Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

This report summarises the results of a brief exploration to establish the quantity and quality of existing high-level evidence on the procedure of interest.

Topic:	Daily online Image-Guided Radiotherapy (IGRT) for people undergoing radical prostate cancer treatment
Topic proposer	Jake Tanguay
Report identifier	RT10
Topic exploration report number:	TER038
Prepared by	Cedar (Cardiff & Vale University Health Board)
Report date	8 March 2019

Purpose

On behalf of Health Technology Wales, Cedar researchers conducted a rapid review of evidence on the implementation and use of daily online IGRT for people undergoing radical prostate cancer treatment. This exploratory summary will inform the prioritisation of radiotherapy procedures to be introduced at Velindre Cancer Centre (VCC), alongside expert opinion and other considerations. It could also be used to clarify the scope of an evidence appraisal. Some of the background information and resource impact considerations was submitted by clinical teams at VCC.

Background

The main objective of radiotherapy treatment is to destroy tumours without harming the healthy tissues which surround them. Imaging in radiotherapy is used to establish accurate diagnoses and staging by evaluating the growth rate and malignant potential of a tumour. Imaging is also used to accurately identify the specific location of the margins of a tumour to inform treatment planning. Radiotherapy procedures are therefore improved when there is an increased certainty in the anatomical location of the tumour margins, and in the precision of treatment delivery. The primary outcome measure is a reduction in the Planning Treatment Volume (PTV). This refers to the volume of the anatomical area of the tumour being targeted for treatment, and includes both the Clinical Target Volume (CTV) and an additional safety margin. The size of this safety margin (indicated by the CTV to PTV ratio), depends on positional uncertainties.

IGRT can be scheduled weekly or daily with fiducial markers (FM) and/or cone-beam computed tomography (CBCT). The goal of treatment is to accurately target the cancer cells and to minimise the risk of harm to surrounding healthy tissues [1]. However, the use of FM is associated with downsides such as the risk of sepsis, increase in staff time and costs [2].

Proposed PICO	
Population	Patients with prostate cancer who require radical radiotherapy (not palliative)
Intervention	*Daily online* image-guided radiotherapy (IGRT)
Comparator	Weekly IGRT
Outcome measures	Reduction in Planning Target Volume (PTV) Proportion of patients who require revision of their treatment plan Costs of: • Initial implementation (including capital costs and training where relevant) • Ongoing service provision (e.g. staff time for treatment planning and delivery; consumables; maintenance of equipment) Patients' QoL Incidence of sepsis Adverse events (e.g. urinary toxicity, diarrhoea, fatigue)

Summary of findings

It is not clear from the background and the costs table provided by the topic referrer what is the current and proposed change in practice. Thus, evidence for weekly and daily IGRT, as well as CBCT and FM, was provided.

Clinical evidence

Two randomised controlled studies (RCTs; De Crevoisier et al. (2018) and Tondel, H. (2018)) and 11 more observational/comparative studies were identified. De Crevoisier et al. (2018) looked at daily vs. weekly IGRT with both CBCT and FM whereas Tondel et al. (2018) evaluated weekly offline orthogonal portal imaging with FM and daily IGRT with CBCT and FM.

The evidence from RCTs suggests that daily IGRT with CBCT and FM showed no advantage with respect to patient-reported side effects at the end of radiotherapy as compared to weekly offline portal imaging with FM (Tondel et al. 2018). However, De Crevoisier et al. (2018) reported that compared with weekly control, daily IGRT in prostate cancer significantly improves biochemical progression-free and clinical progression-free interval, and rectal toxicity.

Mixed comparators in RCTs and other publications do not allow comparison of results between studies. Also, full papers were not available for all evidence identified. Based on topic exploration, the high-quality evidence for clinical effectiveness is limited.

Economic evidence

The topic exploration identified 2 economic evaluations (Perrier et al. (2013); Pommier et al. (2012)).

Perrier et al. (2013) evaluated the data derived from the randomised controlled study (de Crevoisier et al. 2016) comparing the daily or weekly IGRT with CBCT or FM. The analysis includes detailed information about required staff time, room occupation time and mean cost per treatment fraction, according to IGRT modality and control frequency. Also, cost-sensitivities of CBCT- and FM-based IGRT with daily or weekly control were assessed. The costs of weekly imaging frequency were lower than daily frequency for both CBCT and FM.

Pommier et al. (2012) randomly assessed the additional costs of daily versus weekly IGRT using CBCT or FM. We were unable to access the full text of this publication. Based on the abstract, the average additional cost per patient was higher in case of daily than weekly IGRT for both CBCT and FM.

The economic evidence for this topic is very limited. Good levels of detail were provided for the topic for which full paper was available.

Economic impact

Based on information provided by the topic referrer, there is no need to purchase any additional equipment or organise the training for staff. The majority of staff are capable of planning the treatment for patients with prostate cancer. The intervention will not save time in the other parts of a patient's pathway.

The proposed intervention would only benefit prostate patients with a radical intern and excluding those undergoing high-dose palliative radiotherapy. Thus, for the cohort of 300 patients per year, it is estimated that an additional 5 mins per each fraction (n=20) will be required. The additional time required (500 hours for all patients for all fractions) is estimated to incur the cost of £23,410 (there is no information where the cost per hour came from or why it was doubled). Also, 10% of patients would require an adaptive investigation requiring 4 hours per patient. The cost of adding 120 hours per annum (300 patients*0.1*4hours) for re-planning by physicists would incur the cost of £2,809.20 (there is no information where the cost per hour came from).

In summary, the total intervention cost, compared to the standard care in VCC now, would incur the cost of **£26,219.20** (£23,410 + £2,809.20) per annum.

Prioritisation criteria

Clinical impact (Potential for the technology to have an impact on patient-related health outcomes):
The high-quality evidence for this topic is limited - only two relevant RCTs were found. The intervention has the potential to improve clinical outcomes, however, more comparable data is required.

Budget impact (Impact of the technology on health care spending):
Based on the costs and savings provided by the topic referrer, the change in treatment will incur cost of £26,219.20 per annum for all patients.

Population impact (The size of the population that would be affected by the technology):
The topic proposer estimated that 300 patients will benefit from the change which accounts for approximately 11.8% ((300/2552)*100%) of all prostate patients in Wales (based on the data provided by Welsh Cancer Intelligence and Surveillance Unit, the incidence of prostate cancer in 2015 was 2552 patients).

Equity (The technology has the potential to introduce, increase, or decrease equity in health status):
No equity issues identified.

Questions for researcher

Based on the sources you have identified, is your impression that the evidence is likely to:

- favour implementation of the procedure?
- favour standard care?
- be inconclusive?

The evidence identified is inconclusive. There is no guidance or systematic review which would summarise the information for this topic and only two relevant RCTs are available. It is likely that the limited evidence identified will give inconclusive results.

Questions for topic proposer

- What source of information was used to provide the cost of physician time (£23.41 per hour)? Why some costs are doubled? Are there any additional costs included?
- How was the number of eligible patients calculated? Does the number of patients is likely to increase in coming years?
- Your proposal mentioned the Calypso system and potential savings. Can you explain how the Calypso system would decrease the time needed for treatment?
- What is the cost of implantation of fiducial markers and was it taken into account when completing the form?
- The change in practice requires additional 620 hours per annum of clinicians' time. Will it affect (e.g. delay) the treatment of other VCC patients?

Sources of evidence

- De Crevoisier, R. et al. 2018. Daily versus weekly prostate cancer image guided radiation therapy: Phase 3 multicenter randomized trial. International Journal of Radiation Oncology • Biology • Physics 102(5), pp. 1420 - 1429. (restricted access, NCT00433706)
- Perrier, L. et al. 2013. Cost of prostate image-guided radiation therapy: Results of a randomized trial. Radiotherapy and Oncology 106, pp. 50 – 58. (NCT00433706)
- Pommier, P. et al. 2012. Prospective economic evaluation of image-guided radiation therapy for prostate cancer in the framework of the national programme for innovative and costly therapies assessment. Cancer/Radiothérapie 16(5 – 6), pp. 444 – 451. (restricted access)
- Tondel, H. et al. 2018. Radiotherapy for prostate cancer – Does daily image guidance with tighter margins improve patient reported outcomes compared to weekly orthogonal verified irradiation? Results from a randomized controlled trial. Radiotherapy and Oncology 126, pp. 229 – 235. (NCT01550237)

References

[1] The Royal College of Radiologists. 2016. Radiotherapy dose fractionation Second edition. Available at: https://www.rcr.ac.uk/system/files/publication/field_publication_files/bfco163_dose_fractionation_2nd_ed_march2017.pdf [Accessed: 28/11/2018]

[2] O'Neill A.G.M *et al*. 2016. Fiducial marker guided prostate radiotherapy: a review. *The British Journal of Radiology* 89(1068).

Appendix – Brief literature search results

Resource	Results
UK guidelines and guidance	
e.g. NICE; Healthcare Improvement Scotland; Guidelines International Network; SIGN	NICE CG175 Prostate cancer: diagnosis and management (January 2014) HIS – no evidence identified GIN – no evidence identified SIGN – no evidence identified
Secondary literature and economic evaluations	
e.g.Cochrane library; Medline *systematic reviews, meta-analyses, economic evaluations*	**Economic evaluation:** • Perrier, L. *et al*. 2013. Cost of prostate image-guided radiation therapy: Results of a randomized trial. *Radiotherapy and Oncology* 106, pp. 50 – 58. (NCT00433706) • Pommier, P. *et al*. 2012. Prospective economic evaluation of image-guided radiation therapy for prostate cancer in the framework of the national programme for innovative and costly therapies assessment. *Cancer/Radiothérapie* 16(5 – 6), pp. 444 – 451. (access restricted)
Primary studies	
Medline *RCTs; observational studies*	**RCTs:** • De Crevoisier, R. *et al*. 2018. Daily versus weekly prostate cancer image guided radiation therapy: Phase 3 multicenter randomized trial. *International Journal of Radiation Oncology • Biology • Physics* 102(5), pp. 1420 - 1429. (restricted access, NCT00433706) • Tondel, H. *et al*. 2018. Radiotherapy for prostate cancer – Does daily image guidance with tighter margins improve patient reported outcomes compared to weekly orthogonal verified irradiation? Results from a randomized controlled trial. *Radiotherapy and Oncology* 126, pp. 229 – 235. (NCT01550237) **Other studies:** • Ariyaratne, H. *et al*. 2016. Image-guided radiotherapy for prostate cancer with cone beam CT: dosimetric effects of imaging frequency and PTV margin. *Radiotherapy and Oncology* 121, pp. 103 – 108. • Barney, B.M. *et al*. 2011. Image-Guided Radiotherapy (IGRT) for Prostate Cancer Comparing kV Imaging of Fiducial Markers With Cone Beam Computed Tomography (CBCT). *International Journal of Radiation Oncology • Biology • Physics* 80(1), pp. 301 – 305. (access restricted) • Bell, K. *et al*. 2017. Influence of daily imaging on plan quality and normal tissue toxicity for prostate cancer radiotherapy. *Radiation oncology* 12(1) pp. 1 - 11. • Berlin, A. *et al*. 2015. Phase 2 trial of guideline-based postoperative image guided intensity modulated radiation therapy for prostate cancer: Toxicity, biochemical, and patient-reported health-related quality-of-life outcomes. *Practical radiation oncology* 5(5), pp. e473 – e482. • Katsumi, H. *et al*. 2018. The potential failure risk of the cone-beam computed tomography-based planning target volume margin definition for prostate image-guided radiotherapy based on a prospective single-institutional hybrid analysis. *Radiation oncology* 13(1), pp. 1 – 14.

	• Maund, I.F. *et al*. 2014. Image-guided radiotherapy of the prostate using daily CBCT: the feasibility and likely benefit of implementing a margin reduction. *The British Journal of Radiology* 87:20140459. • Qin, A. *et al*. 2015. Evaluation of online/offline image guidance/adaptation approaches for prostate cancer radiation therapy. *International Journal of Radiation Oncology • Biology • Physics* 91(5), pp. 1026 – 1033. • Rudat, V. *et al*. 2016. Image-guided intensity-modulated radiotherapy of prostate cancer: Analysis of interfractional errors and acute toxicity. *Strahlentherapie und Onkologie* 192(2), pp. 109 – 117. • Shi, W. *et al*. 2011. Evaluation of kV Cone-Beam CT Performance for Prostate IGRT A Comparison of Automatic Grey-Value Alignment to Implanted Fiducial-Marker Alignment. *American Journal of Clinical Oncology – Cancer Clinical Trials* 34(1), pp. 16 – 21. • Vanasek, J. *et al*. 2014. Searching for an appropriate image-guided radiotherapy method in prostate cancer--implications for safety margin. *Tumori* 100(5), pp. 518 – 523. • Yukihiro, H. Long-term Follow-up Results of CT-guided Daily Adaptive Radiation Therapy for Localized Prostate Cancer. *Anticancer research* 38(10), pp. 5959 – 5962.
Cochrane *trials database*	None
Ongoing secondary research	
Clinicaltrials.gov	1. NCT02034955 Prostatectomy Adaptive Radiation Therapy (ART) – Active, not recruiting 2. NCT02353819 Stereotactic Ablative Radiotherapy (SABR) of Pelvis and Prostate Targets For High Risk Prostate Cancer – Recruiting 3. NCT01550237 Curative Image Guided Radiotherapy for Prostate Cancer (RIC) – Active, not recruiting (randomised controlled trial)
Other sources	
Topic referrer	• Li, W. et al. 2016. How long does it take? An analysis of volumetric image assessment time. Radiotherapy and Oncology, 119(1), 150-153.
Citation tracking in Google Scholar	• Arabloo, J. et al. 2016. Health technology assessment of image-guided radiotherapy (IGRT): A systematic review of current evidence. Medical Journal of the Islamic Republic of Iran 30(318), pp. 1 – 8.

Date of search:	5th December 2018
Concepts searched:	**Cochrane Library**: MeSH: 'radiotherapy', 'cone-beam computed tomography', 'prostatic neoplasm', 'fiducial markers', 'radiotherapy, image-guided' **Medline:** 1 Prostatic Neoplasms/ (114788) 3 Radiotherapy, Image-Guided/ (2454) 4 Daily.ti,ab (466966) 1 and 2 and 3 (133)