

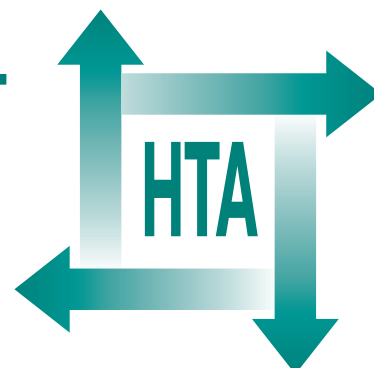
Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers

K Facey, I Bradbury, G Laking and E Payne



October 2007

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Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers

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The research reported in this monograph was commissioned by the HTA Programme as project number 05/01/01. The contractual start date was in August 2005. The draft report began editorial review in June 2006 and was accepted for publication in April 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

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Objectives: To assess the clinical effectiveness of positron emission tomography (PET) using 2-[¹⁸F]-fluoro-2-deoxy-D-glucose (FDG) in breast, colorectal, head and neck, lung, lymphoma, melanoma, oesophageal and thyroid cancers. Management decisions relating to diagnosis, staging/restaging, recurrence, treatment response and radiotherapy (RT) planning were evaluated separately.

Data sources: Major electronic databases were searched up to August 2005 and a survey of UK PET facilities was performed in February 2006.

Review methods: This assessment augments the systematic search undertaken in a previous review. Studies were limited to those using commercial dedicated PET or PET/computed tomography (CT) devices with FDG, in one of the eight cancers.

Results: The new search identified six systematic reviews and 158 primary studies. An economic model for England showed that in non-small cell lung cancer (NSCLC) FDG-PET was cost-effective in CT node-negative patients, but not in CT node-positive patients. A less robust model also showed that FDG-PET was cost-effective in RT planning for NSCLC. A model for Scotland showed that in late-stage Hodgkin's lymphoma (HL), FDG-PET was cost-effective for restaging after induction therapy. For staging/restaging colorectal cancer, FDG-PET changed patient management in a way that can impact on curative therapy. For detection of solitary pulmonary nodule (SPN) there was also impact on patient management, but the resulting effect on patient outcomes was unclear. FDG-PET had an impact on patient management across paediatric lymphoma decisions, but further study of individual management decisions is required. For other cancer management decisions, the evidence on patient management is weak. FDG-PET was accurate in detecting distant metastases across several sites, but

sensitivity was variable for detection of lymph-node metastases and poor in early stage disease where sentinel lymph-node biopsy would be used and for small lesions. There were 61 studies of treatment response. These were generally small and covered all cancers except melanoma. They showed that FDG-PET imaging could be correlated with response, in some cases, but the impact on patient management was not documented. There were 17 small studies of RT planning in four cancers; here, FDG-PET led to alteration of RT volumes and doses, but the impact on patient outcomes was not studied. FDG-PET improved diagnostic accuracy compared with alternatives in a number of other cancer management decisions, but more comparative evidence is needed. There were 23 studies of PET/CT in six cancers (excluding breast and melanoma). In these FDG-PET/CT generally improved accuracy by 10–15% over PET, resolving some equivocal images. The survey of PET facilities in the UK showed that PET and PET/CT are being used for a variety of cancer indications. PET facilities are not distributed evenly across the UK and use is inconsistent. Various research studies are underway in most centres, but only a few of these are collaborative studies. There is major variation in throughput and cost per scan (£635–1300).

Conclusions: The strongest evidence for the clinical effectiveness of FDG-PET is in staging NSCLC, restaging HL, staging/restaging colorectal cancer and detection of SPN. Some of these may still require clinical audit to augment the evidence base. Other management decisions require further research to show the impact of FDG-PET on patient management or added value in the diagnostic pathway. It is likely that capital investment will be in the newer PET/CT technology, for which there is less evidence. However, as this technology appears to be slightly more accurate

than PET/CT, the PET clinical effectiveness results presented here can be extrapolated to cover PET/CT. PET research could be undertaken on FDG-PET or FDG-PET/CT, using a standard cancer work-up process on typical patients who are seen within the NHS in England. For treatment response and RT planning, the

need for larger studies using consistent methods across the UK is highlighted as a priority for all cancers. For all studies, consideration should be given to collaboration across sites nationally and internationally, taking cognisance of the work of the National Cancer Research Institute.



Contents

List of abbreviations	vii	6 Conclusions	65
Executive summary	xi	Implications for healthcare	65
1 Background	1	Recommendations for FDG-PET or FDG-PET/CT research	65
The systematic review	1	Acknowledgements	71
Comparators in the cancer work-up	1	References	73
The technology	1	Appendix 1 Search strategy	87
2 Research questions (scope of report)	5	Appendix 2 Methodologies for combining diagnostic study summaries	89
3 Review methods	7	Appendix 3 Flowchart for selection of English systematic reviews	91
Systematic search process	7	Appendix 4 Flowchart for selection of systematic reviews in languages other than English	93
Selection of papers	8	Appendix 5 Flowchart for selection of English primary studies	95
Data extraction and quality assessment	9	Appendix 6 Flowchart for selection of primary studies in languages other than English	97
Methodologies used for summarising diagnostic studies	12	Appendix 7 Data extraction tables	99
Methodology for treatment response	13	Appendix 8 Cost-effectiveness studies	249
Other data sources	13	Appendix 9 Questionnaire for survey of UK PET facilities	253
4 Results of the review	15	Appendix 10 Survey of PET facilities in the UK (March 2006)	255
Quantity and quality of research	15	Appendix 11 HTA project: NSCLC staging	267
Assessment of clinical effectiveness of FDG-PET	16	Health Technology Assessment reports published to date	269
Breast cancer	16	Health Technology Assessment Programme	285
Colorectal cancer	19		
Head and neck cancer	24		
Lung cancer	30		
Lymphoma	36		
Malignant melanoma	41		
Oesophageal cancer	43		
Thyroid cancer	46		
PET/CT: mixed cancers	48		
Potential harm	49		
Cost-effectiveness	49		
Survey of PET and PET/CT facilities in the UK	50		
5 Discussion	51		
Statement of the principal findings of the systematic review	51		
Other HTAs of PET	54		
The technology	55		
Organisational issues related to PET imaging	56		
Systematic review methods for FDG-PET ..	58		
Additional research and evaluative implementation	59		
Strengths and limitations of this report	64		



List of abbreviations

2D	two-dimensional	CE	conventional evaluation
3D	three-dimensional	CEA	carcinoembryonic antigen
ABVD	adriamycin, bleomycin, vinblastine, dacarbazine (chemotherapy)	CECT	contrast-enhanced computed tomography
AC	adenocarcinoma	CENTRAL	Cochrane Central Register of Clinical Trials
AETS	Agencia de Evaluacion de Tecnologias Sanitarias	chemo	chemotherapy
AHRQ	Agency for Healthcare Research and Quality	CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone (chemotherapy)
AJCC	American Joint Committee on Cancer	CI	confidence interval
ALN	axillary lymph node	CLM	colorectal liver metastases
ALND	axillary lymph-node dissection	Comp.	comparator
ARSAC	Administration of Radioactive Substance Advisory Council	CR	complete response
ASCT	autologous stem cell transplantation	CRT	chemoradiotherapy
AUC	area under the curve	CT	computed tomography
BCBS	Blue Cross Blue Shield association (USA)	CT/MRI	comparative group in analysis including patients who have undergone either CT or MRI, or both CT and MRI
BMB	bone-marrow biopsy	CWU	conventional work-up
BS	bone scintigraphy	CXR	chest X-ray
BSA	body surface area	DA	discriminant analysis
CBV	cyclophosphamide, BCNU (busulphan), etoposide (VP-16)	DACEHTA	Danish Centre for Evaluation and Health Technology Assessment
CCR	continuing clinical response	DARE	Database of Abstracts of Reviews of Effectiveness
CDET	coincidence detection emission tomography		

continued

List of abbreviations continued

DFS	disease-free survival	¹³¹ I	iodine-131
DOR	diagnostic odds ratio	ICER	incremental cost-effectiveness ratio
DRE	digital rectal examination	ICT	induction chemotherapy
endosc.	endoscopy	INAHTA	International Network of Agencies for Health Technology Assessment
ESR	erythrocyte sedimentation rate	IPI	International Prognostic Index
EUS	endoscopic ultrasound	IWC	International Workshop Criteria
F	female	KCE	Health Care Knowledge Centre (Belgium)
FD	fractal dimension	LN	lymph node
FDG	2-[¹⁸ F]-fluoro-2-deoxy-D-glucose	LR	likelihood ratio
FLT	[¹⁸ F]3'-deoxy-3'-fluorothymidine	LSO	lutetium oxyorthosilicate
FN	false negative	<i>m</i>	number of lesions
FNAB	fine-needle aspiration biopsy	M	male
FP	false positive	mets	metastases
FPR	false-positive rate	MI	morphological imaging
FPSS	FDG-PET search strategy	MIJN	Mijnhout strategy
Ga-67	gallium-67 citrate	MRC	Medical Research Council
GEJ	gastro-oesophageal junction	MRI	magnetic resonance imaging
GI	gastrointestinal	MRI/CT	magnetic resonance imaging or computed tomography
GTV	gross tumour volume	MRND	modified radical neck dissection
HAS	Haute Autorité de Santé	MRU	minimum residual uptake
HDT	high-dose therapy	MSAC	Medical Services Advisory Committee
H&E	haematoxylin and eosin	<i>n</i>	number of patients
HL	Hodgkin's lymphoma		
HTBS	Health Technology Board for Scotland		
hTg	human thyroglobulin		

continued

List of abbreviations continued

NA	not applicable	Prob.	probability
NCRI	National Cancer Research Institute	PS	primary study
NCRN	National Cancer Research Network	PTV	planning target volume
NHL	non-Hodgkin's lymphoma	QALY	quality-adjusted life-year
NICE	National Institute for Health and Clinical Excellence	QoL	quality of life
NLR	non-linear regression	QUADAS	Quality Assessment of Studies of Diagnostic Accuracy
NMP	nuclear medicine physician	RCR	Royal College of Radiologists
NPV	negative predictive value	RCT	randomised controlled trial
NR	no response, not recorded	RECIST	Response Evaluation Criteria in Solid Tumours
NRR	National Research Register	Ref.	references
ns	not significant	ROC	receiver operating characteristic
NSCLC	non-small cell lung cancer	ROI	region of interest
OPT	occult primary tumour	RT	radiotherapy
OS	overall survival	SCC	squamous cell carcinoma
PD	progressive disease	SCLC	small cell lung cancer
PET	positron emission tomography	SD	stable disease
PET/CT	integrated PET/CT device	sens.	sensitivity
PET+CT	visual correlation of PET and CT	SLN	sentinel lymph node
PFS	progression-free survival	SLNB	sentinel lymph-node biopsy
PMR	partial metabolic response	SNB	sentinel node biopsy
PNS	paraneoplastic neurological syndrome	spec.	specificity
PR	partial response	SPECT	single-photon emission computed tomography
Prev.	prevalence	SPN	solitary pulmonary nodule

continued

List of abbreviations continued

SR	systematic review	$^{99m}\text{Tc(V)DMSA}$	pentavalent technetium-99m-dimercaptosuccinic acid
sROC	summary receiver operating characteristic	TCP	tumour control probability
SRS	somatostatin receptor scanning	Tg	thyroglobulin
STARD	Standards for Reporting of Diagnostic Accuracy	^{201}Tl	thallium-201
SUV	standardised uptake value	TN	true negative
ΔSUV	change in SUV	TP	true positive
^{99m}Tc	Technetium-99m	TPR	true-positive rate
$^{99m}\text{Tc TF}$	Technetium-99m tetrofosmin	UCL	University College London
$^{99m}\text{Tc-MIBI}$	technetium-99m-2-methoxyisobutylisonitrile	US	ultrasound
$^{99m}\text{Tc-TOC}$	technetium-99m-labelled somatostatin analogue, $^{99m}\text{Tc-EDDA/HYNIC-TOC}$	VAS	visual analogue scale
		WB	whole body
		WBS	whole-body scan

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.



Executive summary

Background

Staging the extent of disease in primary or recurrent cancer requires a range of diagnostic tests to identify the primary tumour and any metastases. Most of the imaging methods are anatomical, e.g. computed tomography (CT). Positron emission tomography using 2-[¹⁸F]-fluoro-2-deoxy-D-glucose (FDG-PET) is an alternative form of diagnostic imaging based on tissue function, which can help to identify active tumours. This health technology assessment evaluates the use of FDG-PET in eight cancers. It encompasses both dedicated PET and newer PET/CT technology that integrates PET and CT into one device.

Objectives

The aim of this review was to assess the clinical effectiveness of FDG-PET in breast, colorectal, head and neck, lung, lymphoma, melanoma, oesophageal and thyroid cancers. For each cancer, use of FDG-PET to aid management decisions relating to diagnosis, staging/restaging, recurrence, treatment response and radiotherapy (RT) planning were evaluated.

Methods

Data sources

This report augments the systematic search undertaken in a previous rapid review. It uses a systematic search undertaken in August 2005 that identified systematic reviews and primary studies not included in the previous review and a survey of UK PET facilities performed in February 2006.

Study selection

Studies were limited to those using commercial dedicated PET or PET/CT devices with FDG, in one of the eight cancers. The most recent robust systematic reviews were identified, along with additional primary studies that were prospective and included at least 12 patients. Treatment response and RT planning studies were included if they had at least six patients and for PET/CT retrospective studies were included. All selections

were made by two researchers independently using predefined inclusion criteria.

Data extraction

Data extraction forms were created for each study to identify key features of study design and conduct according to the Quality Assessment of Studies of Diagnostic Accuracy (QUADAS) quality checklist.

Data synthesis

Given the variety of methods used in the individual publications, the evidence has been summarised in qualitative form.

Results

From this new search, six systematic reviews and 158 primary studies were included in the systematic review.

Cost-effectiveness

An English economic model shows that in non-small cell lung cancer (NSCLC) FDG-PET was cost-effective in CT node-negative patients, but not in CT node-positive patients. There is some evidence to suggest that FDG-PET may also be cost-effective in RT planning, but this model is less robust.

A Scottish model shows that in late-stage Hodgkin's lymphoma (HL), FDG-PET was cost-effective for restaging after induction therapy.

Patient management

For staging/restaging colorectal cancer, FDG-PET changed patient management in a way that can impact on curative therapy.

For detection of solitary pulmonary nodule (SPN) there is evidence of impact on patient management, but the impact on patient outcomes is unclear.

FDG-PET had an impact on patient management across paediatric lymphoma decisions, but further study of individual management decisions is required. For other cancer management decisions, the evidence on patient management is weak.

Diagnostic accuracy

FDG-PET was accurate in detecting distant metastases across several sites, but sensitivity was variable for detection of lymph-node metastases and poor in early-stage disease, where sentinel lymph-node biopsy would be used and for small lesions.

FDG-PET had improved diagnostic accuracy over alternatives in:

- colorectal recurrence
- detection of occult and synchronous head and neck tumours, where other tests have failed
- staging regional lymph nodes in clinically node-positive necks
- restaging/recurrence in head and neck
- staging SCLC
- staging lymphoma
- restaging NHL
- staging oesophageal
- recurrent epithelial thyroid cancer, where elevated biomarkers are not confirmed by ¹³¹I scintigraphy.

Some evidence of the diagnostic accuracy of FDG-PET exists for the following cancers, but more comparative evidence is needed:

- locoregional recurrence in breast
- staging/restaging/recurrence in breast
- staging lymph nodes in colorectal cancer
- diagnosis of occult SCLC
- staging late-stage melanoma
- recurrent melanoma
- restaging thyroid
- recurrent medullary thyroid cancer, where elevated biomarkers are not confirmed by ¹³¹I scintigraphy
- clinically suspected recurrent thyroid cancer with no other markers.

Treatment response/RT planning

There were 61 studies of treatment response in all cancers except for melanoma. Most studies were small and evaluated a range of treatments, at different time-points, with a variety of imaging processes and analytical techniques. They showed that FDG-PET imaging could be correlated with response, in some cases, but the impact on patient management was not documented.

There were 17 small studies on RT planning in four cancers. FDG-PET led to alteration of RT volumes and doses, but the impact on patient outcomes was not studied.

PET/CT

There were 23 studies of PET/CT in six cancers (excluding breast and melanoma). Most studies combined different groups of patients to assess primary and recurrent tumours for staging and restaging. These showed that FDG-PET/CT generally improved accuracy by 10–15% over PET, resolving some equivocal images.

Survey

The survey of PET facilities in the UK showed that PET and PET/CT are being used for a variety of cancer indications. The distribution of PET facilities is not evenly spread across the UK and uses are not consistent. FDG deliveries are often required twice a day and most units use a commercial provider. Various research studies are underway in most centres, but only a few of these are collaborative studies. There is major variation in throughput and cost per scan (£635–1300).

Conclusions

Implications for healthcare

The strongest evidence for the clinical effectiveness of PET is in staging NSCLC, restaging HL, staging/restaging colorectal cancer and detection of SPN. Some of these may still require clinical audit to augment the evidence base. Other management decisions require further research to show the impact of FDG-PET on patient management or added value in the diagnostic pathway.

It is likely that new capital investment will be in the newer PET/CT technology, for which there is less evidence. However, as this technology appears to be slightly more accurate than PET/CT, the PET clinical effectiveness results presented here can be extrapolated to cover PET/CT.

Recommendations for research

PET research could be undertaken on FDG-PET or FDG-PET/CT, using a standard cancer work-up process on typical patients who are seen within the NHS in England. For treatment response and RT planning, the need for larger studies using consistent methods across the UK is highlighted as a priority for all cancers.

For all studies, consideration should be given to collaboration across sites nationally and internationally, taking cognisance of the work of the National Cancer Research Institute.

Chapter I

Background

The systematic review

This health technology assessment (HTA) is a systematic review of positron emission tomography using 2-[¹⁸F]-fluoro-2-deoxy-D-glucose (FDG-PET) in cancer management. It augments an ultra rapid review¹ that was carried out in the summer of 2004.

This report presents a systematic review of the clinical effectiveness of FDG-PET used in the clinical work-up of eight cancers: breast, colorectal, head and neck, lung, lymphoma, melanoma, oesophageal and thyroid. It augments the ultra rapid review by critically appraising new primary studies in each cancer, evaluating the use of FDG-PET in treatment response and radiotherapy (RT) planning studies, and evaluating the newer technology of integrated PET/CT separately. It also presents a survey of PET facilities across the UK.

Comparators in the cancer work-up

The diagnosis, staging, review and response assessment of any cancer is complex. The clinical work-up involves a variety of diagnostic tests with clinical or imaging follow-up if necessary. The tests will vary depending on the type and location of the tumour(s), but could involve

- physical examination
- X-ray
- blood tests
- bronchoscopy
- ultrasound
- endoscopy
- whole-body scintigraphy
- computed tomography (CT)
- magnetic resonance imaging (MRI)
- biopsy and other tests.

Guidance on appropriate work-ups is presented by the National Institute for Health and Clinical Excellence (NICE) in its cancer guidance for all of the cancers of interest in this HTA apart from thyroid cancer (<http://www.nice.org.uk/guidance/topic/cancer>).

FDG-PET may be used at different points in a cancer work-up, in addition to other tests, or in a subset of patients who are positive with a specific test (e.g. CT), or as a replacement for another test or procedure. In all cases the clinical effectiveness is demonstrated by the added value of PET in the whole clinical work-up.

The technology

PET

CT and MRI are high-resolution anatomical imaging techniques that are commonly used in cancer to detect potential tumours. However, there is concern about the inability of these imaging modalities to identify small masses and distinguish between scar tissue and active tumour. PET is an imaging method that can be used to establish the metabolic or functional parameters of tissue and so it should be able to differentiate active tumours more clearly.

PET imaging uses a radiopharmaceutical, which requires a cyclotron for its production. The biological rationale for using the glucose analogue FDG in cancer imaging is that tumours tend to absorb glucose at a rapid rate, owing to increased expression of the transporter enzyme Glut-1. Inside the cell the fluorine atom on the FDG molecule prevents its further metabolism. The metabolically trapped FDG thus accumulates and so can be imaged. Tumours can be identified as regions of high accumulation of FDG. This rationale is valid for most regions of the body, with the exception of tissues in which glucose metabolism is normally high; these include the brain, heart muscle, skeletal muscle, brown fat (a specialised kind of heat-generating fat located mainly between the shoulder blades) and inflammation. FDG tumour imaging is also poor in the region of the bladder, since FDG is excreted into the urine. FDG uptake is also reduced when the blood sugar level is high, as in poorly controlled diabetes. For some tumours (e.g. melanoma), the signal-to-noise ratio may also be high.

Figure 1 shows a PET scanner in use in the UK.



FIGURE 1 PET imager at John Mallard PET Centre, Aberdeen (image reproduced with kind permission of Professor Peter Sharp)

FDG accumulation is evaluated with PET imaging. The definition of increased uptake may be based on the reader's qualitative visual impression, or more formally by using indices such as the standardised uptake value (SUV) (tissue radioactivity concentration divided by the total injected dose, normalised to body size). As PET images lack anatomical information, PET and CT images are normally compared to determine the location of a site of accumulation. This may be done by direct visual means, or alternatively by computer-based image fusion.

The size of lesion that can be detected by PET is limited by several factors, including the physics of positron emission, the spatial resolution of the scanner (typically 4.5–6 mm in the centre of the axial field) and safe dosing limits of FDG.

For further information about the physical properties of PET imaging see Section 2.5.1 of the Scottish HTA on PET imaging.²

PET is an evolving technology that has developed in the past 15 years to allow whole-body and three-dimensional (3D) imaging, use of new scintillator materials, iterative 3D reconstruction algorithms and the combination of PET with other imaging devices.³ These developments have



FIGURE 2 PET/CT imager at NHS Grampian (image reproduced with kind permission of Professor Peter Sharp)

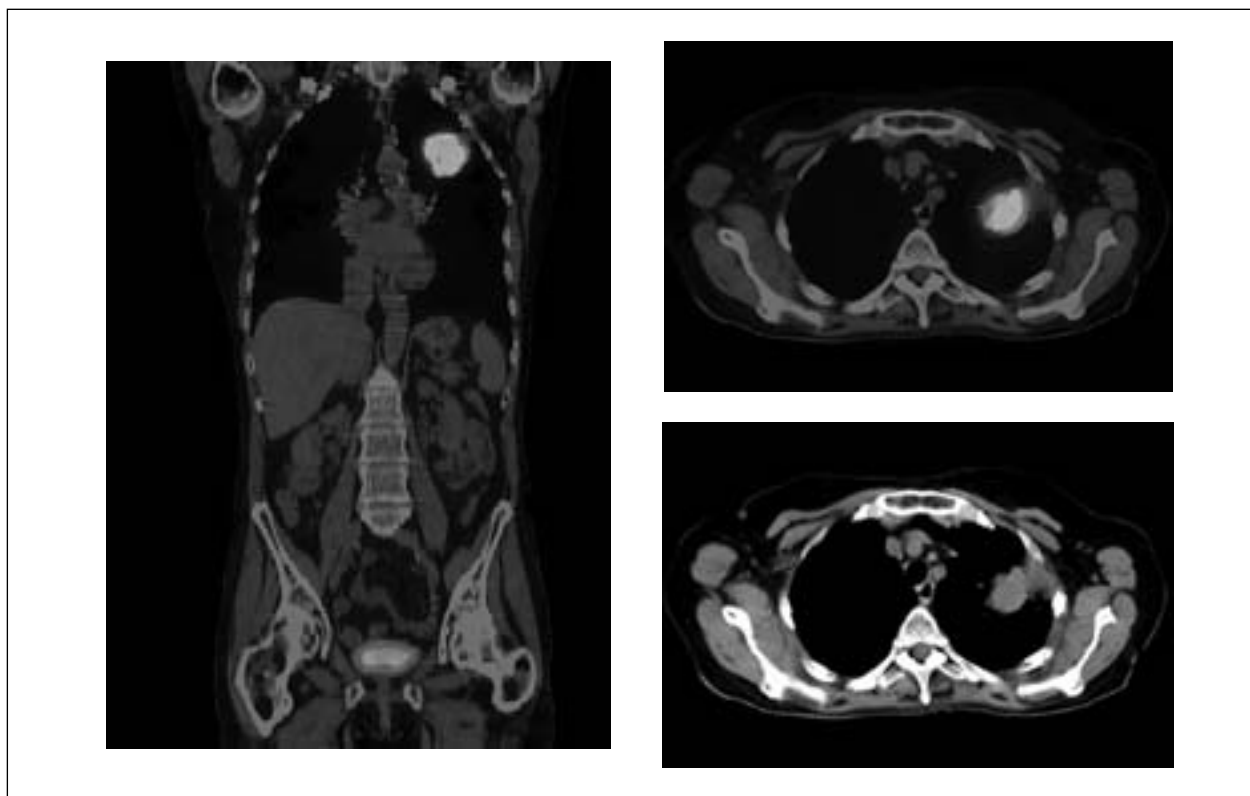


FIGURE 3 Lung cancer FDG-PET/CT scan (© Alliance Medical; images courtesy of Alliance Medical)

helped to improve the quality of the image and contributed to the more widespread use and study of PET in a variety of conditions.

PET/CT

PET/CT is a newer form of the technology that combines PET and CT cameras in tandem in a single unit (*Figure 2*). It permits rapid sequential acquisition of both kinds of image, without the need for the patient to change position. This allows registration of the PET image with the anatomical image on the CT scan and so improves the technical quality of computer-based fusion images. The combined device can be used to correct for photon attenuation in PET, thus eliminating the need for a PET transmission scan.³

Messa and colleagues⁴ provide an overview of PET/CT. They present the technical characteristics of three common PET/CT systems (GE Discovery

LS, CTI REVEAL/Siemens BIOGRAPH and Philips Gemini), the process for obtaining the image, clinical applications and future developments.

Figure 3 shows an FDG-PET/CT scan of a patient with known cancer of the lung. A CT scan (lower right frame) suggested that the mass extended into the chest wall in the left upper zone. The FDG-PET/CT scan was used for disease staging to determine the true extent of the disease. The FDG-PET/CT scan (upper right frame) revealed the large mass and showed clearly that the mass did not extend into the chest wall, so the patient was downstaged and FDG-PET/CT enabled an attempt at curative surgery.

Cherry³ notes that within 5 years of the introduction of the first PET/CT scanner they have accounted for more than 90% of all PET scanner sales.

Chapter 2

Research questions (scope of report)

The key research question for this report was: what is the clinical effectiveness of FDG-PET for the management of the following cancers:

- breast
- colorectal
- head and neck (mouth, lip, tongue; pharynx, larynx)
- lung (non-small cell, small cell and solitary pulmonary nodule)
- lymphoma (Hodgkin's and non-Hodgkin's)
- malignant melanoma
- oesophageal
- thyroid?

The report assesses dedicated PET scanners using FDG. Gamma cameras and other radiopharmaceutical tracers are excluded. The newer technology of integrated PET/CT is assessed separately.

Cancers other than the eight listed have been excluded. Within head and neck cancer, carcinoma of the mouth, lip, tongue, pharynx and larynx were included. Brain tumours were excluded. Nasopharyngeal carcinoma was also excluded (as these are rare in the UK and the only studies were in Oriental populations that were not considered similar to the UK population).

Since the ultra rapid review in these cancers,¹ an English clinical guideline on lung cancer has been published by NICE. This guideline is based on a systematic review, which includes assessment of the clinical effectiveness and cost-effectiveness of FDG-PET.⁵ To avoid duplication of work, this systematic review just sought to identify any evidence that might add to this national guideline, so is somewhat more focused to the UK context than the other searches.

The cancer management decisions studied were:

- diagnosis (detection of cancer before confirmation of disease)
- staging (occurs after histological confirmation and before initial therapy)
- recurrence (detection of malignancy in follow-up after disease-free period, often when suspicion is raised by other follow-up tests)
- restaging (occurs after initial therapy or when recurrence has been confirmed)
- assessment of treatment response (during or immediately after therapy)
- RT planning (before RT to plan target volume and dose).

Note that there may be some ambiguity in classification of studies in restaging and assessment of treatment response immediately after therapy.

For diagnosis, staging/restaging and recurrence, FDG-PET is used to detect malignant lesions, either the primary tumour or local or distant metastases.

In response assessment, FDG-PET is used to estimate changes in FDG uptake by the tumour during therapy, in the expectation that these will be correlated to, but occur earlier than, clinical or pathological changes.

In RT planning, FDG-PET is used to delineate more accurately target region for radiotherapy.

PET imaging has been proposed for use in other applications than cancer (e.g. ischaemic heart disease and neurology),⁶ but these are outside the scope of this report.

Chapter 3

Review methods

Systematic search process

This report updates a previous systematic review of FDG-PET in the eight selected cancers.¹ Searches for the previous report were undertaken in May 2004 and only sought to identify English systematic reviews, hence it was termed an ultra rapid review.

This systematic literature search included:

- English systematic reviews published since the search for the ultra rapid review (May 2004)
- systematic reviews published in a Western European, non-English language since 1966 (with those prior to 2000 deselected by hand)
- English and non-English primary studies since 2000.

Sources searched for systematic reviews

MEDLINE, MEDLINE in-process and other non-indexed citations and EMBASE were searched in August 2005 for systematic reviews of FDG-PET or FDG-PET/CT in cancer. The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness (DARE) and the HTA database (International database of HTA reports) were also searched in August 2005.

Members of the International Network of Agencies for Health Technology Assessment (INAHTA) were contacted in August 2005 for details of systematic reviews not yet listed on the HTA database, or to clarify incomplete HTA database entries.

Sources searched for primary studies

The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE in-process and other non-indexed citations, and EMBASE were searched in August 2005 for primary studies of FDG-PET or FDG-PET/CT in cancer.

Search strategy development

A generic cancer search strategy was used to reduce the margin for error in selecting search terms. Items related to cancers excluded from this review were deselected during the first screen of abstracts.

A filter, developed by Jadad and colleagues,⁷ was used in MEDLINE and EMBASE to select potential systematic reviews. Primary studies were selected during the second screen of abstracts.

To ensure comprehensive identification of all relevant papers and to compare search strategies, the following processes were used.

In the ultra rapid review:

- an FDG-PET search strategy (FPSS) was devised
- an FDG-PET search strategy recommended by Mijnhout⁸ was also used
- each of the FDG-PET search strategies was combined with the cancer strategy and a systematic review filter, and the results were compared
- no additional reviews were retrieved using the Mijnhout strategy, so the results from the FPSS were used in the ultra rapid review.

In this HTA:

- the FPSS from the ultra rapid review was used
- an updated version of the Mijnhout strategy⁹ (MIJN) was also used
- each of the FDG-PET strategies was combined with the cancer strategy, date, language and human limits were applied, and a systematic review filter was used for the searches of systematic reviews
- the results from both FDG-PET strategies were included in the review
- the results from both FDG-PET strategies were tagged, so that the progress of the items retrieved by each could be monitored throughout the review process.

It was expected that the FPSS would retrieve many more items because its aim is to be sensitive, whereas MIJN is designed to be more precise for identifying FDG-PET studies.

Search strategies were compared:

- to determine how many additional papers from the FPSS would be selected at the abstract, full paper and inclusion stages

- to assess whether the time taken to process the larger number of results was beneficial in terms of the number of any additional papers included in the review.

The search strategies used in MEDLINE are presented in Appendix 1. Details of all the strategies can be obtained from the authors.

Selection of papers

The information specialist undertook an initial selection of articles based on abstracts, deleting duplicate references, papers not studying humans, those not studying FDG-PET and those clearly studying a cancer outside the scope of this report. These initial selections were checked by another reviewer.

The second stage of abstract review used separate selection criteria for systematic reviews, primary studies, treatment response studies and FDG-PET/CT. The latter studies had sparser evidence and so used more lenient inclusion criteria.

Systematic reviews

Inclusion criteria:

- dedicated FDG-PET in the stated cancers in humans
- evidence related to diagnostic accuracy, change in patient management, clinical outcomes, treatment response or RT planning
- robust qualitative or quantitative systematic reviews
- studies in English, French, German, Spanish or Italian.

Exclusion criteria:

- gamma PET (dual-headed camera)
- coincidence detection emission tomography (CDET)
- tracers other than FDG
- systematic reviews that have been superseded
- reports that cost more than £50 to obtain
- no English abstract available
- published as (conference) abstract only
- lung cancer systematic reviews that added nothing to the NICE guideline.

PET primary studies

Inclusion criteria:

- prospective study of dedicated FDG-PET in a single cancer of interest
- published after the search date of a robust

- systematic review covering that cancer management decision
- clinical study published as a full article in a peer-reviewed journal
- evidence related to diagnostic accuracy, change in patient management or clinical outcomes
- at least 12 human patients with the cancer of interest
- patient pathway similar to that used in the UK
- suitable reference standard used in diagnostic studies
- studies in English, French, German, Spanish or Italian.

Exclusion criteria:

- evaluations of gamma PET or CDET
- abstracts from conferences, etc.
- preliminary or interim analyses or case series that were later augmented
- retrospective studies
- tracers other than FDG
- cancers other than the eight specified
- mixed cancers that were not reported separately with at least 12 patients in one cancer
- review/editorial
- PET technical papers (e.g. SUVs, FDG uptake, phantom studies, quantitation papers)
- abstract does not allow study characteristics to be determined
- reports that cost more than £50 to obtain
- no English abstract available
- studies in non-English languages that were duplicated in English papers
- lung cancer studies that added nothing to the NICE guideline.

Treatment response/planning

Inclusion criteria:

- clinical study of FDG-PET in a peer-reviewed journal
- evidence showing use of PET to inform treatment assessment or RT planning
- prospective study in one cancer of interest
- patient pathway similar to that used in the UK (comparator that fits in English pathway)
- at least six patients
- studies in English, French, German, Spanish or Italian.

Exclusion criteria:

- evaluations of gamma PET or CDET
- abstracts from conferences, etc.
- tracers other than FDG
- cancers other than the eight specified

- mixed cancers where results by cancer cannot be obtained
- retrospective studies
- abstract does not allow study characteristics to be determined
- reports that cost more than £50 to obtain
- no English abstract available
- non-English studies that were duplicated in English papers
- SUV studies that only evaluated prognosis, not treatment response or planning with a view to evaluating patient management.

PET/CT primary studies

Inclusion criteria:

- clinical study of a commercial integrated PET/CT device using FDG
- prospective or retrospective study published in a peer-reviewed journal
- evidence related to diagnostic accuracy, change in patient management or clinical outcomes
- at least 12 human patients with the cancer of interest
- patient pathway similar to that used in the UK (comparator that fits in English pathway)
- suitable reference standard used in diagnostic studies
- studies in English, French, German, Spanish or Italian.

Exclusion criteria:

- evaluations of gamma PET, CDET or PET
- abstracts from conferences, etc.
- tracers other than FDG
- cancers other than the eight specified
- abstract does not allow study characteristics to be determined
- reports that cost more than £50 to obtain
- no English abstract available
- non-English studies that were duplicated in English papers
- PET technical papers.

Papers were selected by independent review of titles and abstracts by two researchers, and medical

queries were resolved by the medical adviser. Differences in selections were resolved and full papers obtained. Papers were then reviewed independently by two reviewers again according to the selection criteria.

Data extraction and quality assessment

Data were extracted into separate tables for systematic reviews and primary studies and are presented in this order for each cancer management decision.

Systematic reviews

The ultra rapid review,¹ which this report updates, included all robust systematic reviews of FDG-PET in the eight cancers. Studies that were completely superseded by a more recent review were excluded. The data extraction tables in Section 5.3.1 of the ultra rapid review show that most of the systematic reviews had some studies in common and so were not independent pieces of evidence. Consequently, this systematic review has selected the most recently published robust systematic review available for each cancer management decision. Only where reports present results in different ways that inform the understanding of the evidence are two systematic reviews presented.

Robustness is defined here as clear presentation of the systematic search methodology (date of search, sources, etc.), clear inclusion criteria and valid critical assessment methods (that discuss bias and are methodologically sound). Results from these systematic reviews are presented using the analytical methods used in the published papers, with separate comments about study quality, data and analytical caveats.

The hierarchy of diagnostic efficacy established by Fryback and Thornbury,¹⁰ as outlined in *Table 1*, was used as a framework to quantify the level of evidence available for each cancer management decision in the systematic reviews. This review

TABLE 1 Hierarchy of diagnostic efficacy

1	Technical	Technical imaging quality
2	Diagnostic accuracy	Sensitivity, specificity, positive predictive value, negative predictive value
3	Diagnostic thinking	Likelihood ratio (Bayesian approach using pretest and post-test probabilities)
4	Therapeutic	Changes in therapeutic choices (patient management)
5	Patient outcome	Improvement in morbidity/mortality
6	Societal	Cost-benefit analysis

focuses on all evidence between hierarchies 2 and 5 (excluding technical imaging quality data) and mentions the societal level of evidence (cost-effectiveness/cost-benefit) when it is available.

Primary studies related to diagnostic efficacy

As outlined in *Table 1*, there are various levels at which diagnostic efficacy might be studied and this will lead to different forms of primary study. A diagnostic accuracy study is normally a case series of patients and can provide evidence about diagnostic accuracy, diagnostic thinking and some limited information about therapeutic efficacy. Stronger evidence to support therapeutic efficacy is provided from a study specifically designed to collect documented information about the impact of FDG-PET on therapeutic choices. Such a study could be a (before-and-after) case series or a randomised controlled trial (RCT) and may involve a wider multidisciplinary team or teams than would be involved in a diagnostic accuracy study. Some information about patient outcomes may be obtained from a case series with a good period of follow-up for all patients, but definitive evidence can only be obtained from an RCT. Cost-benefit evidence arises from well-conducted economic evaluations.

In this report, emphasis is placed on quality assessment of diagnostic accuracy studies, as more than 95% of the studies extracted for this systematic review fall into this category.

Diagnostic accuracy studies need to be assessed using criteria that can help to determine the diagnostic performance of the technology and its clinical utility. This requires assessment of the robustness of the study and its applicability to the local clinical setting (including its place in the clinical pathway, relevance to the population and potential impact).

One of the assessment guides most commonly used in HTA reports is that now published by the Veterans Administration Technology Assessment Program.¹¹ It lists criteria that seek to avoid the potential biases that can arise in diagnostic accuracy studies and guides the evaluation of clinical impact. European regulatory guidance is also available on features that will contribute to the robust design of studies to evaluate diagnostic agents.¹²

More recently, comprehensive guidelines on the assessment of diagnostic technologies have been published by the Medical Services Advisory

Committee (MSAC).¹³ They clearly explain the diagnostic assessment context and present a detailed process for identifying, appraising and analysing evidence from diagnostic studies.

In terms of appraising quality, Chapter 8 of the MSAC guidelines focuses on two main areas that can compromise quality, namely variation and bias. They note that biases can be related to:

- selection (study population especially chosen and/or not representative)
- imperfect reference standard (better standard exists)
- performance (provision of care other than the experimental intervention)
- attrition (outcomes not available for all patients who entered the study)
- detection (method of measuring outcomes)
- verification (reference standard only undertaken on specific patients, often led by the index test, or different tests used to verify a positive and negative result)
- review (index test and reference standard not interpreted independently)
- clinical review (clinical data available when interpreting index test)
- diagnosis review (reference standard interpreted with knowledge of index test)
- treatment (reference standard evaluated later than index and after treatment has started)
- disease progression (long interval between index test and reference standard)
- incorporation (index test is used in establishing final diagnosis)
- handling of equivocal results (exclusion or different interpretation of equivocal results).

However, some of these biases actually contribute to the external validity of a study or are ethically necessary. For example, for verification purposes it may be unethical to conduct the reference test of biopsy in patients who show no sign of recurrence or it would be unclear where to biopsy if the question related to distant metastases. Similarly, for review it may be standard clinical practice to biopsy patients unblinded to other results.

The appendices of the MSAC guidelines present two checklists that are being increasingly used to help judge the quality of diagnostic studies. The STARD initiative (Standards for Reporting of Diagnostic Accuracy) presents a 25-point checklist for reporting of studies, which has been widely published across a variety of medical journals (e.g. Bossuyt, 2003).¹⁴ The QUADAS tool (Quality Assessment of Studies of Diagnostic Accuracy) is a

14-point checklist (with a yes/no/unclear response) that was designed for use in systematic reviews. It was created using a Delphi process involving a group of nine experts in diagnostic research and assesses the population, reference standard, disease progression bias, verification bias, review bias, clinical review bias,¹⁵ incorporation bias, test execution, attrition and equivocal results.

For this systematic review a descriptive approach to assessing the studies was considered more appropriate as the inclusion criteria had been

designed to exclude poorer quality studies (small, retrospective, mixed cancers, poor or partial reports). *Table 2* shows how the 14 questions of the QUADAS checklist were addressed in this systematic review.

Considering other forms of study in the hierarchy of diagnostic efficacy, quality assessments have not been developed for patient management studies, so standard principles of good study design and analysis apply. Issues to be considered in a case series include a detailed protocol with predefined

TABLE 2 Use of the QUADAS questionnaire to assess study quality in this review

QUADAS question	Assessment process
1. Was the spectrum of patients representative of the patients who will receive the test in practice?	Data extraction described the country of study, patient population and demographics to allow comparison with English population. Study excluded if population very different from UK
2. Were selection criteria clearly described?	Only prospective studies included. Described in data extraction and if selection criteria were broad this was clearly explained
3. Is the reference standard likely to correctly classify the target condition?	No reference standard led to exclusion. Older reference standards were noted in data extraction and results (e.g. some superseded by sentinel lymph-node biopsy)
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Outlined in data extraction where information available and long periods noted as potential bias
5. Did the whole sample, or a random selection of the sample, receive verification using a reference standard of diagnosis?	Details of how many patients received each reference standard documented in data extraction form; clear forms of verification bias not resulting from clinical need noted
6. Did patients receive the same reference standard regardless of the index test result?	
7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	
8. Was the execution of the index test described in sufficient detail to permit replication of the test?	Full details of specification of PET, FDG dose and attenuation correction provided. Studies with non-commercial devices excluded. Extreme FDG doses noted
9. Was the execution of the reference standard described in sufficient detail to permit its replication?	Nature of reference standard was identified (e.g. histopathology or follow-up). For follow-up, the period was stated where given and for imaging follow-up, the methods of imaging were stated
10. Were the index test results interpreted without knowledge of the results of the reference standard?	Reported in data extraction, stating who did the interpretation and whether blinded
11. Were the reference standard results interpreted without knowledge of the results of the index test?	Not fully evaluated given this information is often not reported and there is a role for such comparisons to support external validity
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not fully evaluated as this is rarely reported in sufficient detail to allow such judgements
13. Were uninterpretable/intermediate test results reported?	Status of equivocal results stated where reported
14. Were withdrawals from the study explained?	Attrition from various tests explained in data extraction

end-points, a sample size that is sufficient to detect a clinically important difference, and methods to encourage complete and accurate data collection that are unbiased and use appropriate analytical techniques. Similar principles apply to an RCT, but the methods of randomisation and blinding would also be considered important.¹⁶

Economic evaluations were judged according to the clarity of model, generalisability to the patients and clinical pathway that would be used in England, and validity of model inputs. If models satisfied these criteria, results were presented with assessments of uncertainty.

Primary studies of treatment response/RT planning

Treatment response studies fall into two categories:

- to predict response early in the course of therapy to permit its continuation or alteration
- to assess response after therapy to determine subsequent management options.

The second form of assessment after therapy is similar to that performed in a diagnostic accuracy study of restaging to assess whether a residual mass is malignant. Consequently, in this report this assessment after therapy is presented as restaging.

Early treatment response studies are quite different from diagnostic accuracy studies as they assess a change in the tumour activity. These studies are more akin to standard clinical trials and should be judged accordingly. However, the PET process may be more complex if a dynamic PET scan (akin to a video) is required as opposed to the standard static scan (akin to a photograph) used in other management decisions. Furthermore the estimation of tumour activity can be complex (see 'Methodology for treatment response', p. 13). So analytical methods need to be carefully reviewed and the ability to replicate the results in clinical practice needs to be judged.

Similarly, RT planning studies use FDG-PET to help to delineate the target volume and dose for radiation therapy and so can be assessed as a clinical study. RT planning studies are generally simpler than treatment response studies as they merely seek to evaluate the location of FDG uptake, so outcomes are straightforward and simple analytical techniques can be used.

Methodologies used for summarising diagnostic studies

In diagnostic studies, 2×2 tables are formed describing the result of the diagnostic test and the true state of 'disease' (e.g. tumour present/absent), as shown in *Table 3*.

The most common method of evaluating diagnostic accuracy is by the calculation of sensitivity and specificity.

Sensitivity is the probability of a positive test result given the subject has the tumour (proportion of malignancies correctly detected):

$$\text{Sensitivity (sens.)} = \text{TP}/(\text{TP} + \text{FN})$$

Specificity is the probability of a negative test result given the subject does not have the tumour:

$$\text{Specificity (spec.)} = \text{TN}/(\text{TN} + \text{FP})$$

Accuracy is calculated as:

$$(\text{TP} + \text{TN})/(\text{TP} + \text{FN} + \text{TN} + \text{FP})$$

When the prevalence (prev.) of a condition is known, the negative predictive value (NPV) can be calculated:

$$\text{NPV} = \frac{(\text{prev. benign})(\text{spec.})}{\{(\text{prev. benign})(\text{spec.}) + (\text{prev. malignant})(1 - \text{sens.})\}}$$

To summarise the discriminative value of a test, the diagnostic odds ratio (DOR) is often used. This is the ratio of the odds of a positive test result in patients with a tumour over the odds of a positive test result in patients without a tumour.

$$\text{DOR} = \frac{\text{Sensitivity}/(1 - \text{Sensitivity})}{(1 - \text{Specificity})/\text{Specificity}}$$

DOR equal to 1 implies that the odds of a positive result in those with and without tumour is equal, so the test has no discriminative power. Values greater than 1 imply better discrimination of those with tumour, with higher levels implying better discrimination.

TABLE 3 Diagnostic study outcomes

Test result	Tumour	
	Present	Absent
Positive	True positive (TP)	False positive (FP)
Negative	False negative (FN)	True negative (TN)

One method of summarising diagnostic study results is to create a pooled estimate of sensitivity and a separate pooled estimate of specificity. For such summaries, two forms of meta-analysis model can be used: a fixed-effects model, which only includes within-study variation, or a random-effects model that includes within-study and between-study variation. The latter gives wider confidence intervals and is probably more appropriate given the heterogeneity apparent among most studies. However, in some cases a random-effects model may give a negative variance estimate, indicating that the true between-study variance is small. In this situation, a fixed-effects model should be used.

Sensitivity and specificity are interrelated and depend on the characteristics of the tumours in the study. Separate analyses of sensitivity and specificity ignore this and tend to underestimate the true parameters. Alternative methods of summarising the sensitivity and specificity across studies are the summary receiver operating characteristic (ROC), or the likelihood ratio. These are described in Appendix 2.

Methodology for treatment response

Treatment response studies often involve repeated scans over time to determine a change in the metabolic function of the tumour (FDG uptake) that might correlate with treatment response. To determine 'treatment response' most studies use the Response Evaluation Criteria in Solid Tumours, established in 2000 (RECIST, <http://imaging.cancer.gov/clinicaltrials/imaging/>). This uses the four categories of complete response (CR), partial response (PR), progressive disease (PD) or stable disease (SD).

Since treatment response assessment is concerned with changes in FDG uptake over time, most studies include a pretreatment 'baseline' scan in addition to one or more scans during treatment to assess response. However, for restaging assessments, response is simply assessed by absence of FDG uptake at one evaluation post-treatment, in tumours known to be generally FDG-avid.

A variety of potential parameters that measure the FDG uptake are plausible. The simplest outcome is change in SUV before and during treatment. SUV measurements attempt to standardise the imaged tumour uptake of FDG to the dose of FDG/unit of surface area. More complex assessments include repeated SUV measurements or non-linear models to estimate FDG uptake from a dynamic scan. Hence, analyses vary from simple calculations to more advanced analytical techniques.

When dynamic scans are used, non-linear regression (NLR) modelling from a full-compartment model represents, in theory, the best available method for the measurement of tumour glucose metabolism, but this requires relatively sophisticated mathematical modelling.^{17,18} An alternative approach is to use the Patlak slope, which is an approximate graphical solution for the multicompartment model of FDG distribution.¹⁹ Its calculation requires two or more venous blood samples to estimate FDG plasma distribution.

Other data sources

In addition to the systematic review, a survey was undertaken of PET facilities in the UK. This used a questionnaire created by the research team that is summarised qualitatively.

Chapter 4

Results of the review

Quantity and quality of research

Quantity of evidence from systematic searches

Appendices 3–6 present flowcharts that depict the search and selection process for systematic reviews and primary studies published in English and other languages.

This report is built on a systematic review of systematic reviews published in English, which included 18 systematic reviews. For each cancer management decision, the most recent and robust of these systematic reviews has been presented in this HTA.

A total of 103 ‘new’ English or non-English systematic reviews were found from the new search for this study. Several of these systematic reviews had appeared in the previous ultra rapid review and so only six new systematic reviews were included in this systematic review, while four were referred to in the discussion or other sections.

The search for primary studies used a broad search strategy for papers published since 2000 relating to PET in any cancer. This resulted in a large number of potential records published in English (3386). Of these, 338 full papers were obtained and 152 were included in the systematic review of clinical effectiveness.

From 410 potential records of primary studies in non-English languages, 29 full papers were obtained and six were included in this systematic review. These papers were professionally translated.

Overview of quality of studies

Diagnostic efficacy

The inclusion and exclusion criteria for individual studies varied across systematic reviews. A few only included prospective, comparative studies. However, given the quality of data available, most included retrospective studies and comparator analyses were often not derived from head-to-head comparisons. Some, but not all, excluded those with fewer than ten patients.

Only prospective primary studies that were undertaken in the late 1990s or early 2000s and

included at least 12 patients were included in this systematic review. They were assessed according to the quality criteria outlined in *Table 2* (p. 11). Of all the quality aspects, the PET scanning process is of particular note as this was generally well reported and seems to have improved from earlier reported studies. Other aspects of quality were more difficult to judge.

In most recent studies, the average FDG dose was approximately 370 MBq, but this varied among studies. The appropriate dose of FDG depends on the protocol for acquisition and sensitivity of the scanner. In one study the dose was as low as 180 MBq, while another used 525 MBq. There is a suggestion that the newer lutetium oxyorthosilicate (LSO) scanners may need a higher dose,²⁰ but the impact of the lower dose is unclear and may have affected the sensitivity.

The majority of studies did not state whether the studied series of patients had entered consecutively. Hence, there may have been selection bias. Furthermore, only a handful of studies stated a sample size calculation. Some studies were small, so estimates of diagnostic accuracy could have altered quite substantially if just one or two patients had been reclassified.

Most comparators seem to be a reasonable reflection of recent or current practice in England, but in some cases care is needed because a suboptimal comparator may have been used and there are few studies of PET/CT versus newer comparators (see the section ‘The technology’, p. 55).

The most difficult issue to judge from these studies was the quality of the reference standard. Histopathology is currently the best reference standard in the setting of potentially curative surgical treatment. However, if surgery is not planned, or if metastases are at distant sites that are imprecise, or at multiple sites, biopsy may not be suitable. In this case follow-up clinical procedures and imaging are required. In most cases the follow-up period was stated and appeared to be of reasonable length. This is important as good follow-up can give an indication of longer term outcomes such as disease-free and overall survival.

Studies often present a mixture of reference standards without explaining the reason. Moreover, in some cases, the people who were biopsied were dependent on PET results, thus leading to overestimation of sensitivity (verification bias). Blinding of the reference standard was not always stated and in some cases was clearly guided by the PET results.

Analyses were generally simple and clearly presented. However, the unit of analysis for calculation of diagnostic accuracy differed among papers and included patients, nodal regions, individual lymph nodes or individual sites of metastases. In some cases the number of lesions per patient was large, so results could be influenced by a few patients. Furthermore, lesions are clearly not independent. Consequently, the focus of this review has been placed on analyses by patient, where they are presented.

Patient management/outcomes

This review found several dedicated patient management studies that were specifically designed to show the impact of PET on diagnostic understanding and decision-making. Several were of high quality, with specifically designed questionnaires issued before and after PET. Some were compromised by only issuing the questionnaires in retrospect and several had poor response rates.

Many diagnostic studies also made claims about patient management that were more anecdotal. In these, changes in management may have been amalgamated with changes in staging. The influence of PET on the change is often unclear as other elements of the cancer workup may also have influenced the cancer decision. Furthermore, the changes can range from undertaking additional imaging procedures to altering therapy to curative surgery.

It is unclear whether systematic reviews and HTAs have extracted all relevant information on patient management as their focus was probably diagnostic accuracy. In many cases few details are provided about the actual changes in management.

Few studies evaluated patient outcomes. Anecdotal evidence was provided from follow-up in some case series, but a few RCTs have also been performed.

Treatment response

To assess early treatment response a wide variety of possible target outcomes (complete pathological response, complete clinical response, partial

response, etc.) and possible metabolic predictors (change in SUV, absolute SUV, visual responder, etc.) has been used. Without careful prior specification and reporting, it can be difficult to discern whether a particular result arises due to optimal selection of target, metabolic response and cut-off. It is particularly important in this setting that results are replicated on independent data sets to ensure that valid error estimates are produced,²¹ but this does not seem to have happened in many PET treatment response studies.

RT planning

Several good preliminary clinical studies were found for RT planning in various cancers, but the impact of PET beyond altering radiation dose and volume has not been studied.

Assessment of clinical effectiveness of FDG-PET

The following sections present the evidence from the recent, robust systematic reviews and new primary studies. For each of the eight cancers the evidence relating to each management decision is presented for FDG-PET, followed by all evidence on FDG-PET/CT in that cancer. These sections are followed by information from studies of FDG-PET/CT that each include a variety of cancers, information on risks associated with PET scanning and a brief summary of cost-effectiveness studies.

All systematic reviews and new prospective, primary studies are described in more detail in Appendix 7, in the order presented in these sections. In all cases, only the lead author of a paper is referenced and PET refers to FDG-PET throughout this chapter and in the data extractions in Appendix 7.

Breast cancer

Data extractions are presented in Appendix 7 (from p. 99).

Diagnosis

One systematic review (SR) from the Agency for Healthcare Research and Quality (AHRQ)²² presented studies in patients with suspected breast cancer who had been referred for biopsy with no palpable lymph nodes, with the intention of using PET to avoid biopsy if PET was negative. A summary receiver operating characteristic (sROC) analysis of 13 studies predicted PET sensitivity of 89% at specificity of 80%. However, the individual risk of false negative was considered too high

when the only benefit was avoiding biopsy, as this would be outweighed by not receiving optimal treatment early if a result was false negative. Therefore, the AHRQ report suggested that PET scanning is insufficiently accurate to be recommended for diagnosis of breast cancer (as an alternative to biopsy). This report found no studies of PET in cases with low suspicion findings on mammography that had been referred for 3–6-month imaging follow-up.

Heinisch (2003)²³ was the only additional primary study (PS) that assessed a form of diagnosis. It evaluated 36 women in Austria with suspicious lesions on mammography or clinical examination prior to surgery, to diagnose more accurately the primary tumour. Sensitivity was 76% for PET compared with 95% for MRI. The same specificity was found for both imaging methods of 73%. This study noted that PET appeared less able to detect smaller lesions.

Staging: axillary lymph nodes

The Blue Cross Blue Shield (BCBS) systematic review²⁴ included eight diagnostic studies, with a total of 337 patients. It suggests that PET scanning cannot be used to avoid axillary lymph-node dissection (ALND) in patients with clinically N0 axillae, because of unacceptably low sensitivity [estimated sensitivity in the four studies found using sentinel lymph-node biopsy (SLNB) plus ALND as reference standard ranged from 20 to 50%]. With this level of false negatives, if patients did not go on to have standard diagnostic tests, modelling suggests that resulting suboptimal treatment would be associated with a reduction in 10-year survival of 8.2%.

Four additional primary studies evaluated PET for staging axillary lymph nodes. The first two studies used ALND with SLNB. Wahl^{25,26} used only ALND²⁷ and Zornoza used ALND or SLNB plus ALND.²⁸

Fehr (2004)²⁵ investigated the accuracy of PET in 24 patients in Switzerland and found a sensitivity of 20% (two out of eight), with a specificity of 13 out of 14.

Lovrics (2004)²⁶ reported a study of 90 patients in Canada that showed a sensitivity of PET of 36% (nine out of 25) and specificity of 97%.

Wahl (2004)²⁷ reported a large, carefully designed multicentre study of 325 patients in the USA. The sensitivity and specificity of PET scanning were 61% and 80%, respectively. They also showed that the sensitivity of PET (although not its specificity)

varied noticeably among three readers (from 54 to 67%).

Zornoza (2004)²⁸ studied 200 patients in Spain. For the first 100 patients, ALND was used as the reference standard. For the second 100 patients, SLNB was used, followed by ALND in those positive by PET or SLNB. Results are only reported for all patients combined and show PET sensitivity of 84% (90 out of 107) with specificity of 98% (91 out of 93). This author and Fehr²⁵ suggest that PET scanning may be useful if it is followed by SLNB when there is no suspicious uptake, but the cost-effectiveness of this approach is unclear.

The two studies that did not use SLNB in any or all patients showed higher sensitivity, but these estimates are probably inflated.

Locoregional recurrence

BCBS (2003)²⁴ reported three studies of the accuracy of PET to diagnose locoregional recurrence in 142 patients with clinical suspicion of recurrence. In the largest study in 75 patients, PET sensitivity was 80%, compared with 93% on CT or MRI (CT/MRI). Specificities were greater than 95%. The report concluded that PET sensitivity was somewhat lower than CT/MRI for this purpose, but the specificity was similar.

One additional primary study by Goerres (2003)²⁹ on 32 women in Switzerland reported higher sensitivity of PET than MRI (100% versus 79%) but lower specificity (72% versus 94%).

Staging/restaging/recurrence

A recent systematic review by Isasi³⁰ includes studies published between January 1995 and June 2004. Eighteen studies were found that evaluated PET for the detection of distant metastases in primary or recurrent cancer or in those with recurrence suspected from clinical or radiological findings. Seven studies were retrospective, six prospective and there were five where this was unclear. The 16 studies that reported patient-based results provided an sROC estimate of maximum joint sensitivity, specificity of 86%. The authors report that PET appeared to be more accurate than CT in one study and more sensitive but less specific than MRI in another study. The analyses do not differentiate between detection of locoregional recurrence and distant recurrence, or between initial staging and restaging on recurrence. However, the authors note that locoregional and distant recurrence have different detectability and clinical impact.

Isasi notes that four of the 18 studies reported changes in patient management, but the actual changes are not reported.

One additional primary study was found by Uematsu (2004),³¹ which focused specifically on the detection of bone metastases in 15 primary/recurrent patients in Japan. An analysis of 900 lesions showed that single-photon emission computed tomography (SPECT) had higher sensitivity (85%) than PET (17%).

Treatment response

In a systematic review, Krak³² assessed eight studies, published between 1993 and 2003, evaluating the value of midcourse PET scanning to predict response to chemotherapy in locally advanced breast cancer. As there were substantial differences between study protocols the results were not combined in a meta-analysis.

The studies were small (between five and 28 patients per study with at least one scan after the start of treatment), and used a variety of monitoring times, a variety of target responses and a variety of monitoring methods. The authors recommend:

- replication in independent studies
- the use of automated region of interest (ROI) definition
- that the use of dynamic scans and appropriate analytical methods should be investigated.

They also note that there is no reliable evidence that PET scanning can predict response in axillary lymph nodes, or that post-treatment scans are able to detect microscopic residual foci of disease.

One new primary study (Kim, 2004)³³ was performed in 50 women with large or locally advanced primary breast cancer in Korea. It showed that changes in SUV between pretherapy and post-therapy scans were able to differentiate responders from non-responders with 85% sensitivity and 83% specificity.

Finally, two small primary studies, with nine³⁴ patients and 11 patients,³⁵ showed that midcycle PET scans may also be able to predict clinical response to chemotherapy in metastatic breast cancer.

Mixed management decisions – patient management

Owing to the paucity of evidence on patient management, this retrospective study is

presented here for discussion purposes. It does not have a data extraction table as relevant points are highlighted in the text.

Yap (2001)³⁶ reports a survey in the USA that sought to determine the impact of PET on breast cancer patients. Two questionnaires were used. One related to the stage and planned management before PET. The post-PET questionnaire sought to determine any changes caused by PET and identify what the changes were. These changes were then classified as intermodality (e.g. surgery to RT), intramodality (change of chemotherapeutic agent) or no change. The pre- and post-PET questionnaires were completed at the same time, 1 week after the PET scan. If both questionnaires were returned this was considered to be a ‘completed questionnaire’. Between 1998 and 2000, 160 breast cancer patients had PET scans and questionnaires were returned for 50 of these patients (31%) from 32 referring physicians (oncologists, surgeons and GPs). The main reasons for patient referral were for restaging (52%), diagnosis (16%), monitoring course of disease (14%) and treatment response (8%). In this mixed group of patients, PET upstaged 14 patients (28%) and downstaged four (8%). There were intermodality changes in 14 patients (28%) and intramodality changes in 15 (30%).

This study is subject to a number of biases. The results are difficult to interpret as the survey covers such a mixed group of breast cancer patients, including some areas where PET would not be considered for use in the UK and using referral patterns that would not be appropriate (GPs). The questionnaires were supplied retrospectively at the same time, which could have introduced recall bias. It would have been preferable to document the pre-PET questionnaire before the results of PET were known, but the straightforward approach used was taken to minimise ‘administrative burden’ and to increase the likelihood of response. Despite this, the response rate was poor at only 31%. If a conservative approach was taken and non-responders were assumed to have no change in management, the number that had change in staging would have been 18 out of 160 patients (11%).

PET/CT

There were no published studies of PET/CT for management of breast cancer.

Breast cancer overview

PET

Diagnosis

- One SR with 13 PSs, and one additional PS studied patients with suspected breast cancer who were referred for biopsy, but with no palpable lymph nodes. PET was not sufficiently sensitive to be used for primary diagnosis as an alternative to lymph-node dissection.
- In low-suspicion cases, just referred for follow-up, there were no studies of PET.

Staging axillary lymph nodes

- One SR with eight PSs, and two additional PSs showed that PET had low sensitivity (20–50%) for detection of axillary lymph-node metastases when SLNB+ALND was used as the reference standard.

Locoregional recurrence

- There is some evidence (one SR with three PSs) that PET had lower sensitivity than CT/MRI for detection of locoregional recurrence, but a new PS suggests that PET may be more sensitive but less specific than MRI.

Staging/restaging/recurrence

- Evidence (one SR with 18 PSs) from a mixed set of trials for staging/restaging (to detect distant metastases) and to detect suspected recurrence showed that PET had joint sensitivity, specificity of 86%. There were few comparative analyses and results by population were not differentiated.
- One small study suggested that PET was less sensitive than SPECT for bone metastases.
- There is little evidence of change in patient management.

Treatment response

- There is evidence (one SR with eight PSs, and one PS) that PET scans midtherapy could predict response to neoadjuvant chemotherapy in locally advanced breast cancer.
- Two small primary studies used PET midcycle to predict clinical response to chemotherapy in metastatic breast cancer.
- More studies are needed looking at response in lymph nodes.

PET/CT

- No studies had been published for breast cancer management up to August 2005.

Colorectal cancer

Data extractions are presented in Appendix 7 (from p. 108).

Diagnosis

The systematic review of PET undertaken by the Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)⁶ included assessment of studies to detect the primary tumour in colorectal cancer. It found two small diagnostic studies with a total of 40 patients. These showed sensitivity of PET as greater than 85%, with specificity of 67% reported in one study.

One additional primary study by Friedland (2005)³⁷ studied 45 patients in the USA with neoplastic colonic polyps and sought to detect early-stage colon cancer or colonic adenoma. PET had a sensitivity of 62% to detect malignant lesions, with specificity of 100%. It was noted that PET only detected one in six tumours that were less than 2 cm.

Staging

There are numerous studies of PET for staging or restaging colorectal cancer, particularly for the detection of hepatic metastases. Often it is unclear whether the population included has primary or recurrent cancer, but where possible this has been identified.

Two primary studies evaluated PET before initial therapy for colorectal cancer.

Heriot (2004)³⁸ studied 46 patients in Australia with stage II–IV adenocarcinoma within 15 cm of the dentate line who were being considered for adjuvant preoperative therapy. Eighteen patients (39%) had their staging altered, which led to change in management in eight patients (17%), with six avoiding futile surgery and two having the RT field altered.

Kantorová (2003)³⁹ studied 38 patients in the Czech Republic referred for surgery. PET detected the primary tumour in 95% of patients, compared with 49% on CT and 14% on ultrasound (US). In the seven patients with lymph-node metastases, PET had a sensitivity of 29% and specificity of 88%. CT and US did not detect any of these lymph-node metastases. Nine patients had liver metastases, for which PET had 78% sensitivity, CT 67% and US 25%; all had high specificity. PET altered treatment for six patients (16%).

Staging/restaging

One systematic review assessed detection of hepatic metastases from primary or recurrent colorectal cancer.

Kinkel (2002)⁴⁰ included studies on a variety of imaging methods. In the nine PET studies, PET specificity was at least 85%, with sensitivity of 90% and 95% confidence interval (CI) 80% to 97%. For the other imaging methods, in studies where the specificity was at least 85%, the sensitivity was 72% for CT, 76% for MRI and 55% for US. This suggests that PET had higher sensitivity than other imaging modalities. However, these are indirect comparisons and the trials for CT and US included cancers of the stomach and oesophagus, so comparative analyses are subject to bias. Also, this systematic review probably reports mixed lesion-based and patient-based analyses and so may overestimate the sensitivity on a per-patient basis.

Five additional primary studies reported staging/restaging in those considered eligible for resection of colorectal liver metastases. Five studies of PET/CT in mixed populations are also presented in the section 'PET/CT' (p. 22).

Arulampalam (2004)⁴¹ presents a UK study of 31 patients who underwent PET or PET/CT scanning. The sensitivity of PET to detect hepatic metastases was 100%, compared with 47% on CT. Both had 91% specificity (one FP due to fibrous stroma). Twelve patients (39%) had management changed as a result of PET or PET/CT: seven avoided futile surgery, one had more extensive surgery and four had chemotherapy.

Desai (2003)⁴² studied 114 patients in the USA, 89 with presumed recurrent disease and 25 with presumed isolated liver metastases. The study had a 3-year follow-up. From CT 42 patients were staged to be resectable, but PET found multiple lesions in 17 of these, leaving 25 resectable. Of these, five had isolated extrahepatic lesions or recurrent disease. PET was not able to detect lesions below 1 cm.

Rosa (2004)⁴³ reports a German two-centre study in 58 patients. PET was concordant with standard staging work-up in 46 out of 58 patients; only one of these was incorrect, an FP caused by pneumonitis. In the 12 discordant patients (21%), PET correctly diagnosed extrahepatic disease, which resulted in upstaging meaning that futile liver resection was avoided.

Topal (2001)⁴⁴ reported a study of 91 patients in Belgium. PET was concordant with standard work-up including other imaging in 68 (75%) patients. PET provided additional information in 11% patients, but incorrectly upstaged 7% and incorrectly downstaged 8%. The documentation for these changes was unclear and how this additional information might have impacted patient management was not discussed.

Truant (2005)⁴⁵ studied 53 patients in France. All analyses were lesion based. For hepatic metastases PET and CT had sensitivities of 79%, but PET had a higher specificity of 80% versus 25% on CT. In the abdominal cavity, both PET and CT had specificities over 90%, but lower sensitivities with 63% for PET and 25% for CT. There were four lesions outside the abdominal cavity that both PET and CT detected, with high specificity. PET could have had a major influence on patient management in five patients (9%), three avoiding surgery, one extending surgery and one being advised surgery. There were also three patients in whom PET incorrectly upstaged the patient.

Staging/restaging/recurrence

One systematic review collated evidence on staging/restaging colorectal cancer and detection of recurrence.

Dietlein (2003)⁴⁶ undertook a systematic review, which included 15 studies that had at least 35 patients, with suspected recurrent colorectal cancer or colorectal liver metastases (could be primary or recurrent populations). The paper presents a good critique of the biases that arose in the studies (in particular, selection bias, verification bias and reviewer bias). Five studies including 445 patients were used to create pooled estimates of diagnostic accuracy in restaging. PET had a sensitivity and specificity (with 95% CIs) of 94% (91 to 96%) and 78% (69 to 86%), while for CT the sensitivity and specificity were 73% (68 to 78%) and 62% (52 to 72%).

Dietlein summarised ten studies in a total of 741 patients that provided evidence of change in patient management. The paper states that PET correctly changed staging in 27% of patients. However, Table 8 of the paper states that there were 195 correct upstagings and 59 correct downstagings; this gives a total of 254, which is 34%. There were 16 incorrect upstagings and ten incorrect downstagings, making a total of 4% that had staging changed incorrectly as a result of PET. This led to changes in management ranging from 20 to 59%. The paper quotes an

overall 34%, but the median percentage change is lower at 24% (calculated by this author). No details are given of the actual changes in patient management and it is unclear how PET contributed to them.

Recurrence

The systematic review from DACEHTA⁶ includes 13 studies in those suspected to have recurrent colorectal cancer from clinical symptoms, elevated carcinoembryonic antigen (CEA), and so on. PET sensitivity was greater than 85% in all but one study, with specificity ranging from 43 to over 90%. Sensitivity and specificity appeared to be higher than CT and similar to MRI. These accuracy figures probably include lesion- and patient-based analyses.

There were four additional primary studies that assessed some element of colorectal cancer recurrence.

The first two evaluated patients with suspected recurrence.

Fukunaga (2005)⁴⁷ studied 42 patients in Japan with suspected recurrence of colorectal cancer. PET and CT images obtained from separate devices were combined using software fusion. Fused PET/CT resulted in 39 correct classifications, compared with 37 on PET and 33 on CT.

Montravers (2004)⁴⁸ studied 239 patients in France with suspected recurrent colorectal cancer. PET sensitivity was 90%, with specificity 64%. However for tumours of 1 cm or less, PET sensitivity was reduced to 44%.

The other two studies monitored for recurrence in those without symptoms.

Langenhoff (2002)⁴⁹ studied 23 patients in The Netherlands with unresectable hepatic metastases after local ablative therapy to evaluate time to detection of recurrence. PET identified recurrence locally, outside treated area or extrahepatic more quickly than CT or through elevated CEA. PET was the only imaging modality to detect recurrence in all patients, but it also gave two FPs.

Selvaggi (2003)⁵⁰ studied 49 patients in Italy who had received a curative resection and had no signs of recurrence after regular colonoscopy and CT and MRI follow-up for 2 years. PET detected six hypermetabolic sites in five patients, four of which were TPs. This led to clinical management changes for two patients.

Treatment response

Six studies examined the utility of PET to predict response to therapy for colorectal cancer (in most cases this was after neoadjuvant therapy). Note that Guillem (2004)⁵¹ is a follow-up of the study reported in Guillem (2000).⁵²

Amthauer (2004)⁵³ studied 20 patients in Germany with locally advanced colorectal cancer. The study showed that changes in SUV (using an optimal cut-off) predicted response better than did endoscopic ultrasound (EUS).

Calvo (2004)⁵⁴ studied 25 patients with locally advanced colorectal cancer in Spain and showed that post-treatment SUV was smaller in the patients who responded.

Capirci (2004)⁵⁵ was a study of 81 patients in Italy. PET was used to restage patients with stage II–III adenocarcinoma who had received neoadjuvant chemoradiotherapy (CRT) and were to undergo surgery 8–9 weeks later. In terms of clinical response ten out of 12 clinical responders were PET negative. The distribution across clinical stages was more difficult to interpret, with several false negatives. In terms of pathological response, 22 out of 28 complete responders were PET negative. It was noted that the six FPs may have been due to inflammatory radiation reactions.

Denecke (2005)⁵⁶ studied 23 patients in Germany with locally advanced colorectal cancer and showed that changes in SUV between pretherapy and post-therapy PET scans are better able to predict response than are changes in MRI or CT. Again, this study used an 'optimal' SUV cut-off determined in the study and these results were not replicated on independent data.

Dimitrakopoulou-Strauss (2003)⁵⁷ studied 28 patients with colorectal cancer in Germany, undertaking three dynamic scans per patient (before treatment, after one cycle and after therapy). They showed that discriminant analysis based on fractal dimensions of the first two scans provided the best prediction, but that the accuracy achieved was rather low, with 75% of those with PD/SD correctly predicted, but only 10% with PR.

Guillem (2000)⁵² studied 15 patients in the USA who received CRT for locally advanced rectal cancer, showing that visually interpreted changes on PET images appeared to provide a superior correlation with pathological results to changes on

CT images. Guillem (2004)⁵¹ updated this to show that changes in SUV were correlated with overall survival.

RT planning

There was one study of RT planning in colorectal cancer.

Ciernik (2005)⁵⁸ used an automatic region-growing algorithm with CT and with PET, to estimate treatment volumes for radiotherapy. (A PET/CT system was used, but fused images were not used.) The resulting regions were closely correlated, but the study presented no outcome data and was only performed in 11 patients in Switzerland.

Mixed management decisions – patient management

Owing to the paucity of evidence on patient management, this retrospective study is presented here for discussion purposes.

Meta (2001)⁵⁹ reports a survey in the USA that sought to determine the impact of PET on colorectal cancer patients. Two questionnaires were used retrospectively using identical methods to those reported by Yap (2001)³⁶ in the section ‘Mixed management decisions – patient management’ (p. 18). (Likewise, the caveats regarding the Yap study apply here.) Between 1998 and 2000, 146 colorectal cancer patients had PET scans. Questionnaires were returned for 60 of these patients (41%) from oncologists, surgeons, GPs and pulmonologists. The main reasons for patient referral were for staging (55%), monitoring course of disease (23%), diagnosis (12%) and treatment response (2%). In this mixed group of patients, PET upstaged 20 patients (33%; 14% of total) and downstaged five (8%; 3% of total). There were intermodality changes in 22 patients (37%) and intramodality changes in 11 patients (18%).

PET/CT

Five studies of integrated PET/CT were identified.

Ciernik (2005)⁵⁸ also used a PET/CT device to study RT planning in colorectal cancer; but as only the PET data were used, this is reported in the section ‘RT planning’ above.

Staging/restaging

Arulampalam⁴¹ used PET and PET/CT in one study, while Fukunaga⁴⁷ used software fusion. These studies are reported in the previous PET sections.

Francis (2003)⁶⁰ prospectively studied 17 patients with primary or metastatic tumours in the UK comparing FLT and FDG tracers. Six patients had primary tumours. In addition, there were six lung and six peritoneal tumours. FDG PET/CT detected all tumours (100% sensitivity), with just one FP peritoneal mass. There were 32 liver metastases and FDG PET/CT detected all but one of these, which was 1 cm.

Selzner (2004)⁶¹ undertook a prospective study in 76 patients with hepatic metastases considered suitable for resection in Switzerland. For hepatic metastases, PET/CT and CT had similar sensitivities of approximately 90%, but the specificity of PET/CT was higher at 90% versus 70% on CT. For local recurrence, the specificity of PET/CT and CT was each 98%, but the sensitivity of PET/CT was much higher at 93% versus 53% on CT. PET/CT resulted in a change in treatment in 16 patients (21%).

Recurrence/restaging

Cohade (2003)⁶² was a retrospective study of 44 patients in the USA who had already been treated for colorectal cancer to determine recurrence or restaging after therapy and one patient with primary cancer. In a lesion-based analysis, PET/CT had similar sensitivity to PET, 86% versus 88%. The specificity of PET/CT was low at 67%, but somewhat better than that of PET at 56%. For the patient-based analysis, PET and PET/CT assessed recurrence correctly in all patients, but in other sites there were incorrect assessments in eight patients on PET versus four patients on PET/CT.

Even-Sapir (2004)⁶³ was a retrospective study of 62 patients in Israel with suspected recurrent colorectal cancer. PET/CT had a sensitivity of 96% for detecting recurrence versus 88% on PET. Specificity was 89% on PET/CT versus 74% on PET. Compared with CT or rising CEA, PET/CT produced findings of ‘clinical relevance’ in 29 (47%) patients.

Kim (2004)⁶⁴ undertook a retrospective study of 51 patients with suspected recurrence of colorectal cancer in the USA. For PET/CT the area under the sROC was 0.95, compared with 0.82 for PET. Analyses by lesion showed higher sensitivity for PET/CT (89%) than PET (74%). The specificity was over 90% for both. PET/CT correctly staged 88% of patients versus 71% on PET.

Colorectal cancer overview

PET

Diagnosis

- One SR found two small studies using PET to diagnose colorectal cancer. This was augmented by one new study. These showed that PET had good sensitivity to detect primary tumours larger than 2 cm, but not for smaller tumours, and specificity varied.
- In the UK, it is unlikely that PET would be used routinely before biopsy as a tool for diagnosis.

Staging

- One diagnostic study of staging showed that PET (like other imaging methods) had poor sensitivity to detect regional lymph-node involvement, but better sensitivity for liver metastases and the primary tumour. Specificity was high in all situations.
- One study of patient management in primary cancer showed that eight out of 46 patients (17%) had their therapy altered as a result of PET.

Staging/restaging/recurrence

- One SR with nine PSs and five additional PSs in primary and recurrent populations showed PET to be more accurate than comparators for detection of liver metastases.
- One SR with 15 PSs collated evidence on a mixed population including those with suspected recurrence. It confirmed the other SRs, finding PET sensitivity to be approximately 90%, versus 73% on CT. PET specificity was at least 85%.
- In this mixed-population SR, evidence on change in management was reported in ten studies, showing 20–59% change in patient management. Three of the new PSs showed that PET influenced or could have influenced therapy in 9%, 21% or 39% of patients. Two studies noted that 6% and 15% had staging incorrectly changed.

Recurrence

- One SR with 13 PSs, and two additional PSs showed that PET was more accurate than CT for detecting recurrence, with sensitivity at least 85% and wide-ranging specificities. The SR suggested similar accuracy to MRI, but one

PS showed that PET identified a small number of sites that MRI did not detect.

- In two studies it was noted that the sensitivity of PET to detect lesions smaller than 1 cm was poor.
- Change in therapy as a result of PET was recorded in two studies as two out of 49 patients (4%) and 17 out of 114 patients (15%).
- There were two studies of PET used in monitoring for recurrence. One found that PET detected recurrence more quickly than CT. In the other, PET identified recurrence that led to management changes in two out of 49 patients.

Treatment response

- Six studies, one in more than 80 patients, provided evidence that changes in SUV between pretherapy and post-therapy scans may predict response in the majority of patients.
- One small study reported changes in patient management.

RT planning

- One small Swiss study showed that PET and CT produced similar RT planning regions.

PET/CT

Staging/restaging

- There were two prospective PSs of PET/CT in a total of 93 patients. They showed that PET/CT had high sensitivity to detect primary tumours and liver metastases.
- The largest study showed that the specificity of PET/CT to detect liver metastases was 20% higher than CT.
- For local recurrence, both PET/CT and CT had high specificity, but PET/CT had 40% higher sensitivity than CT.

Recurrence/restaging

- There were three retrospective PSs of PET/CT versus PET in 157 patients. One study showed that both assessed recurrence accurately, while another showed slightly better sensitivity of PET/CT (96% versus 88%) and higher specificity (89% versus 74%). In the other trial 88% of patients were correctly staged with PET/CT versus 71% of patients with PET.

Head and neck cancer

Data extractions are presented in Appendix 7 (from p. 131).

Diagnosis

The systematic review by Vermeersch (2003)⁶⁵ found four studies comparing PET to CT or MRI for the primary diagnosis of head and neck cancer. The sensitivity of PET ranged from 85 to 95%, compared with 67 to 88% for CT/MRI. The specificity of PET ranged between 80 and 100%, with 45–75% for CT/MRI. They conclude that CT/MRI is needed for anatomical localisation, but that PET may be valuable in addition.

There was one new primary study of diagnosis.

Khan (2004)⁶⁶ assessed 45 patients in Japan with uncertain diagnosis after conventional work-up (CWU). Relative to neck dissection or biopsy of suspicious regions, PET yielded a sensitivity of 23 out of 25 (92%) with 65% specificity.

Diagnosis: detection of synchronous primaries

The systematic review by Vermeersch (2003)⁶⁵ included four diagnostic studies evaluating synchronous primaries and distant metastases in patients with squamous cell carcinoma (SCC) head and neck cancer. PET appeared to detect some, but not all tumours that some other diagnostic methods failed to identify.

Nishiyama (2005)⁶⁷ assessed the ability of PET to detect additional simultaneous tumours in 53 patients diagnosed with head and neck cancer in Japan. PET found five out of six second tumours, compared with two out of six found by routine methods. PET also discovered distant metastases in two patients, but missed distant metastases in three other patients.

Diagnosis: detection of occult primary tumour

Two systematic reviews by BCBS (2000)⁶⁸ and MSAC (2001)⁶⁹ reported eight studies in 166 patients evaluating the diagnostic accuracy of PET to detect occult primaries following the detection of cervical lymph-node metastases. Seven of the same studies were included in each systematic review, but different study groupings are reported. In each SR, the rate of true-positive (TPR) PET results was approximately 30%. BCBS showed that this rate was consistent when PET was used after all other diagnostic tests had been negative or if used when some other tests may have been positive. MSAC showed that the TPR was consistent in studies of SCC and in studies of

mixed populations. MSAC also reported that in four studies PET assisted in the detection of primary tumours in 26 out of 90 patients, with consequent management changes in 19 patients (21%).

Two additional primary studies were published in this indication and one study on PET/CT is presented in the section 'Detection of occult primary tumour' (p. 27).

Miller (2005)⁷⁰ reports that in 26 patients investigated for tumour of unknown origin in the USA, PET discovered eight of the 12 tumours found by panendoscopy and multiple biopsies, with one FP. The tumours missed by PET were small (<5 mm).

Stoeckli (2003)⁷¹ reported on 18 patients in Switzerland with lymph-node disease from tumour of unknown origin. In eight out of 18 patients a tumour was found by panendoscopy; five of these were found by PET, with one FP site.

Staging lymph nodes

Goerres (2003),⁷² Vermeersch (2003)⁶⁵ and the BCBS HTA (2000)⁶⁸ presented systematic reviews of the use of PET in staging regional lymph-node involvement in primary head and neck cancer.

Goerres reported 11 studies in SCC and adenocarcinoma (AC). They performed an sROC analysis that estimated PET sensitivity to be 81% with specificity of 79%. Using Swiss pretest probabilities, they estimated the per-patient positive likelihood ratio to be 3.9, with a negative likelihood ratio of 0.24.

Vermeersch included 17 studies in SCC that compared PET with CT or MRI. Substantial methodological differences were reported between studies. In six studies, PET sensitivity was at least 80% and specificity at least 90%. This level of accuracy was only achieved for one CT/MRI study.

The BCBS HTA⁶⁸ is an older systematic review including mainly SCC patients, but it clearly presents two comparative analyses of PET versus CT and MRI. Both showed PET to have slightly superior sensitivity and specificity to the comparative imaging method. The first against CT (four studies, 123 patients) showed sensitivities of 81% for PET and 72% for CT, with specificities 97% and 89%. The second (three studies, 106 patients) produced sensitivities of 91% for PET and 82% for MRI, with specificities of 88% and 83%, respectively.

Twelve further primary studies were found for staging regional lymph-node involvement. In all studies the reference standard was histopathology from neck dissection and most patients were male. These results are presented by stage of disease. Four studies of PET/CT in mixed populations are presented in the section 'Mixed stages of head and neck cancer', p. 28).

Clinically N0

Brouwer (2004)⁷³ compared PET to CT, MRI and US-guided fine-needle aspiration biopsy (FNAB) in 15 patients in The Netherlands with clinically N0 necks. Unfortunately, only PET was performed on all patients, making the comparisons difficult to interpret. PET sensitivity was two out of three, with specificity 11 out of 12. The authors note that small (<6 mm) lymph nodes were problematic for PET to detect.

Civantos (2003)⁷⁴ reported a study of 18 patients in the USA with SCC in clinically N0 necks. The sensitivity of PET for lymph-node metastases was three out of 11, versus ten out of 11 for SLNB.

Hyde (2003)⁷⁵ compared SLNB to PET in 29 patients in the UK with clinically N0 necks. Four node-positive necks were detected on dissection; SLNB found three of these. PET failed to detect any of the malignancies, but had two FPs.

Stoekli (2002)⁷⁶ found that SLNB detected all five occult lymph-node metastases in 12 patients in Switzerland, with no FPs, whereas PET only detected two out of five, with one FP.

Stages T1–T3

Kovacs (2004)⁷⁷ reported a somewhat complex comparison of PET against CT in 62 patients with primary T1–T3 head and neck cancer (SCC) in Germany. After PET and CT imaging, one cycle of chemotherapy was given, then 3–4 weeks later SLNB and surgery were performed on selected patients. PET was less sensitive than CT (72% versus 88%) (five FNs on PET) and specificities were comparable (82% versus 77%). The use of SLNB on PET-negative patients led to detection of the remaining true-positive patients. This combination of PET and SLNB resulted in radical dissections to 35 neck sides, whereas 45 would have been needed with the traditional CT-based algorithm (if FNs were operated on too).

Schmid (2003)⁷⁸ examined the effect of adding PET to CWU in staging locally advanced (N2 or T3) head and neck cancer in Switzerland. PET

detected three additional patients with positive lymph nodes, correctly downstaged two, but also had two FNs.

Stages not clearly specified

Bruschini (2003)⁷⁹ compared PET with CT in 22 patients in Italy. PET sensitivity was 93% (14 out of 15), with no FPs, versus CT sensitivity of 73%, again with no FPs. The patient whose lymph-node metastasis was missed had a small lymph-node focus of disease.

Dammann (2005)⁸⁰ reports a comparison between PET, CT and MRI for 64 patients in Germany. Analysis of 293 nodal regions found that 40 were positive. In nodal analysis, PET had sensitivity and specificity of 85% and 95%, compared with 80% and 93% on CT, and 93% and 94% on MRI.

Ng (2005)⁸¹ compared PET with CT or MRI in 124 patients with newly diagnosed SCC in Taiwan. Comparators differed by patients, with 82 patients receiving MRI and 42 receiving CT. Results were only reported at a nodal level, with 95 positive nodes and 398 negative nodes. CT/MRI had sensitivity of 53% and specificity of 94%. PET had sensitivity of 75% and specificity of 93%, whereas software-fused PET + CT/MRI had sensitivity of 78% and specificity of 94%. The imaging techniques were unable to detect small nodes: the mean diameter of nodes falsely negative on PET was 4.3 mm.

Schwartz (2003)⁸³ reported on 33 patients in the USA with SCC staged using PET before surgery. In the 13 patients who underwent neck dissection, all six positive heminecks were detected by PET, with one out of ten FP.

Schwartz (2005)⁸³ reported on 20 patients in the USA where CT was compared with software-fused PET+CT. CT alone detected 21 out of 27 positive nodes (sensitivity 78%), with one FP (specificity of 99%), whereas PET+ CT detected 26 out of 27 (sensitivity 96%), again with one FP.

Yen (2005)⁸⁴ reported a study in Taiwan that compared CWU (including CT and MRI for all patients) with and without PET for staging primary buccal mucosa (SCC). Patients found to have positive nodes by CWU or CWU + PET received RT or CRT as well as surgery. Although this was a two-group comparative study the groups were not constructed by randomisation, but on the basis of willingness to pay for PET scanning. This resulted in 27 patients in the CWU group and 32 in the CWU + PET group. This selection

procedure could clearly have led to bias, but the patient characteristics appeared to be similar in the two groups. PET scans detected nine TP lymph nodes missed by CWU, but there was only one fewer futile operation in the CWU + PET group and no evidence of any difference in locoregional recurrence between the groups.

Restaging/recurrence

Systematic reviews by Vermeersch (2003),⁶⁵ Goerres (2003)⁷² and MSAC (2001)⁶⁹ assessed the accuracy of PET on staging residual or detecting recurrent head and neck cancer.

Vermeersch retrieved 15 comparative studies in SCC, showing that PET sensitivity was at least 80% and specificity at least 90%. PET appeared to be more accurate than CT or MRI, but there was poor standardisation of patient groups, comparators and reference standards.

Goerres calculated a positive likelihood ratio of 4.0 and negative likelihood ratio 0.16, from ten studies in SCC and AC, but the studies suffered from the deficiencies noted above.

MSAC documented similar diagnostic accuracy in studies with mainly SCC patients, but also reported changes in patient management in eight studies. In one study, PET correctly predicted the need for panendoscopy in 11 out of 38 patients, not determined by CT/MRI. In other studies, PET correctly indicated the need for biopsy in an additional five out of 17 patients, detected distant metastases in seven out of 22 patients (avoiding futile surgery) and in another study 23 out of 66 patients had their management correctly changed. However, none of these changes was clearly documented.

There was also one additional study in a mixed primary/recurrent population and seven that evaluated restaging or recurrent disease.

Dresel (2001)⁸⁵ studied a mixed population of 54 patients with suspected primary ($n = 32$) or recurrent ($n = 16$) head and neck cancer in Germany. Forty-eight patients had tumours. PET had improved sensitivity (98%) compared with CT (52%) to detect the primary tumour and improved specificity to detect lymph-node metastases (97% for PET and 50% for CT).

Conessa (2004)⁸⁶ studied 42 patients in France who underwent PET scans 3–6 months after surgery for head and neck cancer. The reference standard was progression during follow-up for

negative sites and biopsy for positive sites. PET found all six recurrences (100% sensitivity) with specificity of 81%.

Kubota (2004)⁸⁷ studied 36 patients in Japan with possible recurrence of head and neck cancer. Patients received PET and MRI or CT scans a median of 4 months after the end of therapy. PET detected 14 out of 16 true recurrences (sensitivity of 88%) with 78% specificity, whereas CT/MRI had sensitivity of 75%, with specificity of 30%.

Kunkel (2002)⁸⁸ studied 97 patients in the USA who underwent PET scanning between 4 and 9 months after the end of therapy. PET identified 65 out of 78 sites of progression in 49 patients. PET sensitivity was 87% for local and nodal disease, but 71% for distant disease. The specificity for detection of local recurrence was 67%, but over 90% for nodal or distant metastases.

Yao (2004)⁸⁹ studied 12 patients in the USA with persistent lymphadenopathy after CRT for head and neck cancer (SCC). PET sensitivity was four out of four. The FP rate for visual interpretation was three out of eight, or for SUV > 3 was one out of eight.

Goerres (2004)⁹⁰ studied 26 patients in Switzerland with locally advanced head and neck cancer, scanned 6–8 weeks after the end of CRT to assess residual disease. The reference standard was progression during follow-up for negative sites and biopsy for positive sites. PET sensitivity was ten out of 11 (91%), with one FP in 15 patients (specificity of 93%). In five of the ten truly positive patients there was no previous clinical evidence of the disease found by PET. So, PET changed management correctly in five out of 26 patients (19%).

Porceddu (2005)⁹¹ studied 39 patients in Australia with locally advanced head and neck cancer, scanned 8–12 weeks after the end of CRT to assess residual disease. PET sensitivity was five out of ten (50%) (five out of six for local disease) and PET gave two FPs in 27 negative patients (specificity 93%).

Ware (2004)⁹² studied 53 Australian patients with residual abnormalities on conventional evaluation (CE) after definitive treatment for head and neck SCC. Forty-six of the patients were evaluable, of whom 25 had residual disease. PET correctly identified 19, with one FP and six FNs (two of whom had 'equivocal' PET results), whereas CE had, by definition, 21 FPs. PET resulted in major

management changes from the pre-PET plans in 21 patients (in the majority of cases, the replacement of surgery by 'watchful waiting'). Patient outcomes suggested that these management changes were correct in 19 out of 21 patients.

Treatment response

Six studies examined the utility of PET to predict response to therapy (mainly after neoadjuvant therapy) in head and neck cancer.

Dietz (2002)⁹³ studied 20 patients in Germany with larynx and hypopharynx SCC who received neoadjuvant CRT and larynx-preserving surgery. Sixteen patients underwent CT scans both before and after therapy, and 14 also received an additional scan after 6 months. Three patients with small primary tumours were falsely negative on the original scan and omitted from subsequent analyses. At the post-therapy scan eight out of 13 were correctly classified by PET as without residual disease; five were FP.

Kitagawa (2003)⁹⁴ studied 20 patients receiving neoadjuvant CRT for head and neck cancer in Japan. An SUV cut-off of 4 for the post-CRT scan distinguished 14 pathological CRs from four pathological PRs, with two CRs wrongly classified.

Kitagawa (2003)⁹⁵ studied 23 patients given arterial chemotherapy and RT in Japan. Post-treatment PET scans exhibited similar sensitivity and slightly higher specificity than CT or MRI for residual disease in the primary tumour, and comparable specificity in lymph-node disease. The authors claim that eight out of 23 patients avoided surgery as a result of PET scanning. However, it is not clear whether this was relative to the decision that would have been made by other imaging techniques.

Kunkel (2003)⁹⁶ studied 35 patients in Germany who received RT for stage III or IV oral SCC. Twenty-seven of the patients also received cisplatin chemotherapy, and underwent a PET scan 4 weeks after the completion of therapy. A PET 'response', defined as no lesion with SUV above 4, was associated with significantly improved survival ($p = 0.046$); PET status remained significant after adjustment for nodal status, tumour grade and cisplatin.

McCullum (2004)⁹⁷ studied 40 patients with stage IV head and neck cancer in the USA given induction chemotherapy followed by CRT. Thirty-three patients underwent PET scans after induction chemotherapy, of whom 26 were

biopsied to determine pathological status. Then, 37 underwent PET scanning after CRT, of whom 24 were biopsied. After induction chemotherapy, PET detected all three with residual disease, but was falsely positive in eight out of 23. After CRT, PET detected six out of nine patients with residual nodal disease and was falsely positive in seven out of 15.

Nam (2005)⁹⁸ studied 24 patients given 'definitive' RT for SCC head and neck cancer in Korea. PET identified two out of three patients with residual disease, but may have produced six FPs (unclear reporting).

RT planning

There were three studies of PET to supplement CT or MRI for RT planning in head and neck cancer. Three studies on PET/CT are presented in the section 'RT planning', (p. 28).

Nishioka (2002)⁹⁹ compared visually fused PET+CT or PET+MRI with CT or MRI for RT planning in 21 patients in Japan. They found that the primary tumour volumes were similar in all but two patients, but that the number of irradiated nodes increased from 28 on CT or MRI to 39 on PET + CT or PET + MRI.

Scarfone (2004)¹⁰⁰ reported a very small study (six patients), in which the CT gross tumour volume (GTV) was modified for five out of six patients by the software fused PET+CT image (in the sixth patient no FDG uptake was visible).

Schwartz (2005)¹⁰¹ reported an early-stage modelling study in 20 patients in the USA. It showed that in five patients with high FDG uptake located away from critical normal neck structures, the use of PET+CT fused images could markedly reduce the dose to the contralateral parotid gland and to the laryngeal cartilage, while increasing the dose to the tumour region.

PET/CT

Detection of occult primary tumour

One prospective German study by Freudenberg (2005)¹⁰² evaluated the use of PET/CT to detect occult primary tumour in 21 patients with cervical lymph-node metastases. PET/CT detected the occult primary tumour in 12 (57%) patients. This was just one more than that detected by fused PET + CT or PET alone. PET and PET/CT were both more sensitive than CT, which only detected five of the occult primary tumours. The TP rate in this study was much higher than those reported on PET (30%).

Mixed stages of head and neck cancer

There were four studies of PET/CT in head and neck cancer, which included a variety of patients with known or suspected primary, occult or recurrent head and neck cancer in each study.

One study, by Zimmer (2005),¹⁰³ is not summarised here because it studies a prototype scanner that is not available commercially. (It combined a Siemens CT scanner and a Siemens ECAT ART PET scanner mounted on the same assembly.)

Branstetter (2005)¹⁰⁴ was a prospective study of 64 patients in the USA. The area under the sROC for the patient analysis was 0.98 for PET/CT versus 0.96 for PET and 0.87 for CT. By-lesion analyses showed similar specificities of PET/CT and PET at approximately 90%, but higher sensitivity of PET/CT at 98% versus 87% on PET.

Rödel (2004)¹⁰⁵ was a study on 51 patients in Germany. It is unclear whether it was prospective. Analysis by lesion gave similar sensitivities for PET and PET/CT at 95% with higher specificity of PET/CT at 78% versus 65% on PET. PET/CT altered seven equivocal PET findings to benign, three positives on PET to negatives and three negatives on PET to positives.

Schöder (2004)¹⁰⁶ was a retrospective study in 60 head and neck and eight thyroid patients in the USA. Most patients had SCC. On PET, 157 areas showed increased FDG uptake and PET/CT improved anatomical localisation in 98 of these. However, the accuracy was only slightly higher on PET/CT (97%) than on PET (92%). PET/CT led to change in patient management in 12 patients.

Zanation (2005)¹⁰⁷ was a retrospective diagnostic study of 87 patients with 97 scans in the USA. For all lesions combined, the sensitivity of PET/CT was 75%, with specificity 69%. The accuracy by patient was 69%. PET/CT resulted in a change in management in 22% of patients.

RT planning

There were three primary studies of PET/CT in radiotherapy planning in head and neck cancer.

Ciernik (2003)¹⁰⁸ was a prospective study of 12 patients in Switzerland who were to undergo curative RT. Compared with CT, PET/CT resulted in a GTV increase of at least 25% in two patients and GTV reduction of at least 25% in four patients. The mean planning target volume (PTV) change was 20%.

Koshy (2005)¹⁰⁹ was a retrospective study of 36 patients in the USA scheduled for RT. PET/CT altered staging in only five patients (14%), but changed management in nine patients (25%), five of these related to alteration of RT volume.

Paulino (2005)¹¹⁰ reported on the use of PET/CT imaging in comparison to CT alone for RT planning in 40 patients with SCC head and neck cancer in the USA. The median GTVs for PET/CT and CT were 20.3 and 37.2 cm³, respectively. PET/CT resulted in a smaller GTV in 30 patients, a larger GTV in seven and similar GTV in three. The PET region was not always a subset of the CT region and they report that if the CT GTV was used, in 25% of patients the irradiation of the PET/CT-GTV would have been 'less than optimal', that is, underdosed.

Head and neck cancer overview

PET

Diagnosis

- One SR of four PSs, and one additional PS showed that PET was more sensitive and specific than CT/MRI for diagnosis. PET cannot currently replace these modalities because of the need for anatomical localisation, but may be helpful where doubt exists.
- One SR with four PSs, and one additional PS showed that PET could detect some, but not all synchronous primaries that other methods failed to detect.
- Two SRs (each with eight PSs) and two additional PSs showed that PET can detect occult primary tumours in patients with cervical lymph-node metastases. Even in those where other imaging methods have failed, the TP rate of PET is 30%. Tumours missed by PET in one study were smaller than 0.5 cm.
- There is some evidence of change in patient management. This is not clearly documented, but savings in panendoscopy and multiple biopsies are suggested.

Staging regional lymph nodes

- Three SRs and 12 additional PSs studied PET in staging regional lymph-node involvement.
- Four studies in patients with clinically N0 necks showed that PET sensitivity was much lower than that of SLNB.
- Eight studies in populations of mixed or unspecified stage patients showed that PET or PET + CT had sensitivity of approximately 80% and specificity of 80–97%. This was comparable to or better than CT or MRI in most studies.
- One of these studies used SLNB on PET negative necks to improve sensitivity.
- There is little evidence of documented change in management, but one PS showed that PET + SLNB reduced the number of radical neck dissections from 45 out of 62 compared with 35 out of 62 on CT.

Restaging/recurrence

- Two SRs with 15 and ten PSs, and seven additional PSs showed that PET sensitivity was approximately 80%, with specificity at least

90%, which was somewhat more accurate than CT/MRI for restaging or recurrence.

- Another SR reported similar accuracy and eight studies with some evidence of change in patient management. The strongest evidence was detection of distant metastases in seven out of 22 patients. Most other changes were related to further diagnostic tests, were poorly documented, and no clear links with improvement in outcomes were made.

Treatment response

- Six studies in a total of 162 patients used PET to predict response to therapy. These studied different therapies and patient populations and did not clearly demonstrate the value of PET, with a number of false classifications of response. One study states that eight out of 23 patients had their treatment changed, but the precise influence of PET is unclear.

RT planning

- Three studies in 47 patients used PET in RT planning, which resulted in change in GTV or the number of irradiated nodes in several patients.

PET/CT

Diagnosis

- One prospective study showed that PET/CT detected one more occult primary tumour (12 out of 21) than PET and both methods were more sensitive than CT.

Mixed diagnosis/staging/restaging

- There were four studies of PET/CT in various stages of head and neck cancer, at least two of which were retrospective. These showed that PET/CT had slightly higher accuracy than PET, by about 10% (sometimes higher sensitivity, sometimes higher specificity). Two studies reported change in management in approximately 20% of patients, but this was not clearly documented.

RT planning

- Three studies in a total of 88 patients used PET/CT for RT planning and showed changes in volume or dose compared with CT.

Lung cancer

Background to lung cancer search

In 2005, NICE issued a clinical guideline for lung cancer including systematic reviews of PET prepared by the English National Collaborating Centre for Acute Care.⁵ Throughout this systematic review, this document is referred to as 'the NICE guideline'. As this guideline is based on systematic reviews with clinical expert input directly relevant to England and Wales, it forms the basis of this review of PET in lung cancer. For non-small cell cancer staging, NICE undertook economic evaluations in the English context, which showed convincing evidence of cost-effectiveness. Consequently, the literature search for additional primary studies of staging non-small cell lung cancer (NSCLC) only looked for studies that might alter the NICE guidance. For small cell lung cancer (SCLC) and solitary pulmonary nodule (SPN), the evidence from NICE was not so strong (no local economic modelling), so all new primary studies were considered.

The results in this section are presented for NSCLC first, followed by SCLC and SPN.

Data extractions are presented in Appendix 7 (from p. 160).

NSCLC: diagnosis

The HTA from DACEHTA⁶ identified ten diagnostic studies that sought to identify the primary tumour in patients with suspected NSCLC. The prevalence of malignancy varied across trials, but was generally quite high, and several trials had sensitivities of 100% for PET or PET + CT.

The use of PET for diagnosis of NSCLC to differentiate benign from malignant tumour (without biopsy) would not be seen as appropriate in the UK.

NSCLC: staging

The NICE guideline⁵ identified key systematic reviews and additional primary studies.

For mediastinal staging, the main body of evidence comes from two systematic reviews. The first, by Toloza (2003),¹¹¹ studied all patients despite their CT results and included 18 studies in 1045 patients. It found PET sensitivity of 84% and specificity of 89%. Three new primary studies found lower levels of accuracy with sensitivity below 70% and specificity 84% at the highest. The other systematic review was an HTA from the Health Technology Board for Scotland (HTBS)²

that differentiated between CT node-positive and CT node-negative patients. Seventeen diagnostic studies were identified and from an sROC analysis the PET sensitivity and specificity were estimated to be 90% and 93% for CT node-negative patients and 94% and 71% for CT node-positive patients.

The HTBS systematic review also showed that PET had sensitivity of 93% to detect any distant metastases, with specificity of 96%. The NICE guideline goes on to report good accuracy of PET for most individual sites (apart from the brain, where sensitivity was only 60%). The guideline indicated that from 1515 patients, a mean of 15% had unexpected distant metastases detected by PET, and PET led to change in management in 25% of patients.

The HTBS report also presented two RCTs evaluating the ability of PET to detect distant metastases and help to avoid thoracotomy. Patients with NSCLC were randomised to CWU with or without PET. At the time of publication, only one of these trials was fully published and the trials appeared to give conflicting results.

One trial in Europe²⁶⁹ included 188 patients who were node negative on CT. At randomisation, 70% had stage I/II NSCLC, 34% were stage IIIA and 5% were stage IIIB (plus one patient in stage IV). The primary outcome was futile thoracotomy, where a thoracotomy was considered futile if the patient had benign disease, exploratory thoracotomy, were at stage IIIA–N2/IIIB or there was postoperative relapse or death within 12 months of randomisation. Significant benefit was reported, with fewer futile thoracotomies (19 versus 39) when PET was added into the standard cancer work-up. This relative reduction of 51% was highly significant ($p = 0.003$). The halving of futile thoracotomies was consistent across stages, with 16 versus 31 futile thoracotomies on PET versus CWU in the patients classified as stage I/II at randomisation.

One trial in Australia was only published in abstract form at the time of the HTBS HTA. It was an interim report of 164 patients that could find little impact of PET, with over 96% of patients receiving thoracotomies and focus on total thoracotomies rather than futile thoracotomies. This trial has now been published in full (Viney, 2004)¹¹² for the full complement of 183 patients. The final staging of patients was similar to the staging at randomisation in the European trial, with 68% in stage I/II, 21% in stage IIIA, 2% in stage IIIB, 3% in stage IV and five patients (5%)

without tumour. The results focused on the PET-only patients and confirm the results presented in the abstract. As the investigators in this trial did not consider thoracotomy on stage IIIA disease to be futile, only six patients did not undergo thoracotomy. Hence, PET had no impact on the thoracotomies performed. It is noted that PET led to further investigations or change in management in 12 patients.

Viney¹¹² suggests that the result in the European trial was dominated by patients with stage III disease, but given the differences in reporting, this staging effect is difficult to see. Another reason for the difference between the trials could have arisen because surgeons in Australia were prepared to operate on N2 patients, which would have been considered futile in the European trial.

An additional primary study of PET/CT in staging NSCLC is presented in the section 'Staging' (p. 33).

The HTBS HTA reported an economic evaluation for Scotland considering seven pathways for staging NSCLC, four of which included PET. The model has since been updated to correct a mistake.¹¹³ In CT node-negative patients the most cost-effective strategy was to undertake PET then surgery for M0 N0/1 patients, non-surgical treatment for M1 N0/1, mediastinoscopy for other PET positive and surgery for negatives. Compared with sending directly to surgery, this had an incremental cost-effectiveness ratio (ICER) of £7900 per quality-adjusted life-year (QALY). In CT node-positive patients the cost-effectiveness of this strategy involving PET compared with mediastinoscopy then surgery was £58,951. NICE has indicated that it would generally accept a cost-effectiveness ratio of less than £20,000 per QALY as cost-effective and there should be strong reasons for accepting as cost-effective interventions with an ICER of over £30,000 per QALY.¹¹⁴ On these grounds, as PET is just one part of a diagnostic pathway, it would appear difficult to justify the cost-effectiveness of PET in CT node-positive patients.

The NICE guidelines⁵ presented an economic model for England and Wales that modified the HTBS model in CT node-negative patients. Compared with thoracotomy, PET resulted in 22% fewer futile thoracotomies for an ICER of £7200 per QALY. Probabilistic sensitivity analyses were undertaken and it was shown that even with uncertainty in the parameters the cost-effectiveness was unlikely to exceed £30,000 per QALY. The cost-effectiveness in CT node-positive

patients is not reported. This revised model provides a similar result to that in the earlier Scottish model. This gives some confidence relating to the robustness of the results.

The NICE guideline states that the published evidence is inconclusive for the UK, but suggests that PET is clinically and cost-effective to select patients with normal sized lymph nodes for surgery. It goes on to define clear diagnostic pathways for all patients and recommends that patients who have limited (one or two stations) N2/3 disease on CT that is of uncertain pathological significance, but are otherwise candidates for surgical resection, should have a PET scan. The evidence for this particular finding is not stated and given the poor cost-effectiveness of PET in the Scottish model, is presumably led by expert judgement. In addition, a peer reviewer noted that the utility of PET is different in non-bronchoalveolar cell carcinoma compared with bronchoalveolar cell carcinoma (owing to the lower FDG uptake in the latter).

NSCLC: recurrence

There were no studies of PET to detect NSCLC recurrence published after 2000. One study of PET/CT in recurrence is reported in the section 'Recurrence' (p. 33).

NSCLC: treatment response

Six primary studies were found which assessed the ability of PET to detect residual disease after neoadjuvant therapy in potentially curable NSCLC. One study used PET after palliative chemotherapy.

Choi (2002)¹¹⁵ investigated the use of residual glucose metabolism obtained from dynamic scans in 29 patients with locally advanced NSCLC in the USA. Residual glucose metabolism appeared to be predictive of tumour control (stable disease). A false-negative rate of three in 16 is reported. This is derived from a logistic regression model fitted to the data and has not been tested on a further sample, so it is likely to be an overestimate of accuracy.

Five other studies (two in Germany^{116,117} and three in the USA¹¹⁸⁻¹²⁰) all used static scans performed before and after neoadjuvant therapy to predict residual disease. The studies from the USA all report substantial proportions of FN nodal results from PET scanning: Port¹¹⁹ reports five out of 13 for N1/2 disease, Ryu¹²⁰ five out of 13 for N1/2 disease and Cerfolio¹¹⁸ nine out of 11 for N1

disease and four out of 15 for N2 disease. Port¹¹⁹ explicitly states that PET did not perform better than CT for this purpose (six FNs). Contrary to this, Cerfolio's results suggest some advantage for PET in paratracheal disease (no PET FNs from eight stations versus four out of eight for CT).¹¹⁸ In any event, it is clear that negative PET or CT nodal results after neoadjuvant therapy do not guarantee freedom from residual disease.

One study by Weber (2003)¹²¹ examined the use of an early PET scan to predict response to palliative chemotherapy in 57 patients with advanced (stage IIIB or IV) NSCLC in Germany. In this study a PET scan was performed on day 21 of the therapy course and changes from a baseline scan were used to predict clinical response. Twenty out of 28 metabolic responders had a clinical response at the end of therapy, compared with one out of 27 metabolic non-responders.

NSCLC: RT planning

For the NICE guideline, a systematic review of PET in RT planning was undertaken. It found four studies that studied RT planning in NSCLC. One study included 11 patients, while the others had 26–30 patients. The one retrospective study noted the largest change in RT therapy, of 31%. Others identified change in staging due to identification of distant metastases (3 out of 11 and 3 out of 27 patients), while the largest study indicated that PET induced change from radical to palliative therapy in 23% of patients, owing to detection of distant metastases.

The NICE guideline⁵ summarises this evidence by saying that the pooled weighted average for therapy changes as a result of PET was 42%. It is difficult to see how this follows on from the results presented in the individual studies. Furthermore, there is no discussion of the size or quality of studies, but NICE grades this evidence highly at level 2+. The conclusions are that "patients who are potential candidates for radical RT would benefit from a FDG-PET scan prior to their treatment".

There were four additional studies of PET to supplement CT for radiotherapy planning in NSCLC.

Bradley (2004)¹²² reports a study comparing visually fused PET + CT against CT in 24 patients in the USA. The PTV was changed in 14 patients (it was reduced in three and increased in 11 by the finding of unsuspected nodal disease).

De Ruysscher (2005)¹²³ reports the only outcome data found for RT planning. RT fields were planned for 44 patients with stage I–III NSCLC in The Netherlands, Germany or the UK using visually fused PET + CT. They report that RT dose escalation up to 64.8 Gy over 24 days was possible. After a median of 16 months' follow-up, isolated nodal failure outside the radiation field (i.e. unaccompanied by any other failure) occurred in only one patient.

Schmücking (2003)¹¹⁶ reported that in 27 patients in Germany, the PTV from visually fused PET+CT was between 3 and 21% larger than the CT PTV, whereas the volume of lung tissue assumed to be normal, which received less than 20 Gy, reduced by between 5 and 17%.

Van Der Wel (2005)¹²⁴ presents results from a modelling study in 21 patients in The Netherlands or the UK with N2/3 M0 NSCLC, comparing visually fused PET + CT images to CT. They show that the mean GTV (\pm standard deviation) reduced from $13.7 \pm 3.8 \text{ cm}^3$ on CT to $9.9 \pm 4.0 \text{ cm}^3$ on PET. The mean dose to presumed unaffected oesophagus reduced from 29.8 ± 2.5 to 23.7 ± 3.1 Gy and the estimated mean probability of tumour control increased from 12.5% to 18.3%.

An economic evaluation of PET in RT planning in England and Wales was undertaken for the NICE guideline. Compared with going directly to radical RT, PET resulted in 32% fewer courses of futile radical RT and 2.5% receiving curative surgery. Adverse impacts included 5% missed RT courses and 6% more futile thoracotomy. The cost-effectiveness was estimated to be £9500 per QALY and from probabilistic sensitivity analyses was not likely to exceed £30,000. Hence, it was concluded that PET is cost-effective in patients being considered for radical RT.

This model is of particular interest because it is a new model and directly relevant to the English situation. However, the anticipated effect is based on four studies involving fewer than 100 patients in total, with few of these patients contributing information. New studies in a further 116 patients have been published. Also, it was not based on randomised data, so it is subject to uncertainty about the nature of the interaction between FDG images and effective treatment volumes that is difficult to quantify. Consequently, further development and validation of the model would be useful as clinical experience grows.

NSCLC: mixed management decisions – patient management

As for other cancers, there are two reports from the USA of surveys of referring physicians evaluating the impact of PET using two retrospective questionnaires. These are not reported here as they appear to cover diagnosis and staging of all forms of pulmonary malignancies¹²⁵ or all forms of lung cancer.¹²⁶

NSCLC: PET/CT

Staging

There are three primary studies of PET/CT in NSCLC staging. In the first two studies, some patients had received neoadjuvant therapy before planned surgery and the PET scan.

Some authors report PET/CT results in studies earlier than those presented here,^{127–129} but they use fusion or visual correlation of images from separate devices.

Antoch (2003)¹³⁰ prospectively studied 27 patients in Germany and showed that PET/CT correctly staged 26 patients, compared with 20 on PET and 19 on CT. Compared with PET alone, PET/CT led to correct alteration of staging in seven patients (26%).

Cerfolio (2004)¹³¹ prospectively studied 129 patients in the USA. PET/CT correctly staged more patients than PET, but a fairly large number of patients were still incorrectly staged by PET/CT (31 overstaged, 12 understaged). The number of patients with a metastasis at an individual site was small (fewer than eight), but PET/CT generally had fewer FPs than PET, particularly in the bone (three on PET/CT versus 6 on PET).

Lardinois (2003)¹³² prospectively studied 49 patients undergoing primary staging in Switzerland. PET/CT correctly classified more tumours or nodes than visually correlated PET + CT, PET or CECT. Compared with PET + CT, integrated PET/CT provided 'additional information' in 20 (41%) of patients. This generally related to anatomical information such as exact location of lymph nodes, chest-wall infiltration or mediastinal invasion, with differentiation of tumour and inflammation in seven patients and location of distant metastases in two patients.

Recurrence

Keidar (2004)¹³³ prospectively studied 42 patients mainly in stages I and II in Israel. They found high sensitivity of PET/CT and PET at 96%, but lower specificity for PET at 53%, compared with 82% with PET/CT. PET/CT contributed to change in management in 12 patients (29%).

NSCLC overview

PET

Diagnosis

- One SR described ten PSs that used FDG-PET to identify the primary tumour, but PET would not routinely be used for this purpose without biopsy.

Staging

- The NICE guideline presents an SR of 18 PSs which showed that for mediastinal staging (ignoring CT) PET had sensitivity of 84% and specificity of 89%. Somewhat lower values were observed in three additional PSs.
- Using CT before PET, another SR of 17 PSs showed PET to have sensitivity of at least 90% whatever the CT result, but poorer specificity in those who were CT node positive (71% versus 93% in CT node negative).
- The same SR of 17 studies showed that PET had sensitivity and specificity of over 90% for detection of any distant metastases. The NICE guideline shows this level of accuracy for individual metastatic sites apart from the brain. Change in management was reported in 25% of patients, but documentation is generally poor.
- An RCT in Europe showed that PET significantly reduced the number of futile thoracotomies. However, an Australian RCT found that PET did not affect the total number of thoracotomies when surgeons were prepared to operate up to stage IIIa of disease.
- A Scottish model and more recent English economic model exist for the use of PET in staging, which assume that operations on stage IIIA disease are futile. Both show that in CT node-negative patients, the addition of PET was cost-effective (approximately £7500 per QALY). The Scottish model also reports that in CT node-positive patients the ICER is £58,951, which would not normally be considered as cost-effective.

Treatment response

- Six PSs used PET to assess residual disease after neoadjuvant therapy. Five of these used

static PET scans and show that both CT and PET had some FNs. This may be because PET misses residual disease. In one study PET appeared no better than CT, but another reports a lower FN rate for PET.

- One PS in 57 patients used PET during palliative chemotherapy and found that 20 out of 28 metabolic responders on PET had CR at the end of therapy versus one out of 27 metabolic non-responders.

RT planning

- The NICE guideline found four PSs using PET to assess a total of 94 patients before radical RT. The largest study in 30 patients found that PET changed RT from radical to palliative in seven patients (23%). Four additional PSs in 116 patients showed some change in volume and dose as a result of PET.
- One of the new studies followed up patients for 16 months and showed that nodal failure outside the radiation field occurred in only one patient.
- NICE undertook an economic evaluation of PET in RT planning, which suggested that PET is cost-effective. However, this model was only based on less than half the data currently available and uncertainties may be difficult to quantify.

PET/CT

Staging

- PET/CT has been evaluated for staging in three prospective PSs in a total of 205 patients (in some cases after neoadjuvant therapy before planned surgery). All studies showed that PET/CT staged more patients correctly than PET, but a large study of 129 patients in the USA noted that 33% of patients were still incorrectly staged.

Suspected recurrence

- There is one prospective PS studying suspected recurrence in 42 patients, which showed greater specificity of PET/CT than PET and that PET/CT contributed to change in management in 29% of patients.

SCLC: diagnosis

The only systematic review of SCLC diagnosis was published by AHRQ in 2004 and relates to occult SCLC in patients with suspected paraneoplastic neurological syndrome (PNS).¹³⁴ In 43 subjects, PET detected nine out of ten primary tumours, but only three of these were SCLC. No additional primary studies were found and so there is insufficient evidence from which to draw any conclusions.

SCLC: staging

The AHRQ HTA¹³⁴ presents five diagnostic studies of staging SCLC. These were small, but showed PET to have sensitivity of at least 89% and specificity of 100% across both limited and extensive disease populations.

A substantial new study by Brink (2004)¹³⁵ included 120 patients from Germany; 63% had extensive disease. PET showed sensitivity and specificity over 90% for detection of lymph nodes and for detection of distant metastases (apart from those in the brain). PET was concordant with conventional imaging in 63% of patients and for most of the discordant readings PET was correct. PET resulted in 8% of patients being correctly upstaged to extensive disease and 3% being correctly downstaged to limited disease. Just one patient was incorrectly staged with PET, owing to a missed brain metastasis.

A study of 25 patients in the USA by Bradley (2004)¹³⁶ included just 13% of patients with extensive disease. However, this study also found that 8% of patients were upstaged as a result of PET.

The NICE guideline summarises a systematic review of five studies in SCLC (not PET related), which showed that two-thirds of patients with SCLC present with metastatic (extensive) disease, most commonly in the liver and bone. They state that given this disease presentation, investigation for distant metastases is always indicated for SCLC. It is noted that for symptomatic patients the choice and site of staging examination should be guided by clinical examination. For asymptomatic patients CT of the chest, upper abdomen or bone scan should be performed sequentially, stopping once a metastatic site has been found.

NICE does not mention the use of PET for SCLC. However, the new German study by Brink¹³⁵

suggests that PET may be of value in detecting distant metastases not identified by other imaging modalities and that the population studied is similar to that in the UK. Clear evidence of change in patient management and patient outcomes is lacking.

SCLC: restaging

Two small diagnostic studies in a total of 58 patients are summarised in the AHRQ HTA of PET in restaging SCLC to detect residual disease.¹³⁴ The sensitivity of PET was above 95% in the two studies, but specificity was only 41% in one study. No new studies in restaging SCLC were identified.

SCLC overview**PET****Diagnosis**

- One SR identified one PS that used PET to detect occult SCLC in 43 subjects with suspected PNS, but the number with SCLC or PNS was small and no conclusions can be drawn.

Staging

- One SR of five PSs showed PET to have sensitivity and specificity of at least 89%.
- Of two new PSs, one in 120 patients provides substantial additional information. It mirrors the presentation of English patients well, with approximately two-thirds having extensive (metastatic) disease. PET showed sensitivity and specificity of over 90% for detection of lymph nodes and detection of distant metastases (apart from those in the brain).
- In this new study, PET upstaged 8% and downstaged 3% of patients, with just one patient staged incorrectly. The other study was smaller, but also found that PET upstaged 8% of patients. It was unclear how this led to change in management.

Restaging

- One SR reported two small PSs in a total of 58 patients. PET sensitivity was above 95%, but specificity was only 41%.

PET/CT

- No studies had been published for SCLC management up to August 2005.

SPN: diagnosis (characterisation)

Gould (2001)¹³⁷ reports a systematic review including an sROC analysis of 13 studies specifically evaluating SPN. PET sensitivity was 94% at median specificity of 83%. It is noted that only eight of the 450 patients had SPNs smaller than 1 cm.

The NICE guideline⁵ presents different results from the Gould systematic review.¹³⁷ The results from the mixed population of patients with masses and pulmonary nodules are presented, along with two additional primary studies. NICE concluded that PET provides good sensitivity and reasonable specificity for characterisation of SPNs and masses as FDG-avid. It was noted that there may be some concern about the effectiveness of PET for characterisation of nodules smaller than 1.5 cm, but the published studies do not allow such an effect to be investigated.

A new meta-analysis was undertaken for the Health Care Knowledge Centre (Belgium) (KCE) report (2005)¹³⁸ on 32 studies. An sROC analysis showed a sensitivity for PET of 95% to characterise SPN, at median specificity of 77%. This is consistent with the results of Gould¹³⁷ and NICE.

Two additional primary studies of pulmonary nodules were found: Nomori (2005)¹³⁹ and Buck (2005).¹⁴⁰ Both of these evaluated any number of pulmonary nodules (not just solitary) in a variety of patients (including those with lung metastases, NSCLC or SCLC). Consequently, these studies were excluded as they add little to the evidence from the systematic reviews.

One of the new studies identified by NICE was a well-planned change in management study using a set of three questionnaires for each patient. All questionnaires were returned for 76% of the 164 patients. In these 125 patients, it was shown that PET contributed to understanding in 58% of patients, improved diagnosis in 26% of patients and contributed to change in treatment in 43 patients (34%; 26% of total), 36 avoided surgery, seven had surgery.

As the specificity of PET is not that high, the NICE guideline suggests that PET may be useful in low-risk patients (risk based on smoking history, haemoptysis and size) to provide confidence with a negative scan and the ability to adopt a watch-and-wait policy in follow-up. For those with intermediate risk a tissue biopsy would be performed; if this was not possible PET may be useful.

SPN: other management decisions

For patients with SPN, PET has only been studied for diagnosis. Other management questions have not been studied.

SPN overview**PET****Diagnosis (FDG-avid characterisation)**

- In a robust meta-analysis of 13 PSs identifying patients with SPN, the sensitivity of PET was 94% with specificity of 83%.
- Concerns are raised about the effectiveness of PET to characterise small nodules (<1–1.5 cm), but this could not be investigated from the available data as few patients with such small nodules were studied.
- NICE suggests that given the reasonable specificity of PET, PET may be better used in low-risk patients where negatives can be followed up with a watch-and-wait process.
- Of two new PSs, one large, well-designed study showed strong evidence that PET can contribute to the decision-making process and that PET led to change in treatment (surgery) in at least 26% of patients.

For SPN, PET has only been studied for characterisation of the nodule as FDG-avid.

PET/CT

- No studies had been published on SPN up to August 2005.

Lymphoma

Data extractions are presented in Appendix 7 (from p. 182).

Diagnosis

One study of PET used for diagnosis of eight patients with gastric non-Hodgkin's lymphoma (NHL) has been published and is reported in the MSAC HTA (2001).⁶⁹ This was too small to draw any conclusions from, but it is unlikely that PET would be used routinely for diagnosis.

Staging

The MSAC (2001)⁶⁹ assesses evidence from seven studies in 369 patients with Hodgkin's lymphoma (HL) or NHL. The studies showed PET sensitivity ranging from 79 to 100% and specificity between 90 and 100%. In two of these studies, PET appeared to be more accurate than CT for

staging lymph-node involvement, but these only involved 27 patients. Most papers state that there was some change in management or staging. One study stated that PET's change in staging was acted upon in 28 out of 49 patients. In another, PET changed management in ten out of 50 (20%) patients versus seven out of 50 from gallium-67 (Ga-67) scanning. The actual changes in management are not clearly documented.

Seven additional primary studies were found in this indication. There were also three studies of PET/CT in mixed populations (see the section 'PET/CT', p. 38).

Delbeke (2002)¹⁴¹ studied PET added to CWU in 45 patients (23 NHL) in the USA. PET correctly upstaged five, correctly downstaged two and incorrectly downstaged three patients. Management was changed in six patients (13%) as a result of PET scanning.

Hong (2003)¹⁴² reports a comparison of PET, CT and Ga scanning in 30 patients, 26 with NHL, in Korea. This study included nine patients for restaging. Any finding with consensus (two-thirds) support was regarded as accurate, with other findings resolved by follow-up. Nodal analysis of 536 lesions showed that PET and CT had similar accuracy for detection of nodal lesions, with sensitivities of at least 93% and specificities of at least 99%, whereas Ga scanning had sensitivity of only 26%. For extranodal lesions, the sensitivities of PET and CT were both 88% versus 38% on Ga scanning. All modalities had specificity of 100%.

Jerusalem (2001)¹⁴³ presented results from staging 42 patients with low-grade NHL in Belgium. They suggest that in this indication PET must be combined with bone-marrow biopsy (BMB) and indicate that the combination of PET and BMB resulted in stage changes for five patients (12%) relative to CWU including BMB. However, no management changes occurred.

Naumann (2004)¹⁴⁴ examined the effect of using PET to supplement CWU in 88 patients with early HL in Germany. Eleven of these were patients presenting for restaging. Concordant findings were assumed to be correct. Discordances between PET and CWU were resolved by follow-up. In this study 18 out of 88 patients had discordant findings: 11 PET TP, one TN and six FN. PET would have changed management correctly in ten patients (11%), but incorrectly in the six FN patients.

Sasaki (2002)¹⁴⁵ reports a comparison of CWU + PET versus CWU + Ga scanning in 46 patients (42 with NHL) in Japan. Patients with all stages of lymphoma were included, but the majority (33) had high-grade disease and four had recurrent disease. Consensus of imaging and CWU was used to establish reference. Discordant findings were resolved by response to treatment and follow-up results. The combination of CWU and PET had superior sensitivity to CWU + Ga in both nodal [152 out of 152 (100%) versus 112 out of 152 (74%)] and extranodal disease [18 out of 19 (95%) versus 14 out of 19 (74%)]. The addition of PET to CWU correctly upstaged eight patients, which resulted in changes to the clinical management in all these eight (17%). PET incorrectly upstaged five patients.

Shen (2002)¹⁴⁶ reports a comparison of PET and Ga scanning in 30 patients (14 HL, 16 NHL) in Taiwan. He reports that the PET sensitivity was 96% (24 out of 25) versus 72% (18 out of 25) for Ga scans.

Yamamoto (2004)¹⁴⁷ reports a study in 28 NHL patients in Japan, where a total of 66 nodal lesions were found. PET found all 66 lesions, whereas Ga scanning found 32. PET detected 18 out of 23 extranodal lesions compared with 12 on Ga scanning. Five extranodal lesions were not found by either imaging method. The lesions missed by Ga were generally abdominal, whereas those missed by PET were more widely distributed small foci.

Restaging: assessment of response at the end of induction therapy

Patients with residual masses after therapy for lymphoma present a major therapeutic challenge because of uncertainty over the value of more intensive therapy. The HTBS HTA² included eight PET and six CT studies in patients with HL and NHL in its systematic review. Analyses of PET, with or without CT before PET, showed that PET and CT had similar sensitivity of 75–80% for the detection of active residual disease. However, PET had superior specificity of approximately 90% versus 45% on CT. The older MSAC HTA⁶⁹ supports these conclusions and suggests that post-therapy scans may have value in predicting patient prognosis.

The new primary studies found relating to restaging are dealt with in two groups in this subsection:

- scans *after* therapy to predict prognosis and inform subsequent treatment
- the investigation of known residual masses *after* therapy.

The use of PET *during* therapy will be assessed in the later section on treatment response.

Post-treatment prognosis to inform patient management

Five studies used PET to predict prognosis. It is presumed that this information would have been used to inform subsequent treatment, but none of these studies reports how PET was used to change management.

Friedberg (2004)¹⁴⁸ compared PET and Ga post-therapy scanning in 36 newly diagnosed HL patients in the USA. Most patients received chemotherapy or CRT. PET scanning 1 month post-therapy predicted four of the five patients who developed progressive disease, whereas Ga scanning predicted two out of five.

Juweid (2005)¹⁴⁹ studied 54 NHL patients given chemotherapy in the USA and Germany. The study showed that using a post-therapy scan to modify the International Workshop Criteria (IWC) for response results in a classification with stronger correlation to progression-free survival (PFS) than using the IWC alone.

Lavelly (2003)¹⁵⁰ presents the results of using post-treatment PET scans to assess the prognosis of 20 HL and 20 NHL patients after chemotherapy or CRT in the USA. Although the numbers receiving RT were small, there is some evidence to suggest that negative post-RT PET scans were a better predictor of freedom from relapse than negative scans after therapy in patients receiving chemotherapy alone.

De Wit (2001)¹⁵¹ compared the use of PET, CT and erythrocyte sedimentation rate (ESR) to predict prognosis in HL. In 33 patients treated in Germany, ten relapses occurred. PET predicted all ten, with five FPs, whereas CT predicted seven out of ten, with 17 FPs, and ESR identified five out of ten, with seven FPs.

Zinzani (2002)¹⁵² studied 56 patients with bulky (>5 cm) abdominal disease in Italy (13 HL). They compared the ability of post-treatment PET and CT scans to predict prognosis. PET and CT had similar sensitivity for relapse prediction (nine out of eleven versus eight out of eleven), but PET was much more specific (four FP versus 41 FPs).

Investigation of residual mass

Three studies evaluated the use of PET to investigate residual masses.

Jerusalem (2003)¹⁵³ studied 36 patients in Belgium with HL. Nineteen of them had residual masses visible on CT 1 month after therapy. Positive PET scans in this group predicted two out of two relapses over a median follow-up of 2 years, with three FPs. Among the 17 patients without residual mass on CT, PET predicted all three relapses, with three FPs.

Naumann (2001)¹⁵⁴ studied 42 HL patients and 15 NHL patients in Germany with residual masses (≥ 1 cm) on CT after therapy. Within the area of the residual mass, PET scanning predicted the only relapse, with three FPs among the HL patients, and four out of six relapses, with two FNs but no FPs in the NHL patients.

Panizo (2004)¹⁵⁵ studied 29 patients in Spain with HL and residual mass of at least 2 cm on CT scan. All patients received RT before the PET scan. Positive PET scans predicted all nine relapses, with three FPs.

The Scottish HTA of PET² undertook an economic evaluation in restaging advanced HL (assessment of residual mass) in 2002. The model predicted that with CT 36% of patients would receive unnecessary consolidation RT. However, if CT node-positive patients were then imaged by PET, this would reduce to 6%, and if CT was not used at all just 4% would have unnecessary RT. The model showed that PET without CT, or in CT node-positive patients, was highly cost-effective. Probabilistic sensitivity analysis showed that across a range of input values, the willingness to pay needed only to be £5000 per life-year (as shown by the 95% or 99% point on the cost-effectiveness acceptability curves for three age sectors and each gender).

Treatment response: assessment during therapy

Nine published studies investigated the use of PET for response assessment midtherapy.

Becherer (2002)¹⁵⁶ examined the value of a PET scan after ICT in 16 patients (ten HL) in Austria. The absence of metabolic response predicted seven out of eight relapses over 1 year, with no FPs.

Cremerius (2002)¹⁵⁷ studied 24 patients with NHL in Germany scheduled for high-dose chemotherapy and autologous stem cell transplantation (ASCT). Early scans after three cycles of induction chemotherapy (ICT) were not

predictive of PFS. However, changes in FDG uptake between a scan taken after three cycles of ICT and one taken after completion of ICT did predict PFS.

Filmont (2002)¹⁵⁸ studied 43 patients (12 HL) in the USA. PET scan results either after ICT or after ASCT predicted 6-month status better than CT scans done at the same time.

Haioun (2005)¹⁵⁹ studied 90 patients with aggressive NHL in France, receiving ICT [+ ASCT if high risk on the International Prognostic Index (IPI)]. In those patients who were PET negative after two cycles of ICT, 2-year survival was 90%, versus 61% in PET-positive patients. FDG uptake was significantly associated with 2-year survival, independently of IPI and treatment regimen.

Hutchings (2005)¹⁶⁰ studied 85 patients with HL in the UK. PET scans were taken after two or three cycles of chemotherapy. In the 12 that progressed, PET was positive in eight and showed minimal uptake in one other patient. There were also five FPs and eight others with minimal uptake. Overall, midtherapy negative or minimal disease PET scan was a significant predictor of improved PFS.

Schot (2003)¹⁶¹ studied 46 patients with recurrent lymphoma (33 with NHL) in The Netherlands. All patients were given ICT followed by high-dose therapy and ASCT. PET scans were performed before and after ICT. Patients with persistent uptake after ICT had a relative risk of progression over 2 years of 2.6 (95% CI 1.0 to 6.9).

Spaepen (2002)¹⁶² studied 70 patients with aggressive NHL receiving chemotherapy in Belgium. PET scans were performed after three or four cycles. Thirty-seven patients had negative midtreatment PET scans and 31 out of 37 were still in remission after a median follow-up of 1107 days. None of the 33 with FDG uptake at midcycle was in remission after 33 days.

Torizuka (2004)¹⁶³ studied the ability of PET scans to predict PFS after two out of three cycles of the chemotherapy regimen adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) in 20 HL patients in Japan. He showed that the presence of persistent FDG uptake was a significant predictor of PFS. Using a cut-off of 60% as PET positive resulted in correct prediction of all ten clinical responders, while nine out of ten non-responders fell below the cut-off.

Zijlstra (2003)¹⁶⁴ compared the prognostic value of PET and Ga scanning after two cycles of the chemotherapy regimen cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) in 26 patients with NHL in The Netherlands. FDG uptake correlated more closely with status after 16 months follow-up than did Ga uptake.

Mixed management decisions – patient management

Owing to the paucity of evidence on patient management and paediatrics, these retrospective studies are presented here for discussion purposes.

Schöder (2001)¹⁶⁵ reports a survey in the USA that sought to determine the impact of PET on colorectal cancer patients. Two questionnaires were used retrospectively using identical methods to those reported by Yap.³⁶ (Likewise, the caveats regarding the Yap study apply here.) Between 1998 and 2000, 108 patients with lymphoma had PET scans. Questionnaires were returned for 52 (18 HL, 34 NHL) of these patients (48%) from oncologists, general physicians and GPs. The main reasons for patient referral were for staging (37%), treatment response (25%), monitoring course of disease and restaging (13%) and diagnosis (10%). In this mixed group of patients, PET upstaged 11 patients (21%; 10% of total) and downstaged 12 (23%, 11% of total). There were intermodality changes in 22 patients (42%) and intramodality changes in five (10%).

Wegner (2005)¹⁶⁶ presents a survey based on a modified form of this questionnaire for a mixed group of paediatric oncology patients referred for a PET scan between 1992 and 2002. In this group, 60 children with lymphoma received 80 PET scans and 63 questionnaires were returned (79%). It is not stated when the questionnaire was issued in relation to the PET scan (presumably it could have been several years, given the early start date of this retrospective study). However, the response rate in this study was higher than in similar studies. PET was used to assess residual masses (31 scans), to assess treatment response (11), to detect recurrence (ten), for staging (five), for diagnosis (three), and for monitoring the course of the disease (three). PET altered treatment in 20 out of 63 cases (32%; 25% of total). PET findings were confirmed in 44 cases. PET was incorrect in nine out of 63 cases (14%) (all with HL). There were five FPs, but only one affected management and it was not detrimental to the patients. There were four FNs that were stated not to cause detrimental change.

PET/CT

There were three published studies of PET/CT for management of lymphoma. All studies included both HL and NHL and were retrospective.

Allen-Auerbach (2004)¹⁶⁷ studied 73 lymphoma patients (53 NHL) undergoing staging or restaging/recurrence in the USA. This was probably a retrospective study. Approximately half of the patients had malignancies. PET/CT and PET both resulted in the correct staging of 61 patients and the incorrect staging of five patients. PET/CT was correct in seven patients where PET was incorrect. This led to two patients being upstaged and one being downstaged (4%). The sensitivity of PET and PET/CT was 88%, but the specificity of PET/CT was higher (92%) than PET (82%).

Freudenberg (2004)¹⁶⁸ reports a study of the restaging/recurrence of 27 lymphoma patients

(18 HL) in Germany. Fourteen patients had nodal or extranodal lesions. The specificity of PET, PET + CT or PET/CT was 100%, compared with 54% on CT. PET/CT or PET + CT sensitivity was 93%, compared with 86% on PET and 78% on CT. Compared with PET, PET/CT correctly upstaged two patients and downstaged one patient (11%).

Schaefer (2004)¹⁶⁹ studied 60 patients with lymphoma (42 NHL) requiring staging/restaging/recurrence evaluations in Switzerland. PET/CT was slightly more accurate than contrast-enhanced computed tomography (CECT) for determining nodal involvement, but in terms of distant metastases, PET/CT had superior sensitivity of 88% versus 50% on CECT. PET/CT provided additional information in nine patients, compared with two on CECT.

Lymphoma overview**PET****Diagnosis**

- FDG-PET has only been evaluated for diagnosis in one study of fewer than ten patients. However, since histological confirmation is always required, PET is not likely to be used routinely for the diagnosis of lymphoma.

Staging

- Evidence from one SR reviewing seven PSs, and seven additional PSs shows that PET had specificity of at least 90% and sensitivity of 79–100% (or $\geq 90\%$ in the new studies).
- PET consistently showed superior sensitivity to Ga scanning. Two older studies suggested PET was more accurate than CT for staging lymph-node involvement, but one new study showed them to be comparable.
- There was evidence that all imaging methods may miss small disease foci.
- There is some evidence of management/staging changes in 10–20% of patients from diagnostic accuracy studies, but the changes are not well documented.

Restaging

- Five new PSs showed that PET was a better predictor of relapse after therapy than CT. There is no evidence that this information has been used to inform subsequent treatment.
- There is evidence (one SR reviewing eight PSs of PET, and three additional PSs) that

post-therapy PET had similar sensitivity and better specificity than Ga scanning and CT scanning to evaluate residual masses.

- An economic evaluation in advanced HL showed that PET was highly cost-effective (£5000 per life-year) and predicted large savings in unnecessary consolidation RT when used instead of CT, or after CT-positive scans.

Treatment response

- There is evidence from nine PSs that midtherapy scans may be predictive of outcome midtherapy. As yet, however, there is no evidence of any associated changes in management (such as intensification or switch in therapy) consequent upon this.

Paediatrics

- A survey of 60 children with NHL and HL who had undergone PET scans for a variety of management reasons achieved a 79% response rate. It showed that PET altered treatment in at least 25% of cases. There were five FPs and four FNs, all in HL.

PET/CT**Mixed management decisions**

- Three retrospective PSs in mixed populations suggest that PET/CT was more accurate than CT. The accuracy of PET was fairly high in these studies, but PET/CT appears to add value in a few patients, with changes in PET staging in three out of 71 and three out of 27 patients in two studies.

Malignant melanoma

Data extractions are presented in Appendix 7 (from p. 208).

Staging

The only systematic reviews involving staging malignant melanoma are mixed with restaging studies. These are presented in the section 'Staging/restaging' below. There are 12 primary studies in staging alone, presented here by stage of disease.

Early-stage disease

Nine studies included patients with early-stage disease. Most patients had cutaneous melanoma greater than 1 mm Breslow thickness and used PET to detect micrometastatic disease. In most cases, SLNB and histopathology were the reference standards.

Acland (2001)¹⁷⁰ reports a trial of 50 patients in the UK, in which 14 patients had positive sentinel lymph nodes (SLNs). PET did not detect any of these and so had a sensitivity of 0%. For other sites, PET had six FPs.

Belhocine (2002)¹⁷¹ studied 21 stage I/II patients in Belgium. Six had positive SLNs. PET detected one of these, which was 1.8 cm, but missed the other five, all of which were smaller than 1 cm. The sensitivity of PET was 14%, compared with 86% for SLNB.

Fink (2004)¹⁷² studied 48 stage I/II patients in Austria. Eight had positive SLNs. PET detected the largest one (1.1 cm), but the other seven were not detected by PET, resulting in a sensitivity of 13%.

Hafner (2004)¹⁷³ studied 100 newly diagnosed patients in Switzerland who had 26 positive SLNs. The sensitivity of all imaging methods to detect regional lymph-node involvement was poor, being 8% for PET or US. PET also had two FPs for distant metastases.

Havenga (2003)¹⁷⁴ studied 55 patients, with 43 positive SLNs in The Netherlands. Two of the lymph-node metastases were detected by PET (sensitivity 15%). PET also had five FPs.

Kokoska (2001)¹⁷⁵ studied 18 patients in the USA. The majority of patients were in stage II and 17 had positive SLNs. PET sensitivity was 40%.

Longo (2003)¹⁷⁶ studied 25 stage I/II patients in the USA. Nine had positive SLNs, which were all detected by SLNB. PET detected only 2 (sensitivity 22%).

Reinhardt (2002)¹⁷⁷ studied 67 patients in Germany. In this study, PET detected ten out of 11 positive lymph-node metastases and all 13 distant metastases. (It is unclear why this study gives such markedly better results than all other studies.)

Wagner (2005)¹⁷⁸ studied 144 early-stage patients in the USA. Forty of these patients had 43 positive lymph-node regions. In an analysis of 184 lymph-node regions, PET had a sensitivity of 21% compared with 98% on SLNB. Both had specificity greater than 95%. In a patient-based analysis of distant metastases, PET had poor sensitivity of 4%, with specificity of 86%.

Later stage disease

Ghanem (2005)¹⁷⁹ studied 35 patients in Germany to detect liver metastases (stage not specified). PET was less sensitive than MRI (83% versus 100%). Both had a specificity of 97%.

Gulec (2005)¹⁸⁰ studied 49 stage III/IV patients in the USA. PET had sensitivity of 100% and specificity of 75% in lesions larger than 1 cm, but sensitivity of only 13% with specificity of 33% in lesions 1 cm or smaller. Despite this, PET was superior to CWU (involving CT and MRI) and led to change in treatment in 24 patients (49%).

Vereecken (2005)¹⁸¹ studied 43 patients in Belgium. Most were in stages III/IV and 39 had positive SLNs. PET had sensitivity of 40%, detecting metastases between 0.2 and 0.5 cm, but missing other metastases between 0.1 and 0.4 cm. There were 28 FP sites, 19 of which could be explained by other cancers, inflammation, and so on.

Staging/restaging

Two systematic reviews mixed studies with primary and recurrent malignant melanoma, to evaluate the accuracy of PET in detection of regional or distant metastases. Some of the same studies were assessed in each systematic review, but PET accuracy results are presented in quite different ways, so both are reported.

The systematic review by Mijnhout (2001)¹⁸² included 11 studies, six of which were included in an sROC analysis. This resulted in sensitivity of PET of 78%, with specificity of 88% and a high DOR of 33. The studies included were published before 2000, when the reference standard was histopathology or follow-up imaging. In the only study that used SLNB, PET had low sensitivity (17%) in stage I/II patients and this study was excluded from the sROC analysis as it created heterogeneity. The other studies did not include stage I patients.

DACEHTA (2001)⁶ included 15 studies in their systematic review. The studies additional to Mijnhout¹⁸² confirm his results showing sensitivities of 78% or more, with specificities ranging from 44 to 95%. Three studies presented comparisons to CT and showed that PET had higher sensitivity.

An older systematic review by MSAC (2000)¹⁸³ reported that in one study, PET changed management in 22 out of 100 patients.

Three additional primary studies in mixed primary and recurrent populations were found.

Finkelstein (2004)¹⁸⁴ evaluated 18 stage IV patients (five of whom had local recurrence) in the USA. PET had sensitivity of 79% and specificity of 87%, which was comparable to the accuracy with standard work-up (with CT and MRI), with sensitivity of 76% and specificity of 87%. For SLNB, the sensitivity was somewhat higher at 88%, with specificity of 91%.

Jenicke (2001)¹⁸⁵ studied 35 patients with advanced malignant melanoma and used PET for staging and follow-up. Compared with CWU of chest X-ray (CXR) and CT/MRI, PET upstaged 14 patients (40%) and downstaged four (11%). However, it is unclear whether these were all correct staging alterations.

Kurli (2005)¹⁸⁶ studied 20 patients with suspected metastatic choroidal uveal melanomas (only two were primary staging). PET detected malignant disease in ten patients, two of which were other cancers. PET also detected three other lesions, but they were below the SUV cut-off of 2.5 and so were discounted as benign, which was correct.

Recurrence

Two primary studies used PET in patients with suspected recurrence of melanoma.

Mijnhout (2002)¹⁸⁷ studied 68 patients in The Netherlands, with mainly stage III/IV suspected

recurrent melanoma. This was a well-designed patient management trial using three questionnaires issued at three time-points: before and after PET and after 6 months follow-up. Three completed questionnaires were returned for 58 out of 68 (85%) patients. In these 58 patients, PET improved diagnostic understanding in 57% patients (mainly due to better detection of distant metastases and improved specificity). PET contributed to change in therapy in 40% of patients (34% of total) and led to suboptimal treatment in 3% of patients.

Stas (2002)¹⁸⁸ studied 84 patients with suspected recurrent melanoma in Belgium. A lesion-based analysis showed that the sensitivity of PET for all tumour sites, or lung alone or lymph nodes alone was at least 85%, with specificity of at least 90%. For skin, the sensitivity was also 86%, but the specificity was poor at just 25%. For brain, the sensitivity was poor at just 22%. PET led to change in therapy (correctly) in 26 patients (30%): ten were downstaged, nine avoided nodal dissection, three widened surgical field and four were upstaged).

Mixed management decisions – patient management

Owing to the paucity of evidence on patient management, this retrospective study is presented here for discussion purposes.

Wong (2002)¹⁸⁹ reports a survey in the USA that sought to determine the impact of PET on patients with malignant melanoma. Two questionnaires were issued using identical methods to those reported by Yap.³⁶ (Likewise, the caveats regarding the Yap study apply here.) Of 146 patients with melanoma who had PET scans for various reasons, questionnaires were returned for 51 (35% response). PET upstaged ten patients (20%; 7% of total) and downstaged five (10%; 3% of total). There were intermodality changes in 15 patients (29%) and intramodality changes in nine (18%).

Melanoma overview

PET

Staging

- Twelve new PSs used PET for staging, using SLNB as the comparator or reference standard.
- Nine of these PSs showed highly consistent results that PET had poor sensitivity (generally <20%) to detect regional lymph-node activity in early-stage patients. This appears to be due to the small size of the micrometastases.
- For distant metastases, there were several FPs and one study in which the sensitivity was only 4%.
- PET sensitivity varied between 40 and 100% in the three PSs in later stage disease. Again, sensitivity in small lesions was poor.
- For later stage disease, comparative results are varied. In one study PET was less sensitive than MRI, but in another PET was superior to CT/MRI and led to more changes in treatment.

Staging/restaging

- Two older SRs in 11 and 15 PSs report accuracy results in mixed populations and do not differentiate stage of patients.

- Only one study in these systematic reviews used SLNB, but it was excluded owing to low sensitivity and because it created heterogeneity. As SLNB is now considered the best reference standard, emphasis should be placed on the newer primary studies that use SLNB, which evaluate accuracy by stage of disease.

Recurrence

- There were two primary studies on suspected recurrent melanoma. One of these demonstrated that PET had sensitivity and specificity of at least 85% for all tumour sites combined and for the individual areas of lung and lymph nodes. PET accuracy was poorer in skin and brain metastases.
- The diagnostic accuracy study also reported that PET affected 30% of patients' therapy. The other study was a well-designed patient management study, which found that PET contributed to change in therapy in at least 34% of patients.

PET/CT

- No studies had been published on melanoma up to August 2005.

Oesophageal cancer

Data extractions are presented in Appendix 7 (from p. 223).

Diagnosis

The systematic review undertaken by MSAC (2001)¹⁹⁰ reviewed eight studies that assessed diagnosis of oesophageal cancer. All showed PET to have high sensitivity for identification and visualisation of the primary tumour, but one study noted that sensitivity was only 38% in patients with early-stage disease. As the studies only included patients with oesophageal cancer, specificity could not be determined.

There were no new primary studies of PET in diagnosis of oesophageal cancer, but PET would not generally be used for this purpose.

Staging

The BCBS HTA (2002)¹⁹¹ evaluated the diagnostic accuracy at all possible sites that would be considered when staging primary oesophageal cancer. Some studies are reported in multiple sections, but different regions are assessed. The studies included patients with SCC and AC.

In this HTA, nine studies evaluated PET for detection of locoregional lymph nodes. A random effects meta-analysis gave estimates of sensitivity of 51% for PET and 42% for CT. The specificity for PET was 89% compared with 87% on CT. The 95% confidence intervals were overlapping.

Four studies reported the accuracy of PET in detecting distant lymph-node metastases. Two of these were comparative and showed that PET had better sensitivity than CT and specificity of at least 90%. However, in one of these studies, PET sensitivity was still low, at 25%.

Three comparative studies assessed diagnostic accuracy in all lymph nodes regardless of region. Analyses are probably by lymph-node region and show that PET sensitivity was higher than CT, but was still below 55% in two studies. The specificity of PET was greater than 95% in all studies, which was similar to or higher than that of CT.

Three comparative studies evaluated the accuracy of PET for staging distant metastases. PET showed superior sensitivity (69%, 74%, 100%) to CT or EUS and specificity of at least 90%.

Five of these studies present some evidence of the impact on patient management, with the focus on use of PET to predict survival. This suggested that when PET detected distant metastases or showed SUV above 7, survival was shorter. However, these findings are tentative and need to be confirmed with robust modelling.

Van Westreenen (2004)¹⁹² undertook a more recent systematic review that assessed the use of PET for staging patients with primary oesophageal cancer before surgery. They included 12 diagnostic studies and found that for locoregional metastases PET had a sensitivity of 51% and specificity of 84%, and for distant metastases PET had a sensitivity of 67% and specificity of 97%. These results are consistent with those reported by BCBS, despite different analytical methods and inclusion criteria.

There were four additional primary studies in staging oesophageal cancer.

Choi (2004)¹⁹³ studied 69 patients in Korea referred for surgery with visible or palpable lymph nodes. They undertook multivariate survival analysis and found that performance of neoadjuvant therapy and number of PET-positive nodes were significant independent predictors of disease-free survival (DFS). For survival, clinical stage, pathological stage, tumour length on PET and number of PET-positive nodes were all independent predictors.

Heeren (2004)¹⁹⁴ studied 74 patients with cancer of the thoracic oesophagus or gastro-oesophageal junction (GEJ) in The Netherlands (62 AC). PET did not detect 5% of primary tumours (all were <0.5 cm). For detecting regional lymph nodes, PET had sensitivity of 55% and specificity of 37%, which lay between that of CT and EUS. For distant lymph-node metastases, PET sensitivity was higher (71%) than comparators and all had high specificity (97%). Similarly, PET was more sensitive (78%) than CT/EUS in detecting distant metastases.

Libérale (2004)¹⁹⁵ studied 58 patients in Belgium with cancer of the oesophagus or GEJ (31 SCC). PET and CT had similar sensitivity for detecting the primary tumour (~85%). In lesion-based analyses, PET had low sensitivity of 38% to detect distant nodal metastases. However, the sensitivity of CT+EUS was also low, at 25%. The specificity of PET for distant nodal metastases was 81%. For distant metastases, PET had better sensitivity than CT (88% versus 44%) and specificity of 88%.

Sihvo (2004)¹⁹⁶ studied 55 patients with AC of the oesophagus or GEJ, in Finland. PET had sensitivity of 82% for detection of the primary tumour. The tumours that were not detected were smaller, with an average size of 1.4 cm. EUS had higher sensitivity of 96%. For locoregional nodal metastases PET and CT had lower sensitivity (35–50%) than EUS (85%). Adding PET or CT to EUS did not improve the sensitivity, but did improve the specificity of EUS from 53% on its own to 100% when all three tests were performed. The sensitivity of PET to detect distant metastases was 53%; this increased to 64% when CT was added and 74% when EUS was also added. Specificity for distant metastases was high for all diagnostic procedures. This paper notes that PET appears to have limitations in detecting small volumes of AC tissue in the oesophageal region.

Treatment response

Treatment response studies in oesophageal cancer have used PET to determine whether there is any residual disease after neoadjuvant therapy.

A recent systematic review was published by Westerterp (2005)¹⁹⁷ comparing CT, EUS and PET after neoadjuvant therapy in patients with oesophageal cancer considered suitable for surgery. This systematic review was published after the search date for this literature review, but was reported comprehensively in the KCE HTA.¹³⁸ Four studies of PET, three of CT and four of EUS were included in sROC analyses. The maximum joint sensitivity and specificity values were 54% for CT, 85% for PET and 86% for EUS. No head-to-head comparisons were made in any of the studies. It is noted that EUS was not feasible in 6% of patients, compared with 1% for PET. Hence, given comparable accuracy, PET may be advantageous owing to reduced morbidity.

One new primary study of PET was found in this literature search, with another new study in PET/CT reported in the section 'PET/CT' below.

Wieder (2004)¹⁹⁸ studied 38 patients given neoadjuvant CRT. A subset of 27 received PET scans before therapy and on day 14 of treatment. In these patients a fall in SUV of at least 30% was both sensitive and specific for predicting complete response, with sensitivity of 93% and specificity of 88%. The same level of metabolic response was also associated with a significant difference in survival (38 months for those with SUV decrease $\geq 30\%$ versus 18 months).

RT planning

There were two preliminary studies of PET added to CT for RT planning in oesophageal cancer.

Konski (2005)¹⁹⁹ studied 25 patients in the USA and Vrieze (2004)²⁰⁰ studied 30 patients in Belgium. These studies showed that PET resulted in different target volumes from those planned using CT. Konski claims that both PET and EUS increase the oncologist's ability to determine GTV, but shows that EUS is significantly better than PET in determining lymph-node disease. Neither study presents any outcome data to demonstrate that the PET-determined volumes more accurately reflect the tumour.

PET/CT

There was one published study of PET/CT in treatment response in oesophageal cancer.

Cerfolio (2005)²⁰¹ compared the value of post-treatment CT, EUS and PET/CT to determine pathological response. They prospectively studied 48 patients, of whom 15 were complete responders. PET was more sensitive for the evaluation of response (87%) than CT (27%) or EUS (20%). Although PET/CT was more accurate for the detection of N1 disease, it still yielded three out of eight FNs, and none of the methods perfectly distinguished T4 from T1–3 disease.

Oesophageal cancer overview**PET****Diagnosis**

- One SR of eight PSs showed PET to have high sensitivity for diagnosis, but noted low sensitivity in early-stage disease. There were no new PSs and it is unlikely that PET would be used in this way in the UK, as endoscopy (with US) would be standard practice.

Staging

- One SR involving up to nine studies per metastatic site and one SR involving 12 studies assessed PET in staging patients with SCC and AC. The sensitivity of PET to detect locoregional lymph nodes was low, at approximately 51%, but this was a little higher than CT (42%). Specificities of the PET and CT were similar at approximately 85%.
- From an sROC analysis, PET sensitivity for detecting distant metastases was 67% at 97% specificity. In comparative studies, PET appeared to be more accurate than CT.
- There were four additional PSs. Three of these were diagnostic studies that confirmed the low sensitivity for locoregional lymph-node

metastases, but two showed slightly higher levels of sensitivity for distant metastases (71%, 88%), whereas one showed a lower level of 53% (or 64% when CT was added).

Treatment response

- There is evidence (one SR with four PSs of PET in an sROC analysis, and one further PS) that PET may be superior to CT and comparable with EUS for response assessment and to assess prognosis after neoadjuvant therapy.
- There is some evidence that PET is less sensitive in predicting response in small primary tumours.

RT planning

- There were two PSs in 55 patients that showed that when PET was used in RT planning it resulted in different target volumes.

PET/CT**Treatment response**

- One prospective PS showed that PET was more sensitive than CT and EUS for assessment of treatment response after treatment (87% versus 27% and 20%).

Thyroid cancer

Data extractions are presented in Appendix 7 (from p. 233).

Diagnosis

There were no systematic reviews assessing PET for diagnosis of thyroid cancer, but there was one primary study.

Kresnik (2003)²⁰² studied 43 patients with suspicious thyroid nodules, in Austria. Sixteen of the patients had malignant tumours ranging in diameter from 0.7 to 8 cm. All tumours were detected by PET, giving PET a sensitivity of 100%. When PET positive was defined as SUV \geq 2, the specificity of PET was 63%.

Restaging

There were no systematic reviews that studied PET in staging or restaging thyroid carcinoma and no primary studies of PET in staging.

There were four primary studies in restaging. The first was in patients with metastases, while the others used PET a few weeks after therapy to detect malignant lesions.

Gotthardt (2004)²⁰³ studied 26 patients in Germany who had medullary thyroid cancer, with known or occult metastases and elevated calcitonin and/or CEA levels. CT was able to detect more tumour sites than PET in seven patients (at liver, cervical lymph node and lung). PET detected bone metastases in two patients that CT did not detect.

Hsu (2002)²⁰⁴ studied 15 patients in Taiwan with 'local invasion' or aggressive differentiated thyroid cancer who had undergone therapy. Detection was considered by site, but the maximum number of patients to have lesions in any one site was three. From the small numbers, it seems that PET detected more patients as positive in each of the malignant sites than iodine-131 (¹³¹I) whole-body scan (WBS) or thallium-201 (²⁰¹Tl) WBS.

Iwata (2004)²⁰⁵ studied 19 patients with metastatic differentiated thyroid cancer in Japan. PET imaging was performed 2 weeks after replacement doses of thyroxine had been stopped. In a lesion-based analysis of 32 lesions, PET had sensitivity of 81%, compared with 63% on technetium-99m-2-methoxyisobutylisonitrile (^{99m}Tc-MIBI) and 69% on ¹³¹I. Small lung metastases in two patients were not detected by any modality.

Shiga (2001)²⁰⁶ studied 32 patients in Japan with recurrent or metastatic differentiated thyroid cancer, imaged 3 weeks after thyroxine therapy. In

a lesion-based analysis of 47 lesions, PET had sensitivity of 47%, compared with 70% on ¹³¹I and 45% on ²⁰¹Tl. In this study, only 185 MBq FDG was given and there was no attenuation correction, so this may have affected the accuracy of PET.

Recurrence

Two systematic reviews assess the use of PET to detect recurrent thyroid cancer. They present accuracy by different groupings of carcinoma and so both reviews are presented here.

The first set of studies was in previously treated patients with recurrence suspected owing to elevated biomarkers, but not confirmed by ¹³¹I scintigraphy.

Hooft (2001)²⁰⁷ presents 11 diagnostic studies in patients with thyroid cancer, excluding those with medullary or Hürthle thyroid cancer, where possible. PET identified possible disease in 115 out of the 140 patients scanned, but adequate reference standards were only available for about half of these patients. In these, PET had sensitivity of 90% and there were six FPs.

An HTA published by AHRQ (2002)²⁰⁸ included 11 diagnostic studies of epithelial thyroid cancer (follicular, papillary, mixed follicular/papillary, differentiated, well-differentiated Hürthle). A random-effects meta-analysis estimated the sensitivity of PET to be 84% (95% CI 73 to 91%), with specificity of 56% (95% CI 27 to 82%). As the wide confidence interval for specificity shows, there was heterogeneity among the studies for this parameter. Some form of patient management evidence was presented in seven studies. It is noted that the actions taken following a positive PET scan varied among studies and that not all patients received treatment despite a positive PET scan.

The AHRQ HTA intended to evaluate recurrence of medullary thyroid cancer in a separate analysis. Owing to the paucity of data it included studies with small patient numbers and from six studies only 17 patients could contribute to a diagnostic accuracy analysis. Hence, no conclusions could be drawn from such a small data set.

Studies in those with just clinical suspicion of recurrence, without elevated biomarkers and no evidence of disease on ¹³¹I scintigraphy, were reviewed in one of the systematic reviews.

Hooft (2001)²⁰⁷ found five such studies with the mixed group of thyroid cancers, excluding medullary and Hürthle. The number in each study ranged from two to 21, with a total of just 50 patients. Reference standards were not adequate in

all patients, but from the information available there was one FN and six FPs. The FP rate was noted to be higher than in the patients with elevated biomarkers.

Seven new primary studies in recurrent thyroid cancer were found, and two in PET/CT are presented in the section 'PET/CT', next column).

Five studies evaluated patients with well-differentiated thyroid cancer who had previously undergone treatment. In the first three studies, recurrence was suspected by elevated thyroglobulin levels but negative ^{131}I scintigraphy and no palpable lesions.

Chen (2003)²⁰⁹ studied 23 patients in Taiwan and showed that PET had better sensitivity than SPECT (91% versus 50%) and both had two FNs.

Frilling (2001)²¹⁰ studied 24 patients in Germany. In a lesion-based analysis of 32 lesions, PET had sensitivity of 95% and specificity of 25%. PET altered surgical strategy in nine patients (38%).

Gabriel (2004)²¹¹ studied 36 patients in Austria. In a patient-based analysis, PET had sensitivity of 88% versus 63% on technetium-99m-labelled somatostatin analogue, $^{99\text{m}}\text{Tc}$ -EDDA/HYNIC-TOC ($^{99\text{m}}\text{Tc}$ -TOC). The specificities were two out of four (50%) on PET four out of ten and 100% on $^{99\text{m}}\text{Tc}$ -TOC.

Groheux (2005)²¹² studied 39 patients in France with suspected relapse, although it is not stated how this was suspected. A patient-based analysis showed a sensitivity of 68% and specificity of 71%. In two patients surgery was abandoned and in ten the option of revision was taken or reinforced.

Yeo (2001)²¹³ studied 96 patients in Korea with suspected metastases (reason for suspicion not stated). In 37 of these patients PET showed FDG uptake in cervical lymph nodes, 22 of which were chosen for dissection. This led to 85 lymph-node groups and resulted in PET sensitivity of 80% and specificity of 83%. This is a peculiar design, as it is unclear how the 22 areas were chosen from the total positive set and results are therefore clearly biased.

Two studies evaluated recurrent medullary thyroid cancer.

De Groot (2004)²¹⁴ studied 26 patients with recurrence suspected by elevated calcitonin or CEA levels. Concordance of PET with pentavalent technetium-99m-dimercaptosuccinic acid [$^{99\text{m}}\text{Tc}$ (V)DMSA] scintigraphy, ^{111}In -octreotide

scintigraphy and morphological imaging (CT, MRI and US) plus bone scintigraphy was evaluated. PET identified more lesions than any other method. However, it was assumed that all these patients were in fact positive and so the sensitivity of all methods was low, with PET at 41%, the two scintigraphy methods at 17% and 14%, and the morphological imaging plus bone scintigraphy at 30%. PET led to surgical intervention in nine patients and cancer was confirmed in eight of these.

Szakáll (2002)²¹⁵ studied 40 patients in Hungary with recurrence suspected by elevated calcitonin levels. PET detected lesions in 38 out of 40 patients (sensitivity 95%). CT detected lesions in 29 patients (sensitivity 73%), MRI in 23 out of 35 patients (sensitivity 66%) and ^{131}I -MIBG (meta-iodobenzylguanidine) planar scintigraphy detected lesions in just three patients. PET detected more foci in the neck and mediastinum than other imaging techniques. PET failed to detect some lesions in the lung and liver, in particular, pulmonary metastases smaller than 1 cm visualised by CT were not detected by PET.

Treatment response

One primary study by Boerner (2002)²¹⁶ investigates the use of FDG-PET for response prediction and monitoring in advanced thyroid cancer treated with isotretinoin. Twenty-one patients in Germany were scanned before treatment, 3, 6 and 9 months after the start of treatment, and 3 months after discontinuation. There was a non-significant trend towards lower FDG uptake at 3 months in tumours with better long-term outcome.

PET/CT

There are two studies of PET/CT in suspected recurrence of differentiated thyroid cancer in patients with elevated thyroglobulin and negative ^{131}I scintigraphy.

Nahas (2005)²¹⁷ presented a prospective diagnostic study of 33 patients in the USA. Twenty patients were operated on. As they had histopathology, they formed the basis of the analysis, which showed that PET/CT had sensitivity of 66% and specificity of 100%. A retrospective review of patient records suggested that PET/CT altered management in 40% of patients.

Ong (2005)²¹⁸ was a retrospective study of 17 patients in Singapore, in which PET detected lesions in 15 patients (all 17 assumed to be positive). However, in some patients there was a long delay between the PET scan and the last scintigraphy (2 years), so disease may have progressed further by the time of the PET scan.

Thyroid cancer overview

PET

Diagnosis

- One PS sought to diagnose cancer in patients with suspicious thyroid nodules. PET detected all malignant tumours, but specificity was only 63%.
- In the UK, it is unlikely that PET would be used before diagnosis was confirmed by biopsy.

Restaging

- There were no studies of PET in staging, but four new PSs in a total of 92 patients in restaging. In one study CT detected more tumour sites than PET.
- Based on a small number of patients/lesions, PET appeared to have slightly better accuracy than WBS with various tracers in two studies, but not in the third (but this used a low dose of FDG).

Recurrence

- Two SRs presented studies in different populations of patients with suspected recurrence.
- In those with elevated biomarkers, not confirmed by ¹³¹I scintigraphy:
 - A meta-analysis in 11 studies (excluding medullary) showed sensitivity of 84% and specificity of 56% (with wide variability).
 - Four out of five new PS studies showed PET sensitivity of at least 80%, with specificity ranging from 25 to 83%.
 - The SR noted that actions taken following a positive PET scan vary among studies, but

two of the new PSs noted that PET altered the surgical strategy in nine out of 24 patients (38%) and two out of 39 (5%).

- One SR found six studies in medullary cancer, but this involved just 17 patients. Two additional PSs studied 66 medullary thyroid patients. Sensitivity of PET varied between the studies (41% versus 95%), but PET identified more lesions than other methods.
- In one medullary cancer study, PET led to correct surgical intervention in eight out of 26 patients. It was noted that PET failed to detect lesions that were smaller than 1 cm.
- One of the SRs found five studies in those with clinical suspicion of recurrence (without elevated biomarkers). This only involved a total of 50 patients and the FP rate was noted to be higher than in those with elevated biomarkers.
- There is little evidence of how PET has been used to alter patient management.

Treatment response

- There is just one PS of PET for response prediction in 21 patients that showed a trend towards lower FDG uptake at 3 months in tumours with better long-term outcome.

PET/CT

Recurrence

- There are two new PSs of PET/CT in a total of 50 patients with suspected recurrence. Both seem to be highly selected populations with few TNs, so specificity figures are unreliable. In the larger prospective study, PET/CT had a sensitivity of 66%.

PET/CT: mixed cancers

Any studies in mixed cancers for which diagnostic accuracy results in individual cancers could be obtained are presented in the previous cancer sections. Studies in mixed cancers that could not be separated are strictly outside the search, but certain PET/CT studies are discussed because they provide insight into the use of this newer technology.

HTAs from the Spanish HTA Agency (AETS)²¹⁹ and the French Agency (HAS)²²⁰ present systematic reviews of PET/CT (see Appendix 7, from p. 247). These are interesting summaries of the variety of studies arising with this new technology. However, the reviews contain

heterogeneous studies, using different forms of PET and CT integration (hybrid machines and software fusion) and present accuracy results summarised over a variety of cancers. This makes it difficult to interpret the results, but the conclusions of the reports are interesting and consistent. They state that PET/CT provides a faster attenuation correction and better localisation of FDG uptake than PET alone and it can resolve some results that are equivocal on PET. However, questions remain about the potential clinical impact, specific indications for use and cost-effectiveness.

In addition to the systematic review, HAS performed a survey of healthcare organisations in France in June 2004. Of the 60 organisations, 93% responded. The survey showed that there were

nine PET and 23 PET/CT systems in use in France, and 23 new sites were expecting to install PET/CT. Uses in oncology included cancer of the lung, lymphoma, colon and digestive system. The estimated capital outlay for a PET/CT system in France was €2.5 million, compared with €1.75 million for a PET system. The estimated operating budget was €2–2.2 million for 2000 examinations per annum (eight or nine patients per day). This is approximately €250,000 more than for PET and approximately €140 more than PET per examination.

A number of PET/CT papers record experience with new PET/CT machines within an institution. These often summarise PET/CT accuracy for all presenting patients, no matter what tumour or management reason. A good example of one of these that provides some information about patient management is the study by Bar-Shalom (2003).²²¹ They present the impact of an integrated PET/CT device on 204 consecutive patients entering a clinic in Israel with suspected or known malignancy for a variety of management decisions (64 with lung cancer, 34 gastrointestinal tumours, 33 lymphoma, 20 SPN, 16 genitourinary tract tumours, 13 breast cancer, ten skin tumours, five sarcoma, four head and neck cancer, five other cancers). In the 204 patients, 586 suspected sites were fully investigated and PET/CT provided additional information compared with PET or CECT in 99 (49%) patients. This led to an impact on patient management in 28 patients (14%): 12 with lung cancer or SPN, eight with colorectal cancer and eight others. The additional information meant that five patients did not need further evaluation, in seven patients PET/CT guided further diagnostic procedures and in 16 (8%) PET assisted in optimisation of treatment strategy. This study shows how the extra information obtained by PET/CT affects patient management, but that only 8% of patients had their treatment strategy altered as a result of PET/CT.

Potential harm

Most published evidence focuses on the benefits of FDG-PET. A few HTAs present information about safety, concluding that there is little risk arising from the actual imaging procedure given the small doses of radiopharmaceuticals that are used. Picano (2004)²²² is concerned that doctors do not fully understand the long-term health risks associated with radiological imaging, particularly in this environment where imaging of all forms is

increasing. However, it could be that doctors understand the risks, but disregard or overly discount them when weighing risk against benefit.

For PET, probably the greatest potential harm will arise if there is a change in patient management on the basis of an erroneous FDG-PET result that leads to the patient having suboptimal treatment¹² (e.g. an FP PET result leading to the patient being denied curative surgery).

There is also potential harm for staff undertaking the radiopharmaceutical production and transportation, and those involved in the scanning preparation and process. In the UK, these processes are governed by national guidelines such as those produced by the Medicines and Healthcare Products Regulatory Agency and the Administration of Radioactive Substances Advisory Committee and by local clinical governance processes. All these seek to minimise the risk to staff.

Cost-effectiveness

This study was not intended to evaluate economic reviews of PET and so did not undertake a search of all economic sources. However, during the systematic review for clinical effectiveness, some studies of cost-effectiveness were identified. These were verified against those found by a more systematic search in the KCE HTA¹³⁸ and it was found that this research identified all relevant models. All economic models evaluated FDG-PET.

The NICE guideline on lung cancer⁵ presented the most useful information on cost-effectiveness in NSCLC, because this was a recent economic evaluation modelling the English context. Likewise, the Scottish model of restaging HL² is relevant to the English context. The information on these models has been reported in the main body of evidence for each cancer.

Several models simply 'localised' existing models by substituting local costs in the model. Five new cost-effectiveness models were found that provided a new decision tree:

- Comber:²²³ characterisation of SPN in Australia
- Hollenbeak:²²⁴ staging clinical N0 head and neck cancer in the USA
- Park:²²⁵ recurrent colorectal cancer in the USA
- Sloka:²²⁶ suspected recurrence of colorectal cancer in Canada
- Wallace:²²⁷ staging oesophageal cancer in the USA.

The papers all present well-constructed models, which are summarised in Appendix 8. For the studies in SPN and head and neck cancer, the accuracy data are derived from a small number of early studies. None of these models considers the English or even a European context. Consequently, patient populations, epidemiology and resource use may be quite different. Hence no conclusions can be drawn and the models could be usefully reworked with updated data in the English context.

A recent paper by von Schulthess²²⁸ suggested that the cost-effectiveness of PET/CT will be superior to that of PET in some indications, because of both the potential for increased patient throughput and the possible greater accuracy of PET/CT. However, no published studies of the cost-effectiveness of PET/CT were found in this review and this is clearly an area for targeted research.

Survey of PET and PET/CT facilities in the UK

In February–March 2006, a survey of UK PET facilities was undertaken (Appendix 9). As the UK-PET Special Interest Group (www-pet.umds.ac.uk/UKPET) had produced a survey of PET facilities in the UK in September 2003, members of this network were targeted.

Responses were received from ten of the 11 who had responded to the 2003 survey. The non-responder was UMS Neuromed Ltd, which has withdrawn from PET provision in the UK. Responses were also received from two new units at the Cheltenham Imaging Centre and Lodestone Diagnostic Imaging, Guildford.

The responses from the 12 units are summarised in Appendix 10. Information was received from nine units in England, one in Scotland and one in Northern Ireland. The responses were comprehensive and informative about the current situation of PET provision in the UK. Just a few questions were not answered owing to commercially sensitive information.

The location of sites shows that fixed PET facilities are not evenly distributed across the UK, with fewer sites in the north.

Most units have PET/CT machines or are upgrading to PET/CT, and some have more than one machine. Eight units use a commercial provider to supply FDG. Three units have a local supply, but in one case (Christie) this is not always used owing to delays in receipt of the FDG and unreliability of the service.

The PET facilities are used for a wide range of cancer applications and cover the range of cancers studied in this report (except for thyroid). A few centres also use PET for other cancers such as brain/spine, sarcoma, pancreas, pelvic, gastrointestinal, testes, ovary and uterus.

All non-commercial imaging units have research and clinical studies underway. Some of these are coordinated across the UK by the Medical Research Council (MRC) and several centres are involved in the major MRC RCT evaluating the impact of PET on restaging HL. Most have audits in place and one notes that PET audits are part of the normal annual audit process in the hospital.

The greatest variation in results occurs in the assessment of patient throughput and running costs. A commercial provider indicates that their throughput can be 4000 scans per year. Individual units note throughputs of 300–3000 scans per year. Costs per scan range from £635 to £1300. The resource issues clearly rely on local circumstances and available funding, but there would not appear to be a consistent approach to process or funding in England. In contrast to this, in Scotland a national service is being established that seeks to ensure equitable and appropriate access for all patients who may benefit from a PET scan across Scotland.

Several difficulties in establishing and running a PET facility were highlighted in England. These include:

- funding clinical services
- accessing FDG to allow 09.00h clinic start and reliability of FDG service
- staff recruitment, training and retention
- making PET integral to the decision making of the local multidisciplinary cancer team
- appropriate administrative processes (including data transfer).

Chapter 5

Discussion

Statement of the principal findings of the systematic review

For a diagnostic technology, there is a hierarchy of clinical effectiveness evidence (see the section 'Systematic reviews', p. 9), ranging from diagnostic studies showing the accuracy to detect a lesion, to change in patient management (obtaining optimal therapy), change in patient outcomes (improved survival or quality of life) and cost-effectiveness (value for money). The evidence for the eight cancers studied in this systematic review is presented in this framework, from the highest level down. In addition, a category is added where the risk of using FDG-PET may outweigh its benefit, and treatment response and RT planning are evaluated separately.

The published evidence includes some uses of PET that are unlikely to be considered for routine use in the UK given current cancer pathways and cost constraints (e.g. for recurrence monitoring). The evidence for these is not presented here, but does appear in the final summary in *Table 7* (p. 66).

Most of the evidence found relates to PET, with relatively few studies of the newer technology PET/CT. This is to be expected as this new technology came on stream around the year 2000. Since then, expertise with the technology has been developed and so reports of its use are only just being published. Given the rapid uptake of PET/CT instead of PET, this creates a dilemma in evaluating the evidence base. However, it would appear that a general statement can be made about the slightly superior accuracy of PET/CT over PET, so the results from the older technology can be 'bridged' to the new technology.

Cost-effectiveness

There are two recent economic models in the English setting evaluating the use of FDG-PET for staging NSCLC, before surgery and before radical RT.

FDG-PET is shown to be cost-effective for staging NSCLC before surgery in those who are CT node-negative. The model is robust and confirms an earlier Scottish model. There is no English model

for staging NSCLC in CT node-positive patients, but the Scottish model indicates that this is not cost-effective unless willingness to pay is over £60,000 per QALY.

The English model in radical RT finds FDG-PET to be cost-effective, but is based on a small number of patients who had management changes as a result of FDG-PET. Four new studies of FDG-PET in this indication are available that could improve the robustness of the model.

The Scottish HTA of FDG-PET undertook an economic evaluation in restaging advanced HL to assess residual mass. This model was undertaken in 2002 and so is somewhat out of date, but is probably a fair reflection of the English clinical pathway. It showed that FDG-PET was highly cost-effective compared with strategies without FDG-PET and could replace CT in the diagnostic pathway. The major impact on reducing unnecessary consolidation RT found in this model is being tested in a large, multicentre clinical trial in the UK.

Other cost-effectiveness models exist for the use of FDG-PET in SPN, head and neck cancer, recurrent colorectal cancer and staging oesophageal cancer. These are all based in North American or Australian settings, where patient presentation, clinical intervention and resource use may be quite different. Hence, these models should be repeated in an English setting using the most up-to-date inputs.

There is a suggestion that PET/CT may be more cost-effective than PET owing to the increased throughput, lower FDG costs and market popularity of the units. However, no cost-effectiveness studies of PET/CT were found in this systematic review, so this is yet to be proven.

Patient outcomes

There have been no clinical studies which demonstrate that FDG-PET leads to improvement in patient outcomes. Some studies make survival predictions and assess disease progression in follow-up, but these are difficult to judge outside a randomised setting as the impact of the FDG-PET imaging may be confounded with other actions.

One major evaluation of patient outcomes after use of FDG-PET in restaging HL is underway in the UK. This major multicentre RCT has been carefully designed and has the potential to provide high-quality information (see the section ‘Overview’, p. 59).

Patient management

The quality of evidence showing how FDG-PET affects patient management varies widely, from two RCTs in staging NSCLC to anecdotal evidence in diagnostic studies. The latter often make claims of large benefits of 40 or 50% of patients who have had management changed, but it is often unclear whether FDG-PET is the sole reason for the change in management or what that change in management is. In some cases, it is further imaging. This is likely to show less impact of FDG-PET than when a possible distant metastasis is discounted and curative therapy can be given. Change in staging is also reported, without clear explanation of what that means in terms of change in treatment. The more reliable evidence on patient management would suggest that FDG-PET influences therapy change in 10–30% of patients.

Evidence relating to the impact of PET on patient management arises from studies undertaken around the world. However, changes in management depend heavily on local approaches to treatment (as shown by the two NSCLC RCTs discussed in ‘NSLCLC: staging’, p. 30). Consequently, published results should be interpreted in the light of local protocols.

From the evidence, FDG-PET appears to be able to influence therapy in a substantial way (that will impact on curative treatment) for the following cancer management decision:

- staging/restaging colorectal cancer to detect distant metastases.

In this cancer management decision, no further evidence of patient outcomes is probably needed as there is a strong link between the patient management change and outcome.

There is also strong evidence relating to the impact of PET on surgical treatment for:

- characterisation of FDG-avid SPNs (>1 cm).

However, most research in SPN has been undertaken in the USA, where the form of disease may be different to that in typical English patients.

Consequently, some additional clinical evaluation in a standard UK clinical setting would be helpful.

Diagnostic accuracy

The diagnostic accuracy of FDG-PET could be studied in two ways: in studies that report results of FDG-PET alone when added to the CWU, or comparative results where FDG-PET is compared to the standard imaging procedure, such as CT or MRI. However, most studies in this review have studied FDG-PET as a supplement to, rather than replacement for, other diagnostic techniques. Even in those studies where PET was read independently of other techniques, the additional information provided by PET scanning is evaluated.

The diagnostic studies found in the literature originate from all over the world, but show fairly consistent results when the stage of disease being considered is similar. Hence, these would seem applicable to the English context.

Overall, published studies show that FDG-PET had good accuracy to detect distant metastases, but sensitivity tended to be poor for bone, brain and soft-tissue metastases. FDG-PET sensitivity was lower in early-stage disease and in all cases where lesions were small (<1 cm). Like comparators, FDG-PET accuracy was lower in oesophageal and thyroid cancer.

From the evidence obtained, FDG-PET has been shown to have improved diagnostic accuracy over alternatives in:

- detection of colorectal cancer recurrence
- diagnosis of head and neck cancer when other tests have failed (including occult primary tumour and synchronous primaries)
- staging regional lymph nodes in clinically N+ necks
- restaging/recurrence of head and neck cancer
- staging SCLC
- restaging NHL
- staging lymphoma
- staging oesophageal cancer
- detection of recurrence of epithelial thyroid cancer in patients with elevated biomarkers not confirmed by ¹³¹I scintigraphy.

There is little evidence to show the impact of PET on management in these cancers from well-designed patient management studies.

Some evidence of the diagnostic accuracy of FDG-PET exists for the following cancer management

decisions, but evidence rests on one or two trials and further comparative work is needed:

- locoregional recurrence in breast cancer
- staging/restaging/recurrence in breast cancer
- staging lymph-node involvement in colorectal cancer
- diagnosis of occult SCLC in patients with PNS
- staging late-stage melanoma
- detection of recurrent melanoma
- restaging thyroid cancer
- detection of recurrence of medullary thyroid cancer in patients with elevated biomarkers not confirmed by ^{131}I scintigraphy
- detection of recurrence of thyroid cancer in clinical suspicion of recurrence but no elevated biomarkers or ^{131}I scintigraphy confirmation.

For paediatric lymphoma some evidence of change in patient management across a mixture of management decisions exists. Good-quality comparative diagnostic studies in each lymphoma management decision would be beneficial in this population.

Poor benefit: risk

Risks arise with FDG-PET if it is used to replace more sensitive procedures that can better identify patients who need curative therapy. In particular, FDG-PET is less sensitive than biopsy for:

- diagnosis or staging of breast cancer to avoid axillary lymph-node dissection
- diagnosis of colorectal cancer
- diagnosis of lung cancer
- diagnosis of oesophageal cancer
- diagnosis of thyroid cancer

and less sensitive than SLNB for:

- staging regional lymph nodes in clinically N0 necks
- staging early-stage melanoma.

Treatment response

The possible gains from reproducible, accurate treatment monitoring are substantial, as outlined by Laking and Price,²²⁹ including accelerated drug development, improved use of sequential therapies and increased opportunity to tailor therapies to patients.

In the literature search, 22 studies of PET to assess treatment response midtherapy were found for:

- locally advanced breast cancer (nine studies)
- metastatic breast cancer (two studies)

- colorectal cancer (one study using dynamic scans)
- advanced NSCLC (one study)
- lymphoma (nine studies)
- advanced thyroid cancer (one study).

Thirty-nine studies reported on use of PET to assess treatment response at the end of therapy in:

- locally advanced colorectal cancer (four studies plus one follow-up report)
- head and neck cancer (six studies)
- potentially curable NSCLC (six studies)
- lymphoma (11 studies to assess residual mass and five to predict prognosis)
- oesophageal (five studies of PET and one study of PET/CT).

Many of these studies were small (including fewer than 12 patients), evaluating different treatment questions with a diversity of response targets and monitoring methods. There is little evidence of change in patient management, even anecdotally, and no published evidence of successful applications to drug development.

Further well-planned studies are needed, including consistent definitions of monitoring methods, patient populations and response targets, which will allow replication and synthesis, to provide a stronger evidence base. This needs to be combined with methodological work evaluating the appropriateness of SUV end-points and cut-offs, appropriate correction methods and the use of dynamic scanning evaluated in a multidisciplinary team framework (see 'Treatment response', p. 63).

Juweid and Cheson²³⁰ note that there is no published evidence that FDG-PET has been used to alter patient management, and recommend that trials should be performed to show whether treatment response assessment does alter treatment, and ultimately the effect of that on patient outcome.

RT planning

The use of FDG-PET to supplement CT or MRI for RT planning is a topic of interest in the FDG-PET community. The literature search retrieved 17 primary studies (mainly evaluating replacement of CT before radical RT) in:

- colorectal cancer (one study)
- head and neck cancer (three studies of PET and three of PET/CT),
- NSCLC (eight studies)
- oesophageal cancer (two studies).

The studies were small and used different methods to determine the treatment volume. Review of these studies suggests that it would be helpful to establish consensus standards for translating FDG-PET images into volumes for use in RT planning, to promote consistency across future studies and reproducibility in clinical practice.

Only one study provided any outcome data,¹²³ evaluating nodal failure outside the radiation field after 16 months' follow-up in NSCLC. Collection of such outcome data should be encouraged and optimally RCTs should be performed to demonstrate definitively the added value of FDG-PET/CT in RT planning.

PET/CT

Twenty-three publications evaluating integrated FDG-PET/CT machines in individual cancers were included in this systematic review. FDG-PET/CT studies existed for all cancers apart from breast and malignant melanoma. A variety of cancer management decisions was studied (including treatment response and RT planning). Half of the published studies were undertaken in the USA, four in Switzerland, four in Germany, two in Israel, one in England and one in Singapore.

The sparsity of studies in FDG-PET/CT and mixed populations studied does not allow definitive conclusions to be made about the effectiveness of PET/CT for each management decision. However, the published studies show that FDG-PET/CT tended to be more accurate than FDG-PET, by about 10–15%, resolving some, but not all, equivocal images. Consequently, if this report is used to evaluate potential uses of a PET/CT unit, the FDG-PET results can be reviewed noting the additional accuracy likely with FDG-PET/CT.

Other HTAs of PET

Many HTA agencies have undertaken HTAs of PET across all indications of PET in cancer, neurology and cardiology. The current status of projects and recent publications can be found on the website of the INAHTA (www.inahta.org/HTA/PET/).

There has been a suggestion that for PET, reports from HTA agencies have given different conclusions and the value of HTA in determining the usefulness of PET is questioned.²³¹ However, HTA agencies have explained that despite the broad context of social and organisational issues

that have been considered in individual country's HTAs, HTA reports of PET have in fact reached similar conclusions and the main differences arise from the evidence available at the time of the report.²³² As the presentation of HTAs in the ultra rapid review¹ showed, it is evident that differences also exist due to different inclusion criteria and definitions of patient pathways that reflect the national norm and different levels of sophistication of analytical methodology. However, the conclusions, if not all elements of methodology, are comparable across reports.

INAHTA has recently published its second joint report on PET diffusion and assessment. The first part of the report presents a survey of INAHTA members.²³³ Twenty-seven agencies from 19 countries around the world responded to the survey during the period of 2003–2004. The survey concluded that dedicated PET systems were most common, but that mobile scanners and gamma cameras were used occasionally. They list the number of PET scanners per million population in each country, ranging from 1.26 per million in Belgium to 0.28 per million in the UK and 0.25 per million in The Netherlands. Interest in PET/CT was noted “despite limited assessment of impact on service planning”.

In the survey, PET was most frequently used in cancer. In addition to the cancers studied in this report, PET was being used for (number of agencies):

- brain tumours (3)
- glioma (2)
- CNS (2)
- cervical (1)
- gastric (1)
- ovarian (1)
- prostate (1)
- sarcoma (1).

In neurology, six agencies reported that PET was being used in epilepsy and four indicated use in dementia. For cardiology, five agencies reported use of PET in myocardial viability/perfusion.

All countries had some form of public funding for clinical use of PET, but this was often linked to data collection to accumulate evidence to refine clinical use and better determine cost-effectiveness. For example, Australia^{13,69,183}, has granted funding for promising FDG-PET indications on an interim basis to enable the collection of further data. In Spain, the Catalonian Agency for HTA and Research devised an FDG-PET monitoring proposal when

FDG-PET and FDG-PET/CT were first introduced in 2000.²³⁴ The aim was to promote suitable adoption of the technology in the early stages of dissemination when there was little knowledge of its added value or cost-effectiveness. This has included provision of questionnaires to determine the impact of FDG-PET on patient management. These have been completed in 35% of cases. For some cancers this has provided valuable information, for example, in lung cancer there has been a reduction in the number of mediastinoscopies and surgery with an increase in chemotherapy and surgery with neoadjuvant therapy.

Examples of the use of HTA to inform decisions about the diffusion and clinical use of PET were presented at a workshop in 2004 and are summarised in the second part of the INAHTA joint report.²³⁵ Presentations were heard from four countries in Europe, the USA (Veterans Health Administration) and Australia. One of the conclusions was that to manage the uncertainty in the evidence base, continuous quality improvement should be used. This requires systematic processes for data collection and regular dissemination of findings to help providers to increase the most appropriate use of the PET.

The technology

PET/CT

Several PET/CT studies summarise a series of patients undergoing scanning with a variety of tumours. These are of little value to assess diagnostic accuracy within cancers, but provide some useful insights about the running of this newer technology.

One study published in the UK by Costa (2003)²³⁶ describes the use of a new PET/CT scanner (Discovery LS) at University College Hospital, London. They note that in a typical adult a 370-MBq dose of FDG is effective and that in the first 8 months of operation 535 patients were scanned in their unit. Of these, 477 were for FDG studies in cancer:

- colorectal cancer (113 patients)
- lymphoma (95)
- lung cancer (84)
- PNS (30)
- oesophageal cancer (23)
- CNS tumours (19)
- occult tumours (18)
- sarcoma (10)
- infection/malignancy (9)

- breast cancer (7)
- head and neck and gynaecological tumours (6)
- testicular cancer (5)
- melanoma (4)
- various others in small numbers.

Costa studied the average time needed for a five-bed position whole-body two-dimensional (2D) PET scan (with a GE Advance PET machine) compared with that on the PET/CT machine, over a number of procedures. This showed a reduction in the average time taken to undertake the scan from 54 minutes on PET to 41 minutes on PET/CT. This included 10 minutes in each session to put the patient on the bed, prepare them and take them off the bed. This study used 5-minute emission times per bed position in the PET/CT machine, if these were reduced to 3 minutes each, this would have reduced the PET/CT overall scan time to 31 minutes. Furthermore, this study was undertaken in 2002 and since that time the technology and fusion software have continued to improve, which is likely to reduce scan times even further.

Hany (2002)²³⁷ presents results from a prospective study of 53 patients scanned on a Discovery LS machine in Switzerland (19 NSCLC staging, seven suspected lung cancer recurrence, 14 head and neck staging/restaging, 13 various recurrent tumours). Clinical and histopathology data were used as reference standards. With FDG-PET alone, 38 patients were correctly staged, 11 patients were understaged and three were overstaged. (It is unclear what happened to the 53rd patient.) Using FDG-PET/CT with low-dose CT (10 mA), 48 patients were correctly staged, four patients were understaged and one was overstaged. Using FDG-PET/CT with a 40-mA dose for CT, 49 patients were diagnosed correctly, three patients were understaged and one was overstaged. This demonstrates that FDG-PET/CT could reduce the incidence of FNs even with low-dose CT.

Cherry³ notes that important challenges remain such as the differing effects of physiological motion and the effect of CT contrast agents, but like PET it is likely that this technology will evolve rapidly. Hence, it will be important to keep the effectiveness of PET/CT under review as new studies are published.

Other radiopharmaceuticals

Around the world (from Australia, to Europe and America) PET and PET/CT are only currently reimbursed for use with FDG because FDG-PET has the strongest evidence base. Likewise, this report has only evaluated FDG-PET and

FDG-PET/CT. However, there are technical limitations with FDG (as mentioned in the section 'PET', p. 1) that mean it is not ideal for some cancers and management questions, and so other radiopharmaceutical tracers are being developed.

In a recent editorial of the PET Centre of Excellence newsletter²³⁸ the main areas of opportunity for development were considered to be:

- proliferation tracers, particularly for treatment response and early assessment of the effect of RT therapy, [¹⁸F]3'-deoxy-3'-fluorothymidine (FLT)
- amino acid tracers (e.g. methionine labelled with ¹¹C for brain tumours, but the difficulties of clinical imaging and short-half life are noted with this tracer)
- cell membrane synthesis tracers (e.g. fluorocholine), for cancers where FDG does not perform well, such as prostate cancer (where accumulation of FDG in the urine compromises imaging of organs adjacent to the bladder)
- cell membrane receptor tracers comprises a wide-ranging group to assess presence of tumour-specific phenotypes (e.g. fluoroestradiol, a marker of cell-surface oestrogen receptor expression in breast cancer).

These tracers offer comparators for FDG-PET and as they emerge into clinical practice will need to be evaluated in well-designed studies.

Development of other imaging technologies

This report has sought to evaluate FDG-PET and the newer technology FDG-PET/CT. However, it is not just PET technology that is evolving. Other processes in the diagnostic pathway are evolving. Comparators, such as CT and MRI, have also evolved since the time of many of the reported studies. High-resolution, rapid, multislice CT scanners may offer more information than the older forms of CT used in most studies.^{239,240} Indeed, a recent study showed comparable accuracy of contrast-enhanced helical CT and FDG-PET for staging NSCLC, noting that both provide complementary information.²⁴¹

Whole-body MRI has also been suggested as a potential new tool for cancer staging and it is pleasing to see one new study that compares the newer technologies. Antoch (2003)²⁴² compared whole-body MRI (1.5 tesla) with whole-body PET/CT using a Siemens Biograph device on 98 patients undergoing tumour staging for a variety

of cancers (82 primary staging). Histopathology, clinical and imaging follow-up were used as the reference standards. PET/CT correctly staged 75 (77%) of patients compared with 53 patients (54%) on MRI. With PET/CT 11 patients were overstaged and 12 understaged, compared with 19 overstaged on MRI and 26 understaged with MRI. Compared with MRI, PET/CT had a direct impact on treatment strategy in 12 patients (12%).

An academic unit has created fusion software for PET and MRI (<http://www.research.ucdavis.edu/ncd.cfm?caseno=2005-584>), but there is no commercially available combined PET/MRI imager. Although development of a combined PET/MRI imaging unit started at the same time as the development of PET/CT it has proved technologically more challenging.³ It is anticipated that PET/MRI units could be developed for research purposes in the next 13 years. However, the cost is likely to be \$2.5–3 million higher than PET/CT, so it will be necessary to establish the comparative clinical benefits and optimal case-mix and caseloads to determine cost-effectiveness.²⁴³

Further studies comparing PET/CT with the most up-to-date comparators are needed.

Reference standards

This study has shown that the choice of reference standard can have a major impact on apparent diagnostic accuracy. For example, several earlier studies in breast cancer and melanoma that did not use SLNB showed disproportionately high accuracy of PET. Furukawa and Guyatt²⁴⁴ pointed out that a reference (gold) standard may be problematic when it is ill-defined or cannot be agreed upon. Also, an old reference standard may become less relevant in the setting of a new treatment. For example, conventional haematoxylin and eosin (H&E) stained histopathomorphology may be less relevant than knowledge of tumour oncogene expression in predicting benefit from treatment with imatinib.²⁴⁵ However, even when a reference standard is well defined, agreed on and manifestly relevant to selection for a given treatment, it still may fail as the basis for evaluation of newer tests. This can happen when new tests reveal some clinically relevant heterogeneity within the reference standard categories.²⁴⁶

Organisational issues related to PET imaging

In 2005, the Department of Health published a framework for the development of PET services

in England.²⁴⁷ It seeks to provide advice on the current status of PET, the evidence base, number of scanners needed, workforce and training issues, costs and research. This adds to the more detailed costing work that was undertaken for the Scottish HTA.² Section 9.6 and Appendix 24 of that HTA outline all costs to be considered for four FDG-PET configurations: two with a cyclotron in a hospital, one using radiopharmaceuticals from another source and one for a mobile unit. In addition to the capital costs of a system, annual running costs were estimated to be approximately £1.1 million at 2002 prices, with cost per scan ranging from £677 to approximately £900.

The PET framework states that in the immediate future most PET scans will continue to be for cancer, with the strongest evidence of benefit in lung cancer, lymphoma and colorectal cancer.

The PET framework states that there is currently approximately one PET scanner per 5 million people in the UK. However, on the basis of current evidence and consensus among experts, 40,000 scans per annum are needed across England (800 scans per million population) over the next 3–5 years. They note that this is likely to rise as evidence gets stronger. They assume that the throughput of scanners would be 2000–2500 scans per annum for clinical use. Hence, facilities should be developed to serve approximately 2.5 million people (0.4 scanners per million population). They note that development of PET services outside London is a priority and there is an urgent need to consider workforce development.

The framework presents consensus among experts that PET/CT scanners have considerable advantages over fused PET and CT images and so the integrated machines are recommended for future installations. The capital cost of installing a PET/CT scanner with associated building costs is expected to be approximately £2–2.6 million. The annual running costs are estimated to be £1.5–2 million. This would lead to a cost per scan of approximately £750–1000. They propose that a network of cyclotrons is established across England, with each one costing approximately £3.5 million.

This framework was launched with an announcement that there would be £20 million capital investment in the NHS in England from 2006/07 for the next 2 years to build new PET/CT scanning facilities.

The PET framework was supported by a report from the Royal College of Radiologists (RCR)²⁴⁸ outlining a ‘hub’ (expert support, with most having a cyclotron) and satellite PET/CT service for England. This RCR report assumed one PET/CT scanner per 1.5 million people (0.67 per million population) would be needed initially. The report outlined the staffing requirements, the use of PET in the cancer multidisciplinary team decision-making process and audit requirements.

It is interesting to note that the RCR report was based on the assumption of one scanner per 1.5 million people, but the final PET framework was based on one scanner per 2.5 million people.

Bedford and Maisey (2004)²⁴⁹ assessed the UK requirements for PET (based on 2003 data). They developed a clinical pathway for all forms of lung cancer in England, populated with cancer incidence, local and published data and compared this across Europe. It assumed a scanning capacity of 2,500 scans per annum. For lung cancer they noted a requirement of approximately 30,000 scans per annum and assuming lung cancer to be one quarter of the total scans, this led to an estimated requirement of 121,585 scans per annum for all cancers. This is approximately 2,000 per million population (i.e. 0.82 scanners per million population). However, it is unclear how it has been determined that lung cancer would only provide 25% of the scans, which clearly has a major impact on the capacity figures.

Groves²⁵⁰ noted that many PET capacity calculations assume that patients have one scan. They evaluated patient records over almost 5 years from the Institute of Nuclear Medicine, UCL. From 2268 patients, 418 (18%) had more than one PET or PET/CT scan. The majority (313) of patients had two scans, but nine patients had more than five scans. Ninety-six per cent of the repeat scans were for cancer (20 different primary tumours). Repeat scans were used for evaluating disease progression, staging, treatment response and primary staging. Lymphoma was the cancer that most commonly required a repeat scan, then colorectal cancer and paraneoplastic syndrome.

The KCE HTA¹³⁸ undertook calculations of the capacity required for clinical and research use across all indications (including neurology and cardiology) in Belgium. This detailed approach, estimating the local epidemiology, number of scans per indication, and so on, for all cancer would be helpful to see on a UK-wide or an

English basis. When undertaking such calculations it is important to agree for each cancer what level of evidence is needed to permit routine clinical use, when use may be permitted conditional on local, regional or national audits, and when further research is required. The permitted level of evidence may depend on the reliability of the current diagnostic pathway, the additional value of PET and the kind of change that PET may bring (more imaging versus switch to curative surgery). It is hoped that the results presented in Chapter 6 of this report would aid such calculations.

Systematic review methods for FDG-PET

Search strategy for primary English studies

A new search strategy was developed for this HTA, called FPSS (see the section ‘Search strategy development’, p. 7). It found 18 additional relevant papers that were not found by the published strategy MIJN⁹ (Table 4). Details of FPSS and MIJN can be found in Appendix 1.

When assessing why some of the papers were not found by MIJN, it was discovered that the MIJN strategy had been misinterpreted for this review: the CAS Registry/EC Number/Name of Substance (CEN) field in MEDLINE had not been searched. This shows that when interpreting strategies designed by other searchers, or when translating them for different versions of a database, variations can be introduced, altering the published sensitivity and precision scores assigned to the strategy.

It is estimated that 13 additional papers would still not have been found by MIJN, had the CEN field been searched according to the MIJN strategy. These 13 references were all in English and not retrieved by MIJN because fluorodeoxyglucose F-18 was not mentioned in their titles, abstracts, subject headings or CEN field (Table 5). MIJN combines the PET terms and FDG terms using AND, so that any references that do not specify FDG would be excluded by this strategy.

Of the 13 additional papers identified by FPSS, nine were used in the systematic review (one breast,²⁶ two colorectal,^{38,42} three head and neck,^{70,74,90} one NSCLC,¹¹⁹ one melanoma,¹⁷² one thyroid PET/CT²¹⁷) and four in other sections of the report.

It is unlikely that the extra time needed to screen over 1000 additional abstracts and identify the extra 6.7% of papers (compared to correct MIJN) identified from the FPSS would have yielded a different conclusion to the review. However, if the aim of the review is to be all-inclusive, then the extra time and cost to identify the few additional papers may be justified.

Primary studies in languages other than English

The authors have limited understanding of German, French and a little Spanish, therefore it was necessary for non-English language papers to be translated for use in the systematic review. Translation is costly, at a rate of approximately £117 per 1000 words for common European languages. To minimise costs, it was essential to identify abstracts or papers that should be

TABLE 4 Comparison of search strategies, excluding CEN

Results from MIJN (excluding the CEN field)	Results from FPSS	Stage of review
2038	1348 extra to MIJN	Total search results after deduplication
289	38 extra to MIJN ^a	Included at abstract review stage
176	18 extra to MIJN	Included in the review after full paper evaluated

^a Plus one other item from CENTRAL, not attributable to either strategy.

TABLE 5 Comparison of search strategies, including CEN

Results from MIJN (including the CEN field)	Results from FPSS	Stage of review
181	13 extra to MIJN	Included in the review after full paper evaluated (after checking with amended version of MIJN strategy post-review)

excluded before translation. This was fairly easily done by translation of important words such as retrospective, knowing translations of the relevant cancers and by reading the results tables. From the selected studies, systematic reviews were translated in full, but for primary studies, only the methods and results sections were translated, omitting the introduction and discussion sections. This methodology helped to reduce translation costs substantially.

As noted in the next section, great care must be taken to examine duplicate reporting between non-English and English publications.

Twenty-five potentially relevant papers were identified by the searches for which English abstracts could not be found. Abstracts in other languages were found for six of these papers, after which two could be excluded. Guidance on carrying out reviews from bodies such as the Cochrane Collaboration and the NHS Centre for Reviews and Dissemination states that, "if reviews include only trials reported in English language, their results and inferences would be biased".²⁵¹

There is a need for abstracts of non-English-language papers to be translated and included in bibliographic databases to allow unbiased evaluation of research in systematic reviews. However, if no English abstract can be readily found, the reviewers may have to obtain the papers and then consider exclusion, before or after translation. This could prove extremely costly and time-consuming. The alternative is to exclude papers without English abstracts.

Multiple publications of the same study

In undertaking the systematic review of non-English literature it has become clear that a few papers are published first in another language and that the same study is later published in an English-language journal. For example, Steinert²⁵² first published a lymphoma PET/CT study in a German journal. It was a poor-quality paper with few details about the study design or imaging methodology. However, the same study was published in much greater detail in English in the same year, but with a different lead author.¹⁶⁹ In another case, the English version³⁸ was an exact translation of the foreign paper.

Other forms of duplication that can occur with diagnostic studies are the repeated presentation of a growing series of patients. The worst example of this was a Taiwanese study from which four papers were published on an emerging series of 13,²⁵³

15,²⁵⁴ 20²⁵⁵ and 23²⁰⁹ patients. In all papers patient listings are provided, so it is clear from patient characteristics that the same patients are involved. The 'case numbers' are reordered in each paper so that they appear in a different sequence, but the age/gender/PET/comparator results can all be matched across the papers. Each paper had a different lead author from a different centre, but the same authors were involved in several of the papers. The papers were published in three different journals: *Anticancer Research* (two in the same year), *Endocrine Research* and *Academic Radiology*.

This form of repeat reporting, with clear attempts to rejig the patient sequence and leading authors to avoid identification is poor science and such practice should be brought to the attention of journals. It reinforces the necessity to check carefully for such duplicate reporting in systematic reviews to avoid the bias that could be introduced by assessing these papers as independent studies.

Exclusion of papers costing more than £50

The exclusion of papers costing more than £50 affected three systematic reviews published in English by Hayes Inc.^{256–258} Each report cost US \$600. The reports were a 2002 report on 'other malignancies', a 2003 report on thyroid cancer and a 2004 PET/CT report. It was not possible to judge the relevance of these reports as no abstracts were provided on the HTA database. Hence, these reports were excluded because they did not have English abstracts available at reasonable cost. These exclusions are unlikely to have had an impact, as primary studies following the most robust published SR were included in this SR.

Two primary studies in non-English languages were excluded after abstract selection because they were not available in the UK and so would have cost too much to obtain. The studies used PET to assess early treatment response in neoadjuvant therapy. Delrio²⁵⁹ studied patients with cancer of the lower rectum, while Ollivier²⁶⁰ studied patients with breast cancer. Both abstracts were poor, with no details of study design or even the number of patients.

Additional research and evaluative implementation

Overview

For most cancer management decisions more evidence is required to determine the added value

of PET in terms of diagnostic accuracy, documented change in patient therapy or changes in patient outcome. Conversely, there are a number of cancers where the evidence of diagnostic accuracy is conclusive and further studies would not be worthwhile.

From the thousands of studies reviewed, only a few studied children or allowed patients under the age of 18 to enter. This is a major gap in the evidence base that could be filled by well-controlled research. Indeed, the potential use of PET in lymphoma has been noted in the NICE guidance on cancer in children and young people²⁶¹ and some evidence of the influence of PET on patient management exists.¹⁶⁴ However, as noted in the RCR report,²⁴⁸ PET investigations on children should only be undertaken in centres that have specialist paediatric skills and it is recommended that there are two such designated centres in England.

The majority of publications have come from countries such as the USA and Germany, which have been using PET in routine practice for many years. Few studies have been published from English centres, but given the good nationwide collaboration regarding cancer research it would seem highly feasible and robust studies of PET should be encouraged in the UK. Such studies should be of adequate size to estimate the parameter of interest with sufficient certainty, following a clear study protocol to ensure that all involved understand the implications of the trial and use of PET.

In February 2006, the National Research Register (NRR) showed approximately 25 primary studies underway on PET or PET/CT in the UK. The studies in cancers of interest in this review are presented in *Table 6*.

Not all studies are registered on the NRR, but it is interesting to see where efforts are being targeted, and that in only two studies does there appear to be collaboration among centres.

Other studies of PET or PET/CT are listed on the NRR in cancers not evaluated in this report:

- detection of bone metastases (primary tumours not stated)
- staging stage I non-seminomatous germ-cell tumours
- relapse in stage I seminomatous germ cell tumours
- treatment response after salvage chemotherapy in relapsed germ-cell cancer
- characterisation of diffusion tensor abnormalities in cerebral gliomas
- assessment of cancer physiology in glioma
- microglial infiltrate in low-grade and anaplastic diffuse astrocytoma
- staging stage I teratoma
- development of PET pharmacodynamic endpoints for inhibitors of basic fibroblast growth factor (bFGF)
- pharmacokinetics/pharmacodynamics
- RT planning in carcinoma of the cervix.

In March–May 2006 there was a call for research proposals from the English Department of Health that was focused on new technologies. The ‘Technology Platform Funding (diagnostic imaging)’ scheme particularly encouraged proposals on PET or PET/CT, so it is hoped that this will lead to new research initiatives in England that lead to publications in peer-reviewed journals.

Diagnostic studies

As noted in the section ‘Data extraction and quality assessment’, (p. 9), clear standards for the design and reporting of diagnostic studies have been published. Unfortunately, fundamental weaknesses are often still apparent in studies. Furukawa and Guyatt²⁴⁴ wrote an editorial on recent systematic reviews that evaluated sources of bias. They note that the issues that appear repeatedly are poor selection of patients, inconsistent use of reference standard and lack of blinding.

To design a robust diagnostic study, the following issues should be considered:

- Take account of previously published studies using FDG-PET in a similar patient pathway to ensure that the new study will add value.
- Identify any relevant new research underway.
- Use a prospective study design of consecutive eligible patients.
- Study a clearly defined population similar to those who would receive the test in clinical practice, following a standard patient pathway evaluating all decisions relevant to the patient at that time.
- Include patients with and without the characteristic to be determined.
- Clearly document the PET imaging process.
- Use a comparator that reflects standard or upcoming practice in UK.
- Decide whether PET is an addition or replacement to a current diagnostic test.

TABLE 6 *Trials in progress in the UK*

Centre	Cancer management	Study	No. of patients	Study period
Institute of Nuclear Medicine, UCL	Recurrent advanced head and neck	Diagnostic vs MRI	40	May 2004 to May 2008
Royal Marsden	Head and neck	RT planning	20	April 2004 to March 2006
UCL	SCC head and neck	RT planning compared with FLT-PET, using serial scans	20	October 2004 to September 2006
Christie	Head and neck unspecified	Diagnostic?	NR	Up to March 2007
Multicentre NCRN	Stage Ia/Ila HL restaging after three cycles of ABVD	RCT: those with negative PET scan randomised to consolidation RT or no further treatment. Outcomes include recurrence in residual mass negative on PET and DFS	320	April 2004 to April 2007
Royal Marsden	Lymphoma restaging	Diagnostic with estimates of DFS	60	October 2005 to October 2007
UCL	Lymphoma	Treatment response to low-intensity bone-marrow transplant	40	February 2002 to July 2007
Royal Marsden	NSCLC	Treatment response to erlotinib	35	December 2005 to December 2007
Papworth/Lister	NSCLC tumour angiogenesis	Basic research	100	July 2005 to June 2010
Royal Marsden	Oesophageal	RT planning	18	April 2005 to December 2006
Christie	Mixed tumours including head and neck, colorectal, lung, breast, lymphoma	Correlation with standard CWU	10 per tumour type	December 1999 to December 2007

NCRN, National Cancer Research Network; NR, not reported.

- Use valid reference standards that are fully explained, evaluated blind by more than one person if possible.
- Avoid verification bias, so that the decision to perform the reference standard is not dependent on the results of test under study.
- As a secondary outcome, document the impact of PET on patient management for each patient.

This review has found several meta-analyses in high-quality medical journals. In most cases, the quality of these meta-analyses was excellent, with clear explanation of methodology and results. Such analyses are highly informative and can often provide sufficient evidence of diagnostic accuracy if a number of small diagnostic studies in similar populations have already been published, and should be encouraged.

Patient management

To provide evidence on change in patient management/patient outcome, an RCT is preferable. For evaluation of patient outcomes, if the cancer is in a later stage, survival is the easiest outcome to study, but care should be taken to try to achieve complete follow-up for all patients to achieve a robust analysis.

To determine change in patient management, high-quality prospective studies of a consecutive sequence of patients can also be valuable if they are well designed, well documented and give comparable results across studies. A good example of such a study is shown by Kalff and colleagues,²⁶² in patients with recurrent colorectal cancer thought suitable for resection after CWU (including CT). The referring oncologist was asked to state their proposed management plan after the CWU on the

PET referral form. There was no restriction in the treatment options, so physicians were able to choose combinations thought appropriate for the individual patient. After 1 month, physicians provided information on how patients were managed after the PET scan and documentation of operative findings and laboratory reports were provided. After at least 6 months, information from further diagnostic tests was obtained and the patient outcome was determined from the referring physician and medical records.

Another example of an evaluation in routine practice is provided by Hillner and colleagues.²⁶³ They report a study within the Medicare system in the USA to determine the impact of PET on 248 patients with a variety of cancers, referred by 71 physicians. The physicians completed questionnaires before and after the PET study was undertaken. The first questionnaire identified the primary reason for the PET investigation, the probability of cancer and what would be done if PET was not available. After PET, the questionnaire determined how patient staging was changed, whether new lesions were identified, whether additional tests could be avoided and a final question outlining the details of the post-PET management plan.

This form of study with before and after questionnaires of the impact of PET has been used in a number of published cancer studies included in this review. Such study designs do not appear too cumbersome and may well be possible in routine clinical practice in the UK. However, it is important to encourage as complete a return of questionnaires as possible and so obtaining the commitment of members of the multidisciplinary cancer team for such research is key. Indeed, it has already been stated that oncologists should take a leading role in the design of such studies to focus on the emerging and future value of PET in their practice.²⁶⁴

Audit

From the survey of PET facilities in the UK (see the section 'Cost-effectiveness', p. 49) it is clear that a number of hospitals are using clinical audit as an integral part of the process for developing PET. Audit studies can be helpful not only to give an evaluation of the impact of PET, but also to monitor appropriate use and provide resource information that may feed into an economic model.

In the UK, Gopalan and colleagues²⁶⁵ reported that a simple audit form was issued for patients

referred for FDG-PET scans, mainly for oncology, at two centres in London. The form used scales and yes/no answers to determine whether PET provided new or false information (score of 1–5), how staging was altered and the clinical view of the value of the information (from misleading to therapy change). The audit form was issued with the formal clinical report but from a total of 1500 patients, there was only a return rate of 22%. Such a low response rate affects the validity of conclusions and so more needs to be done to encourage response. One way to do this is to make completion of such audit forms mandatory.

In the USA, Medicare is expanding its coverage for PET imaging, by instigating a National Oncological PET Registry (NOPR). For use of PET in cancer indications not reimbursed by Medicare (e.g. brain, cervical, SCLC, pancreatic, ovarian, testicular), physicians will complete short surveys before and after the PET scan. Data will be analysed centrally and the effect of PET on intended management will be assessed. This national, Internet-based, audited registry was launched on 8 May 2006. Full details of the protocols for data collection and analysis can be found on the NOPR website (www.cancerpetregistry.org/).

As outlined in 'Other HTAs of PET' (p. 52), systematic processes for data collection and regular dissemination of findings can help to determine the most appropriate use of the PET. Ideally, this should be centrally coordinated to ensure common study methodologies and maximum use of all available evidence.

Patient outcomes

RCTs are the optimal form of study to answer definitively questions about the additional value of PET in terms of patient outcomes, but few RCTs of PET have been undertaken. This study reports just two published RCTs. Both are in staging NSCLC.^{112,269} From the HTA database, it has also been determined that two others are underway or have recently finished.

U. Lassen (DACEHTA: personal communication, 2005) provides further details about one trial. It is a multicentre RCT in staging NSCLC in Denmark where patients are randomised to either PET/CT prior to mediastinoscopy or just mediastinoscopy (see data extraction in Appendix 11). It was planned to recruit 430 patients, but after more than 3 years of recruitment, only half that number have been recruited despite enrolling extra

centres. The reason for this is considered to be due to competing studies and the desire to use other forms of imaging technology not in the protocol (SPECT). It is likely that recruitment will be stopped after a planned interim analysis, whatever the results of that analysis.

An RCT has also been sponsored by ZonMw in The Netherlands,²⁶⁶ randomising patients to NSCLC staging with or without PET early in the diagnostic work-up. The aim here was to improve the accuracy and speed of staging. This study has successfully recruited the planned 465 patients and is in the process of assessment.

It is interesting that the only RCTs that have been performed are in NSCLC staging and that recruitment has been a difficulty in one of the trials. It is important that sponsoring bodies learn from the successes and difficulties in undertaking such RCTs as these are costly enterprises and will be compromised if they do not recruit sufficient patients. We look with interest to see the progress of the major UK multicentre RCT in restaging HL, that is outlined in *Table 6*.

Qualitative research

The studies reported here have focused mainly on diagnostic or predictive accuracy, with some attempts, mainly model based, to estimate the value of PET scanning to assist management change and improve outcomes such as overall or progression-free survival. However, very little has been reported on the impact of PET scan information on the patient's decision-making processes. Important questions in this respect include the utility value of the information gain and patient decision-regret caused by falsely positive (or negative) scans that may have led to inappropriate management changes or unneeded investigations.

Ongoing work by Kee²⁶⁷ is seeking to elicit patient utilities for health states determined by PET. Before undergoing PET, patients with NSCLC are interviewed with a set of cards that describe experiences and outcomes of different treatments. Patients are asked to use a visual analogue scale (VAS) to value the avoidance of a needless thoracotomy, compared with other treatments with or without the chance of cure. From the first 25 patients, the VAS score for being true negative after PET was 90 and for true positive 72. The VAS score for false positive was 12 and for false negative was 24 (non-significant difference). The authors note that this information is valuable for economic evaluations, but further work should

assess utilities after patients have experienced the outcomes.

Such qualitative research could be highly informative and should be encouraged.

Treatment response

PET scanning is used for assessment of treatment response by estimating changes in FDG uptake by the tumour during therapy, in the expectation that these will be correlated to, but occur earlier than, clinical or pathological response. Theoretically, the best measurement of FDG uptake is provided by an appropriate analysis of data derived from a combination of dynamic PET scanning and venous blood samples, allowing the analyst to determine the relationship between tumour uptake and the plasma concentration of FDG. The use of dynamic scans would increase the time required per patient and would probably increase the cost per scan.

For dynamic scans NLR from a full-compartment model can be used to measure tumour glucose metabolism. However, three papers^{17,18,268} compare a range of simpler methods to the gold-standard of NLR modelling. They conclude that a simplified kinetic method requiring only venous blood samples and the use of a corrected SUV are reasonable alternatives to NLR. Krak¹⁷ and Hoekstra¹⁸ suggest adjusting SUV for lean body mass and correcting for plasma glucose, whereas Kroep²⁶⁸ suggests adjustment for total body weight and no correction. Alternatively, Dimitrakopoulou-Strauss⁵⁷ suggests the use of a non-compartmental 'fractal dimension' model to analyse dynamic scans.

It remains unclear whether dynamic imaging and NLR or Patlak modelling are required to obtain the best possible results from therapy monitoring and indeed whether the additional burdens imposed by dynamic scanning and venous blood sampling required for some methods are practicable in routine clinical practice. Further larger scale, prospective comparisons of the methods would be valuable to resolve this issue.

In practice it is unlikely that a 'mechanical' cut-off-based approach to defining treatment response will be used; rather, the treatment response assessment will be a collaborative exercise. Consequently, the design and conduct of treatment response studies require better collaboration between radiologists and oncologists/haematologists than is apparent in

some studies reported to date, as it will be important to demonstrate the properties of such 'softer' response assessments.

PET/CT

There are relatively few studies with the newer PET/CT technology and many of these are of poorer quality, studying a mixture of cancer patients retrospectively. Good-quality studies with PET/CT could be highly informative for current clinical practice, to demonstrate both clinical effectiveness and cost-effectiveness. Furthermore, it will be important to keep revising systematic reviews of PET/CT, such as this, to keep abreast of the full evidence base as technology evolves.

Collaborative research

As a result of the PET service framework,²⁴⁷ there are plans to extend PET scanning facilities across England and there is increased interest at a regional level for investment in PET. This will provide important opportunities for UK research and consideration should be given to collaboration across sites nationally and internationally. Maximum use should be made of cancer collaborative networks, to encourage working to a common protocol with central analysis of the data.

The National Cancer Research Institute (NCRI) (www.ncri.org.uk) is a partnership of major UK cancer research funding bodies from the government, charity and private sectors. In response to a request from the Department of Health, NCRI convened a strategic planning group to coordinate development of a research strategy for PET scanning in cancer. The impetus for this work on PET arose from the increasing use of PET for the management of cancer, the potential for its use as an investigative method for the study of drug action and development of new therapeutic approaches in cancer. Workshops have been held with a wide variety of experts and stakeholders to determine the clinical uses of PET and related health economic issues, and to discuss the potential for translational research and cancer biology, together with the technological base needed to support these areas of investigation. Discussions have considered the current state of play of PET research in the UK, analysing the needs, barriers and opportunities. NCRI published a full report of this work in early 2007, along with an announcement regarding its proposals to promote more PET research in the UK.

Strengths and limitations of this report

This systematic review has certain strengths, including the following.

- It uses recent robust systematic reviews augmented by new, higher quality primary studies.
- It includes papers published in Western European non-English languages and translated professionally. (This was thought to be particularly important for this technology, which is in much more widespread use in Western Europe, particularly Germany and Belgium.)
- This is the first systematic review of PET/CT to be written in English.
- This is the first comprehensive systematic review of PET/CT to focus on treatment response and RT planning that discusses the differences between these and other diagnostic accuracy trials.
- It contains a detailed discussion of future research priorities and appropriate methodologies.
- The systematic review was guided by a research specification setting out the research methods, scope of studies to be included and data extraction process.
- A detailed survey of PET facilities in the UK was undertaken.
- Clarification was sought on individual HTAs and papers with authors. This was more successful for HTAs than individual papers, where few responses were received.

Conversely, this systematic review has a number of limitations, including:

- No new meta-analyses were performed.
- No new economic modelling was undertaken.
- The scope of the report was limited and so only eight cancers were evaluated and other indications such as neurology and cardiology could not be covered.
- Only the tracer FDG was evaluated.
- Papers beyond August 2005 were not included and this is a drawback given the rapidly evolving technology.

Chapter 6

Conclusions

Implications for healthcare

A large number of primary research studies, HTAs and systematic reviews has been undertaken to evaluate the potential benefit of FDG-PET in the management of breast cancer, colorectal cancer, head and neck cancer, lung cancer, lymphoma, malignant melanoma, oesophageal cancer and thyroid cancer. FDG-PET appears to have a role to play for some of these cancers in staging and assessing recurrent/residual disease. FDG-PET appears to add little benefit in diagnosis, except in head and neck tumours and for characterisation of FDG-avid SPNs. FDG-PET appears to be particularly beneficial for the identification of distant metastases in the later stages of disease when tumours are larger or when other results have been equivocal. The summary of evidence for the clinical effectiveness of FDG-PET in each cancer is presented in *Table 7*.

For the newer technology of FDG-PET/CT, fewer studies have been published for specific cancer management decisions. However, the published studies showed that FDG-PET/CT tended to be more accurate than FDG-PET, by about 10–15%, resolving some, but not all, equivocal images.

When prioritising clinical use of PET or research proposals it would be helpful to consider areas where current diagnostic techniques are poor and where there is substantial benefit to be gained from altering a treatment management decision. Often, focus has been placed on avoiding futile therapy that may cause harm (e.g. futile thoracotomy in NSCLC or unnecessary radiotherapy in after induction therapy in HL), but it would also be helpful to identify change in treatment that would lead to curative surgery (e.g. from palliative to curative therapy). In all cases, the use of PET by the multidisciplinary cancer team should be discussed and potential changes in decisions agreed for local pathways.

Recommendations for FDG-PET or FDG-PET/CT research

PET research could be undertaken on FDG-PET or FDG-PET/CT, using a standard English cancer

work-up process on typical patients seen within the NHS. This HTA report has summarised the strength of evidence for diagnostic efficacy (as per the hierarchy in *Table 1*, p. 9) for each cancer management decision. So it is possible to tabulate what would be required for each cancer to achieve the next level of efficacy. This is presented in *Table 8*.

However, this builds on the research that has been published internationally and not necessarily on the research needed to answer the most important clinical questions in the UK. Other multidisciplinary cancer and research groups need to use this information alongside clinical needs and priorities to determine where PET research should be focused.

In general, it is clear that better clinical studies of treatment response and radiation planning are required in all cancers. Treatment response studies need to be designed using consensus recommendations to agree the issues outlined in the section ‘Treatment response’ (p. 63), then documentation of the change in patient management instigated as a result of PET is required. For radiation planning, a common methodology for translating PET information into the radiation volume and dose should be agreed, then studies with longer follow-ups that can detect relapses and record survival are needed. After this, RCTs to show the impact of PET on patient outcomes would be ideal. Furthermore, there is a paucity of qualitative evidence to show the impact of PET on patients’ decision-making. Such evidence is valuable and the utilities could be used in economic models.

When prioritising research proposals it would be helpful to consider areas where current diagnostic techniques are poor and where there is substantial benefit to be gained from altering a treatment management decision, which can be recognised for the typical population of NHS patients, particularly taking account of stage of disease at presentation and clinical treatment attitudes.

TABLE 7 Summary of FDG-PET clinical effectiveness by cancer

Type of cancer	Cancer management decision	Evidence
Breast	Diagnosis in patients referred for breast biopsy with abnormal mammogram but no palpable lymph nodes	Not sufficiently sensitive to avoid biopsy
Breast	Diagnosis in patients with low-suspicion findings on mammography who have been referred for 3–6 months' imaging follow-up	No evidence
Breast	Staging ALNs in patients with no palpable ALN metastases and no evidence of distant metastases	Low sensitivity in some studies, so FDG-PET does not obviate the need for ALND
Breast	Locoregional recurrence	Four small studies show variable levels of FDG-PET sensitivity compared with CT or MRI
Breast	Staging/restaging/recurrence	FDG-PET sens., spec. ~85%. Little comparative evidence
Breast	Treatment response for neoadjuvant chemotherapy in locally advanced breast cancer using midtherapy FDG-PET scans	Several studies show that FDG-FDG-PET can predict response, but variety of methods used to evaluate metabolic change in relation to response
Breast	Treatment response for chemotherapy in metastatic breast cancer using midtherapy FDG-PET scans	Two studies on 20 patients show that FDG-PET can predict response
Colorectal	Diagnosis: detection of malignant primary tumour	Poor sensitivity for small tumours, biopsy still needed
Colorectal	Staging: lymph-node metastases	FDG-PET detected 2/7 LNs in one study, compared with 0 on CT or US. Two studies showed change in management in 16%
Colorectal	Staging/restaging: hepatic metastases	FDG-PET more sensitive than CT to detect hepatic and extrahepatic metastases. 13 studies report some form of patient management changes affecting 9–59% of patients
Colorectal	Recurrence: detection in those with clinical symptoms	FDG-PET sens. \geq 85%, spec. varies down to 43%. Accuracy better than CT, similar to MRI
Colorectal	Monitoring for recurrence	Two diagnostic accuracy studies. Unlikely to be used in this way in the UK
Colorectal	Treatment response for neoadjuvant therapy in locally advanced colorectal cancer using FDG-PET scan during or after treatment	Six studies show that FDG-PET is correlated with response
Colorectal	RT planning	One study ($n = 11$) showed FDG-PET to be comparable to CT
Colorectal	PET/CT	10–15% more sensitive or specific than FDG-PET
Head and neck	Diagnosis: when CT/MRI results are equivocal	Evidence of improved accuracy over CT/MRI, but these still needed for anatomical localisation
Head and neck	Diagnosis: detection of synchronous primaries	FDG-PET can detect some but not all synchronous primaries that may be missed by other modalities
Suspected head and neck	Diagnosis: detection of occult primary tumour	FDG-PET detects 30% of primary tumours, including those missed by other modalities
Head and neck	Staging: regional lymph nodes	In clinically N0 necks, FDG-PET less sensitive than SLNB. Other stages, FDG-PET comparable or more accurate than CT/MRI. Little evidence of change in patient management
Head and neck	Restaging/recurrence	FDG-PET may be more accurate than CT/MRI. Some evidence of change in patient management, but mainly related to change in diagnostic procedures

continued

TABLE 7 Summary of FDG-PET clinical effectiveness by cancer (cont'd)

Type of cancer	Cancer management decision	Evidence
Head and neck	Treatment response: various populations	Six studies in which FDG-PET did not consistently predict response. Change in therapy reported in 8/23 in one study
Head and neck	RT planning	Six studies show that FDG-PET and FDG-PET/CT impact radiation volume
Lung: NSCLC	Diagnosis	Some diagnostic evidence, but would not be used without biopsy
Lung: NSCLC	Staging	Evidence of change in management in European RCT. CT node negative, cost-effective; CT node positive, -£59,000 per QALY, so not cost-effective. Preliminary qualitative evidence regarding impact on patient decision-making
Lung: NSCLC	Recurrence	One diagnostic study on FDG-PET/CT
Lung: NSCLC	Treatment response for neoadjuvant therapy using FDG-PET scans at the end of treatment	Evidence to show that FDG-PET correlates with response, but may miss some residual disease
Lung: NSCLC	Treatment response for palliative chemotherapy using FDG-PET scans during therapy	Only one study
Lung: NSCLC	RT planning	Studies show FDG-PET affects radiation volume and dose. One study presents evidence on outcomes during follow-up
Lung: NSCLC	PET/CT	FDG-PET/CT provided better anatomical information and improved staging compared with FDG-PET alone, but some patients were still incorrectly staged with FDG-PET/CT
Lung: SCLC	Diagnosis of occult SCLC cancer in subjects with suspected paraneoplastic syndrome	One diagnostic study in 43 subjects, three SCLC tumours detected by PET
Lung: SCLC	Staging	PET has high sens. and spec. for detecting LN and distant metastases. 8% upstaged, but change in patient management not clear
Lung: SCLC	Restaging	Two diagnostic accuracy studies ($n = 58$) show PET sens. > 95%, but specificity only 41%, unlikely to be used for this in UK
Lung: SPN	Diagnosis (characterisation of FDG-avid nodules)	Several studies show FDG-PET sens. >90%, spec. ~80%. Concerns about ability to detect tumours <1.5 cm. One well-designed study documents change in treatment (to receive or avoid futile surgery)
Lymphoma: NHL	Diagnosis of primary gastric NHL	One study ($n = 8$); not likely to be used for this in UK
Lymphoma: NHL and HL	Staging	FDG-PET more sensitive than Ga scanning, comparable or better accuracy to CT. Some evidence of management/staging changes in diagnostic accuracy studies
Lymphoma: NHL	Restaging to assess residual tumour masses after induction therapy	FDG-PET more specific than Ga or CT
Lymphoma: HL	Restaging to assess residual tumour masses after induction therapy	FDG-PET more specific than Ga or CT. Cost-effectiveness shown in Scottish model in advanced disease. Large UK MRC RCT of patient outcomes underway in early disease
Lymphoma	Treatment response to assess response to chemotherapy midtherapy	Several studies show that FDG-PET can predict response

continued

TABLE 7 Summary of FDG-PET clinical effectiveness by cancer (cont'd)

Type of cancer	Cancer management decision	Evidence
Lymphoma	Paediatrics: all stages	One study in 80 children shows evidence of change in treatment in at least 25% of cases. PET only incorrect in HL
Lymphoma	PET/CT	FDG-PET/CT slightly improves accuracy and alters staging in some
Malignant melanoma	Staging: early-stage disease	FDG-PET less sensitive than SLNB due to inability to detect small lesions
Malignant melanoma	Staging: later stage disease	Unclear whether superior to CT/MRI and has poor accuracy for small lesions
Malignant melanoma	Recurrence	One diagnostic study and one patient management study report that FDG-PET influenced management in at least 30% of patients
Oesophageal	Diagnosis: detection of primary tumour	Diagnostic accuracy studies show accuracy, but unlikely to be used without biopsy in the UK
Oesophageal	Staging: lymph-node metastases	Sensitivity lower than for other indications at ~50%, but comparable to or a little better than CT
Oesophageal	Staging: distant metastases	Sensitivity of 67%, lower than for other cancers but somewhat better than CT
Oesophageal	Treatment response: restaging after patients have received neoadjuvant therapy	Studies show that FDG-PET may be superior to CT and comparable or superior to EUS, but small residual masses may be missed
Thyroid	Diagnosis	One study. Would not be used without biopsy in UK
Thyroid	Restaging	Four diagnostic accuracy studies (total $n < 100$) suggest PET had better sensitivity than scintigraphy, but in one study CT detected more tumour sites than PET
Thyroid: excluding medullary	Recurrence in those with elevated biomarkers not confirmed by ¹³¹ I scintigraphy	Sensitivity of $\geq 80\%$, but low specificity compared with other cancers. Some evidence of PET influencing surgical strategy
Thyroid: medullary	Recurrence in those with elevated biomarkers not confirmed by scintigraphy	Sensitivity of FDG-PET varied across studies, but generally more accurate than comparators in lesions > 1 cm
Thyroid: excluding medullary and Hürthle	Recurrence in those with just clinical suspicion of recurrence (no elevation of biomarkers)	Only 50 patients reported; need more diagnostic evidence
Thyroid	Treatment response after isotretinoin in advanced disease: FDG-PET during treatment and after discontinuation	One study in 21 patients suggested an association between FDG uptake and response
Thyroid	PET/CT for assessment of recurrence	Two small, low-quality studies with no comparison to FDG-PET

ALN, axillary lymph node; LN, lymph node.

TABLE 8 FDG-PET or FDG-PET/CT research needed to increase the published evidence base

Cancer management decision	Research objective
All cancers	Qualitative patient research
All cancers: treatment response	Change in patient management using consistent methods (types of scan, outcomes, analytical methods)
All cancers: RT planning	Impact on patient outcomes, taking account of operator dependency to interpret the volumes and provide treatment, to ensure generalisability across sites
Breast; locoregional recurrence	Comparative diagnostic studies with documentation of change in patient management
Breast; staging/restaging/recurrence	Comparative diagnostic studies in separate primary and recurrent populations, evaluating metastases by site with documentation of change in patient management
Colorectal; staging: detection of lymph-node metastases	Comparative diagnostic accuracy study with change in patient management; or meta-analysis to extract this information from earlier SRs that presented results for mixed primary/recurrent populations
Colorectal; recurrence in those with clinical symptoms	Patient management/patient outcomes, particularly in comparison to MRI
Head and neck; diagnosis of primary tumour when CT/MRI equivocal	Clinical audit to show how PET will be used to alter therapy
Head and neck; diagnosis of synchronous primary tumour when other methods failed	Clinical audit to show how PET will be used to alter therapy
Head and neck; diagnosis of occult primary tumour when other methods failed	Clinical audit to show how PET will be used to alter therapy
Head and neck; staging: regional lymph-node involvement in clinically N+ necks	Patient management where curative options are available or patient outcomes when only palliative changes are possible
Head and neck; restaging/recurrence	Patient outcomes or an economic model
Lung: SCLC; diagnosis of occult SCLC cancer in subjects with suspected paraneoplastic syndrome	Diagnostic accuracy study with documentation of change in patient management. Given small patient numbers, this should be studied by collaborative research
Lung: SCLC; staging	RCT of patient outcomes
Lung: SPN; diagnosis (characterisation)	Clinical audit to demonstrate impact on English patients and populate economic model
Lymphoma; staging	Impact on therapy and outcomes
Lymphoma: NHL; restaging to assess residual tumour masses after induction therapy	RCT of patient outcomes
Lymphoma: paediatrics	Comparative diagnostic accuracy studies with patient management for each management decision, undertaken in paediatric unit(s), particularly in NHL
Malignant melanoma; staging: later stage disease	Comparative diagnostic accuracy studies showing change in patient management
Malignant melanoma; recurrence	Comparative diagnostic accuracy studies with assessment of QoL in longer term follow-up
Oesophageal; staging: detection of lymph-node metastases	Comparative studies of patient management or outcome stratified by SCC/AC
Oesophageal; staging: detection of distant metastases	Comparative studies of patient management or outcome stratified by SCC/AC

continued

TABLE 8 FDG-PET or FDG-PET/CT research needed to increase the published evidence base (cont'd)

Cancer management decision	Research objective
Thyroid; restaging	Diagnostic studies comparing to CT and various forms of scintigraphy
Thyroid: excluding medullary; recurrence in those with elevated biomarkers not confirmed by ¹³¹ I scintigraphy	Patient management with follow-up to assessment outcomes such as hospitalisation
Thyroid: medullary; recurrence in those with elevated biomarkers not confirmed by scintigraphy	Diagnostic accuracy studies with assessment of change in patient management
Thyroid: excluding medullary and Hürthle; recurrence in those with just clinical suspicion of recurrence	Diagnostic accuracy studies with assessment of change in patient management
QoL, quality of life.	



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Contribution of authors

Karen Facey (Evidence-Based Health Policy Consultant) managed the project, undertook the systematic review with Ian Bradbury (Senior Lecturer in Statistics) and has responsibility for the final report. Liz Payne (Information Specialist) had responsibility for the systematic searching including initial selections, report write-ups, comparison of search strategies and reference formatting. Ian Bradbury helped to design the project and perform the systematic review, and performed the critical appraisal for three of the cancers and all treatment response, RT planning and cost-effectiveness sections. George Laking (Clinical Research Fellow) acted as a medical/PET cancer expert during the design, critical appraisal and reporting of this study.



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Appendix I

Search strategy

Two search strategies were used to search OVID MEDLINE. The strategies were adapted for the other databases searched. Full details of the strategies used for each database can be obtained from the authors.

Basic PET-FDG terms

- 1 Tomography, Emission-Computed/
- 2 (positron adj emission adj tomography).ti,ab.
- 3 PET.ti,ab.
- 4 PET-FDG.ti,ab.
- 5 1 or 2 or 3 or 4
- 6 Fluorodeoxyglucose F18/
- 7 18f fluorodeoxyglucose.ti,ab.
- 8 18fdg.ti,ab.
- 9 2-fluoro-2-deoxy-d-glucose.ti,ab.
- 10 2-fluoro-2-deoxyglucose.ti,ab.
- 11 18f-fdg.ti,ab.
- 12 fluorine-18-fluorodeoxyglucose.ti,ab.
- 13 6 or 7 or 8 or 9 or 10 or 11 or 12
- 14 5 or 13

Alternative PET-FDG terms

From Mijnhout,⁸ PET-FDG updated search strategy 2004

- 15 DEOXYGLUCOSE/
- 16 deoxyglucose.ti,ab.
- 17 desoxyglucose.ti,ab.
- 18 desoxy-glucose.ti,ab.
- 19 deoxy-d-glucose.ti,ab.
- 20 desoxy-d-glucose.ti,ab.
- 21 2deoxyglucose.ti,ab.
- 22 2deoxy-d-glucose.ti,ab.
- 23 fluorodeoxyglucose.ti,ab.
- 24 fluorodesoxyglucose.ti,ab.
- 25 fludeoxyglucose.ti,ab.
- 26 fluordeoxyglucose.ti,ab.
- 27 fluordesoxyglucose.ti,ab.
- 28 18fluorodeoxyglucose.ti,ab.
- 29 18fluorodesoxyglucose.ti,ab.
- 30 18fluordeoxyglucose.ti,ab.
- 31 fdg\$.ti,ab.
- 32 18fdg\$.ti,ab.
- 33 18f-dg\$.ti,ab.
- 34 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
- 35 fluor.ti,ab.
- 36 2fluor\$.ti,ab.

- 37 fluoro.ti,ab.
- 38 fluorodeoxy.ti,ab.
- 39 fludeoxy.ti,ab.
- 40 fluorine.ti,ab.
- 41 18f.ti,ab.
- 42 18flu\$.ti,ab.
- 43 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
- 44 glucose.ti,ab.
- 45 pet.ti,ab.
- 46 petscan\$.ti,ab.
- 47 Tomography, Emission-Computed/
- 48 pet ct.ti,ab.
- 49 emission.ti,ab.
- 50 tomograph.ti,ab.
- 51 tomographs.ti,ab.
- 52 tomographic\$.ti,ab.
- 53 tomography.ti,ab.
- 54 tomographies.ti,ab.
- 55 50 or 51 or 52 or 53 or 54
- 56 49 and 55
- 57 45 or 46 or 47 or 48 or 56
- 58 43 and 44
- 59 34 or 58
- 60 57 and 59

Cancer terms

- 61 exp Neoplasms/
- 62 Neoplasm Staging/
- 63 cancer\$.ti,ab.
- 64 tumor\$.ti,ab.
- 65 tumour\$.ti,ab.
- 66 carcinoma\$.ti,ab.
- 67 neoplasm\$.ti,ab.
- 68 lymphoma.ti,ab.
- 69 melanoma.ti,ab.
- 70 staging.ti,ab.
- 71 metastas\$.ti,ab.
- 72 metastatic.ti,ab.
- 73 exp Neoplasm Metastasis/
- 74 exp neoplastic processes/
- 75 neoplastic process\$.ti,ab.
- 76 non small cell.ti,ab.
- 77 adenocarcinoma\$.ti,ab.
- 78 squamous cell.ti,ab.
- 79 nsclc.ti,ab.
- 80 osteosarcoma\$.ti,ab.
- 81 phyllodes.ti,ab.
- 82 cystosarcoma\$.ti,ab.
- 83 fibroadenoma\$.ti,ab.
- 84 (non adj small adj cell).ti,ab.

- 85 (non adj2 small adj2 cell).ti,ab.
 86 (nonsmall adj2 cell).ti,ab.
 87 plasmacytoma\$.ti,ab.
 88 myeloma.ti,ab.
 89 multiple myeloma.ti,ab.
 90 lymphoblastoma\$.ti,ab.
 91 lymphocytoma\$.ti,ab.
 92 lymphosarcoma\$.ti,ab.
 93 immunocytoma.ti,ab.
 94 sarcoma\$.ti,ab.
 95 hodgkin\$.ti,ab.
 96 (nonhodgkin\$ or non hodgkin\$.ti,ab.
 97 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68
 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or
 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83
 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or
 91 or 92 or 93 or 94 or 95 or 96

Limits

- 98 limit to year="2000 - 2005"
 99 not (comment or editorial or letter or case
 reports).pt. (**exclude comments, letters,
 editorials, case reports**)
 100 limit to human

Systematic review filter

- 101 (integrative research review\$ or research
 integration).ti,ab.
 102 ((methodologic\$ adj10 review\$) or
 (methodologic\$ adj10 overview\$)).ti,ab.
 103 ((quantitativ\$ adj10 review\$) or (quantitativ\$
 adj10 overview\$) or (quantitativ\$ adj10
 synthes\$)).ti,ab.
 104 ((systematic adj10 review\$) or (systematic
 adj10 overview\$)).ti,ab.

- 105 (metaanal\$ or meta anal\$.ti,ab.
 106 meta-analysis/
 107 meta analysis.pt.
 108 101 or 102 or 103 or 104 or 105 or 106 or
 107
 109 (review-tutorial or review-academic or
 review).pt.
 110 (pooling or pooled analys\$ or mantel
 haenszel\$.ti,ab.
 111 (peto\$ or der simonian or dersimonian or
 fixed effect\$.ti,ab.
 112 109 or 110
 113 108 and 111
 114 107 or 112
 115 (letter or editorial or comment).pt.
 116 73 not 74

Strategy 1

Systematic reviews:

Basic PET-FDG terms + Cancer terms, limits
 applied + Systematic review filter

Primary studies:

Basic PET-FDG terms + Cancer terms, limits
 applied, Systematic reviews excluded

Strategy 2

Systematic reviews:

Mijnhout PET-FDG terms + Cancer terms, limits
 applied + Systematic review filter

Primary studies:

Mijnhout PET-FDG terms + Cancer terms, limits
 applied, Systematic reviews excluded

Appendix 2

Methodologies for combining diagnostic study summaries

sROC

The summary receiver operating characteristic (sROC) is used to combine results from several diagnostic studies, where each reports an estimated false-positive rate (FPR) and an estimated true-positive rate (TPR). The method involves the following steps:

1. Convert each FPR to its logistic transform U and each TPR to its logistic transform V after increasing each observed frequency by adding $1/2$.
2. For each study calculate $D = V - U$, which is the log odds ratio of TPR and FPR, and $S = V + U$, an implied function of test threshold; then plot each study's point (S_i, D_i).
3. Fit a least squares regression line to these points (or resistant regression line), with D as the dependent variable and S as the independent variable.
4. Back-transform the line to ROC space.

The method as normally applied assumes that there are no major sources of between-study heterogeneity. If the data points (S_i, D_i) do not fit a straight line, sROC curves should not be reported.

A variety of methods has been used to produce summary estimates of sensitivity and specificity from sROC curves, which are supplements to the graphical presentation of the sROC curve. Many authors report the estimated sensitivity corresponding to the observed median specificity. One group¹⁷⁰ prefers to report the estimated joint maximum sensitivity and specificity. An alternative is to use the sROC point of mean pooled sensitivity.

An alternative method of analysis for sROC curves is to use Bayesian methodology, as outlined in Appendix 19 of HTA10.¹ The results from this can then be fed directly into Bayesian economic models.

Likelihood ratios

Likelihood ratios (LRs) provide an alternative means of describing the properties of a diagnostic test.

A positive likelihood ratio (LR+) indicates how many more times likely a positive test result would be when there is a tumour, than when there is no tumour.

$$\begin{aligned} \text{LR+} &= \frac{\text{Pr}(\text{Test +ve} \mid \text{Tumour})}{\text{Pr}(\text{Test +ve} \mid \text{No tumour})} \\ \text{or} &= \text{Sensitivity} / (1 - \text{Specificity}) \end{aligned}$$

A negative likelihood ratio (LR-) indicates how many times more likely a negative test result would be when there is tumour, than when there is no tumour.

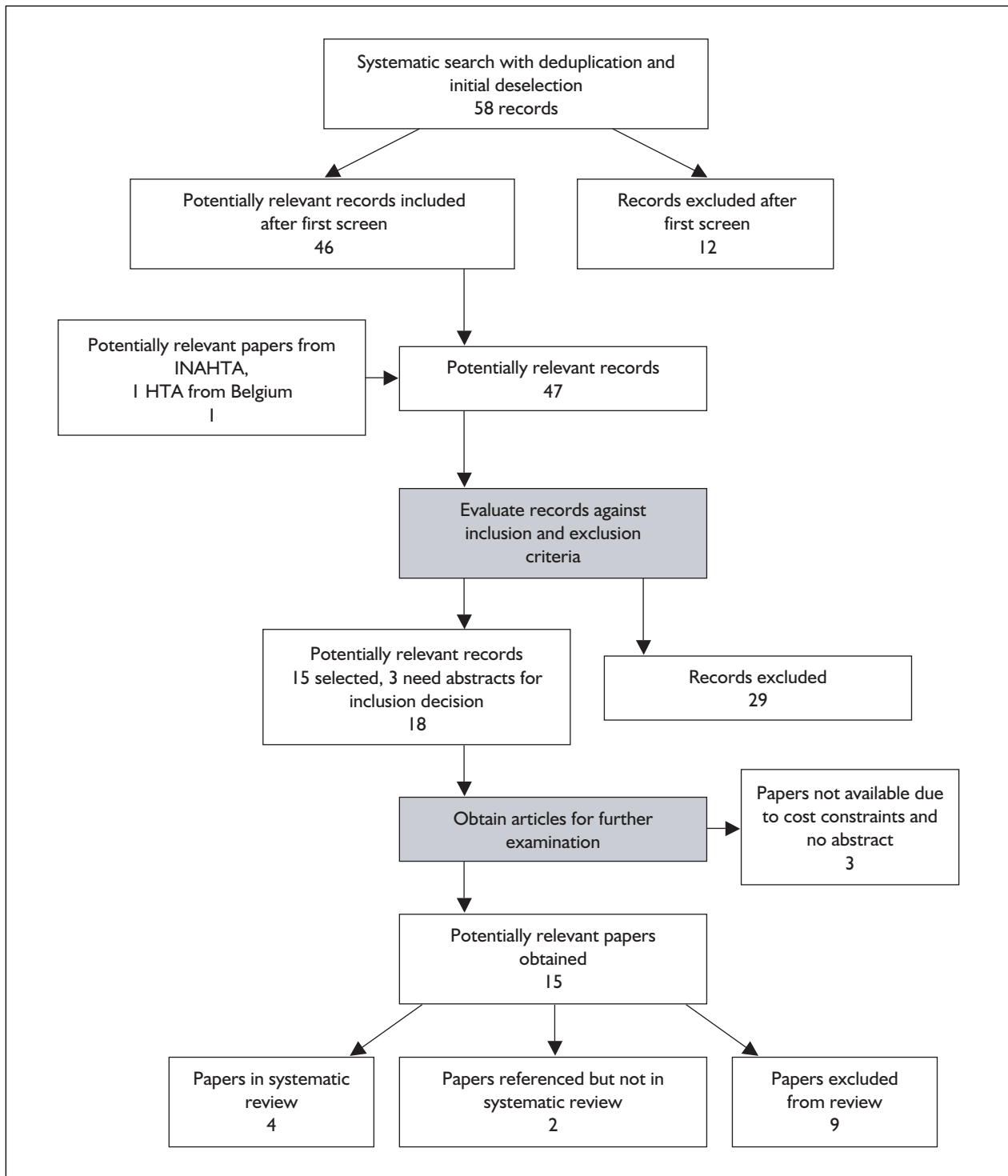
$$\text{LR-} = (1 - \text{Sensitivity}) / \text{Specificity}$$

Positive likelihood ratios can be combined across studies by taking weighted means, with the weights given by:

$$w_i = \frac{1}{\text{var LR+}_i} = \frac{1}{\text{TP}_i} + \frac{1}{\text{FP}_i} - \frac{1}{(\text{TP}_i + \text{FN}_i)} - \frac{1}{(\text{TN}_i + \text{FP}_i)}$$

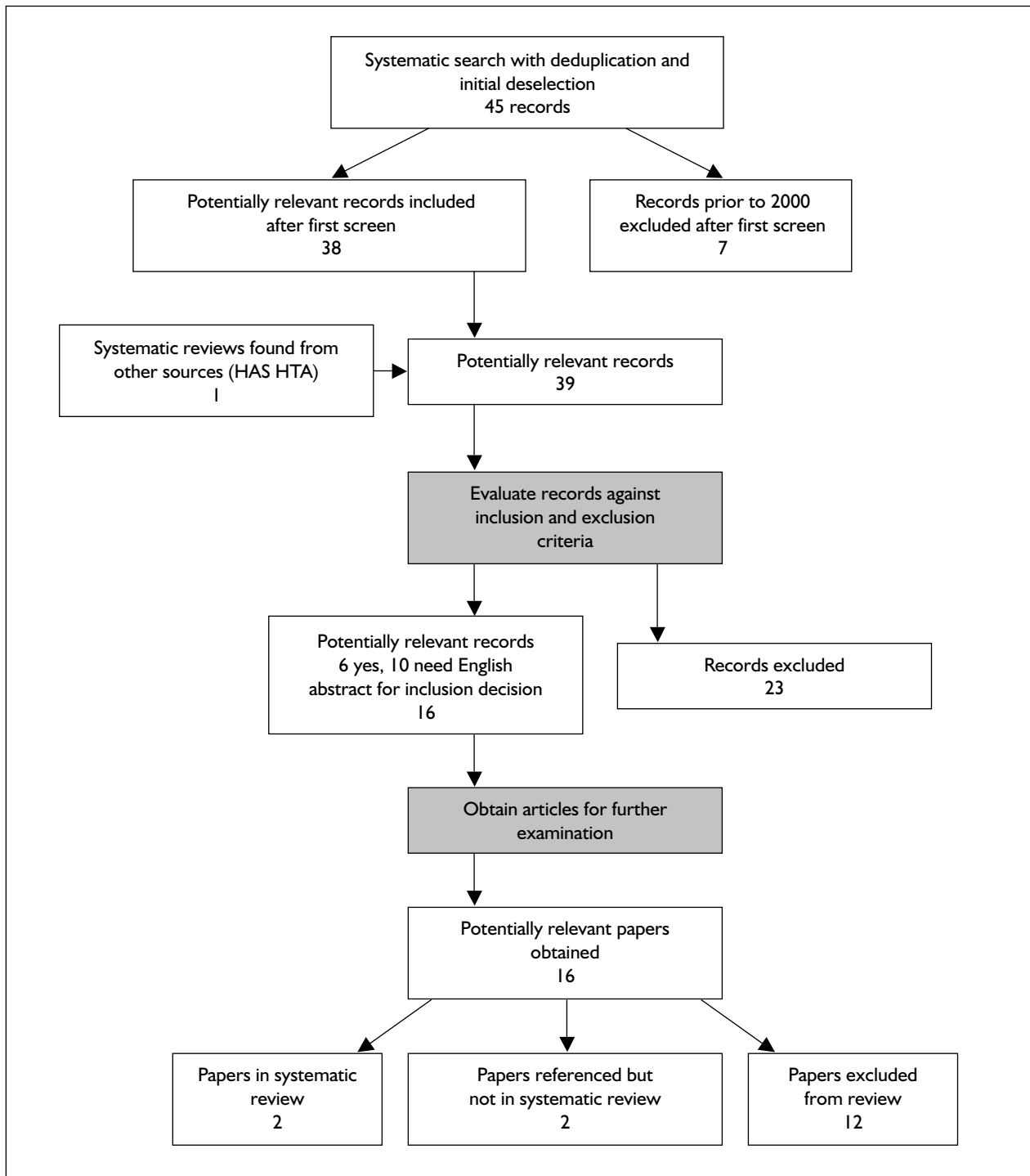
Appendix 3

Flowchart for selection of English systematic reviews



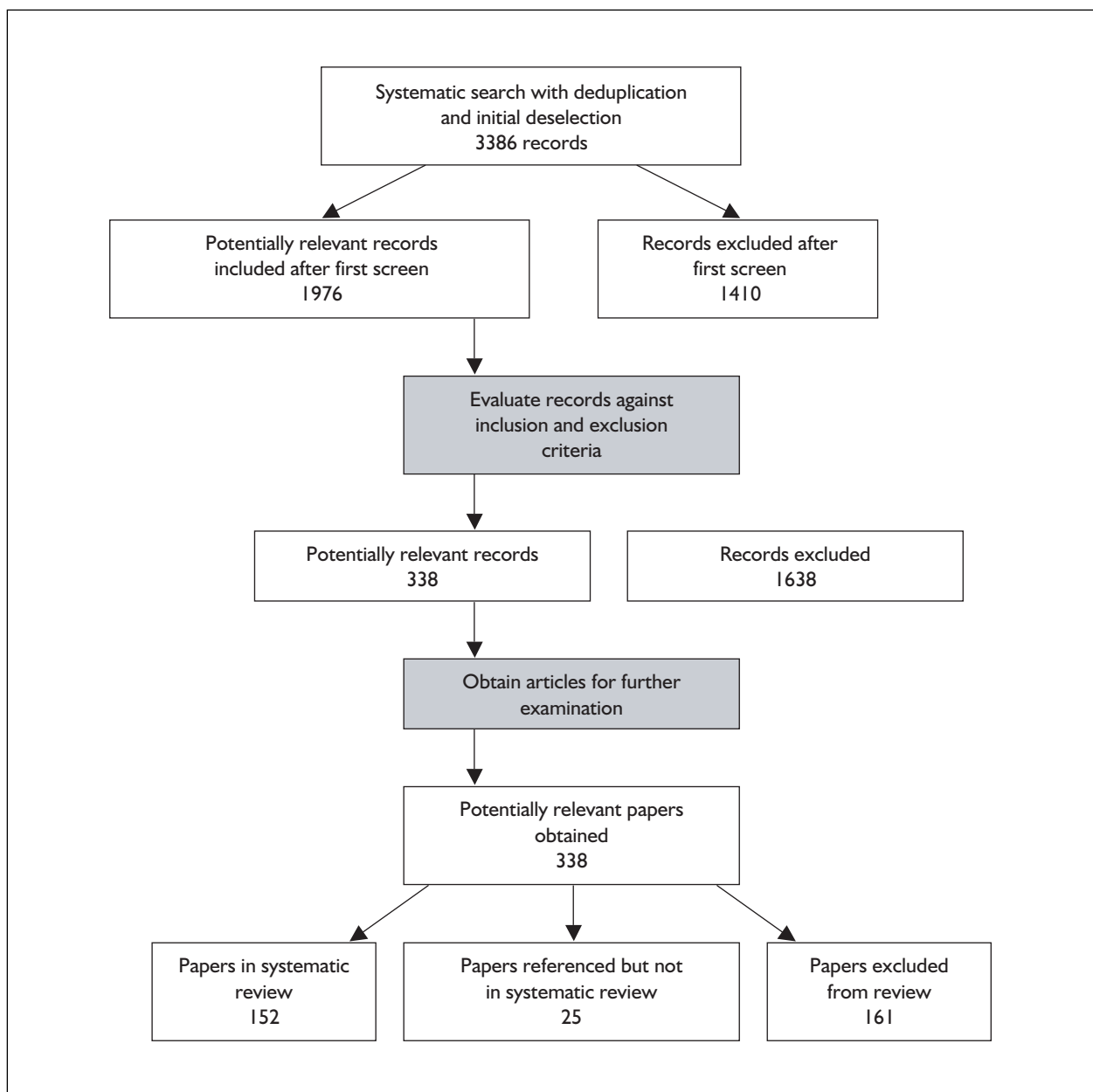
Appendix 4

Flowchart for selection of systematic reviews in languages other than English



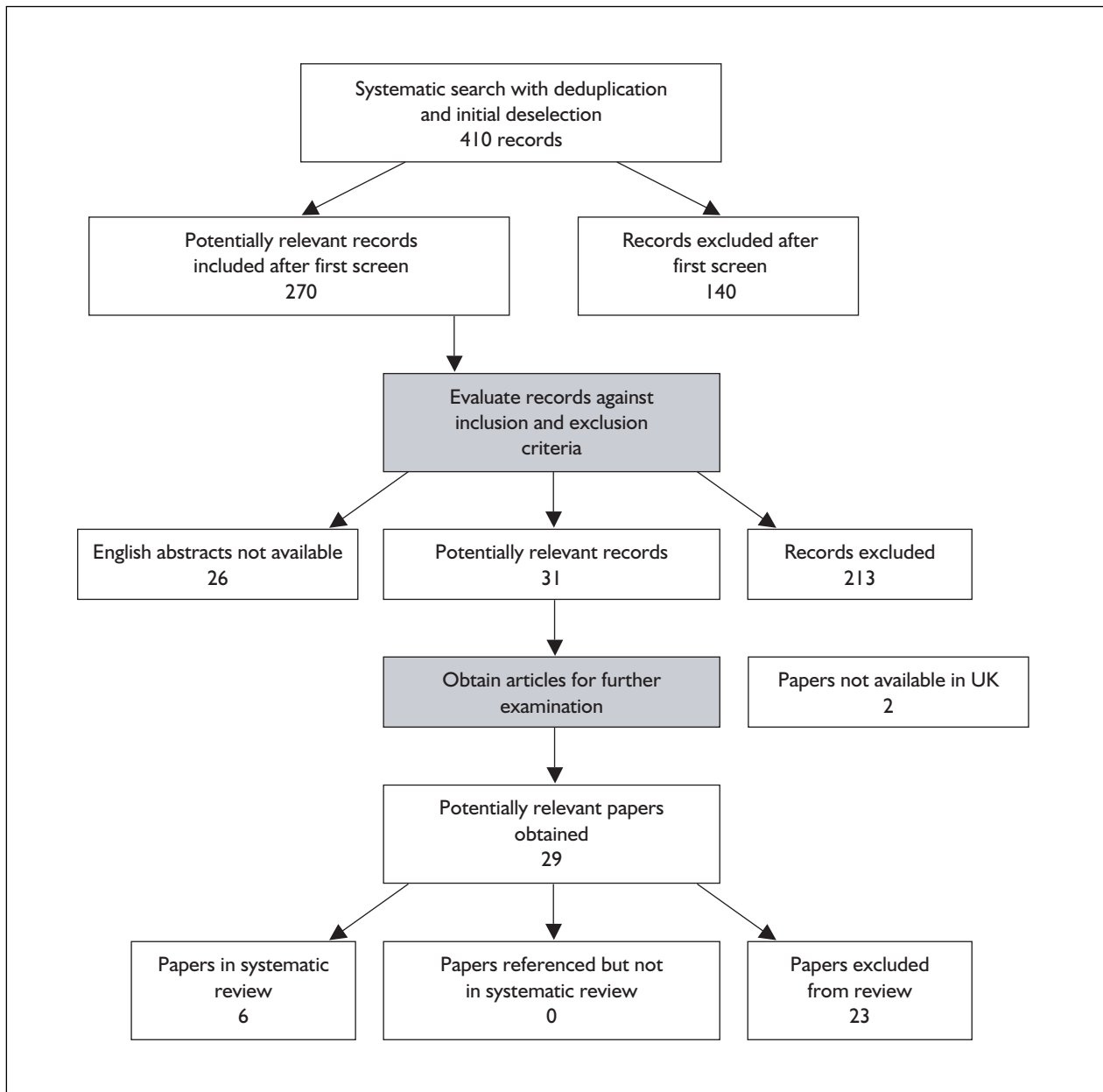
Appendix 5

Flowchart for selection of English primary studies



Appendix 6

Flowchart for selection of primary studies in languages other than English



Appendix 7

Data extraction tables

Breast cancer

Breast cancer: diagnosis Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
<p><i>Diagnosis</i></p> <p>A. In patients who have an abnormal mammogram or palpable breast mass and have been referred for breast biopsy, to avoid breast biopsy when PET is negative</p> <p>Reference standards: cytological aspiration and histopathology</p>	<p>AHRQ, USA, 2001²²</p> <p>(Up to March 2001)</p>	<p>A. 13 hierarchy 2 studies ($n = 16-144$/study, total $n = 606$)</p> <p>Ten studies with patient data ($n = 415$)</p> <p>Random-effects meta-analysis of ten studies gives estimate (95% CI)</p> <p>PET sens. 89% (84 to 93%)</p> <p>PET spec. 80% (70 to 87%)</p> <p>sROC analysis of all 13 studies predicts</p> <p>PET sens. = 89%, spec. = 80%</p> <p>NPV = 88%, so for an individual patient with PET negative and prior prob. (prevalence) of malignancy of 0.5, risk of FN = 12%, for prior prob. of malignancy of 0.75, risk of FN = 29%</p>	<p>No separate sROC of patient-based studies, but results identical to patient-based meta-analysis</p> <p>Individual risk of FN considered too high when benefit is only avoiding biopsy</p> <p>Trials only include patients with suspicious mammograms or palpable masses, so prevalence is high and mean tumour size was large, ranging from 2 to 4 cm with prior prob. of malignancy of 0.5–0.95, compared with 0.2–0.3 in the general population. Hence, report states that evidence is required in other patients</p>
<p>B. In patients who have low-suspicion findings on mammography and other routine imaging, and have been referred for 3–6-month imaging follow-up, to elect early biopsy or avoid short-interval imaging follow-up</p>		<p>B. No studies</p>	
<p>Prob., probability.</p>			

Additional primary study**Author, year, country, study period**Heinisch, 2003,²³ Austria, NR**Article number**

EP 538

Cancer/management decision

Women with suspected breast cancer scheduled for surgical investigation of breast lesions found on mammogram or clinically

Diagnosis: detection of primary lesion before surgery

Design of study/patient characteristics

Diagnostic accuracy study

36 women; mean age 48 years (range 25–77 years)

PET specification

ECAT ART, 120–180 MBq FDG; attenuation correction not stated

Visual interpretation by two NMPs, not blinded to clinical, US or mammography

Reference tests/comparators

Ref.: histopathology from surgery

Comp.: dynamic contrast-enhanced MRI within 1 week

Results

$n = 36$; 40 lesions analysed

25 malignant lesions (in 21 women)

	TP	FN	TN	FP
PET	16	5	11	4
MRI	20	1	11	4

PET poorer in detecting small lesions (< 10 mm)

Comp., comparator; NMP, nuclear medicine physician; Ref., references.

Breast cancer: staging axillary lymph nodes

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
<p><i>Staging</i></p> <p>Extent of tumour in ALN in patients with confirmed primary breast malignancy, no palpable ALN mets (cN0) and no evidence of distant mets</p> <p>(Those with palpable nodes are likely to undergo ALND even if imaging does not detect mets, so PET unlikely to have impact and not assessed here)</p> <p>Reference standards: ALND: some side-effects, but may have some curative potential (four studies) ALND + SNB: new, less invasive (four studies)</p>	<p>BCBS, USA, 2003²⁴</p> <p>(Up to October 2003)</p>	<p>Eight hierarchy 2 studies, ($n = 15-129$/study, total $n = 337$)</p> <p>Six studies with cN0 patients only, two with 71% and 94% cN0</p> <p>ALND as ref.: PET sens. = 40–93% PET spec. = 87–100% ALND + SNB as ref.: PET sens. = 20–50% PET spec. = 82–100%</p> <p>NPV for PET with ALND ref.: 68–96% ALND + SNB ref.: 57–80%</p> <p>Prevalence of node-positive disease = 33–64%, so 36–67% patients with PET negative would have axillary disease undetected if further tests were not undertaken</p>	<p>Most studies prospective, with $n > 30$ in five studies</p> <p>The studies with mixed population did not analyse cN0 separately, but acceptable as percentage of patients was high</p> <p>PET accuracy lower when evaluated against the more sensitive reference of ALND+SNB</p> <p>Report shows that if 50–80% with undetected axillary mets did not go on to have reference standard tests, undertreatment would be associated with absolute difference in 10-year survival of 8.2%</p> <p>Paper concludes that given high individual risk of FNs, PET cannot be reliably used to avoid ALND</p>
mets, metastases; SNB, sentinel node biopsy.			

Additional primary studies

Author, year, country, study period	Article number															
Fehr, 2004, ²⁵ Switzerland, NR	EP 100															
<p>Cancer/management decision Patients with primary breast cancer and primary tumour diameter ≤ 3 cm, no palpable nodes Staging (axillary nodes) within 1 week of surgery</p> <p>Design of study/patient characteristics Diagnostic accuracy study 24 women; mean age 56 years Follow-up: none</p> <p>PET specification GE Advance; FDG 600–700 MBq, attenuation correction Visual interpretation method NR</p> <p>Reference tests/comparators Ref.: ALND Comp.: SLNB at time of surgery</p> <p>Results $n = 24$</p> <table border="1"> <thead> <tr> <th></th> <th>TP</th> <th>FN</th> <th>TN</th> <th>FP</th> </tr> </thead> <tbody> <tr> <td>PET</td> <td>2</td> <td>8</td> <td>13</td> <td>1</td> </tr> <tr> <td>SLNB</td> <td>10</td> <td>0</td> <td>14</td> <td>0</td> </tr> </tbody> </table>			TP	FN	TN	FP	PET	2	8	13	1	SLNB	10	0	14	0
	TP	FN	TN	FP												
PET	2	8	13	1												
SLNB	10	0	14	0												

Author, year, country, study periodLovrics, 2004,²⁶ Canada, 1999–2003**Article number**

EP 2318

Cancer/management decision

Women with primary breast cancer scheduled for surgery (PET within 14 days of surgery)
Staging axillary nodes

Design of study/patient characteristics

Diagnostic accuracy study
98 patients; patient characteristics NR
Follow-up: none

PET specification

ECAT ART; 5 mCi MBq FDG; attenuation correction NR
Visual interpretation by one NMP, blinding NR

Reference tests/comparators

Ref.: histopathology (ALND) from surgery
Comp.: SLNB

Results

90 received PET and standard ALND
(routine H&E staining, not detecting micrometastatic disease)
25/90 positive
PET: 9/25 TP, 2/65 FP
SLNB: 100% sens. and spec.

72 micrometastatic lesions also detected
22/72 disease positive
PET: 6/22 TP, 2/50 FP

Author, year, country, study periodWahl, 2004,²⁷ USA, 1996–2000**Article number**

EP 761

Cancer/management decision/cancer work-up

Newly diagnosed breast cancer scheduled for ALND
Staging (axillary nodes)
CWU: clinical exam then surgery within 1 month

Design of study/patient characteristics

Diagnostic multicentre study
Sample size based on power calculation: 414 patients needed to give CI half-width 0.06 if sens. and spec. in range 0.8–0.9
325 assessable women recruited; mean age 52 ± 11 years
Stage: T1, 4; T1a, 22; T1b, 58; T1c, 116; T2, 87; T3, 5; Tx, 3
Follow-up: none

PET specification

ECAT Exact HR+ (82%), GE Advance (18%); 17.3 ± 3 mCi; attenuation correction
Three NMPs blinded to other data

Reference tests/comparators

Ref.: ALND
Comp.: None

Results

Mean sens. 61%, mean spec. 80%. Sens. and spec. also presented by reader:

	Sens. estimate	Sens. 95% CI	Spec. estimate	Spec. 95% CI
Reader 1	0.62	0.53 to 0.71	0.81	0.54 to 0.73
Reader 2	0.67	0.57 to 0.76	0.79	0.73 to 0.84
Reader 3	0.54	0.44 to 0.63	0.81	0.74 to 0.86

Comments

Recommend using SLNB in cases with no PET uptake

Author, year, country, study periodZornoza, 2004,²⁸ Spain, NR**Article number**

EP 797

Cancer/management decision

Patients with breast cancer, to detect axillary nodes
Staging

Design of study/patient characteristics

Diagnostic accuracy study
Consecutive series of 200 women; median age 52 years (range 25–74 years)
Stage: 0, 8; I, 54; II, 138; average tumour size 2.4 cm (0.5–4.2 cm)
Follow-up: none

PET specification

ECAT Exact HR+; FDG 370 MBq; attenuation correction
Two NMPs blinded to other data

Reference tests/comparators

Ref.: SLNB or ALND (first 100 PET then ALND, second 100 PET, then SLNB, then ALND for SLNB or PET +ve patients)
Comp.: none

Results

$n = 200$

	TP	FN	TN	FP
PET	90	17	91	2

Breast cancer: locoregional recurrence

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
Locoregional recurrence in patients with breast cancer (may include those who present with arm pain or other symptoms referable to the brachial plexus)	BCBS, USA, 2003 ²⁴ (January 1966 to October 2003)	Three hierarchy 2 comparative studies (<i>n</i> = 10–75/study, total <i>n</i> = 142) 1. New retrospective study, in mixed population, only 25/57 suspected recurrent/metastatic disease 2. <i>n</i> = 10 3. Prospective study, <i>n</i> = 75 PET: sens. = 80%, spec. = 96% CT/MRI: sens. = 93%, spec. = 98%	Seven non-comparative studies excluded Report states total <i>n</i> = 152, but tables and other text imply <i>n</i> = 142 1. Report states there were data inconsistencies and confused reporting with locoregional and distant mets combined and other patients in total group 3. PET spec. comparable to CT/MRI, but PET sens. lower than CT/MRI and report expresses concerns about description of reference standard and thus validity of accuracy calculations
Reference standard: histopathology/follow-up			

Additional primary study

Author, year, country, study period Goerres, 2003, ²⁹ Switzerland, 2000–2001	Article number EP 514			
Cancer/management decision/cancer work-up Women in follow-up, with suspected recurrence of breast cancer Detection of recurrence CWU: PET and MRI within 4 weeks of each other				
Design of study/patient characteristics Diagnostic accuracy study Series of 32 women; mean age 57 ± 10 years Imaging median 32 months after initial therapy Follow-up: 12–15 months				
PET specification GE Advance; FDG 386 MBq, attenuation correction Visual interpretation by two NMPs, blinding NR				
Reference tests/comparators Ref.: histopathology by biopsy for 17/32, remaining 15 follow-up Comp.: MRI				
Results <i>n</i> = 32				
	TP	FN	TN	FP
PET	14	0	13	5
MRI	11	3	17	1
Five distant mets found on PET, but outside MRI field Suggested algorithm PET first, MRI if PET +ve; both +ve suggests therapy, otherwise wait				

Breast cancer: staging/restaging/recurrence

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
Staging/restaging	Isasi, 2005 ³⁰	18 hierarchy 2 studies Two lesion based, not reported here	Seven retrospective, six prospective, five unclear
Detection of distant metastasis/recurrence in patients with diagnosis of breast cancer and suspicious clinical or radiological findings (14 studies)	(1995 to June 2004)	16 patient-based studies (eight comparative)	Four reported patient management, but details not provided
Reference standard: histopathology and/or follow-up		Median: PET sens. 93%, spec. 82%	PET had higher sens. and spec. than CWU. PET had higher sens. and spec. than CT (one study). PET had higher sens. but lower spec. than MRI (one study)
		Pooled: PET sens. 90%, spec. 87%	
		sROC, PET: Max. joint sens., spec. 86%	

Additional primary study

Author, year, country, study period	Article number			
Uematsu, 2005, ³¹ Japan, NR	EP 357			
Cancer/management decision/cancer work-up				
Women with primary or recurrent breast cancer				
Staging/restaging for detection of bone mets				
CWU: includes bone scan (within 49 days of PET)				
Design of study/patient characteristics				
Diagnostic accuracy study				
15 women; eight patients restaging, seven initial staging				
Age range 39–68 years				
PET specification				
GE Advance; FDG 220–240 MBq; attenuation correction				
Visual assessment by two NMPs, blinding NR				
Reference tests/comparators				
Refs: CT, MRI and clinical follow-up				
Comp.: SPECT				
Results				
Results reported by lesion, 900 lesions in 15 women				
	TP	FN	TN	FP
SPECT	139	24	729	8
PET	27	136	737	0

Breast cancer: treatment response

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
<p><i>Treatment response</i></p> <p>Response to chemotherapy in locally advanced breast cancer</p> <p>Reference standard: various</p>	<p>Krak, 2004³²</p> <p>(1993–2003)</p> <p>(month not stated)</p>	<p>Eight studies</p> <p><i>Study design</i></p> <p>Number of patients in each study with at least one post-treatment PET scan ranged from 5 to 28</p> <p>Six studies included midpoint scan, five included a scan after one cycle</p> <p>Five used SUV-corrected weight, one SUV corrected for BSA, one tumour to non-tumour ratio, one Patlak slope alone</p> <p><i>Study results</i></p> <p>Reduction in FDG uptake after one cycle predicts response in primary tumours</p> <p>Automated ROI definition and simplified kinetic method using venous blood samples during scanning is argued to be preferable to SUV</p>	<p>Heterogeneous treatment regimens, PET interpretation methods, response criteria and analytical methods</p> <p>Quality of studies generally poor. No consistent target or cut-off definitions. Lack of replication in independent data set. No accurate results for monitoring response in ALN</p> <p>PET unable to detect very small residual foci</p>
BSA, body surface area.			

Additional primary studies

<p>Author, year, country, study period</p> <p>Kim, 2004,³³ Korea, NR</p>	<p>Article number</p> <p>EP 195</p>
<p>Cancer/management decision</p> <p>Women with large or locally advanced primary breast tumour</p> <p>Response assessment to neoadjuvant chemotherapy</p>	
<p>Design of study/patient characteristics</p> <p>Treatment response</p> <p>PET pre- and post-chemo before surgery</p> <p>50 women; patient characteristics not stated</p>	
<p>PET specification</p> <p>GE Advance; FDG 370–555 Mbq; attenuation correction</p> <p>SUV from manual ROI by two NMPs</p>	
<p>Reference tests</p> <p>Ref.: pathological response from surgery</p>	
<p>Results</p> <p>4 CR, 23 PR, 23 no response</p> <p>Δ SUV cut-off of 88% had sens. and spec. 100% and 56.5% for CR vs PR</p> <p>Δ SUV cut-off of 79% had sens. and spec. 85.2% and 82.6% for response vs non-response</p>	
<p>Comments</p> <p>Post-hoc cut-offs</p>	

Author, year, country, study periodGennari, 2000,³⁴ Italy, NR**Article number**

EP 898

Cancer/management decision

Women with metastatic breast cancer
Early assessment of disease response to chemo

Design of study/patient characteristics

Treatment response
PET 1 week pretherapy, day 8 (after course 1), end of planned course
13 patients; patient characteristics not stated
Nine patients completed chemo course

PET specification

ECAT 931/4; FDG 370 MBq; attenuation correction
SUV from manual ROI

Reference tests

Ref.: CWU (physical exam, CXR, CT, MRI, bone scan)

Results

6/9 responders: average SUV drop after one cycle 18% vs no fall in remaining three

Comments

Unclear why this is not in BCBS, 2003²⁴

Author, year, country, study periodSchwarz, 2005,³⁵ Germany, 1997–2000**Article number**

EP 1305

Cancer/management decision

Women with metastatic breast cancer
Early prediction of response to chemo

Design of study/patient characteristics

Treatment response
PET pre-chemo, after one cycle and after two cycles
Substudy of Phase III RCT of chemo (epirubicin + cyclophosphamide vs epirubicin + paclitaxel)
11 patients; age range 34–68 years; nine given paclitaxel

PET specification

Exact 47/921; FDG 240–400 MBq; not corrected
Visual interpretation by one reader

Reference tests

Ref.: conventional imaging after up to ten cycles of chemo

Results

Same classifications for both one- and two-cycle scans
Six metabolic responders, five non-responders
Complete correspondence to conventional response assessment

SUV levels as proportion of baseline

Responders: 72% ± 21% after cycle 1, 54% ± 16% after cycle 2
Non-responders: 94% ± 19% cycle 1, 76% ± 9% cycle 2

Chemo, chemotherapy.

Colorectal cancer

Colorectal cancer: diagnosis

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
Detection of malignant primary tumour	DACEHTA, Denmark, 2001 ⁶	Two hierarchy 2 studies <i>n</i> = 16, 24	Insufficient evidence to draw any conclusions
Reference standard: histopathology in one, not stated in other	(1990 to May 2001)	PET sens. >85% PET spec. = 67% in one study, not recorded in other	

Additional primary study

<p>Author, year, country, study period Friedland, 2005,³⁷ USA, NR</p>	<p>Article number EP 113</p>
<p>Cancer/management decision/cancer work-up Patients with neoplastic colonic polyps Detection of (colonic adenoma or) early-stage colon cancer CWU = colonoscopy</p>	
<p>Design of study/patient characteristics Diagnostic accuracy 45 patients (13 with cancer); demographics NR Follow-up: none</p>	
<p>PET specification CTI ECAT Exact; FDG 370–666 MBq; attenuation correction Visual interpretation by two experienced physicians blinded to clinical history</p>	
<p>Reference tests/comparators Ref.: histopathology by colonoscopy or surgery Comp.: none</p>	
<p>Results PET sens. 62% (8/13) PET poorly sensitive for cancer <2 cm, detecting only 17% (1/6) No FPs, so 100% spec.</p>	
<p>Comments Unusual study in early population, FNs for smaller lesions</p>	

Colorectal cancer: staging**Primary studies****Author, year, country, study period**Heriot, 2004,³⁸ Australia, 1998–2001**Article number**

EP 2246

Cancer/management decision/cancer work-up

Primary rectal (advanced: stage II–IV), with biopsy-proven adenocarcinoma within 15 cm of dentate line

Staging for consideration of adjuvant preoperative therapy

CWU = abdominal CT, pelvic MRI or endoscopic abdominal US or both

Design of study/patient characteristics

Patient management study, with changes in management documented before and after PET

46 patients; 33 M, 13 F; 21–84 years

Follow-up: mean 12 months (range 1–44 months)

PET specification

GE Quest 300-H; 70–120 MBq; attenuation correction

Visual interpretation

Reference tests/comparators

Ref.: follow-up histopathology of operative findings, clinical follow-up

Comp.: CWU

Results

18/46 (39%) change in staging

Pre-PET	Post-PET			
	I	II	III	IV
I	0	0	1	0
II	0	11	1	2
III	0	0	12	7
IV	0	4	1	7

8/46 management changed (six cancelled surgery, two RT field changed)

Two other patients had management changes not related to PET (patient choice, rapid disease progression)

Author, year, country, study periodKantorová, 2003,³⁹ Czech Republic, NR**Article number**

EP 580

Cancer/management decision/cancer work-up

Colorectal cancer histologically proven by colonoscopy

Staging before potential surgery

CWU = CXR, US, CT

Design of study/patient characteristics

Diagnostic accuracy study plus evaluation of change in patient management by comparing medical records before and after PET

38 patients; 27 M, 11 F; average age 66 years (range 38–83 years)

Follow-up: NR

PET specification

CTI/Siemens ECAT Exact; FDG 525 MBq per 70 kg body weight

Visual interpretation by one NMP

Reference tests/comparatorsRef.: following surgery detailed histopathology of many LNs, allowing microscopic tumours to be detected ($n = 36$), clinical follow-up ($n = 2$)

Comp.: Siemens Somatron Plus 3 CT Scanner, US

Results*Primary tumour sensitivity*PET = 35/37 (95%), CT = 17/35^a (49%), US = 5/36^a (14%)*Lymph nodes*

	TP	FN	TN	FP	
PET	2	5	22	3	sens. = .29%, spec. = .88%
CT, US detected 0/7 (0%)					

Liver mets

	PET	CT	US
Sens.	7/9 (78%)	6/9 (67%)	2/8 ^a (25%)
Spec.	24/25 (96%)	23/23 ^a (100%)	24/24 ^a (100%)

PET changed treatment modality for 3/38 patients and range of surgery for 5/38 patients. Overall, PET changed treatment methods for 6/38 (16%) patients.

Comments

^a It appears that not all imaging results were available for all patients

Colorectal cancer: staging/restaging

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
Staging Detection of hepatic metastases from primary or recurrent colorectal carcinoma Reference standards: histopathology, core biopsy, cytology, or follow-up (min. 6 months)	Kinkel, 2002 ⁴⁰ (December 1985 to December 2000)	Hierarchy 2 evidence: nine PET studies ($n = 423$), 11 MRI studies ($n = 401$), 25 CT studies ($n = 1371/1747$), nine US studies ($n = 509/686$) Studies reporting sens. and spec.: 7/9 PET, 20/25 CT, 4/11 MRI, 8/9 US PET spec. $\geq 85\%$ in all studies For comparators, those studies with spec. $\geq 85\%$ show following sens. (95% CI): PET 90% (80 to 97%) CT 72% (63 to 80%) MRI 76% (57 to 91%) US 55% (41 to 68%) Two papers report management change after PET in 61–94% of patients, but details not provided	Includes seven studies published before 1990 PET and MRI studies: all patients had colorectal cancer CT and US studies: any non-hypermetabolic GI tract tumour (e.g. stomach and oesophagus) Imaging methods poorly reported in original papers sROC not performed because the data did not fit the statistical model. Instead, they stratified studies by specificity and reported weighted mean sensitivity within the strata PET has high sensitivity compared with three other imaging comparators
GI, gastrointestinal.			

Additional primary studies**Author, year, country, study period**Arulampalam, 2004,⁴¹ UK, 1999–2002**Article number**

EP 14

Cancer/management decisionPatients with confirmed CLM referred for hepatic resection to one surgeon
(Re)staging before surgery**Design of study/patient characteristics**Diagnostic accuracy study plus evaluation of change in patient management
31 patients; 15 M, 16 F; 41–82 years
Follow-up: median 21 months (range 5–33 months)**PET and PET/CT specification**

GE Advance 300-H up to December 2001; GE Discovery LS PET/Ct January–May 2002; FDG 330–380 MBq; attenuation correction

Visual interpretation by two NMPs

Reference tests/comparators

Ref.: surgical findings, histopathology, clinical follow-up, radiology

Comp: spiral CT

ResultsThree patients had index CLM on CT, but not PET with no evidence of mets in median of 9 months' follow-up
28/31 patients had an index CLM on both CT and PET referred for surgery

	TP	FN	TN	FP	Sens.	Spec.	PPV	NPV
PET	17	0	10	1	100	91	94	100
CT	8	9	10	1	47	91	89	53

FP was a patient with an area of fibrous stroma

CT FNs occurred in 5/10 patients with multiple CLM and 4/7 patients with extrahepatic metastatic disease. No FNs in patients with solitary CLM

12/31 patients had management changed as a "direct result of findings on FDG-PET": laparotomy avoided = 7; more extensive surgery = 1; palliative chemotherapy = 4

Comments

Unclear whether primary or recurrent populations

Mixed results from two machines: PET and PET/CT

Documentation methods for change in patient management unclear

Need comparison with MRI

PET sensitivity much better than CT, particularly for multiple CLM and extrahepatic disease

23% patients avoided surgery and associated surgical morbidity

Author, year, country, study periodDesai, 2003,⁴² USA, 1998–1999**Article number**

EP 2188

Cancer/management decision/cancer work-up

Recurrent colorectal cancer: patients with rising CEA in routine follow-up or those with planned reoperation for mets, all by one surgeon

Restaging to avoid futile laparotomy

CWU = CT + laparoscopy in those PET and CT positive, when possible

Design of study/patient characteristics

Change in patient management (avoidance of futile laparotomy)

114 patients: 89 presumed recurrent disease; 25 presumed isolated liver mets

60 M, 54 F; mean age 62 years

Follow-up: 3 years

PET specification

Siemens ECAT Exact 922; FDG 10 mCi; WB + separate scan for brain

Fourier rebinding/ordered subsets reconstruction

Interpretation by two PET NMPs, with knowledge of CT results

Reference tests/comparators

Ref.: surgery or follow-up

Comp.: CT performed up to 2 months before PET in another centre

Results

Pilot in first 26 patients performed laparotomy regardless of PET findings

	Pos.	Neg.	Sens.	
Surgery	26	0		
CT	10	16	38%	
PET	23	3	88%	(three patients had diffuse peritoneal disease)

All 114 patients (mean survival 16 months)

CT found 42 patients to be resectable (mean survival 17 months). Of these 42, PET found 17 with multiple foci (one alive at 3-year follow-up), leaving 25 resectable. "40% saved non-therapeutic laparotomy"

Of the 25 considered resectable by PET and CT:

13 had no other evidence of disease (assessed by laparoscopy) and so surgery was not undertaken.

After surgery seven had isolated liver mets; none alive at 3-year follow-up.

Five had isolated extrahepatic foci of recurrent disease: all alive at 3-year follow-up

PET not able to detect small volume disease and underestimates the extent of lesions < 1 cm

Five patients with negative PET scans had peritoneal carcinomatosis or positive portal LNs. Negative PET with other positive imaging does not obviate the need for further surgery

Author, year, country, study periodRosa, 2004,⁴³ Germany, NR**Article number**

EP 301

Cancer/management decision/cancer work-up

Patients with suspected CLM, studied in two centres with PET

Staging/restaging before hepatic resection

CWU = physical exam, CEA, abdominal US at 3- or 12-monthly intervals after colorectal resection, plus colonoscopy before PET

Design of study/patient characteristics

Change in patient management, surgeon documented decision before and after PET

58 patients; 34 M, 24 F; age 33–81 years

Follow-up: 6–24 months

PET specification

Siemens/CTI ECAT Exact PET scanner in each centre; FDG 185 MBq in one centre, 370 MBq in the other centre

All patients catheterised for continuous flushing of bladder; blood glucose < 140 mg/dl

Visual interpretation blinded to other imaging, image reader(s) NR

Reference tests/comparators

Ref.: histopathology or imaging follow-up

Comp.: CT of thorax, abdomen and pelvis, abdominal US, colonoscopy

Results

46/58 patients PET concordant with CT/US/colonoscopy. In 43 of these 46, no extrahepatic disease was correctly detected, in two lung mets were correctly detected, there was one FP where pneumonitis was detected as a lung mets

In the 12 discordant cases PET correctly diagnosed extrahepatic disease, mainly in the lung

PET correctly upstaged 12/58 patients (21%), so liver resection was not undertaken and chemo or no further therapy was given

Comments

Catheterisation. Documentation of change in patient management limited to one sentence.

Author, year, country, study periodTopal, 2001,⁴⁴ Belgium, 1990–1998**Article number**

EP 1133

Cancer/management decision

Patients considered eligible for resection of CLM

Staging/restaging

Design of study/patient characteristics

Change in patient management

91 patients (27 synchronous CLM, 64 metachronous CLM)

65 M, 26 F; mean age 61 years (range 36–79 years)

Follow-up: mean 23 months (range 0.5–92 months)

PET specification

Reported in another paper

PET <2 months after CWU and within 1 month before surgery

Interpretation by one PET experienced NMP blinded to intraoperative data

Reference tests/comparators

Ref.: histopathology, intraoperative findings and follow-up

Comp.: CWU

Results

PET was concordant with CWU in 68 patients (75%)

PET provided additional information in ten patients (11%): five bilobar (one underwent extended left hepatectomy, four partial liver resection), one local rectal recurrence (surgical resection), one pulmonary mets (resection), one oesophageal cancer (CRT), one cerebral mets, one coeliac LN mets

PET falsely upstaged six patients (7%): false identification of two peritoneal mets, one pulmonary mets, one bilobar, one mediastinal LN mets, one axillary LN mets

PET falsely downstaged seven patients (8%): missed three with bilobar mets (lesions measuring 5–15 mm), one peritoneal mets (5 mm), one local recurrence, two portal LN non-enlargement; three of these were excluded intraoperatively from liver resection

Comments

No clear documentation of how the changes in stage were documented and the resulting change in treatment is not clear in all cases

Author, year, country, study periodTruant, 2005,⁴⁵ France, 2001–2002**Article number**

EP 350

Cancer/management decision/cancer work-up

Patients considered eligible for resection of CLM

Staging/restaging

CWU = abdominal CT and CXR or thoracic CT

Design of study/patient characteristics

Diagnostic accuracy study

53 patients (119 lesions across all sites); 40 M, 13 F; mean age 63 years (range 44–78 years)

27 synchronous CLM, 26 metachronous

Follow-up: NR

PET specification

GEMS PET Advance scanner; FDG 370 MBq; attenuation correction

PET within 2 months of laparotomy

Visual interpretation by two experienced NMPs blinded to previous imaging results

Reference tests/comparatorsRef.: histopathology ($n = 33$ lesions), follow-up ($n = 4$ lesions) for discordant PET vs CT readings

Comp.: CT (80% of patients on MX Twin Philips) within 2 months of resection

Results*CLM (lesion-based analysis)*

	TP	FN	FP	TN	Sens.	Spec.
PET	78	21	1	4	79% ^a	80%
CT	78	21	3	1	79%	25%

^a After exclusion of five patients who showed unfavourable metabolic conditions*Abdominal cavity (lesion-based analysis)*

	TP	FN	FP	TN	Sens.	Spec.
PET	5	3	1	46	63%	98%
CT	2	6	4	43	25%	91%

Extra-abdominal organs (lesion-based analysis)

	TP	FN	FP	TN	Sens.	Spec.
PET	4	0	2	73	100%	97%
CT	4	0	0	75	100%	100%

PET was concordant with CWU in 41 patients and all these underwent complete resection

In two patients, bilobar hepatic involvement was not detected by PET or CT and two-stage hepatectomy was required

PET gave “additional information that might influence or alter surgical management” in ten patients; of these, PET could have been “strongly beneficial to the management” of five patients (9%), could have influenced management in another two patients and could have had a negative impact in three patients

For the five beneficial patients, three had irresectable extrahepatic disease detected by PET and so would have avoided surgery, one had locoregional recurrence and so would have had complete resection, one had lymph-node involvement disproved so hepatic resection would have been encouraged

The three negative impacts related to FPs, suggesting that the patient was inoperable

Comments

Purported change in management figures not impressive and show potential for negative consequences due to FPs

CLM, colorectal liver metastases; WB, whole body.

Colorectal cancer: staging/restaging/recurrence

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
Restaging (plus staging ^a) in patients who are candidates for resection of colorectal liver mets Reference standards: histopathology, clinical follow-up (min. 6 months)	Dietlein, 2003 ⁴⁶ (1997–2002)	15 studies Five studies ($n = 445$) assessed the identification of local recurrence and mets Estimates (95% CI): PET: Sens. 94% (91 to 96%) Spec. 78% (69 to 86%) LR+ = 4.3, LR- = 0.08 CT: Sens. 73% (68 to 78%) Spec. 62% (52 to 72%) LR+ = 1.9, LR- = 0.43 Ten studies had hierarchy 4 evidence ($n = 741$) Staging correctly changed: 27% (24 to 30%) Staging incorrect: 4% (2 to 5%) Change in management: 34% (31 to 38%)	Only studies that fulfilled the criteria laid out by the EMEA ¹² and had ≥ 35 patients were included in analysis Paper gives full critique of the potential biases and study weaknesses Simple pooled analysis of accuracy, estimating sens. and spec. independently Hierarchy 5 evidence from modelling estimated 3-year survival rate following surgery would have been $>70\%$ if selection of patients had included PET
^a Some of the papers included mixed patients with primary or recurrent cancer.			

Colorectal cancer: recurrence

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
Evaluation of recurrence in cases suspected by clinical symptoms, elevated CEA, etc. Reference standard: histopathology	DACEHTA, Denmark, 2001 ⁶ (1990 to May 2001)	13 hierarchy 2 studies with PET ($n = 15-105/\text{study}$) PET sens. $\geq 85\%$ in all but one study, 79% in other study PET spec. $\geq 90\%$ in seven studies, 43–83% in other studies Sens. and spec. higher than CT in four studies, similar or better than MRI in four studies	Analysis probably mixed by patient and lesion

Additional primary studies

Author, year, country, study period	Article number
Fukunaga, 2005, ⁴⁷ Japan, 2000–2003	EP 1336
<p>Cancer/management decision/cancer work-up Patients with clinically suspected local recurrence of rectal cancer after curative resection (median time since operation 24 months, range 5–112 months) Restaging CWU = CT/MRI suggestive of recurrence ($n = 22$), local symptoms ($n = 13$), increased CEA ($n = 7$)</p> <p>Design of study/patient characteristics Change in patient management using scoring system: PET compared with fused PET/CT for detection of colorectal cancer recurrence 42 patients (two others excluded: one died before confirmation of diagnosis, one bladder cancer) 32 M, 10 F; mean age 61 years (range 40–79 years) Follow-up: median 36 months (range 13–45 months) for those with postoperative change</p> <p>PET specification Japanese Shimadzu Headtome V FDG 370 MBq, bladder continuously flushed by catheter with saline Visual interpretation by one NMP and one surgeon, blinded to CT Digital fusion of CT and PET using Japanese commercial software Evaluated by two independent oncologists, blinded to PET and CT results</p> <p>Reference tests/comparators Ref.: surgical pathology ($n = 17$), biopsy ($n = 4$), clinical and radiology follow-up ($n = 21$) Comp.: CT read by senior radiologist, blinded to PET</p> <p>Results Correct classifications: CT = 33/42, PET = 37/42, fused PET/CT = 39/42 Incorrect classifications: CT = 9/42, PET = 5/42, fused PET/CT = 3/42 Fused PET/CT provided additional information (exact location for surgery and eligibility for chemo) in 7/9 patients incorrectly diagnosed by CT Fused PET/CT provided information on exact location of recurrence in 2/5 patients with incorrect PET diagnoses Overall fused PET/CT provided additional information in 8/42 patients compared with CT or PET alone. Fused PET/CT negatively affected patient management in one patient. Fused PET/CT missed small volume disease in two patients In 5/42 cases, fused PET/CT changed patient management by identifying the exact location of tumour for radical surgery. In six other patients the treatment was 'modified' on the basis of correct fused PET/CT diagnosis</p> <p>Comments Unclear presentation of patient management results</p>	

Author, year, country, study periodMontravers, 2004,⁴⁸ France, 2000–2002**Article number**

EP 249

Cancer/management decision/cancer work-up

Patients who had previously been treated for primary colorectal cancer with suspected recurrence or for preoperative staging or evaluation of efficacy of treatment for recurrence

Restaging

CWU = CEA and/or CA 19-9 assays, abdominal US, CXR and CT, MRI and endoscopy depending on problem

Design of study/patient characteristics

Diagnostic accuracy study with comparison of a previous series imaged using CDET; only PET results and study characteristics presented here

(303 patients entered in study period with 354 PET exams)

$n = 239$ of these exams were eligible with histopathology or sufficient follow-up

167 M, 137 F; mean age 60 years (range 23–88 years)

Follow-up: mean 11 months (range 6–22 months)

PET specification

ADAC C-PET; FDG 2 MBq/kg; attenuation correction

Patients with blood glucose > 7.5 mmol/l excluded

Scans evaluated by observer informed of CWU, but not of patient's final outcome

Reference tests/comparators

Ref.: histopathology in those who underwent surgery; follow-up in others

Comp.: CDET on an earlier set of patients (NR here)

Results

PET scans with histological evidence ($n = 94$ scans)

	Sens.	Spec.
All tumours	75/83 (90%)	7/11 (64%)
Tumours ≤ 10 mm	14/32 (44%)	7/7 (100%)
Tumours > 10 mm	43/48 (90%)	4/5 (80%)

PET scans with follow-up ($n = 145$ scans)

	Sens.	Spec.
All tumours	94%	64%

Comments

Unclear reporting of scans vs patients in the results and subgroup figures (numerator and denominator) do not add up to 'all tumours' figures

Author, year, country, study periodLangenhoff, 2002,⁴⁹ Netherlands, 1998–2000**Article number**

EP 615

Cancer/management decision/cancer work-up

Patients with unresectable CLM followed up after local ablative therapy

Restaging

CWU = CEA, CT, PET immediately after ablative therapy ('preoperative') and 3 weeks after (postoperative)

Postoperative assessments used as reference

Design of study/patient characteristics

Diagnostic accuracy study

23 patients; 15 M, 8 F; 51–78 years

Follow-up: CWU after postoperative assessment, 6 weeks after ablation and then every 3 months. Mean 16 months (range 10–21 months)

PET specification

Siemens ECAT-ART; FDG 200–220 MBq; attenuation correction

Scans evaluated by at least two NMPs

Reference tests/comparators

Ref.: clinical and imaging follow-up

Comp.: Siemens Somatom Volume Zoom Spiral CT, images interpreted by two independent reviewers. PET and CT images evaluated by one independent investigator blinded to CEA

Results

Recurrence	No. of patients	n, positive (mean time of detection – months)		
		PET	CT	CEA
Local	4	5 ^a (3.8)	4 (8.5)	2 (11)
Outside treated area	11	11 (8.1)	11 (11.7)	7 (12.3)
Extrahepatic	9	10 (8.4)	8 (9.8)	5 (12.6)

^a Abscess gave FP. Also noted that equivocal but not clear PET positive findings were apparent in these five patients at the 3-week postoperative assessment

Author, year, country, study periodSelvaggi, 2003,⁵⁰ Italy

Original resection: 1993–1998, then 2-year follow-up for recurrence to 1995–2000

Article number

EP 707

Cancer/management decision/cancer work-up

FDG-PET for detection of early recurrence of colorectal cancer in patients previously treated with curative resection

Recurrence screening in patients with no other evidence of recurrence, 2 years after resection

CWU = colonoscopy, CT and MRI: 1 or 6 months, 1 and 2 years after curative resection, clinical exam every 3 months

Design of study/patient characteristics

Diagnostic accuracy study plus evaluation of change in patient management

49 patients received initial curative resection, 31 disease free at 2 years

19 M, 12 F; mean age 62 years (range 43–79 years)

Follow-up: median 21 months (range 5–33 months)

PET specification

Siemens PET Exact 47; FDG 370 MBq; 3D

Evaluated by two independent NMPs blinded to other results

Reference tests/comparators

Ref.: surgical findings, histopathology, clinical and radiology follow-up

Comp.: CT, MRI, colonoscopy

Results

n = 31 disease free at 2 years

PET detected six sites with increased metabolic activity in five patients

All five underwent surgery. TP = 4, FP = 1, PET sens. = 100%, spec. = 83%

Clinical management changed in two cases (6%)

Comments

Unusual study design (using PET when no other methods indicate recurrence) unlikely to be used this way in England

Colorectal cancer: treatment response**Primary studies**

Author, year, country, study period Amthauer, 2004, ⁵³ Germany, NR		Article number EP 8		
Cancer/management decision Locally advanced rectal cancer Response assessment to neoadjuvant CRT and regional hyperthermia				
Design of study/patient characteristics Treatment response, substudy of Phase III RCT PET and EUS, pre- and post-neoadjuvant therapy, within 1 month of start and 1 month of end 20 patients (14 M); age range 21–69 years				
PET specification ECAT Exact 47; FDG 5 MBq/kg; attenuation correction Visual interpretation by two NMPs blinded to EUS and pathology results				
Reference tests/comparators Ref.: histopathology from resection Comp.: EUS restaging in 17 patients				
Results 13/20 responders PET results based on optimal SUV cut-off (36.1% decrease)				
	TP	FN	TN	FP
PET	13	0	6	1
EUS	4	8	4	1

Author, year, country, study period Calvo, 2004, ⁵⁴ Spain, 1997–1999		Article number EP 43		
Cancer/management decision T2–4 rectal cancer Response to neoadjuvant CRT (5-FU + RT)				
Design of study/patient characteristics Treatment response PET done before CRT and 4–5 weeks after CRT (just before surgery) 25 patients; 14 M; age NR Follow-up: median 39 months				
PET specification Posicam H7L-R scanner; FDG 5 MBq/kg; attenuation correction NR SUV calculated by one NMP				
Reference tests/comparators Ref.: histopathology from resection (and recurrence related to initial SUV)				
Results 14/21 tumours downstaged after CRT Mean SUV significantly lower in downstaged group 1.9 vs 3.3, $p = 0.03$ Initial SUV >6 ($n =$) 3-year survival 60% vs 93% for the remainder				

Author, year, country, study periodCapirci, 2004,⁵⁵ Italy, 2000–2003**Article number**

EP 45

Cancer/management decision/cancer work-up

Restaging after neoadjuvant CRT in patients with histologically proven adenocarcinoma in clinical stage II–III all to undergo surgery 8–9 weeks after end of CRT

CWU (4 weeks after end of CRT) = DRE, proctoscopy with multiple biopsies, endoscopic rectal US, CT or MRI pelvic scan

Design of study/patient characteristics

Diagnostic accuracy study

81 patients; gender and age NR

Follow-up: NR

PET specification

Siemens ECAT Exact 47; FDG 440 MBq

Visual interpretation by two independent NMPs, independent of other results

PET positive is intense, discrete or mild uptake, negative with faint, diffuse or absent uptake

Reference tests/comparators

Ref.: pathological exam of resected specimen

Comp.: CWU

Results

	Clinical CR	Clinical stage			Total (PET)
		I	II	III	
PET negative	10	27	7	7	51
PET positive	2	13	8	7	30
Total at CWU	12	40	15	14	81

	Pathological CR	Pathological stage				Total (PET)
		0	I	II	III	
PET negative	22	1	17	3	8	51
PET positive	6	1	8	7	8	30
Total at CWU	28	2	25	10	16	81

PET sens. 45%; PET spec. 79%; PPV = 77%; NPV = 43%

Hard to differentiate PET uptake at primary site from lymph-nodes mets

Note that 6/28 patients on PET FP might be caused by inflammatory actinic reaction

Low sensitivity may be due to small dimension of residual neoplastic mass and low metabolic activity of cancer cells after CRT

Author, year, country, study periodDenecke, 2005,⁵⁶ Germany, NR**Article number**

EP 1299

Cancer/management decision

Locally advanced rectal cancer

Response to neoadjuvant CRT

Design of study/patient characteristics

Treatment response, substudy of RCT

PET, CT and MRI pre- and post-neoadjuvant therapy. Scans within 1 month of start and 1 month of end. Resection done in all patients

23 patients; 16 M; mean age 53 ± 12 years, T3, 20, T4, 3**PET specification**

ECAT Exact 47; FDG 5 MBq/kg; attenuation correction

Two NMPs blind to other data, SUV for interpretation

Reference tests/comparators

Ref.: histopathology from resection

Comp.: CT and MRI (in subsets); one radiologist, assessment based on change in T score

Results

Note that 'optimal' SUV cut-off selected post-hoc; results reported based on this selection

13 responses, ten stable disease (path), Δ SUV of 36%

CT (done in 23): sens. 54% (6 FN), spec. 80% (2 FP)

PET (done in 23): sens. 100% (0 FN), spec. 67% (1 FP)

MRI (done in 10): sens. 71% (2 FN), spec. 60% (4 FP)

Author, year, country, study periodDimitrakopoulou-Strauss, 2003,⁵⁷ Germany, NR**Article number**

EP 478

Cancer/management decision

Metastatic colorectal cancer all patients previously treated with 5-FU + folinic acid

Treatment response to chemotherapy of 5-FU + folinic acid + oxaliplatin as second line therapy

Design of study/patient characteristics

Treatment response

28 patients with metastatic disease (55 sites, 50 liver, three lung, two local)

Three PET scans; 1–7 days before chemo, after one cycle, immediately before restaging (3 months after therapy end)

PET specificationECAT Exact HR+; FDG 300–370 MBq; dynamic scan for 60 minutes (23 frame, 100×1 min, 5×2 , 8×5)

Data analysis using PMod: visual analysis, SUV, FD model

DA used to predict categories of response

Reference tests/comparators

Ref.: clinical response 3 months post-therapy (PD, SD, PR)

Results

Visual analysis 'not helpful'

DA generally overpredicts PD and underpredicts PR

FD from both early PET scans give best overall accuracy (17/21 PD, 11/14 SD, 1/10 PR)

Comments

Further analysis: 2/7 PET +ve and stage I–II relapsed, 6/6 PET +ve stage III/IV

Author, year, country, study periodGuillem, 2000,⁵² USA, 1997–1998**Article number**

EP 911

Cancer/management decision

Primary rectal cancer given CRT (5040 Gy + 5-FU and leucovorin)
Assessment of response to CRT

Design of study/patient characteristics

Treatment response: PET and CT before and 5 weeks after treatment
Unselected series of 15 patients; patient characteristics not recorded

PET specification

GE Advance; 10–15 mCi; attenuation correction
Visual assessment by four NMPs, blinded to other data

SUV (max. in region and average over region)

Change in PET lesion size

 Δ TLG**Reference tests/comparators**

Ref.: pathological response after surgery graded by two pathologists independent of imaging tests

Comp.: CT (change in lesion size) + range of PET assessments

Results

	Response identified	Complete concordance with path	Overestimate	Underestimate
Visual	15/15	9	5	1
Δ TLG	15/15	6	4	5
SUV max.	15/15	5	3	7
SUV average	15/15	5	3	7
PET size	13/15	3/13	4/13	6/13
CT size	7/9	2/9	1/9	6/9

Author, year, country, study periodGuillem, 2004,⁵¹ USA, 1997–1998**Article number**

EP 132

Cancer/management decision

Rectal cancer: T3/T4 or N1 disease
Response assessment after CRT

Design of study/patient characteristics

Treatment response: PET pre- and post-CRT (~ 5 weeks post)
Series of 15 patients; patient characteristics NR
Follow-up: median 42 months

PET specification

GE Advance; 10–15 mCi; attenuation correction
Visual interpretation by four NMPs + Δ SUV

Reference tests/comparators

Ref.: pathology from resection and follow-up

Results

All patients had some response

 Δ SUV cut-off of 63.5 selects patients with improved DFS ($p = 0.08$)

DA, discriminant analysis; DRE, digital rectal examination; Δ , change; FD, fractal dimension; 5-FU, 5-Fluorouracil; TLG, total lesion glycolysis.

Colorectal cancer: RT planning**Primary study****Author, year, country, study period**Ciernik, 2005,⁵⁸ Switzerland, NR**Article number**

EP 69

Cancer/management decisionRectal cancer patients suitable for radical RT
RT planning**Design of study/patient characteristics**

RT planning

Development of automatic treatment volume method using PET data from PET/CT system

11 patients

PET/CT specification

Discovery LS; FDG 370 MBq; attenuation correction

Planning using Swiss software (PMOD) and the Pinnacle3 planning system

PET-based GTV estimated using region-growing algorithm based on 40% contour of PET signal (i.e. 40% of maximum)

Reference tests/comparators

Comparator: CT-based GTV

ResultsCorrelation between PET and CT volumes $r^2 = 0.84$

PET and CT volumes obtained quickly, and may be valuable for presurgery RT planning. However, further validation needed

Colorectal cancer: PET/CT – staging/restaging

Primary studies

Author, year, country, study period
Francis, 2003,⁶⁰ UK, NR
Article number

EP 502

Cancer/management decision/cancer work-up

Surgical or oncological outpatients with primary colorectal cancer, metastatic colorectal cancer or both

Staging/restaging

CWU = multislice CT

Design of study/patient characteristics

Prospective comparative SUV uptake study with diagnostic accuracy information

17 patients (50 lesions); 11 M, 6 F; mean age 70 years (range 50–87 years)

Follow-up: NR

PET/CT specification

GE Discovery LS PET/CT in 2D mode; FDG 332–401 MBq

Readers: NR

Reference tests/comparators

Ref.: histopathology (12 lesions), laparotomy (13 lesions), clinical and radiological follow-up (25 lesions)

Comp.: FLT-PET (dose 312–432 MBq)

Results

		Sens.			
		FDG	FLT	FDG	FLT
Primary tumour	TP:	6/6	6/6	100%	100%
Lung lesion	TP:	6/6	5/6	100%	92%
Peritoneal tumour	TP:	6/6	6/6		
	FP:	1 (fat necrosis)			
Liver mets	TP:	31/32	11/32		

For FDG the mets that was missed was small (1 cm)

No significant correlation between FDG and FLT uptake

Poor sens. of FLT in detecting CLM makes it a poor staging tool for colorectal cancer

Author, year, country, study periodSelzner, 2004,⁶¹ Switzerland, 2002–2003**Article number**

EP 321

Cancer/management decision/cancer work-up

Patients with CLM considered suitable for surgery

Staging/restaging

CWU: CECT of chest and abdomen, colonoscopy within 6 months of surgery

Design of study/patient characteristics

Patient management using documented treatment plan pre- and post-PET/CT plus diagnostic information

76 patients; 52 M, 24 F; median age 63 years (range 35–78 years)

PET/CT specification

GE Discovery LS PET/CT; FDG 370 MBq; attenuation correction

Visual interpretation by radiologist and NMP, blinded to other imaging

Reference tests/comparators

Ref.: histopathology and surgical findings with intraoperative US

Comp.: contrast-enhanced Siemens Somatom Volume Zoom CT

Results (calculated from other published summaries)*Liver mets (intrahepatic and extrahepatic)*

	TP	FN	TN	FP	Sens.	Spec.
PET/CT	60	6	9	1	91%	90%
CT	61	5	7	3	92%	70%

Local recurrence at primary colorectal site

	TP	FN	TN	FP	Sens.	Spec.
PET/CT	14	1	60	1	93%	98%
CT	8	7	60	1	53%	98%

In 16 patients (21%) PET/CT findings resulted in a change in treatment. In ten PET/CT found extrahepatic disease and so patients did not have resection. In six PET/CT found positive nodes in the hepatoduodenal ligament and the surgical strategy was changed to liver resection and removal of the periportal nodes

CECT, contrast-enhanced computed tomography.

Colorectal cancer: PET/CT – recurrence/restaging

Primary studies

Author, year, country, study period
Cohade, 2003,⁶² USA, 2001
Article number

EP 461

Cancer/management decision

Patients with history of colorectal cancer with suspected recurrence or for assessment of therapy response (plus one for staging of primary cancer)

Restaging

Design of study/patient characteristics

Retrospective diagnostic accuracy study

45 patients (36 with reference standard data); 28 M, 17 F; mean age 61 years (range 36–83 years)

Follow-up: 25 patients had at least 6 months follow-up

PET/CT specification

GE Discovery LS PET/CT; FDG 555–740 MBq; attenuation correction

Did not include patients with blood glucose levels > 11.1 mmol/l

Reference tests/comparators

Ref.: histopathology, clinical and radiological follow-up in 36 patients

Comp.: FDG-PET

Results
Lesion analysis ($n = 122$)

	Sens. (95% CI)	Spec. (95% CI)
PET	88% (80 to 93%)	56% (34 to 75%)
PET/CT	86% (77 to 91%)	67% (44 to 84%)

Patient analysis ($n = 36$)

Primary or local recurrence:

PET and PET/CT correctly assessed all patients

In other sites:

PET was incorrect in eight patients (4 FN, 4 FP), PET/CT was only incorrect in three of these (1 FN, 2 FP)

PET/CT also had another one FP (due to peritoneal implants) where PET was correct

Comments

Retrospective, ref. standard not clear on all patients, so subset analysed

High FDG dose

Author, year, country, study periodEven-Sapir, 2004,⁶³ Israel, NR**Article number**

EP 98

Cancer/management decision

Patients who have undergone surgical removal of rectal cancer with suspected recurrence

Detection of recurrence

Reasons for referral = elevated CEA, suspected pelvic recurrence on CT or colonoscopy, identification of presumably resectable mets, therapy response, suspected secondary primary, anal pain

Design of study/patient characteristics

Retrospective diagnostic accuracy study

62 patients (45 anterior resection, 17 abdominoperineal resection; three with CRT before surgery, 16 CRT and three RT after surgery)

37 M, 25 F; mean age 62 years

Referral period after surgery: mean 32 months (range 6–81 months)

Follow-up: mean 8 months (clinical follow-up and final diagnosis of scintigraphic lesions by two physicians independent of image interpretation; histopathology; imaging by CT, MRI, US, PET/CT)

PET/CT specification

GE Discovery LS PET/CT; iodinated oral contrast for last 42 patients; FDG 666 MBq

Scans permitted in patients with diabetes with blood glucose levels ≤ 8.3 mmol/l

Visual interpretation; scans read by two experienced PET/CT readers

Reference tests/comparators

Ref.: imaging or clinical follow-up, histopathology, treatment response after successful therapy

Comp.: PET image from the PET/CT machine (without the CT image) evaluated at least 1 week apart from combined image, in different order; CT performed within prior 6 weeks

Results

19 patients had no disease, 19 extrapelvic mets only, 16 pelvic recurrence only, eight pelvic recurrence and extrapelvic mets

Pelvic recurrence

	Sens.	Spec.	PPV	NPV
PET	88% (21/24)	74% (28/38)	68%	90%
PET/CT	96% (23/24)	89% (34/38)	85%	97%

PET/CT significantly more sensitive and specific (χ^2) than PET*Presacral region*

30 patients had abnormal findings on low-dose CT

Of these 30, PET/CT TP = 7, TN = 22, FP = 1, sens. = 100%, spec. = 96%

PET/CT findings 'of clinical relevance' in 29 (47%) patients

In 16 patients with rising CEA, PET/CT detected tumours in 13 patients (nine chemo, four surgery)

In 22 patients with suspicious CT or colonoscopy, PET/CT positive in 13 (eight surgery)

PET/CT true negative in nine

PET/CT depicted pelvic recurrence in 23/24 patients; 12 of the 23 were referred for surgery (plus the one FN)

Comments

Retrospective study

Author, year, country, study periodKim, 2005,⁶⁴ USA, 2002–2003**Article number**

EP 193

Cancer/management decision/cancer work-up

Patients with suspected or biopsy-proven recurrent colorectal cancer

Restaging

CWU = biopsy or other imaging tests, tumour markers or clinical symptoms

Design of study/patient characteristics

Retrospective study of diagnostic accuracy

51 patients ($n = 34$ with CT within 4 weeks of PET/CT)

30 M, 21 F; mean age 65 years

Follow-up: at least 6 months

PET/CT specification

CTI Reveal RT PET/CT; FDG 7.77 MBq/kg; attenuation correction

Digital fusion using Miranda Solutions software

Images interpreted by three NMPs blinded to clinical data, each took one-third of patients and did not look at different images of the same patient

Reference tests/comparators

Ref.: histopathology and clinical–radiological follow-up

Comp.: PET and fused PET/CT

Results

AUC for ROC

PET = 0.82 PET/CT = 0.95 ($p = 0.01$)*By-lesion analysis: 143 regions*

	Sens. (95% CI)	Spec. (95% CI)
PET/CT	89% (73 to 97%)	98% (93 to 99%)
PET	74% (57 to 88%)	93% (86 to 97%)

Staging accuracy (95% CI)

	Correct	Upstaging	Understaging
PET/CT	88% (76 to 96%)	4% (0.5 to 13%)	8% (2 to 19%)
PET	71% (56 to 83%)	14% (6 to 26%)	16% (7 to 29%)

Software fusion failed (distance between PET and CT landmarks >2 cm) in 8/34 (24%) patients, so $n = 26$, with 67 regions

	Sens. (95% CI)	Spec. (95% CI)
PET/CT	93% (66 to 99%)	98% (88 to 99%)
PET/CT fusion	93% (66 to 99%)	96% (87 to 99%)

Figures for PET/CT would be reduced if those who had failed fused images were included as failures, resulting in accuracy of 45%

Comments

Retrospective study

AUC, area under the curve.

Head and neck cancer

Head and neck cancer: diagnosis

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions																											
<i>Diagnosis in addition to other imaging</i>	Vermeersch, 2003 ⁶⁵	Four hierarchy 2 comparative studies with CT/MRI	Routine diagnosis is generally made with physical exam, CT/MRI and/or US, and endoscopy with biopsies																											
Primary head and neck cancer: SCC of upper aerodigestive tract, including oral cavity, nasopharynx, oropharynx, hypopharynx and larynx	(1989 to February 2003)	Study sizes not reported	Morphological imaging such as CT/MRI is irreplaceable to determine the extension of the tumour in adjacent structure, but may lack specificity																											
Reference standards: NR		<table border="1"> <thead> <tr> <th></th> <th>Sens.</th> <th>Spec.</th> </tr> </thead> <tbody> <tr> <td>1. PET</td> <td>87%</td> <td>80%</td> </tr> <tr> <td>CT/MRI</td> <td>88%</td> <td>50%</td> </tr> <tr> <td>2. PET</td> <td>87%</td> <td>67%</td> </tr> <tr> <td>CT/MRI</td> <td>67%</td> <td>44%</td> </tr> <tr> <td>3. PET</td> <td>95%</td> <td>92%</td> </tr> <tr> <td>CT/MRI</td> <td>68%</td> <td>69%</td> </tr> <tr> <td>4. PET</td> <td>85%</td> <td>100%</td> </tr> <tr> <td>CT/MRI</td> <td>88%</td> <td>75%</td> </tr> </tbody> </table>		Sens.	Spec.	1. PET	87%	80%	CT/MRI	88%	50%	2. PET	87%	67%	CT/MRI	67%	44%	3. PET	95%	92%	CT/MRI	68%	69%	4. PET	85%	100%	CT/MRI	88%	75%	'Where doubt exists' PET may be used to improve specificity of CT/MRI
	Sens.	Spec.																												
1. PET	87%	80%																												
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CT/MRI	68%	69%																												
4. PET	85%	100%																												
CT/MRI	88%	75%																												
		PET spec. higher than CT/MRI spec. ($p = 0.06$)																												

Additional primary study

Author, year, country, study period Khan, 2004, ⁶⁶ Japan, 2000–2003	Article number EP 192			
Cancer/management decision Head and neck cancer patients with uncertain clinical evaluation (involving other imaging) Primary diagnosis; patients referred for definitive diagnosis				
Design of study/patient characteristics Diagnostic accuracy study 45 patients; 28 M; mean age 61 years (range 29–84 years)				
PET specification Shimadzu SET 2400; FDG 370 MBq; attenuation correction Visual interpretation of PET by two NMPs				
Reference tests/comparators Ref.: neck dissection or biopsy of suspicious areas (30 dissections)				
Results 25/45 malignant lesions Patient-based analysis				
	FN	TP	TN	FP
PET	2	23	13	7

Head and neck cancer: detection of synchronous primaries

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
Staging and identification of synchronous primaries	Vermeersch, 2003 ⁶⁵	Four hierarchy 2 studies reported in narrative	Results by lesion and patient
SCC of upper aerodigestive tract, including oral cavity, nasopharynx, oropharynx, hypopharynx and larynx	(1989 to February 2003)	1. (<i>n</i> = 59) PET superior 'accuracy' to bronchoscopy for detection of synchronous lung lesions (80% vs 50%)	1. Unclear whether this referred to diagnostic accuracy or sensitivity
Detecting distant metastases and synchronous primaries in patients diagnosed with primary squamous cell head and neck cancer		2. (<i>n</i> = 45) 2 TP, 4 FP in chest	2. No pathological data
Reference standard: histopathology, clinical or radiographic follow-up		3. (<i>n</i> = 28) TP=9/10, TN=17/18	
		4. (<i>n</i> = 12) PET detected mediastinal disease in two patients, not otherwise detected	

Additional primary study

Author, year, country, study period Nishiyama, 2005, ⁶⁷ Japan, 2002–2003	Article number EP 262
Cancer/management decision Newly diagnosed head and neck cancer given clinical exam (endoscopy, CT, CXR, neck/abdomen US) Detection of synchronous primary tumour	
Design of study/patient characteristics Diagnostic accuracy study 53 patients	
PET specification Exact HR+; FDG 3 MBq/kg; attenuation correction Visual interpretation by two NMPs	
Reference tests/comparators Ref.. pathology after biopsy or 6-month follow-up	
Results Ten patients with distant sites of FDG uptake 5/10 second primary (two gastric, one rectal, one pancreas, one thyroid) One prostate missed Routine methods found 2/6 Five others; two TPs for distant mets	

Head and neck cancer: diagnosis of occult primary tumour

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
<p>Diagnosis of occult primary tumour following detection of metastases to cervical lymph nodes</p> <p>and</p> <p>A. Primary tumour not identified by clinical examination/imaging</p> <p>or</p> <p>B. Result of other imaging modalities not necessarily negative</p> <p>Reference standard: histopathology</p>	<p>BCBS, 2000⁶⁸</p> <p>(Up to May 2000)</p> <p>One study here not included in MSAC,⁶⁹ study here updated in MSAC⁶⁹</p>	<p>Eight hierarchy 2 studies ($n = 10-29$/study, total $n = 138$)</p> <p>PET overall accuracy TP = 32% (range 13-56%) FP range = 0-40% Sens. = 69% (range 44-100%) Spec. = 69% (range 20-100%)</p> <p>A. Four studies, Pooled TP=28%</p> <p>B. Four studies, Pooled TP PET=36%</p> <p>Study TPs: 1. ($n = 15$) PET = 47%, CT/MRI = 33% 2. ($n = 13$) PET = 31%, endosc. = 8% 3. ($n = 10$) PET = 50%, CT = 0% 4. ($n = 20$) PET = 35%, MRI = 36%, CT = 22%</p>	<p>Small studies with a variety of comparators</p> <p>No pooled analysis of sens.</p> <p>Primary tumour identified in one in four patients where tumour was not detected by other means</p> <p>Benefit over MRI unclear</p>
<p>Diagnosis of occult primary tumour following detection of metastases to cervical LNs of:</p> <p>1. Occult SCC primary tumour</p> <p>or</p> <p>2. Occult SCC or other histopathology (mixed study populations)</p> <p>Reference standards: PET-directed biopsies plus clinical follow-up</p>	<p>MSAC, Australia, 2001 [Part 2(ii)]⁶⁹</p> <p>(Up to March 2001)</p>	<p>Overall, eight hierarchy 2 studies ($n = 166$)</p> <p>1. Five studies, TP = 27%</p> <p>2. Three studies, TP = 33%</p> <p>Approx. two-thirds of primaries in head and neck, one-third in breast, two with mixed pathology identified primary breast primary tumour</p> <p>Overall, four studies reported hierarchy 4 evidence PET assisted detection of primary tumours in 26/90 patients, which led to changes in planned management in 19 patients</p> <p>Overall, three studies included some information about survival (hierarchy 5)</p>	<p>Similar results for SCC vs mixed mets</p> <p>Max. n for survival evaluation in a study was 29 and information did not always include patients with PET-identified primary tumours, so insufficient data to draw any conclusions</p>
endosc., endoscopy.			

Additional primary studies

Author, year, country, study period Miller, 2005, ⁷⁰ USA, NR	Article number EP 1911
Cancer/management decision Patients with biopsy results from cervical lymph nodes showing SCC and no visible primary site on nasopharyngoscopy, laryngoscopy, CT or MRI Detection of occult primary head and neck cancer	
Design of study/patient characteristics Diagnostic accuracy study <i>n</i> = 26	
PET specification PET device not stated; FDG 14.7 mCi Visual interpretation No further details given	
Reference tests/comparators Ref.: panendoscopy and biopsy of tongue base, nasopharynx, tonsils and any sites suspicious on PET	
Results Eight primaries detected by PET One PET FP Four PET FNs (foci 0.8 mm, 1, 2 and 5 mm)	

Author, year, country, study period Stoekli, 2003, ⁷¹ Switzerland, 1999–2001	Article number EP 725
Cancer/management decision Patients with cervical LN mets from unknown primary tumour Detection of occult primary SCC in head and neck	
Design of study/patient characteristics Diagnostic accuracy study 18 consecutive patients; 15 M; age range 38–86 years Stage: N1, 8; N2b, 8; N2c, 1; N3, 1	
PET and PET/CT specification GE Advance (<i>n</i> = 10) or GE Discovery LS (<i>n</i> = 8); FDG 300–400 MBq; attenuation correction Visual interpretation by two NMPs	
Reference tests/comparators Ref.: panendoscopy (oral cavity, oropharynx, nasopharynx, oesophagus, larynx)	
Results 8/18 tumours found by panendoscopy 5/8 PET positive 9/10 PET negative	

Head and neck cancer: staging lymph nodes

Systematic reviews

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions																		
Staging SCC and AC, sites not specified Regional lymph-node involvement in patients with cytologically or histologically proven primary head and neck cancer Reference standard: histopathology	Goerres, 2003 ⁷² (Up to October 2001) Includes three studies not included by Vermeersch ⁶⁵	11 hierarchy 3 studies (<i>n</i> = 8–106 patients/study) Positive and negative log likelihoods calculated as weighted means and reported by patient and by lymph node, with 95% CIs By lymph node (<i>n</i> = 3294): LR+ 17.3 (10.9 to 27.3) LR– 0.19 (0.13 to 0.27) By patient (<i>n</i> = 369): LR+ 3.9 (2.6 to 5.9) LR– 0.24 (0.14 to 0.41) PET sens. = 81%, spec. = 79%	Few details given of the included studies No comparative data presented Some small studies, but with large numbers of lymph nodes/patients; analysis by patient more reliable in methodological terms Pretest probabilities from register of 98 Swiss patients, combined with LR to give post-test probabilities																		
Staging SCC of upper aerodigestive tract, including oral cavity, nasopharynx, oropharynx, hypopharynx and larynx Regional lymph-node involvement in primary squamous cell head and neck cancer Reference standard: NR	Vermeersch, 2003 ⁶⁵ (1989 to February 2003) Includes nine studies not included by Goerres ⁷²	17 hierarchy 2 comparative studies using CT or MRI Study sizes not reported sROC curve, but no estimates reported sens. ≥80% and spec. ≥90% in six PET vs one CT/MRI study PET significantly higher sens. (<i>p</i> = 0.01) and higher spec. (<i>p</i> = 0.01) than CT/MRI	Little standardisation across studies of CT/MRI-positive definition, patient population or reference standard Results by lesion and patient not differentiated As the studies used disparate populations, authors restricted analysis to a pairwise comparison of PET with CT/MRI. Analysis by each comparator would have been preferable																		
Staging Diverse malignancies (mainly SCC), including lip and oral cavity, nasopharynx, oropharynx, hypopharynx, larynx and salivary glands Regional lymph-node mets following confirmed primary head and neck cancer, to determine whether to perform neck dissection or irradiation Reference standard: NR	BCBS, USA, 2000 ⁶⁸ (Up to May 2000)	17 hierarchy 2 studies based on neck sides, lesions or patients (eight studies, <i>n</i> = 239) Comparative pooled (by patient) results: (Four studies, <i>n</i> = 123) <table border="1" style="margin-left: auto; margin-right: auto;"><thead><tr><th></th><th>Sens.</th><th>Spec.</th></tr></thead><tbody><tr><td>PET</td><td>81%</td><td>97%</td></tr><tr><td>CT</td><td>72%</td><td>89%</td></tr></tbody></table> (Three studies, <i>n</i> = 106) <table border="1" style="margin-left: auto; margin-right: auto;"><thead><tr><th></th><th>Sens.</th><th>Spec.</th></tr></thead><tbody><tr><td>PET</td><td>91%</td><td>88%</td></tr><tr><td>MRI</td><td>82%</td><td>83%</td></tr></tbody></table>		Sens.	Spec.	PET	81%	97%	CT	72%	89%		Sens.	Spec.	PET	91%	88%	MRI	82%	83%	sROC analysis not performed
	Sens.	Spec.																			
PET	81%	97%																			
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	Sens.	Spec.																			
PET	91%	88%																			
MRI	82%	83%																			
		One small study evaluated value of PET in addition to other imaging Correct stage classifications: CT = 9/13, CT+PET = 12/13, 13 MRI = 2/5, MRI+PET = 5/5 patients																			

Additional primary studies: clinical N0

Author, year, country, study period Brouwer, 2004, ⁷³ Netherlands, 2001–2002	Article number EP 39			
Cancer/management decision Patients with proven head and neck tumour and no clinical evidence of neck region disease Staging to detect metastatic disease				
Design of study/patient characteristics Diagnostic accuracy study 15 patients				
PET specification ECAT Exact HR+; FDG 370–490 MBq; no attenuation correction Visual interpretation of PET by one NMP, blinded PET in all 3 weeks before radical surgery including neck dissection				
Reference tests/comparators Ref.: neck dissection followed by histopathology Comp.: CT (7), MRI (7), US-guided FNAB (11)				
Results				
	TP	FN	FP	TN
CT	0	3	0	4
MRI	2	0	0	5
US FNAB	2	0	0	9
PET	2	1	1	11
Comments Comments that small nodes (<6 mm) are problematic for PET, and that occult nodes are ~1–2 mm				

Author, year, country, study period Civantos, 2003, ⁷⁴ USA, 1997–2002	Article number EP 2166			
Cancer/management decision Patients with untreated oral SCC <6 cm diameter, no clinically suspicious nodes Staging with PET and SLNB				
Design of study/patient characteristics Diagnostic accuracy study: PET then SLNB and surgery 18 patients; 16 M; mean age 62 years (range 34–79 years)				
PET specification Not specified Visual interpretation				
Reference tests/comparators Ref.: neck dissection followed by histopathology (all necks dissected)				
Results <i>Patient based</i>				
	FN	TP	TN	FP
PET	8	3	7	0
SLNB	1	10	7	0

Author, year, country, study periodHyde, 2003,⁷⁵ UK, 1998–2002**Article number**

EP 560

Cancer/management decision

Patients with biopsy-proven head and neck cancer who have a clinically N0 neck
Staging

Design of study/patient characteristics

Diagnostic accuracy study
19 patients: 16 given MRI, three CT
10 M; mean age 62 years (range 44–80 years)

PET specification

GE Advance; mean FDG dose 340 MBq (range 237–370 MBq); attenuation correction
Visual interpretation
PET within 2 weeks before surgery (neck dissection)

Reference tests/comparators

Ref.: neck dissection then pathology
Comp.: SLNB

Results

Four TP
SLNB detected three, no FPs
PET detected none, two FPs

Comments

Comment: “PET may be less useful”

Author, year, country, study periodStoekli, 2002,⁷⁶ Switzerland, NR**Article number**

EP 1117

Cancer/management decision

Clinical N0 oral and oropharyngeal SCC patients scheduled for surgery
Staging

Design of study/patient characteristics

Diagnostic accuracy study
PET done at least 24 hours before surgery
12 consecutive patients; 10 M; age range 39–81 years
Stage: T2, 10; T1, 2

PET specification

GE Advance; FDG 300–400 MBq; attenuation correction
Visual interpretation by two NMPs

Reference tests/comparators

Ref.: neck dissection
Comp.: SLNB

Results

5/12 occult LN mets
All found on SLNB and no FPs
PET 2/5 found, one FP

Additional primary studies: stages T1–T3**Author, year, country, study period**Kovacs, 2004,⁷⁷ Germany, 2000–2003**Article number**

EP 201

Cancer/management decision

Patients with untreated T1–T3 oral or oropharyngeal SCC
Staging with SLNB

Design of study/patient characteristics

Diagnostic accuracy study

PET and CT, then one cycle high-dose selective chemo of primary region, then after 3–4 weeks SLNB and surgery
Others SLNB, then dissection of positive cases

62 patients; 36 M; mean age 62 years (range 44–77 years)
Stage: T1, 15; T2, 35; T3, 12

PET specification

ECAT Exact 47; FDG 370 MBq; attenuation correction
Visual interpretation of PET

Reference tests/comparators

Ref.: neck dissection followed by histopathology or follow-up of negative cases
(all PET +ve necks dissected)

Results*Patient-based analysis*

	FN	TP	TN	FP
CT	2	15	34	10
PET	5	13	36	8

35 neck sides detected based on PET/SLNB. CT would have produced 45
SLNB needed because of micrometastases

Author, year, country, study periodSchmid, 2003,⁷⁸ Switzerland, 2000–2002**Article number**

EP 699

Cancer/management decision/cancer work-up

Newly diagnosed locally advanced head and neck SCC (N2+ or T3)
Staging

CWU: biopsy, endoscopy, CXR, CT (skull base to clavicles) then RT

Design of study/patient characteristics

Diagnostic accuracy study

PET within 2 weeks before RT

48 patients; 42 M; mean age 61 years (range 35–85 years)

PET or PET/CT specification

GE Advance or Discovery LS, FDG 350–430 MBq; attenuation correction
Visual interpretation of PET by two NMPs, aware of other data

Reference tests/comparators

Ref.: distant findings confirmed by biopsy, locoregional findings used to extend RT field planned from CWU

Results*Lymph-node mets:*

41/48 concordant with CWU

Of the seven discordant LN scans, five PET scans were correct

PET identified three additional LN mets and four fewer LN mets (2 FNs, too close primary)

Other positives on PET:

PET suggested distant mets in four patients (2 FP)

PET suggested second primary in two patients (1 FP)

Additional primary studies: other/unspecified stages

Author, year, country, study period Bruschini, 2003, ⁷⁹ Italy, NR	Article number EP 2144
Cancer/management decision Head and neck cancer Staging	
Design of study/patient characteristics Diagnostic accuracy study 22 patients; 19 M; mean age 63 ± 9 years	
PET specification ECAT Exact HR+; FDG 370 MBq; attenuation correction Visual interpretation of PET	
Reference tests/comparators Ref.: neck dissection followed by histopathology Comp.: CT	
Results PET correct in 17/21 primary sites CT correct in 15/21 PET sens. 14/15, spec. 7/7 CT sens. 11/15, spec. 4/7 Smallest PET +ve node 0.9 cm	

Author, year, country, study period Dammann, 2005, ⁸⁰ Germany, NR	Article number EP 77			
Cancer/management decision Head and neck cancer Staging				
Design of study/patient characteristics Diagnostic accuracy study PET, CT and MRI within 5 days of each other, then surgery (radical + neck dissection) within 2 weeks 64 patients; 43 M; mean age 56 years (range 26–83 years)				
PET specification GE Advance; FDG 300–400 MBq; attenuation correction Visual interpretation of PET by two NMPs, blinded				
Reference tests/comparators Ref.: neck dissection followed by histopathology Comp.: CT and MRI each read by two radiologists				
Results Results given for 67 suspected primary sites and 293 nodal regions				
<i>Primary</i>				
	TP	FN	TN	FP
CT	36	21	8	0
MRI	54	5	5	3
PET	51	8	5	3
<i>Nodal</i>				
	TP	FN	TN	FP
CT	32	8	236	17
MRI	37	3	239	14
PET	34	6	241	12

Author, year, country, study periodNg, 2005,⁸¹ Taiwan, NR**Article number**

EP 1507

Cancer/management decision/cancer work-up

Newly diagnosed SCC of the oral cavity scheduled for neck dissection

Staging: nodal mets

CWU: PET and CT or MRI < 1 week apart, ~2 weeks presurgery

Design of study/patient characteristics

Diagnostic accuracy study

124 consecutive patients; 121 M, 3 F; mean age 51 years (range 26–82 years)

Diabetes excluded (fasting glucose > 200 ng/ml)

Stage: T1, 16; T2, 56; T3, 19; T4, 33

PET specification

ECAT Exact HR+, FDG 370 MBq; attenuation correction

Visual interpretation of PET by three NMPs (blinded)

Reference tests/comparators

Ref.: histopathology

Comp.: 82 MRI, 42 CT, visual interpretation by two radiologists (blinded)

Results*Primary tumour:*

PET detected 122/124 primary sites (missed one small primary and mislocated one)

CT or MRI detected 108/124 primaries

Nodal disease

	FN	TP	TN	FP
CT/MRI	45	50	376	22
PET	24	71	370	28
PET+CT/MRI	21	74	376	22

PET FN: mean nodal size 4.3 mm

PET TP: mean nodal size 9 mm

Author, year, country, study periodSchwartz, 2003,⁸² USA, 2000–2002**Article number**

EP 704

Cancer/management decision

Stage II–IV SCC of oral cavity

Staging

CWU: head and neck CT, CXR and LFTs (chest/abdomen CT done only to examine abnormalities found on PET)

Design of study/patient characteristics

Diagnostic accuracy study

33 patients; all male; mean age 60 years (range 47–79 years)

PET specification

GE Advance; FDG 260–370 MBq

Visual assessment by one NMP

Reference tests/comparators

Ref.: neck dissection in 13 cases, otherwise confirmation attempted for positive findings by biopsy, no confirmation of negative findings

Results*Neck dissections*

6/6 positive hemi-necks identified by PET, 9/10 negative ones correctly identified

Distant disease

7/33 had distant disease discovered by PET; two of these were understaged by other methods. One FP for distant disease by PET

LFT, liver function test.

Author, year, country, study periodSchwartz, 2005,⁸³ USA, 2000–2003**Article number**

EP 319

Cancer/management decision

Head and neck cancer patients referred for RT
Staging

Design of study/patient characteristics

Diagnostic accuracy study of PET+CT
20 patients had neck dissection after PET scan and before RT
CT and PET done at same facility and software fused (not rigidly aligned)
Mean age 61 years (range 42–78 years)

PET specification

GE Advance; FDG 259–370 MBq
CT and PET software fused
Result read by two NMPs

Reference tests/comparators

Ref.: pathology after neck dissection
Comp.: CT read by two radiologists

Results

Results for 96 nodal levels

Primary

	TP	FN	TN	FP
CT	21	6	68	1
PET+CT	26	1	68	1

Estimated GTV similar for both methods

Author, year, country, study periodYen, 2005,⁸⁴ Taiwan, 2002–2004**Article number**

EP 387

Cancer/management decision/cancer work-up

Buccal mucosa SCC
Staging
CWU: endoscopy, CXR, liver US, WB bone scan. All received CT and MRI

Design of study/patient characteristics

Diagnostic accuracy study
CWU ± PET (division based on willingness to pay)
51 assessed in each group, well balanced on age, gender, stage and primary treatment

PET specification

ECAT Exact HR+; FDG 370 MBq; attenuation correction
Visual interpretation of PET by three NMPs, blinded

Reference tests/comparators

Ref.: neck dissection followed by histopathology
Comp.: CT/MRI

Results

These results for the CWU+PET group only; accuracy figures not presented for CWU alone

	FN	TP	TN	FP
CT/MRI, LN	15	25	254	12
PET, LN	6	34	259	7
CT/MRI, all lesions	15	76	254	12
PET, all lesions	6	84	259	7

PET FNs in small (2–6 mm) nodes

One fewer 'futile' operations in the CWU+PET group, but no difference in locoregional recurrence

Comments

"Although PET is superior to CT/MRI in identifying cervical nodal metastases, it does not improve locoregional recurrence"

Head and neck cancer: restaging/recurrence

Systematic reviews

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
<p><i>Restaging/recurrence</i></p> <p>SCC of upper aerodigestive tract, including oral cavity, nasopharynx, oropharynx, hypopharynx and larynx</p> <p>Staging regional LN involvement in residual or recurrent squamous cell head and neck cancer</p> <p>Reference standard: NR</p>	<p>Vermeersch, 2003⁶⁵</p> <p>(1989 to February 2003)</p> <p>Includes nine studies not in Goerres⁷²</p>	<p>15 hierarchy 2 comparative studies of PET and CT/MRI</p> <p>Study sizes not reported</p> <p>sROC curve, but no estimates reported</p> <p>Sens. $\geq 80\%$, spec. $\geq 90\%$ in six PET and one CT/MRI study</p> <p>PET significantly higher sens. ($p = 0.01$) and spec. ($p = 0.02$) than CT/MRI</p>	<p>Little standardisation across studies of CT/MRI positive definition, patient group or reference standard</p> <p>Results by lesion and patient</p> <p>Separate analyses of CT and MRI comparators would have been preferable, but combined sensitivity of comparators appears lower than PET</p>
<p><i>Progression</i></p> <p>SCC and AC, sites not specified</p> <p>Restaging regional LN involvement in patients with recurrent head and neck cancer, investigation at follow-up visit (≥ 1 month after end of treatment)</p> <p>Reference standard: histopathology</p>	<p>Goerres, 2003⁷²</p> <p>(Up to October 2001)</p> <p>Includes three studies not in Vermeersch⁶⁵</p>	<p>Ten hierarchy 3 studies ($n = 13-50$/study, total $n = 350$)</p> <p>Positive and negative log-likelihoods calculated as weighted means and reported by patient</p> <p>By patient: LR+ 4.0 (2.8 to 5.6) LR- 0.16 (0.10 to 0.25)</p> <p>PET sens. = 88%, spec. = 78%</p>	<p>No comparative data presented</p> <p>Few details given of the included studies</p> <p>Generally small studies</p>
<p><i>Restaging/recurrence</i></p> <p>Predominantly SCC of the upper aerodigestive tract</p> <p>Assessment of residual or recurrent head and neck cancer</p> <p>Reference standards: clinical follow-up, sometimes with histopathology of lesions obtained by biopsy or surgery</p>	<p>MSAC, Australia, 2001 [Part 2 (ii)]⁶⁹</p> <p>(Up to March 2001)</p>	<p>15 hierarchy 2 comparative studies vs CT/MRI analysed by patient ($n = 10-66$/study)</p> <p>Sens. $\geq 85\%$ for PET in 14/15 studies, CT/MRI in 4/15</p> <p>Spec. $\geq 80\%$ for PET in 10/15 studies, CT/MRI in 6/15 studies</p> <p>Eight studies with hierarchy 4 evidence</p> <p>In one study PET correctly predicted need for panendoscopy in 30/38 patients vs 19/38 for CT+MRI</p> <p>Three other notable studies:</p> <ol style="list-style-type: none"> 1. PET correctly indicated need for biopsy in 16/17 patients vs 11/17 for CT/MRI. PET correctly avoided biopsy in 14/21 cases 2. Distant mets identified by PET in 7/22 patients and treatment changed from surgery to palliation 3. 26/66 patients had management changed following PET, 23 of these cases found to be correct 	<p>Most studies assessed detection in patients who had undergone radiation</p> <p>PET had higher sens. than comparators and similar or higher spec.</p> <p>In some cases PET accuracy was slightly better for local disease compared with nodal disease</p> <p>Several of these were small studies with incomplete details of how management was changed</p>

Primary study**Author, year, country, study period**Dresel, 2001,⁸⁵ Germany, NR**Article number**

FP 55

Cancer/management decision

Suspected primary or recurrent head and neck cancer

Diagnosis/staging or recurrence

Design of study/patient characteristics

Diagnostic study

 $n = 54$; 30 M, 24 F; age range 32–67 years

Follow-up: period NR

PET specification

Siemens ECAT Exact HR+; FDG 185–350 MBq; attenuation correction NR

Visual interpretation of PET by two NMPs, aware of other data

Visual interpretation by two experienced examiners, blinded

Reference tests/comparators

Ref.: histology or follow-up

Comp.: Somatom Plus 4 CT (and hybrid PET, but not reported here)

Results

Of the 54 patients, 48 had tumours (32 primary, 16 recurrent)

Primary tumour

	TP	FN	TN	FP	Sens.	Spec.
PET	47	1	0	0	98%	–
CT	25	23	0	0	52%	–

LN mets

	TP	FN	TN	FP	Sens.	Spec.
PET	17	1	35	1	94%	97%
CT	15	3	18	18	83%	50%

PET identified 11 patients with distant mets in lung, bone and liver. Those in lung and liver led to upstaging; those in bone needed to be confirmed by bone scintigraphy, which identified more lesions

PET identified secondary tumours in four patients (three in head and neck region)

Additional primary studies**Author, year, country, study period**Conessa, 2004,⁸⁶ France, 1999–2002**Article number**

EP 72

Cancer/management decisionPatients who have received RT (66–70 Gy 5-MV photons) after chemo or surgery for head and neck cancer
Restaging**Design of study/patient characteristics**

Diagnostic accuracy study

PET 3–6 months postsurgery

42 unselected patients; 37 M; mean age 60 years (range 43–78 years)

20 oropharynx, ten larynx, ten hypopharynx, five oral cavity

Follow-up: median 17 months

PET specification

C-PET (Phillips); 4–7 mCi; attenuation correction

Visual interpretation of PET by one reader

Reference tests/comparators

Positive PET, biopsy; negative PET, follow-up

Results

	TP	FN	TN	FP
PET	6	0	29	7

CT and MRI gave no further useful information

Author, year, country, study periodKubota, 2004,⁸⁷ Japan, NR**Article number**

EP 203

Cancer/management decision

Suspected recurrent head and neck cancer who have received CRT

Detection of recurrence

Design of study/patient characteristics

Diagnostic accuracy study

Median interval from end of therapy to PET 4 months (range 1–60 months)

MRI or CT done at same time

37 patients, one excluded because of high plasma glucose

No further details of patient characteristics

Follow-up: > 1 year for PET negatives

PET specification

Shimadzu SET 2400 W; FDG 370 MBq; attenuation correction

Visual interpretation with knowledge of clinical data, not of other imaging

Reference tests/comparators

Ref.: biopsy for positive sites, follow-up for negatives

Results

	TP	FN	TN	FP
PET	14	2	21	6
MRI/CT	12	4	8	19

Author, year, country, study periodKunkel, 2003,⁸⁸ Germany/USA, 1997–2002**Article number**

EP 609

Cancer/management decision

Patients who have undergone radical surgery or surgery + RT for primary recurrent head and neck cancer
 Recurrence suspected 6–9 months postresection (min. 4 months post-RT completion)

Design of study/patient characteristics

Diagnostic accuracy study

97 patients; mean age 55 years (range 29–81 years)

Follow-up to recurrence, death or ≥ 6 months post-PET scan (35-month median follow-up)**PET specification**

ECAT Exact 952; FDG 370 MBq; attenuation correction

Visual reading by two NMPs (using all available clinical data) + SUV calculation

SUV ≤ 4 used as predictor for successful resection**Reference tests/comparators**

Evidence of progression during follow-up

Results

78 sites of progression seen during follow-up (in 49/97 patients)

PET identified 65/78

Smallest lesion detected 1 cm

Performance table (denominators not given)

	Sens.	Spec.	Prev.	PPV	NPV
Local	0.87	0.67	0.32	0.55	0.92
LN mets	0.87	0.99	0.15	0.96	0.98
Distant mets	0.71	0.93	0.18	0.67	0.94

3-year survival rates: 86% PET negative, 44% PET positive

Still predictive after control for stage, age, RT and prior tumour history ($p < 0.001$)**Comments**

No clear evidence that patient management was actual change in any patient, but the authors claim that PET result will be important in determining patient management. For example, PET-negative patients could be offered early reconstructive therapy

Author, year, country, study periodYao, 2004,⁸⁹ USA, 2000–2002**Article number**

EP 381

Cancer/management decisionPatients with head and neck SCC who have received definitive RT \pm chemo

Restaging: prediction of need for neck dissection

Design of study/patient characteristics

Diagnostic accuracy study

PET and CT done 2.5–6 months post-treatment

41 patients; 12 had persistent lymphadenopathy, study focuses on these patients

All 12 M; age range 40–74 years

Pretreatment LN sizes 1.1–6 cm

PET specification

CTI HR+; FDG 10–15 mCi; attenuation correction

SUV calculated

Reference tests/comparators

Ref.: neck dissection or fine-needle aspiration of residual nodes followed by histopathology

ResultsTwo definitions used for PET +ve: (i) any increased uptake; (ii) SUV ≥ 3

	TP	FN	TN	FP
PET: any increase	4	0	5	3
PET: SUV ≥ 3	4	0	7	1

Comments

Not clear, but probably post-hoc selected cut-off

Author, year, country, study periodGoerres, 2004,⁹⁰ Switzerland, NR**Article number**

EP 2217

Cancer/management decision

Advanced head and neck cancer patients who have received CRT

Restaging: early follow-up

Design of study/patient characteristics

Diagnostic accuracy study

PET scan 6–8 weeks after end of therapy

Clinical exam 2 days after PET or < 12 days before

26 patients initially stage III/IV

25 received RT (median dose 70 Gy in 6 weeks) + cisplatin, one RT only

Mean age 56 ± 9 years

Follow-up: ≥6 months

PET specification

GE Advance; FDG 300–400 MBq; attenuation correction

Visual reading by one NMP, blinded

Reference tests/comparators

Biopsy for PET positive sites, follow-up for negative sites

Results

	TP	FN	TN	FP
PET	10	1	14	1

5/10 PET-positive findings not seen clinically and management changed in 5/26

Author, year, country, study periodPorceddu, 2005,⁹¹ Australia, 1996–2002**Article number**

EP 288

Cancer/management decision

Patients with node-positive III–IV head and neck SCC after CRT with complete regression of primary tumour + residual neck nodes clinically pathological confirmation or > 12 months follow-up

Restaging: detection of residual neck node disease

Design of study/patient characteristics

Diagnostic accuracy study

39 patients; 29 M; median age 55 years (range 37–89 years)

35 treated with 70 Gy + concomitant cisplatin or carboplatin in 34; four with concomitant boost RT or accelerated RT

Follow-up: median 34 months

PET specification

GE Quest 300H; FDG NR; attenuation correction

Visual interpretation; no further details given

31 scans performed within 8–12 weeks of CRT. Median time to scan 12 weeks for all patients

Reference tests/comparators

Biopsy or evidence of progression during follow-up

Results

32 PET negative: one neck recurrence and four distant in these patients (5 FN, 27 TN)

Seven PET positive: five confirmed by biopsy (5 TP), other two FPs

Comments

On the basis of these results, the authors suggest that patients who achieved a complete response at the primary site but have a residual abnormality in the neck that is negative on PET scan 12 weeks after treatment are unlikely to need neck dissection

Author, year, country, study periodWare, 2004,⁹² Australia, 1996–1999**Article number**

EP 1631

Cancer/management decision

Head and neck SCC patients who have received 'definitive' therapy but had residual abnormality on CE

Restaging: early follow-up

Design of study/patient characteristics

Diagnostic accuracy study + change in planned management

PET scan ≥ 8 weeks after end of therapy, CE before PET for all but one patient

PET within 31 days of CE for 45 patients, 31–77 days for seven patients

Disease location: oral cavity 4, oropharynx 23, nasopharynx 2, hypopharynx 7, larynx 12, paranasal sinus 1, unknown 4

Initial stage: I, 1; II, 7; III, 6; IV, 36; unknown, 3

Primary therapy: surgery 5, surgery + RT 8, RT 8, CRT 29, chemo then RT or surgery 3

Age, gender: NR

PET specification

GE Quest 400H; FDG dose NR; attenuation correction

Visual reading by one NMP with access to clinical data

Reference tests/comparators

All non-PET information including CT, MRI/US, clinical assessment and biopsy for PET. Follow-up for negative sites median 55 months (range 41–76 months)

Pre-PET treatment plan based on CE, then post-PET uses PET information as well

High impact if intent or mode changed, low if PET and pre-PET consistent, none if PET differs from CE, but no change to plan

Results

FN declared if any evidence of recurrence not predicted by diagnostic method unless death or treatment intervened

PET result	No. patients	No. evaluable	No. correct
Negative	43	32	30
Systemic	6	5	5
Second primary	1	1	1
Equivocal	3	0	–

PET positive in 20/46; 19/20 TP

PET negative in 24; TN in 20, two equivocal, both positive

CE TP in 24/46

CE FP in 21/46, FN (by biopsy) in one

PET changed management in 21; validity established in 20/21, correct in 19/20

15 patients' management was not changed according to PET; validity was established in 12. In eight of these management directed by PET would have been correct

21 high impact; 14 surgery to obs., one investigative diagnostic procedure to obs., two RT/surgery+RT to obs., one palliative RT to radical RT, one surgery to palliation, one surgery to BSC, one surgery to investigative diagnostic procedure

5-year survival: 45%

Disease extent by CE: non-significant predictor ($p = 0.089$, one-sided trend test)Disease extent by PET: significant predictor ($p < 0.001$)

Obs., observation; BSC, best supportive care.

Head and neck cancer: treatment response

Primary studies

Author, year, country, study period Dietz, 2004, ⁹³ Germany, NR	Article number FP 50
Cancer/management decision Larynx and hypopharynx SCC patients receiving larynx-preserving surgery Detection of residual disease	
Design of study/patient characteristics Treatment response 20 patients PET before therapy, 16 immediately after, 14 after 6 months follow-up 20 patients; 15 cases given CRT, five treated 'otherwise'; 19 M; median age 60 years (range 47–79 years)	
PET specification Device NR; FDG 240 MBq; attenuation correction SUV for interpretation >3 positive, <2.5 negative, rest borderline	
Reference tests/comparators Refs: pretreatment CT + endoscopy and biopsy; post-treatment follow-up CT, endoscopy, US and biopsy	
Results All three scans only performed in 13 patients Three patients had only pretreatment scans Three patients initially FN (all small tumours) Immediate post-therapy, without three FNs, no FNs, 8/13 correct, 5/13 FPs At 6 months, without three FNs, 9/11 correct, one FP, one FN	

Author, year, country, study period Kitagawa, 2003, ⁹⁴ Japan, NR	Article number EP 590
Cancer/management decision Primary head and neck cancer patients receiving neoadjuvant CRT Evaluation of clinical response	
Design of study/patient characteristics Treatment response All PET scanned before treatment, then pretreatment biopsy, then PET scan and surgery post-treatment 20 patients; 17 M; mean age 62 years (range 47–78 years)	
PET specification GE Advance; FDG 244–488 MBq; attenuation correction SUV corrected for body weight	
Reference tests/comparators Ref.: histopathology	
Results 16/20 CR, other four PR Post-SUV < 4: 14/14 CR Post-SUV > 4: 4/6 PR	

Author, year, country, study period Kitagawa, 2003, ⁹⁵ Japan, NR	Article number EP 591
Cancer/management decision Head and neck cancer patients given two courses of arterial chemo (adriamycin, 5-FU, carboplatin) + 30–40 Gy RT Response assessment	
Design of study/patient characteristics Treatment response PET before and ≥ 4 weeks (mean 38 days) after CRT 23 patients	
PET specification GE Advance; FDG 244–488 MBq; attenuation correction 18 patients also dynamic scan for 60 minutes (only static images used) All forms of image evaluated blind (number of readers not specified), visually and by SUV (for PET)	
Reference tests/comparators Ref.: histopathology from surgery or biopsy Comp.: CT/MRI MRI before ($n = 23$) and after ($n = 20$) CT before (22) and after (21) Ga scan (20) before only	
Results PET 100% sensitive for primary lesion (CT 15/22, MRI 18/23, Ga 8/20) PET sens. for residual tumour 4/4 (CT 3/4 MRI 3/3) PET spec. for residual tumour 17/19 (CT 10/17, MRI 7/17) <i>Lymph nodes</i> No pathological evidence of post-treatment node involvement, so no sensitivity PET specificity 17/23 (CT 16/21, MRI 17/20) <i>Patient management</i> PET results allowed eight patients to avoid surgery (not clear whether this is relative to other imaging methods or to no imaging)	

Author, year, country, study period Kunkel, 2003, ⁹⁶ Germany, 1995–1999	Article number EP 610
Cancer/management decision Patients with stage III or IV oral SCC given neoadjuvant RT \pm cisplatin chemo before 'curative' resection Treatment response: restaging 4 weeks after RT	
Design of study/patient characteristics Treatment response 35 patients, 27 also received cisplatin chemotherapy Follow-up: mean 41 months	
PET specification ECAT EXACT 922; FDG 350 MBq; attenuation correction SUV calculated from manual ROI Predefined SUV cut-off (4) used to define PET positive	
Reference tests/comparators Ref.: disease-specific survival and OS	
Results 7/28 PET negative vs 5/7 PET positive died ($p = 0.046$) Disease-specific deaths 2/28 vs 4/7 ($p = 0.018$) PET still significant predictor after adjustment for nodal status, tumour grade and cisplatin use	
OS, overall survival.	

Author, year, country, study periodMcCollum, 2004,⁹⁷ USA, 1999–2002**Article number**

EP 235

Cancer/management decision

Head and neck cancer patients receiving ICT (5-FU + docetaxel or cisplatin) and CRT (RT + carboplatin)
Response assessment

Design of study/patient characteristics

Treatment response
PET after ICT and after CRT
40 patients; 31 M; 35 stage IV; median age 54 years (range 29–78 years)
Follow-up: median 21 months

PET specification

GE Advance; FDG 370–555 MBq; attenuation correction
SUV from manual ROI by two NMPs

Reference tests/comparators

Biopsy post-ICT
Biopsy or follow-up post-CRT

Results

33 had PET after ICT, 26 biopsied

	TP	FN	TN	FP
PET	3	0	15	8

37 had PET after CRT, 24 biopsied

	TP	FN	TN	FP
PET	6	3	8	7

13 follow-up only; no evidence of disease in the five that were positive on PET

Comments

Post-hoc cut-offs

Author, year, country, study periodNam, 2005,⁹⁸ Korea, 2001–2002**Article number**

EP 256

Cancer/management decision

SCC head and neck patients treated with definitive RT
Response evaluation in head and neck cancer

Design of study/patient characteristics

Treatment response
PET, CT/MRI, physical exam, panendoscopy, CXR, clinical chemistry 4 weeks before RT
PET + clinical work-up (no CT/MRI, but including panendoscopy) 4–6 weeks post-RT
24 patients; 23 M; median age 59 years (range 17–78 years)

PET specification

Device not specified; FDG 15 mCi MBq; attenuation correction
SUV of 3 used to distinguish tumour

Reference tests/comparators

Biopsy done at each site with SUV > 3 after RT

Results

In two patients raised SUV correctly predicted residual disease, one FN, 6 FP (but unclear write-up)

Head and neck cancer: RT planning

Primary studies

Author, year, country, study period Nishioka, 2002, ⁹⁹ Japan, NR	Article number EP 657
Cancer/management decision Patients with head and neck cancer referred for RT RT planning	
Design of study/patient characteristics RT planning CT or MRI primary planning tool; patients immobilised by mask and head support, then localised using laser beam system to facilitate PET placement <i>n</i> = 21	
PET specification Visually fused PET+CT or PET+MRI No detail given	
Reference tests/comparators Comp.: CT or MRI	
Results Primary tumour volume similar for CT/MRI and when PET added, apart from two patients (49% increase in one, 45% decrease in one) Total number of nodes to irradiate increased from 28 on CT/MRI to 39 on PET+CT or PET+MRI	

Author, year, country, study period Scarfone, 2004, ¹⁰⁰ USA, NR	Article number EP 309
Cancer/management decision Patients with head and neck cancer scheduled for RT RT planning	
Design of study/patient characteristics RT planning CT simulation used for planning; PET images on same day, using laser alignment <i>n</i> = 6; 3 M; age range 41–83 years	
PET specification GE Advance; FDG 370 MBq; attenuation correction PET+CT fused image interpreted for planning without reference to CT GTV	
Reference tests/comparators Comp.: CT	
Results Patient 1: no PET uptake, so PET GTV set equal to CT GTV Patient 2: two CT volumes, one increased based on PET Patient 3: three CT volumes, all increased on PET Patient 4: single CT volume, increased based on PET Patient 5: two CT volumes, one increased by PET, the other PET negative, but still interpreted as malignant disease Patient 6: three CT, all modified, one PET volume added PET+CT > CT by 3.3 cm ³	

Author, year, country, study periodSchwartz, 2005,¹⁰¹ USA, 2000–2003**Article number**

EP 1569

Cancer/management decision

Head and neck cancer patients scheduled for RT before neck dissection

RT planning

Design of study/patient characteristics

RT planning

CT and PET done with patients immobilised on backboard, then registered by software

20 patients; all male; median age 61 years (range 42–78 years)

PET specification

Exact 922; FDG 200–350 MBq

CT GTV and PTV defined independently of PET

PET+CT GTV and PTV defined using visually fused images

PET-negative regions omitted from GTV, volumes assessed using CT image

Reference tests/comparators

Comparator: CT

Ref.: regions checked on dissection

Results

Major differences: mean contralateral parotid dose 210.6 cGy (PET) vs 5122 cGy (CT) and mean laryngeal dose 4046 vs 5999

PET missed one neck node

Head and neck cancer: PET/CT – diagnosis of occult primary tumour**Primary study****Author, year, country, study period**Freudenberg, 2005,¹⁰² Germany, 2001–2003**Article number**

EP 109

Cancer/management decision

Detection of occult primary tumour of the head and neck in patients with cervical LN mets

Diagnosis (detection) of OPT

Design of study/patient characteristics

Prospective diagnostic accuracy study (image evaluation retrospectively)

 $n = 21$; 14 SCC, four AC, three undifferentiated

16 M, 5 F; mean age 64 years (range 26–94 years)

Follow-up: NR

PET/CT specification

Siemens Biograph; FDG 360 MBq, SUV >2.5 considered positive

Visual interpretation by two NMPs for PET, two radiologists for CT, both blinded

Reference tests/comparators

Ref.: histopathology (14), clinical follow-up (7)

Comp.: PET, CT

Results $n = 21$

	TP	FP
PET/CT	12 (57%)	0
Fused PET+CT	11 (52%)	1
PET	11 (52%)	3
CT	5 (23%)	3

OPT, occult primary tumour.

Head and neck cancer: PET/CT – mixed cancer management decisions

Primary studies

Author, year, country, study period Branstetter, 2005, ¹⁰⁴ USA, 2002	Article number EP 1717														
Cancer/management decision Patients with suspected or known head and neck cancer Various: staging ($n = 11$); detection of OPT ($n = 8$); recurrence ($n = 46$)															
Design of study/patient characteristics Prospective diagnostic accuracy study $n = 65$ consecutive patients; 42 M, 23 F; mean age 63 years (range 43–83 years) Follow-up: mean 9 months (range 6–12 months)															
PET/CT specification Two commercially available PET/CT systems used: first not named, combining an EXACT HR+ PET with a Somatom Emotion CT; second CTI Reveal; FDG 296–555 MBq; patients with blood glucose level > 200 –250 mg/dl were rescheduled Visual interpretation by one neuroradiologist and one NMP For PET: blinded to concurrent CT, but access to all previous clinical and imaging data PET/CT interpreted after PET and with access to all information															
Reference tests/comparators Ref.: biopsy, clinical and imaging follow-up Comp.: PET, CT															
Results $n = 64$ patients with follow-up 125 lesions in 58 patients (46 true malignancies) 50 identified by PET and CT 46 identified with CT but not PET 26 identified with PET but not CT Three only identified by PET/CT															
<i>By-lesion analysis</i>															
	<table border="1"> <thead> <tr> <th></th> <th>Sens.</th> <th>Spec.</th> </tr> </thead> <tbody> <tr> <td>PET/CT</td> <td>98%</td> <td>92%</td> </tr> <tr> <td>PET</td> <td>87%</td> <td>91%</td> </tr> <tr> <td>CT</td> <td>74%</td> <td>75%</td> </tr> </tbody> </table>		Sens.	Spec.	PET/CT	98%	92%	PET	87%	91%	CT	74%	75%		
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<i>By-patient analysis</i> PET/CT or PET significantly different from CT in pairwise tests ($p < 0.05$) PET/CT vs PET, $p = 0.14$															

Author, year, country, study periodRödel, 2004,¹⁰⁵ Germany, NR**Article number**

FP 198

Cancer/management decision

Patients with head and neck cancer

Various: 14 primary tumours, 11 recurrent tumours, 22 OPT, four NR

Design of study/patient characteristicsDiagnostic accuracy study^a $n = 51$ patients; 34 M, 17 F; mean age 58 ± 17 years

Follow-up: NR

PET/CT specification

Siemens Biograph; FDG 370 MBq

Visual interpretation separately by experienced independent examiners, with subsequent comparison

SUV >3 implies PET positive**Reference tests/comparators**

Ref.: histopathology, follow-up

Comp.: PET, CT

Results

153 lesions

Various analyses comparing PET and CT not presented here

	Sens.	Spec.
PET	95%	65%
CT	80%	76%
PET/CT	96%	78%

Diagnostic advantage of PET/CT compared with PET or CT, in terms of lesions

	Change in findings	No. (%)
CT	Questionable to malignant	27 (18)
CT	Questionable to benign	4 (3)
CT	Malignant to benign	2 (1)
CT	Unremarkable to malignant	2 (1)
CT	Total	35 (23)
PET	Questionable to malignant	0 (0)
PET	Questionable to benign	7 (5)
PET	Malignant to benign	3 (2)
PET	Unremarkable to malignant	3 (2)
PET	Total	13 (9)

PET/CT altered equivocal CT findings mainly to malignant, whereas all questionable PET findings were altered to benign

Comments

^a Records how many patients have been studied since the introduction of the PET/CT machine, so this could be a retrospective analysis, but the study protocol for giving PET is quite clear and no reference is made to referring to patient case notes

Author, year, country, study periodSchöder, 2004,¹⁰⁶ USA, 2001–2002**Article number**

EP 314

Cancer/management decisionPatients with head and neck ($n = 60$) or thyroid cancer ($n = 8$)Various: staging ($n = 16$); detection of OPT ($n = 8$); restaging after chemo or RT ($n = 10$), recurrence ($n = 34$)**Design of study/patient characteristics**

Retrospective diagnostic accuracy study

 $n = 68$; 44 M, 24 F; mean age 58 years (range 14–81 years)

52 SCC; eight OPT; eight recurrent or metastatic thyroid cancer

Follow-up: ≥ 3 months**PET/CT specification**

Siemens Biograph or GE Discovery LS; FDG 444–555 MBq

Retrospective interpretation in consensus by one experienced NMP and one experienced radiologist, with knowledge of patient history but not any other imaging studies

Reference tests/comparators

Ref.: for lesions: 31 histopathology, 16 clear clinical findings, 82 follow-up, 26 no ref.

Comp.: none

Results

157 areas had FDG uptake on PET

PET/CT improved anatomical localisation on 98 of these

42/56 (74%) in previously treated areas vs 58/101 (58%) untreated areas
(note: adds to 100 not 98) $n = 131$ lesions with ref. standard

	Accuracy	
	Ignoring equivocal ^a	Equivocal counted as correct if cancer not missed
PET	92%	91%
PET/CT	97%	96%

^a 18 lesions equivocal.

Four FPs for both: one tonsillitis, three related to RT

33 PET abnormalities were reclassified after PET/CT plus two newly diagnosed with PET/CT

31 of these had ref. standard and information

21 definite benign, six definite malignancies, three equivocal benign, one equivocal malignant

Change in patient management ascribed to 17 lesions in 12 (18%) patients

Two surgery initiated, one surgery altered, eight avoided follow-up, one guide nodal biopsy

Comments

Includes eight patients with recurrent or metastatic thyroid cancer

Hoped that PET/CT would remove all equivocal cases, but there were still 18/157 (11%), compared with 39 equivocal lesions on PET

Author, year, country, study periodZanation, 2005,¹⁰⁷ USA, 2003–2004**Article number**

EP 1667

Cancer/management decision

Patients with head and neck cancer

Various: staging (15 scans); detection of OPT (10); distant mets (25); recurrence (47)

Design of study/patient characteristics

Retrospective diagnostic accuracy study (querying PET/CT records for head and neck cases)

Medical records reviewed by two independent reviewers

 $n = 87$ patients with 97 scans included; 65 M, 22 F; mean age 61 years (range 18–84 years)

Stage: I–II, 26; III–IV, 45 (others NR)

Follow-up: ≥ 2 months, mean 8 months**PET/CT specification**

Siemens Biograph; 'appropriate dose' of FDG

Visually interpreted by attending radiologist, with any image described as hypermetabolic and not considered benign regarded as positive

Reference tests/comparators

Ref.: histopathology (64% of patients) or clinical and/or other radiological exam

Comp.: none

Results*Diagnostic accuracy of each scan by site ($n = 97$ scans)*

Site	Sens.	Spec.	Accuracy
All	75%	69%	72%
Primary	83%	82%	83%
Regional	89%	93%	90%
Distant	97%	91%	96%

Accuracy by patient = 69%

Accuracy results also presented by scan and patient according to reason for obtaining scan

21/97 (22%) of scans resulted in some change in patient management

PET/CT accuracy was stratified into three 4-month periods. Stated that no significant differences in accuracy at any of the periods

Comments

Unclear presentation of change in patient management as many more patients are referred to than the 21; some are clearly overlapping explanations

Interesting mention of learning curve

Head and neck cancer: PET/CT – RT planning

Primary studies

Author, year, country, study period Ciernik, 2003, ¹⁰⁸ Switzerland, NR	Article number EP 459
Cancer/management decision Patients with head and neck cancer presenting for curative RT RT planning for target volume delineation in RT	
Design of study/patient characteristics Prospective RT planning PET/CT study Including a total of 39 consecutive patients presenting with a variety of cancers (other cancers had fewer than 12 patients) <i>n</i> = 12 with head and neck cancer; 11 M, 1 F; mean age 64 years (range 55–78 years) Tumour stage: IIB–IVA Follow-up: none stated	
PET/CT specification Discovery LS; FDG 370 MBq Images transferred electronically into RT planning software; target volumes independently defined by two radiation oncologists evaluating first with CT, then with PET/CT	
Reference tests/comparators Ref.: none Comp.: CT	
Results PET/CT compared with CT GTV increase $\geq 25\%$ in 2/12 patients and GTV reduction $\geq 25\%$ in 4/12 patients Mean GTV change $32 \pm 11\%$. Mean PTV change $20 \pm 5\%$	

Author, year, country, study period Koshy, 2005, ¹⁰⁹ USA, NR	Article number EP 1428
Cancer/management decision Patients with SCC head and neck cancer (including three with OPT) scheduled for RT [no clinical or radiological evidence (CT, MRI, CXR) of distant mets or synchronous tumours], with RT planned using a CT simulation scan Staging before RT	
Design of study/patient characteristics Retrospective study of RT planning <i>n</i> = 36 consecutive patients; 28 M, 8 F; mean age 56 years (range 32–80 years) All but one patient newly diagnosed Follow-up: NR	
PET/CT specification GE Discovery LS; FDG 370–444 MBq; patients immobilised with head mask Visual interpretation by a nuclear radiologist or NMP, unblinded	
Reference tests/comparators Ref.: histopathology, additional imaging, clinical follow-up Comp.: CWU	
Results PET/CT altered TNM score in 13 patients (36%) and AJCC stage in five (14%) Although changes in TN did not frequently have an impact on overall stage, they had an important impact on radiation volume and dose Overall PET/CT changed management in nine patients (25%): Five changed in RT volume, four of these also had a change in dose (generally increased) Three changed in chemotherapy (one not given due to downstaging, two altered given distant mets) One underwent lobectomy following detection of mass	

Author, year, country, study periodPaulino, 2005,¹¹⁰ USA, 2002–2004**Article number**

EP 280

Cancer/management decisionPatients with head and neck cancer referred for RT
RT planning**Design of study/patient characteristics**RT planning
CT simulation using head mask and fixed carriage position
PET under same conditions $n = 40$; 32 M

38 stage III–IV

PET/CT specificationDiscovery LS, FDG 370–444 MBq; attenuation correction
PET/CT interpreted by NMP using all available data
GTV determined (for both PET/CT and CT) by two oncologists**Reference tests/comparators**

Comp.: CT

ResultsMedian GTV: PET/CT 20.3 cm³, CT 37.2 cm³

30 cases PET/CT < CT, three PET/CT = CT

In 25% of patients PET/CT-GTV underdosed if CT-GTV used

Current practice to use the larger volume

Lung cancer

NSCLC: diagnosis

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions																					
<p><i>Diagnosis</i></p> <p>Investigation of primary tumours, to determine whether malignant or benign</p> <p>Reference standard: histopathology, with follow-up in two trials</p>	<p>DACEHTA, Denmark, 2001⁶</p> <p>(1990 to May 2001)</p>	<p>Ten hierarchy 2 studies involving PET or PET+CT</p> <p>Two PET+CT vs CT trials</p> <table border="1"> <thead> <tr> <th></th> <th>Sens.</th> <th>Spec.</th> </tr> </thead> <tbody> <tr> <td colspan="3">1. (<i>m</i> = 48 lesions)</td> </tr> <tr> <td>PET+CT</td> <td>100%</td> <td>58–63%</td> </tr> <tr> <td>CT</td> <td>33–41%</td> <td>52%</td> </tr> <tr> <td colspan="3">2. (<i>m</i> = 100 lesions)</td> </tr> <tr> <td>PET+CT</td> <td>100%</td> <td>99%</td> </tr> <tr> <td>CT</td> <td>100%</td> <td>94%</td> </tr> </tbody> </table> <p>One other study compared PET vs CT, both had sens. of 100%, spec. not calculated</p>		Sens.	Spec.	1. (<i>m</i> = 48 lesions)			PET+CT	100%	58–63%	CT	33–41%	52%	2. (<i>m</i> = 100 lesions)			PET+CT	100%	99%	CT	100%	94%	<p>Unclear reporting of lesions vs patients, so total <i>n</i> unclear</p> <p>No pooled analysis</p> <p>PET+CT trials not reported by patient</p> <p>1. 32 malignant, 16 benign</p> <p>2. High accuracy for CT with or without PET, so probably a highly selected population</p> <p>Appropriateness of this form of investigation given CWU in England is unclear</p>
	Sens.	Spec.																						
1. (<i>m</i> = 48 lesions)																								
PET+CT	100%	58–63%																						
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PET+CT	100%	99%																						
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NSCLC: staging

Systematic reviews

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions									
<p><i>Staging</i></p> <p>Mediastinal nodal staging in patients with known or suspected NSCLC</p> <p>(PET without CT)</p> <p>Reference standard: histocytology</p>	<p>National Collaborating Centre for Acute Care (for NICE), UK, 2005⁵</p> <p>(Up to December 2003)</p>	<p>Tolosa (2003)¹¹¹ systematic review of 18 studies plus three additional prospective studies</p> <p>Systematic review ($n = 1045$) PET sens.: 84% (95% CI 78 to 89%) PET spec.: 89% (95% CI 83 to 93%)</p> <p>Three primary studies ($n = 584$) PET sens.: 61–68% PET spec.: 72–84%</p>	<p>PET allows reasonably accurate determination of mediastinal disease.</p> <p>However, there are FPs, so tissue sampling may still be needed</p>									
<p><i>Staging</i></p> <p>Mediastinal nodal staging in patients with NSCLC to identify those with enlarged LNs who would not be suitable for thoracotomy</p> <p>Additional use of PET considered after CT +ve or CT –ve</p> <p>Reference standard: cytohistopathology</p>	<p>National Collaborating Centre for Acute Care (for NICE), UK, 2005⁵</p> <p>(1990 to December 2003)</p>	<p>HTBS HTA² of 17 hierarchy 2 studies including CT evaluation plus one additional prospective study</p> <p>sROC: Pooled PET spec. calculated and PET sens. read off sROC</p> <table border="1"> <thead> <tr> <th></th> <th>Sens.</th> <th>Spec.</th> </tr> </thead> <tbody> <tr> <td>CT–</td> <td>90%</td> <td>93%</td> </tr> <tr> <td>CT+</td> <td>94%</td> <td>71%</td> </tr> </tbody> </table>		Sens.	Spec.	CT–	90%	93%	CT+	94%	71%	<p>Several methodological weaknesses in the individual studies and heterogeneity of patients included but the consistency of results suggests they are reliable</p> <p>High FP for CT+ means that PET cannot be relied upon</p> <p>There is evidence to support the use of PET for potential candidates for surgery who are negative for mediastinal disease on CT</p>
	Sens.	Spec.										
CT–	90%	93%										
CT+	94%	71%										
<p><i>Staging</i></p> <p>Detection of any distant mets in patients with proven or suspected NSCLC</p> <p>Reference standard: histopathology or follow-up</p>	<p>National Collaborating Centre for Acute Care (for NICE), UK, 2005⁵</p> <p>(1990 to December 2003)</p>	<p>HTBS HTA of 17 hierarchy 2 studies including CT evaluation, plus two additional studies with diagnostic information</p> <p>sROC analysis ($n = 1202 + 144 + 287$) PET sens. = 93%, spec. = 96%</p> <p>($n = 1515$) Mean 15% (range 8–39%) patients had unexpected distant mets detected by PET, which led to change in management in 25% of patients</p>	<p>Heterogeneity of studies, some only included potential candidates for surgery, others included all NSCLC patients</p> <p>Additional studies</p> <p>Generally poor documentation of change in patient management</p>									

continued

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions												
<p><i>Staging</i></p> <p>Detection of specific distant mets in patients with newly diagnosed NSCLC</p> <p>Reference standard: histopathology and follow-up</p>	<p>National Collaborating Centre for Acute Care (for NICE), UK, 2005⁵</p> <p>(Up to December 2003)</p>	<p><i>Brain</i></p> <p>One prospective study of PET vs CT+MRI (<i>n</i> = 100) CT+MR 100% accurate, PET sens. = 60%, spec. = 99%</p> <p><i>Liver</i></p> <p>One prospective study of PET vs CT (<i>n</i> = 78) CT sens. = 100%, spec. = 95% PET 100% accurate</p> <p><i>Adrenal</i></p> <p>Three prospective PET studies (<i>n</i> = 100, 27, 33) Sens. 84^a to 100%, spec. 80 to 100% ^a Data extraction table indicates 94%</p> <p><i>Bone mets</i></p> <p>Three prospective PET studies (<i>n</i> = 110, 48, 100) Sens. 90 to 94%, spec. 82 to 99%</p>	<p>One heterogeneous study suggests MRI+CT is better than PET for detection of brain mets</p> <p>Insufficient evidence to depart from the current practice of routinely scanning the liver and kidney with CT during staging</p> <p>Other studies evaluate MRI and bone scintigraphy and suggest that PET is more accurate, but these three heterogeneous studies are insufficient to make a recommendation that departs from clinical practice</p>												
<p><i>Staging</i></p> <p>Detection of distant mets (or locoregional recurrence in RCT1) in patients with NSCLC considered medically fit for thoracotomy</p>	<p>HTBS, Scotland, 2002²</p> <p>(1990 to October 2001)</p>	<p>One hierarchy 4 RCT and one hierarchy 4/5 RCT</p> <p>Randomisation to CWU or CWU + PET</p> <p>RCT1: Europe (<i>n</i> = 188, stage I–III)</p> <p><i>Futile thoracotomy</i></p> <table border="1"> <thead> <tr> <th>Stage</th> <th>I/II</th> <th>III</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td>CWU</td> <td>31/68</td> <td>8/28</td> <td>39/96</td> </tr> <tr> <td>CWU+PET</td> <td>16/64</td> <td>3/27^a</td> <td>19/92</td> </tr> </tbody> </table> <p>^a Plus one stage IV in CWU+PET with no thoracotomy.</p> <p>Overall, significant difference, χ^2-test (<i>p</i> = 0.003)</p> <p>RCT2: Australia (abstract) (<i>n</i> = 164)</p> <p><i>Thoracotomies</i></p> <p>CWU = 98% CWU + PET = 96% (futile rate not stated)</p> <p>Death rates after median 10 months follow-up: 16% vs 15% (ns)</p> <p>(Full study reported as Viney, 2004,¹¹² data extraction)</p>	Stage	I/II	III	Total	CWU	31/68	8/28	39/96	CWU+PET	16/64	3/27 ^a	19/92	<p>RCT2 total <i>n</i> = 179, only conference abstract (full paper summarised below)</p> <p>Results look disparate, but RCT2 only included earlier stage patients and futility of operations was judged differently in each trial. In RCT1 thoracotomy on N2 disease was considered futile, whereas in RCT2 such surgery was considered appropriate. Also, only RCT1 used PET to exclude benign lesions.</p> <p>In both RCTs, positive PET only affected patient management if confirmed by biopsy or other imaging. Such confirmation may impose additional costs and delays on the patient</p>
Stage	I/II	III	Total												
CWU	31/68	8/28	39/96												
CWU+PET	16/64	3/27 ^a	19/92												

Additional primary study**Author, year, country, study period**Viney, 2004,¹¹² Australia, 1999–2000**Article number**

URR25

Cancer/management decision

Patients with cytologically established diagnosis of NSCLC
Staging to avoid futile thoracotomy

Design of study/patient characteristics

RCT of change in patient management
Sample size to detect a 10% change in the proportion of patients undergoing thoracotomy

$n = 183$: 91 PET+CWU, 92 to CWU only
134 M, 49 F; median age 67 years (range 42–82 years)

Follow-up: ≥ 12 months

PET specification

Siemens ECAT 951R; FDG 5–7 MBq/kg; attenuation correction
Visual interpretation by one PET physician

Reference tests/comparators

Ref.: biopsy, mediastinoscopy or surgery
Comp.: CWU = CXR and CT scan (of thorax, upper abdomen and brain) and bone scans performed in those with signs and symptoms of bony metastatic disease

Results*Staging comparison*

PET	True stage				
	0	I/II	III A	III B	IV
0	2	0	0	0	0
I/II	2	53	6	0	0
III A	0	1	11	1	0
III B	0	4	1	1	0
IV	0	1	0	0	2
None	1	3	1	0	1

0, benign; none, no scan

PET+CWU led to further investigations or change in management in 12/184 (7%) patients

Few patients avoided thoracotomy: 4/91 PET+CWU vs 2/92 CWU ($p = 0.2$)

At the time of the study, surgeons felt that surgery on stage IIIA patients who were CT negative was appropriate, so PET did not influence the management of such patients upstaged by PET. It is noted that neoadjuvant chemotherapy is now standard and thus PET would have more impact

Estimated 12-month survival rates were 80% for PET+CWU vs 77% for CWU

Economic models

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
Staging Patients with NSCLC considered eligible for surgery	HTBS, Scotland, 2002, ² HTBS, Scotland, 2005 (correction) ¹¹³ UK Data inputs and costs from 2001	Economic model, NHS Scotland perspective <i>Strategies for CT+ and CT- separately</i> 1. Thoracotomy 2. Non-surgical treatment 3. Mediastinoscopy then thoracotomy for N0/I 4. Mediastinoscopy then PET for N0/I and thoracotomy for PET -ve 5. PET then thoracotomy for M0 N0/I 6. PET then mediastinoscopy for PET -ve and surgery for -ve 7. PET then surgery for M0 N0/I, non-surgical treatment for M1 N0/I, mediastinoscopy for other PET +ve and surgery for -ve <i>For CT+ and CT-</i> Strategies 1, 3 and 7 have higher mean QALY per patient and life expectancy. Of these, strategy 7 avoids the most futile thoracotomies <i>CT-</i> Strategy 7 (with PET) compared with strategy 1 (thoracotomy) results in an ICER of £7900 per QALY Strategy 3 (mediastinoscopy) compared with strategy 1 results in an ICER of £18,590 per QALY <i>CT+</i> Strategy 7 compared with strategy 3 results in an ICER of £58,951 per QALY	Original report misspecified CT- model, updated results presented here All patients except those who have successful surgery go on to have non-surgical care

continued

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
<p><i>Staging</i></p> <p>Patients with NSCLC with normal-sized lymph nodes (CT-) considered eligible for surgery</p>	<p>National Collaborating Centre for Acute Care (for NICE), UK, 2005⁵</p> <p>Data inputs and costs from 2003</p>	<p>Economic model, NHS perspective</p> <p><i>Strategies</i></p> <ol style="list-style-type: none"> 1. Thoracotomy 2. Mediastinoscopy then radical RT for N2/3 or thoracotomy for N0/I 3. PET then palliative care for M1 or radical RT for M0 N2/3 or thoracotomy for M0 N0/I <p>(All patients except those who have successful surgery go on to have palliative care)</p> <p>PET strategy compared with thoracotomy:</p> <ul style="list-style-type: none"> - 22% fewer futile thoracotomies - 0.7% fewer surgical deaths - improved life expectancy of 0.04 years per patient <p>Cost savings from avoiding thoracotomies offset some of the cost of PET, resulting in an estimated ICER of £7200 per QALY</p> <p>PET compared to mediastinoscopy:</p> <ul style="list-style-type: none"> - 8% fewer futile thoracotomies - 0.7% fewer surgical deaths - 7% fewer futile radical RT courses <p>Model dominated: PET is cost saving compared with mediastinoscopy</p>	<p>Based on model used by HTBS but making sensible alterations to model distant mets, etc., better, included radical RT in pathway and alter some costs, e.g. increase cost of mediastinoscopy</p> <p>CT+ not modelled</p> <p>Cost-effectiveness only sensitive to unit costs and so only when cost of PET scanning high and cost of thoracotomy low does the estimate of cost-effectiveness exceed £30,000 per QALY</p> <p>Results similar to the revised HTBS results for CT-, unclear why CT+ not modelled as this was much higher cost per QALY in HTBS</p>

NSCLC: treatment response**Primary studies****Author, year, country, study period**Choi, 2002,¹¹⁵ USA, NR**Article number**

EP 457

Cancer/management decisionLocally advanced NSCLC patients receiving CRT (RT, 42 Gy; CT, two courses of 5-FU, cyclophosphamide, cisplatin)
Treatment response**Design of study/patient characteristics**

Treatment response: complementary study to Phase II CRT study

PET before and 2 weeks after CRT

Relationship between probability of tumour response to (C)RT and glucose metabolic rate measured by FDG-PET

29 patients with 30 lesions; 16 M; median age 60 years (range 42–78 years)

Pancoast tumours, 2; IIIa, 18; IIIb, 7; stump recurrence, 2; contralateral lesion, 1

PET specification

Scanditronix PC4096-16WB; FDG 370 MBq

Dynamic imaging and arterial input measurements for 13 patients, simplified kinetic method for remainder (~1 hour scan time)

Reference tests/comparators

Ref.: pathology from resection

Results

Pathological CR 11/29 patients, 14/30 lesions

CR in 6/6 when residual metabolic rate $<0.05 \mu\text{mol/minute/g}$, 0/6 if $>0.13 \mu\text{mol/minute/g}$

Residual metabolic rate significant in logistic regression

Using cut-off of 0.5 from logistic regression:

Classification for tumour control

Model prediction	Control	
	Yes	No
Yes	12	3
No	2	13

Author, year, country, study periodSchmücking, 2003,¹¹⁶ Germany, NR**Article number**

EP 702

Cancer/management decision

Patients with NSCLC

Treatment response and RT planning

Design of study/patient characteristics

Treatment response and planning

Three groups receiving PET scans:

63 for primary staging (results not shown here)

34 response to neoadjuvant chemo

27 RT planning

No details of patient characteristics reported

PET specification

Device NR; FDG 350–600 MBq; attenuation correction

Visual interpretation after CT image fusion

Reference tests/comparators

Ref.: histopathology for response to neoadjuvant chemo

Results*Treatment response*

All patients with PET CR free of vital tumour, no patient without PET CR free of vital tumour (no numbers reported)

RT planning

PTV 3–21% higher with PET

Volume of normal lung receiving > 20 Gy reduced by 5–17%

Author, year, country, study periodSchmücking, 2005,¹¹⁷ Germany, NR**Article number**

FP 217

Cancer/management decision

NSCLC patients on CRT

Response assessment

Design of study/patient characteristics

Treatment response

RCT comparing (1) CRT then chemo vs (2) chemo then CRT, then surgery

PET pre- and post-neoadjuvant therapy (before surgery). CT at the same time

32 patients

PET specification

No details of PET scanning process reported

PET and CT software fused

PET CR defined as SUV < 2.5

Reference tests/comparators

Histopathology from surgery

Results*Primary tumour*

PET CR in 17; 16 had good path response, one FN

Lymph nodes

PET CR in ten; all had good path response, five FPs

CR vs no CR $p = 0.008$ for OS

2-year survival 76% vs 20%

Author, year, country, study periodCerfolio, 2003,¹¹⁸ USA, 2000–2002**Article number**

EP 447

Cancer/management decisionNSCLC patients who have received preoperative C(R)T
Therapy response; detection of residual disease**Design of study/patient characteristics**Treatment response
PET and CT pre- and post-neoadjuvant C(R)T
Scans within 1 month of start and 1 month of end34 patients; 24 M; mean age 63 years (range 42–76 years)
Stage: T2N0, 7; T3N0, 8; T4N0, 1; N1, 7; N2, 11

Seven CRT; 27 chemo only

PET specificationECAT Exact PET scanner; FDG 370 MBq
Analysis done on attenuation-corrected scans
ROI drawn by investigator, SUV by software**Reference tests/comparators**Ref.: pathology after thoracotomy and LN removal or fine-needle biopsy
Comp.: CT**Results**

	Primary		NI nodes	
	Path +	Path –	Path +	Path –
PET	+	31	0	2
	–	1	2	9
CT	Path +	Path –	Path +	Path –
	+	31	0	3
	–	1	2	8

Results

	Paratracheal N2		Other N2	
	Path +	Path –	Path +	Path –
PET	3	7	0	4
	60	0	48	4
CT	Path +	Path –	Path +	Path –
	4	4	1	2
	59	3	47	6

Path, pathology.

Author, year, country, study periodPort, 2004,¹¹⁹ USA, NR**Article number**

EP 2400

Cancer/management decisionNSCLC patients receiving neoadjuvant chemo before resection
Assessment of response**Design of study/patient characteristics**Treatment response
PET scans before and 2 weeks after chemo

25 patients; 17 M; age NR

PET specificationDedicated PET scanner (no details given)
Predefined major PET response: >50% fall in SUV**Reference tests/comparators**

Ref.: histopathology

ResultsAccuracy for N1 + N2 disease (compared to N0):
12 N0 disease, PET three FPs
13 N1/2 disease, PET five FNs

CT five FPs, six FNs

Author, year, country, study periodRyu, 2002,¹²⁰ USA, 1993–1998**Article number**

EP 1083

Cancer/management decisionNSCLC patients given CRT before resection
Restaging NSCLC**Design of study/patient characteristics**Treatment response
PET before neoadjuvant CRT and 2 weeks after completion
 $n = 26$; median age 62 years (range 47–72 years)**PET specification**Scanditronix PC4096–16WB; FDG 370 MBq; attenuation correction
Two NMPs, visual + SUV using manual ROI**Reference tests/comparators**

Ref.: pathology from resection

Results*Primary tumour* (sens. and spec. to detect residual disease)

	TP	FN	TN	FP
Visual	12	6	5	3
SUV	15	2	4	2

Lymph nodes (only visual assessment presented, for nodal levels)

	TP	FN	TN	FP
Visual	7	5	37	3

Comments

SUV value of 3 used as cut-off (prespecified)

Author, year, country, study periodWeber, 2003,¹²¹ Germany, NR**Article number**

EP 765

Cancer/management decisionAdvanced NSCLC patients given palliative chemo
Prediction of response using early PET**Design of study/patient characteristics**Treatment response
Baseline PET 1 week pretherapy and day 21 of therapy
57 patients; 45 M; mean age 60 ± 9 years
Stage: IIIB, 9; IV, 48**PET specification**ECAT Exact; FDG 300–400 MBq; attenuation correction
SUV cut-off + FDG net-influx modelling for subset**Reference tests/comparators**

Ref.: EORTC RECIST response criteria after complete treatment

Results

SUV cut-off (20% change used, a priori selection from earlier studies)

20/28 PET responders had a RECIST response
1/27 PET non-responders had a RECIST response

FDG net influx (available in 32 from dynamic scanning) also predicts response

NSCLC: RT planning

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
Planning/staging in candidates for radical radiotherapy	National Collaborating Centre for Acute Care (for NICE), UK, 2005 ⁵ (Up to December 2003)	No SRs, three prospective studies and one retrospective study (n = 26, retrospective) 31% had therapy change (dose, volume or intent) (n = 11) Three patients had stage change (n = 27) PET detected unexpected mets in three patients vs 0 on SPECT (n = 30) PET led to change from radical to palliative treatment due to distant mets in seven (23%)	NICE guideline concludes that patients who are potential candidates for radical radiotherapy would benefit from a PET scan before treatment

Additional primary studies

Author, year, country, study period Bradley, 2004, ¹²² USA, NR	Article number EP 32
Cancer/management decision NSCLC patients referred for radical RT RT planning	
Design of study/patient characteristics RT planning 26 patients for CT simulation used for RT planning and compared to PET	
PET specification ECAT Exact HR+; FDG 15 mCi PET/CT fusion: patients located in same position for CT and PET, using localisation guides and laser positioning CT PTV estimated by radiation oncologist PET and CT fused by software, then separate oncologist estimated PTV	
Reference tests/comparators Comp.: CT	
Results Two M1 disease found by PET, so 24 went on to have radical RT 14 different GTV (reduced in three, increased in 11)	

Author, year, country, study periodDe Ruyscher, 2005,¹²³ Netherlands, Germany, UK, NR**Article number**

EP 1295

Cancer/management decision

Patients with stage I–III NSCLC referred for irradiation of mediastinal nodes
RT planning

Design of study/patient characteristics

RT planning: prospective Phase I study

Scans before chemo

No distant mets on CT or PET, then LN selected by PET and localised on CT after visual fusion

44 patients; 27 M; median age 68 years

Pre-RT chemo done in 20

Follow-up: median 16 months

PET specification

ECAT Exact 922; FDG 200–350 MBq; attenuation correction

Reference tests/comparators

Ref.: progression defined by review after quarterly follow-ups

Results

29 patients 61.2 Gy, others 64.8 Gy

11 local recurrence, 18 any recurrence or failure (two nodal failure outside PTV)

Toxicity grade (number of patients)

0 (no toxicity) (27)

1 (15)

2 (1)

5 (highest level) (1)

Author, year, country, study periodSchmücking, 2003,¹¹⁶ Germany, NR**Article number**

EP 702

Cancer/management decision

Patients with NSCLC

Treatment response and RT planning

Design of study/patient characteristics

Treatment response and planning

Three groups of receiving PET scans:

63 for primary staging (results not shown here)

34 response to neoadjuvant chemo

27 RT planning

No details of patient characteristics reported

PET specification

Device NR; FDG 350–600 MBq; attenuation correction

Visual interpretation after CT image fusion

Reference tests/comparators

Ref.: histopathology for response to neoadjuvant chemo

Results*Treatment response*

All patients with PET CR free of vital tumour, no patient without PET CR free of vital tumour (no numbers reported)

RT planning

PTV 3–21% higher with PET

Volume of normal lung receiving > 20 Gy reduced by 5–17%

<p>Author, year, country, study period Van Der Wel, 2005,¹²⁴ Netherlands/UK, NR</p> <p>Cancer/management decision/CWU Pathologically proven N2–3 M0 NSCLC RT planning CWU: bronchoscopy, CT</p> <p>Design of study/patient characteristics RT planning using visually fused PET+CT 21 consecutive patients</p> <p>PET specification ECAT Exact 922; FDG 200–350 MBq CT GTV and PTV defined independently of PET PET+CT GTV and PTV defined using visually fused images PET-negative regions omitted from GTV, volumes assessed using CT image</p> <p>TCP calculated for each PTV, given assumptions about geographical misses and probability that imaging is discordant with true status</p> <p>Reference tests/comparators Comp.: CT</p> <p>Results <i>Nodal GTV</i> CT: 13.7 ± 3.8 cm³ PET: 9.9 ± 4.0 cm³</p> <p><i>Mean oesophageal dose</i> CT: 29.8 ± 2.5 Gy PET: 23.7 ± 3.1 Gy</p> <p>14 plans changed; 11 decreased volume Estimated TCP 12.5% vs 18.3%</p>	<p>Article number EP 361</p>
TCP, tumour control probability.	

Economic model

Cancer management decision	Source	Evidence	Data caveats/conclusions
<p><i>Staging</i></p> <p>Patients with NSCLC considered eligible for radical RT (mainly with enlarged LNs on CT: CT+)</p>	<p>National Collaborating Centre for Acute Care (for NICE), UK, 2005⁵</p> <p>Data inputs and costs from 2003</p>	<p>Economic model, NHS perspective</p> <p><i>Strategies</i></p> <ol style="list-style-type: none"> 1. Radical RT 2. PET then palliative care for M1 or radical RT for M0 N2/3 or thoracotomy for M0 N0/I <p>(All patients except those who have successful surgery go on to have palliative care)</p> <p>PET compared with radical RT resulted in benefits of</p> <ul style="list-style-type: none"> • 32% fewer courses of futile radical RT • 2.5% receiving curative surgery <p>adverse impacts of</p> <ul style="list-style-type: none"> • 5% missed RT courses • 6% more futile thoracotomy • 0.3% surgical death <p>ICER was £9500 per QALY</p>	<p>Cost-effectiveness only sensitive to unit costs and so only when cost of PET scanning exceeds the cost of radical RT or radical RT is more effective than surgery does the ICER exceed £30,000 per QALY</p>

NSCLC: PET/CT – staging**Primary studies****Author, year, country, study period**Antoch, 2003,¹³⁰ Germany, NR**Article number**

EP 410

Cancer/management decision

Patients with NSCLC before surgery

Staging: primary ($n = 19$), post-neoadjuvant therapy ($n = 8$)**Design of study/patient characteristics**

Prospective diagnostic accuracy study

 $n = 27$ patients; 23 M; mean age 57 years (range 39–70 years); 4 F; mean age 48 years (range 40–57 years)

Follow-up: mean 142 days

PET/CT specification

Siemens biograph; FDG 350 MBq

PET, CT and PET/CT visually interpreted by three independent teams

Reference tests/comparators

Ref.: histopathology and radiological follow-up for those with distant mets

Comp.: Siemens ECAT Exact HR+, Somatom CT

Results

Stages up to IIb considered resectable, IIIa suitable for neoadjuvant therapy

 $n = 27$ *Patients correctly staged*

PET/CT	PET	CT
26	20	19

PET/CT significantly better than PET or CT

Analyses also presented to show that PET/CT enabled more accurate T, N and M staging

Compared to PET alone, PET/CT led to correct alteration of staging in seven patients (26%), four to higher stage, three to lower stage

This led to changes in treatment plan for four patients (15%) (two to non-resectable, one to resectable, one neoadjuvant to palliative)

PET not superior to PET/CT in any patient

Author, year, country, study periodCerfolio, 2004,¹³¹ USA, 2002–2003**Article number**

EP 49

Cancer/management decision

Patients with histopathologically proven NSCLC before scanning or after surgery (all were operated upon)

Staging: primary or post-neoadjuvant chemo

Design of study/patient characteristics

Prospective diagnostic accuracy study

Patients with type I diabetes or preoperative RT excluded

n = 129 patients; 77 M, 52 F; median age 66 years (range 24–87 years)

Follow-up: NR

PET/CT specification

GE Discovery LS; FDG 555 MBq; PET/CT and CT scan within 4 weeks of surgery

Visual interpretation by a radiologist with CT scan to correlate findings visually

Reference tests/comparators

Ref.: histopathology

Comp.: PET

Results*n* = 129*Accuracy of staging*

Stage	Total	Patients correctly staged		Patients overstaged		Patients understaged	
		PET/CT	PET	PET/CT	PET	PET/CT	PET
0 ^a	10	9	7	1	3	0	0
I	42	22	14	19	20	4	7
II	17	12	6	3	4	2	7
IIIA	23	16	11	6	8	1	4
IIIB	9	5	3	2	6	3	0
IV	19	17	16	0	0	2	3

^a CR after preoperative chemo and pulmonary resection

PET/CT better than PET, particularly for staging levels I and II

Another analysis excluded 33 patients who underwent neoadjuvant chemo before surgery; this confirmed these results

Similar results were shown when the accuracy of PET/CT and PET was compared in terms of the elements of TNM staging and analysis of each LN station

Identification of mets

19 patients with confirmed M1 disease (three with multiple sites)

Most common site for FPs was in the bone

Site	Total	TP		FP	
		PET/CT	PET	PET/CT	PET
Bone	7	7	6	3	6
Chest	5	4	5	2	3
Liver	4	4	4	0	2
Adrenal	3	2	2	1	1
GI	2	2	1	0	1
Brain	1	1	0	1	1
Thyroid	0	0	0	1	?
Scrotum	0	0	0	1	0

PET/CT changed management in 12 patients (9%): four N2 disease, five N1 disease, three M1 disease

PET changed management in one patient, detecting N2 disease that PET/CT did not detect

Author, year, country, study periodLardinois, 2003,¹³² Switzerland, 2001–2002**Article number**

EP 2299

Cancer/management decisionPatients with proven or suspected NSCLC
Staging**Design of study/patient characteristics**

Prospective diagnostic accuracy study

n = 49 consecutive patients; 28 M, 21 F; mean age 62 years (range 46–81 years)

AC, 28; SCC, 13; large cell carcinoma, 8

Follow-up: NR

PET/CT specification

GE Discovery LS; FDG 350–400 MBq

Visual interpretation of PET alone by two experienced NMPs aware of previous imaging tests

Visual interpretation of PET/CT by combined team of NMPs and a chest radiologist

Reference tests/comparators

Ref.: histopathology or for mets other imaging methods where biopsy not ethically justifiable

Comp.: CECT, PET, visual correlation of PET+CT

Results*Tumour staging (n = 40)*

	Classification		
	Correct	Equivocal	Incorrect
CECT	23	8	9
PET	16	16	8
PET+CT visual	26	5	9
PET/CT integrated	35	4	1

PET/CT significantly higher diagnostic accuracy than CT or PET ($p \leq 0.001$) or PET + CT ($p = 0.01$)*Nodal staging (n = 37)*

	Classification		
	Correct	Equivocal	Incorrect
CECT	22	2	13
PET	18	14	5
PET+CT visual	22	4	11
PET/CT integrated	30	1	6

PET/CT provided additional information in 20/49 patients (41%) beyond that provided by visual correlation of PET and CT
For these 20 patients there were 24 additional pieces of information:

nine, exact location of LNs

three, precise evaluation of chest-wall infiltration

three, mediastinal invasion

seven, differentiation between tumour and peritumoral inflammation or atelectasis

two, exact location of distant mets

Comments

Unclear why PET alone results appear to have so many equivocals and thus look worse than CECT

NSCLC: PET/CT – recurrence**Primary study****Author, year, country, study period**Keidar, 2004,¹³³ Israel, 2001–2002**Article number**

EP 188

Cancer/management decision

Patients with suspected recurrent NSCLC or in whom extent of recurrent disease is unclear, who had no evidence of malignancy for ≥ 6 months after initial therapy

Detection/restaging recurrent disease

Design of study/patient characteristics

Prospective diagnostic accuracy study with patient management

$n = 42$; 28 M, 14 F; mean age 66 years (range 35–82 years)

Stage: IA, 1 I; IB, 14; IIA, 4; IIB, 10; IIIA, 1; IIIB, 1; IV, 1

Follow-up: ≥ 18 months

PET/CT specification

GE Discovery LS; FDG 370–555 MBq

Visual interpretation of PET alone by two experienced NMPs aware of previous imaging tests

Visual interpretation of PET/CT by combined team of NMPs and a chest radiologist

Reference tests/comparators

Ref.: biopsy ($n = 15$), clinical or imaging follow-up

Comp.: PET

Results

$n = 42$

	TP	TN	FP	FN	Sens. (95% CI)	Spec. (95% CI)
PET	24	9	8	1	96% (80 to 99%)	53% (31 to 74%)
PET/CT	24	14	3	1	96% (80 to 99%)	82% (59 to 94%)

PET/CT contributed to change in management in 12 (29%) patients

In five identified that FDG uptake was benign and so further investigations were not needed

In one precise location of malignant sites was identified, allowing RT

In three size/location of radiation field was altered

In three additional mets were identified leading to altered radiation field and/or chemo

SCLC: diagnosis

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
<p><i>Diagnosis</i></p> <p>Of occult SCLC in patients with suspected PNS in whom conventional imaging was negative</p> <p>Reference standards: histopathology and follow-up</p>	<p>AHRQ, USA, 2004¹³⁴</p> <p>(1990 to April 2003)</p>	<p>One hierarchy 2 study, $n = 43$</p> <p>Identification of <i>any</i> cancer PET sens., spec. = 90%</p>	<p>Of the 9/10 cancers identified by PET, only three were SCLC</p> <p>Of the 26/29 correct negative scans, two were paraneoplastic</p> <p>Only five patients had conditions of interest, so very preliminary results</p>

SCLC: staging

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
Staging	AHRQ, USA, 2004 ¹³⁴	Five hierarchy 2 studies ($n = 3-30$ /study)	No joint presentation of sens./spec. in sROC
In patients with histologically confirmed SCLC, to determine extent of disease	(1990 to April 2003)	PET sens. = 89–100%, spec. = 100%	Few studies could calculate spec. as no patients were truly 'negative'
Reference standards: clinical follow-up and histopathology in three studies		In largest study with $n = 30$, CT/MRI comparator had sens. = 65%, spec. = 100%	Some studies differentiated between 'limited' and 'extensive' disease, but PET was not used to identify this 'stage' of disease, merely noted that accuracy was high for PET despite stage of disease
		In second largest study, $n = 25$, CT was comparator with sens. = 93%, spec. = 90%	

Additional primary studies

Author, year, country, study period Brink, 2004, ¹³⁵ Germany, 1999–2003	Article number EP 36			
Cancer/management decision Patients with histologically confirmed SCLC Staging				
Design of study/patient characteristics Diagnostic accuracy study 120 patients; 90 M, 30 F; mean age 61 ± 9 years 37% limited disease, 63% extensive disease Follow-up: NR				
PET specification Siemens ECAT Exact 922; FDG 5 MBq/kg; attenuation correction Within max. of 26 days of CT (mean = 12 days) Visual interpretation by two experienced investigators, blinded				
Reference tests/comparators Ref.: histopathology or all available clinical and imaging data including those from follow-up Comp.: CWU = bronchoscopy, thoracic and abdominal CECT, as indicated cranial MRI or CT, WBS, SPECT. Iliac crest BMB ($n = 84$)				
Results PET concordant with other imaging in 75/120 patients PET discordant in 45 patients at 65 sites 47/65 sites PET correct, 10/54 PET incorrect, eight could not be validated PET correctly upstaged 10/120 patients (8%) to extensive disease (ED) and treatment was altered to just chemo instead of CRT PET correctly downstaged 3/120 patients (3%) who then received CRT PET missed brain involvement in one patient				
	Primary tumour ($n = 120$)	LN mets ED ($n = 118$)	Distant mets (not brain) ($n = 70$)	Brain mets ($n = 91$)
PET sens.	100%	100%	98%	46%
PET spec.	–	98%	92%	97%
CWU sens.	100%	70%	83%	100%
CWU spec.	–	94%	79%	100%

Author, year, country, study periodBradley, 2004,¹³⁶ USA, 2001–2003**Article number**

EP 32

Cancer/management decision

Patients with newly diagnosed histologically or cytologically confirmed SCLC
Staging

Design of study/patient characteristics

Diagnostic accuracy study

25 patients entered, 24 had PET; 11 M, 14 F; mean age 60 years (range 33–90 years)

Follow-up: NR

PET specification

Siemens ECAT HR+; FDG 10–15 mCi; attenuation correction

PET not performed in fasting blood glucose > 150 mg/dl

Visual interpretation by two experienced NMPs, blinded and unblinded

Reference tests/comparators

Ref.: depending on site of met: thin-cut guided CT or US-guided FNAB where feasible, FNA cytology of liver, adrenal biopsy, bone scintigraphy, X-rays, CT or MRI

Comp.: none

Results

Blinded results presented

Primary tumour

PET sens. = 100%

PET identified unsuspected primary tumour or nodal mets in 7/24 (29%) patients; this allowed targeted radiation

Extensive disease

PET identified mets in 3/24 patients; two of these (8%) were upstaged

Unblinded and blinded results same in 20/24 patients

In four patients, CT altered the interpretation. Three of these changes were accurate

SCLC: restaging

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
<p>Restaging after initial treatment for SCLC with chemotherapy and/or radiation, to detect residual disease or new site</p> <p>Reference standard: clinical follow-up</p>	<p>AHRQ, USA, 2004¹³⁴</p> <p>(1990 to April 2003)</p>	<p>Two small hierarchy 2 studies</p> <p>1. $n = 46$ Survival at 1 year PET sens. = 96%, spec. = 41%</p> <p>2. $n = 12$ Recurrence PET sens. = 100%, spec. = 80%</p>	<p>1. Report states $n = 38$, but summary table for survival shows data for 38 post-treatment plus eight initial (so presume the initials were treated as all were positive)</p>

SPN: diagnosis

Systematic reviews

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
<p><i>Diagnosis</i></p> <p>To differentiate between malignant and benign solitary pulmonary nodule, i.e. a lesion "less than 3–4 cm in diameter"</p> <p>Some studies included patients with known or suspected lung cancer and assessed 'mass lesions'; others used gamma cameras</p> <p>Reference standards: histopathology and 2-year clinical follow-up</p>	<p>Gould, 2001¹³⁷</p> <p>(Up to September 2000)</p>	<p>13 hierarchy 2 studies of PET studying SPNs ($n = 19-100$/study, $m = 19-87$/study, total 450 SPNs)</p> <p><i>sROC analysis</i> Maximum joint sens. and spec. for identifying an SPN with PET 90% (95% CI 86 to 93%)</p> <p>PET sens. = 94% (95% CI 89 to 97%) at median spec. of 83%</p> <p>Only eight results for lesions < 1 cm: three TPs, two TNs, three FNs</p>	<p>Six studies on SPN, seven others included SPN subgroups, so fewer SPNs than total patients</p> <p>Total of 40 studies in the meta-analysis</p> <p>PET not read blind to other imaging or clinical data in ~50% of studies (although these reported <i>lower</i> DORs than those read blindly)</p> <p>Accuracy apparently better in studies reported pre-1997 (but not significantly so)</p> <p>No comparator tests reported in meta-analysis</p> <p>Conclusion was that PET has high sens. and intermediate spec. for lesions > 1 cm</p>
<p><i>Diagnosis</i></p> <p>To detect masses and SPNs</p> <p>Reference standards: histopathology and clinical follow-up</p>	<p>National Collaborating Centre for Acute Care (for NICE), UK, 2005⁵</p> <p>(Up to December 2003)</p>	<p>Gould SR of 40 studies plus 13 hierarchy 2 studies¹³⁷</p> <p>Gould overall <i>sROC</i> analysis PET sens. of 97% at median specificity of 78%</p> <p>In additional studies range of PET sens. is 72–100%, with specs from 67 to 100%</p> <p>One of the additional studies in 164 patients documented change in management using three questionnaires. 76% returned all questionnaires. In these, 58% PET contributed to understanding and in 26% PET improved diagnosis. PET contributed to change in treatment in 43 patients (36 avoided surgery, seven had surgery)</p>	<p>All studies of Gould included (including those on gamma camera)</p> <p>PET appears to have good sens. and reasonable spec. for detection of SPNs and masses</p> <p>Noted that there is some concern that PET would not be effective at imaging smaller nodules (< 1.5 cm), but results are not broken down to show this. However, for such small nodules results may be less reliable</p> <p>PET guideline main text states that PET resulted in beneficial change of treatment in 50%, but unclear where this arises from</p>

Lymphoma

Lymphoma: diagnosis Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
Diagnosis Of primary gastric NHL	MSAC, Australia, 2001 [Part 2(ii)] ⁶⁹ (Up to March 2001)	One study in eight patients with NHL and seven controls	Study too small to draw any conclusions

Lymphoma: staging

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
<p>Staging</p> <p>NHL and HL</p> <p>Identification of more advanced, non-bulky or bulky disease, to inform initial therapy</p> <p>Reference standards:</p> <ul style="list-style-type: none"> conventional staging (including CT, US, bone scan, histopathology, MRI, laparotomy, clinical exam, X-ray) CT and clinical follow-up histopathology and clinical follow-up 	<p>MSAC, Australia, 2001 [Part 2(ii)]⁶⁹</p> <p>(Up to March 2001)</p>	<p>Seven hierarchy 2 studies ($n = 11-93$/study)</p> <p>No pooled analyses PET sens. = 79-100% PET spec. = 90-100%</p> <p>Two studies ($n = 52, 76$) assessed bone with comparators of biopsy or scintigraphy. All had spec. >90%. PET sens. 79%, 100% vs comparator sens. 58%, 80%</p> <p>One study ($n = 93$) used Ga-67 scan as comparator, sens. >85% for PET and comparator, spec. NR</p> <p>Only two small studies used CT as comparator, total $n = 27$</p> <p>11 papers indicated how PET changed staging and some indicated how this changed management, but evidence generally relates to a couple of patients in each study, with few details</p> <p>Two more substantive write-ups:</p> <p>1. PET vs Ga-67 ($n = 50$) Upstaged: PET eight, Ga seven Changed management: PET ten, Ga seven</p> <p>2. $n = 49$ Upstaged: PET 27 Downstaged: PET two All but one treated according to PET staging</p>	<p>Overall 18 papers were found, but confirmation of results was only performed in a subset of patients, so sens. and spec. could not be calculated for all papers</p> <p>No differentiation between the two forms of lymphoma and some analyses not patient based</p> <p>Multiple papers appeared on similar sets of patients. Unclear whether they were the same patients. The two studies of bone evaluations may be the same set of patients</p> <p>In most papers, unclear whether change in staging was correct or how management was changed</p> <p>1. PET altered management to: palliative RT (2), RT to chemotherapy (2), chemoradiation to chemotherapy (1), modification of RT field (5)</p> <p>2. No details of changes in management</p>

Additional primary studies

Author, year, country, study period Delbeke, 2002, ¹⁴¹ USA, NR	Article number EP 1297
Cancer/management decision/CWU Lymphoma patients (untreated) Staging CWU: physical examination, CT, BMB (all within 4 weeks)	
Design of study/patient characteristics Patient management 45 patients; 27 M; mean age 35 ± 16 years 22 HL; 23 NHL	
PET specification ECAT 933/08/16; FDG 370 MBq; no attenuation correction Visual interpretation	
Reference tests/comparators Consensus of imaging and CWU used to establish reference. Discordant findings resolved by response to treatment and follow-up results	
Results PET correctly upstaged five, correctly downstaged two and incorrectly downstaged three. Six patients had a change in clinical management because of PET scanning	
Comments There was no evidence that the change in management was documented on a form	

Author, year, country, study periodHong, 2003,¹⁴² Korea, 2000–2001**Article number**

EP 554

Cancer/management decision

Proven malignant lymphoma

Staging (+ nine restaging)

CWU: CT, Ga scan, bone scan, BMB

Design of study/patient characteristics

Diagnostic accuracy study

PET within 2 weeks of CWU

30 consecutive patients; mean age 49 years (range 20–81 years); 19 M, 11 F

Four with HL; 26 with NHL

21/30 were examined by FDG-PET for initial staging work-up

9/30 for restaging after chemo or RT

PET specification

GE Advance; FDG 370 MBq; attenuation correction

Visual interpretation by two NMPs

Reference tests/comparators

Consensus of imaging methods (2/3) used to establish reference. Discordant findings resolved by response to treatment and follow-up results

Comps: CT, Ga scan

Results*Nodal results*

	TP	FN	TN	FP
PET	83	6	447	0
CT	88	1	443	4
Ga	23	66	446	1

Extranodal results

	TP	FN	TN	FP
PET	14	2	314	0
CT	14	2	314	0
Ga	6	10	314	0

Author, year, country, study period Jerusalem 2001, ¹⁴³ Belgium, 1994–1999	Article number EP 949
Cancer/management decision/CWU Verified low-grade NHL Staging CWU: lab screen; clinical exam; CXR; head and neck X-ray; gastroscopy; CT chest, abdomen and pelvis; BMB. LN > 1 cm suspicious	
Design of study/patient characteristics Diagnostic accuracy study PET performed at same time as CWU 42 patients; mean age 62 years (range 37–76 years) 11 small lymphocytic, seven follicular small cleaved, 17 follicular mixed small and large, four MALT, three mantle cell	
PET specification PENN 240-M; FDG 200–300 MBq; attenuation correction Visual interpretation by two NMPs	
Reference tests/comparators Refs: PET alone +ve: biopsy; all methods +ve: classed as TP; all methods –ve: classed as TN; discordant (PET –ve, CWU +ve): follow-up	
Results Authors state that PET has to be combined with BMB and so only present PET+BMB results Compared to CWU, PET+BMB had same stage in 37, lower stage in three, higher in two No changes to management resulting from PET	
Comments Fairly old study	
MALT, mucosa-associated lymphoid tissue.	

Author, year, country, study period Naumann, 2004, ¹⁴⁴ Germany, 1997–2002	Article number EP 258
Cancer/management decision Early-stage HL Staging (+ restaging) CWU: CXR, US, CT, full lab ESR, posterior iliac crest biopsy for bone-marrow evaluation. Subsequent MRI or bone scan performed in cases of suspected osseous involvement (defined as LN \geq 1 cm)	
Design of study/patient characteristics Diagnostic accuracy study performing PET after CWU 88 consecutive patients; 57 M; mean age 34 years (range 17–83 years) Primary HL, 77; recurrent HL, 11	
PET specification ECAT Exact-HR+; FDG 300–370 MBq; attenuation correction Visual interpretation and SUV calculated by two NMPs	
Reference tests/comparators Lesions not generally biopsied. Discordant findings between PET and conventional work-up resolved by follow-up and response to therapy	
Results 18/88 discordant results PET TP, 11; PET TN, 1; PET FN, 6 They state that PET would have changed management in 16 (nine intensified), but take no account of the six FNs, which would have led to incorrect changes	

Author, year, country, study periodSasaki, 2002,¹⁴⁵ Japan, NR**Article number**

EP 695

Cancer/management decision/CWU

Lymphoma

Staging (+ restaging)

CWU: physical exam, CT, GI studies and BMB

Design of study/patient characteristics

Diagnostic accuracy study plus assessment of impact on decision-making

46 patients (43 NHL, three HL); four recurrent disease, others primary; 28 M, mean age 60 years (range 23–90 years)

Histopathology and grade		Stage				Total
		I	II	III	IV	
NHL	Low	2	0	0	1	3
	Intermediate	0	0	1	0	1
	High	11	3	13	6	33
	Unclassified	4	1	2	1	8
Total		1	0	0	0	1
		18	4	16	8	46

Follow-up: more than 6 months after treatment

PET specification

ECAT Exact HR+; FDG mean 271 ± 103 MBq; attenuation correction

Visual interpretation by three NMPs

Reference tests/comparators

Consensus of imaging and CWU used to establish reference. Discordant findings resolved by response to treatment and follow-up results

Comps: CWU+Ga-67; CWU

Results*Nodal involvement (lesion level)*

	TP	FN	TN	FP
CWU	98	54	718	4
CWU+Ga	112	40	718	4
CWU+PET	152	0	713	9

Extranodal lesions

Results presented somewhat oddly; sensitivities and PPV presented:

CWU: sens. 13/19, PPV 13/13

CWU+Ga: sens. 14/19, PPV 14/14

CWU+PET: sens. 18//19, PPV 18/19

CWU+PET accurately upstaged eight and falsely upstaged five; the eight correctly upstaged had different management

PPV; positive predictive value.

Author, year, country, study periodShen, 2002,¹⁴⁶ Taiwan, NR**Article number**

EP 1104

Cancer/management decision

Lymphoma

Staging

Design of study/patient characteristics

Diagnostic accuracy study

30 (14 HL); 16 M; age range 28–65 years

PET specification

ECAT Exact HR+; FDG 370 MBq; attenuation correction

Visual interpretation of PET (no further details)

Reference tests/comparators

Ref.: CT/MRI + clinical + biopsy

Comp.: Ga scan

Results

Reported for 25 patients (unclear why five are missing)

Sens.: PET, 24/25; Ga, 18/25

Author, year, country, study periodYamamoto, 2004,¹⁴⁷ Japan, 1999–2002**Article number**

EP 1653

Cancer/management decision

NHL

Staging

Design of study/patient characteristics

Diagnostic accuracy study

28 patients; 14 M; mean age 57 ± 15 years

13 low-grade, eight intermediate, seven high-grade

PET specification

ECAT Exact HR+; FDG 185 MBq; attenuation correction

Visual interpretation of PET by two NMP; PET, SPECT and CT interpreted together

Reference tests/comparators

Ref.: CT + clinical + biopsy when possible.

Lesions considered negative if no change over 6 months

Comp.: Ga SPECT (SPECT and PET performed within 1 month of each other)

Results*66 confirmed nodal lesions*

32 identified by PET and Ga SPECT, 34 identified only by PET

No evidence for differences by histopathology or location

23 confirmed extranodal lesions

12 identified by PET and Ga SPECT, six only by PET, five by neither

PET +ve, SPECT –ve lesions: three stomach, one colon, one ileum

Nine patients upstaged by PET compared to SPECT; no discussion of management changes

Lymphoma: restaging

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
<p><i>Restaging</i> (treatment response)</p> <p>NHL and HL</p> <p>To identify residual tumour masses, following partial or complete response to induction therapy, to avoid unnecessary consolidation RT if there is no active residual disease</p> <p>Reference standard: clinical follow-up (min. 6 months, most ~2 years)</p>	<p>HTBS, Scotland, 2002²</p> <p>(Up to April 2002)</p>	<p>Eight hierarchy 2 PET studies, six for CT</p> <p>Bayesian model used for sROC analysis to input to economic model</p> <p>Estimates (95% CI):</p> <p><i>CT +ve</i></p> <p>Seven studies, <i>n</i> = 246</p> <p>PET sens. = 80% (59 to 94%)</p> <p>PET spec. = 89% (74 to 97%)</p> <p><i>Without CT information</i></p> <p>Seven studies, <i>n</i> = 384</p> <p>PET sens. = 81% (63 to 92%)</p> <p>PET spec. = 95% (90 to 99%)</p> <p><i>CT</i></p> <p>Six studies, <i>n</i> = 266</p> <p>CT sens. = 75% (58 to 88%)</p> <p>CT spec. = 45% (27 to 64%)</p>	<p>One PET study excluded because scanner was judged to have substandard performance</p> <p>No differentiation between the two forms of lymphoma</p> <p>Sens. of PET and CT comparable</p> <p>CT spec. low, but PET spec. much higher (CIs do not overlap) and variability reduced if PET used without CT information</p>

Additional primary studies: post-treatment prognosis**Author, year, country, study period**Friedberg, 2004,¹⁴⁸ USA, NR**Article number**

EP 112

Cancer/management decisionNewly diagnosed HL patients receiving chemo or CRT
Restaging/treatment response: prognosis**Design of study/patient characteristics**

Diagnostic accuracy study

All received pretreatment PET and Ga scan

Second group received scans 1 month after end of therapy

22 received midtherapy (post-cycle 3) scans

36 patients: four received RT only, 32 either chemo or CRT; 23 M; median age 30 years (range 18–60 years)

PET specification

ECAT Exact HR +; FDG 370 MBq

Visual interpretation by two NMPs, blinded

Reference tests/comparators

Ref.: clinical follow-up

Comp.: Ga scan

Results*Pretherapy scans*

Three patients upstaged by PET (all with below-diaphragm disease)

Midtherapy scan

	CCR	PD
PET+/Ga+	0	2
PET+/Ga-	1	2
PET-/Ga+	1	0
PET-/Ga-	15	1

Post-therapy scan+

	CCR	PD
PET+/Ga+	1	2
PET+/Ga-	3	2
PET-/Ga+	0	0
PET-/Ga-	23	1

Author, year, country, study periodJuweid, 2005,¹⁴⁹ USA/Germany, 1994–2002**Article number**

EP 177

Cancer/management decision

NHL patients given four or eight cycles of anthracycline-based chemo
Response assessment

Design of study/patient characteristics

Treatment response
PET and CT within 16 weeks of end of chemo
54 consecutive patients, median age 58 years (range 21–79 years)
Stage: I/II, 19; III/IV, 35

PET specification

GE 4096, GE Advance or ECAT Exact HR+; FDG 10–15 mCi; attenuation correction
Blinded visual interpretation by one NMP, then reviewed with clinical and CT data

Reference tests/comparators

Ref.: PFS within each category
Comp.: IWC compared to IWC+PET

IWC:

- CR: complete disappearance of all disease
- CRu: no more than one residual mass, $\geq 75\%$ regression
- PR: $\geq 50\%$ reduction in sum of product of greatest diameters of six largest masses (SPD) + no new mass
- SD: by exclusion
- PD: $\geq 50\%$ increase in SPD or new disease sites

IWC+PET:

- CR if PET completely negative; if IWC PD the new (PET –ve) lesion must be ≥ 1.5 cm diameter; if BMB was positive pretreatment it must clear
- CRu only if BMB indeterminate

PD: any new site < 1.5 cm or PET +ve site ≥ 1.5 cm

Results

IWC	IWC+PET				
	CR	CRu	PR	SD	PD
CR	17	0	0	0	0
CRu	5	0	2	0	0
PR	10	0	9	0	0
SD	2	0	1	6	0
PD	1	0	0	0	1

2-year PFS

	IWC		IWC+PET	
	Estimate	95% CI	Estimate	95% CI
CR	88.2	72.9 to 100	91.4	82.2 to 100
CRu	85.7	55.8 to 100	NA	NA
PR	68.4	47.5 to 89.3	41.7	13.9 to 69.6
SD	33.3	2.5 to 64.1	16.7	0 to 46.5
PD	50.0	0 to 100	0	0 to 97.5

3-year PFS

	IWC		IWC+PET	
	Estimate	95% CI	Estimate	95% CI
CR	74.1	51.7 to 96.5	79.9	65.1 to 94.7
CRu	85.7	55.8 to 100	NA	NA
PR	62.2	39.9 to 84.5	41.7	13.9 to 69.6
SD	33.3	2.5 to 64.1	16.7	0 to 46.5
PD	50.0	0 to 100	0	0 to 97.5

CRU, complete response unconfirmed.

Author, year, country, study periodLavelly, 2003,¹⁵⁰ USA, 1995–2001**Article number**

EP 618

Cancer/management decision

Newly diagnosed HL and NHL after first line chemo or CRT

Response assessment: predicting recurrence of disease and determining fields of radiation

Design of study/patient characteristics

Treatment response

Patients received currently accepted chemo (MOPP/ABVD) for HL and CHOP for NHL

Follow-up PET scan median 1 month (range 1–8 months) after completion of therapy

40 patients (20 with HL, 20 with NHL)

HL: 11 M, 9 F; median age 30 years (range 10–65 years)

NHL: 17 M, 3 F; median age 39 years (range 6–77 years)

28 received chemo alone as primary therapy, 12 CRT

(Radiation therapy, field and dose: 30–40 Gy for HL; 36–46 Gy for NHL, for specific site of disease)

First line therapy consisted of either chemo alone (HL $n = 12$, NHL $n = 16$) or chemo plus involved-field radiation therapy (HL $n = 8$, NHL $n = 4$)**PET specification**

GE Advance or ECAT 933; FDG 370 MBq; attenuation correction

Visual interpretation

Reference tests/comparators

Clinical follow-up using laboratory studies: CT, MRI; Ga-SPECT

Results*HL chemo only*

9/12 PET –ve: two original site recurrence

HL chemo + RT

7/8 PET –ve: no recurrence at original site

NHL chemo alone

12/16 PET –ve: three original site recurrence

NHL chemo + RT

3/4 PET –ve: no recurrence at original site

Comments

Includes children

Author, year, country, study periodDe Wit, 2001,¹⁵¹ Germany, NR**Article number**

EP 862

Cancer/management decision

HL

Post-treatment PET to predict DFS

Design of study/patient characteristics

Treatment response prediction

37 patients, but 50 'studies': 39 residual masses and 11 'clinical signs of disease progression'

(17 studies in 17 patients done between CT and RT)

33 studies in 26 patients after completion of all therapy

Seven patients received two separate chemo courses and were scanned twice; not possible to separate out these data

Follow-up: median 26 months

PET specification

Exact 47; FDG 250–400 MBq; no attenuation correction

Visual interpretation

Reference tests/comparators

Ref.: clinical exam and CT/X-ray or US (45) histopathology (5)

Comp.: CT and ESR

Results

Only report here on the 33 post-therapy

	TP	FP	TN	FN
CT (<i>n</i> = 33)	7	17	6	3
PET (<i>n</i> = 33)	10	5	18	0
ESR (<i>n</i> = 32)	5	7	17	3

Author, year, country, study periodZinzani, 2002,¹⁵² Italy, 1996–2000**Article number**

EP 796

Cancer/management decisionLymphoma patients with abdominal disease ≥ 5 cm who have received chemo or CRT

Restaging: follow-up of lymphoma with abdominal presentation

Design of study/patient characteristics

Diagnostic accuracy

Scanning 2 months after RT, 1 month after chemo

59 patients with HL (16) or NHL (43); 20 bulky disease ≥ 10 cm

49% received CRT; 31 M; mean age 51 years (range 17–81 years)

Follow-up: median 24 months

PET specification

Exact 47; FDG 444 MBq; attenuation correction

Visual interpretation by two NMPs independently

Reference tests/comparators

Ref.: clinical assessment after follow-up

Comp.: CT read by single radiologist

Results

	No.	CCR	Relapse
CT-/PET –	7	7	0
CT-/PET +	3	0	3
CT+/PET +	10	4	6
CT+/PET –	39	37	2

CCR, continuing clinical response.

Additional primary studies: investigation of residual mass

Author, year, country, study period Jerusalem, 2003, ¹⁵³ Belgium, 1994–1999	Article number EP 572
Cancer/management decision Histologically verified HL Early detection of relapse in routine follow-up	
Design of study/patient characteristics Diagnostic accuracy/treatment response 1 month after treatment, evaluation of treatment response was carried out by CT and PET every 4–6 months for next 2–3 years Follow-up every 4 months for 2 years; methods included clinical examination and lab screening 36 consecutive patients with histologically verified HL; 13 M, 23 F	
PET specification Penn Pet 240-H Scanner; FDG 300–400 MBq; attenuation correction Visual interpretation by two NMPs	
Reference tests/comparators Ref.: clinical follow-up using CT, FDG-PET, laboratory screening, radiological studies (CXR, CT)	
Results <i>Follow-up results</i>	
Residual mass on CT $n = 19$	Positive PET $n = 5$ (relapse $n = 2$, no relapse $n = 3$) Negative PET $n = 14$ (no relapse $n = 14$)
No residual mass on CT $n = 17$	Positive PET $n = 6$ (relapse $n = 3$, no relapse $n = 3$) Negative PET $n = 11$ (no relapse $n = 11$)

Author, year, country, study periodNaumann, 2001,¹⁵⁴ Germany, NR**Article number**

EP 1044

Cancer/management decision

HL or NHL

Post-treatment evaluation of residual mass

Design of study/patient characteristics

Diagnostic accuracy study

58 patients with primary or recurrent lymphoma (43 HL, 15 NHL)

All had CR except for residual mass ≥ 1 cm on CT. PET scan after CT. No therapy received after PET scan done
 $n = 58$

43 HL; median age 34 years (range 17–69 years); 30 had some RT

15 NHL; median age 44 years (range 20–68 years); four had some RT

Follow-up: median 35 months

PET specification

ECAT Exact HR+; FDG 300–370 MBq; attenuation correction

Visual assessment by two NMPs+SUV (cut-off of 3.0 prespecified)

Reference tests/comparators

Ref.: clinical follow-up

Comp.: none

Results*Results reported by patient: residual mass*

PET result	Lymphoma	<i>n</i>	Residual relapse	CCR
Positive	HL	4	1	3
	NHL	4	4	0
	Total	8	5	3
Negative	HL	36	0	36
	NHL	10	1	9
	Total	46	1	45
Questionable	HL	3	0	3
	NHL	1	1	0
	Total	4	1	3

Results reported by patient: outside mass

PET result	Lymphoma	<i>n</i>	Residual relapse	CCR
Positive	HL	2	0	2
	NHL	2	2	0
	Total	4	2	2
Negative	HL	28	0	28
	NHL	8	1	7
	Total	26	1	35
Questionable	HL	11	0	11
	NHL	2	1	1
	Total	13	1	12

Patients with SUV ≥ 3.0 had a poorer prognosis (5/8 recurrences) than patients with SUV < 3.0 (2/50)

Author, year, country, study periodPanizo, 2004,¹⁵⁵ Spain, 1997–2002**Article number**

EP 273

Cancer/management decisionHL patients with mediastinal residual mass ≥ 2 cm on CT scan

Evaluation of residual mediastinal masses

Design of study/patient characteristics

Diagnostic accuracy study

Patients' IPI was calculated followed by radiation treatment before PET scan

Salvage therapy was heterogeneous and included CHT regimens and/or ASCT

(No therapy after PET scan)

29 consecutive HL patients; 9 M, 20 F; age NR

IPI

IPI	Cases
1	1
2	3
3	10
4	4
5	6
6	3
7	0

Bulky mass	Cases
Yes	22
No	7

Follow-up: NR

PET specification

Siemens ECAT Exact HR+

Reference tests/comparators

Clinical follow-up

Results*PET positive*

12 patients (41%) (including those that relapsed/progressed) had a positive PET scan: three of these (25%) remain in continuous CR after 3, 30 and 58 months; nine of these (75%) either progressed or relapsed; three of these patients had FPs, unrelated to HL

PET negative

17 (59%) had a negative PET scan. All of these (100%) maintained their continuous response throughout the entire observation time

There were no FNs on PET

Comparison of the two groups in relation to DFS at 1 year (i.e. FP/FN) was: 100% vs $20 \pm 5\%$

Economic model

Cancer management decision	Source	Evidence	Data caveats/conclusions
<p><i>Restaging</i></p> <p>HL</p> <p>To identify residual tumour masses, following partial or complete response to induction therapy, to avoid unnecessary consolidation RT if there is no active residual disease</p> <p>Reference standard: clinical follow-up (min. 6 months, most ~2 years)</p>	<p>HTBS, Scotland, 2002²</p> <p>(2002 data inputs and costs)</p>	<p>Cost-effectiveness model for Scotland</p> <p>Compares five strategies:</p> <ol style="list-style-type: none"> 1. All to surveillance 2. All to RT 3. CT -ve to surveillance, CT +ve to RT 4. CT -ve to surveillance, CT +ve to PET <ul style="list-style-type: none"> • PET +ve to RT • PET -ve to surveillance 5. PET -ve to surveillance, PET +ve to RT <p>Models run for men and women aged 20, 40 and 60 years</p> <p>All models show that strategy 5 is most cost-effective, if willingness to pay is \geq£5000 per life-year gained</p> <p>Model predicts a reduction in unnecessary consolidation RT from 36% using CT to 4% using PET instead of CT (strategy 5), or 6% using CT and PET (strategy 4)</p>	<p>No verification in clinical practice, but model robust to a variety of sensitivity analyses and cost-effectiveness clear from probabilistic sensitivity analyses</p>

Lymphoma: treatment response

Primary studies

Author, year, country, study period

Becherer, 2002,¹⁵⁶ Austria, 1998–2000

Article number

EP 820

Cancer/management decision

Lymphoma patients who have received high-dose therapy with stem cell transplantation
Predicting relapse

Design of study/patient characteristics

Treatment response

Patients underwent autologous or allogeneic HDT/SCT with a PET scan interposed between induction or reinduction therapy which might have been combined with irradiation and HDT/SCT (11 also had baseline scan)

$n = 16$; 9 M, 7 F

NHL: $n = 10$; mean age 44 years (range 25–56 years)

HL: $n = 6$; mean age 32 years (range 19–48 years)

Follow-up: ≥ 11 month

PET specification

GE Advance; FDG 370 MBq; attenuation correction

Visual interpretation

Reference tests/comparators

Ref.: Cheson response criteria using CT and BMB 28 days post-HDT/SCT (US and MRI optional) and clinical follow-up

Results

Five PET CR at intermediate scan: all still in CCR

Three PET PR: two in CCR, one relapsed after 6 months

Eight PET NR: seven relapsed (within 6 months), one transplant-related mortality

Author, year, country, study periodCremerius, 2002,¹⁵⁷ Germany, NR**Article number**

EP 466

Cancer/management decisionNHL scheduled for HDT and ASCT
Predictive value**Design of study/patient characteristics**

Treatment response

Patients received induction therapy (five to seven cycles of polychemotherapy). HDT was performed on most patients (CBV scheme) on days 1–3, autologous stem cells were reinfused on day 5

24 consecutive patients; 10 M; mean age 52 years (range 22–69 years)

23 patients received first line therapy

One patient suffered from relapsed lymphoma 4 years after HDT and ASCT as initial treatment

One patient excluded (progressed during induction therapy)

Initial histopathology

Follicular lymphoma grade 1, 3; grade 2, 1; grade 3, 5

Diffuse large B-cell lymphoma = 8

Large cell anaplastic lymphoma = 2

Mediastinal large B-cell lymphoma = 2

T-cell lymphoma (unclassified) = 1

HDC: cyclophosphamide, etoposide, BCNU = 21; Endoxan = 3

Additional RT in nine patients

PET performed up to four times:

PET1: preinduction chemo

PET2: after three cycles of induction chemo

PET3: after completion of induction therapy/before HDT and ASCT

PET4: after recovery from ASCT or completion of additional involved-field radiation (6–14 weeks after ASCT)

PET specification

ECAT Exact 922 or Siemens ECAT 953; FDG 150–300 MBq; attenuation correction

If sequential scans available fall of 25% in SUV scored as PMR. Clearance of all lesions (or fall in SUV to <3.5) CMR

Reference tests/comparators

Clinical follow-up using laboratory studies, CT and MRI

Results

Early PET scans (after three cycles) not predictive of PFS

Metabolic response based on change from PET2 to PET3 associated with PFS (size of change for prediction not specified)

Similarly, PET3 to PET4 (19 patients with PMR median PFS 25 months vs four patients)

BCNU (busulphan), etoposide (VP-16); CBV, cyclophosphamide; PMR, partial metabolic response.

Author, year, country, study periodFilmont, 2003,¹⁵⁸ USA, NR**Article number**

EP 498

Cancer/management decision

Patients with aggressive lymphoma undergoing ASCT

Prediction of clinical outcome

Design of study/patient characteristics

Treatment response

PET before and after ASCT in two groups with different timings of PET

 $n = 43$

Group 1: PET 2–5 weeks after initiation of standard chemo before ASCT

 $n = 20$; 6 HL, 14 NHL; 13 M, 7 F; median age 46 years (range 17–68 years)

Group 2: PET within a median of 2.4 months (range 2–6 months) after ASCT

 $n = 23$; 6 HL, 17 NHL; 12 M, 11 F; age range 17–65 yearsFollow-up: ≥ 6 months after ASCT**PET specification**

ECAT Exact HR+; FDG 370–550 MBq; attenuation correction for 22/43 patients

Visual interpretation

Reference tests/comparators

Ref.: PFS from clinical follow-up

Comp.: CT

Results*Group 1*

8/20 disease free after 13.3 months' median follow-up (post-ASCT)

PET: sens. TP in 11/12 with relapse, spec. TN in 7/8

CT: similar sens. (10/12), poorer spec. (2/8)

Group 2

9/23 disease free after 16.5 months' median follow-up (post-ASCT)

PET: sens. TP in 13/14 with relapse, spec. TN in 8/9

CT: same sens. (13/14), poorer spec. (3/9)

PET better predictor of PFS than CT, in both groups

Author, year, country, study periodHaïoun, 2005,¹⁵⁹ France, 2000–2004**Article number**

EP 1361

Cancer/management decision

Patients with aggressive NHL (large B-cell or peripheral T-cell) give induction chemo, possibly plus high dose and ABSCT in four cycles

Assessment of response

Design of study/patient characteristics

Treatment response

PET before chemo, then after two and four cycles of induction

Induction therapy

If <60 years: rituximab, adriamycin, cyclophosphamide, vincristine, bleomycin, prednisone

If >60 years: rituximab+CHOP

If <60 years and two or three high-risk factors on IPI: high-dose chemo + ABSCT if at least partial response to induction

90 patients; 56 M; median age 53 years (range 17–78 years)

IPI status: low 16%, low–intermediate 26%, high–intermediate 33%, high 26%

PET specification

ADAC C-PET; 2 MBq/kg; attenuation correction

Visual interpretation by two observers, blinded

Reference tests/comparators

Refs: Cheson response criteria: clinical exam, lab screen, CT, BMB if marrow invaded at baseline. Restaging every 6 months; 2-year median follow-up

Results

54 PET –ve after two cycles

No patient PET –ve at this time became PET +ve after four cycles, so two-cycle results reported

PET –ve at two cycles: results at final follow-up

CR	CR post-salvage	PR	Progressive disease	Dead
40	7	1	1	5

PET +ve at two cycles: results at final follow-up

CR	CR post-salvage	PR	Progressive disease	Dead
18	2	0	0	16

Overall survival:

PET –ve 90%, PET +ve 61%

$p = 0.006$, independent of IPI and regimen

ABSCT, autologous blood stem cell transplantation.

Author, year, country, study period Hutchings, 2005, ¹⁶⁰ UK, 1993–2004	Article number EP 1385
Cancer/management decision HL undergoing chemotherapy Prediction of outcome after treatment	
Design of study/patient characteristics Treatment response All patients PET after two or three cycles, 42 PET at end of treatment as well 85 patients; 43 M; mean age 38 years (range 15–73 years) Stage: I, 13; II, 44; III, 16; IV, 12 79 received ABVD Follow-up: median 20 months (range 6–125 months)	
PET specification ECAT 951R; FDG 350 MBq; attenuation correction Visual interpretation by two NMPs, scored as negative, positive, MRU	
Reference tests/comparators Ref.: OS and DFS	
Results 55 PET after two cycles, 30 after three 63 negative, nine MRU, 13 positive 12 progressions: eight positive, one MRU, three negative Cox model for DFS: Ann Arbor stage and PET result both significant predictors ($p < 0.001$) MRU and negative 'close' (hazard ratio 1.24, $p > 0.5$) OS 'small number of events'	
Comments Further analysis: 2/7 PET +ve and stage I–II relapsed, 6/6 PET +ve stage III/IV	
MRU, minimum residual uptake.	

Author, year, country, study period Schot, 2003, ¹⁶¹ Netherlands, 1999–2002	Article number EP 703
Cancer/management decision Relapsed lymphoma patients given second line induction therapy + ASCT Prediction of outcome	
Design of study/patient characteristics Treatment response Second line therapy, followed by high-dose therapy + ASCT for responders (these patients included in PET study) PET before and after induction chemo 46 patients; 13 HL; 29 M; median age 52 years (range 21–65 years) Follow-up: median 24 months	
PET specification Exact 4HR+; dose NR; attenuation correction Visual assessment	
Reference tests/comparators Ref.: PFS	
Results Relative risk of progression with persistent lesion 2.59 (95% CI 1.01 to 6.90) Reduction in perceived intensity <90% (19/40) vs >90% Relative risk 2.85 (95% CI 1.15 to 7.05)	

Author, year, country, study periodSpaepen, 2002,¹⁶² Belgium, 1995–1999**Article number**

EP 719

Cancer/management decision

Patients with aggressive NHL undergoing chemo
Midtreatment PET scan to assess treatment response

Design of study/patient characteristics

Treatment response study
PET scan after three or four cycles of treatment
70 patients; 56 patients 12 weeks CHOP, 14 similar regimens; 52 M; age range 3–76 years
IPI: low, 26; low–intermediate, 22; high–intermediate, 17; high, 5
Follow-up: median 1107 days

PET specification

CTI ECAT 931; FDG 370–555 MBq; attenuation correction NR
Scans scored as negative or positive by two NMPs with knowledge of initial staging data, but no other information

Reference tests/comparators

Response assessment 3 months post-treatment by conventional methods (clinical, lab tests, CT, BMB, CXR and MRI scan)
Also follow-up for progression

Results

37 patients PET negative at midtreatment, 31 of these CR
Five CR at 3 months, relapsed (median PFS 365 days)
One remaining patient had bone-marrow involvement and achieved CR after further therapy
33 PET positive: no continuing CR

Author, year, country, study periodTorizuka, 2004,¹⁶³ Japan, NR**Article number**

EP 741

Cancer/management decision

NHL and HL patients undergoing chemo
Early therapy monitoring

Design of study/patient characteristics

Treatment response
PET before therapy then after one or two cycles of chemo
20 patients, 17 NHL; mean age 55 years (range 29–72 years)
Stage: II, 2; III, 8; IV, 7
Follow-up: 24 months

PET specification

Hamamatsu Phoyonics SHR 22000; FDG 200–500 MBq; attenuation correction
Visual interpretation of PET using all available data + SUV

Reference tests/comparators

Ref.: follow-up

Results

Ten clinical CR after chemo
All 20 abnormal PET at baseline, four negative after two cycles
Sens. and spec. for prediction of disease at 24 months 14/16 (sens.) and 2/4 (spec.)
Post-hoc cut-off of 60% for predicting CR at therapy end separated ten CR from nine out of ten non-responders

Author, year, country, study period
Zijlstra, 2003,¹⁶⁴ Netherlands, 1998–2000

Article number
EP 794

Cancer/management decision
NHL patients treated with CHOP
Midtreatment PET as prognostic tool

Design of study/patient characteristics
Treatment response
Baseline CT, chest node biopsies, BMB
PET and Ga scan 2 weeks after second CHOP cycle
26 patients; 14 M; median age 55 years (range 22–77 years)
Stage: I, 5; II, 11; III, 4; IV, 6
Follow-up: 16 months

PET specification
ECAT Exact HR+; FDG 350–420 MBq; attenuation correction
Visual interpretation of PET by four NMPs using pretreatment data

Reference tests/comparators
Ref.: PFS
Comp.: Ga scan (interpreted similarly to PET)

Results
Negative PET: 64% progression free follow-up, vs 50% for negative Ga
Positive PET: 25% progression free follow-up, vs 42% for negative Ga

Lymphoma: PET/CT – staging/restaging/recurrence**Primary studies**

Author, year, country, study period Allen-Auerbach, 2004, ¹⁶⁷ USA, 2002–2003	Article number EP 6									
Cancer/management decision Patients with lymphoma (20 HL, 53 NHL) Staging ($n = 14$) and restaging ($n = 59$)										
Design of study/patient characteristics Retrospective diagnostic accuracy study $n = 73$; 36 M, 37 F; mean age 51 ± 17 years Follow-up: mean 10 months (range 1–78 weeks)										
PET/CT specification CPS Innovations Reveal RT; FDG 7.8 MBq/kg Visual interpretation of PET images by consensus of two NMPs, radiologist subsequently added for interpretation of PET/CT images										
Reference tests/comparators Ref.: biopsy ($n = 26$), clinical follow-up (all), other imaging ($n = 52$) Comp.: PET										
Results 34/73 had malignancies PET and PET/CT concordantly correct in 61 patients, concordantly incorrect in 5 patients, PET/CT correct in seven patients where PET was incorrect										
	<table border="1"> <thead> <tr> <th></th> <th>Sens. (95% CI)</th> <th>Spec. (95% CI)</th> </tr> </thead> <tbody> <tr> <td>PET</td> <td>88% (69 to 91%)</td> <td>82% (70 to 93%)</td> </tr> <tr> <td>PET/CT</td> <td>91% (76 to 98%)</td> <td>92% (82 to 99%)</td> </tr> </tbody> </table>		Sens. (95% CI)	Spec. (95% CI)	PET	88% (69 to 91%)	82% (70 to 93%)	PET/CT	91% (76 to 98%)	92% (82 to 99%)
	Sens. (95% CI)	Spec. (95% CI)								
PET	88% (69 to 91%)	82% (70 to 93%)								
PET/CT	91% (76 to 98%)	92% (82 to 99%)								
PET/CT correctly changed stage assigned by PET in 7/73 patients (10%) (two upstaged, five downstaged)										
Comments States that a “reliable reference standard was established”, so presume this was a retrospective review of available patients Some patients had short follow-up										

Author, year, country, study periodFreudenberg, 2004,¹⁶⁸ Germany, NR**Article number**

EP 110

Cancer/management decisionPatients with lymphoma (18 HL, 9 NHL) undergoing clinical restaging post-therapy
Restaging**Design of study/patient characteristics**

Retrospective diagnostic accuracy study

 $n = 27$; 16 M, 11 F; mean age 46 years (range 19–70 years)Follow-up: ≥ 12 months**PET/CT specification**Siemens Biograph; FDG 360 ± 20 MBq/kgPET: Visual interpretation by two experienced NMPs in consensus, blinded to other imaging, $SUV \geq 2.5 =$ PET positive

CT: two radiologists, blinded to other imaging

PET and CT then read side by side in consensus

PET/CT then viewed by all physicians

Reference tests/comparators

Ref.: biopsy (seven lesions), clinical follow-up and other imaging

Comp.: PET, CT, PET+CT

Results

14/27 had recurrence

86 positive LNs found in 23/135 LN regions

Two patients with extranodal involvement

Patient-based analysis

	Sens.	Spec.
CT	78%	54%
PET	86%	100%
PET+CT	93%	100%
PET/CT	93%	100%

Compared with CT, PET/CT correctly upstaged six patients (26%) and downstaged seven (26%)

Compared with PET, PET/CT correctly upstaged two patients and downstaged one patient

Author, year, country, study periodSchaefer, 2004,¹⁶⁹ Switzerland, 2001–2002**Article number**

EP 310

Cancer/management decision

Patients with lymphoma (42 HL, 18 high-grade NHL)
 Staging/restaging/recurrence

Design of study/patient characteristics

Retrospective diagnostic accuracy study
n = 60; 37 M, 23 F; mean age 40 years
 Follow-up: NR

PET/CT specification

GE Discovery LS; FDG 370 MBq/kg
 Visual interpretation by two NMPs when there were discrepant findings

Reference tests/comparators

Ref.: biopsy (20 patients); clinical, laboratory or other imaging follow-up (all patients)
 Comp.: CECT within 24 days of PET/CT

Results

Patient-based analysis (*n* = 60)

LN involvement

	Sens.	Spec.
CECT	88%	86%
PET/CT	94%	100%

Organ involvement

	Sens.	Spec.
CECT	50%	90%
PET/CT	88%	100%

Main reason for FP in CECT was due to lung infiltration

CECT missed bone involvement that PET/CT detected

PET/CT provided additional information in nine patients (15%) compared with two patients for CECT

Comments

This is an English publication of Steinert (2004)²⁵²

Malignant melanoma

Malignant melanoma: staging – early-stage disease

Primary studies

Author, year, country, study period

Acland, 2001,¹⁷⁰ UK, NR

Article number

EP 805

Cancer/management decision

Patients with primary cutaneous melanoma (> 1 mm Breslow thickness)^a to detect micrometastatic disease in the regional draining LNs

Staging

Design of study/patient characteristics

Diagnostic accuracy study

n = 50; 27 M, 23 F; mean age 53 years (range 26–89 years)

^a (one patient had lesion of 0.8 mm, but with evidence of lymphatic invasion on histopathology, as allowed in study design)

Follow-up: mean 13 months (range 5–26 months)

PET specification

Siemens ECAT 951R; FDG 350MBq; no attenuation correction; diabetics excluded

Visual interpretation by two NMPs, blinding not stated

Reference tests/comparators

Ref.: SLNB + histopathology

Comp.: SLNB

Results

SLNB as reference

14 patients had positive sentinel LNs

Mean Breslow thickness 1.9 mm (range 1.0–4.2 mm), eight lesions < 1.5 mm thickness

PET detected 0/14, giving sens. = 0% (95% CI 0 to 23%)

PET positive for seven patients in other sites: one papillary carcinoma, three due to physiological uptake, three no evidence of disease after follow-up for 12–15 months

So seven FPs for metastatic melanoma, six FPs for any cancer

PET is not sufficiently sensitive to detect small deposits within clinically normal LNs. PET has little to contribute as a staging procedure in this group of patients

Author, year, country, study periodBelhocine, 2002,¹⁷¹ Belgium, NR**Article number**

EP 425

Cancer/management decision

Patients with stage I or II melanoma

Staging

Design of study/patient characteristics

Diagnostic accuracy study in two centres

 $n = 21$ consecutive patients; 10 M, 11 F; mean age 58 ± 11 years

Breslow thickness 0.5–4.6 mm (mean 1.9 mm)

Follow-up: median 12 months

PET specificationUGM PENN 240H ($n = 13$); ADAC C-PET ($n = 8$); FDG 259–333 MBq; attenuation correction

Visual interpretation in routine clinical fashion; blinding NR

Reference tests/comparators

Ref.: histopathology

Comp.: SLNB within 1 week of PET

Results

6/21 had a positive SLN

	TP	FN	TN	FP	Sens. (95% CI)	Spec. (95% CI)
PET	1 (1.8 cm)	5 (all < 1 cm)	13	1	14% (0 to 28%)	93% (83 to 103%)
SLNB	NR	NR	NR	NR	86% (72 to 100%)	100% (100 to 100%)

Comments

CI approximations clearly permit values over 100%

Author, year, country, study periodFink, 2004,¹⁷² Austria, 1998–2002**Article number**

EP 103

Cancer/management decision

Patients with newly diagnosed stage I/II primary cutaneous melanoma, Breslow thickness > 1 mm

Staging

Design of study/patient characteristics

Diagnostic accuracy study

 $n = 48$ consecutive patients; 25 M, 23 F; mean age 54 years (range 21–83 years)

Mean tumour thickness = 2.9 mm (range 1–14 mm)

Follow-up: 12 months

PET specification

Siemens ECAT ART; FDG 250 MBq; attenuation correction

Visual interpretation by two experienced NMPs, blinding NR

Reference tests/comparatorsRef.: histopathology in those with positive sentinel nodes ($n = 8$), follow-up in others

Comp.: none

Results

8/48 (17%) had positive SLNB

Mean size of LN mets 3.4 mm (range 0.2–11 mm)

PET: one TP (the largest met at 11 mm), seven FN, 40 TNs, no FPs

Sens. = 13% (95% CI 2 to 47%), spec. = 100%

Author, year, country, study periodHafner, 2004,¹⁷³ Switzerland, 1999–2002**Article number**

EP 2235

Cancer/management decision/cancer work-upPatients with newly diagnosed primary cutaneous melanoma (Breslow thickness ≥ 1 mm)

Staging

CWU: CXR, abdominal and regional LN US

Design of study/patient characteristics

Diagnostic accuracy study

 $n = 100$ consecutive patients eligible for the study; 55 M, 45 F; mean age 56 years (range 18–79 years)

AJCC T status: 38 T2 (1–2 mm); 43 T3 (2.01–4 mm); 19 T4 (>4 mm)

Follow-up: median? = 20 months (range 8–39 months)

PET specification

Siemens ECAT 95 IR; FDG 350 MBq; attenuation correction NR

Visual interpretation by one NMP, blinding NR

Reference tests/comparators

Ref.: SLNB

Comp.: clinical exam, US

Results

26 positive sentinel LNs

Regional LN mets $m = 26$: PET and US each detected 2/26

	Sens. (95% CI)	Spec. (95% CI)
Clinical exam	12% (6 to 28%)	100% (95 to 100%)
PET	8% (1 to 25%)	100% (95 to 100%)
US	8% (1 to 25%)	88% (78 to 94%)
US+PET	12% (6 to 28%)	88% (78 to 94%)

Distant mets $m = 0$; PET two FPs, US three FPs

	Sens.	Spec. (95% CI)
CXR	–	96% (90 to 99%)
Abdominal US	–	97% (91 to 99%)
PET	–	98% (93 to 100%)
CXR+US+PET	–	88% (78 to 94%)

Macroscopic mets can be reliably detected by physical exam and LN US, followed up by FNAB

Mets with a diameter <4 mm can only be reliably diagnosed by SLNB

AJCC, American Joint Committee on Cancer.

Author, year, country, study periodHavenga, 2003,¹⁷⁴ Netherlands, NR**Article number**

EP 535

Cancer/management decision

Patients with primary cutaneous melanoma (> 1 mm Breslow thickness and no palpable regional LNs)
Staging

Design of study/patient characteristics

Diagnostic accuracy study

n = 55 in two centres; 26 M, 29 F; median age 54 years (range 15–77 years)

Median Breslow thickness = 2.4 mm (range 1–13 mm)

Follow-up: NR, but in two patients with distant mets, follow-up periods of 12 and 38 months noted

PET specification

In 45 patients: Siemens ECAT-ART; FDG 200–220 MBq; attenuation correction

In 10 patients: Siemens ECAT 951/31 or Siemens ECAT HR+; FDG 386–603 MBq; attenuation correction

Method of interpretation NR

Reference tests/comparators

Ref.: SLNB

Comp.: none

Results

SLNB positive in 43

LN mets

13 showed SLNB proven LN mets

2/13 detected by PET (calculated sens. = 15%)

Five FPs

In the 11 PET FNs, the SLN was ≤2 mm in eight patients, 4–5 mm in two patients and 11 mm in one patient

Distant mets

PET detected eight possible distant mets, one TP, seven FPs (one was another cancer)

(Sens. and spec. not calculated as ref. standard for this unclear)

Comments

Much higher dose of FDG used in one centre. Results not differentiated by centre, so influence of this cannot be investigated

Author, year, country, study periodKokoska, 2001,¹⁷⁵ USA, 1998–2000**Article number**

EP 974

Cancer/management decision

Patients with melanoma of the head and neck, Breslow depth > 1 mm

Staging

Design of study/patient characteristics

Diagnostic accuracy study

n = 18; 13 M, 5 F; mean age 68 years (range 52–83 years)

AJCC stage: I, 2; II, 12; III, 2; 2 unknown

Mean tumour thickness = 3.2 mm (range 0.5–12 mm)

Follow-up: mean 19 months

PET specification

Siemens ECAT 951/31; FDG 370 MBq; attenuation correction

No details of interpretation methods

Reference tests/comparatorsRef.: SLNB (*n* = 17), elective node dissection (*n* = 1)

Comp.: none

Results*n* = 18

17 positive sentinel LNs (94%)

PET sens. 40% for detecting regional mets

Spec. cannot be reported in the absence of long-term follow-up

Comments

Unclear reporting of true and false results for PET

Author, year, country, study periodLongo, 2003,¹⁷⁶ USA, NR**Article number**

EP 628

Cancer/management decision

Patients with stage I and II cutaneous melanoma (> 1 mm Breslow thickness), for detection of LN mets
Staging

Design of study/patient characteristics

Diagnostic accuracy study

 $n = 25$; 12 M, 13 F; mean age 54 years (range 18–76 years)

Follow-up: median 15 months (range 10–29 months)

PET specification

ADAC C-PET-250; FDG 2 MBq/kg; attenuation correction; excluded those with diabetes

Visual interpretation: professionals NR

Reference tests/comparators

Ref.: histopathology and clinical follow-up

Comp.: SLNB

Results**SLNB**

9/25 (36%) had positive SLNB. After follow-up no other patients showed clinical signs of recurrence, so sens. = 100%

PET

PET correctly identified 2/9 cases of LN mets with macroscopic involvement, sens. = 22%

Most nodes detected by SLNB were microscopic and not detected by PET

CommentsDiscussion states that the spherical volume that could be detected by a PET scanner with a spatial resolution of 5–6 mm is in the range of 65–113 mm³**Author, year, country, study period**Reinhardt, 2002,¹⁷⁷ Germany, NR**Article number**

EP 681

Cancer/management decision

Patients with cutaneous melanoma with Breslow thickness >0.75 mm

Staging

Design of study/patient characteristics

Diagnostic accuracy study

 $n = 67$; 47 M, 20 F; mean age 56 years (range 18–85 years)Breslow thickness 0.76–1.49 mm in 14 patients; 1.5–2.49 mm in 26; 2.5–3.99 mm in 17; ≥ 4 mm in ten

Follow-up: NR

PET specification

Siemens ECAT Exact 921/47; FDG 200–400 MBq; attenuation correction

Visual interpretation by two experienced NMPs, blinded

Reference tests/comparators

Ref.: histopathology, imaging (US, CT, MRI) and/or clinical follow-up

Comp.: S-100B protein in serum

Results $n = 67$ **PET**

43 negative: 41 TNs (as determined by clinical data), two FNs for distant mets

11 with LN mets: one of these FP, ten TP

13 with distant mets: 13 TPs

For LN or distant mets, PET sens. = 92%, spec. = 98%

S-100B protein, with cut-off value of 0.2 $\mu\text{g/l}$: sens. = 67%, spec. = 95%**Comments**

Use of ref. standard unclear and period for clinical follow-up when used as a ref. standard not stated

Author, year, country, study periodWagner, 2005,¹⁷⁸ USA, NR**Article number**

EP 1627

Cancer/management decision/cancer work-up

Patients with early-stage cutaneous melanoma (> 1 mm Breslow thickness, local disease recurrence or solitary in-transit mets) to detect occult LN and distant mets

Staging (five with local recurrence)

CWU: CXR, blood tests, conventional imaging

Design of study/patient characteristics

Diagnostic accuracy study

$n = 144$; 74 M, 70 F; mean age 54 years (range 24–79 years)

Follow-up: median 41 months

PET specification

Siemens ECAT 951/31R; FDG 10 mCi; attenuation correction

Visual interpretation by one NMP, blinded

Reference tests/comparators

Ref.: for LNs: histopathology; for distant mets and recurrence: histopathology and 3–6-month clinical and imaging follow-up

Comp.: none

Results*Occult LN mets*

$n = 144$, 184 LN regions subjected to SLNB

40 patients with 43 positive LN regions

	TP	FN	TN	FP	Sens. (95% CI)	Spec. (95% CI)
PET	9	34	137	4	21% (10 to 36%)	97% (93 to 99%)
SLNB	42	1	137	0	98%	100%

37 regions were <80 mm³ volume and only four of these were detected by PET

Distant mets

Lesion analysis:

34 patients, 47 lesions in scan area (seven in brain, outside scan area)

PET sens. = 5/47 (11%) (95% CI 4 to 23%)

Patient analysis:

140 patients with at least 6 months follow-up, 136 without brain/scalp recurrence

	TP	FN	TN	FP	Sens. (95% CI)	Spec. (95% CI)
PET	1	24	96	15	4% (0.1 to 20%)	86% (79 to 92%)

Malignant melanoma: staging – later stage disease**Primary studies**

Author, year, country, study period Ghanem, 2005, ¹⁷⁹ Germany, NR	Article number EP 1340	
Cancer/management decision Patients with malignant melanoma Staging for detection of liver mets		
Design of study/patient characteristics Diagnostic accuracy study <i>n</i> = 35; M/F not stated; median age 58 years (range 24–85 years) Follow-up: 3–15 months		
PET specification Siemens ECAT Exact; FDG 360 ± 30 MBq; attenuation correction PET: visual interpretation by two NMPs, blinded to MRI MRI: two radiologists, blinded to PET		
Reference tests/comparators Ref.: MRI, follow-up investigations (including CT) Comp.: MRI (Siemens Magnetom Expert, 1.5 T)		
Results <i>n</i> = 35, comparison of PET and MRI 27 concordant scans indicated no liver mets Four concordant scans indicated liver mets Four discordant scans, MRI one FP, PET one FP, PET one FN; in one patient more mets detected on PET		
	Sens.	Spec.
PET	83%	97%
MRI	100%	97%
Comments Ref. standard mainly based on comparison to MRI, which may not be perfect in all situations		

Author, year, country, study periodGulec, 2003,¹⁸⁰ USA, NR**Article number**

EP 527

Cancer/management decision/cancer work-up

Patients with suspected metastatic melanoma

Staging

CWU: brain MRI, chest, abdomen, pelvis CT (for subset)

Design of study/patient characteristics

Diagnostic accuracy study and "impact on surgical decision making" (no documentation)

 $n = 49$ consecutive patients; 30 M, 19 F; mean age 51 years (range 25–83 years)

AJCC stage: III/IV, 46; II, 3 with high-risk primaries and suspicious symptoms

Follow-up: median NR

PET specification

PET model not stated; FDG 10–15 mCi; attenuation correction NR

Visual interpretation blinded, but professionals NR

Reference tests/comparators

Ref.: histopathology

Comp.: CWU for subset and "conventional metastatic survey"

Results $n = 49$

51 lesions evaluated, 44 were melanoma

	Lesions > 1 cm ($n = 29$)		Lesions \leq 1 cm ($n = 15$)	
	Sens.	Spec.	Sens.	Spec.
PET	100%	75%	13%	33%

When compared with a conventional metastatic survey on the 49 patients, PET detected greater extent of metastatic disease in 27 patients (55%), same extent of disease in 18 (37%) and less disease in four (8%) (two mets in brain, one skeletal, one subcutaneous)

In the 27 patients with full CWU, PET detected greater extent of disease in 52%, same in 41%, less in 7%

PET prompted treatment changes in 24 patients (49%): in 12 the planned operation was cancelled, in six additional operations were performed and in six medical therapy was changed

Comments

Major claims for change in treatment management, but no explanation as to how this was documented and unclear what is meant by 'metastatic survey' and why not everyone received the CWU

Author, year, country, study periodVereecken, 2005,¹⁸¹ Belgium, 2000–2001**Article number**

EP 365

Cancer/management decision

Patients with melanoma at intermediate or high risk of recurrence, scheduled for SLNB and complementary excision
Staging

Design of study/patient characteristics

Diagnostic accuracy study

 $n = 43$; 20 M, 23 F; mean age 53 years (range 22–78 years)

AJCC stage: II, 9; III, 17; IV, 15; V, 2

Follow-up: 6 months

PET specification

ECAT; FDG dose and attenuation correction NR

Professional responsible for interpretation NR; blinded

PET scan with other imaging, 3 days before surgery

Reference tests/comparators

Ref.: histopathology (SLNB) and imaging (CT/MRI) and clinical follow-up

Comp.: none

Results

39/43 had sentinel LNs identified

From these 39, 63 LNs were biopsied

14 positive LNs from ten patients:

PET sens. = 40%

Four TPs: (2, 3, 4, 5 mm)

Six FNs: (1, 2, 2, 4, 4, 4 mm)

PET positive in 29 patients

Four LNs

19 other reasons (inflammation, other cancers, prostatitis, etc.)

Nine other positives that remain unexplained after 6 months follow-up

Comments

Results not presented clearly; the positive results probably have some patients in more than one category

Malignant melanoma: staging/restaging

Systematic reviews

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions																														
<p><i>Staging/restaging</i></p> <p>Identification of regional or systemic metastatic spread in patients with primary or suspected recurrent melanoma, in patients with histologically proven cutaneous melanoma</p> <p>Reference standards: histopathology, follow-up, imaging for two studies with primary cases, SNB for one</p>	<p>Mijnhout, 2001¹⁸²</p> <p>(Up to July 1999)</p>	<p>11 hierarchy 2 studies ($n = 12-100/\text{study}$)</p> <p>Seven studies provided enough data to calculate index test characteristics, six in sROC analysis</p> <p>Both distant and regional spread included in the pooled analysis ($n = 360$)</p> <p>sROC, random effects model Sens. (95% CI): PET 78% (70 to 84%) Spec. (95% CI): PET 88% (82 to 92%)</p> <p>Overall DOR = 33.1 DOR (95% CI) by AJCC stage before PET: III: 18.3 (0.4 to 127.5) II: 5.5 (1.0 to 31.5) I: 7.4 (0.1 to 462.5) (excluding low outlier with stage I/II patients)</p> <p>MSAC, 2000¹⁸³ included all the studies presented here and notes that one study reported that 22/100 patients had change in management as a result of PET</p>	<p>Five studies in recurrent, one in primary, five mixed</p> <p>Six in distant mets, four local LN mets, one both</p> <p>Poor reporting of sens./spec. for comparators</p> <p>Study ($n = 74$) using SNB as ref.: showed very low sensitivity (17%) in stage I/II patients and excluded from meta-analysis, so heterogeneity is greater than model shows</p> <p>Only one other study with one stage I patient</p> <p>Deterministic value of PET looks better in stage III patients</p> <p>At outset, author notes that PET has been promoted for recurrence, but some controversy over use in primary disease. There are no analyses by primary vs recurrent. MSAC, 2000¹⁸³ studied only recurrent, but only found one study; this author found more studies</p>																														
<p><i>Staging/restaging</i></p> <p>In patients with primary or suspected recurrent malignant melanoma</p>	<p>DACEHTA, Denmark, 2001⁶</p> <p>(1990 to May 2001)</p> <p>(Nine of these in Mijnhout,¹⁸² five later ones from 1999/2000 included here plus one from 1995)</p>	<p>15 hierarchy 3 studies ($n = 12-100/\text{study}$)</p> <p>Four out of five studies published after Mijnhout show PET sens. >85%, one study in stage II patients shows PET sens. = 78% PET spec.: 95%, 84%, 44%, 56%, 87%</p> <p>Three studies showed CT comparators:</p> <table border="1"> <thead> <tr> <th></th> <th>Sens.</th> <th>Spec.</th> </tr> </thead> <tbody> <tr> <td>1. ($n = 76$)</td> <td></td> <td></td> </tr> <tr> <td>PET</td> <td>94%</td> <td>83%</td> </tr> <tr> <td>CT</td> <td>55%</td> <td>84%</td> </tr> <tr> <td>2. ($n = 50$)</td> <td></td> <td></td> </tr> <tr> <td>PET</td> <td>100%</td> <td>95%</td> </tr> <tr> <td>CT</td> <td>92%</td> <td>82%</td> </tr> <tr> <td>3. ($n = 38$)</td> <td></td> <td></td> </tr> <tr> <td>PET</td> <td>97%</td> <td>56%</td> </tr> <tr> <td>CT</td> <td>62%</td> <td>22%</td> </tr> </tbody> </table>		Sens.	Spec.	1. ($n = 76$)			PET	94%	83%	CT	55%	84%	2. ($n = 50$)			PET	100%	95%	CT	92%	82%	3. ($n = 38$)			PET	97%	56%	CT	62%	22%	<p>Population not clearly delineated</p> <p>Analysis probably mixed by patient and lesion</p> <p>Author notes that many studies found that PET had highest precision with visceral and lymphatic mets, while CT was better for diagnosing smaller pulmonary mets</p>
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Additional primary studies**Author, year, country, study period**Finkelstein, 2004,¹⁸⁴ USA, 2000–2001**Article number**

EP 104

Cancer/management decision/cancer work-up

Patients with stage IV melanoma undergoing metastasectomy

Staging (five with local recurrence)

CWU: CT in all, + MRI of liver/abdomen in three patients (within 2 weeks of surgery)

Design of study/patient characteristics

Diagnostic accuracy study

 $n = 18$; 11 M, 7 F; excluded patients with brain mets; median age 42 years

Follow-up: median 24 months

PET specificationGE Advance; FDG ~15 mCi if weight <200 lb (91 kg) or ~20 mCi if ≥ 200 lb (91 kg); attenuation correction

PET: visual interpretation by one NMP, blinded

CT (+MRI) + PET: one NMP, unblinded, and one surgeon familiar with patient history

Reference tests/comparatorsRef.: histopathology ($m = 40$) or 3-monthly CT/MRI imaging follow-up ($m = 54$)

Comp.: CT/MRI

Results $n = 18$ (20 operations), $m = 94$ lesions

	TP	FN	TN	FP	Sens.	Spec.
CT (+MRI)	37	12	39	6	76%	87%
PET	38	10	40	6	79%	87%
SLNB	42	6	42	4	88%	91%

Author, year, country, study periodJenicke, 2001,¹⁸⁵ Germany, NR**Article number**

EP 1827

Cancer/management decision/cancer work-up

Patients with advanced malignant melanoma (mainly suspected to be stage III and IV)

Staging (primary and follow-up)

CWU: CXR, CT or MRI of chest, brain and abdomen

Design of study/patient characteristics

Diagnostic accuracy study

 $n = 35$ for primary staging, $n = 20$ for follow-up staging; 22 M, 13 F; age range 31–81 years; Breslow thickness range: 0.4–8.3 mm

Follow-up: NR

PET specification

Siemens ECAT Exact 47 (921); FDG 370 MBq; attenuation correction NR

Visual interpretation by two independent NMPs, blinded

Reference tests/comparators

Ref.: histopathology

Comp.: CWU

Results

CWU

	I	II	III	IV	
Primary staging	5	7	23	0	($n = 35$)
Follow-up staging	2 (3 ND)	2 (4 ND)	13 (8 ND)	3	($n = 20$)

Upstaged to IV: one from stage II, two from stage III

PET

	I–II	III	IV	
Primary staging	9	21	5	($n = 35$)
Follow-up staging	4 (3 ND)	7 (ND 9)	10 (ND 2)	($n = 20$)

Upstaged to IV: one from stage II, six from stage III

PET concurred with CWU in 17 patients (49%)

PET upstaged 14 patients (40%) and downstaged four (11%)

Comments

Follow-up process NR

It is unclear whether the changes in staging due to PET are correct or not

Author, year, country, study periodKurli, 2005,¹⁸⁶ USA, NR**Article number**

EP 1440

Cancer/management decision/cancer work-up

Patients with suspected metastatic choroidal (uveal) melanomas

Restaging (two staging)

CWU: CECT, MRI, FNAB

Design of study/patient characteristics

Diagnostic accuracy study

20 patients (18 during follow-up; two before primary treatment); 11 M, 9 F; mean age 69 years (range 46–95 years)

AJCC tumour size: T1, 3; T2, 10; T3, 7

Follow-up: 6–154 months

PET specification

Model NR; target FDG dose 5 mCi/kg; attenuation correction; SUV >2.5 = positive

Reference tests/comparators

Ref.: histopathology in the eight PET-detected patients

Comp.: None

Results $n = 20$ **PET**

Ten TPs (eight with hepatic and other mets to melanoma, two with other primaries)

No FNs (in three patients PET detected benign lesions, but these could be differentiated by the SUV cut-off)

Comments

Poor use of ref. standard only on the PET positives

Malignant melanoma: recurrence**Primary studies****Author, year, country, study period**Mijnhout, 2002,¹⁸⁷ Netherlands, 1997–2000**Article number**

EP 1019

Cancer/management decision

Patients with suspected recurrent melanoma with a diagnostic problem^a unresolved by conventional work-up
Restaging

Design of study/patient characteristics

Change in diagnostic understanding and patient management measured on a scale in a questionnaire at three time-points: before, directly after PET and 6 months later (clinical value design)
Results validated by two independent observers with patient notes

68 consecutive patients, 58 of whom were evaluable (with three completed patient management forms); 32 M, 26 F; mean age 51 years (range 22–80 years)
AJCC stage: I/II, 4; III, 22; IV, 32
Follow-up: 6 months

PET specification

Siemens ECAT Exact HR+; FDG 370 MBq; attenuation correction NR
Visual interpretation by two observers, unblinded

Reference tests/comparators

Ref.: NA

Comp.: CWU

Results^a Problem leading to PET referral:

39 related to surgical therapy, 11 to determine eligibility for chemo or RT or to monitor therapy response, seven suspected recurrence, and one to localise primary after mets found

PET improved diagnostic understanding in 57% of patients (often due to detection of distant mets outside range of conventional imaging and improved specificity, rather than sens. of PET)

PET had no effect in 36% of patients

PET confused clinicians in 7% of patients (two FPs, one FN which was positive on other scans)

(There were also seven other FNs, but these were FN on other scans as well, so no confusion was caused)

PET contributed to change in planned therapy in 40% of patients, increased confidence in chosen treatment in 40%, had no influence in 17% and led to wrong treatment in 3%

The validation process showed that 9% (5/58) of ratings were incorrect (in either direction)

Comments

Good patient management design

Author, year, country, study periodStas, 2002,¹⁸⁸ Belgium, 1995–1998**Article number**

EP 723

Cancer/management decision

Patients with suspected recurrent melanoma who had not had RT to the recurrence site or chemo, within the last 8 months
Restaging

Design of study/patient characteristics

Diagnostic accuracy study with evaluation of change in patient management

$n = 84$; 35 M, 49 F

Follow-up: ≥ 12 months or until death

PET specification

Siemens 931/08/12 or ECAT Exact HR+; FDG 6.5 MBq/kg (max. 555 MBq); no attenuation correction; scan undertaken within 1 month of referral

Visual interpretation by NMPs (number not stated); blinded

Reference tests/comparators

Ref.: histopathology (21% of lesions), clinical imaging and clinical follow-up (70% of lesions); considered not appropriate for further investigation given numerous other mets (9% lesions)

Comp.: conventional imaging (depending on clinical problem: CXR, US, CT, MRI, nuclear bone scans, endoscopy)

Results

Lesion-based analysis: diagnostic accuracy

644 areas assessed, 599 related to melanoma, 'definite statement' about 546

PET scan concordant with conventional imaging (Conv. im.) in 73%

Site	% Sens.		% Spec.	
	PET	Conv. im.	PET	Conv. im.
All sites	85	81	90	87
Brain	22	67	97	100
Lung	91	82	97	91
Liver	67	75	99	93
Skin/subcutaneous	86	80	25	25
LN's	89	83	90	72

Patient-based analysis: change in management

30 patients concordant staging (including two FPs and one FN)

66 patients discordant, PET correct in 31, false in 16, showed false and correct results in 19

In 26 of these patients (30% of the total), the choice of therapy relied essentially on PET:

ten downstaging of mets to avoid systemic therapy, nine no nodal uptake and so avoidance of nodal dissection, three widening of surgical field, four detection of mets so avoidance of futile surgery

In the other 40 PET did not influence therapy

Comments

12 patients had two PET scans and two had three scans. Unclear how these multiple scans were analysed

Diagnostic accuracy not presented clearly by patient

The numbers of patients in the concordant/discordant change in management summaries add up to more than the total number of patients

Impact of PET on treatment management not clearly documented

Oesophageal cancer

Oesophageal cancer: diagnosis

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
<p><i>Diagnosis</i></p> <p>SCC, AC</p> <p>Assessment of primary tumour in patients with oesophageal cancer</p> <p>Reference standard: histopathology</p>	<p>MSAC, Australia, 2001 [Part 2(i)]¹⁹⁰</p> <p>(Up to March 2001)</p>	<p>In four studies PET was able to identify all primary tumours</p> <p>In another four studies, high PET sens. = 95–99% for primary tumour visualisation</p> <p>Low PET sens. of 38% for patients with early-stage disease (T1) vs 100% for patients with T2–T4 lesions</p>	<p>Some authors suggest that although overall accuracy of PET is high, it may not be useful for determining stage of primary tumour given limited ability to define tissue planes in relation to other structures</p>

Oesophageal cancer: staging

Systematic reviews

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions																																				
Staging SCC, AC Locoregional LNs in patients with biopsy-proven oesophageal cancer Reference standard: histopathology	BCBS, USA, 2002 ¹⁹¹ (Up to March 2002)	Nine hierarchy 2 studies, Seven comparative ($n = 302$) Random effects meta-analysis by patient <i>Sens. (95% CI)</i> PET 51% (31 to 70%) CT 42% (25 to 61%) <i>Spec. (95% CI)</i> PET 89% (81 to 94%) CT 87% (67 to 96%) sROC analysis, ns AUC: PET = 0.85, CT = 0.66 Only one study involving EUS $n = 39$, SCC/AC <table border="1"><thead><tr><th></th><th>Sens.</th><th>Spec.</th></tr></thead><tbody><tr><td>PET</td><td>33%</td><td>89%</td></tr><tr><td>CT</td><td>0%</td><td>100%</td></tr><tr><td>EUS</td><td>81%</td><td>67%</td></tr><tr><td>CT+EUS</td><td>62%</td><td>67%</td></tr></tbody></table>		Sens.	Spec.	PET	33%	89%	CT	0%	100%	EUS	81%	67%	CT+EUS	62%	67%	For all oesophageal indications in this HTA, there were several instances of centres producing multiple publications. Each analysis used just one paper from each centre PET spec. similar to CT and slightly higher sens., but PET sens. is low at only ~50% In one study, PET sens. much lower than EUS, which contradicts another study reported in the earlier HTA by MSAC																					
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Staging Distant LNs in patients with biopsy-proven oesophageal cancer SCC, AC Reference standard: histopathology	BCBS, USA, 2002 ¹⁹¹ (Up to March 2002)	Four hierarchy 2 studies, Two comparative studies ($n = 77$) <table border="1"><thead><tr><th></th><th>Sens.</th><th>Spec.</th></tr></thead><tbody><tr><td colspan="3">1. $n = 42$, SCC/AC</td></tr><tr><td>PET</td><td>77%</td><td>90%</td></tr><tr><td>CT</td><td>46%</td><td>69%</td></tr><tr><td colspan="3">2. $n = 35$, SCC/AC</td></tr><tr><td>PET</td><td>25%</td><td>96%</td></tr><tr><td>CT</td><td>0%</td><td>100%</td></tr></tbody></table>		Sens.	Spec.	1. $n = 42$, SCC/AC			PET	77%	90%	CT	46%	69%	2. $n = 35$, SCC/AC			PET	25%	96%	CT	0%	100%	One study reported twice, second study combining regional and distant LNs not included here PET sens. higher than CT, with high spec., but low sens. in one study															
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Staging All LNs (no specific region) in patients with biopsy-proven oesophageal cancer SCC, AC Reference standards: histopathology plus clinical follow-up in 9% of patients in study 3	BCBS, USA, 2002 ¹⁹¹ (Up to March 2002)	Three hierarchy 2 comparative studies ($n = 201$) <table border="1"><thead><tr><th></th><th>Sens.</th><th>Spec.</th></tr></thead><tbody><tr><td colspan="3">1. $n = 53$, $m = 436$, SCC</td></tr><tr><td>PET</td><td>52%</td><td>94%</td></tr><tr><td>CT</td><td>15%</td><td>97%</td></tr><tr><td colspan="3">2. $n = 39$, $m = 221$, SCC/AC</td></tr><tr><td>PET</td><td>39%</td><td>97%</td></tr><tr><td>CT</td><td>22%</td><td>96%</td></tr><tr><td>EUS</td><td>63%</td><td>88%</td></tr><tr><td>CT+EUS</td><td>54%</td><td>90%</td></tr><tr><td colspan="3">3. $n = 109$, $m = 276$, NR</td></tr><tr><td>PET</td><td>80%</td><td>95%</td></tr><tr><td>CT</td><td>68%</td><td>81%</td></tr></tbody></table>		Sens.	Spec.	1. $n = 53$, $m = 436$, SCC			PET	52%	94%	CT	15%	97%	2. $n = 39$, $m = 221$, SCC/AC			PET	39%	97%	CT	22%	96%	EUS	63%	88%	CT+EUS	54%	90%	3. $n = 109$, $m = 276$, NR			PET	80%	95%	CT	68%	81%	Analysis probably by LNs or node regions PET appeared to have higher sens. than CT and similar or higher spec., but PET sens. lower than EUS sens. in one study
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continued

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions																																				
<p>Staging</p> <p>Distant sites, other than LNs, in patients with biopsy-proven oesophageal cancer</p> <p>SCC, AC</p> <p>Reference standards: histopathology, follow-up</p>	<p>BCBS, USA, 2002¹⁹¹</p> <p>(Up to March 2002)</p>	<p>Three hierarchy 2 comparative studies ($n = 196$)</p> <table border="1"> <thead> <tr> <th></th> <th>Sens.</th> <th>Spec.</th> </tr> </thead> <tbody> <tr> <td>1. $n = 79$, SCC/AC</td> <td></td> <td></td> </tr> <tr> <td>PET</td> <td>74%</td> <td>90%</td> </tr> <tr> <td>CT</td> <td>41%</td> <td>83%</td> </tr> <tr> <td>EUS</td> <td>42%</td> <td>94%</td> </tr> <tr> <td>CT+EUS</td> <td>47%</td> <td>78%</td> </tr> <tr> <td>2. $n = 91$, $m = 100$, SCC/AC</td> <td></td> <td></td> </tr> <tr> <td>PET</td> <td>69%</td> <td>93%</td> </tr> <tr> <td>CT</td> <td>46%</td> <td>74%</td> </tr> <tr> <td>3. $n = 26$, SCC/AC</td> <td></td> <td></td> </tr> <tr> <td>PET</td> <td>100%</td> <td>90%</td> </tr> <tr> <td>CT</td> <td>50%</td> <td>95%</td> </tr> </tbody> </table>		Sens.	Spec.	1. $n = 79$, SCC/AC			PET	74%	90%	CT	41%	83%	EUS	42%	94%	CT+EUS	47%	78%	2. $n = 91$, $m = 100$, SCC/AC			PET	69%	93%	CT	46%	74%	3. $n = 26$, SCC/AC			PET	100%	90%	CT	50%	95%	<p>Author states that only one study avoided verification bias, only one interpreted PET blind and none interpreted reference standard blind to PET; thus insufficient evidence to permit conclusions about diagnostic performance</p> <p>Despite this, PET had much higher sens. and similar or higher spec. than CT or EUS in all three studies</p>
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<p>Staging</p> <p>Overview of all diagnostic studies for oesophageal cancer (to obtain higher level evidence)</p> <p>SCC, AC</p>	<p>BCBS, USA, 2002¹⁹¹</p> <p>(Up to March 2002)</p>	<p>MSAC¹⁹⁰ reports five studies with some hierarchy 4 evidence mainly predicting surgery that would be avoided</p> <p>BCBS¹⁹¹ reports two survival analyses determining predictive value of PET</p> <p>1. $n = 91$ 30-month survival: PET predicted disease state Local, survival = 60%, Distant, survival = 20% ($p = 0.01$) CT predicted disease state Local, survival = 52%, Distant, survival = 38% ($p > 0.05$)</p> <p>2. $n = 48$ SUV predictive of median survival: SUV > 7, survival = 10 months SUV ≤ 7, survival = 35 months</p>	<p>Insufficient evidence to quantify actual change in patient management</p> <p>Not robust category 5 evidence</p> <p>30-month survival stated to be significantly better when PET predicted local disease. However, analysis unclear and probably not robust</p> <p>Authors note that robust multivariate analyses including other potential prognostic factors are required</p>																																				
<p>Staging prior to surgery</p> <p>Locoregional mets</p>	<p>van Westreenen, 2004¹⁹²</p> <p>(Up to June 2003)</p>	<p>12 hierarchy 2 studies, eight prospective, six entered consecutive patients</p> <p>PET ($n = 421$)</p> <p>Sens. (95% CI): 51% (34 to 69%)</p> <p>Spec. (95% CI): 84% (76 to 91%)</p>	<p>Several design deficiencies were apparent in some studies:</p> <p>PET and reference test not evaluated independently of other tests; ref. test only performed on those identified by index test; retrospective</p>																																				
<p>Staging prior to surgery</p> <p>Distant mets</p>	<p>van Westreenen, 2004¹⁹²</p> <p>(Up to June 2003)</p>	<p>12 hierarchy 2 studies</p> <p>PET ($n = 452$)</p> <p>Sens. (95% CI): 67% (58 to 76%)</p> <p>Spec. (95% CI): 97% (90 to 100%)</p>	<p>Several design deficiencies were apparent in some studies:</p> <p>PET and reference test not evaluated independently of other tests; ref. test only performed on those identified by index test; retrospective</p>																																				

Additional primary studies**Author, year, country, study period**Choi, 2004,¹⁹³ Korea, 1997–2000**Article number**

EP 65

Cancer/management decision/cancer work-up

Patients with newly diagnosed primary oesophageal SCC undergoing curative oesophagectomy with dissection of visible or palpable LNs

Staging

CWU = bone scintigraphy, oesophagogastroduodenoscopy, bronchoscopy, EUS, abdominal or neck US, CT, PET within 3 weeks of diagnosis

Design of study/patient characteristics

Study to determine predictors for disease progression

89 patients entered, 69 patients analysed (20 could not be resected or withdrew consent); 64 M, 5 F; mean age 63 years

Follow-up: chemo and RT given according to physician's choice after surgery. Follow-up with variety of tests (not including PET) every 2–4 months in first year then every 4–6 months next 2 years, annually thereafter. Max. follow-up = 80 months

PET specification

GE Advance; FDG 370 MBq; attenuation correction

Visual interpretation by two NMPs, blinded

Reference tests/comparators

Ref.: histopathology performed on suspicious findings to determine disease return

Comp.: none

Results

Multivariate survival analyses

For DFS: performance of neoadjuvant therapy and number of PET-positive nodes were independent significant predictors

For survival: clinical stage, pathological stage, tumour length on PET and number of PET-positive nodes were independent significant predictors

Comments

Completeness of follow-up NR. This is crucial for such a survival analysis

Author, year, country, study periodHeeren, 2004,¹⁹⁴ Netherlands, 1996–2002**Article number**

EP 146

Cancer/management decision/cancer work-up

Patients with resectable carcinoma of the thoracic oesophagus or GEJ

Staging

CWU = CT, EUS in 52 patients, US of neck: within 2 weeks of PET

Design of study/patient characteristics

Diagnostic accuracy study

74 consecutive patients (62 AC, 12 SCC); 40 patients resection with curative attempt, 28 not resectable or exploratory laparotomy only; 60 M, 14 F; mean age 62 years (range 21–78 years)

Follow-up: 6 months

PET specification

Siemens ECAT; FDG 400–580 MBq; attenuation correction

Visual interpretation by two NMPs, blinded

Reference tests/comparators

Ref.: histopathology performed blinded or FNAB or follow-up

Comp.: blinded CT (at least three different machines)

Results

PET missed 5% of primary tumours, all were <0.5 cm

Nodal mets (n = 61)

	Sens.	Spec.	
PET	55%	71%	
CT	44%	90%	(n = 60)
EUS	69%	76%	(n = 43)

"PET does not add much in the detection of regional nodes"

Distant nodal mets (n = 72)

	Sens.	Spec.	
PET	71%	98%	
CT	21%	98%	
EUS	14%	97%	(n = 52)
CT/EUS	29%	96%	

Combined distant node and organ mets (n = 71)

	Sens.	Spec.
PET	78%	98%
CT/EUS	37%	87%

2/15 patients correctly upstaged by PET avoided surgery, the other 13 needed laparotomy to confirm distant or nodal liver mets

Comments

Surgery still needed for confirmation in some of those who were upstaged

Author, year, country, study periodLiberale, 2004,¹⁹⁵ Belgium, 1998–2002**Article number**

EP 222

Cancer/management decision/cancer work-upPatients with *de novo* oesophageal or GEJ cancer**Staging**

CWU = lab tests, fibre-optic bronchoscopy, ENT and physical exam, barium swallow, EUS, CT

Design of study/patient characteristics

Diagnostic accuracy study

58 patients; (31 SCC, 26 AC); 47 M, 11 F; mean age 60 years (range 37–80 years)

Follow-up: NR

PET specification

Siemens 962HR+; FDG 6.5 MBq/kg

Visual interpretation by one NMP, not blinded

Reference tests/comparators

Ref.: histopathology

Comp.: CT (Somatom Plus 4 or Volume Zoom)

Results*Primary tumour* (n = 58)

	Sens.	
PET	87%	7 FN tumour sizes (0.3, 0.9, 1, 1.5, 3, 4 cm) (one not stated)
CT	84%	

Distant nodal mets (n = 24, 468 LNs)

(27 operated patients without neoadjuvant therapy minus three with stenotic tumour that could not be staged with EUS)

	Sens.	Spec.
PET	38%	81%
CT+EUS	25%	50%

Distant mets (n = 58)

	Sens.	Spec.
PET	88%	88%
CT	44%	95%

PET sens. significantly higher than CT

PET detected distant mets in seven patients (12%) not detected by CT

Author, year, country, study periodSihvo, 2004,¹⁹⁶ Finland, 1998–2003**Article number**

EP 2441

Cancer/management decision/cancer work-up

Patients with AC of the oesophagus or oesophogastric junction considered eligible for resection

Staging

CWU = endoscopy, CT, EUS

Design of study/patient characteristics

Diagnostic accuracy study with survival calculations

55 patients (20 oesophagus, 35 junction); 43 received lymphadenectomy, 12 exploratory surgery with palliative care; 42 M, 13 F; mean age ~59 years

Follow-up: NR, but several years in many patients

PET specification

GE Advance scanner; median FDG 370 MBq; first 19 patients without attenuation correction; no direct coregistration of PET and CT

Reader not stated, but CT and radiology reports were available when PET image read

Reference tests/comparators

Ref.: histopathology

Comp.: CT, EUS

Results*Primary tumour (n = 55)*

	Sens.	
PET	82%	Mean tumour size for 10 FN = 1.4 cm and for 44 TP = 5.4 cm
CT	69%	
CT+PET	85%	
EUS	96%	

Locoregional nodal mets (n = 43)

	Sens.	Spec.
PET	35%	100%
CT	42%	82%
CT+PET	50%	100%
EUS	85%	53%
EUS+CT	85%	82%
EUS+CT+PET	85%	100%

PET sens. significantly lower than EUS, but PET spec. significantly higher than EUS

Distant mets (n = 55)

	Sens.	Spec.
PET	53%	89%
CT	32%	97%
CT+PET	64%	100%
EUS+CT	42%	100%
EUS+CT+PET	74%	100%

PET could neither identify very small primary tumours nor detect small mets such as intra-abdominal carcinomatosis

The largest primary tumour that PET could not detect was 3 cm

PET has limitations in detecting small volumes of AC tissue in the oesophageal region

Comments

It was noted that although the PET image reconstruction was changed partway through the trial this had not affected tumour detection in a previous trial, so all images were analysed together

Oesophageal cancer: treatment response

Systematic review

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
Assessment of response after neoadjuvant therapy in patients with oesophageal cancer eligible for curative surgery	Westerterp, 2005 ¹⁹⁷ (Up to January 2004)	Seven hierarchy 2 studies of PET, four in sROC; four of CT, three in sROC; 13 of EUS, four in sROC	Studies of variable quality, and half the EUS studies were retrospective compared with one on PET or CT
Reference standard: histopathology		sROC max. joint sens., spec. CT 54% EUS 86% PET 85%	CT studies were of lower quality and there were differences in neoadjuvant therapeutic schemes across trials, so it is particularly unfortunate that no comparative studies exist
		Overall accuracy of PET significantly higher than CT and comparable with EUS	PET appears to have similar accuracy to EUS and given its lower morbidity may be a promising tool for assessment of response to neoadjuvant therapy
		In all PET studies a significantly longer survival was found in metabolic responders	
		EUS was not feasible in 6% of patients, vs 1% of PET patients	

Adapted from KCE HTA (2005).¹³⁸

Additional primary study

Author, year, country, study period Wieder, 2004, ¹⁹⁸ Germany, NR	Article number EP 373										
Cancer/management decision Oesophageal cancer patients scheduled for neoadjuvant chemotherapy and surgery Response to treatment											
Design of study/patient characteristics Treatment response Therapy CRT with 5-FU + 40 Gy RT PET before and 3–4 weeks after CRT In 27 patients PET also performed 14 days after start of CRT											
38 consecutive patients; 33 patients evaluable (both post-CRT PET and resection), 23 evaluable for the benefit of mid-CRT scanning to predict response											
PET specification ECAT Exact HR+; 300–400 MBq; attenuation correction SUV cut-off used											
Reference tests/comparator Ref.: histopathology after resection Comp.: clinical response by CT, EUS and bronchoscopy											
Results Post-hoc cut-off of $\Delta\text{SUV} \geq 30\%$ for midtreatment prediction of response											
	<table border="1"> <thead> <tr> <th></th> <th>TP</th> <th>FN</th> <th>TN</th> <th>FP</th> </tr> </thead> <tbody> <tr> <td>PET</td> <td>14</td> <td>1</td> <td>7</td> <td>1</td> </tr> </tbody> </table>		TP	FN	TN	FP	PET	14	1	7	1
	TP	FN	TN	FP							
PET	14	1	7	1							
Median survival in group with $\Delta\text{SUV} \geq 30\%$ was 38 months vs 18 months											

Oesophageal cancer: RT planning**Primary studies****Author, year, country, study period**Konski, 2005,¹⁹⁹ USA, 2002–(end NR)**Article number**

EP 198

Cancer/management decisionOesophageal cancer patients with CT simulation for RT planning
RT planning**Design of study/patient characteristics**RT planning
Tumour length compared for PET, CT and EUS

25 patients

PET specification

Discovery LS; FDG 8.1 MBq/kg (PET only image used from PET/CT) positioned in same location as for CT simulation using guidance lasers

PET, EUS and CT length estimated independently, using SUV cut-offs for PET

Reference tests/comparatorsComp.: CT (all), EUS (*n* = 17)**Results**

Location	PET SUV 2	PET SUV 2.5	PET SUV 3	EUS	CT
Upper/mid (<i>n</i> = 8)	5.5 cm (3.7–7.4)	5.4 cm (3.5–7.3)	5.1 cm (3.2–7.1)	5.4 cm (2.9–8.0)	7.6 cm (5.2–10)
Lower (<i>n</i> = 8)	5.6 cm (4.4–8.1)	6.7 cm (5.6–7.8)	6.4 cm (5.3–7.6)	5.5 cm (4.1–6.9)	7.6 cm (5.8–9.5)
GEj (<i>n</i> = 9)	4.5 cm (2.6–6.3)	4.0 cm (2.1–5.9)	3.6 cm (1.7–5.6)	4.4 cm (2.9–6.0)	5.8 cm (4.1–7.6)

PET apparently less good at detecting LNs than EUS

Author, year, country, study periodVrieze, 2004,²⁰⁰ Belgium, NR**Article number**

EP 368

Cancer/management decisionOesophageal cancer scheduled for preoperative planning
RT planning**Design of study/patient characteristics**

RT planning

30 patients entered into study for preoperative planning; 24 actually analysed

PET specification

NR

Reference tests/comparators

Comps: CT and EUS

Results

PET suggested different volume in 14 patients (eight smaller, six larger)

Comments

Suggested interpretation is that larger PET areas should be regarded as correct

Poor-quality reporting

Oesophageal cancer: PET/CT – treatment response

Primary study

Author, year, country, study period
Cerfolio, 2005,²⁰¹ USA, 2002–2004
Article number

EP 48

Cancer/management decision
Oesophageal cancer receiving CRT (cisplatin chemo) before resection
Predict response to CRT
Design of study/patient characteristics
Treatment response
Imaging before and after CRT48 patients; 41 M; median age 68 years (range 48–76 years)
43 AC, five SCC

Stage:

	Pre	Post
0	0	15
I	0	5
IIa	22	10
IIb	5	4
III	15	2
T4	2	1
IV (M1a)	3	5
IV (M1b)	1	6

PET/CT specification
GE Discovery; 555 MBq; attenuation correction
CT image used for anatomical localisation of PET
SUV from ROI drawn on image
Reference tests/comparators
Ref.: pathology after resection or biopsy
Comp.: CT and EUS
Results

Path	T0			T1–3			T4		
	CT	EUS	PET/CT	CT	EUS	PET/CT	CT	EUS	PET/CT
T0	4	3	13	12	13	3	0	0	0
T1–3	4	1	4	18	20	18	0	1	0
T4	0	0	0	2	3	1	1	0	2

Path	CT				EUS				PET/CT			
	TP	FP	FN	TN	TP	FP	FN	TN	TP	FP	FN	TN
NI	1	2	7	31	1	2	7	31	5	0	3	33
M1a	0	0	6	42	2	0	4	42	2	1	4	41
CR	4	3	11	30	3	2	12	31	13	4	2	29

Sens. for CR: CT 27%, EUS 20%, PET 87%

Spec. for CR: 91%, 94%, 88%

Thyroid cancer

Thyroid cancer: diagnosis

Primary study

Author, year, country, study period

Kresnik, 2003,²⁰² Austria, NR

Article number

EP 605

Cancer/management decision

Patients with suspicious thyroid nodules (indicating follicular or Hürthle cell proliferation) in an endemic goitre area, scheduled for surgical resection, with normal TSH levels

Diagnosis/preoperative assessment

Design of study/patient characteristics

Diagnostic accuracy study of thyroid nodules

43 patients; 9 M, 34 F; mean age 55 years

Follow-up: NR

PET specification

Siemens ECAT ART; FDG 180 MBq; attenuation correction

Visual interpretation by two NMPs, blinded, plus quantitative SUV

Reference tests/comparators

Ref.: histopathology

Comp.: none

Results

Out of 43 patients, 16 had malignant tumours (11 papillary, three follicular, two anaplastic)

Tumour diameter ranged from 0.7 to 8 cm

All tumours visible on PET. Mean (SD) SUV = 3.7 (1.9) (range 2.2–9.3)

When SUV = 2 used as PET +ve threshold this led to PET sens. = 100%, PET spec. = 63%

Comments

Low dose of FDG

Thyroid cancer: restaging

Primary studies

Author, year, country, study period	Article number
Gotthardt, 2004, ²⁰³ Germany, NR	EP 126
<p>Cancer/management decision/cancer work-up Patients with medullary thyroid cancer, with known or occult mets, all with elevated calcitonin and/or CEA levels Restaging CWU = SRS, CT</p>	
<p>Design of study/patient characteristics Diagnostic accuracy study 26 consecutive patients; 15 M, 11 F; median age 45 years (range 16–75 years) Follow-up: 2–13 months</p>	
<p>PET specification Siemens ECAT; FDG 400–500 MBq; attenuation correction Visual interpretation by two NMPs, blinded</p>	
<p>Reference tests/comparators Ref.: other imaging Comp.: Siemens Somatom 2 CT, SRS</p>	
<p>Results From 183 tumours sites in 26 patients Tumour sites classified as 'sure' PET = 57%, CT = 65%, SRS = 48% Median number of tumour sites per patient detected by PET was 3.5 vs 5 on CT In 9/26 patients the number of lesions detected by PET and CT was discordant: In two patients PET was superior to CT, with PET identifying bone-marrow involvement In seven patients CT was superior to PET in detecting liver, cervical LN and lung lesions CT had three FPs. FPs for other modalities NR Dependent on the reference standard, CT scanning is similar to or slightly better than PET. SRS is clearly inferior to both methods</p>	
<p>Comments Poor reference: diagnostic performance alters depending on comparator imaging technique Short follow-up in some patients</p>	
<p>SRS, somatostatin receptor scanning.</p>	

Author, year, country, study periodHsu, 2002,²⁰⁴ Taiwan, NR**Article number**

EP 556

Cancer/management decision/cancer work-up

Patients with local invasion or aggressive differentiated thyroid cancer who had undergone thyroidectomy and ¹³¹I ablation or therapy

Restaging

CWU = serum Tg, ²⁰¹Tl WBS from gamma camera, thyroxin therapy

Design of study/patient characteristics

Diagnostic accuracy study

15 patients; 5 M, 10 F; mean age 49 years (range 29–72 years); mean duration of disease 6 years

Follow-up: NR

PET specification

Scanditronix PC 4096–15WB; FDG 370 MBq; attenuation correction

PET performed while patient on thyroxin before ¹³¹I uptake evaluation

Visual interpretation; readers not specified

Reference tests/comparators

Histopathology or ¹³¹I uptake

Comparator: ²⁰¹Tl WBS while patient on thyroxin and before ¹³¹I uptake evaluation

Results

PET: one FN demonstrated by ¹³¹I uptake

The following are TP by patient:

Lesion	PET	¹³¹ I WBS	²⁰¹ Tl WBS
Neck–local	2	0	0
Neck–lymph	3	1	1
Mediastinum	3	2	1
Lung–diffuse	0	2	0
Lung–focal	1	1	0
Lung–small nodule	3	0	0
Bone	2	2	2

(different patients)

Tg, thyroglobulin.

Author, year, country, study periodIwata, 2004,²⁰⁵ Japan, 1999–2001**Article number**

EP 170

Cancer/management decision/cancer work-up

Patients with metastatic differentiated thyroid cancer given replacement doses of thyroxin, imaging performed approximately 2 weeks after therapy stopped

Restaging

CWU = CXR, neck US, CT, MRI, bone scans, Tg levels, histopathology

Design of study/patient characteristics

Diagnostic accuracy study

19 patients (16 papillary, three follicular); 8 M, 11 F; mean age 60 years (range 38–72 years)

Follow-up: period of 5 years

PET specification

GE Advance; FDG 370 MBq, attenuation correction in all but first five patients

Visual interpretation by three experienced NMPs

Reference tests/comparators

Ref.: histopathology in some and other imaging

Comp.: ^{99m}Tc-MIBI SPECT, ¹³¹I scintigraphy

Results

32 lesions

PET	^{99m} Tc-MIBI		¹³¹ I	
	Pos.	Neg.	Pos.	Neg.
Pos.	19	7	17	9
Neg.	1	5	5	1

Lesion sens.: PET = 81%, ^{99m}Tc-MIBI = 63%, ¹³¹I = 69%

Maximal diameter of FDG-positive lesions was significantly greater than FDG negative lesions (mean 2 cm vs 1.2 cm)

Small lung mets in one patient were not detected by any modality

PET: two FPs

Comments

Ref. standard not clear

Author, year, country, study periodShiga, 2001,²⁰⁶ Japan, NR**Article number**

EP 1105

Cancer/management decision/cancer work-up

Patients with recurrent or metastatic differentiated thyroid cancer after thyroidectomy, given thyroxin but imaging performed 3 weeks after therapy stopped

Restaging

CWU = hTg and cytology or ¹³¹I scintigraphy, ²⁰¹Tl scintigraphy, CT, ultrasound, MRI, CXR, bone scintigraphy

Design of study/patient characteristics

Diagnostic accuracy study

32 patients (27 papillary, five follicular); 10 M, 22 F; mean age 54 years (range 30–77 years)

Follow-up: NR

PET specification

CTI ECAT Exact 47; FDG 185 MBq; no attenuation correction

Visual interpretation by at least two experienced NMPs

Reference tests/comparators

Ref.: other imaging, unclear whether histopathology was used

Comp.: ¹³¹I and ²⁰¹Tl scintigraphy

Results

47 lesions

PET	¹³¹ I		²⁰¹ Tl	
	Pos.	Neg.	Pos.	Neg.
Pos.	13	9	20	2
Neg.	20	5	1	24

PET concordant with ¹³¹I in only 38% of lesions, but PET concordant with ²⁰¹Tl in 94% of lesions

Lesion sens: PET = 47%, ¹³¹I = 70%, ²⁰¹Tl = 45%

Six lesions were not detected by any modality

Comments

Low FDG dose and no attenuation correction may have meant PET was less accurate

¹³¹I sens. similar to that in other Japanese study

hTg, human thyroglobulin.

Thyroid cancer: recurrence

Systematic reviews

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions
<p>Detection of recurrent disease in previously treated patients with elevated biomarkers not confirmed by ¹³¹I scintigraphy</p> <p><i>Excluding medullary or Hürthle cancer where possible</i></p> <p>Reference standards: histopathology, imaging, follow-up</p>	<p>Hooft, 2001²⁰⁷</p> <p>(Up to October 2000)</p> <p>(Includes six of the epithelial and two of the medullary studies in the AHRQ report)</p>	<p>11 hierarchy 2 studies (total $n = 156$)</p> <p>PET found 'possible disease' in 115/140 patients, but adequate validation only done on 68 of them, 90% of which were recurrent disease</p> <p>PET missed recurrence in six cases (FN); six FPs</p>	<p>Inadequate reference standards in some studies</p> <p>Unable to extract adequate data to undertake planned meta-analyses, so only narrative reports presented, with no calculations of sens. or spec.</p>
<p>Detection of recurrent disease in previously treated patients who have suspected metastatic disease with elevated biomarkers not confirmed by ¹³¹I scintigraphy</p> <p><i>Epithelial</i> (follicular, papillary, mixed follicular–papillary, differentiated, well-differentiated, Hürthle)</p> <p>Reference standards: histopathology, imaging, follow-up</p>	<p>AHRQ (Balk), USA, 2002²⁰⁸</p> <p>(1980 to September 2001)</p> <p>Includes six of the studies in Hooft²⁰⁷)</p>	<p>11 studies with hierarchy 2 evidence on at least ten patients (total $n = 244$)</p> <p>~65% papillary cancers, ~35% follicular cancers</p> <p>Random effects meta-analysis: Sens. (95% CI): PET 84% (73 to 91%) Spec. (95% CI): PET 56% (27 to 82%)</p> <p>Seven studies included some hierarchy 4 evidence about outcome following positive PET</p> <p>In five studies, 27–97% (overall 71%) had treatment for recurrence In four studies, 0–48% had successful treatment or cure In three studies, 34% of patients treated after positive PET had recurrence In four studies, 21% of patients had no change in management despite positive PET</p>	<p>One updated report excluded; there may be one more, but primary reporting unclear</p> <p>Only two studies clearly prospective</p> <p>Subgroup analyses reported for Hürthle and poorly differentiated tumours, but small n</p> <p>Author notes heterogeneity, so estimates are considered preliminary to be "interpreted with caution"</p> <p>However, heterogeneity is predominantly for spec., sens. quite high given negative for other imaging</p> <p>Definitions of cure and recurrence were not consistent and generally poorly reported</p>
<p>Detection of recurrent disease in patients with elevated biomarkers, not confirmed by other imaging</p> <p><i>Medullary</i></p> <p>Reference standards: histopathology, imaging, follow-up</p>	<p>AHRQ (Balk), USA, 2002²⁰⁸</p> <p>(1980 to September 2001)</p>	<p>Six hierarchy 2 studies (total $n = 17$)</p>	<p>Studies with fewer than ten patients included given paucity of evidence</p> <p>Too few patients to draw any conclusions</p>

continued

Cancer management decision	Source (search period)	Evidence	Data caveats/conclusions								
<p>Detection of recurrent disease in patients <i>without</i> elevated biomarkers and no evidence of disease by ^{131}I scintigraphy, but with clinical suspicion of recurrence (e.g. equivocal imaging results)</p> <p><i>Medullary or Hürthle thyroid cancer excluded where possible</i></p> <p>Reference standards: histopathology, imaging, follow-up</p>	<p>Hooft, 2001²⁰⁷</p> <p>(Up to October 2000)</p>	<p>Five hierarchy 2 studies ($n = 2-21/\text{study}$, total $n = 50$)</p> <p>16 positive PET scans</p> <table border="1"> <thead> <tr> <th>TP</th> <th>FN</th> <th>FP</th> <th>TN</th> </tr> </thead> <tbody> <tr> <td>5</td> <td>1</td> <td>6</td> <td>30</td> </tr> </tbody> </table> <p>(eight with unclear results)</p>	TP	FN	FP	TN	5	1	6	30	<p>Authors unable to extract adequate data to undertake the planned meta-analyses, so only narrative reports presented, with no sens. or spec. calculations</p> <p>Inadequate verification (neither pathology nor follow-up) in some studies</p> <p>Noted that FP rate higher than in the group with elevated biomarkers</p>
TP	FN	FP	TN								
5	1	6	30								

Additional primary studies: well-differentiated thyroid carcinoma

<p>Author, year, country, study period Chen, 2003,²⁰⁹ Taiwan, NR</p> <p>Cancer/management decision/cancer work-up Patients with well-differentiated thyroid who underwent nearly total thyroidectomy and ^{131}I ablation/therapy. In follow-up all had negative ^{131}I WBS and elevated hTg levels under TSH</p> <p>Recurrence CWU = neck ultrasound, CT, $^{99\text{m}}\text{Tc}$ MDP WB bone scan</p> <p>Design of study/patient characteristics Diagnostic accuracy study 23 patients; 8 M, 15 F; age range 29–71 years Follow-up: ≥ 1 year</p> <p>PET specification CTI-Siemens ECAT HR+; FDG 370 MBq; attenuation correction NR Visual interpretation by at least two of three experienced NMPs, blinded to other results</p> <p>Reference tests/comparators Histopathology in patients positive under any test, clinical follow-up of ≥ 1 year in the rest Comp.: 740 MBq $^{99\text{m}}\text{Tc}$ TF SPECT</p> <p>Results PET detected mets in 20 patients; SPECT detected mets in 11 patients Two FNs for PET and SPECT (both with military pulmonary mets) (other patient was not positive under any imaging test)</p> <p>So derived calculation of PET sens. = 91% and SPECT sens. = 50%</p> <p>Comments Worst example of repeat reporting of a series of patients, this being the fourth paper reported on this expanding cohort of patients, but this added a SPECT comparator. Lead authors different in each. In four different journals, but clearly the same patients. Previous papers were Wu (2003)^{253,254} and Hung (2003)²⁵⁵</p>	<p>Article number EP 454</p>
<p>MDP, Medronate.</p>	

Author, year, country, study periodFrilling, 2001,²¹⁰ Germany, 1992–2000**Article number**

EP 894

Cancer/management decision/cancer work-up

Patients with well-differentiated thyroid cancer who had undergone thyroidectomy and at least one postoperative radioiodine treatment, with negative ¹³¹I scans but suspicion of tumour recurrence due to abnormal thyroglobulin levels

Recurrence

CWU = CXR, cervical US (sometimes with FNAB), CT in those with positive PET

Design of study/patient characteristics

Diagnostic accuracy study with statements re patient management

n = 24; 25 patients with the signs of recurrence from a total cohort of 189 patients; one 8-year-old excluded; 8 M, 17F; mean age 53 years (range 21–81 years)

Follow-up: Not stated

PET specification

CTI ECAT Exact HR; FDG 400 MBq; attenuation correction

Exclude patients with blood glucose > 130 mg/ml

Visual interpretation by two experienced NMPs

Reference tests/comparators

Ref.: histopathology

Comp.: Philips SR 8000 CT

Results

32 lesions (four benign)

	Sens. (95% CI)	Spec. (95% CI)
PET	95% (81 to 99%)	25% (1 to 81%)

Owing to unsuspected findings on PET, the initial surgical strategy was altered in nine patients (not clearly documented)

Comments

Long study period, unclear whether the subset of patients studied here was spread over that period; if so, standard care may have altered over this 8-year period

Change in patient management not clearly documented

Author, year, country, study periodGabriel, 2004,²¹¹ Austria, NR**Article number**

EP 117

Cancer/management decision/cancer work-up

Patients with local differentiated thyroid cancer (follicular, papillary or Hürthle) who had undergone thyroidectomy and ablation therapy, who had suspected recurrence or resistant disease (with increasing Tg) but negative ¹³¹I WBS

Recurrence

CWU = radioiodine therapy, CXR, US, WBS

Design of study/patient characteristicsDiagnostic accuracy study of ^{99m}Tc-TOC involving PET comparison

54 patients for ^{99m}Tc-TOC; subset of 36 (18 M, 18 F) received PET; mean age of the 54 patients = 64 years (range 22–90 years)

Follow-up: ≥ 1 year

PET specification

GE Advance; FDG 370 MBq; attenuation correction

Visual interpretation by two NMPs, blinded

Reference tests/comparators

Ref.: selection of histopathology, CT, MRI, BS, US, surgery

Comp.: ^{99m}Tc-TOC**Results**

(n = 36)

	Sens.	Spec.
PET	88% (28/32)	50% (2/4)
^{99m} Tc-TOC	63% (20/32)	100% (4/4)

Comments

Unclear how imaging reference was chosen for each patient

BS, bone scintigraphy.

Author, year, country, study periodGroheux, 2005,²¹² France, 2002–2004**Article number**

FP 82 (from translation)

Cancer/management decision/cancer work-upPatients with suspected relapse of differentiated thyroid cancer after thyroidectomy and ¹³¹I therapy

Recurrence

CWU = ¹³¹I scintigraphy, hormone substitution (at low TSH)**Design of study/patient characteristics**

Diagnostic accuracy study and discussion of patient management

39 patients (32 papillary, four follicular, three oncocytic); 10 M, 22 F; mean age 49 years (range 25–82 years)

Follow-up: NR

PET specification

GEMS (in 2D mode); FDG 4.5 MBq/kg; attenuation correction; excluded diabetics

Visual interpretation by at least two experienced NMPs, blinded

Reference tests/comparatorsRef.: histopathology (*n* = 12), cytology (*n* = 6), thyroglobulin assay (*n* = 10), imaging and lab tests (*n* = 11)

Comp.: none

Results*n* = 39 (71 lesions)

	TP	FN	TN	FP
PET	17	8	10	4

Sens. = 68%, spec. = 71%

In 27/39 (69%), PET altered the evaluation of the extent of disease

In 11/39 (28%), PET changed 'therapeutic attitude' (or 12 patients; see following)

In ten patients the option of revision was taken or reinforced (?unclear how this is *change*)

In one patient, surgery abandoned due to multiple mets

In one patient, surgery abandoned due to futility

Comments

Confirmation of any one of the four ref. standards methods was sufficient to put PET as TP, but some elements may be poor standards (e.g. other imaging)

Author, year, country, study periodYeo, 2001,²¹³ Korea, 1995–1999**Article number**

EP 1177

Cancer/management decision/cancer work-upPatients with differentiated thyroid cancer who have undergone thyroidectomy and ablation who have negative ¹³¹I body scans but suspected metastases

Recurrence

CWU = thyroglobulin levels or anatomical images

Design of study/patient characteristics

Diagnostic accuracy study

96 patients entered, 37 patients with PET showing uptake in cervical LNs

22 patients where PET identified cervical LN lesions and who had LN dissection

All 22 papillary carcinoma; 5 M, 17 F; mean age 41 years (range 17–72 years)

Follow-up: NR

PET specification

CTI ECAT Exact 47; FDG 370–555 MBq; attenuation correction

Visual interpretation by two experienced NMPs, blinding NR

Reference tests/comparators

Ref.: histopathology in the chosen set, but interval between PET scan and dissection was mean of 59 days (range 19–200 days)

Comp.: none

Results

22 patients underwent PET-directed LN dissection, yielding 85 LN groups

PET sens. = 80%, spec. = 83%

10/11 FN ≤ 1 cm

CommentsResults only evaluated in patients showing PET positive and then only for a subset for whom operations were undertaken
Long interval between PET scan and ref. standard dissection

Additional primary studies: medullary thyroid carcinoma**Author, year, country, study period**de Groot, 2004,²¹⁴ Netherlands, 1998–2002**Article number**

EP 81

Cancer/management decision/cancer work-up

Patients with medullary thyroid cancer with elevated serum calcitonin or CEA levels after adequate initial surgical treatment, excluding patients with palpable lesions

Recurrence

CWU = at least two imaging procedures, form depending on hospital and suspected site of lesion including ^{99m}Tc(V)DMSA scintigraphy, ¹¹¹In-octreotide scintigraphy, MRI, CT, US. All performed ≥2 months after therapy and completed within 18 months

Design of study/patient characteristics

Diagnostic accuracy study

26 consecutive patients; 15 M, 11 F; median age 51 years (range 15–75 years)

Median time since initial therapy 54 months

Follow-up: NR

PET specification

CTI-Siemens ECAT 951/31 or ECAT HR+; FDG 400 MBq; attenuation correction

Visual interpretation by at least two of three experienced NMPs, blinded to other results

Reference tests/comparators

Ref.: histopathology or confirmation in at least two consecutive morphological scans or with two different imaging methods

Comps: ^{99m}Tc(V)DMSA scintigraphy, ¹¹¹In-octreotide scintigraphy, MI (CT, MRI and US) + BS

Results*Concordance between imaging methods*

		^{99m} Tc(V)DMSA scintigraphy		¹¹¹ In-octreotide scintigraphy		MI+BS	
		+	–	+	–	+	–
PET	+	5	7	4	6	9	3
PET	–	1	12	0	11	2	11
<i>n</i>		25		21		25	

PET identified the most number of lesions of any imaging method in 13 patients

In 11 patients all imaging techniques failed to detect any lesions; considered FNs, but no mets discovered in follow-up.

No TNs

Stated sens.

PET = 41%, ^{99m}Tc(V)DMSA = 17%, ¹¹¹In-octreotide = 14%, MI+BS = 30%

(unclear how these figures derived)

PET +ve led to surgical intervention in nine patients (removal of residual tumour or mets) and cancer was confirmed in eight patients

Comments

Not all patients had results for all tests, so some figures difficult to follow

Unclear accuracy calculations given concordance figures

MI, morphological imaging.

Author, year, country, study periodSzakáll, 2002,²¹⁵ Hungary, NR**Article number**

EP 1121

Cancer/management decision/cancer workup

Patients with a history of medullary thyroid cancer who had undergone surgery (and had elevated calcitonin levels)

Recurrence

CWU = calcitonin and CEA levels, diagnostic imaging ≥ 2 months after any therapy**Design of study/patient characteristics**

Diagnostic accuracy study

40 patients; 18 M, 22 F; mean age 48 years (range 23–69 years)

Follow-up: mean 81 months (range 17–379 months)

PET specification

GE 4096 Plus scanner; FDG 5.55 MBq/kg, no attenuation correction

Visual interpretation by two experts, blinding NR

Reference tests/comparators

Histopathology in some patients, radiology in some, clinical follow-up in some

Comps: CT (native and contrast enhanced, using Siemens Somatom HR), MRI (Siemens Megatom 1.5 T)

Results

PET scans detected lesions in 38/40 patients

The two patients negative on PET were also negative on CT and MRI, but were considered FN given the elevated calcitonin levels

Number of patients with lesions

Lesion site	PET	CT	MRI	¹³¹ I-MIBG planar scintigraphy
LN	38	26	19	3
Liver	7	9	6	0
Lung	2	5	2	0
Bone	5	0	1	1
Breast	1	1	1	0
Total patients with positive scans	38	29	23 ^a	3

^a Scans not done in five patients

PET detected more foci in the neck and mediastinum (33 regions) than other imaging methods (MRI 11 regions, CT 14 regions)

PET failed to detect many lesions in the lung and liver. Small pulmonary mets (< 1 cm) detected by CT (and MRI) were not visualised by PET

LN mets were verified by histopathology in ten patients. In 15 patients imaging follow-up verified LN involvement or other mets. Two of the PET-detected bone mets appear to be FP. The data on some patients still require validation

Comments

Poor use of ref. standard; similar methods not used in all patients, selection probably driven by imaging results, true results unclear

Thyroid cancer: treatment response

Primary study

Author, year, country, study period

 Boerner, 2002,²¹⁶ Germany, NR

Article number

EP 824

Cancer/management decision

 Patients with recurrent or metastatic differentiated thyroid cancer receiving isotretinoin therapy
 Monitoring response

Design of study/patient characteristics

Treatment response

 PET, ¹³¹I scans and hTg measurements before and 3, 6, 9 months after start of isotretinoin therapy

Outcome measurement based on WHO criteria (CT, US and MRI morphology)

23 patients; 11 M; age range 24–76 years

PET specification

ECAT Exact 922; FDG 5 MBq/kg; attenuation correction

Visual interpretation by three NMPs and SUVs calculated

Reference tests/comparators

Ref.: clinical response

Comp.: hTg

Results

 Marginally significant trend ($p = 0.052$) towards lower SUVs at 3 months in patients with CR ($n = 2$) or PR ($n = 7$)

SUVs (means): CR, 0.0; PR, 1.6; SD, 3.3; PD, 5.2

No relationship between response and hTg

Thyroid cancer: PET/CT recurrence**Primary studies****Author, year, country, study period**Nahas, 2005,²¹⁷ USA, NR**Article number**

EP 2360

Cancer/management decision/cancer work-up

Patients with papillary thyroid cancer treated by thyroidectomy and ¹³¹I treatment, with suspected recurrence due to elevated Tg but negative ¹³¹I WBS

Recurrence

CWU to determine requirement for surgery: palpation of the head and neck, serum Tg, FNAB, US, CT, MRI and PET were also used

Design of study/patient characteristics

Diagnostic accuracy study, with change in patient management assessed retrospectively

33 papillary carcinoma patients; 13 M, 20 F; mean age 44 years (range 12–72 years)

20 operated on

Follow-up: NR

PET specification

GE Discovery LS PET/CT; FDG dose not stated

Visual interpretation by NMPs and radiologists (number and blinding NR)

Reference tests/comparators

Ref.: histopathology in those who underwent surgery

Comp.: none

Results

20 patients chosen for operation, with 36 lesions

Lesion accuracy

	TP	FN	TN	FP
PET/CT	21	11	4	0

Sens. = 66%, spec. = 100%

33 patients had patient management assessed by retrospective review of case notes without PET/CT and treatment plan created. Additional value of PET/CT then determined.

PET/CT altered management in 13/33 patients (40%), supported management plan in 9/33 (27%), and did not contribute to management plan in 11/33 (33%).

Patient characteristics were similar across these three groups

Comments

Diagnostic accuracy based on selected group

Author, year, country, study periodOng, 2005,²¹⁸ Singapore, 2003–2004**Article number**

EP 1524

Cancer/management decision/cancer work-upPatients with differentiated thyroid cancer after thyroidectomy and at least one dose of ¹³¹I, with elevated hTg and negative ¹³¹I WBS

Recurrence

CWU = ¹³¹I WBS**Design of study/patient characteristics**

Retrospective diagnostic accuracy study

17 patients (15 papillary, one follicular, one Hürthle); 6 M, 11 F; mean age 54 years (range 35–83 years)

Follow-up: NR

PET specification

Siemens PET/CT scanner (model not stated); 333–444 MBq (15 within 3 months of WBS, two within 2 years)

Visual interpretation by two NMPs

Reference tests/comparators

Ref.: histopathology in four patients, all others assumed to be positive

Comp.: none

Results

Assuming all 17 patients are TPs

PET detected lesions in 15 patients (sens. = 88%)

Comments

Poor study: long delay between WBS and PET/CT evaluation for some patients, limited use of ref. standard

PET/CT: mixed cancers

Systematic reviews

Cancers	Source (search period)	Evidence	Data caveats/conclusions
Various Some studies with single cancers and some with a variety of cancers	AETS (Garrido), Spain, 2004 ²¹⁹ (Up to November/December 2003)	16 studies, 293 patients 12 prospective, four retrospective 11 hybrid PET/CT, five fusion of PET and CT Six studies included sufficient data for meta-analysis <i>Meta-analysis</i> Includes five studies: Vansteenkiste ¹²⁸ (NSCLC, fusion), Antoch ¹³⁰ (NSCLC), Lardinois ¹³² (NSCLC), Bristow ²⁷¹ (ovarian), Antoch ²⁴¹ (various cancers) Hany ²³⁶ excluded (various cancers) due to heterogeneity Sens. 0.87 (95% CI 0.80 to 0.92) Spec. 0.89 (95% CI 0.82 to 0.94) DOR 41.5 (95% CI 21.6 to 136.3) Positive likelihood ratio = 6.15 Negative likelihood ratio = 0.17 <i>Subgroup of three NSCLC studies</i> <i>Staging</i> Sens. 0.85 (95% CI 0.74 to 0.92) Spec. 0.84 (95% CI 0.70 to 0.93) DOR 17.8 (95% CI -1.3 to 36.9) <i>Tumoral restaging</i> Sens. 0.89 (95% CI 0.84 to 0.94) Spec. 0.87 (95% CI 0.78 to 0.93) DOR 16.2 (95% CI 1.1 to 31.3) For five studies of restaging, metaregressions identified publication year, number of patients and study quality as significant factors	Advantages: less time consuming than PET, simultaneous acquisition of PET and CT images limits alignment problems and changes of patient's position Diagnostic accuracy for tumoral restaging (detection of locoregional recurrence and distant mets) is a little better than for N staging PET/CT helps to reduce the number of non-conclusive lesions Unclear which clinical indications could be established more accurately with PET/CT Need cost-effectiveness studies
Various	HAS, France, 2005 ²²⁰ (December 2002 to November 2004, augmenting the report from CEDIT in 2002) ²⁷² English and French publications	13 studies comparing PET/CT with PET (including two fusion studies) Six studies in cancer of interest: one head and neck, four NSCLC, one lymphoma Seven studies in other cancers or mixed cancers: one bone mets, three digestive, three gynaecological Tended to show that PET/CT had improved sens. and especially improved spec. compared with PET	Potential for replacing PET/CT with PET and the potential clinical impact of PET/CT could not be assessed. Neither could the clinical benefit of increasing the number of detectors in the PET/CT systems PET/CT is more expensive per scan Clinical and economic studies of the value of PET/CT compared with PET are needed

Appendix 8

Cost-effectiveness studies

Author, year, country	Article number
Comber, 2003, ²²³ Australia	EP 464
Cancer/management decision	
Impact of QECT on cost-effectiveness of PET in staging SPN	
Design of study/patient characteristics	
Cost-effectiveness model for SPN diagnosis, comparing four strategies:	
<ul style="list-style-type: none"> • CT • CT then QECT if CT not benign • CT then PET if CT not benign • CT then QECT if CT not benign then PET if QECT positive 	
Data sources	
<i>Accuracy data</i>	
PET and CT from literature	
QECT from one multicentre study (356 patients)	
<i>Stage and life expectancy</i>	
Not used	
<i>Costs</i>	
Costs from Australian system, except QECT: assigned the cost of CT angiography	
<i>Mortality and QoL</i>	
Missed malignant nodules and resected benign assigned equal value of 0	
Other outcomes value 1	
Follow-up for nodules declared benign: four CXRs over 2 years	
<i>Sensitivity analysis</i>	
Ratio PET:surgery costs and prevalence of malignancy examined in two-way sensitivity analysis	
Results	
At Australian values (54% prevalence, PET:surgery 16%) CT+QECT least cost (\$5560/patient), then CT+QECT+PET (\$5910/patient)	
Most cost-effective is CT+QECT+PET (ICER \$12,059.18/patient), then CT+PET (\$12,300/patient)	
As prevalence and cost rise CT+QECT performs better	
UK values suggest CT+QECT cost-effective	
Comments	
Some concern that QECT not a mature technology	
QECT, quantitative contrast-enhanced computed tomography.	

Author, year, country Hollenbeak, 2001, ²²⁴ USA	Article number EP 933
Cancer/management decision Cost-effectiveness of PET in the N0 neck	
Design of study/patient characteristics Cost-effectiveness model of approaches with and without PET to assess whether patients with clinically and CT N0 neck should receive treatment or be followed up Immediate treatment by modified radical neck dissection (MRND) or radiotherapy Treatment on relapse after observation by RND+RT	
Data sources	
<i>Accuracy data</i> From literature review	
<i>Stage and Life expectancy</i> SEER database	
<i>Costs</i> Average for large Midwest hospital	
<i>Mortality and QoL</i> Utilities elicited from eight head and neck surgery residents (MRND highest utility at 0.93, RND+RT lowest at 0.68)	
<i>Sensitivity analysis</i> Done for scan costs and prevalence of occult mets	
Results PET cost-effective (\$250 per QALY, \$8718 per life-year) If prevalence in the interval [16%, 33%] PET ICER below \$50,000 per QALY	
Comments No sensitivity analysis done on PET accuracy	
MRND, modified radical neck dissection.	

Author, year, countryPark, 2001,²²⁵ USA**Article number**

EP 1058

Cancer/management decision

Cost-effectiveness of PET in recurrent colorectal cancer

Design of study/patient characteristics

Comparison of CT vs CT+PET prior to the decision on hepatic surgery in patients with rising (>5 ng/ml) CEA at some point after primary surgery

Decision-tree model comparing CT and CT+PET

Key assumptions:

- any site suspicious on PET or CT can be biopsied with perfect accuracy
- surgery will be offered to any patient apparently having only liver mets
- any patient with only liver mets will in fact be resectable
- any patient found to be negative for recurrence will be 'recycled' through the decision tree once; the transition probabilities on the two cycles are assumed to be independent

Data sources

All data except life expectancies and costs derived from literature search (MEDLINE, 1980–1998, details not given)

Life expectancies estimated by authors

Cost data sources NR

One-way sensitivity analysis done to find thresholds for all variables

In a separate analysis all 'PET-favourable' variables (PET sens. and spec.) penalised by 15% and CT sens., spec. inflated by 15%

Results

Baseline ICER for PET+CT \$16,437: 167 surgeries avoided in 6000 patients

PET penalised 15%: ICER \$33,556

PET penalised + CT 15% inflation: ICER \$111,000

One-way sensitivity analysis

ICER <\$50,000 if prevalence of recurrence greater than 49%

CT sensitivity and biopsy specificity important (CT sens. > 88% or biopsy spec. <80.3% CT+PET ICER > \$50,000)

If life expectancy of patient untreated, with recurrence >2.569 years (vs baseline 2 years), PET+CT ICER > \$50,000

If life expectancy patient with recurrence, chemo alone, <1.75 years (vs baseline 2.663 years) ICER > \$50,000

Comments

Inadequate referencing of literature review to allow adequacy of data sources to be assessed

Author, year, countrySloka, 2004,²²⁶ Canada**Article number**

ESR 41

Cancer/management decision/cancer work-up

Cost-effectiveness of PET in recurrent colorectal cancer

Design of study/patient characteristics

Comparison of CT vs CT+PET before colonoscopy

Data sources*Accuracy data*

PET and CT from meta-analysis using all published studies (not all prospective, not all read independently)

Note that for all studies PET more accurate than CT

Stage and life expectancy

Literature

Costs

Canadian fee schedules

Mortality and QoL

Literature

Sensitivity analysis

One-way analysis performed

Results

125 futile operations avoided per 1000 patients

PET+CT cost-saving (\$1758) + 38-day increase in life expectancy for the baseline case (65-year-old man)

If PET is more accurate than CT, PET+CT remains preferred unless > 95% have non-resectable disease

Author, year, countryWallace, 2002,²²⁷ USA**Article number**

EP 2491

Cancer/management decision

Cost effectiveness for staging oesophageal cancer

Design of study/patient characteristics

Cost-effectiveness model for staging oesophageal cancer, comparing six strategies:

- CT
- CT+EUS
- CT+TL
- CT+EUS + TL
- CT+PET + EUS
- PET+EUS

Data sources*Accuracy data*

CT+EUS: previously published meta-analysis

T/L: one study, suggesting perfect sens. and spec.

PET: five studies

Stage and life expectancy

SEER database

Costs

Medicare

Mortality and QoL

Expert opinion

Results

CT+EUS dominates all other strategies except PET+EUS

ICER for PET+EUS is \$60,544 per QALY. Robust to sensitivity analyses

Benefit chiefly from avoidance of 'futile' operations

TL, thorascopy/laparoscopy.

Appendix 9

Questionnaire for survey of UK PET facilities

RESPONDENT'S DETAILS:

Name of respondent	
Institutional affiliation	
Address	
Telephone	
Email	
Population served by PET centre	

1. Device spec

1a. List the specifications of the PET and PET/CT devices used in your institution.

1b. If you are planning to install a PET or PET/CT facility in the next 12 months, please indicate the type of device to be installed.

1c. This survey has been sent to all centres listed on the UK PET Special Interest Group website <http://www-pet.umds.ac.uk/UKPET/page.php?5> . If you know of any new sites that have been established or are in planning stages, please list them here.

2. Source of FDG

2a. Where do you source FDG from?

2b. How many deliveries of FDG are received per day?

2c. What distance is that from your facility?

2d. What transport system do you use?

3. Uses of PET

3a. List the routine clinical uses for which FDG-PET is used in your institution.

3b. List any clinical studies or audit underway with FDG-PET in your institution.

3c. List research studies planned or underway with FDG-PET.

3d. Explain how your institution decided what indications, audits or studies FDG-PET should be used for.

4. Capacity and costs

4a. What are the annual throughputs for FDG-PET using the different machines you have? (Give details of any recent capacity calculations)

4b. If mobile PET is used, indicate frequency of mobile provision and number of scans per day.

4c. What is the approximate annual running cost of each PET and PET/CT unit?

4d. What is the estimated cost/scan?

5. Difficulties in establishing a PET facility

5a. Outline any difficulties you faced in setting up your PET facility.

**Please return this survey by 10 March 2006 to Karen Facey
by email to k.facey@btinternet.com
or by fax on 01360 660316.**

Appendix 10

Survey of PET facilities in the UK (March 2006)

Section 1 and 2 responses: device and FDG source

Centre and contact	Device	FDG source/deliveries per day
<p>Alliance Medical Leisl Anderson landerson@alliance.co.uk</p> <p>Postal addresses given for contacts at all hospital sites</p>	<p>PET/CT: One Siemens Biograph LSO (London) One GE Discovery STE (London) One GE Discovery ST (Birmingham) Three GE Discovery ST (Mobile)</p> <p>PET: One GE Advance NXi (Mobile)</p> <p>Several multislice PET/CT scanners to be installed across Europe</p>	<p>PETNET (London) and Erigal (Keele University Science Park)</p> <p>For fixed sites in London, PETNET is approximately 17 miles</p> <p>For fixed site in Birmingham, Erigal is approximately 45 miles</p> <p>Mobile scanners: various distances</p> <p>Each FDG provider employs its own transport courier</p> <p>On average, two deliveries</p>
<p>Cheltenham Imaging Centre Nigel Benatar nigel@cobaltappeal.com</p>	<p>Philips Gemini GXL PET/CT (due to go online April 2006)</p>	<p>Erigal (Keele)</p> <p>~100 miles by courier van</p> <p>One delivery planned initially</p>
<p>Christie Hospital Peter Julyan peter.julyan@physics.cr.man.ac.uk</p>	<p>GE Advance PET</p> <p>Out to tender for replacement PET/CT</p>	<p>Erigal (Keele) or local production from Clatterbridge cyclotron at the Patterson Institute of Radiochemistry</p> <p>Distance unknown, but important to note that commercial delivery from Erigal arrives by 09.00 h, compared with 12.00 h arrival from 'local' site</p> <p>All transport by Strand</p> <p>Normally one delivery (up to six doses)</p>
<p>Hammersmith Hospitals NHS Trust David Towey dtowey@hhnt.nhs.uk</p>	<p>Siemens ART-Rotapet</p> <p>PET/CT to be installed in next 12 months</p>	<p>PETNET</p> <p>Distance unknown, transport by Extran Medica</p> <p>One delivery</p>

continued

Centre and contact	Device	FDG source/deliveries per day
InHealth Group Alan Gibson Alan.Gibson@inhealthgroup.com	PET/CT: Philips Gemini GXL (16-slice) (one on fixed site, one mobile) Siemens Biograph 16 (fixed) PET: GE Advance (fixed) GE Advance NXi (mobile) Plan to install five to seven centres with PET/CT 16-slice or possibly 64-slice	PETNET mainly, other sources include Erigal and some NHS sites 0 or 17 miles for fixed sites For mobile sites, delivery up to 4–5 hours from facility is possible with high output to obtain a small number of usable doses Transported by specialist radiopharmacy logistics company Two deliveries, but could increase to three if demand justifies
Institute of Nuclear Medicine – University College London Peter Ell peter.ell@uclh.nhs.uk	GE Discovery PET/CT: 16-slice (plan to upgrade to 64-slice PET/CT in October 2006) GE Discovery LS PET/CT: four-slice (plan to upgrade to 16-slice PET/CT in April 2006) ° Plan to build cyclotron	PETNET° 1–2 hours by courier One or two deliveries
Lodestone Guildford Diagnostic Imaging Deanna Murray gharris@lodestone.co.uk	GE Discovery LS PET/CT	PETNET 50 miles by Exran Medica One or two deliveries
NHS Grampian Peter Sharp p.sharp@biomed.abdn.ac.uk	GE Discovery ST Enhanced 16 PET/CT (newly installed, March 2006)	On site Delivered as required
Northern Ireland Regional PET Institute Peter Jarritt peter.jarritt@mpa.n-i.nhs.uk	GE Discovery LS with four-slice spiral Lightspeed CT	M2i Blackrock Clinic, Dublin 110 miles by car One delivery
Paul Strickland Scanner Centre John Lowe john.lowe@paulstrickland-scannercentre.org.uk	GE Discovery ST four-slice PET/CT with associated computers	PETNET On site Two deliveries

continued

Centre and contact	Device	FDG source/deliveries per day
PET Imaging Centre at St Thomas Paul Marsden paul.marsden@kcl.ac.uk	Two GE STs, four-slice	Cyclotron on site One or two deliveries
Royal Marsden NHS Foundation Trust Gary Cook, Bernadette Cronin, Mike Partridge m.partridge@physics.org	Philips Gemini PET/CT, GSO full body PET scanner with I37-Cs transmission source and two-slice CT	PETNET 50 miles by road One or two deliveries
1 mile = 1.61 km.		

Question 3a responses: routine clinical cases

Centre	Population	Routine clinical uses for cancer and rationale	
Alliance Medical	Mobile PET to Manchester (two sites), Wirral, Sheffield, Birmingham, Bath, Reading and Cardiff	Clinical oncology Indications decided by local sites	
	Mobile PET/CT to Preston, Sheffield, Hull, Cambridge, Oxford, Brighton, Southampton, Maidstone, Bournemouth, Guildford		
	Static sites: Birmingham, London (two sites)		
Cheltenham Imaging Centre	1.5 million	Lung	Suitability for radical therapy Recurrence SPN
		Lymphoma	Staging Monitoring treatment response Recurrence
		Colorectal	Recurrence
		Oesophagus	Suitability for radical surgery
		Thyroid	Raised thyroglobulin, negative ¹³¹ I scan
		Melanoma	Before resection of first mets
		Brain/spine	Recurrence
		Sarcoma	Staging non-skeletal mets recurrence
		Department of Health guidelines/local PCT approved indications	
<i>continued</i>			

Centre	Population	Routine clinical uses for cancer and rationale	
Christie Hospital	3 million	NSCLC	Staging before surgery or radical RT
		SPN	Diagnosis only when biopsy not safe or practicable
		Colorectal	Restaging before surgery for removal of hepatic or pulmonary metastatic disease
		Colorectal	Recurrence in the presacral region after surgery and RT
		HL	Restaging: residual mass
		Oesophageal	Staging before radical surgery
		Head and neck	Unknown primary, assessment of malignant neck nodes
Various national guidelines			
Hammersmith Hospitals NHS Trust	Not stated	Carcinoma	Precise indications not stated
		Indications according to ARSAC licence and proven results for effective use of FDG	
InHealth Group	Mobiles, across the UK Two fixed sites in London serving London population and UK referrals One fixed site in Nottingham to serve regional cancer network	Lung	Staging/restaging/recurrence
		NHL, HL	
		Colorectal	
		Oesophageal	
		Head and neck	
		Melanoma	
		Breast	
		Pancreas	
		Thyroid	
		PNS	
		Brain	
		Germ cell	
		Ovarian	
		Cervical	
Others based on evidence-based practice, NICE guidelines and ARSAC licence holders' recommendations			
Institute of Nuclear Medicine – University College London	Supraregional activity	Lung	Staging/restaging/recurrence
		NHL, HL	
		Colorectal	
		Oesophageal	
		Head and neck	
		Melanoma	
		Breast	
		Pancreas	
		PNS	
		Pelvic	
		Others	
Determined from literature, college recommendations and knowledge from expert symposia			

continued

Centre	Population	Routine clinical uses for cancer and rationale	
Lodestone Guildford Diagnostic Imaging	Across the UK	Lung	Staging
		Lymphoma	Restaging
		GI	Staging
		Breast	Restaging
		Melanoma	
		Others	
NHS Grampian	5.1 million (whole of Scotland, but second scanner due to serve in 2007)	Lung	All according to nationally agreed protocols
		Colorectal	
		Lymphoma	
		Other conditions	Decided on case-by-case basis
		Indications decided from HTBS HTA (2002) ² and recommendations of a Scottish Executive Health Department Implementation Group, with discussion on longer term demand by regional planning groups	
Northern Ireland	1.7 million	Lung	SPN diagnosis and pretreatment staging (mainly NSCLC)
		Colorectal	Recurrence
		Melanoma	Staging
		Head and neck	
		Oesophagus	Staging
		Lymphoma recurrence	Staging, restaging after induction therapy,
		Others	Justified by ARSAC certificate holder
		ICSCNM guidelines originally to restrict demand, now for referrals	
Paul Strickland Scanner Centre	Local CTC serves 2 million plus referrals from Western England, Wales and Midlands	Oncology	Precise indications not stated
		Evidence-based practice with regular critical review of recent publications, taking account of NICE guidelines and relevant intercollegiate, RCR and RCP reports	
PET Imaging Centre at St Thomas	National (English) referrals	Lungs, bronchus, trachea (30% of total workload)	80% staging 15% SPN 5% recurrence
		NHL (15.5%)	60% restaging 26% staging 14% recurrence
		HL (9.5%)	60% restaging 20% staging 20% recurrence
		Colorectal (11%)	60% recurrence 30% staging 10% other
		Skin	
		Breast	
		Head and neck	~ 15%
		Oesophageal	
		Unknown primary	

continued

Centre	Population	Routine clinical uses for cancer and rationale	
		Testes	
		Ovary	
		Uterus	
		Stomach	~15%
		Sarcoma	
		Other low-prevalence cancers	
		Non-cancer	~4%
		Determined from literature, 15 years' experience, locally produced and widely adopted list of approved indications	
Royal Marsden NHS Foundation Trust	Mainly local cancer network, plus referrals from UK and abroad	Lung	Staging before radical surgery
		Lung	Staging before RT
		Lung	SPN
		Lymphoma	Restaging – residual mass
		Lymphoma	Staging equivocal stage I
		Colorectal	Staging before hepatic surgery
		Colorectal	Rising CEA with negative imaging
		Clinical indications agreed with PCT	
ARSAC, Administration of Radioactive Substance Advisory Council; ICSCNM, Intercollegiate Standing Committee on Nuclear Medicine; PCT, primary care trust; RCP, Royal College of Physicians.			

Other section 3 responses: research use

Centre	PET cancer research and audit (ongoing or planned)
Alliance Medical	<p>Various research studies coordinated by local sites and facilitated by Alliance Medical, including new research collaborations being planned</p> <p>Fixed sites at London and Birmingham undertaking various research studies and audits</p>
Cheltenham Imaging Centre	None
Christie Hospital	<p>Clinical studies – various</p> <p>Research studies</p> <ul style="list-style-type: none"> • pharmacodynamics in various drug trials • multicentre trials in restaging HL • various non-FDG projects, e.g. pharmacokinetics on labelled drugs
Hammersmith Hospitals NHS Trust	<p>Research dependent on clinical interest and ethical approval, but research time limited as they cannot impinge on clinical scan time:</p> <ul style="list-style-type: none"> • sarcoid • CAPD
InHealth Group	Participate in and support research carried out and coordinated by local clinicians; studies confidential
Institute of Nuclear Medicine – University College London	<p>Audit in collaboration with MD Anderson (USA) as part of the standard annual audit programme</p> <p>A variety of studies underway (cannot be stated due to intellectual property)</p>
Lodestone Guildford Diagnostic Imaging	None stated
NHS Grampian	<p>Research studies:</p> <ul style="list-style-type: none"> • measuring response to chemotherapy in oesophageal cancer • effect of ketogenic diets on brain metabolism <p>Audit:</p> <p>Implementation of PET in Scotland overseen by a National Advisory Group to monitor implementation of PET services across Scotland to “ensure equitable and appropriate access for all patients who might benefit from a PET scan as well as monitor future requirements”.</p> <p>Monthly reports on the number of scans, types of tumour, etc., will be reviewed and tumour-specific protocols, data sets and audit reporting mechanisms will be developed</p>
Northern Ireland Regional PET Institute	<p>Research:</p> <ul style="list-style-type: none"> • radiotherapy planning in NSCLC • comparison of FDG SUV and dynamic perfusion CT in NSCLC, compared with pathology • patient utilities in NSCLC • various MRC multicentre trials <p>Audit (regional):</p> <ul style="list-style-type: none"> • service response times for use of FDG in staging of lung cancer

continued

Centre	PET cancer research and audit (ongoing or planned)
Paul Strickland Scanner Centre	<p>Research:</p> <ul style="list-style-type: none"> • multicentre RCT in stage Ia/Ia HL • phase I pilot evaluating serial PET/CT images during conventionally fractionated RT with and without concurrent chemotherapy for SCC of the head and neck • evaluation of VoLumen (oral contrast) on the bowel • multicentre trial in RT planning for head and neck or lung cancer <p>Clinical studies:</p> <ul style="list-style-type: none"> • assessment of oesophageal cancer • comparison of 2D/3D imaging • patterns of intrinsic laryngeal muscle uptake • PET as an independent prognostic marker in occult head and neck cancer • normal palatine tonsil FDG uptake <p>Audits:</p> <ul style="list-style-type: none"> • rare head and neck cancers • pulmonary carcinoid tumours • occult head and neck primary tumours • clinical indications for PET/CT at the Centre and in Bedfordshire and Hertfordshire
PET Imaging Centre at St Thomas	A variety of studies underway
Royal Marsden NHS Foundation Trust	<p>Research/clinical studies agreed by LREC and Committee for Clinical Research:</p> <ul style="list-style-type: none"> • national HL trial • five phase I trials monitoring response • response to Tarceva in metastatic lung cancer • RT planning in oesophageal cancer • dual-phase imaging to assess residual masses in lymphoma • research study in lung cancer <p>Audits agreed with Clinical Audit Committee:</p> <ul style="list-style-type: none"> • staging preoperative oesophageal cancer • staging in colorectal cancer with rising CEA, negative imaging • assessing residual masses in lymphoma
LREC, local research ethics committee.	

Section 4 responses: capacity and costs

Centre	Throughput	Costs
Alliance Medical	Fixed: Up to 4000/year (16/day, 5 days/week, 50 weeks) Mobile: Throughputs vary by site. Mainly weekly or fortnightly utilisation. PET up to eight patients/day PET/CT up to 12 patients/day	Not stated
Cheltenham Imaging Centre	Not yet in operation (Aim to scan 12–15/day)	Estimated cost/scan = £800 (dependent on total number of patients scanned)
Christie Hospital	2005: 300 patients/year Plus mobile for last 6 months for 1 day/week 2006/07: funding for 1100 patients/year with extended facilities and new equipment	Estimated cost/scan = £820
Hammersmith Hospitals NHS Trust	600/year	£175,000 for FDG costs alone (no other costs quoted) Estimated cost/scan = £820
InHealth Group	At most sites maximum capacity could be 6 days/week, 12 hours/day, 50 weeks/year With maintenance at weekend, this implies that 3500 scans would be possible per machine Mobile PET scheduled to meet customer requirements and typically operated up to 12 hours/day Both fixed and mobile can provide 12 scans/day and, depending on case-mix and patient flow, up to 16	Prices for scan vary between £800 and £1300 including FDG, depending on volume and type of scan
Institute of Nuclear Medicine – University College London	Owing to migration and staff shortages only one scanner fully operational, performing eight to ten scans/day New unit designed to house eight to ten patients simultaneously injected and awaiting scan By October WB scan will be 15–20 minutes/scan	Mixed NHS and R&D funding Estimated cost to NHS/scan = £900

continued

Centre	Throughput	Costs
Lodestone Guildford Diagnostic Imaging	Not stated	Not stated
Northern Ireland Regional PET Institute	1500/year currently funded Approved capacity: 2000/year	£1.1 million Estimated cost/scan = £700 plus capital costs
NHS Grampian	Estimated 1300/year in 2006/07 2300/year in 2007/08 2800/year maximum capacity Cost of scans for approved indications was calculated and Health Department has agreed ~£1 million to be ring-fenced in health budget for 2006/07. This is planned to rise to £5 million in future years as the service develops	Revenue costs (including capital charges) For PET alone (assuming 1000 scans/year): Fixed: £499,000 Variable: £31,000 For FDG: £300/scan + VAT Estimated cost/scan = £800 + VAT ^a (assuming 1000 scans per annum, will reduce as capacity increases)
Paul Strickland Scanner Centre	3000/year last year Currently 320/month (workload could decline as new PET centres open in West Country and Midlands)	Annual running costs: £1.9 million including FDG and staffing (based on 3000 patients/year) Estimated cost/scan = £635
PET Imaging Centre at St Thomas	18 scans/day total for two scanners	Confidential
Royal Marsden NHS Foundation Trust	<800/year, PCT funding limited to ~400	Annual running costs (approx.): Total: £735,000 Staff: £320,000 Maintenance: £115,000 FDG/consumables: £300,000 (800 patients/year) Estimated cost/scan = £1100
^a Value-added tax (VAT) is charged at 17.5%. R&D, research and development.		

Section 5 responses: difficulties

Centre	Difficulties establishing PET facility
Alliance Medical	Close working with local site and staff is essential to ensure smooth running and seamless integration of service into local hospital, working as an extension of the imaging department Essential not to underestimate the amount of time needed to adjust to increase in administration such as scheduling patients, reporting and issuing results
Cheltenham Imaging Centre	None as yet at this early stage of installation
Christie Hospital	Obtaining funding for clinical work has taken a long time despite having the facility and staff for 6 years and having performed a range of research work
Hammersmith Hospitals NHS Trust	FDG originally bought on site, which was much cheaper, but they could not produce FDG until 11.00 h and so this limited number of patients that could be scanned. PETNET is more expensive, but more reliable Staff training Increasing staff doses (<i>of radiation?</i>)
InHealth Group	Lack of funding available for scanning. Availability of FDG if demand increases
Institute of Nuclear Medicine – University College London	Various difficulties over 10 years
Lodestone Guildford Diagnostic Imaging	None stated
NHS Grampian	As this was part of a national scheme, time was lost deciding where the scanners should be located, particularly because two other cancer centres in Scotland are geographically close National issues about provision of FDG and other radiopharmaceuticals. This facility has its own cyclotron, but it was not feasible to use this for the whole of Scotland. Discussions with a private supplier in central Scotland did not reach fruition and this delayed the process As this first scanner for the national Scottish scheme is going to an established PET centre, most of the technical problems have already been resolved An initial issue about payment for scans was decided on a national level
Northern Ireland Regional PET Institute	Staffing, especially radiologists Servicing multidisciplinary meetings with data transfer, storage, etc. Timeliness of response and report into clinical practice. Systems not used to a 7–14-day turnaround in Northern Ireland
Paul Strickland Scanner Centre	As the second PET centre in England in 1997 there were many difficulties. Specialists had little awareness of PET and budget holders could not understand the high cost of the imaging procedure This is a registered charity and not part of the NHS. Although located on NHS grounds, there was no NHS subsidy. It took several years to create service-level agreements with NHS trusts
PET Imaging Centre at St Thomas	Set up 15 years ago, so issues were different. Current difficulties in maintaining operation are recruitment and retention of trained staff at all levels in all areas, particularly in the face of competition
Royal Marsden NHS Foundation Trust	Staff recruitment and subsequent training NHS funding Difficulty in accessing FDG Limited number of FDG suppliers, causes problems when there are production failures

Appendix II

HTA project: NSCLC staging

Author, year, country, study period

Lassen, DACEHTA, 2006, Denmark, 2003–ongoing

Article number

Personal communication

Cancer/management decision

Patients considered to have operable NSCLC after CT staging
Staging to avoid futile thoracotomy

Design of study/patient characteristics

RCT of patients to

1. PET/CT then mediastinoscopy (unless PET +ve results in a positive biopsy indicating stage IV disease)
2. Mediastinoscopy

Excluded patients with diabetes, radiologically M1 disease, estimated FEV₁ < 30% after surgery

To detect change in patient management, diagnostic accuracy, cost-effectiveness

Planned sample size of 430, assuming 60% of the referred patients with stage I–IIIa will undergo thoracotomy, to observe absolute difference of 15% in number of thoracotomies

Interim analysis after 220 patients using Peto rule

Follow-up: min. 18 months planned

PET/CT specification

GE Discovery LS; FDG approximately 400 MBq

Visual interpretation by an experienced NMP and an experienced radiologist, blinded for analysis but unblinded to determine whether further tests are needed

Reference tests/comparators

Refs: LN biopsy

liver: biopsy unless MRI or US indicate benign cyst

adrenal: no biopsy needed for PET –ve, if CT indicates benign

bone: X-ray, CT, MRI or BS, biopsy if equivocal

brain: CT, MRI

Comp.: CWU without PET/CT

Results

After more than 3 years only 209 patients have been randomised

Recruitment has been much slower than anticipated, partly due to other competing studies and violations of study protocol (use of SPECT)

Interim analysis planned in spring 2006, but it is likely that the study will be closed at this point whatever the result of the interim analysis owing to the slow recruitment

FEV₁, forced expiratory volume in 1 second.



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No. 29

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No. 32

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.

By Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N.

No. 33

Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.

By Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

No. 34

Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.

By David AS, Adams C.

No. 35

A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.

By Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, *et al.*

No. 36

Cost analysis of child health surveillance.

By Sanderson D, Wright D, Acton C, Duree D.

Volume 6, 2002**No. 1**

A study of the methods used to select review criteria for clinical audit.

By Hearnshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

No. 2

Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.

By Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, *et al.*

No. 3

Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation.

By Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, *et al.*

No. 4

A systematic review of discharge arrangements for older people.

By Parker SG, Peet SM, McPherson A, Cannaby AM, Baker R, Wilson A, *et al.*

No. 5

The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.

By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

No. 6

The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.

By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 7

The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.

By Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, *et al.*

No. 8

Promoting physical activity in South Asian Muslim women through 'exercise on prescription'.

By Carroll B, Ali N, Azam N.

No. 9

Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.

By Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, *et al.*

No. 10

A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models.

By Richards RG, Sampson FC, Beard SM, Tappenden P.

No. 11

Screening for gestational diabetes: a systematic review and economic evaluation.

By Scott DA, Loveman E, McIntyre L, Waugh N.

No. 12

The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation.

By Clegg AJ, Colquitt J, Sidhu MK, Royle P, Loveman E, Walker A.

No. 13

The clinical effectiveness of trastuzumab for breast cancer: a systematic review.

By Lewis R, Bagnall A-M, Forbes C, Shirran E, Duffy S, Kleijnen J, *et al.*

No. 14

The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation.

By Lewis R, Bagnall A-M, King S, Woolcott N, Forbes C, Shirran L, *et al.*

No. 15

A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease.

By Vale L, Wyness L, McCormack K, McKenzie L, Brazzelli M, Stearns SC.

No. 16

The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation.

By Woolcott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al.*

No. 17

A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.

By Cummins C, Connock M, Fry-Smith A, Burls A.

No. 18

Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation.

By Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, *et al.*

No. 19

Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation.

By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, *et al.*

No. 20

Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.

By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Frementle N, Vail A.

No. 21

The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.

By Jobanputra P, Barton P, Bryan S, Burls A.

No. 22

A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.

By Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

No. 23

A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.

By Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, Reimsma R.

No. 24

A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change.

By Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, *et al.*

No. 25

A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists.

By Robinson M, Ginnelly L, Sculpher M, Jones L, Riemsma R, Palmer S, *et al.*

No. 26

A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS.

By Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, *et al.*

No. 27

A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic.

By Caine N, Sharples LD, Hollingworth W, French J, Keogan M, Exley A, *et al.*

No. 28

Clinical effectiveness and cost – consequences of selective serotonin reuptake inhibitors in the treatment of sex offenders.

By Adi Y, Ashcroft D, Browne K, Beech A, Fry-Smith A, Hyde C.

No. 29

Treatment of established osteoporosis: a systematic review and cost-utility analysis.

By Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M.

No. 30

Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial.

By Elliott RA Payne K, Moore JK, Davies LM, Harper NJN, St Leger AS, *et al.*

No. 31

Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice.

By Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, *et al.*

No. 32

The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature.

By Crow R, Gage H, Hampson S, Hart J, Kimber A, Storey L, *et al.*

No. 33

The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.

By Garside R, Round A, Dalziel K, Stein K, Royle R.

No. 34

A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis.

By Suri R, Wallis C, Bush A, Thompson S, Normand C, Flather M, *et al.*

No. 35

A systematic review of the costs and effectiveness of different models of paediatric home care.

By Parker G, Bhakta P, Lovett CA, Paisley S, Olsen R, Turner D, *et al.*

Volume 7, 2003

No. 1

How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study.

By Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J.

No. 2

Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.

By Mowatt G, Vale L, Perez J, Wyness L, Fraser C, MacLeod A, *et al.*

No. 3

Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.

By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burls A.

No. 4

A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.

By Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, *et al.*

No. 5

Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma.

By Riley RD, Burchill SA, Abrams KR, Heny D, Lambert PC, Jones DR, *et al.*

No. 6

The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.

By Roderick P, Davies R, Raftery J, Crabbe D, Pearce R, Bhandari P, *et al.*

No. 7

The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.

By Davenport C, Elley K, Salas C, Taylor-Weetman CL, Fry-Smith A, Bryan S, *et al.*

No. 8

A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women's preferences in the management of menorrhagia.

By Kennedy ADM, Sculpher MJ, Coulter A, Dwyer N, Rees M, Horsley S, *et al.*

No. 9

Clinical effectiveness and cost-utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.

By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

No. 10

Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.

By Grimshaw GM, Szczepura A, Hultén M, MacDonald F, Nevin NC, Sutton F, *et al.*

No. 11

First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).

By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

No. 12

The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.

By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

No. 13

A systematic review of atypical antipsychotics in schizophrenia.

By Bagnall A-M, Jones L, Lewis R, Ginnelly L, Glanville J, Torgerson D, *et al.*

No. 14

Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.

By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, *et al.*

No. 15

Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.

By Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mujica Mota R, *et al.*

No. 16

Screening for fragile X syndrome: a literature review and modelling.

By Song FJ, Barton P, Sleightholme V, Yao GL, Fry-Smith A.

No. 17

Systematic review of endoscopic sinus surgery for nasal polyps.

By Dalziel K, Stein K, Round A, Garside R, Royle P.

No. 18

Towards efficient guidelines: how to monitor guideline use in primary care.

By Hutchinson A, McIntosh A, Cox S, Gilbert C.

No. 19

Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.

By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

No. 20

Prioritisation of health technology assessment. The PATHS model: methods and case studies.

By Townsend J, Buxton M, Harper G.

No. 21

Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence.

By Cody J, Wyness L, Wallace S, Glazener C, Kilonzo M, Stearns S, *et al.*

No. 22

The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation.

By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

No. 23

The role of modelling in prioritising and planning clinical trials.

By Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P.

No. 24

Cost-benefit evaluation of routine influenza immunisation in people 65-74 years of age.

By Allsup S, Gosney M, Haycox A, Regan M.

No. 25

The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.

By Wight J, Chilcott J, Holmes M, Brewer N.

No. 26

Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.

By Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT.

No. 27

Evaluating non-randomised intervention studies.

By Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovich C, Song F, *et al.*

No. 28

A randomised controlled trial to assess the impact of a package comprising a patient-orientated, evidence-based self-help guidebook and patient-centred consultations on disease management and satisfaction in inflammatory bowel disease.

By Kennedy A, Nelson E, Reeves D, Richardson G, Roberts C, Robinson A, *et al.*

No. 29

The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review.

By Dinnes J, Loveman E, McIntyre L, Waugh N.

No. 30

The value of digital imaging in diabetic retinopathy.

By Sharp PF, Olson J, Strachan F, Hipwell J, Ludbrook A, O'Donnell M, *et al.*

No. 31

Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.

By Law M, Wald N, Morris J.

No. 32

Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation.

By Ward S, Kaltenthaler E, Cowan J, Brewer N.

No. 33

Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review.

By Hummel S, Paisley S, Morgan A, Currie E, Brewer N.

No. 34

Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system.

By Royle P, Waugh N.

No. 35

Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.

By Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K.

No. 36

A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses.

By Boland A, Haycox A, Bagust A, Fitzsimmons L.

No. 37

Redesigning postnatal care: a randomised controlled trial of protocol-based midwifery-led care focused on individual women's physical and psychological health needs.

By MacArthur C, Winter HR, Bick DE, Lilford RJ, Lancashire RJ, Knowles H, *et al.*

No. 38

Estimating implied rates of discount in healthcare decision-making.

By West RR, McNabb R, Thompson AGH, Sheldon TA, Grimley Evans J.

No. 39

Systematic review of isolation policies in the hospital management of methicillin-resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic modelling.

By Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, *et al.*

No. 40

Treatments for spasticity and pain in multiple sclerosis: a systematic review.

By Beard S, Hunn A, Wight J.

No. 41

The inclusion of reports of randomised trials published in languages other than English in systematic reviews.

By Moher D, Pham B, Lawson ML, Klassen TP.

No. 42

The impact of screening on future health-promoting behaviours and health beliefs: a systematic review.

By Bankhead CR, Brett J, Bukach C, Webster P, Stewart-Brown S, Munafa M, *et al.*

Volume 8, 2004

No. 1

What is the best imaging strategy for acute stroke?

By Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PAG, Dennis MS, *et al.*

No. 2

Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care.

By Mant J, McManus RJ, Oakes RAL, Delaney BC, Barton PM, Deeks JJ, *et al.*

No. 3

The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.

By Garside R, Stein K, Wyatt K, Round A, Price A.

No. 4

A systematic review of the role of bisphosphonates in metastatic disease.

By Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, *et al.*

No. 5

Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer.

By Jones L, Hawkins N, Westwood M, Wright K, Richardson G, Riemsma R.

No. 6

Effectiveness and efficiency of guideline dissemination and implementation strategies.

By Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, *et al.*

No. 7

Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei.

By Bryant J, Clegg AJ, Sidhu MK, Brodin H, Royle P, Davidson P.

No. 8

Psychological treatment for insomnia in the regulation of long-term hypnotic drug use.

By Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M.

No. 9

Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome.

By Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ.

No. 10

A systematic review and economic evaluation of magnetic resonance cholangiopancreatography compared with diagnostic endoscopic retrograde cholangiopancreatography.

By Kaltenthaler E, Bravo Vergel Y, Chilcott J, Thomas S, Blakeborough T, Walters SJ, *et al.*

No. 11

The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis.

By Barton P, Jobanputra P, Wilson J, Bryan S, Burls A.

No. 12

Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review.

By Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S.

No. 13

Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation.

By Czoski-Murray C, Warren E, Chilcott J, Beverley C, Psyllaki MA, Cowan J.

No. 14

Routine examination of the newborn: the EMREN study. Evaluation of an extension of the midwife role including a randomised controlled trial of appropriately trained midwives and paediatric senior house officers.

By Townsend J, Wolke D, Hayes J, Davé S, Rogers C, Bloomfield L, *et al.*

No. 15

Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach.

By Oliver S, Clarke-Jones L, Rees R, Milne R, Buchanan P, Gabbay J, *et al.*

No. 16

A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery.

By Reeves BC, Angelini GD, Bryan AJ, Taylor FC, Cripps T, Spyt TJ, *et al.*

No. 17

Does early magnetic resonance imaging influence management or improve outcome in patients referred to secondary care with low back pain? A pragmatic randomised controlled trial.

By Gilbert FJ, Grant AM, Gillan MGC, Vale L, Scott NW, Campbell MK, *et al.*

No. 18

The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis.

By Clark W, Jobanputra P, Barton P, Burls A.

No. 19

A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder.

By Bridle C, Palmer S, Bagnall A-M, Darba J, Duffy S, Sculpher M, *et al.*

No. 20

Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis.

By Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N.

No. 21

Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.

By Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, *et al.*

No. 22

Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus.

By Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burls A.

No. 23

Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients.

By Dretzke J, Sandercock J, Bayliss S, Burls A.

No. 24

Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation.

By Dündar Y, Boland A, Strobl J, Dodd S, Haycox A, Bagust A, *et al.*

No. 25

Development and validation of methods for assessing the quality of diagnostic accuracy studies.

By Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J.

No. 26

EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy.

By Garry R, Fountain J, Brown J, Manca A, Mason S, Sculpher M, *et al.*

No. 27

Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon- β and glatiramer acetate for multiple sclerosis.

By Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C.

No. 28

Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.

By Dalziel K, Round A, Stein K, Garside R, Price A.

No. 29

VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers.

By Iglesias C, Nelson EA, Cullum NA, Torgerson DJ on behalf of the VenUS Team.

No. 30

Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.

By Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, *et al.*

No. 31

A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme.

By Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S.

No. 32

The Social Support and Family Health Study: a randomised controlled trial and economic evaluation of two alternative forms of postnatal support for mothers living in disadvantaged inner-city areas.

By Wiggins M, Oakley A, Roberts I, Turner H, Rajan L, Austerberry H, *et al.*

No. 33

Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.

By Green JM, Hewison J, Bekker HL, Bryant, Cuckle HS.

No. 34

Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status.

By Critchley HOD, Warner P, Lee AJ, Brechin S, Guise J, Graham B.

No. 35

Coronary artery stents: a rapid systematic review and economic evaluation.

By Hill R, Bagust A, Bakhai A, Dickson R, Dündar Y, Haycox A, *et al.*

No. 36

Review of guidelines for good practice in decision-analytic modelling in health technology assessment.

By Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al.*

No. 37

Rituximab (MabThera[®]) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation.

By Knight C, Hind D, Brewer N, Abbott V.

No. 38

Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.

By Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, *et al.*

No. 39

Pegylated interferon α -2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.

By Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.

No. 40

Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation.

By Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, *et al.*

No. 41

Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.

By Beswick AD, Rees K, Griebisch I, Taylor FC, Burke M, West RR, *et al.*

No. 42

Involving South Asian patients in clinical trials.

By Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P.

No. 43

Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.

By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

No. 44

Identification and assessment of ongoing trials in health technology assessment reviews.

By Song FJ, Fry-Smith A, Davenport C, Bayliss S, Adi Y, Wilson JS, *et al.*

No. 45

Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine

By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.

No. 46

Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis.

By McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, *et al.*

No. 47

Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.

By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

No. 48

Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.

By Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, *et al.*

No. 49

Generalisability in economic evaluation studies in healthcare: a review and case studies.

By Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, *et al.*

No. 50

Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.

By Wallace P, Barber J, Clayton W, Currell R, Fleming K, Garner P, *et al.*

Volume 9, 2005

No. 1

Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.

By Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, *et al.*

No. 2

Do the findings of case series studies vary significantly according to methodological characteristics?

By Dalziel K, Round A, Stein K, Garside R, Castelnovo E, Payne L.

No. 3

Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.

By Wilson BJ, Torrance N, Mollison J, Wordsworth S, Gray JR, Haites NE, *et al.*

No. 4

Randomised evaluation of alternative electrosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia.

By Fowler C, McAllister W, Plail R, Karim O, Yang Q.

No. 5

A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer.

By Shenfine J, McNamee P, Steen N, Bond J, Griffin SM.

No. 6

Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography.

By Taylor P, Champness J, Given-Wilson R, Johnston K, Potts H.

No. 7

Issues in data monitoring and interim analysis of trials.

By Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, *et al.*

No. 8

Lay public's understanding of equipoise and randomisation in randomised controlled trials.

By Robinson EJ, Kerr CEP, Stevens AJ, Lilford RJ, Braunholtz DA, Edwards SJ, *et al.*

No. 9

Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies.

By Greenhalgh J, Knight C, Hind D, Beverley C, Walters S.

No. 10

Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology.

By Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, *et al.*

No. 11

Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation.

By Green C, Dinnes J, Takeda A, Shepherd J, Hartwell D, Cave C, *et al.*

No. 12

A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy.

By Dinnes J, Deeks J, Kirby J, Roderick P.

No. 13

Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK.

By Willis BH, Barton P, Pearmain P, Bryan S, Hyde C.

No. 14

Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation.

By McCormack K, Wake B, Perez J, Fraser C, Cook J, McIntosh E, *et al.*

No. 15

Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation.

By Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, *et al.*

No. 16

A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine.

By Peveler R, Kendrick T, Buxton M, Longworth L, Baldwin D, Moore M, *et al.*

No. 17

Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation.

By Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, *et al.*

No. 18

A randomised controlled comparison of alternative strategies in stroke care.

By Kalra L, Evans A, Perez I, Knapp M, Swift C, Donaldson N.

No. 19

The investigation and analysis of critical incidents and adverse events in healthcare.

By Woloshynowych M, Rogers S, Taylor-Adams S, Vincent C.

No. 20

Potential use of routine databases in health technology assessment.

By Raftery J, Roderick P, Stevens A.

No. 21

Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study.

By Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, *et al.*

No. 22

A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.

By Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J.

No. 23

A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.

By Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, *et al.*

No. 24

An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.

By Roderick P, Nicholson T, Armitage A, Mehta R, Mullee M, Gerard K, *et al.*

No. 25

Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.

By Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J, *et al.*

No. 26

Indirect comparisons of competing interventions.

By Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, *et al.*

No. 27

Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.

By Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A, *et al.*

No. 28

Outcomes of electrically stimulated gracilis neosphincter surgery.

By Tillin T, Chambers M, Feldman R.

No. 29

The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.

By Garside R, Stein K, Castelnovo E, Pitt M, Ashcroft D, Dimmock P, *et al.*

No. 30

Systematic review on urine albumin testing for early detection of diabetic complications.

By Newman DJ, Mattock MB, Dawney ABS, Kerry S, McGuire A, Yaqoob M, *et al.*

No. 31

Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.

By Cochrane T, Davey RC, Matthes Edwards SM.

No. 32

Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.

By Thomas KJ, MacPherson H, Ratcliffe J, Thorpe L, Brazier J, Campbell M, *et al.*

No. 33

Cost-effectiveness and safety of epidural steroids in the management of sciatica.

By Price C, Arden N, Coglean L, Rogers P.

No. 34

The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.

By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

No. 35

Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials.

By King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, *et al.*

No. 36

The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.

By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

No. 37

A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.

By Kendrick T, Simons L, Mynors-Wallis L, Gray A, Lathlean J, Pickering R, *et al.*

No. 38

The causes and effects of socio-demographic exclusions from clinical trials.

By Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, *et al.*

No. 39

Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.

By Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M, *et al.*

No. 40

A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.

By Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, *et al.*

No. 41

Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty.

By Keating JF, Grant A, Masson M, Scott NW, Forbes JF.

No. 42

Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.

By Durham RC, Chambers JA, Power KG, Sharp DM, Macdonald RR, Major KA, *et al.*

No. 43

The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.

By Castelnovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44

Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.

By Knowles R, Griesch I, Dezateux C, Brown J, Bull C, Wren C.

No. 45

The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.

By Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al.*

No. 46

The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.

By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

No. 47

Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.

By Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al.*

No. 48

Systematic review of effectiveness of different treatments for childhood retinoblastoma.

By McDaid C, Hartley S, Bagnall A-M, Ritchie G, Light K, Riemsma R.

No. 49

Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.

By Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, *et al.*

No. 50

The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.

By Dretzke J, Frew E, Davenport C, Barlow J, Stewart-Brown S, Sandercock J, *et al.*

Volume 10, 2006**No. 1**

The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease.

By Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, *et al.*

No. 2

FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.

By Dennis M, Lewis S, Cranswick G, Forbes J.

No. 3

The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.

By Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, *et al.*

No. 4

A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.

By Whiting P, Gupta R, Burch J, Mujica Mota RE, Wright K, Marson A, *et al.*

No. 5

Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.

By Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

No. 6

Systematic review and evaluation of methods of assessing urinary incontinence.

By Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, *et al.*

No. 7

The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.

By Connock M, Frew E, Evans B-W, Bryan S, Cummins C, Fry-Smith A, *et al.*

No. 8

Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.

By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

No. 9

Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.

By Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al.*

No. 10

Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.

By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

No. 11

Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.

By Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Greaves M, *et al.*

No. 12

A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.

By Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, *et al.*

No. 13

Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).

By Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J, *et al.*

No. 14

The cost-effectiveness of screening for oral cancer in primary care.

By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M *et al.*

No. 15

Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.

By Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, *et al.*

No. 16

Systematic review of the effectiveness and cost-effectiveness of HealOzone[®] for the treatment of occlusal pit/fissure caries and root caries.

By Brazzelli M, McKenzie L, Fielding S, Fraser C, Clarkson J, Kilonzo M, *et al.*

No. 17

Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.

By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, *et al.*

No. 18

Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.

By Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, *et al.*

No. 19

Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.

By Kennedy TM, Chalder T, McCrone P, Darnley S, Knapp M, Jones RH, *et al.*

No. 20

A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1.

By Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, *et al.*

No. 21

Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.

By Wright M, Grieve R, Roberts J, Main J, Thomas HC on behalf of the UK Mild Hepatitis C Trial Investigators.

No. 22

Pressure relieving support surfaces: a randomised evaluation.

By Nixon J, Nelson EA, Cranny G, Iglesias CP, Hawkins K, Cullum NA, *et al.*

No. 23

A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.

By King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, *et al.*

No. 24

The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review.

By Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, *et al.*

No. 25

Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.

By Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ, *et al.*

No. 26

A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.

By Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, *et al.*

No. 27

A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost-utility for these groups in a UK context.

By Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C, *et al.*

No. 28

Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.

By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

No. 29

An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial.

By Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, *et al.*

No. 30

Accurate, practical and cost-effective assessment of carotid stenosis in the UK.

By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, *et al.*

No. 31

Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.

By Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, *et al.*

No. 32

The cost-effectiveness of testing for hepatitis C in former injecting drug users.

By Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, *et al.*

No. 33

Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.

By Kaltenthaler E, Brazier J, De Nigris E, Tumor I, Ferriter M, Beverley C, *et al.*

No. 34

Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.

By Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, *et al.*

No. 35

Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.

By Brazier J, Tumor I, Holmes M, Ferriter M, Parry G, Dent-Brown K, *et al.*

No. 36

Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.

By Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, *et al.*

No. 37

Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.

By O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.

No. 38

A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling.

By Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, *et al.*

No. 39

The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.

By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hillis G.

No. 40

What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).

By Williams J, Russell I, Durai D, Cheung WY, Farrin A, Bloor K, *et al.*

No. 41

The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.

By Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P.

No. 42

A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.

By Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, *et al.*

No. 43

Telemedicine in dermatology: a randomised controlled trial.

By Bowns IR, Collins K, Walters SJ, McDonagh AJG.

No. 44

Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model.

By Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C.

No. 45

Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.

By Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, *et al.*

No. 46

Etanercept and efalizumab for the treatment of psoriasis: a systematic review.

By Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, *et al.*

No. 47

Systematic reviews of clinical decision tools for acute abdominal pain.

By Liu JLY, Wyatt JC, Deeks JJ, Clamp S, Keen J, Verde P, *et al.*

No. 48

Evaluation of the ventricular assist device programme in the UK.

By Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al.*

No. 49

A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children.

By Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, *et al.*

No. 50

Amniocentesis results: investigation of anxiety. The ARIA trial.

By Hewison J, Nixon J, Fountain J, Cocks K, Jones C, Mason G, *et al.*

Volume 11, 2007**No. 1**

Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.

By Dundar Y, Bagust A, Dickson R, Dodd S, Green J, Haycox A, *et al.*

No. 2

A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer.

By Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K, *et al.*

No. 3

A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.

By Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, *et al.*

No. 4

The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women.

By Stevenson M, Davis S, Lloyd-Jones M, Beverley C.

No. 5

A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.

By Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K, *et al.*

No. 6

Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.

By Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, *et al.*

No. 7

Glucocorticoid-induced osteoporosis: a systematic review and cost-utility analysis.

By Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M.

No. 8

Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.

By Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE, *et al.*

No. 9

Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.

By Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, *et al.*

No. 10

Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.

By Isaacs AJ, Critchley JA, See Tai S, Buckingham K, Westley D, Harridge SDR, *et al.*

No. 11

Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.

By Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N.

No. 12

Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.

By Tappenden P, Jones R, Paisley S, Carroll C.

No. 13

A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.

By Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al.*

No. 14

A systematic review and economic evaluation of statins for the prevention of coronary events.

By Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, *et al.*

No. 15

A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.

By Mason A, Weatherly H, Spilsbury K, Arksey H, Golder S, Adamson J, *et al.*

No. 16

Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.

By Weindling AM, Cunningham CC, Glenn SM, Edwards RT, Reeves DJ.

No. 17

Screening for type 2 diabetes: literature review and economic modelling.

By Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, *et al.*

No. 18

The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.

By Garside R, Pitt M, Anderson R, Mealing S, Roome C, Snaith A, *et al.*

No. 19

The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.

By Takeda AL, Jones J, Loveman E, Tan SC, Clegg AJ.

No. 20

A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.

By Collins R, Cranny G, Burch J, Aguiar-Ibáñez R, Craig D, Wright K, *et al.*

No. 21

The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.

By Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS.

No. 22

A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.

By Fayter D, Nixon J, Hartley S, Rithalia A, Butler G, Rudolf M, *et al.*

No. 23

Systematic review of the effectiveness of preventing and treating *Staphylococcus aureus* carriage in reducing peritoneal catheter-related infections.

By McCormack K, Rabindranath K, Kilonzo M, Vale L, Fraser C, McIntyre L, *et al.*

No. 24

The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.

By McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, *et al.*

No. 25

A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.

By Boyle J, McCartney E, Forbes J, O'Hare A.

No. 26

Hormonal therapies for early breast cancer: systematic review and economic evaluation.

By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L.

No. 27

Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review.

By Bryant J, Picot J, Levitt G, Sullivan I, Baxter L, Clegg A.

No. 28

Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.

By McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, *et al.*

No. 29

Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses.

By Colbourn T, Asseburg C, Bojke L, Philips Z, Claxton K, Ades AE, *et al.*

No. 30

Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review.

By Garrison KR, Donell S, Ryder J, Shemilt I, Mugford M, Harvey I, *et al.*

No. 31

A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.

By Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, *et al.*

No. 32

Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen.

By Bamford J, Fortnum H, Bristow K, Smith J, Vamvakas G, Davies L, *et al.*

No. 33

The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation.

By Black C, Cummins E, Royle P, Philip S, Waugh N.

No. 34

Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.

By Thompson Coon J, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, *et al.*

No. 35

The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Home-based compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence.

By Jolly K, Taylor R, Lip GYH, Greenfield S, Raftery J, Mant J, *et al.*

No. 36

A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food.

By Abubakar I, Irvine L, Aldus CF, Wyatt GM, Fordham R, Schelenz S, *et al.*

No. 37

A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial.

By Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, *et al.*

No. 38

Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling.

By Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, *et al.*

No. 39

A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder.

By Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, *et al.*

No. 40

Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation.

By Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A.

No. 41

The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation.

By Burr JM, Mowatt G, Hernández R, Siddiqui MAR, Cook J, Lourenco T, *et al.*

No. 42

Acceptability, benefit and costs of early screening for hearing disability: a study of potential screening tests and models.

By Davis A, Smith P, Ferguson M, Stephens D, Gianopoulos I.

No. 43

Contamination in trials of educational interventions.

By Keogh-Brown MR, Bachmann MO, Shepstone L, Hewitt C, Howe A, Ramsay CR, *et al.*

No. 44

Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers.

By Facey K, Bradbury I, Laking G, Payne E.



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The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (<http://www.hta.ac.uk>) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.