



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:	Whole breast irradiation with supraclavicular fossa (SCF) radiotherapy and axillary radiotherapy for people with early breast cancer following a macrometastatic sentinel node
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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 axillary radiotherapy as an alternative to axillary node clearance for people with early breast cancer following a macrometastatic (>2mm) sentinel node. 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 primary treatment for breast cancer is surgery to remove the tumour in the breast. Sentinel lymph node biopsy (SLNB) is a technique to determine whether cancer has spread to the lymph nodes in the arm pit (axilla). SLNB is done in the same operation to remove the breast tumour.

Patients with tumour deposits of 2mm in size or greater in one or more sentinel nodes require further treatment to the axilla to control the cancer. This can be surgical removal of an area of fat from the axilla containing numerous nodes (axillary node clearance), or application of radiotherapy to the axilla. For patients undergoing whole breast radiotherapy (WBRT) at VCC, another field would be added to include the axilla. For patients who were already due to receive WBRT to include the supraclavicular fossa (SCF), the SCF field would be extended to the axilla.

The RT procedures proposed are consistent with recommendations in latest NICE guidance for early and locally advanced breast cancer: NG101, July 2018.

Proposed PICO	
Population	Patients who have 1 or more disease positive sentinel nodes identified by sentinel lymph node biopsy (macrometastases \geq 2mm in size)
Intervention	Axillary radiotherapy
Comparator	Axillary clearance (surgery)
Outcome measures	Recurrence Disease free survival Overall survival Health related quality of life Adverse events, particularly lymphoedema, shoulder stiffness.

Summary of findings
<p>There is sufficient evidence to support a rapid review of the procedure if required. Evidence has been reviewed by NICE (NG101 Evidence review [B]): Evidence reviews for management of the positive axilla. NICE recommends the procedure as a treatment alternative to axillary surgery.</p> <p>In addition the systematic review and meta-analysis by Zhao et al. 2017 summarises the evidence for this topic (2 randomised studies and 5 non randomised studies).</p> <p>NICE NG101 (2018) makes a number of relevant recommendations, as follows:</p> <p>“1.4.7 Offer further axillary treatment (axillary node clearance or radiotherapy) after SLNB to people who have 1 or more sentinel lymph node macrometastases. [2018]</p> <p>1.4.8 Discuss the benefits and risks of having no further axillary treatment after primary breast-conserving surgery (within clinical trials where available) with women who:</p> <ul style="list-style-type: none"> • have 1 or 2 sentinel lymph node macrometastases and • have been advised to have whole-breast radiotherapy with systemic therapy (which may be endocrine therapy). [2018]” <p>“1.10.3 Offer whole-breast radiotherapy to women with invasive breast cancer who have had breast-conserving surgery with clear margins.”</p> <p>“1.10.10 Offer adjuvant postmastectomy radiotherapy to people with node-positive (macrometastases) invasive breast cancer or involved resection margins.”</p> <p>“1.10.16 Do not offer adjuvant radiotherapy to regional lymph nodes to people with invasive breast cancer who have been shown to have histologically lymph node-negative breast cancer. [2009, amended 2018]</p> <p>1.10.17 Do not offer adjuvant radiotherapy to the axilla after axillary clearance for invasive breast cancer. [2009, amended 2018]</p> <p>1.10.18 Offer adjuvant radiotherapy to the supraclavicular fossa to people with invasive breast cancer and 4 or more involved axillary lymph nodes. [2009]</p> <p>1.10.19 Offer adjuvant radiotherapy to the supraclavicular fossa to people with invasive breast cancer and 1 to 3 positive lymph nodes if they have other poor</p>

prognostic factors (for example, T3 and/or histological grade 3 tumours) and good performance status.[2009]

1.10.20 Consider including the internal mammary chain within the nodal radiotherapy target for people with node-positive (macrometastases) invasive breast cancer [2018]”

With regard to considering surgery versus radiotherapy to treat patients with macrometastases in 1 or more sentinel nodes, NICE makes note that:

“There were unclear benefits and risks of further axillary treatment after primary surgery in people with only 1 or 2 sentinel lymph node macrometastases who have had breast-conserving surgery and have been advised to have whole-breast radiotherapy and systemic therapy, so the committee agreed that the risks and benefits of further treatment should be discussed with this group..... the recommendations will result in a minor change in practice because some centres currently use mainly surgery and may not use radiotherapy. In addition, more time may need to be factored in to plan and deliver radiotherapy treatment.”

The Royal College of Radiologists consensus statement (accessed 7th December 2018) provides the expected standard for further local treatment for the malignant sentinel lymph node in individuals with early invasive breast cancer:

- “Sentinel nodes with isolated tumour cells and/or micrometastases - no further axillary treatment is required in addition to breast-conserving surgery or mastectomy.
- 1-2 sentinel nodes with macrometastases - further axillary treatment is no longer mandatory in breast conservation with whole-breast radiotherapy in patients who are postmenopausal and have T1, Grade 1 or 2, oestrogen receptor positive (ER+) and human epidermal growth factor receptor negative (HER2-) tumours. These patients could also be entered into the POSNOC or equivalent clinical trial.
- Three or more sentinel nodes with macrometastases - patients should usually be recommended to have further axillary treatment.
- Further axillary treatment should usually be recommended for patients undergoing mastectomy or with tumours with one or more of the following features: T3, Grade 3, ER- or HER2+. These patients could also be entered into the POSNOC or equivalent clinical trial.
- No consensus was reached on the management of the axilla for patients with one or more of the following features: premenopausal status, T2 tumours, lymphovascular invasion or extranodal spread.”

The VCC proposal cites the AMAROS study. The AMAROS study was included in the NICE NG101 evidence review [B]: one of two randomised studies: AMAROS and OTOASOR. The AMAROS study reports a lower rate of lymphoedema following axillary RT versus axillary surgery after positive sentinel node biopsy: 23% versus 11% at 5 years, respectively (this study has not been critically appraised in preparation of this exploratory report). The VCC proposal cites the POSNOC trial, which is open to recruitment and compares axillary RT/surgery VERSUS no axillary treatment in patients with positive sentinel node(s).

Economic impact

The NICE guidance did not include any economic studies of radiotherapy to the axilla. The proposal estimates that 70 patients per year will require axillary RT, most likely as patients enrolled in the POSNOC trial. The VCC proposal estimates that the intervention would cost per annum an additional £936.40 (physicist) plus £2,116.30 (consultant) or £955.13 (radiographer instead of consultant) for planning the RT, and then £4,096.75 for delivery of RT. The development cost to lead to initiation of the service is estimated at £5267.25 making the total service cost for axillary RT in year 1 an estimated £12,416.70. All patients would avoid the cost of axillary surgery at other hospitals to VCC.

Prioritisation criteria

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

NICE guidance recommends axillary RT or surgery. The proposal cites data from 1 RCT for lower lymphoedema rate following RT compared to surgery.

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

If patients who would not normally have breast/chest wall RT, then have axillary RT instead of axillary surgery VCC would incur a cost but UHW/UHL/+ other hospitals would avoid costs of surgery. Otherwise for patients already having breast/chest wall RT addition of another field (or extension of SCF to axilla) may be less of an issue for VCC (but still extra) whereas surgical teams avoid the need for further axillary surgery. The reported costs in the proposal are not large and soul deb compared with costs of surgery.

Population impact (The size of the population that would be affected by the technology):

The relevant population is patients with positive sentinel nodes. Would this be about 1 in 4 of 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? - Yes, as per NICE guidance, made clearer by understanding how cases are selected for RT or surgery.
- favour standard care? - see above
- be inconclusive?

Questions for topic proposer

- How are patients selected for axillary RT or surgery? Both are options under NICE guidance. Is there a joint MDT encompassing VCC and surgical expertise making the decision?
- Physicist planning time is estimated at 4 hours*70 patients = 280 hours per annum, but the £936.40 is based on 40*23.41. Is this correct?

Sources of evidence

See Appendix below

Appendix - Brief literature search results

Resource	Results
UK guidelines and guidance	
e.g. NICE ; Healthcare Improvement Scotland ; Guidelines International Network ; SIGN	Royal College Postoperative radiotherapy for breast cancer: UK consensus statements: Axillary management of sentinel lymph node-positive disease* https://www.rcr.ac.uk/clinical-oncology/service-delivery/postoperative-radiotherapy-breast-cancer-uk-consensus-statements NICE NG101 early and locally advanced breast cancer (updated July 2018) https://www.nice.org.uk/guidance/ng101
Secondary literature and economic evaluations	
e.g. Cochrane library ; Medline <i>systematic reviews, meta-analyses, economic evaluations</i>	Can axillary radiotherapy replace axillary dissection for patients with positive sentinel nodes? A systematic review and meta-analysis. Min Zhao, a Wei-Guang Liu, a Lei Zhang, Zi-Ning Jin, Zhan Li, Cheng Liu, Dong-Bao Li, Ying Ma, Jing-Wen Zhang, Feng Jin, and Bo Chen. Chronic Diseases and Translational Medicine Volume 3, Issue 1, 25 March 2017, Pages 41-50 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5627701/
Primary studies	
Medline <i>RCTs; observational studies</i>	Randomised trials (2) Donker M et al. 2014 Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial https://www.clinicalkey.com/service/content/pdf/watermarked/1-s2.0-S1470204514704607.pdf?locale=en_US Optimal treatment of the axilla after positive sentinel lymph node biopsy in primary invasive breast cancer patients (surgery versus radiotherapy)-OTOASOR trial: 5 years follow-up of a randomized clinical trial. A. Sávolt, Z. Mátrai, C.S. Polgár, N. Udvarhelyi, G. Rubovszky, E. Kovacs, P. Musonda, G. Peley. European Journal of Surgical Oncology, 2014-11-01, Volume 40, Issue 11, Pages S37-S38, Copyright © 2014 https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S0748798314006490?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0748798314006490%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ejso.com%2Farticle%2FS0748-7983(14)00649-0%2Fpdf Other literature (may be less applicable) Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. https://www.sciencedirect.com/science/article/pii/S0140673605678877?via%3Dihub EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet, The, 2014-06-21, Volume 383, Issue 9935, Pages 2127-2135

	<p>https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S0140673614604888?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0140673614604888%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.thelancet.com%2Fjournals%2Flancet%2Farticle%2FPIIS0140-6736(14)60488-8%2Ffulltext</p> <p>Avoiding axillary dissection in breast cancer surgery: a randomized trial to assess the role of axillary radiotherapy U. Veronesi R. Orecchia S. Zurrada V. Galimberti A. Luini P. Veronesi G. Gatti G. D'Aiuto L. Cataliotti R. Paolucci ... Annals of Oncology, Volume 16, Issue 3, 1 March 2005, Pages 383-388 https://academic.oup.com/annonc/article/16/3/383/160005</p> <p>POSNO - A Trial Looking at Axillary Treatment in Early Breast Cancer https://clinicaltrials.gov/ct2/show/NCT02401685</p>
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Date of search:	7 th December 2018
Concepts searched:	guidance, breast cancer, radiotherapy, sentinel lymph node biopsy, surgery, axilla