Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	Extreme hypofractionated radiotherapy (EHFRT) for localised prostate cancer
Topic exploration report number:	TER244

Introduction and aims

Health Technology Wales researchers reviewed evidence provided by the topic proposer and searched for additional evidence on extreme hypofractionated radiotherapy (EHFRT) for localised prostate cancer. This can also be referred to as ultra-hypofractionated or stereotactic body radiotherapy. EHFRT is an adaptation to conventional external beam radiotherapy (EBRT) and delivers the same total dosage of radiotherapy in fewer sessions or fractions. The topic proposer suggests that in NHS Wales this could lead to a reduction from 20 to 5 or 7 fractions.

Reducing the number of sessions that the radiotherapy dose is delivered in could lead to cost-savings for the health system and be more convenient for patients and their families. However, this approach may lead to a higher genitourinary and gastrointestinal toxicity, particularly in the period following treatment.

Summary of evidence

Guideline

NICE guideline 'Prostate cancer: diagnosis and management' (NG131) recommends use of moderate hypofractionated radiotherapy of 20 fractions for patients unless contraindications are present. The guideline does not make reference to EHRFT.

Primary Studies

The HYPO-RT-PC trial examined the effectiveness of EHRFT compared to EBRT (Widmark et al. 2019): 1200 patients were randomised to one of the treatments (EHRFT, 7 fractions over 2.5 weeks; EBRT, 39 fractions, over 8 weeks). The study was initially intended to demonstrate superiority of EHRFT but after interim analysis and availability of new evidence, analyses were re-planned to show non-inferiority. At 5 years, estimated failure-free survival in both groups was 84% (HR, 1.002; 95%CI, 0.758-1.325). The study noted that in the short-term, there was a trend towards worse urinary toxicity in the EHRFT group (158, 28% vs 132, 23%; p=0.057) but

that the difference reduced after 1-year follow-up. Another publication reports on the quality of life outcomes from the HYPO-RT-PC trial with a median follow-up of 48 months (Fransson et al. 2021). For seven of ten bowel symptoms, clinically significant deteriorations were significantly higher for EHRFT, but differences were not found for 14 urinary symptoms or sexual functioning.

An earlier trial examined acute toxicity at 12-weeks after EHRFT (Brand et al. 2019). Patients (874 in total) were initially randomised to EBRT with 39 fractions or EHRFT with 5 fractions but a protocol amendment was made to allow the EBRT group to receive moderate hypofractionated therapy with 20 fractions. The study found no differences between grade 2 or more severe toxic events on both gastrointestinal (conventional/moderate, 12% vs extreme, 10%; -1.9pp, 95%CI, -6.2 to 2.4, p=0.38) and genitourinary measures (conventional/moderate, 27% vs extreme, 23%; -4.2pp, 95%CI, -10.0 to 1.7, p=0.16).

A discrete choice experiment examining patient preferences for treatment factors in EHRFT was identified as a conference proceeding (Sigurdson et al. 2020). Details on the setting and methods are limited but the authors report that patients' trade-offs within the experiment indicate that risk of recurrence was seen as most important, followed by risk of long-term toxicity and then risk of short-term toxicity. Only patients over 70 and those who lived more than an hour from the treatment centre appeared to place weight on shorter durations of treatment and the coefficient for this factor was low relative to other factors.

Secondary and Economic Evidence

A systematic review published as a conference proceeding was identified (Jackson et al. 2019). The authors completed their search prior to the availability of the above studies and included 38 prospective series with 6116 patients. A subset of these studies were from comparative trials but only event rates for patients receiving EHRFT were reported. The number of fractions used across studies was not reported. The review reports that pooled recurrence free survival was 95.3% and 93.7% at 5 and 7 years. Estimated late grade 3 or higher toxicity rates were 2.0% for genitourinary and 1.1% for gastrointestinal.

No economic evaluations of EHRRT were identified. However, an economic evaluation of moderately hypofractionated compared to conventional radiotherapy suggest that a reduction in fractions are associated with substantial cost savings to the health system (Ranh Voong et al. 2017).

Areas of uncertainty

There appears to be some variation in findings for short-term toxicity of EHRFT. It is unclear whether this is due to differing approaches to mitigation of adverse effects within the trials or whether the number of fractions used as the comparator has an impact. A more in-depth evidence review could address this point.

EHRFT could reduce the number of times a patient is required to visit a radiotherapy centre as well as the duration of care. However, EHRFT may lead to worse toxicity in the short-term and it is uncertain how patients would balance their preferences for these treatment factors. A single study on patient preferences for these factors was available and input from the PPI standing group and patient groups would be valuable to help address this uncertainty.

Conclusions

Evidence suggests that EHRFT may have equivalent benefits to other forms of radiotherapy for patients and has the potential to make treatment more convenient for patients and reduce resource use in the health system. However, there is mixed evidence on whether EHRFT leads to greater toxicity in the short-term and whether mitigation strategies could reduce any side effects. A full review would be needed to assess these issues in more detail.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland	We did not identify any relevant information or guidance from this source.
Health Technology Assessment Group	We did not identify any relevant information or guidance from this source.
Health Information and Quality Authority	We did not identify any relevant information or guidance from this source.
EUnetHTA	We did not identify any relevant information or guidance from this source.
International HTA Database	We did not identify any relevant information or guidance from this source.
UK guidelines and guidance	
SIGN	We did not identify any relevant information or guidance from this source.
NICE	NICE guideline [NG131] Prostate cancer: diagnosis and management. Published date: 09 May 2019. https://www.nice.org.uk/guidance/ng131
Secondary literature and economic evaluations	
Medline	Ranh Voong et al. (2017). Long-term economic value of hypofractionated prostate radiation: Secondary analysis of a randomized trial. *Advances in Radiation Oncology, 2,* 249-258. https://doi.org/10.1016/j.adro.2017.07.010 Sigurdson et al. (2020). Localized Prostate Cancer Patients' Preferences for Hypofractionated Radiotherapy: A Discrete Choice Experiment. *International Journal of Radiation Oncology Biology Physics, 108,* s145. https://doi.org/10.1016/j.ijrobp.2020.07.889
Other	
Provided by the topic proposer	Fransson et al. (2021). Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer (HYPO-RT-PC): patient-reported quality-of-life outcomes of a randomised, controlled, non-inferiority, phase 3 trial. *The Lancet Oncology, 22,* 235-245. https://doi.org/10.1016/S1470-2045(20)30581-7 Jackson et al. (2019). Stereotactic Body Radiotherapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies. *International Journal of Radiation Biology Physics, 105*, E280-E281. https://doi.org/10.1016/j.ijrobp.2019.06.1912 Widmark et al. (2020). Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *The Lancet, 394,* 385-395. https://doi.org/10.1016/S1470-2045(20)30581-7

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Concepts used:	extreme/ultra hypofractionated, stereotactic body, radiotherapy, prostate cancer