



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:	Internal mammary node irradiation (IMNI) for people with high-risk early breast cancer
Topic proposer	Catherine Pembroke
Report identifier	RT03
Topic exploration report number:	TER031
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 IMNI for people with high-risk 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

There has been some concern regarding the treatment of the internal mammary nodal chain with radiotherapy as there is the potential for long term cardiac toxicity due to the proximity to the heart (Nguyen, 2018). Breast cancer patients with internal mammary node metastasis have a worse prognosis than those who do not, independent of their axillary status (Qiu, 2013). There is evidence to suggest that intramammary lymph node (ILN) metastases are most commonly found concomitantly with axillary lymph node metastases; the incidence of intramammary lymph node metastasis increased significantly ($p < 0.0001$) from 9.1% in patients with negative axillary lymph nodes to 29.1% in those with positive ALNs (Veronesi, 1985).

Recently updated NICE Guidelines suggest that clinicians consider including the internal mammary chain within nodal radiotherapy target for people with node-positive invasive breast cancer (NICE CG101, 2018) and the 2016 National Comprehensive Cancer Network Breast Cancer Clinical Practice Guidelines recommends IMNI for patients with ≥ 4 axillary lymph nodes (ALNs) and strongly considers IMN for patients with 1-3 positive ALNs (Cong 2017).

Proposed PICO	
Population	People with high risk early breast cancer T4 and/ or ≥ 4 axillary lymph node positive)
Intervention	Internal mammary node irradiation
Comparator	Whole breast irradiation \pm supraclavicular fossa radiotherapy
Outcome measures	Overall survival, disease free survival, locoregional recurrence, treatment related adverse events/morbidity, health related quality of life

Summary of findings

The evidence review for the NICE guidelines included 6 studies from which there was moderate quality evidence that internal mammary irradiation reduced locoregional recurrence compared with no radiotherapy. Moderate quality evidence suggested no clinically important increase in disease free survival in patients with 4 or more positive nodes. High quality evidence indicate a clinically meaningful increase in overall survival in patients treated with internal mammary irradiation compared with no radiation (NICE CG101, 2018).

Searches identified evidence which shows that certain patients may benefit from IMNI. One systematic review and meta-analysis (Verma, 2015) reports that although older randomised trials failed to show differences in clinical outcomes or toxicities, more recently published studies suggest a potential benefit with limited data to suggest an overall survival benefit or disease free survival benefit.

Deep inspiration breath hold (DIBH) techniques appear to reduce the dose to the heart (Nguyen, 2018) thus potentially reducing toxicity. Toxicity with modern radiotherapy techniques is low; pulmonary toxicity was a reported 1-5% (Verma, 2015) while the evidence review for the NICE guidelines included moderate evidence that internal mammary irradiation resulted in increased lung toxicity and grade 2+ lymphoedema.

Economic impact

Addition of the internal mammary chain to the radiotherapy field is likely to have a minor effect on the cost. However including the internal mammary chain within the nodal radiotherapy target and using a radiotherapy technique that minimises the dose to the lung and heart is not currently standard practice and will require additional training, technique development and implementation (NICE CG101).

The topic proposal submission estimated that there would be an addition cost of £31,914.25 to account for extra time required in planning radiotherapy and additional training and development costs based on 136 patients per annum.

Prioritisation criteria

Clinical impact (Potential for the technology to have an impact on patient-related health outcomes):

There is major potential to improve clinical outcomes for a small number of patients however the treatment is not without risks which should be considered.

Budget impact (Impact of the technology on health care spending):

The main costs are associated with increased time for treatment planning and training.

Population impact (The size of the population that would be affected by the technology): 2872 people in Wales were diagnosed with breast cancer in 2014 (WCISU). Based on the numbers provided by the topic proposer, this technology would impact approximately 5% of breast cancer 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?

Recently published NICE clinical guidance suggests that there is moderate to high quality evidence from systematic reviews and randomised trials to support the implementation of internal mammary nodal irradiation (IMNI) in high-risk breast cancer patients. It is not clear at this time whether there is evidence for the mode of delivery of radiotherapy (VMAT, IMRT etc) however it is assumed that this information could be more specifically elucidated on full review of the evidence.

Questions for topic proposer

- There needs to be clarity on what the specific question that needs to be addressed is. Are clinicians debating whether IMNI should be given or is the uncertainty about the way in which the radiotherapy is delivered? These are two subtly different questions when designing literature search strategies and extracting data.
- How is high-risk early breast cancer being defined? Based on information from the initial submission it was assumed:
 - patients with T4 breast cancer with or without ALN positive and
 - patients with any T stage with ≥ 4 ALN positive
- Can you clarify how the cost impact has been calculated? It is not clear why the additional time is multiplied by 68 when there are 136 patients annually, particularly as this seems to be multiplied by 2 again in the additional cost column. Although ultimately gives the same cost of £1591.88, we need to be clear where those costs are generated from.
- Could the topic proposer reference the source of the costs used (PSSRU etc)?

Sources of evidence

- Choi J et al (2016) Radiation Pneumonitis in Association with Internal Mammary Node Irradiation in Breast Cancer Patients: an Ancillary Result from the KROG 08-06 Study *Journal of breast cancer*, 19(3), 275-282
- Cong et al (2017) Internal mammary lymph nodes radiotherapy of breast cancer in the era of individualized medicine *Oncotarget* 8;46:81583-81590
- Early and Locally Advanced Breast Cancer: Diagnosis and Management (NICE Clinical Guideline 101; 2018)
 - Included: Choi 2016; Hennequin 2013 ; Matzinger 2010; Poortmans 2015; Thorsen 2016; Whelan 2015
- Nguyen M et al (2018) Cardiac sparing characteristics of internal mammary chain radiotherapy using deep inspiration breath hold for left-sided breast cancer *Radiation Oncology* 13:103
- Veronesi U et al (1985): Prognosis of breast cancer patients after mastectomy and dissection of internal mammary nodes. *Annals of Surgery* 202:702-707
- Verma et al (2016) Role of internal mammary node radiation as a part of modern breast cancer radiation therapy: a systematic review *International Journal of Radiation Oncology, biology, physics* 95;2:617-631
- (WCISU) Wales Cancer Intelligence and Survey Unit <http://www.wcisu.wales.nhs.uk/breast-cancer> [last accessed 22/11/2018]

Appendix - Brief literature search results

Resource	Results
UK guidelines and guidance	
NICE	N=1 Early and Locally Advanced Breast Cancer: Diagnosis and Management (NICE Clinical Guideline 101; 2018)
Healthcare Improvement Scotland	N=0
Guidelines International Network	N=0
SIGN	N=0
Secondary literature and economic evaluations	
e.g. Cochrane library ; Medline <i>systematic reviews, meta-analyses, economic evaluations</i>	N=1 Verma et al (2016) Role of internal mammary node radiation as a part of modern breast cancer radiation therapy: a systematic review International Journal of Radiation Oncology, biology, physics 95;2:617-631
Primary studies	
Medline <i>RCTs; observational studies</i>	N=62 (Searches were limited to 2015 (date of searches in systematic review) onwards and English Language only. Not including a date limit gave 319 results) N=45 possibly relevant following title and abstract review
Cochrane trials database	N=56 studies of which N=9 were possibly relevant following title and abstract review
Ongoing secondary research	
Clinicaltrials.gov	None identified
Date of search:	22 nd November 2018
Concepts searched:	breast neoplasms; carcinoma; radiotherapy; axilla; lymph nodes; internal mammary; metastases