The value of FDG positron emission tomography/computerised tomography (PET/CT) in pre-operative staging of colorectal cancer: a systematic review and economic evaluation

J Brush,[1] K Boyd,[2] F Chappell,[3] F Crawford,[4]* M Dozier,[5] E Fenwick,[2] J Glanville,[6] H McIntosh,[4] A Renehan,[7] D Weller[4] and M Dunlop[8]

[1]Department of Radiology, Western General Hospital, Edinburgh, UK
[2]Institute of Health and Wellbeing, The University of Glasgow, Glasgow, UK
[3]Division of Clinical Neurosciences, The University of Edinburgh, Edinburgh, UK
[4]The Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, UK
[5]The Main Library, The University of Edinburgh, Edinburgh, UK
[6]York Health Economics Consortium, Ltd, The University of York, York, UK
[7]Department of Surgery, The Christie NHS Foundation Trust, The University of Manchester, Manchester, UK
[8]School of Molecular and Clinical Medicine, The University of Edinburgh, Edinburgh, UK

*Corresponding author

Executive summary

Health Technology Assessment 2011; Vol. 15: No. 35
DOI: 10.3310/hta15350

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk

Executive summary

Background

Worldwide, large bowel (colorectal) cancer (CRC) accounts for > 1 million cancers per year or 9% of all new cancer cases. In the UK, CRC is the third most common malignancy (behind lung and breast cancer), with 37,514 new cases registered in 2006, of which around two-thirds (23,384) were in the colon and one-third (14,130) in the rectum.

Treatment of cancers of the colon and rectum differ considerably, but surgical resection is the mainstay of treatment for curative intent. Particularly for rectal cancers, there are a variety of surgical options and combinations with pre-operative therapies including pre-operative radiotherapy or chemoradiotherapy (where both chemotherapy and radiotherapy are delivered together), all with various levels of morbidity and mortality risk. Surgery is also the main treatment with curative potential for recurrent and metastatic (mainly liver) disease. The presence of disease distant to the site of planned surgery affects type and timing of treatments. Together, this wide variation in presentations and extents of treatments underpins the rationale for accurate pre-operative staging.

Following surgical resection, there is a comprehensive assessment of the tumour, its invasion characteristics and its spread. This forms the basis of tumour 'staging'. Over the past two decades, a number of diagnostic tools have entered clinical practice and now facilitate the process of pre-operative staging. A number of imaging modalities are used in the pre-operative staging of CRC, including computerised tomography (CT), magnetic resonance imaging (MRI), ultrasound imaging and positron emission tomography (PET).

This report examines the role of CT in combination with PET scanning ('hybrid' scan) in pre-operative staging for CRC. The literature contains reports on the use of PET scanning alone compared with other imaging modalities for staging CRC, but as this technology is no longer available, the present report is limited to the role of hybrid fluorine-18-deoxyglucose (FDG) PET/CT scanning.

Objectives

- To conduct a systematic review of the diagnostic accuracy and therapeutic impact of FDG PET/CT for the pre-operative staging of primary, recurrent and metastatic cancer.
- To undertake probabilistic decision-analytic modelling (using Monte Carlo simulation).
- To conduct a value of information analysis to help inform whether or not there is potential worth in undertaking further research.

Methods

Data sources

For each aspect of the research – the systematic review and the economic evaluation – a database was assembled from a comprehensive search for published and unpublished studies, which included database searches, reference list searches and contact with experts. All databases were searched from their inception until May 2009 and included BIOSIS Previews; Cumulative Index to Nursing and Allied Health Literature; The Cochrane Library; EMBASE; GlobalHealth; Index

to Theses; MEDLINE; metaRegister of Current Controlled Trials; UK Clinical Research Network; and Web of Science, including Conference Proceedings Citation Index. The software used was Reference Manager version 10 (Thomson Reuters, CA, USA).

In the systematic review no language restrictions were applied and non-English-language studies were read by individuals with language-specific reading skills. Prospective and retrospective patient series (diagnostic cohort) and randomised controlled trials (RCTs) were eligible for inclusion. Both consecutive series and series that are not explicitly reported as consecutive were included.

Adults with known or suspected primary cancer of the colon or rectum undergoing pre-operative staging prior to curative surgery in a secondary care setting with any stage of disease were eligible for inclusion. Studies solely in patients with anal cancer were excluded.

Studies using only integrated FDG PET/CT equipment with both contrast-enhanced and non-contrast-enhanced CT were considered eligible for inclusion and were compared with standard imaging tests including ultrasound, diagnostic CT, MRI and PET, alone or in combination. Histopathology of surgical resected specimens or biopsy is the gold standard for tests used in CRC pre-operative staging. However, some patients do not undergo surgical intervention if their disease is too advanced for curative management, and therefore composite reference standards including imaging tests and clinical follow-up are used.

Data extraction

Two reviewers extracted all data and applied the criteria independently and resolved disagreements by discussion. Data to populate 2 × 2 contingency tables consisting of the numbers of true positives, true negatives, false positives and false negatives using the studies' own definitions were extracted, as were data relating to changes in management. All 14 items from the Quality Assessment of Diagnostic Accuracy Studies checklist were used to assess the methodological quality of the included studies.

Data synthesis

The 2 × 2 tables for the patient-level data were used to calculate sensitivity and specificity with confidence intervals (CIs). Data were plotted graphically in forest plots.

For the economic evaluation, economic models were designed for each of the disease states: primary, recurrent and metastatic. These were developed and populated based on a variety of information sources (in particular published data sources) and literature, and in consultation with clinical experts.

Results

The review found 30 studies that met the eligibility criteria. Only a small number of data were available from two small studies evaluating the use of FDG PET/CT in primary CRC, and there is insufficient evidence to support its routine use at this time. For FDG PET/CT used for the detection of recurrent disease, data were identified from five retrospective studies from which a pooled sensitivity of 91% (95% CI 87% to 95%) and specificity of 91% (95% CI 85% to 95%) were observed. Pooled accuracy data from patients undergoing staging for suspected metastatic disease showed FDG PET/CT to have a pooled sensitivity of 91% (95% CI 87% to 94%) and specificity of 76% (95% CI 58% to 88%), but the poor quality of the studies means the validity of the data may be compromised by several biases. A complementary handsearch study did not yield any additional unique studies relevant to FDG PET/CT.

The economic evaluation found that the cost per correct diagnosis outcome for primary CRC based on the diagnostic test accuracy estimates used in the models favoured the conventional imaging modalities, as did the cost per quality-adjusted life-year (QALY) outcomes. The recurrent models found FDG PET/CT as an add-on device to have an incremental cost-effectiveness ratio (ICER) of £21,409 per QALY in the rectal model and £6189 per QALY in the colon model. The metastatic model produced an ICER of £21,434 per QALY. Considering the National Institute for Health and Clinical Excellence's monetary threshold of £20,000–30,000 per QALY, these ICERs can be considered to be cost-effective.

Conclusions

The systematic review found only a small amount of evidence to support the use of FDG PET/CT in the pre-operative staging of primary, recurrent and metastatic CRC, and although FDG PET/CT was shown to change patient management, the data are divergent and the quality of research is generally poor. None of the economic models reported cost savings, but the approach adopted was conservative in order to determine more reliable results given the lack of current information. FDG PET/CT as an add-on imaging device is cost-effective in the pre-operative staging of recurrent colon, recurrent rectal and metastatic disease but not primary colon or rectal cancers.

Implications for health care

There is uncertainty about the value of using FDG PET/CT in CRC clinical practice, and those practitioners who access this imaging technology should routinely collect data to enable audits of patient outcomes, including detection rates and any changes in management resulting from its use.

Implications for research

An RCT and concurrent economic evaluation is required to evaluate the therapeutic impact and cost-effectiveness of FDG PET/CT compared with conventional imaging (without FDG PET/CT) for the pre-operative staging of recurrent and metastatic CRC.

There is no value in undertaking further research in primary CRC unless FDG PET/CT technology improves, for example if contrast-enhanced PET/CT becomes available then there would be potential value in undertaking an RCT to evaluate the diagnostic test accuracy and cost-effectiveness of contrast-enhanced PET/CT as a replacement for contrast-enhanced CT imaging.

Funding

Funding for this study was provided by the National Institute for Health Research Health Technology Assessment programme.

Publication

Brush J, Boyd K, Chappell F, Crawford F, Dozier M, Fenwick E, *et al.* The value of FDG positron emission tomography/computerised tomography (PET/CT) in pre-operative staging of colorectal cancer: a systematic review and economic evaluation. *Health Technol Assess* 2011;**15**(35).

How to obtain copies of this and other HTA programme reports

An electronic version of this title, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable DVD is also available (see below).

Printed copies of HTA journal series issues cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our despatch agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per issue and for the rest of the world £3 per issue.

How to order:

– fax (with **credit card details**)
– post (with **credit card details** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you to either print out your order or download a blank order form.

Contact details are as follows:

Synergie UK (HTA Department)
Digital House, The Loddon Centre
Wade Road
Basingstoke
Hants RG24 8QW

Email: orders@hta.ac.uk

Tel: 0845 812 4000 – ask for 'HTA Payment Services' (out-of-hours answer-phone service)

Fax: 0845 812 4001 – put 'HTA Order' on the fax header

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *University of Southampton* and drawn on a bank with a UK address.

Paying by credit card
You can order using your credit card by phone, fax or post.

Subscriptions

NHS libraries can subscribe free of charge. Public libraries can subscribe at a reduced cost of £100 for each volume (normally comprising 40–50 titles). The commercial subscription rate is £400 per volume (addresses within the UK) and £600 per volume (addresses outside the UK). Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

How do I get a copy of *HTA on DVD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd/index.shtml). *HTA on DVD* is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 08/65/02. The contractual start date was in April 2009. The draft report began editorial review in April 2010 and was accepted for publication in November 2010. 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.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

ISSN 2046-4932 (DVD)

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by the Charlesworth Group.