Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence

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1. Title of the project

Intensity modulated radiotherapy for treatment of head and neck cancer (HTA 08/01/02)

2. TAR team

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Lead

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3. Plain English Summary

Head and neck cancer includes a group of cancers found in the head and neck region and therefore, comprises different types of diseases.[3] Head and neck cancer is a broad term including cancer with its primary site from the base of the neck upwards. It excludes cancers of the brain, eye, thyroid and malignant melanomas. Examples of head and neck cancers include the mouth, nasal cavity or larynx (voice box). Head and neck cancer frequently spreads to other sites in the head or neck (local metastases), usually spreading through the lymphatic system in the neck. Distant metastases occur less commonly, and metastases from other cancers to the head and neck are rare.

Intensity modulated radiotherapy (IMRT) began in 1982 with a publication presented by Brahme *et al.* [1] in the Karolinska Institute in Stockholm. IMRT is a form of three dimensional radiation therapy. Its main purpose is to produce a three dimensional dose distribution based on multiple external beams radiation that conforms to the shape of the area to be treated. The main advantage of this radiation therapy is that it avoids excessive radiation exposure of normal tissue adjacent to the tumour allowing higher radiation doses being applied to the tumour. IMRT can more accurately wrap around curved structures than 3D conformal radiotherapy (3D CRT). IMRT can be planned using inverse planning software algorithms. These algorithms are based on planning a prescribed dose and distribution of radiation with clinical input and using a computer software to work backwards to determine the optimal direction and intensity of the beams to achieve the required dose prescription.[2]

IMRT requires several steps for both treatment planning and treatment delivery. In treatment planning the clinician needs 3D computer tomography images to determine the tissues at risk and the target tissues in order to develop the treatment plan. The treatment plan should include the dose constraints and requirements and the distribution of radiation. Finally, the treatment delivery involves the patient position and localisation of the target. IMRT delivery is a complex process and therefore quality assurance (QA) is an important component. QA consists of verifying that the treatment planned has been delivered. It also involves testing the equipment precision. QA can be standardised but in some complex cases it may be individualised. Expected benefits of IMRT for treatment of head and neck cancer are reduction in side effects and generally improved quality of life. In patients with head and neck cancer common side effects that are likely to cause patient discomfort are inflammation and ulceration of the mucous membranes lining the mouth and dry mouth due to a lack of saliva.

The aim of this review is to systematically evaluate and appraise the potential clinical and cost-effectiveness of IMRT for the treatment of head and neck cancer. Relevant outcome measures include overall survival, progression-free survival, adverse effects of treatment and health-related quality of life.

Several types of IMRT devices are available in the UK. Where evidence is available an assessment will be undertaken on individual devices. Where evidence is not available then assumptions will be made on the effectiveness of the device.

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 treatment of head and neck cancer?"

4.2 Clear definition of the intervention

The included intervention will be intensity modulated radiotherapy (IMRT) with systems that either do or do not combine the ability to simultaneously image. IMRT will be included whether delivered using forward planning or inverse planning.

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

Treatment for head and neck cancer usually includes radiotherapy and surgery in combination, although radiotherapy may be used alone, for example in the case of unresectable cancers. Sometimes chemotherapy is given along with radiotherapy (chemoradiation).[3] Radiotherapy may be delivered pre-operatively (neoadjuvant radiotherapy) or post-operatively (adjuvant radiotherapy).

4.4 Relevant comparators

In England and Wales, radiotherapy for head and neck cancer is currently delivered using 3-dimensional conformal radiotherapy (3D CRT).

4.5 Population and relevant sub-groups

The population to be studied will comprise adults with head and neck cancer for whom radiotherapy is considered appropriate. Head and neck cancer includes cancer of the following sites: oral cavity (lips, mouth, tongue); salivary glands; paranasal sinuses and nasal cavity; pharynx (nasopharynx, oropharynx, hypopharynx); larynx; ear (external auditory meatus, middle ear). Relevant subgroups include: origin of cancer; stage of cancer; performance status or prognostic biomarkers; previous irradiation to the head and neck.

4.6 Key factors to be addressed

The objectives of the review are:

- To evaluate the clinical effectiveness of IMRT in terms of overall survival and progression-free survival
- To evaluate the side-effect profile of IMRT
- To estimate the incremental cost-effectiveness of IMRT compared with current standard therapy

4.7 Areas outside the scope of the appraisal

Patients with cancers of the brain, eye, thyroid, malignant melanomas, or cancer in the lymph nodes of the upper neck with no evidence of cancer in other parts of the head and neck, will be excluded.

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 adults with head and neck 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. Medline, Embase and CINAHL will be searched via OVID. The Cochrane Database of Systematic Reviews (CDSR), the Cochrane Controlled Trials Register (CCTR) and NHS Centre for Reviews and Dissemination databases (DARE, NHS, EED, HTA) will be searched via Wiley. BIOSIS and Science Citation Index will be searched via ISI.

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, proceedings from relevant conferences will be browsed, for e.g. American Society for Therapeutic Radiology and Oncology (ASTRO) and European Society for Therapeutic and Radiation Oncology (ESTRO). 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 is presented in Appendix 1.

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. IMRT will be included whether delivered using forward planning or inverse planning.

Population

The population will comprise adults with head and neck cancer for whom radiotherapy is considered appropriate. Sites of head and neck cancer considered in the review will include: oral cavity (lips, mouth, tongue); salivary glands; paranasal sinuses and nasal cavity; pharynx (nasopharynx, oropharynx,

hypopharynx); larynx; ear (external auditory meatus, middle ear). Where data are available, the following subgroups will be considered: origin of cancer; stage of cancer; performance status or prognostic biomarkers; previous irradiation to the head and neck.

Comparator

- 3-dimensional conformal radiotherapy (3D CRT)

Outcomes

- overall survival
- progression-free survival
- 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 will be sought that could form a network of trials that compare the technologies with other interventions. In the absence of evidence on clinical endpoints, dosimetric studies will be included.

5.3 *Exclusion criteria*

Patients with cancers of the brain, eye, thyroid, malignant melanomas, or cancer in the lymph nodes of the upper neck with no evidence of cancer in other parts of the head and neck, will be excluded. 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[4], see Appendix 2. 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[5]. 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 head and neck 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[6] together with the Eddy checklist on mathematical models[7] (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 National Health Services and Personal Social Services. A disease treatment pathway model built in Excel will be developed to estimate the cost per QALY gained for IMRT for treatment of head and neck cancer. The model structure will be determined in consultation with clinical experts.

Ideally, the quality of life data regarding the reduced side-effects associated with IMRT for the treatment of head and neck 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 staff resources and equipment required. It is likely that staff training and increased workload will be a key issue, particularly in the initial phase of IMRT implementation.[8] 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.

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.

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 10-11-2008. 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

Julie Olliff is president of the British Institute of Radiology. This is a charitable institute and as such receives support from various sources. Martin Robinson has carried out research with this topic in the past at Weston Park Hospital in Sheffield. He has been involved in projects where various equipment manufacturers have funded a radiographer to assist in the implementation of 'on board imaging' in the short term, however this payment was made to the Weston Park Hospital and this radiographer will not be an author on the report.

Appendix 1

Draft search strategy for MEDLINE

1 exp "Head and Neck Neoplasms"/

2 exp Facial Neoplasms/

3 exp Mouth Neoplasms/

4 exp Salivary Gland Neoplasms/

5 exp Otorhinolaryngologic Neoplasms/

6 exp Nose Neoplasms/

7 exp pharyngeal neoplasms/ or exp oropharyngeal neoplasms/

8 exp Paranasal Sinus Neoplasms/

9 or/1-8

10 (neoplas$ or cancer$ or carcinoma$ or malignan$ or tumor$ or tumour$).tw.

11 (lip$ or oral or oropharyn$ or laryn$ or hypopharyn$ or nasopharyn$ or nasal or paranasal or ear$ or external auditory meatus or face or facial or head or neck).tw.

12 (salivary$ adj2 gland$).tw.

13 11 or 12

14 10 and 13

15 9 or 14

16 Radiotherapy, Intensity-Modulated/

17 intensity-modulated radiotherap$.tw.

18 intensity modulated radiotherap$.tw.

19 intensity-modulated radiation therap$.tw.

20 intensity modulated radiation therap$.tw.

21 IMRT.tw.

22 image guided radiotherap$.tw.

23 igrt.tw.

24 longitudinal wedge$.tw.

25 physical compensat$.tw.

26 mixed energ$.tw.

27 dose compensat$.tw.

28 electronic compensat$.tw.

29 ecompensat$.tw.

30 e compensat$.tw.
31 e-compensat$.tw.
32 forward-plan$.tw.
33 field in field.tw.
34 forward plan$.tw.
35 plan optimisation.tw.
36 plan optimization.tw.
37 or/16-36
38 15 and 37
39 randomized controlled trial.pt.
40 controlled clinical trial.pt.
41 randomized controlled trials/
42 random allocation/
43 double blind method/
44 single blind method/
45 clinical trial.pt.
46 exp Clinical Trial/
47 (clin$ adj25 trial$).ti,ab.
48 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
49 placebos/
50 placebos.ti,ab.
51 random.ti,ab.
52 research design/
53 or/39-52
54 38 and 53
55 exp cohort studies/
56 cohort$.tw.
57 controlled clinical trial.pt.
58 epidemiologic methods/
59 limit 58 to yr=1966-1989
60 exp case-control studies/
61 (case$ and control$).tw.
62 55 or 56 or 57 or 59 or 60 or 61

63 53 or 62

64 38 and 63

Appendix 2 Draft quality assessment

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[4] together with the Eddy checklist on mathematical models employed in technology assessments.[5]

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	

[1] Brahme A., Roos J.E., Lax I. Solution of an integral equation encountered in rotation therapy. Phys Med Biol 1982; **27** 1221-1229.

[2] Intensity-modulated radiotherapy (IMRT) KCE. Belgian Health Care Knowledge Centre. Reports vol. 62C, November 2007.

[3] Guidance on Cancer Services. Improving Outcomes in Head and Neck Cancers. The Manual. NICE November 2004.

[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.

[5] Downs S.H. and Black N. *J Epidemiol Community Health* 1998; **52** 377-384.

[6] Drummond, M and Jefferson, TO Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996; **313** 257-283.

[7] Eddy, DM. *The role of mathematical modelling in Assessing medical technology. Technology Assessment 1985; 144-154.*

[8] 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.