

# **Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation**

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## ***Executive summary***

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## Executive summary

### Background

Prostate cancer (PC) is the most common cancer in men in the UK. Radiotherapy (RT) is a recognised treatment for PC and high-dose conformal radiotherapy (CRT) is the recommended standard of care for localised or locally advanced tumours. Intensity-modulated radiotherapy (IMRT) allows better dose distributions in RT.

### Objectives

This report evaluates the clinical effectiveness and cost-effectiveness of IMRT for the radical treatment of PC.

### Methods

A systematic literature review of the clinical effectiveness and cost-effectiveness of IMRT in PC was conducted. Comparators were three-dimensional conformal radiotherapy (3DCRT) or radical prostatectomy. Outcomes sought were overall survival, biochemical [prostate-specific antigen (PSA)] relapse-free survival, toxicity and health-related quality of life (HRQoL). Fifteen electronic bibliographic databases were searched (including MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), MEDLINE In-Process & Other Non-Indexed Citations, etc.) in January 2009 and updated in May 2009, and the reference lists of relevant articles were checked. Studies only published in languages other than English were excluded.

An economic model was developed to examine the cost-effectiveness of IMRT in comparison to 3DCRT. Four scenarios were modelled based on the studies which reported both PSA survival and late gastrointestinal (GI) toxicity. In two scenarios equal PSA survival was assumed for IMRT and 3DCRT, the other two having greater PSA survival for the IMRT cohort. As there was very limited data on clinical outcomes, the model estimates progression to clinical failure and PC death from the surrogate outcome of PSA failure.

### Results

No randomised controlled trials (RCTs) of IMRT versus 3DCRT in PC were available, but 13 non-randomised studies comparing IMRT with 3DCRT were found, of which five were only available as abstracts. One abstract reported overall survival. Biochemical relapse-free survival was not affected by treatment group, except where there was a dose difference between groups, in which case higher dose IMRT was favoured over lower dose 3DCRT. Most studies reported an advantage for IMRT in GI toxicity, attributed to increased conformality of treatment compared with 3DCRT, particularly with regard to volume of rectum treated. There was some indication that genitourinary (GU) toxicity was worse for patients treated with dose-escalated IMRT, although most studies did not find a significant treatment effect. HRQoL improved for both treatment groups following RT, with any group difference resolved by 6 months after treatment. No comparative studies of IMRT versus prostatectomy were identified. No comparative studies of IMRT in PC patients with bone metastasis were identified.

### Summary of costs

The additional cost of IMRT compared with 3DCRT was estimated to be £1100, arising from additional medical, radiographer and physics staff time.

### Summary of cost-effectiveness

For the scenarios with greater survival for IMRT than 3DCRT-treated patients the results are unambiguous. IMRT either dominates 3DCRT [that is results in more quality-adjusted life-years (QALYs) for lower total costs], or the incremental cost-effectiveness ratio (ICER) is relatively modest (£5000), results which are robust to variation in other key parameters.

The two scenarios where equivalent survival is assumed for IMRT and 3DCRT, and QALY differences between the two cohorts are derived solely from differences in late GI toxicity alone, show IMRT to be borderline cost-effective

depending on the difference in GI toxicity, duration of GI toxicity and the cost difference between IMRT and 3DCRT. At baseline parameter values the scenario with a difference in late GI toxicity of 5% (scenario 1) gave an ICER of £104,000, but scenario 2 with a difference in GI toxicity of 15% gave an ICER of £31,000. The probabilistic analysis of the latter scenario showed that only with a maximum incremental cost-effectiveness ratio (MAICER) of  $\geq$  £30,000 was it probable that IMRT was more cost-effective than 3DCRT. These results are highly sensitive to two very uncertain parameters: the incremental cost of IMRT and the duration of late GI toxicity. Variation of these parameters within plausible bounds can reduce the ICER of IMRT in comparison to 3DCRT to below a threshold of £20,000, or equally push it clearly beyond a threshold of £30,000. The scenarios modelled were all based on studies where both PSA survival and toxicity were reported. To put the values of incidence of late GI toxicity from the modelled studies in context the results of other studies included in the review were considered. These suggest model scenario 2 is more representative of the literature than scenario 1.

For RT to the whole pelvis (usually only considered for men with a > 15% risk of pelvic lymph node involvement) IMRT may be more cost-effective than for treatment of the prostate (and seminal vesicles) alone. A previous report published by Sanguineti *et al.* (Sanguineti G, Cavey ML, Endres EJ, Franzone P, Barra S, Parker BC, *et al.* Does treatment of the pelvic nodes with IMRT increase late rectal toxicity over conformal prostate only radiotherapy to 76 Gy? *Strahlenther Onkol* 2006;182:543–9) reports a difference of 15% in late GI toxicity at only two years, despite the IMRT group receiving whole pelvis RT in comparison to treatment of the prostate only in the comparator (3DCRT) group.

## Discussion

A comprehensive, systematic literature review was undertaken, but the strength of the conclusions

of this review are limited by the lack of RCTs, and any comparative studies for some patient groups. The comparative data of IMRT versus 3DCRT seem to support the theory that higher doses, up to 81 Gy, can improve biochemical survival for patients with localised PC, concurring with data on CRT. The data also suggest that toxicity can be reduced by increasing conformality of treatment, particularly with regard to GI toxicity, which can be more easily achieved with IMRT than 3DCRT. Whether differences in GI toxicity between IMRT and 3DCRT are sufficient for IMRT to be cost-effective is uncertain, depending on the difference in incidence of GI toxicity, its duration and the cost difference between IMRT and 3DCRT.

## Conclusions

### Implications for service provision

Clinical advice suggests that most RT centres already possess the equipment required to deliver IMRT, but that lack of available staff such as medical physicists hinders implementation. 3DCRT may be safely delivered at the currently recommended total dose of 74 Gy, and there is no evidence that PSA survival is improved by giving IMRT at the same dose as 3DCRT. However, there is evidence that IMRT reduces toxicity, in particular late GI toxicity. The magnitude of the difference is uncertain, which, together with uncertainties in other variables such as the difference in cost between IMRT and 3DCRT, in turn makes the cost-effectiveness of IMRT in comparison to 3DCRT uncertain. If a difference in late GI toxicity of 15% is assumed the probability of IMRT being more cost-effective than 3DCRT is only true for a MAICER of  $\geq$  £30,000.

## Publication

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