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 bladder cancer treatment
Topic proposer	Jake Tanguay
Report identifier	RT09
Topic exploration report number:	TER037
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 image-guided radiotherapy (IGRT) for people undergoing radical bladder 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.

The use of daily online imaging ensures that the treatment can be more accurately targeted and may allow higher doses of the radiation to be delivered to the target site while keeping radiation of the surrounding tissues as low as possible. This can allow the most effective does to be delivered to the target site while minimising the risk of side effects of the treatment.

Proposed PICO	
Population	Patients with bladder cancer who require radical radiotherapy
Intervention	Daily online image-guided radiotherapy (IGRT)
Comparator	Weekly IGRT, primarily offline
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) Normal tissue sparing Adverse events Patient QoL

Summary of findings

The evidence identified was limited, with no RCTs identified.

The 2016 Vestergaard et al study concluded that online imaging has a great potential for ensuring target coverage, while maintaining normal tissue sparing in treatment sites. Similar findings were identified in the Vestergaard 2014 and 2013 studies.

Similarly Faroudi et al (2011) found that the use of online adaptive radiotherapy was feasible and reduced the area of normal tissue irradiated without reducing CVT coverage. Tuomikoski et al (2011) concluded that adaptive radiotherapy considerably reduced the radiotherapy dose to the small bowel, while maintaining the dose coverage of CTV at similar level when compared to the conventional treatment.

Faroudi et al (2014) noted that a CTV to PVT margin of 7mm was inadequate in some cases due to fluid load or medication use which resulted in rapid bladder filling.

Economic impact

No economic studies were identified.

Based on the information provided by the topic referrer, VCC already has skills and equipment required to implement these changes. There is no requirement for the purchase of any additional equipment or additional staff training. The technique will not save time in other stages of a patient's treatment pathway.

For the cohort of patients suggested by the proposer, there would be an additional 66.6 hours per annum for treatment delivery equating to an additional 15 minutes per day (based on 40 patients). The costs of this are estimated by the proposer as: additional time per fraction X no

of patients X no of fractions per patient (5 X 40 X 20 = 4000). This result of 4000 minutes is equal to 66.6666 hours per annum. The proposer has estimated the cost of this as 66.6 X £23.41 X 2 giving an overall cost of £3,121.33. It is unclear what the source of this cost is or why it is doubled. The 66.6 used has been rounded down by the proposer from 66.6666 which will have a minor impact on the cost calculation. NB: in the proposal, current treatment options include one fraction of IGRT online and 4 fractions of IGRT offline per patient: it is unclear if these would still be required if the proposed option is implemented. The current calculation assumes that the 20 online fractions are additional to current care.

Additionally, it is estimated that the proposed change in treatment would lead to an increase in the proportion of patients requiring replans. This is estimated at an additional 10 patients at 7.5 hours per replan equating to an additional 75 hours. The proposer has calculated the cost of this as £1,755.80 although it is unclear where this cost originated.

A cost for physics input of £936.41 has been included for validation if the PTV margins change, the source of this is unclear.

Overall the suggested additional total per annum cost for the proposed treatment option is:

£3,121.33 + £ £1,755.80 + £936.41 = £5,831.54

Prioritisation criteria

Clinical impact (Potential for the technology to have an impact on patient-related health outcomes):
Weak evidence available, more evidence and comparative data required. Increased accuracy is likely to result in better outcomes and reduced adverse events however there is a lack of evidence regarding if/how much this technique will change outcomes. No data on long term outcomes is available.

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 a cost of £5,831.54 per annum for based on 40 patients per year.

Population impact (The size of the population that would be affected by the technology):
Topic proposer estimates approx. 40 patients per year. This equates to 0.001% of the population of Wales (3.099 Million people) or 7.89% of the opulation diagnosed with bladder cancer each year (Welsh Cancer Intelligence and Surveillance Unit 2015 data)

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 limited evidence on the superiority of this technique. The study data that is available is limited to small studies. There is a lack of comparative data. No RCTs are available and there is a lack of economic evidence.

Questions for topic proposer

- Please provide the sources of the costs of the staff and other assumptions made in the cost table.
- The additional cost of IGRT is calculated at 66.6 X £23.41 X 2. Please clarify where the X 2 originates.
- Please clarify if the one fraction of IGRT online and 4 fractions of IGRT offline per patient used in current standard care would still be required.
- How accurate is the patient estimate and what is this based on? What are predicted future patient numbers?
- Would the additional IGRT have an impact on capacity and a detrimental effect on other patients?

Sources of evidence

- Collins SD & Leech MM (2018) A review of plan library approaches in adaptive radiotherapy of bladder cancer, Acta Oncologica, 57:5, 566-573
- Vestergaard A, Hafeez S, Muren LP, et al. The potential of MRIguided online adaptive re-optimisation in radiotherapy of urinary bladder cancer. Radiother Oncol. 2016;118:154–159.
- Vestergaard A, Muren LP, Lindberg H, et al. Normal tissue sparing in a phase II trial on daily adaptive plan selection in radiotherapy for urinary bladder cancer. Acta Oncol. 2014 53(8) 997-1004.
- Foroudi F, Pham D, Rolfo A, et al. The outcome of a multi-centre feasibility study of online adaptive radiotherapy for muscle-invasive bladder cancer TROG 10.01 BOLART. Radiother Oncol. 2014;111:316–320.
- Vestergaard A, Muren LP, Sondergaard J, et al. Adaptive plan selection vs. re-optimisation in radiotherapy for bladder cancer: A dose accumulation comparison. Radiother Oncol 2013; 79: 705–12.
- Foroudi F, Wong J, Kron T, et al. Online adaptive radiotherapy for muscle-invasive bladder cancer: results of a pilot study. Int J Radiat Oncol Biol Phys. 2011;81(3):765-71.
- Tuomikoski L, Collan J, Keyrilainen J, et al. Adaptive radiotherapy in muscle invasive urinary bladder cancer—an effective method to reduce the irradiated bowel volume. Radiother Oncol. 2011;99: 61–66.

Appendix – Brief literature search results

Resource	Results
UK guidelines and guidance	
e.g. NICE; Healthcare Improvement Scotland; Guidelines International Network; SIGN	NICE: NICE guideline (NG2) Bladder Cancer Diagnosis and Management. February 2015 HIS: No relevant evidence identified GIN: • EAU Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS). European Association of Urology 2017 • EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. European Association of Urology 2016. • Guideline on Muscle-Invasive and Metastatic Bladder Cancer (European Association of Urology Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement. American Society of Clinical Oncology Clinical Practice 2017 SIGN: No relevant evidence found National Cancer Action Team (Part of the National Cancer Programme). National Radiotherapy Implementation Group Report. Image Guided Radiotherpay (IGRT). Guidance for implementation and use. August 2012
Secondary literature and economic evaluations	
e.g.Cochrane library; Medline *systematic reviews, meta-analyses, economic evaluations*	Collins SD & Leech MM (2018) A review of plan library approaches in adaptive radiotherapy of bladder cancer, Acta Oncologica, 57:5, 566-573
Primary studies	
Medline *RCTs; observational studies*	• Vestergaard A, Muren LP, Lindberg H, et al. Normal tissue sparing in a phase II trial on daily adaptive plan selection in radiotherapy for urinary bladder cancer. Acta Oncol. 2014 53(8) 997-1004. • Foroudi F, Pham D, Bressel M, et al. Bladder cancer radiotherapy margins: A comparison of daily alignment using skin, bone or soft tissue. Clin Oncol 2012; 24: 673-81 • Foroudi F, Wong J, Kron T, et al. Online adaptive radiotherapy for muscle-invasive bladder cancer: results of a pilot study. Int J Radiat Oncol Biol Phys. 2011;81(3):765-71.
Cochrane *trials database*	No relevant trials identified
Ongoing secondary research	
Clinicaltrials.gov	1. NCT011043501: Image-Guided Radiation Therapy for Bladder-Cancer Patients Undergoing Radiotherapy and Concurrent Gemcitabine Chemotherapy. Active not recruiting. 2. NCT00609843: Pilot Study of Lipiodol Demarcation of the Tumour in Bladder Cancer. Completed 3. NCT01142102: Feasibility of Online Adaptive Radiotherapy for Muscle Invasive Bladder Cancer (BOLART). Completed. 4. NCT00913536: Cone Beam Computed Tomography (CT) Bladder. Active, not recuiting. 5. NCT02447549: Study of Tumour Focused Radiotherapy for Bladder Cancer (RAIDER). Recruiting 6. NCT00963404: Image-Guided Tumorboost of Bladder Cancer. Completed

	7. NCT01124682: 3-Dimensional Conformal Radiation Therapy in Treating Patients With Bladder Cancer Who Have Undergone Transurethral Resection of the Bladder. Status unknown
Other sources	
Citation tracking	• Vestergaard A, Hafeez S, Muren LP, et al. The potential of MRIguided online adaptive re-optimisation in radiotherapy of urinary bladder cancer. Radiother Oncol. 2016;118:154–159. • Kibrom AZ, Knight KA. Adaptive radiation therapy for bladder cancer: a review of adaptive techniques used in clinical practice. J Med Radiat Sci. 2015;62(4):277-85. • Foroudi F, Pham D, Rolfo A, et al. The outcome of a multi-centre feasibility study of online adaptive radiotherapy for muscle-invasive bladder cancer TROG 10.01 BOLART. Radiother Oncol. 2014;111:316–320. • Vestergaard A, Muren LP, Sondergaard J, et al. Adaptive plan selection vs. re-optimisation in radiotherapy for bladder cancer: A dose accumulation comparison. Radiother Oncol 2013; 79: 705–12. • Tuomikoski L, Collan J, Keyrilainen J, et al. Adaptive radiotherapy in muscle invasive urinary bladder cancer—an effective method to reduce the irradiated bowel volume. Radiother Oncol. 2011;99: 61–66. • Button MR, Staffurth JN, Clinical Application of Image-guided Radiotherapy in Bladder and Prostate Cancer, Clinical Oncology (2010), doi:10.1016/j.clon.2010.06.020 • Burridge N, Amer A, Marchant T, et al. Online adaptive radiotherapy of the bladder: small bowel irradiated-volume reduction. Int J Radiat Oncol Biol Phys. 2006;66(3):892-7

Date of search:	3rd December 2018
Concepts searched:	**Cochrane Library:** MeSH: ‘radiotherapy’, ‘urinary bladder neoplasm’, ‘radiotherapy, image-guided’ **Medline:** 1 Bladder Neoplasms/ (68604) 2 Radiotherapy, Image-Guided/ (5251) 3 Daily.ti,ab (467383) 4 1 and 2 and 3 (122)