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:	Partial Breast Irradiation (PBI) for people with early breast cancer
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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 Partial breast irradiation (PBI), 40Gy in 15 fractions for people with early breast cancer. 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

Breast radiotherapy is given to some patients following breast conserving surgery to treat early breast cancer and has been shown to reduce the risk of recurrence of cancer. Standard treatment is whole breast radiotherapy (WBRT). Radiotherapy carries the possibility of short- and long-term adverse effects on the breast, and resulting cosmetic changes (such as skin soreness, changes to colour of skin, radiation fibrosis or stiffening of the breast tissue) (NICE 2018).

Partial breast irradiation aims to give the same standard dose of radiotherapy but to only part of the breast where the tumour (removed by surgery) was located, and aims to reduce the risk of cosmetic changes.

Evidence Review H of the NICE guidance for early and locally advanced breast cancer (2018) states:

> "WBRT halves the risk of local recurrence. However, local recurrence rates have fallen dramatically over the last 30 years, so that the absolute benefit of WBRT for some women may not outweigh the potential risks (normal tissue toxicity, cardiac morbidity, second

cancers). For many women, increasingly diagnosed with small screen-detected cancers, it is the late complications of radiotherapy (RT), rather than the risk of local recurrence, that is their predominant concern. Whilst the proportional benefit of radiotherapy is similar across all subgroups of women with breast cancer, the absolute benefit for women with good prognosis tumours is small. The risk of true local recurrence is highest in the area of the breast close to the site of the original tumour raising the possibility that there are women at low risk of local recurrence for whom treatment of the whole breast volume and surrounding tissue is not necessary."

Proposed PICO	
Population	Women who have had breast-conserving surgery for invasive cancer (excluding lobular type) with clear margins and who: • have a low absolute risk of local recurrence (defined as women aged 50 and over with tumours that are 3 cm or less, N0, ER-positive, HER2-negative and grade 1 to 2) and • have been advised to have adjuvant endocrine therapy for a minimum of 5 years (NB: based on NICE recommendation 2018. The NICE PICO specified a broader population: Women (18 or over) with invasive breast cancer (M0) who have undergone breast conserving surgery)
Intervention	Partial breast irradiation (40 Gy in 15 fractions specified by proposer)
Comparator	Whole breast irradiation (40 Gy in 15 fractions specified by proposer)
Outcome measures	Local recurrence rate Treatment-related morbidity Health related Quality of Life (HRQoL) Cosmetic outcome Overall survival Disease-free survival Treatment-related mortality

Summary of findings

There is an adequate body of evidence to support a rapid review. The evidence base has been recently reviewed for NICE guidance and also for a prior Cochrane review, included in the NICE review. Longer term outcomes beyond 5 years are not yet known. NICE reports that five large clinical studies are in progress.

The published NICE guidance on early and locally advanced breast cancer (updated July 2018) makes the following recommendations regarding radiotherapy following breast conserving surgery:

"1.10.3 Offer whole-breast radiotherapy to women with invasive breast cancer who have had breast-conserving surgery with clear margins.

1.10.4 Consider partial breast radiotherapy (as an alternative to whole-breast radiotherapy) for women who have had breast-conserving surgery for invasive cancer (excluding lobular type) with clear margins and who:

- have a low absolute risk of local recurrence (defined as women aged 50 and over with tumours that are 3 cm or less, N0, ER-positive, HER2-negative and grade 1 to 2) and
- have been advised to have adjuvant endocrine therapy for a minimum of 5 years.

1.10.5 When considering partial breast radiotherapy (see recommendation 1.10.4), discuss the benefits and risks, and explain that:

- local recurrence with partial breast radiotherapy at 5 years is equivalent to that with whole-breast radiotherapy
- the risk of local recurrence beyond 5 years is not yet known
- there is a potential reduction in late adverse effects.

1.10.6 When delivering partial breast radiotherapy, use external beam radiotherapy [2018]"

The NICE recommendations quoted above were informed by Evidence Review H Evidence Reviews for Breast Radiotherapy (July 2018). The review states:

"Six randomised trials (N=6215), reported on in 12 publications (The Groupe Européen de Curiethérapie and the European SocieTy for Radiotherapy & Oncology [GEC-ESTRO; Ott 2016; Polgar 2017; Strnad 2016]; Intensity Modulated and Partial Organ Radiotherapy [IMPORT-LOW; Coles 2017] Livi 2015 [Livi 2010; Livi 2015]; Polgár 2007 [Lovey 2007; Polgar 2007; Polgar 2013]; Randomized Trial of Accelerated Partial Breast Irradiation [RAPID; Olivotto 2013]; Rodriguez 2013 [Rodriguez 2013]), and 1 systematic review (Hickey 2016) were included in the review."

The IMPORT LOW randomised study (Coles 2017) cited by the topic proposer is included in NICE Evidence Review H (NICE 2018) and provides a basis for the radiotherapy regimen of 40 Gy in 15 fractions in the proposal. However the other studies in NICE review H use radiotherapy regimens that differ to the LOW IMPACT study (for WBRT and PBRT). The NICE evidence review notes that the guidance recommendations are based on the trials with surgical techniques, radiotherapy regimens and adjuvant endocrine therapy most applicable to the UK: the recommended population for PBI is based on the IMPORT LOW study. The review also states:

"The committee acknowledged that follow-up in the trial most relevant to the UK setting had not yet reached 10 years and that differences in local recurrence may become evident with longer follow-up. For this reason they did not make a strong recommendation in favour of partial breast radiotherapy"

The Cochrane review (published 2016) included seven RCTs and studied 7586 women: (ELIOT; GEC-ESTRO; Livi 2015; Polgár 2007; RAPID; Rodriguez; TARGIT). There appears to be substantial overlap with the NICE review in terms of included studies, although when the Cochrane Review was published the results of IMPORT LOW were not yet available.

The Cochrane review concluded that local recurrence was rare, but more common with PBI than WBRT and the cosmetic outcome (scored by doctors) was worse with PBI. Survival did not differ. Scarring in the breast was worse with PBI. The same number of women developed metastatic breast cancer with either treatment. There appeared to be the same number of women who eventually required mastectomy after both treatments, either due to cancer regrowth in the breast or bad side effects. The Cochrane review noted that at the time of publication there were five big ongoing studies.

The NICE recommendations appear to be influenced by selected evidence with greatest applicability to the UK, particularly the IMPORT LOW trial.

Economic impact

The NICE evidence review included one economic study which included APBI techniques that are not standard current practice in the UK.

The 2018 NICE evidence review states:

> "One relevant study was identified in a literature review of published cost-effectiveness analyses on this topic; Shah 2013 (see appendix H and appendix I for summary and full evidence tables). The study considered the cost-effectiveness of accelerated partial breast radiotherapy (APBRT) techniques in comparison to whole beam radiotherapy (WBRT) techniques. The analysis was a cost-utility analysis measuring effectiveness in terms of quality adjusted life years (QALYs) … Evidence from one cost-utility analysis showed that all APBRT techniques were dominant in comparison to WBRT with IMRT. APBRT using IMRT or 3DCRT were found to be dominant in comparison to WBRT with CRT while other APBRT techniques were found to be more costly and more effective with ICERs of $12,514, $67,329 and $557 per Breast radiotherapy. QALY for single lumen, multi lumen and interstitial APBRT techniques, respectively. The analysis was partially applicable with serious limitations."

The NICE review reports the committee's consideration of the single economic study (Shah 2013) as follows:

> "The analysis was thought to have demonstrated the potential cost-effectiveness of accelerated partial breast radiotherapy in comparison to whole beam therapy. However, as the analysis was not directly applicable to the UK context, it was not thought to give a reliable estimate of cost-effectiveness in the UK context.
>
> In terms of the potential resource impact, the committee considered there would be a potential reduction in costs of treating late effects if partial breast radiotherapy were used but there may also be increased costs in treating local recurrence beyond five years, the balance of these is as yet unknown. The use of partial breast radiotherapy delivered as external beam radiotherapy would not have any implications on planning time, delivery time or patient counselling time, and is already used in most centres in the UK."

The proposal estimates likely impact of implementing this technique to be small, with low likelihood of change to the care pathway, and this is corroborated by the statement by NICE, above. No extra equipment is required. However the proposal states that the suitability of image guided radiotherapy practices and resources would need to be assessed (i.e. access to CT scanners). No additional imaging is required to implement PBI at VCC: no CBCT is required.

The proposal estimates that use of PBI would need an extra 20 minutes per case of consultant time, costed at £1,089.27 per year (252 cases) and also 5 minutes of extra image guidance radiotherapy time per case (if CBCT or IGRT required), costed at £14,748.30.

Set-up (training) costs are estimated in the proposal at £33,232.61.

The proposal makes not of the PRIMETIME randomised controlled trial which is open to recruitment. PRIMETIME will compare breast RT versus no RT according to biomarker risk profile. The relevance to VCC is that some patients eligible for PBI may receive no RT due to their trial participation.

Prioritisation criteria

Clinical impact (Potential for the technology to have an impact on patient-related health outcomes):
It appears that PBRT has similar outcomes to WBRT in terms of recurrence and uncertain benefit in terms of improved cosmetic outcome. Treatment choice seems to depend on staging (risk profile) and patient choice.

Budget impact (Impact of the technology on health care spending):
NICE seemed to conclude the future balance of extra costs/extra savings is unknown. The proposal documents limited local set up costs and ongoing costs.

Population impact (The size of the population that would be affected by the technology):
Breast cancer is the most common cancer in the UK, with approximately 54,000 new cases of invasive disease. Most breast cancers are diagnosed at an early stage, which could make PBRT a fairly common option (VCC proposal states one third of breast RT patients potentially eligible i.e. 252 patients/year at VCC serving SE Wales.

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

Questions for topic proposer

None

Sources of evidence

See Appendix

Appendix – Brief literature search results

Resource	Results
UK guidelines and guidance	
e.g. NICE; Healthcare Improvement Scotland; Guidelines International Network; SIGN	Early and locally advanced breast cancer: diagnosis and management. NICE guideline 101. Published: 18 July 2018. https://www.nice.org.uk/guidance/ng101/resources/early-and-locally-advanced-breast-cancer-diagnosis-and-management-pdf-66141532913605
Secondary literature and economic evaluations	
e.g.Cochrane library; Medline *systematic reviews, meta-analyses, economic evaluations*	Cochrane review: Hickey BE, Lehman M, Francis DP, See AM. Partial breast irradiation for early breast cancer. Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD007077. DOI: 10.1002/14651858.CD007077.pub3. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007077.pub3/media/CDSR/CD007077/CD007077.pdf Shah 2013 Shah, C. Cost-efficacy of acceleration partial-breast irradiation compared with whole-breast irradiation. Breast Cancer Research & Treatment, 2013. 138(1): p. 127-35. [economic study cited in NICE quidance NG101] https://www.ncbi.nlm.nih.gov/pubmed/23329353
Primary studies	
Medline *RCTs; observational studies*	A study looking at radiotherapy for women with a very small risk of their breast cancer returning (PRIMETIME) https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/study-radiotherapy-women-small-risk-breast-cancer-returning-primetime#undefined
Ongoing secondary research	
Clinicaltrials.gov	NICE makes reference to 5 ongoing, large clinical studies.

Date of search:	4th December 2018
Concepts searched:	Not reported.