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 lung cancer treatment
Topic proposer	Mick Button
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Prepared by	Cedar (Cardiff & Vale University Health Board)
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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 lung 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, but also to accurately identify the specific location of the margins of a tumour to inform treatment planning. Radiotherapy procedures are improved when there is an increased certainty in the anatomical location of the tumour margins, and in the precision of treatment delivery.

The key argument for the use of daily online imaging is that timely information increases the target accuracy. Variation in lung density or other anatomical changes may occur due to atelectasis, pleural effusion, pneumonia or pneumonitis (Tvilum et al. 2015). If there are delays between image capture and treatment, imaging may need to be repeated. It is recommended that contemporaneous scans are available at the time of treatment, especially for the radical treatment of borderline lesions (British Thoracic Society, 2010).

Proposed PICO	
Population	Patients with lung cancer who require radical radiotherapy
Intervention	Daily online (adaptive) image-guided radiotherapy (IGRT)
Comparator	Initial online IGRT (fractions 1-3), followed by weekly online IGRT (with offline treatment in between)
Outcome measures	*Interim/proxy measures:* • *Reduction in Planning Target Volume (PTV)* • *Proportion of patients who require revision of their treatment plan* Clinical effectiveness: • Survival/progression-free survival • Local/regional failure-free survival Safety: Toxicity (e.g. pneumonitis) Costs of: • Ongoing service provision (e.g. staff time for treatment planning and delivery; consumables; maintenance of equipment) • Long-term requirement for further treatment if poor control or toxicities (e.g. retreatments, palliative care, clinic attendances/scans)

Summary of findings

Increasing the frequency of imaging is an incremental development rather than a new innovation, but has potential for improving clinical outcomes as well as implications for resource use. The most important question is whether the investment of extra resources is outweighed by an increase in clinical accuracy and treatment effectiveness, without additional harm. The topic proposer argues that daily online imaging will impact on the ability of the multidisciplinary team to rapidly react to any changes which are detected, enabling timely replanning (subject to clinician availability).

An American clinical practice guideline (Bezjak 2015) concluded that “prospective comparative trials are lacking in the comparison of different types of EBRT, such as three-dimensional conformal, intensity-modulated, and image-guided radiotherapy”. The American College of Radiology (2014) advised that “the frequency of IGRT usage should be carefully balanced between the needs of the disease/technique, imaging dose, and resource requirements”. A survey of US clinicians revealed that the most common approach was to use online verification for the first few fractions, followed by off-line verification for all subsequent fractions (Nabavizadeh et al. 2015).

Two observational studies using non-randomised comparator groups reported improved local and locoregional control when using daily online (adaptive) IGRT compared with non-adaptive approaches (Kilburn et al. 2015; Tvilum et al. 2015). Both studies were limited by differences between the groups, and relatively small sample sizes. However they both showed some promise in improving failure-free survival rates, with no significant differences in toxicity.

Kilburn et al. (2015) used a historic comparator group receiving weekly conventional megavoltage (MV) portal imaging (January 2001 to 2009, n=107). Between February 2009 and

September 2012 a further 62 patients were treated with daily IGRT. The authors acknowledged that it was not clear how much the IGRT with CBCT contributed to the improved outcomes, and noted that the results may not be generalisable to other forms of IGRT. Tvilum et al. (2015) reported that re-planning was required for 12/52 (23%) of the adaptive group, and although there was no systematic re-planning in the non-adaptive group, 5/52 (10%) patients were re-planned due to "large changes found accidentally" by radiation therapists.

Dial and Weiss (2016) simulated four treatment scenarios based on data from patients with stage II and III lung cancer: "no adapt"; "midadapt" (implementing a single replan); "weekly adapt"; and "full-adapt" (based on daily replanning). Increasing frequencies of replanning resulted in incremental reductions in radiation doses in adjacent healthy tissues, thereby allowing a corresponding increase in dose to the target areas. However, the magnitude of these benefits reduced with each increment (see Fig. 3 below). About 85% of the benefit was achieved by weekly adaptation. The remaining 15% of benefit was associated with a six-fold increase in workload, suggesting that the effort associated with daily replanning outweighs the potential benefit. However, the authors note that automated methods may provide justification of daily replanning in future. Another important observation made by these authors is that adaptive planning requires imaging, which itself is associated with exposure to radiation.

1793 Dial *et al.*: Lung ART replanning frequency

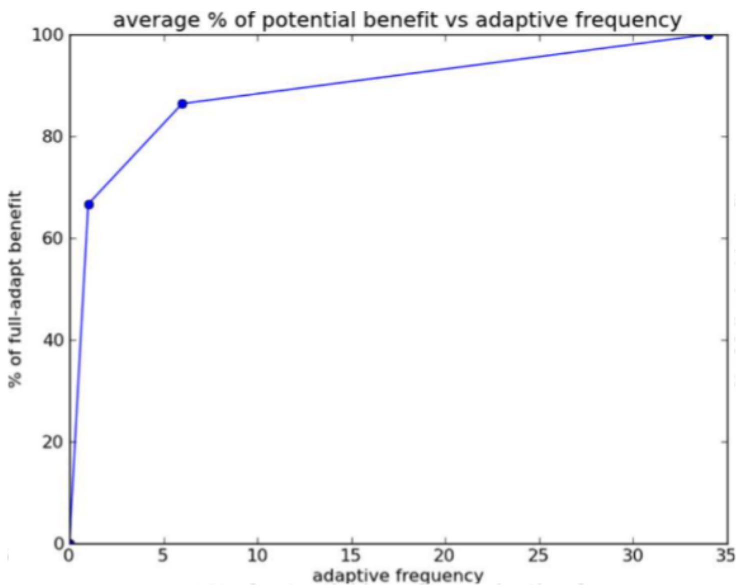

FIG. 3. Percent of potential benefit (i.e., allowable dose to target) as a function of replanning frequency. On average, 65% of benefit was achieved with a single midtreatment adaptation, and 85% was realized after weekly adaptation.

Economic impact

It is understood that the staff at VCC already have the necessary equipment and skills to implement these changes. The main uncertainty is the number of patients who would need replanning during a course of radiotherapy. Current working arrangements are unlikely to allow sufficient time for urgent replanning within 24 hours. The topic proposer has suggested that there would be a need for clinician availability 5 days per week, with capacity to carry out urgent replanning of treatment within 24 hours when required.

For the whole cohort of 156 patients per year, there would be an additional 5 minutes per fraction (n=20) during delivery of IGRT, at a total estimated cost of (£12,173.20). For each patient requiring a new treatment plan, additional costs (totalling £239.15) are introduced by:

- 30 minutes for an additional scan
- 7.5 hours of physicist time
- 60 minutes of consultant availability

If 1 in 10 patients (10%) needs their treatment to be re-planned, this additional cost equates to £3,826.40; when added to the treatment delivery time, the total cost is £17,016.80 per annum. These costs appear to have been underestimated.

Prioritisation criteria

Clinical impact (Potential for the technology to have an impact on patient-related health outcomes):
There is low quality evidence suggesting potential improvement.

Budget impact (Impact of the technology on health care spending):
Estimated costs appear to be conservative, at around £15,000 - £20,000 pa.

Population impact (The size of the population that would be affected by the technology):
Topic proposer estimates 156 patients per year (in the South Wales catchment area of 1.5 million).

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? Yes
- be inconclusive?

This is a relatively minor change to current practice. There is some evidence suggesting that increased frequency of imaging leads to clinical benefits. Modelling indicates that resource burdens could outweigh the benefit of daily replanning. The evidence of clinical effectiveness was from small observational studies, but supplemented by a full systematic literature search may be sufficient to conduct a more comprehensive appraisal.

Questions for topic proposer

- With reference to the study by Tvilum et al. (2015), how much can the differences in the outcomes between the two groups be attributed to the adaptive approach? Could these differences be accounted for by baseline characteristics or changes to treatment other than the frequency of online imaging?
- Would you expect the findings of Dial and Weiss (2016) to apply at VCC? How is their model similar or different to the options available at VCC (ie weekly vs daily IGRT)?
- Were the staff time cost estimates based on salary alone? What about overheads? (The delivery time alone adds 5 hours per week to the use of facilities). What are the costs of maintaining equipment? Would more regular use decrease the lifespan of the imaging device?
- How accurate is the estimate of 156 eligible patients per annum? Is that likely to increase or decrease in future?

Sources of evidence

- Bezjak et al. (2015) Definitive and Adjuvant Radiotherapy in Locally Advanced Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline J Clin Oncol 33(18)::2100-2105. http://ascopubs.org/doi/pdf/10.1200/JCO.2014.59.2360
- The American College of Radiology (2014) ACR-ASTRO Practice Parameter tool. https://www.acr.org/-/media/ACR/Files/Practice-Parameters/IGRT-RO.pdf
- Dial C, and Weiss E. Benefits of adaptive radiation therapy in lung cancer as a function of replanning frequency. Medical Physics, Vol. 43, No. 4, April 2016; 1787-1794.
- Kilburn JM, Soike MH, Lucas JT, et al. Image guided radiotherapy may result in improved local control in locally advanced lung cancer patients. Practical radiation oncology. 2016;6(3):e73-e80. http://dx.doi.org/10.1016/j.prro.2015.10.004.
- MARIE TVILUM 1 , AZZA A. KHALIL 1 , DITTE S. M Ø LLER 2 , LONE HOFFMANN 2 & MARIANNE M. KNAP Clinical outcome of image-guided adaptive radiotherapy in the treatment of lung cancer patients Acta Oncologica, 2015; Early Online: 1–8
- Nabavizadeh et al. 2015 Int J Radiation Oncol Biol Phys, Vol. 94, No. 4, pp. 850e857, 2016, http://dx.doi.org/10.1016/j.ijrobp.2015.09.035

Appendix – Brief literature search results

Resource	Results
UK guidelines and guidance	
e.g. NICE; Healthcare Improvement Scotland; Guidelines International Network; SIGN	NICE CG121 Lung cancer: diagnosis and management (April 2011) HIS – no relevant evidence found. GIN (restricted access): • Adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIA resectable non-small cell lung cancer (McMaster University, 2017) • Definitive and adjuvant radiotherapy in locally-advanced non-small cell lung cancer (ASTRO, US, 2015); • SIGN – CPG137 (2014) Management of Lung Cancer • British Thoracic Society guidelines (2010)
Other sources	
Topic referrer	• Kilburn JM, Soike MH, Lucas JT, et al. Image guided radiotherapy may result in improved local control in locally advanced lung cancer patients. Practical radiation oncology. 2016;6(3):e73-e80. doi:10.1016/j.prro.2015.10.004. • Clinical outcome of image-guided adaptive radiotherapy in the treatment of lung cancer patients MARIE TVILUM 1, AZZA A. KHALIL 1 , DITTE S. M Ø LLER 2 , LONE HOFFMANN 2 & MARIANNE M. KNAP Acta Oncologica, 2015; Early Online: 1-8
Followed up on news article (eCancer News 23/04/2018)	• Johnson-Hart C, Price G, Faivre-Finn C et al. (2018) Residual setup errors towards the heart after image guidance linked with poorer survival in lung cancer patients: do we need stricter IGRT protocols? *International Journal of Radiation Oncology Biology Physics* 102(2): 434-42.
Recommended by Science Direct	• Haslett K, de Ruysscher D, Dziadziuszko R et al. (2018) Short communication: Management of patients with extensive-stage small-cell lung cancer treated with radiotherapy: A survey of practice. *Cancer Treatment and Research Communications* 17: 18-22.

Date of search:	9th December 2018
Concepts searched:	Medline (via Ovid):

Set	Search Statement
1.	(Daily adj3 online).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2.	adaptive.mp.
3.	IGRT.mp.
4.	(image adj guided).mp.
5.	radiotherapy or (radiation adj therapy).mp.
6.	lung.mp.
7.	1 or 2 or 3 or 4
8.	5 and 6
9.	7 and 8
10.	limit 9 to (english language and humans and yr="2009 -Current")
11.	from 10 keep 2,6,11,18,21,32,41,47,51,78,87,98,107,160,170