Technoleg Iechyd Cymru
Health Technology Wales

HEALTH TECHNOLOGY WALES (HTW) GUIDANCE 034 (February 2022)

Extreme hypofractionated radiotherapy (EHFRT) to treat localised prostate cancer

HTW guidance:

The evidence supports the routine adoption of extreme hypofractionated radiotherapy (EHFRT) to treat localised prostate cancer.

EHFRT is associated with equivalent short- and medium-term cancer recurrence and survival outcomes compared with standard care (moderately or conventionally fractionated radiotherapy). EHFRT reduces the number of visits required for treatment and is associated with a low incidence of adverse events.

EHFRT is likely to be cost effective when compared with standard care. Compared with moderately hypofractionated radiotherapy guided by fiducial markers, EHFRT (seven fractions) using fiducial markers is likely to be cost effective if it is delivered in treatment slots of 20 minutes or shorter. If EHFRT is delivered in five fractions, it is likely to be cost effective at all slot lengths up to 30 minutes.

Why did Health Technology Wales (HTW) appraise this topic?

In the UK, prostate cancer is the most common cancer in men. In Wales, more than 2,500 men each year are diagnosed with prostate cancer. Radiotherapy is included as part of primary treatment in approximately 30% of patients diagnosed with prostate cancer.

EHFRT is an adaptation to conventional external beam radiotherapy and delivers the equivalent dose of radiotherapy in fewer sessions or fractions: EHFRT uses five or seven fractions over two weeks whereas standard radiotherapy treatment (moderately fractionated radiotherapy) usually uses 20 fractions over 4 weeks. Shorter treatment duration delivered over fewer treatment sessions has the potential to reduce hospital visits, reduce travelling costs, and alleviate some of the inconvenience of treatment for patients and their families.

This topic was proposed by Dr John Staffurth, Consultant Oncologist, Velindre University NHS Trust.

The status of HTW guidance is that NHS Wales should adopt this guidance or justify why it has not been followed. HTW will evaluate the impact of its guidance.

Evidence Summary

Refer to Evidence Appraisal Report 034 for a full report of the evidence supporting this guidance.

HTW carried out an evidence review to address the following research question: What is the clinical and cost effectiveness of extreme hypofractionated radiotherapy (EHFRT) to treat localised prostate cancer compared to standard care? This review defined localised prostate cancer as TNM classification TXN0M0, i.e., people with a tumour of any T stage, but no node involvement or distant metastasis.

HTW's evidence review found two randomised controlled trials evaluating the clinical effectiveness of EHFRT compared to either conventionally fractionated or moderately hypofractionated radiotherapy, delivered as 39 or 20 fractions, respectively (PACE-B), or conventional fractionated radiotherapy, delivered as 39 fractions (HYPO-RT-PC).

Evidence from HYPO-RT-PC showed no significant difference in the overall, failure-free, and distant metastasis-free survival at five years between the treatment groups (long-term outcome data from PACE-B has not yet been published). In both trials, there were no statistically significant differences in toxicity outcomes between the EHFRT group and the control group at any point after treatment, except for an increase in grade 2 or worse urinary toxicity in the EHFRT group compared to the control group at one-year follow-up, reported in HYPO-RT-PC (6% and 2% of patients treated with EHFRT or control treatment, respectively). After six-years follow-up, there was no difference in the incidence of clinically relevant deterioration between the groups for overall urinary, bowel, sexual and global health in HYPO-RT-PC.

HTW's cost-utility analysis showed that EHFRT has the potential to be cost effective when compared with conventionally fractionated radiotherapy in people with localised prostate cancer, in several key scenarios which explored changes in assumptions about slot times for treatment delivery. If fiducial markers are not used to guide treatment in standard care, EHFRT is estimated to be cost effective when compared with conventional fractionation if it is delivered in seven fractions with slot lengths of 15 minutes, or five fractions of 20 minutes duration. If fiducial markers are used to guide treatment, then EHFRT is estimated to be cost effective when compared with conventional fractionation when seven fractions are delivered in slot lengths of 20 minutes, or five fractions are delivered in slot lengths of 30 minutes.

The appropriate mechanism for patient engagement was determined and the patient perspective was considered where possible. HTW sought to better understand patient decision making and the factors that may influence patient's decisions when offered EHFRT instead of conventional or moderately hypofractionated radiotherapy. Expert comments indicated that shorter and fewer treatment sessions are much preferred by patients and their families.

Appraisal Panel considerations

- The Appraisal Panel heard from patient and public involvement representatives of the benefits that EHFRT would likely bring to patients and their families. EHFRT reduces the number of hospital visits and would reduce the overall burden of travel for patients and their families, which could be very significant for many people across Wales, especially those living in remote and rural communities. Experts and members of the panel also noted that lower numbers of visits may improve overall adherence to treatment, reduce travelling costs for patients and their families as well as result in a desirable reduction in fuel consumption and carbon emissions, potentially resulting in more environmentally sustainable treatment option.

- The Appraisal Panel heard from clinical experts that the demand for external beam radiotherapy treatment for cancer is high and that pressures on the clinical service have been exacerbated by the COVID-19 pandemic. The opportunity to reduce the number of radiotherapy fractions would liberate treatment slots and improve radiotherapy capacity. This would enable greater and more timely access to radiotherapy for people with a range of cancers. Furthermore, a reduction in the time spent visiting hospital for vulnerable patients is desirable to minimise their risk of acquiring transmissible infections.

- The Appraisal Panel concluded that the published evidence relating to the use of EHFRT to treat localised prostate cancer comprises well-conducted, randomised controlled trials (RCTs) and were advised by the clinical experts that the patient cohorts included in these studies are directly relevant to those that are treated for this type of prostate cancer in the UK. It was also concluded from the available evidence that the important clinical outcomes of EHFRT, including overall survival, cancer recurrence, and quality of life are equivalent after treatment when compared to conventionally fractionated or moderately hypofractionated radiotherapy in the short and medium term. In HYPO-RT-PC, the estimated failure-free survival at five years follow-up was 84% in both treatment groups ($p = 0.99$). Overall survival at five years follow-up between the treatment groups was 94% for the EHFRT group and 96% for the control group ($p = 0.951$). HYPO-RT-PC reported quality-of-life outcomes after six years of follow-up: there was no difference in the incidence of clinically relevant deterioration between the treatment groups for overall urinary, bowel, sexual and global health.

- The Appraisal Panel noted that one of the two pivotal RCTs reported a small increase in urinary toxicity (grade 2 or higher) at one-year follow-up in the EHFRT group compared to the control group. However, the panel also noted that at earlier and later time points than one year, the available evidence reports equivalent levels of urinary toxicity for EHFRT and standard care. The panel were further reassured by the clinical experts that the urinary symptoms reported can usually be managed by relatively straightforward interventions such as additional oral medication.

- The Appraisal Panel were advised by the clinical experts that the insertion of fiducial markers is an optimal means of directing radiotherapy treatment (especially at high dose) to best target the treatment on the cancer and reduce the likelihood of adjacent tissue damage and toxicity. The use of fiducial markers is widely used in other parts of the UK but is not yet part of routine practice in Wales. The experts indicated that the adoption of fiducial guided treatment was both desirable and deliverable in the context of further developing EHFRT services in Wales. The Appraisal Panel noted that the use of fiducial markers was included in the treatment of most patients in the RCTs and were advised that this should be regarded as optimal practice when considering the clinical and cost implications of EHFRT. The clinical experts informed the Appraisal Panel that the skills are available for fiducial marker insertion in Wales and that this is done by a variety of specialists including radiologists and urologists.

- The Appraisal Panel noted that the cost-utility analysis results were sensitive to changes in a variety and combination of assumptions including the number of fractions delivered, the slot lengths for delivering the fractions, and the use or not of fiducial markers. The cost-utility analysis estimates that, without the use of fiducial markers in standard care, EHFRT is cost effective when compared with conventional fractionation (20 fractions) provided that the slot times and number of fractions for EHFRT are delivered as follows:
    - 7-fraction EHFRT in slot lengths of 15 minutes
    - 5-fraction EHFRT in slot lengths of 20 minutes
- EHFRT, compared with conventionally fractionated radiotherapy with fiducial markers, was more likely to be cost effective. In the HTW cost-utility analysis, EHFRT was shown to be cost effective when EHFRT was delivered as follows:
    - 7-fraction EHFRT in slot lengths of 20 minutes
    - 5-fraction EHFRT in slot lengths of 30 minutes
- The Appraisal Panel consulted the clinical experts about the likelihood of being able to deliver different fraction times and numbers in NHS Wales. The experts reported that with infrastructure improvements, such as the use of Flattening Filter Free technology (which delivers a higher dose rate of radiation and enables the 'beam on' time to be reduced, minimising intra-fraction motion) and the adoption of fiducial markers, EHFRT is likely to be deliverable in 15 minutes. The experts advised, however, that there would need to be additional training and service modifications to achieve this. Furthermore, the experts advised that EHFRT could be delivered as 5 fractions and it was noted that this was the treatment regimen used in the PACE-B and PACE-C RCTs, in which many UK centres have participated.
- The Appraisal Panel concluded that the evidence shows that the use of EHFRT to treat localised prostate cancer is clinically effective in the short and medium term and likely to be cost effective when delivered as outlined above.
- The Appraisal Panel considered the areas where further research into the use of EHFRT for prostate cancer is needed. The clinical experts advised that more data are needed to understand the potential use of EHFRT in higher risk disease and in younger people with prostate cancer while longer term clinical outcomes from the studies already undertaken would be desirable. It was noted that the PACE-B trial (which has reported interim results) and PACE-C trial (which is ongoing), will provide more evidence to address these gaps within the next three to five years.

Responsibilities for consideration of this Guidance

Health Technology Wales (HTW) was established by Ministerial recommendation[1,2] to support a strategic, national approach to the identification, appraisal and adoption of non-medicine health technologies into health and care settings. The HTW Appraisal Panel comprises senior representation from all Welsh boards with delegated authority to produce guidance 'from NHS Wales, for NHS Wales'. The status of HTW guidance is 'adopt or justify'. There is an expectation from Welsh Government that HTW guidance is implemented with adoption regularly audited by HTW.[3]

The guidance in this document is intended to assist Welsh care system decision makers to make evidence-informed decisions when determining the place of health technologies and thereby improve the quality-of-care services.

The content of this HTW guidance was based upon the evidence and factors available at the time of publication. An international evidence base was reviewed and external topic experts and HTW committee members consulted to contextualise available evidence to Wales. Readers are asked to consider the generalisability of the evidence reviewed to NHS Wales and that new trials and technologies may have emerged since first publication and the evidence presented may no longer be current. It is acknowledged that evidence constitutes only one of the sources needed for decision making and planning.

This guidance does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgment in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

No part of this guidance may be used without the whole of the guidance being quoted in full. This guidance represents the view of HTW at the date noted. HTW guidance is not routinely updated. It may, however, be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the guidance given.

Standard operating procedures outlining HTW's evidence review methods and framework for producing its guidance are available from the HTW website.

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Declarations of interest were sought from all reviewers. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control and the views expressed are those of Health Technology Wales.

Chair, Health Technology Wales Appraisal Panel

1. National Assembly for Wales, Health and Social Care Committee. Access to medical technologies in Wales. December 2014.
2. Response to Recommendations from the Health & Social Care Committee: Inquiry into Access to Medical Technologies in Wales. February 2015.
3. Gething, V. Letter to all Health Board Chairs re Funding for Sacral Nerve Stimulation in Wales. VG_01655_17. September 2017.