NCCHTA

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1. Title of the project

Intensity modulated radiotherapy for treatment of prostate cancer (HTA 08/01/01)

2. TAR team

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3. Plain English Summary

Prostate cancer is the most common cancer in men in the UK and a leading cause of cancer death in men. Incidence in the UK, in common with many other countries, has been rising. In 2004 there were over 31,000 new cases diagnosed in England and Wales. Despite the increase in incidence mortality rates have been relatively stable.[1]

Prostate cancer frequently progresses slowly, and men with less aggressive disease rarely die of their cancer, but this is not the case for those with the most aggressive tumours (poorly differentiated).[2]

For men with disease localised to the prostate the 2008 NICE prostate cancer guideline[3] recommends active surveillance as the first choice of treatment for low risk disease, and radical treatment (3D-conformal radiotherapy or prostatectomy) for those with intermediate risk disease. Radiotherapy is also offered to patients with locally advanced disease (tumours which have spread no further than the pelvic region), and as salvage therapy for those whose initial radical treatment has failed.[3] The NICE scope for this project[4] states that radiotherapy is also useful in managing metastatic disease, especially in bone. Following expert clinical advice the major focus of this review is radical treatment (with a likely focus on primary radical treatment) as: 1) bone metastases are not unique to prostate cancer, 2) minimal data are expected to be available to assess the benefit of intensity-modulated radiotherapy (IMRT) and 3) the use of IMRT for bone metastatic disease is commonly not used as the target areas are frequently not conformal. It is noted however, that Gong et al.[5] suggest that Image-guided intensity modulated radiotherapy can be of benefit to cancer patients with spinal metastasis but did not include prostate cancer patients in their sample.

Radiotherapy is a recognised treatment for prostate cancer and high dose conformal radiotherapy (CFRT) is the recommended standard of care.[3] Radiation therapy, including IMRT, stops cancer cells from dividing and growing, thus slowing tumour growth. Concepts of IMRT were developed by Brahme[6] and Webb[7] and is a technological advance leading on from 3-dimensional conformal radiotherapy (3D-CRT). The basic principle behind IMRT is the use of intensity-modulated beams, which are defined as beams that deliver more than two intensity levels for a single beam direction and a single source position in space.[8] This definition does not take into account the planning methods (i.e. forward or inverse) or delivery methods (multileaf collimater or compensators, step-shoot, or dynamic) of the treatment intensity-modulated radiotherapy or equipment (for example Image-guided IMRT[5]; a form of image-guided radiotherapy (IGRT)) The planning methods for IMRT treatment use software algorithms to plan how to achieve the prescribed radiation dose to different areas of the prostate. IMRT has been rapidly implemented.[9,10,11]

The close proximity of the prostate and the pelvic lymphatics to the bladder, rectum and small bowel encourage the use of IMRT for prostate cancer[12] because IMRT can sculpt the radiation to the target area of the cancer more precisely so toxicity to the surrounding normal tissues may be reduced.[13] However, side

effects can occur during or immediately after treatment (acute effects) or many months or years after completion of treatment (late effects). In prostate cancer, acute effects include genitourinary symptoms (frequency, urgency, urinary retention, bladder spasms, urinary incontinence, haematuria, dysuria)[8] and gastrointestinal symptoms (proctitis, rectal/perirectal pain, rectal bleeding, diarrhoea).[14,15] Late effects include similar urinary symptoms, sexual dysfunction and gastrointestinal symptoms; these late effects may permanently affect quality of life.

Quality assurance (QA) is an important component of IMRT. QA consists of ensuring that the treatment plan is correctly delivered. It involves verifying that the linear accelerator is optimally set up by making direct measurements. IMRT QA can be individualised for each patient as tends to be the case in the United States or a standardised QA procedure, such as used for 3D-CRT, can be adopted as is increasingly the case for prostate IMRT in the UK.

The aim of this review is to systematically evaluate and appraise the potential clinical and cost-effectiveness of IMRT for the treatment of prostate cancer. The outcome measures to be considered will include overall and disease-specific survival, progression-free survival (clinical and biochemical relapse free), adverse effects of treatment and health-related quality of life.

4. Decision problem

4.1 Purpose of the assessment

The assessment will address the question "What is the clinical and cost effectiveness of intensity modulated radiotherapy for the radical treatment of prostate cancer?"

4.2 Clear definition of the intervention

The included intervention will be IMRT with systems that either do or do not combine the ability to simultaneously image (image-guided radiotherapy (IGRT). IMRT using forward planning or inverse planning will be included. IMRT usually involves the combination of different devices for planning, delivery and sometimes also positional verification. It is anticipated that it will be unlikely that an assessment of the cost-effectiveness of different devices can be made.

4.3 Place of the intervention in the treatment pathway(s)

Radiotherapy may be offered as a radical treatment option for patients diagnosed with localised or locally advanced prostate cancer, often with neoadjuvant and/or adjuvant hormone therapy; which is our primary focus. IMRT is offered to some cancer patients with bone metastasis.

4.4 Relevant comparators

For patients with localised tumours the principal alternative radical treatment options are prostatectomy and 3D-CRT. For patients with locally advanced disease radical 3D-CRT is the relevant comparator.

4.5 Population and relevant sub-groups

The population to be studied comprises of adult men with prostate cancer for whom radical radiotherapy is appropriate.

Sub-groups will principally include localised prostate cancer and locally advanced prostate cancer (radiation of prostate only and whole pelvis radiation). For each of these sub-groups the following sub-sub-groups will be considered: stage of cancer, grade of cancer, initial PSA; prognostic risk groups; the use of neoadjuvant/adjuvant hormonal therapy.

It is likely that the focus will ultimately be primary radical treatment but an evaluation of the sub-group of prostate cancer patients with bone metastasis will be undertaken should evidence allow. However minimal pertinent data are anticipated. Furthermore, an evaluation of adjuvant radiotherapy treatment for high risk radical prostatectomy patients and salvage treatment will be considered if the available evidence suggests that it is required. However minimal pertinent data are anticipated.

4.6 Outcomes

The outcomes of the review are:

- survival (overall and disease-specific)
- progression-free survival (clinical or biochemical (PSA) relapse free)
- adverse effects of treatment
- health-related quality of life

4.7 Key factors to be addressed

The objectives of the review are:

- To evaluate the clinical effectiveness of IMRT in terms of survival (overall and disease-specific), and progression-free survival (clinical and biochemical (PSA) relapse free)
- To evaluate the side-effect profile of IMRT compared with current standard therapy
- To estimate the incremental cost-effectiveness of IMRT compared with current standard therapy

4.8 Areas outside the scope of the appraisal

Other less common radical treatment options (internal seed radiotherapy (brachytherapy), cryotherapy etc.) and non-radical treatment options: watchful waiting, active monitoring, hormone therapy alone.

5. Report methods for synthesis of evidence of clinical effectiveness

5.1 Search strategy

A comprehensive search will be undertaken to systematically identify clinical effectiveness and cost effectiveness literature concerning intensity modulated radiotherapy in men with prostate cancer. The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers

The following databases will be searched: Medline (1950-present), Embase (1980-present), CINAHL (1982-present), BIOSIS (1985-present), the Cochrane Database of Systematic Reviews (CDSR) (1991-present), the Cochrane Controlled Trials Register (CCTR) (1991-present), the Science Citation Index (1900-present) and the NHS Centre for Reviews and Dissemination databases (DARE, NHS EED, HTA) (1991-present). Pre-Medline will also be searched to identify any studies not yet indexed on Medline. Current research will be identified through searching the UK Clinical Research Network (UKCRN), National Research Register archive (NRR), the Current Controlled Trials register and the MRC Clinical Trials Register. In addition, abstracts of relevant conferences will be browsed. Any industry submissions, as well as any relevant systematic reviews will also be hand-searched in order to identify any further clinical trials. Searches will not be restricted by date or publication type. The MEDLINE search strategy for randomised clinical trials is presented in Appendix 1. It is anticipated that a search for case-control and cohort studies may also be conducted. In addition, if indirect comparisons are necessary, a further search will be conducted to try to identify a network of trials that connect the intervention and comparator.

5.2 *Inclusion criteria*

Intervention

Intensity modulated radiotherapy (IMRT) with systems that either do or do not combine the ability to simultaneously image (image-guided radiotherapy (IGRT), whether delivered using forward planning or inverse planning.

Population

The population will comprise men with prostate cancer for whom radical radiotherapy is appropriate. Where data are available, the following subgroups will be considered: localised prostate cancer, locally advanced prostate cancer (radiation of prostate only and whole pelvis radiation), bone metastasis in prostate cancer patients, adjuvant radiotherapy treatment for high risk radical prostatectomy patients and salvage

treatment. Stage of cancer, grade of cancer, initial PSA, prognostic risk groups, the use of neoadjuvant/adjuvant hormonal therapy will also be considered.

Comparators

- 3-dimensional conformal radiotherapy (3D CRT), radical prostatectomy

Outcomes

- survival (overall and disease-specific)
- progression-free survival (clinical or biochemical (PSA) relapse free)
- adverse effects of treatment
- health-related quality of life

Study types

According to the accepted hierarchy of evidence, randomised controlled trials and meta-analyses from systematic reviews will be searched initially, as they provide the most authoritative forms of evidence. If sufficient data are not available from RCTs, case-control and cohort studies will be included. If data from head-to-head RCTs are not available, indirect treatment comparison methods may be used, and so data may be sought that could form a network of trials that compare the technologies with other interventions. If direct evidence of treatment toxicity is lacking the inclusion of dosimetric studies will be considered.

5.3 *Exclusion criteria*

Studies only published in languages other than English will be excluded.

Based on the above inclusion/exclusion criteria, study selection will be made by one reviewer, with involvement of a second reviewer when necessary.

5.4 *Data extraction and critical appraisal*

Data will be extracted with no blinding to authors or journal. Data will be extracted by one reviewer using a standardised form, and checked by a second reviewer. Quality of randomised controlled trials will be assessed according to criteria based on NHS CRD Report No.4, see Appendix 2.[16] If no randomised controlled trials are found, quality assessment of other study types will be adapted from the Downs and Black checklist for randomised and non-randomised studies.[17] The purpose of such quality assessment is to provide a narrative account of trial quality for the reader and, where meta-analysis is appropriate, inform potential exclusions from any sensitivity analyses.

5.5 *Data synthesis*

Pre-specified outcomes will be tabulated and discussed within a descriptive synthesis. Where statistical synthesis is appropriate, meta-analyses will be conducted using fixed or random effect models, using

RevMan software. If sufficient trials are available, a sensitivity analysis will be undertaken to see if the removal of poor quality trials affects the results.

5.6 *Methods for estimating quality of life*

Any HRQoL data available from studies accepted into the review will be extracted. In the absence of such evidence, the mathematical model may use indirect evidence on quality of life from alternative sources. Quality of life data will be reviewed and used to generate the quality adjustment weights required for the model.

6. Report methods for synthesising evidence of cost-effectiveness

6.1 Identifying and systematically reviewing published cost-effectiveness studies

Appropriate published cost-effectiveness and cost-utility studies associated with IMRT for treatment of prostate cancer will be identified using an economic search filter which will be integrated into the search strategy detailed in Section 5.1. These will be reviewed and possibly used to inform suitable methodologies for the economic model. The quality of economic literature will be assessed using a combination of key components of the British Medical Journal check list for economic evaluations[18] together with the Eddy checklist on mathematical models[19] (see Appendix 3).

6.2 Methods for estimating costs and cost-effectiveness

An economic evaluation will be carried out from the perspective of the UK NHS and Personal Social Services (PSS). A mathematical model will be developed in Excel to estimate the cost per QALY gained for IMRT for treatment of prostate cancer. The model structure will be determined in consultation with clinical experts. The time horizon of the analysis will be a patient's lifetime. However, the model will be constructed to facilitate the use of shorter horizons. Ideally, the quality of life data regarding the reduced side-effects associated with IMRT for the treatment of prostate cancer will be identified from the literature. Where utility values are not found in the published literature these will have to be estimated from other sources, including but not limited to, comparisons with other conditions with comparable health states and expert opinion. Cost data for the economic model will ideally be derived from the source of clinical effectiveness. If such data are unavailable, cost data will be extracted from a variety of published sources, and if necessary, and available, from interrogations of clinical databases and resource usage records. The costs of implementation of IMRT will consider additional equipment required and staff resources. It is likely that staff training and increased workload will be a key issue, particularly in the first few months of IMRT implementation.[20] The core team will use evidence from the literature and work in collaboration with our advisers to estimate the resources required to implement IMRT.

In a recent review of IMRT in prostate cancer[13] no studies were identified with disease-free or overall survival as outcomes. Studies commonly report outcomes based on the biochemical marker prostate-specific antigen, typically freedom from biochemical recurrence. An international consensus definition is now used (ASTRO 2006), but older studies may use a previous definition (ASTRO 1996) or their own.[21,22] The relationship of freedom from biochemical recurrence with survival is also not straightforward.[23] In order to model lifetime outcomes assumptions will need to be made, based on the literature and in collaboration with our clinical advisors, regarding this relationship.

A sensitivity analysis will be undertaken to identify the key parameters that determine the cost-effectiveness of the intervention with the objective of identifying how secure the results of the economic analyses are, given the available evidence. Uncertainty with respect to model parameters will be explored with a probabilistic sensitivity analysis (PSA), where uncertainty of all input variables is modelled with probability distribution of their value. The information derived from PSA will be summarised graphically using cost effectiveness acceptability curves.[24]

7. Handling the company submission(s)

All data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 14 November 2008. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the TAR team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing de-novo modelling. Any 'commercial in confidence' data taken from a company submission will be highlighted in yellow and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets).

8. Competing interests of authors

John Staffurth

Studied for his MD in IMRT for pelvic malignancies at the Institute for Cancer Research which receives funding from various sources for its IMRT programme. This includes CRUK (programme grant) and commercial collaborators. He sits on the NCRI radiotherapy clinical studies group and its technical sub-group, and on the Radiotherapy Development Board (RCR, IPEM, SoR, ACCORRN, NCRI RT CSG).

He chairs a group developing an IMRT consensus statement which is addressing the following issues relating to IMRT use in the UK: evidence, evaluation, education, and department delivery standards.

Philip Mayles

Uses IMRT in the course of his work at Clatterbridge Centre for Oncology. He receives no payment for this work other than his NHS salary.

Colin Baker

Has an intellectual interest in IMRT from a research perspective, including IMRT for prostate cancer. No direct involvement with manufacturers.

Baker CR, Clements R, Gately A and Budgell GJ (2006) A separated primary and scatter model for independent dose calculation of intensity modulated radiotherapy. Radiotherapy and Oncology 80: 385-390.

Baker CR and Hardy V (2004) Provision of IMRT in the UK II: Current levels, planned expansion and obstacles to implementation. Journal of Radiotherapy in Practice 3 (4): 181-184.

Baker CR and Hardy V (2004) Provision of IMRT in the UK I: A review of planning, delivery and related technologies. Journal of Radiotherapy in Practice 3 (4): 175-180.

Helen Mayles

Uses IMRT in the course of his work at Clatterbridge Centre for Oncology. She receives no payment for this work other than her NHS salary.

David Dearnaley

Is the chief investigator for the CTAAC approved CRUK DoH funded CHHiP Trial, ISRCTN No. 97182923, which is a national study of IMRT using standard or hypofractionated radiation schedules in localised prostate cancer. This trial has facilitated the introduction of high quality IMRT techniques in prostate cancer across the UK.

He is the Chief Investigator of an institutional study of high dose pelvic lymph node irradiation in prostate cancer (EC:1766). Provisional results show a very low level of side effects and an initial draft publication has been submitted which he is happy to make available to the review process.

He has acted as an unpaid advisor to BUPA to establish minimum quality assurance standards for facilities delivering IMRT to private patients.

He has co-authored an article from the Institute of Physics and Engineering in Medicine on the development of IMRT in prostate cancer.

He has no financial interests in any of the technology or radiotherapy companies involved in delivering IMRT.

Jason Cashmore

Has a research contract with one of the linac manufacturers, Elekta, to study unflattened photon beams, i.e. radiotherapy with no flattening filter. The study is not directly tied into IMRT delivery but will contain elements of IMRT research.

Cashmore J, The characterisation of unflattened photon beams from a 6MV linear accelerator. Phys. Med. Biol. 53 (2008) 1933-1946.

ScHARR team

None

Appendix 1

Draft search strategy for MEDLINE

1 Radiotherapy, Intensity-Modulated/
2 intensity modulated radiotherap*.tw.
3 intensity-modulated radiotherap*.tw.
4 intensity modulated radiation therap*.tw.
5 intensity-modulated radiation therap*.tw.
6 imrt.tw. (2343)
7 image guided radiotherap*.tw. (185)
8 igrt.tw.
9 dose compensation.tw.
10 electronic compensation.tw.
11 e compensation.tw.
12 forward planning.tw.
13 inverse planning.tw.
14 field in field.tw.
15 physical compensation.tw.
16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17 Randomized controlled trials as Topic/
18 Randomized controlled trial/
19 Random allocation/
20 Double blind method/
21 Single blind method/
22 Clinical trial/
23 exp Clinical Trials as Topic/
24 16 or 17 or 18 or 19 or 20 or 21 or 22
25 (clinic$ adj trial$1).tw.
26 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
27 Placebos/
28 Placebo$.tw.
29 Randomly allocated.tw.
30 (allocated adj2 random).tw.
31 25 or 26 or 27 or 28 or 29 or 30
32 24 or 31
33 prostatic neoplasms/
34 (prostat$ adj5 (cancer$ or carcin$ or tumor$ or tumour$ or neoplasm$)).tw.

35 ((carcinoma or neoplasia or neoplasm$ or adencarcinoma or cancer$ or tumor$ or tumour$ or malignan$) adj3 prostat$).tw.

36 33 or 34 or 35

37 16 and 32 and 36

Appendix 2: Draft quality assessment

Appendix 2

Randomised controlled trial quality assessment scale based on NHS CRD Report No. 4.
NHS Centre for reviews and Dissemination. *Report 4: Undertaking systematic reviews of research on effectiveness; CRD's guidance for those carrying out or commissioning reviews*. York: University of York; 2001.

	Yes/No/Unclear/ Not Applicable
Was the method used to assign participants to the treatment groups really random?	
What method of assignment was used?	
Was the allocation of treatment concealed?	
What method was used to conceal treatment allocation?	
Was the number of participants who were randomised stated?	
Were the eligibility criteria for study entry specified?	
Were details of baseline comparability presented?	
Was baseline comparability achieved?	
Were participant data analysed by allocated treatment group in accordance with intention-to-treat principle?	
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	
Were the outcome assessors blinded to the treatment allocations?	
Were the individuals who administered the intervention blinded to the treatment allocation?	
Were the participants who received the intervention blinded to the treatment allocation?	

Appendix 3: Critical appraisal checklist for economic evaluations using key components of the British Medical Journal checklist for economic evaluations[18] together with the Eddy[19] checklist on mathematical models employed in technology assessments.

Reference ID		
Title		
Authors		
Year		
Modelling assessments should include:		**Yes/No**
1	A statement of the problem;	
2	A discussion of the need for modelling vs. alternative methodologies	
3	A description of the relevant factors and outcomes;	
4	A description of the model including reasons for this type of model and a specification of the scope including; time frame, perspective, comparators and setting. *Note: n=number of health states within sub-model*	
5	A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence;	
6	A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships, and distributions) and the data;	
7	A list of parameter values that will be used for a base case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis;	
8	The results derived from applying the model for the base case;	
9	The results of the sensitivity analyses; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold.	
10	A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect;	

11	A description of the validation undertaken including; concurrence of experts; internal consistency; external consistency; predictive validity.	
12	A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results;	
13	A description of research in progress that could yield new data that could alter the results of the analysis	

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