Review protocol for 8.4 What are the indications for radiotherapy to internal mammary nodes?

Field (based on PRISMA-P)	Content
Review question	What are the indications for radiotherapy to internal mammary nodes?
Type of review question	Intervention review
Objective of the review	The objective of this review is to determine the incremental benefit of internal mammary node irradiation and identify subgroups of patients with early/locally advanced breast cancer who have most to gain from this treatment. Recommendations will aim to cover which subgroups should be offered such treatment.
Eligibility criteria – population/disease/condition/issue/domain	Adults (18 or over) with invasive breast cancer but no distant metastases (M0) treated with breast conserving surgery or mastectomy (including modified radical mastectomy).
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Radiotherapy to internal mammary nodes (± other nodes)
Eligibility criteria – comparator(s)/control or reference (gold) standard	No internal mammary node radiotherapy (± other nodes)
Outcomes and prioritisation	Critical (up to 3 outcomes) • Locoregional recurrence rate (MID: any statistically significant difference) • Disease-free survival (MID: any statistically significant difference) • Treatment-related morbidity (e.g., pulmonary toxicity [MID: GRADE default values], cardiac toxicity, [MID: GRADE default values], second primary tumours [MID: any statistically significant difference]) Important but not critical • Overall survival (MID: any statistically significant difference) • HRQoL (MID: values from the literature) • 10 year follow-up periods will be prioritised when multiple time points are reported. HRQoL MID values from the literature: • FACT-G total: 3-7 points • FACT-B total: 7-8 points • TOI (trial outcome index) of FACT-B: 5-6 points • BCS of FACT-B: 2-3 points • WHOQOL-100: 1 point

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Eligibility criteria – study design	Systematic reviews/meta-analyses of RCTs RCTs Controlled, non-randomised studies (only if RCTs unavailable or insufficient data to inform decision making; minimum no. of participants 2000 as large numbers will be needed to see effect)
Other inclusion exclusion criteria	Foreign language studies, conference abstracts, and narrative reviews will not routinely be included.
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups (critical outcomes only – excluding treatment-related morbidity): Extent of lymph node metastasis (0, 1-3, 4+) Tumour position (medial, lateral) T stage Laterality (left, right)
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the reviewing team. Quality control will be performed by the senior systematic reviewer. Dual sifting will not be performed for this question as it is an intervention review with a straightforward PICO.
Data management (software)	Study sifting and data extraction will be undertaken in STAR. Pairwise meta-analyses will be performed using Cochrane Reviewer Manager (RevMan 5). GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	The following key databases will be searched: Cochrane Library (CDSR, DARE, CENTRAL, HTA) through Wiley, Medline & Medline in Process and Embase through OVID. Additionally Web of Science may be searched and consideration will be given to subject-specific databases and used as appropriate. Searches will be undertaken from 2006 to capture modern radiotherapy techniques.
Identify if an update	Previous question: What are the indications for radiotherapy to the supraclavicular fossa, internal mammary chain and axilla? Date of search: 28/02/2008 Relevant recommendation(s) from previous guideline: 1) Do not offer adjuvant radiotherapy to the internal mammary chain to patients with early breast cancer who have had breast surgery.
Author contacts	For details please see the guideline in development web site.

Field (based on PRISMA-P)	Content
Highlight if amendment to previous protocol	For details please see Section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see Section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see Section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods chapter
Meta-bias assessment – publication bias, selective reporting bias	For details please see Section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see Sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Dr Jane Barrett in line with section 3 of Developing NICE guidelines: the manual. Staff from NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.

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Name of sponsor	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for the NHS in England.
PROSPERO registration number	N/A

BCS, breast cancer subscale; FACT-B, Functional assessment of cancer therapy – Breast cancer; FACT-G, Functional assessment of cancer therapy – General; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HRQoL, health-related quality of life; MID, minimally important difference; N/A, not applicable; NHS, National Health Service, NICE, National Institute of Health and Care Excellence; NGA, National Guideline Alliance; RCT, randomised controlled trial; RT, radiotherapy; TOI, Trial outcome index; WHOQOL, World Health Organization quality of life