National Institute for Health and Care Excellence

Draft for Consultation

Early and locally advanced breast cancer: diagnosis and management

[H] Evidence reviews for breast radiotherapy

NICE guideline tbc

Evidence reviews

January 2018

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Breast radiotherapy

This evidence report contains information on 4 reviews relating to breast radiotherapy.

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Review question 8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?

Introduction

The number of early breast cancer survivors is increasing. This is the result of a combination of increased incidence of the disease, widespread availability of breast screening and the development of more effective treatment strategies. As a consequence, more women cured of breast cancer will live with the late effects of their treatment.

Breast radiotherapy is associated with a 1-2% excess of non-breast cancer mortality, the majority of which is attributable to cardiac disease. There is a linear, no-threshold relationship between mean heart dose and the risk of subsequent major coronary events. Excluding the heart from the radiotherapy field reduces mean heart dose and therefore the risk of longer term cardiac side effects

The objective of this review is to determine which heart-sparing breast radiotherapy techniques are effective without compromising the treatment of the whole breast volume, and to identify which techniques should be offered to spare the heart during radiotherapy.

PICO table

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults (18 or over) with invasive breast cancer (M0) and/or DCIS receiving whole breast radiotherapy
Intervention	Heart sparing techniques: • Deep inspiration breath-hold • Prone radiotherapy • Shielding • Proton beam radiotherapy
Comparison	• Heart sparing techniques • No heart sparing technique
Outcome	**Critical** • Mean heart dose • Target coverage **Important** • Local recurrence rate • Treatment-related morbidity • Treatment-related mortality

DCIS: Ductal carcinoma in-situ; M0 no distant metastases

For full details see review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

Four observational studies (number of participants, N=236) and 1 randomized cross over study (N=28) were included in the review (Barlett 2017; Barlett 2015; Chi 2015; Czeremszynska 2017; Eldredge Hindy 2015). All 5 studies reported on the mean heart dose. One study (Eldredge Hindy 2015) reported on the target coverage. No studies reported data on local recurrence rate, treatment related morbidity or mortality.

There was no evidence available for shielding and proton beam radiotherapy.

See also the study selection flow chart in appendix C, forest plots in appendix E and study evidence tables in appendix D.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of the included studies

Table 2: Summary of included studies

Study	Additional inclusion/exclusion criteria	Intervention/Comparison
Bartlett 2017	Left sided breast cancer	Intervention arm: Deep inspiration breath-hold Control arm: Free breathing
Bartlett 2015	Left sided breast cancer	Intervention arm: Deep inspiration breath hold Control arm: Prone radiotherapy
Chi 2015	Left sided breast cancer	Intervention arm: Moderate deep inspiration breath-hold Control arm: Free breathing
Czeremszynska 2017	Age <70 years Left sided breast cancer	Intervention arm: Deep inspiration breath-hold Control arm: Free breathing
Eldredge-Hindy 2015	Left sided breast cancer	Intervention arm: Moderate deep inspiration breath-hold with ABC device Control arm: Free breathing

ABC: Active breathing coordinator

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profile for this review question (heart sparing radiotherapy) is presented in Table 3 and Table 4. The evidence was very low quality because of the observational nature of the included studies and small sample size.

Table 3: Summary clinical evidence profile: Comparison 1. Deep inspiration breath-hold versus free breathing

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Free Breathing	Deep Inspiration Breath-Hold			
Mean Heart Dose at RT (Gy)	The mean heart dose at RT in the control groups was 2.4 Gy	The mean mean heart dose at RT in the intervention groups was 1.29 lower (1.81 to 0.77 lower)	-	236 (4 studies[1,2,3,4])	Very low[5,6,7]
Target Coverage at RT Scale from: 0 to 100.	The mean target coverage at RT in the control groups was 86.3 %	The mean target coverage at RT in the intervention groups was 0.5 higher (4.6 lower to 5.6 higher)	-	81 (1 study[1])	Very low[7]

CI: confidence interval; Gy: gray: RT: radiotherapy
[1] Eldredge-Hindy 2015
[2] Chi 2015
[3] Czeremszynska 2017
[4] Barlett 2017
[5] Downgraded by 2 levels for very serious inconsistency as I square=89%
[6] Downgraded by 1 level for indirectness due to inclusion of women with only larger breast volumes (estimated volume>750cm3)
[7] Downgraded by 1 level for serious imprecision, as number of events <400

Table 4: Summary clinical evidence profile: Comparison 2. Deep inspiration breath-hold versus prone radiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Prone RT	Deep Inspiration Breath-Hold			
Mean Heart Dose at RT (Gy)	The mean heart NTD dose at RT in the control groups was 0.66 Gy	The mean heart dose at RT in the intervention groups was 0.22 lower (0.30 to 0.14 lower)	-	28 (1 study[1])	Low[2,3]

CI: Confidence interval; Gy: Gray; NTD: normalized total dose; RT: Radiotherapy;
[1] Barlett 2015
[2] Downgraded by 1 level for serious indirectness as only women with larger breasts included
[3] Downgraded by 1 level for serious imprecision, as number of events <400

See appendix F for full GRADE tables.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Evidence statements

Comparison 1. Deep inspiration breath-hold versus free breathing

Critical outcomes

Mean heart dose

- There is very low quality evidence from four prospective cohort studies (N=236) that deep inhalation breath hold produces clinically meaningful reduction in mean heart dose compared with free breathing at radiotherapy for people with invasive breast cancer and/or ductal carcinoma in situ (DCIS) receiving whole breast radiotherapy.

Target coverage

- There is very low quality evidence from one prospective cohort study (N=81) that deep inspiration breath-hold does not produce clinically meaningful change in target coverage compared to free breathing at radiotherapy for people with invasive breast cancer and/or DCIS receiving whole breast radiotherapy.

Important Outcomes

Local recurrence rate

- No evidence was found for this outcome.

Treatment-related morbidity

- No evidence was found for this outcome.

Treatment-related mortality

- No evidence was found for this outcome.

Comparison 2. Deep inspiration breath-hold versus prone radiotherapy

Critical outcomes

Mean heart dose

- There is low quality evidence from one randomized cross over study (N=28) that deep inhalation breath hold produces clinically meaningful reduction in mean heart dose compared with prone radiotherapy for people with invasive breast cancer and/or DCIS receiving whole breast radiotherapy.

Target coverage

- No evidence was found for this outcome.

Important Outcomes

Local recurrence rate

- No evidence was found for this outcome.

Treatment-related morbidity

- No evidence was found for this outcome.

Treatment-related mortality

- No evidence was found for this outcome.

Other interventions:

- There was no evidence available on shielding or on proton beam radiotherapy

Recommendations

H1. Use a deep inspiratory breath-hold radiotherapy technique for people with left-sided breast cancer to reduce the dose to the heart.

Rationale and impact

Why the committee made the recommendations

There was evidence that deep inspiratory breath-hold radiotherapy techniques reduce the mean radiotherapy heart dose for adults with left-sided invasive breast cancer receiving whole breast radiotherapy. The committee did not identify any harms. There was also evidence that deep inspiration breath-hold radiotherapy techniques did not reduce the target coverage of whole breast radiotherapy.

There was no evidence about the use of deep inspiration breath-hold radiotherapy techniques for people with right-sided breast cancer, so the committee did not make separate recommendations for this subgroup.

Impact of the recommendations on practice

Currently, deep inspiratory breath-hold radiotherapy techniques are not routinely offered to people with invasive breast cancer having whole breast radiotherapy. However, the committee noted that the Royal College of Radiologists has produced consensus statements that advise using this technique, and that many centres already offer it.

The recommendation will ensure consistent practice and ensure that people can access the best care.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

As this review question is considering a heart sparing radiotherapy technique, mean heart dose and target coverage were selected as critical outcomes by the committee. The inclusion of treatment-related morbidities and treatment-related mortality as important outcomes was to allow a balance of the benefits and harms of treatments to be made. Local recurrence rate was identified as other important outcome.

No evidence was available for treatment-related morbidities, treatment-related mortality and local recurrence rate.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE. For comparison of mean heart dose using deep inspiratory breath-hold technique compared to free breathing, the evidence was of a very low quality, and was downgraded due to observational study design and imprecision due to small sample size. For target coverage, the evidence was of very low quality due to observational study design and small sample size.

The quality of evidence for mean heart dose using deep inspiratory breath-hold technique compared to prone radiotherapy was low quality. The evidence quality was downgraded mainly due to uncertainty around the estimate due to small sample size and indirectness due to the inclusion of only women with large breasts.

Benefits and harms

The use of deep inspiratory breath-hold technique during whole breast radiotherapy leads to reduction in mean heart dose without compromising the target coverage. Specifically, it leads to a reduction in mean heart dose by 1.29 Gy, which is almost a 50% reduction in the mean heart dose. The committee discussed that this may potentially lead to reduction in late cardiovascular morbidity/mortality and will be particularly beneficial for people with cardiovascular risk factors. The committee were aware of estimates that a decrease in 1 Gy led to a 7% reduction in cardiovascular morbidity (Darby 2013). The committee noted that reduction in cardiovascular morbidity may also lead to cost reduction to the NHS. The committee also discussed that heart sparing radiotherapy techniques may reduce treatment related anxiety for people undergoing radiotherapy and improve quality of life due to decreased cardiovascular effects.

There was no evidence available regarding treatment related morbidity or mortality and local recurrence rate for deep inspiratory breath hold technique. Based on their experience and expertise, the committee discussed that deep inspiratory breath hold technique only requires a change in position during radiotherapy and is not known to be associated with serious harms. However, the committee discussed that deep inspiratory breath-hold technique may be more demanding for people who may struggle to do this exercise. The committee also discussed that people with disabilities, particularly respiratory compromise, may be unable to perform the breathing exercises required and therefore unable to access the technique.

The committee agreed that although many centres were already offering the breath-hold technique, some centres did not use it routinely and therefore this recommendation would reduce variation in practice across the country.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee discussed that the use of deep inspiratory breath-hold technique will require increased resource use within some radiotherapy departments. This will include a coaching session of up to 45 minutes to train the person to use the technique, an extension to the radiotherapy treatment time of approximately 10 to 15 minutes (as the treatment is paused between breath-holds), and possibly some initial training time for the radiotherapy team to implement the use of routine breath-hold technique. The extended treatment time will also impact on the utilisation of equipment, which may already be used to capacity.

However, these costs may be offset in the longer term by the expected reduction in cardiac events and therefore a reduction in the costs to the NHS of managing these events. Therefore, it is likely that the technique would be cost-effective in cost per QALY terms.

While there may be resource implications for those centres not currently using the technique, the overall resource impact of implementing the recommendation across the NHS was not thought to be significant because the technique is already being used in many centres.

Other factors the committee took into account

The committee noted that deep inspiratory breath-hold technique may also benefit people with right sided breast cancer, particularly when the target volume extends over the midline, but had not looked at evidence for this so were unable to make a specific recommendation for this group of people.

References

Bartlett 2015

Bartlett, F. R., Colgan, R. M., Donovan, E. M., McNair, H. A., Carr, K., Evans, P. M., Griffin, C., Locke, I., Haviland, J. S., Yarnold, J. R., Kirby, A. M. (2015) The UK HeartSpare Study (Stage IB): Randomised comparison of a voluntary breath-hold technique and prone radiotherapy after breast conserving surgery. Radiotherapy and Oncology, 114, 66-72.

Bartlett 2017

Bartlett, F. R., Donovan, E. M., McNair, H. A., Corsini, L. A., Colgan, R. M., Evans, P. M., Maynard, L., Griffin, C., Haviland, J. S., Yarnold, J. R., Kirby, A. M. (2017) The UK HeartSpare Study (Stage II): Multicentre Evaluation of a Voluntary Breath-hold Technique in Patients Receiving Breast Radiotherapy. Clinical Oncology, 29, e51-e56.

Chi 2015

Chi, F., Wu, S., Zhou, J., Li, F., Sun, J., Lin, Q., Lin, H., Guan, X., He, Z. (2015) Dosimetric comparison of moderate deep inspiration breath-hold and free-breathing intensity-modulated radiotherapy for left-sided breast cancer. Cancer/Radiotherapie, 19, 180-186.

Czeremszynska 2017

Czeremszynska, B., Drozda, S., Gorzynski, M., Kepka, L. (2017) Selection of patients with left breast cancer for deep-inspiration breath-hold radiotherapy technique: Results of a prospective study. Reports of Practical Oncology and Radiotherapy, 22, 341-348.

Darby 2013

Darby, S.C., Ewertz M., McGale, P, Bennet A.M., Blom-Goldman, U., Bronnum, D., Correa, C., Cutter, D., Gagliardi, G., Gigante, B., Jensen, M.B., Nisbet, A., Peto, R., Rahimi, K., Taylor, C., Hall, P.(2013) Risk of ischemic heart disease in women after radiotherapy for breast cancer. New England Journal of Medicine, 368(11),987-98.

Eldredge-Hindy 2015

Eldredge-Hindy, H., Lockamy, V., Crawford, A., Nettleton, V., Werner-Wasik, M., Siglin, J., Simone, N. L., Sidhu, K., Anne, P. R. (2015) Active Breathing Coordinator reduces radiation dose to the heart and preserves local control in patients with left breast cancer: Report of a prospective trial. Practical Radiation Oncology, 5, 4-10.

Review question 8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?

Introduction

Adjuvant whole breast radiotherapy is the current standard treatment option for most people with stage 1 and 2 breast cancer after breast-conserving surgery (BCS). Multiple retrospective studies and an overview of randomized trials have established the equivalence of this treatment approach compared with mastectomy in terms of both disease-free and overall survival. Whole breast radiotherapy halves the risk of local recurrence. However, local recurrence rates have fallen dramatically over the last 30 years, so that the absolute benefit of radiotherapy for some individuals may not outweigh the potential risks (for example, normal tissue toxicity, cardiac morbidity, second cancers). For many women, increasingly diagnosed with small screen-detected cancers, it is the late complications of radiotherapy, 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 aim of this review is to determine if specific groups of women can be identified in whom breast radiotherapy does not have a favourable risk/benefit ratio and so can be omitted.

PICO table

See Table 5 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 5: Summary of the protocol (PICO table)

Population	Women (18 or over) with invasive breast cancer (M0) who have undergone breast conserving surgery
Intervention	• No breast radiotherapy
Comparison	Whole breast radiotherapy
Outcome	**Critical** • Local recurrence rate • Treatment-related morbidity • HRQoL **Important** • Overall survival • Disease-free survival • Treatment-related mortality

HRQoL, Health related quality of life; M0, no distant metastases

For full details see review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

Six studies (N=3977) were included in the review (Blamey 1990; Holli 2009; Hughes 2013; Kunkler 2013; Wickberg 2014; Williams 2011). These studies report data from 6 trials: British Association of Surgical Oncologists (BASO) II trial (number of publications, k=1), Cancer and Leukemia Group B (CALGB) 9434 trial (k=1), Holli 2009 (k=1), Postoperative Radiotherapy in Minimum-Risk Elderly (PRIME; k=1), PRIME II (k=1), and Uppsala/Orebro trial (k=1). The BASO II, CALGB, and PRIME II trials compared BCS and endocrine therapy with or without whole breast radiotherapy, Holli 2009 and Uppsala/Orebro trial compared BCS and dissection of the axilla with or without whole breast radiotherapy, and the PRIME trial compared BCS alone with or without whole breast radiotherapy.

All studies reported data for subgroups of interest: T stage 1, (k=2), N stage 0 (k=5), age ≥65 years (k=3), no adjuvant systemic therapy received (k=1), and negative surgical margins (k=5).

The clinical studies included in this evidence review are summarised in Table 6 and evidence from these are summarised in the clinical GRADE evidence profile below (Table 7). See also the study selection flow chart in appendix C, forest plots in appendix E and study evidence tables in appendix D.

This review updates a question from the previous guideline CG80 (NICE 2009). Therefore, studies for this topic identified by the previous guideline are incorporated into forest plots, GRADE evidence profiles, and evidence statements. However, studies are not incorporated where there is more recent data available from the same trial, unless different outcomes are reported, or where a change in protocol from the previous guideline means that studies no longer meet inclusion criteria. Therefore, 21 articles included in the previous guideline were not incorporated into the current results for the following reasons: did not meet current inclusion criteria outlined in review protocol (k=16), more recent data available (k=2), insufficient presentation of results in original article to include in analysis (k=2), does not report data for any subgroups of interest so cannot inform current question (k=1). This resulted in only one article (Whelan 2000) from CG80 being added to the current evidence.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 6: Summary of included studies

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
Blamey 2013	BASO II	Aged <70 with primary operable unilateral invasive breast cancer (N0, M0) Histological grade 1 or specific good prognosis tumours Maximum tumour size 20mm No previous cancer except adequately treated basal cell carcinoma of the skin	• Intervention arm (RT-): WLE (0.5-1cm clear margin). Tamoxifen 20 mg/day for 5 years • Control arm (RT+): WLE (0.5-1 cm clear margin). Tamoxifen 20 mg/day for 5 years. Whole breast radiation total 40-50 Gy in 15-25 fractions.

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
		Excluded if pregnant or lactating Excluded if other diseases precluded adequate surgery, adjuvant therapy, or follow-up	
Holli 2009		Age >40 years Tumour 20mm or less, grade 1 or 2. PR status positive. Low cell proliferation rate Excluded if extensive intraductal component or axillary node metastases	Intervention arm (RT-): segmental breast resection (1 cm margins) and levels I and II dissection of ipsilateral axilla. Control arm (RT+): segmental breast resection (1 cm margins) and levels I and II dissection of ipsilateral axilla. Whole breast radiotherapy total 50 Gy within 5 weeks using 2 Gy daily fractions.
Hughes 2013	CALGB 9343	≥70 years with stage I, N0, ER+ breast cancer No history of cancer other than in situ cervical or non-melanoma skin cancer within 5 years Initially included tumours up to 4cm but reduced to 2cm	Intervention arm (RT-): lumpectomy with a clear margin (no ink on tumour). 20 mg tamoxifen per day for 5 years initiated during or after irradiation. Control arm (RT+): lumpectomy with a clear margin (no ink on tumour). 20 mg tamoxifen per day for 5 years initiated during or after irradiation. RT included tangential fields to the entire breast followed by an electron boost to the lumpectomy site.
Kunkler 2015	PRIME II	≥65 years with T1-T2, N0 hormone receptor positive breast cancer Receiving neoadjuvant hormonal treatment Excluded if history of in-situ or invasive breast cancer of either breast or previous malignant disease in the past year, other than non-melanomatous skin cancer or carcinoma in situ of the cervix	Intervention arm (RT-): No details for breast conserving surgery procedures provided (except ≥1mm margins). Tamoxifen (20 mg daily for 5 years) as the standard adjuvant endocrine treatment but other forms allowed. Control arm (RT+): No details for breast conserving surgery procedures provided (except ≥1mm margins). Tamoxifen (20 mg daily for 5 years) as the standard adjuvant endocrine treatment but other forms allowed. RT total dose 40-50Gy in 15-25 fractions over 3-5 weeks. Boost permitted but not required.
Wickberg 2014	Uppsala/Orebro	≤80 years with unifocal stage 1 invasive breast cancer	Intervention arm (RT-): sector resection and axilla dissected to levels I and II Control arm (RT-): sector resection and axilla dissected to levels I and II. Radiotherapy total dose of 54Gy in 27 fractions
Williams 2011	PRIME	≥ 65 years with T0-2, N0 unilateral breast cancer	BCS complete excision – further details not reported

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
		Receiving adjuvant endocrine therapy. Medically suitable to attend for all treatments and follow-up. Excluded if pure in situ carcinoma or previous/concurrent malignancy within 5 years other than non-melanomatous skin cancer or carcinoma in situ of cervix Excluded if grade 3 cancer	

BASO, British Association of Surgical Oncologists; BCS, Breast conservation surgery; CALGB, Cancer and Leukemia Group B; ER, oestrogen receptor; Gy, gray; PRIME, Postoperative Radiotherapy in Minimum-Risk Elderly; RT, radiotherapy; WLE, wide local excision

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profile for this review question (breast radiotherapy after breast-conserving surgery) is presented in Table 7. The majority of the evidence is moderate or low quality. This is primarily due to small number of events of interest occurring.

Table 7: Summary clinical evidence profile: Comparison 1. No whole breast radiotherapy versus whole breast radiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: RT+	Corresponding risk: RT-			
Overall survival - T stage: 1 (12 year follow-up)	12 yr OS 85%	12 yr OS 77% (73% to 81%)	HR 1.59 (1.29 to 1.96)	263 (1 study)	Moderate[1]
Overall survival - N stage: 0 (5 to 12 year follow-up)	5 yr OS 88%	5 yr OS 85% (83% to 87%)	HR 1.29 (1.12 to 1.5)	1154 (3 studies)	Moderate[2]
Overall survival - Margins: negative (5 to 12 year follow-up)	5 yr OS 88%	5 yr OS 85% (83% to 87%)	HR 1.29 (1.12 to 1.5)	1154 (3 studies)	Moderate[2]
Overall survival - Age: 65+ (5 to 10 year follow-up)	5 yr OS 88%	5 yr OS 87% (85% to 90%)	HR 1.06 (0.87 to 1.3)	891 (2 studies)	High
Overall survival - Adjuvant systemic therapy: none (20 year follow-up)	20 yr OS 50%	20 yr OS 47% (37% to 56%)	HR 1.1 (0.85 to 1.42)	381 (1 study)	Moderate[3]
Local recurrence - T stage: 1 (10 to 12 year follow-up)	90% free from local recurrence at 10 yrs	75% free from local recurrence at 10 yrs (66% to 82%)	HR 2.7 (1.84 to 3.97)	1378 (2 studies)	Moderate[3]
Local recurrence - N stage: 0 (5 to 12 year follow-up)	96% free from local recurrence at 5 yrs	88% free from local recurrence at 5 yrs (83% to 91%)	HR 3.22 (2.31 to 4.49)	3340 (4 studies)	Moderate[3]
Local recurrence - Margins: negative (5 to 12 year follow-up)	96% free from local recurrence at 5 yrs	88% free from local recurrence at 5 yrs (83% to 91%)	HR 3.22 (2.31 to 4.49)	3340 (4 studies)	Moderate[3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: RT+	Corresponding risk: RT-			
Local recurrence - Age: 65+ (5 to 10 year follow-up)	99% free from local recurrence at 5 yrs	95% free from local recurrence at 5 yrs (90% to 97%)	HR 5.35 (2.78 to 10.29)	1962 (2 studies)	Low[1]
Treatment-related morbidity – fractures (cause unspecified; all patients N stage 0, 65+, negative margins; 5 year follow-up)	106 per 1000	116 per 1000 (50 to 272)	RR 1.10 (0.47 to 2.57)	171 (1 study)	Low[4]
Treatment-related morbidity - congestive cardiac failure (all patients N stage 0, 65+, negative margins; 5 year follow-up)	35 per 1000	35 per 1000 (7 to 168)	RR 0.99 (0.21 to 4.76)	171 (1 study)	Low[6]
Treatment-related morbidity - myocardial infarction (all patients N stage 0, 65+, negative margins; 5 year follow-up)	71 per 1000	58 per 1000 (18 to 184)	RR 0.82 (0.26 to 2.6)	171 (1 study)	Low[4]
Treatment-related morbidity - secondary cancer (cause unspecified; all patients N stage 0, 65+, negative margins; 5 year follow-up)	35 per 1000	89 per 1000 (8 to 928)	RR 2.53 (0.24 to 26.51)	1497 (2 studies)	Low[1]
Treatment-related morbidity - score 10+ on HADS depression scale (all patients N stage 0, 65+, negative margins; 5 year follow-up)	10 per 1000	30 per 1000 (3 to 281)	RR 3.12 (0.33 to 29.49)	206 (1 study)	Low[4]
Treatment-related morbidity - score 10+ on HADS anxiety scale (all patients N stage 0, 65+, negative margins; 5 year follow-up)	86 per 1000	119 per 1000 (52 to 270)	RR 1.39 (0.61 to 3.15)	206 (1 study)	Low[4]
HRQoL - EQ5D scale (all patients N stage 0, 65+, negative margins; 5 year follow-up)		The mean HRQoL – EQ5D scale (all patients N stage 0, 65+, negative margins) in the intervention groups was 0.02 lower (0.1 lower to 0.06 higher)		168 (1 study)	Low[5]
HRQoL - reduction in scores on Breast Cancer Chemotherapy Questionnaire (all patients N stage 0, negative margins; 2 month follow-up)	270 per 1000	160 per 1000 (119 to 214)	RR 0.59 (0.44 to 0.79)	720 (1 study)	Not possible to GRADE this outcome due to study included from previous guideline

Rates of overall survival and local recurrence in the control group correspond to the weighted average across included trials or the trial with the shortest follow-up period where these differ across included trials

CI: Confidence interval; EQ5D, EuroQol Research Foundation measure of general health status; HADS: Hospital Anxiety and Depression Scale; HR: Hazard ratio; HRQoL: Health related quality of life; OS: overall survival; RR: Risk ratio;

[1] <300 events

[2] Random effects model with significant heterogeneity - I squared value 74% - not possible to investigate heterogeneity as additional subgroups of interest identified by the GC were not reported for the trials that contributed to this estimate. All estimated effects were in the same direction

[3] Total events <300

[4] <300 events and 95% CI crosses both thresholds for minimally important difference based on GRADE default values (0.80 and 1.25)

[5] N<400

[6]total events<300; not downgraded based on 95% CI due to very small differences in absolute risk

See appendix F for full GRADE tables.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Evidence statements

Comparison 1. No whole breast radiotherapy versus whole breast radiotherapy

Critical outcomes

Local recurrence rate

- There is moderate quality evidence from 2 RCTs (N=1378) that whole breast radiotherapy produces clinically meaningful reductions in local recurrence at 10 to 12 year follow-up compared with no whole breast radiotherapy for women with T stage 1 invasive breast cancer.
- There is moderate quality evidence from 4 RCTs (N=3340) that whole breast radiotherapy produces clinically meaningful reductions in local recurrence at 5 to 12 year follow-up compared with no whole breast radiotherapy for women with N stage 0 invasive breast cancer.
- There is moderate quality evidence from 4 RCTs (N=3340) that whole breast radiotherapy produces clinically meaningful reductions in local recurrence at 5 to 12 year follow-up compared with no whole breast radiotherapy for women with invasive breast cancer and negative surgical margins following breast-conserving surgery.
- There is low quality evidence from 2 RCTs (N=1962) that whole breast radiotherapy produces clinically meaningful reductions in local recurrence at 5 to 10 year follow-up compared with no whole breast radiotherapy for women with invasive breast cancer aged 65 years and over.

Treatment-related morbidity

- There is low quality evidence from 1 RCT (N=171) that whole breast radiotherapy reduces fractures (cause unspecified) at 5 year follow-up compared with no whole breast radiotherapy for women aged 65 years and over with N stage 0 invasive breast cancer and negative surgical margins following breast-conserving surgery. However, this was not statistically or clinically significant.
- There is moderate quality evidence from 1 RCT (N=171) that there is no effect of whole breast radiotherapy on congestive cardiac failure at 5 year follow-up for women aged 65 years and over with N stage 0 invasive breast cancer and negative surgical margins following breast-conserving surgery.
- There is low quality evidence from 1 RCT (N=171) that there was no effect of whole breast radiotherapy following breast-conserving surgery on myocardial infarction at 5 year follow-up for women aged 65 years and over with N stage 0 invasive breast cancer and negative surgical margins.
- There is low quality evidence from 2 RCTs (N=1497) that there was no effect of whole breast radiotherapy following breast-conserving surgery on secondary cancer (cause unspecified) at 5 year follow-up for women aged 65 years and over with N stage 0 invasive breast cancer and negative surgical margins.

Health-realted quality of life

- There is low quality evidence from 1 RCT (N=206) that whole breast radiotherapy produces clinically significant reductions in depression at 5 year follow-up compared with no whole breast radiotherapy for women aged 65 years and over with N stage 0 invasive breast cancer and negative surgical margins following breast-conserving surgery. However, this was not statistically significant.
- There is low quality evidence from 1 RCT (N=206) that whole breast radiotherapy produces clinically significant reductions in anxiety at 5 year follow-up compared with no whole breast radiotherapy for women aged 65 years and over with N stage 0 invasive breast cancer and negative surgical margins following breast-conserving surgery. However, this was not statistically significant.
- There is low quality evidence from 1 RCT (N=168) that there is no effect of radiation on HRQoL, as measured by EQ5D at 5 year follow-up, for women aged 65 years and over with N stage 0 invasive breast cancer and negative surgical margins following breast-conserving surgery.
- There is evidence from 1 RCT (N=720) that that whole breast radiotherapy produces clinically significant improvements in HRQoL, as measured by Breast Cancer Chemotherapy Questionnaire at 2 month follow-up, compared with no whole breast radiotherapy in women with N stage 0 invasive breast cancer and negative surgical margins following breast-conserving surgery. It was not possible to judge the overall quality of this evidence as it was included from the previous NICE guideline (CG80).

Important outcomes

Overall survival

- There is moderate quality evidence from 1 RCT (N=263) that whole breast radiotherapy produces clinically meaningful increases in overall survival at 12 year follow-up compared with no whole breast radiotherapy for women with T stage 1 invasive breast cancer.
- There is moderate quality evidence from 3 RCTs (N=1154) that whole breast radiotherapy produces clinically meaningful increases in overall survival at 5 to 12 year follow-up compared with no whole breast radiotherapy for women with N stage 0 invasive breast cancer.
- There is moderate quality evidence from 3 RCTs (N=1154) that whole breast radiotherapy produces clinically meaningful increases in overall survival at 5 to 12 year follow-up compared with no whole breast radiotherapy for women with invasive breast cancer and negative surgical margins following breast-conserving surgery.
- There is high quality evidence from 2 RCTs (N=891) that there was no effect of whole breast radiotherapy following breast-conserving surgery on overall survival at 5 to 10 year follow-up for women with invasive breast cancer aged 65 years and over.
- There is moderate quality evidence from 1 RCT (N=381) that there was no effect of whole breast radiotherapy on overall survival at 20 year follow-up for women with invasive breast cancer not receiving adjuvant systemic therapy.

Disease-free survival

- No evidence was found for this outcome.

Treatment-related mortality

- No evidence was found for this outcome.

Recommendations

H2. Offer whole breast radiotherapy to women with invasive breast cancer who have had breast-conserving surgery with clear margins.

H3. Consider omitting radiotherapy for women who:

- have had breast-conserving surgery for invasive breast cancer with clear margins **and**
- have a very low absolute risk of local recurrence (defined as women aged 65 and over with tumours that are T1N0, ER-positive, HER2-negative and grade 1 to 2) **and**
- are willing to take adjuvant endocrine therapy for a minimum of 5 years.

H4. When considering omitting radiotherapy (see previous recommendation), discuss the benefits and risks, and explain that:

- without radiotherapy, local recurrence occurs in about 10 women per 1,000 per year, and with radiotherapy occurs in about 2 women per 1,000 per year
- overall survival at 10 years is the same with or without radiotherapy
- there is no increase in serious late effects if radiotherapy is given (for example, congestive cardiac failure, myocardial infarction or secondary cancer).

Rationale and impact

Why the committee made the recommendations

There is evidence that whole breast radiotherapy after breast-conserving surgery reduces the risk of recurrence and increases overall survival. It also decreases rates of depression and anxiety.

However, because the risk of breast cancer recurring at 5 years is very low and there are harms associated with radiotherapy, the benefits of radiotherapy for women with a very low risk of recurrence are less certain. For these women, the committee agreed that healthcare professionals should fully discuss the benefits and risks with women before a decision is made.

Impact of the recommendations on practice

Most women are already offered radiotherapy after breast-conserving surgery so this reflects current practice, but more time may be needed to discuss the balance of benefits and risks with women.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

As the purpose of this review was to determine if the use of radiotherapy could lead to a clinically meaningful reduction in recurrence of breast cancer after surgery in low risk people, and the risks and benefits of this approach were thought to be finely balanced, the committee prioritised local recurrence rate, treatment-related morbidity and health related quality of life as critical outcomes. Overall survival, disease-free survival and treatment-related mortality were selected as important outcomes.

There was no evidence available for disease-free survival and treatment-related mortality. There was also no evidence available for several of the subgroups of interest, specifically positive margins, oestrogen receptor (ER) status, human epidermal growth factor receptor 2

(HER2) status, grade, younger age, women who received adjuvant systemic therapy, T stage 2 and above and N stage 1 and above.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE. The evidence for local recurrence rate ranged from moderate to high across the different subgroups. The evidence for treatment-related morbidity and HRQoL was low quality. The evidence for overall survival across the different subgroups of interest ranged from moderate to high quality (with most of it being moderate quality).

The committee noted that there were high rates of performance bias in the studies due to the inability to blind for whole breast radiotherapy. However they considered this was unlikely to have a significant impact due to the objective nature of the outcomes. There were also high rates of imprecision due to small number of events of interest and small sample sizes.

The evidence showed that whole breast radiotherapy produces clinically meaningful reductions in local recurrence compared with no breast radiotherapy for people with T1 breast cancer, N0 breast cancer, people with invasive breast cancer and negative surgical margins following breast-conserving surgery, and people with invasive breast cancer aged 65 years and over. The committee noted that radiotherapy reduces recurrence rates for all women, but it was important to discuss the benefits and risks with individual patients. Some patients may be very anxious about recurrence, and want everything possible to reduce risk. However, some patients interpret risk more rationally and would rather avoid potential side effects when the risk of recurrence is small.

The evidence showed that whole breast radiotherapy produces clinically significant reductions in anxiety and depression compared with no whole breast radiotherapy for individuals aged 65 years and over with N stage 0 invasive breast cancer and negative surgical margins following breast-conserving surgery. However these data had low event rates and the symptoms of anxiety and depression were only measured at a single time point, not over a period of time. Therefore the Committee were uncertain about the actual effect size for this outcome.

The evidence showed that whole breast radiotherapy produces clinically meaningful increases in overall survival compared with no whole breast radiotherapy for individuals with T stage 1 invasive breast cancer, N stage 0 invasive breast cancer, and in individuals with invasive breast cancer and negative surgical margins following breast-conserving surgery. No clinically meaningful differences in overall survival were found in people aged 65 and over and individuals not receiving adjuvant systemic therapy

Benefits and harms

Given that the evidence showed clinically meaningful reductions in local recurrence, anxiety and depression and increases in overall survival with whole breast radiotherapy for people with invasive breast cancer who have had breast conserving surgery with clear margins, the Committee agreed to offer this treatment to this group.

The absolute risk of local recurrence at 5 years is very low, based on the evidence. There are harms associated with the use of radiotherapy and the benefits on overall survival are only realised in the longer term (5 and 10 year survival is the same with or without radiotherapy). Therefore the benefits of giving radiotherapy to those with a very low absolute risk of recurrence are less certain, particularly if they are willing to take endocrine therapy. Consequently the committee recommended there should be a discussion about the benefits and harms of whole breast radiotherapy with this group of people so that they can make an informed choice about their treatment. Important factors to include in the discussion are the local recurrence rates with and without radiotherapy, that overall survival is the same and that there is no increase in serious late effects with radiotherapy.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee discussed the potential costs and savings of recommendations and agreed that an increase in resources would not be required as the use of whole breast radiotherapy after breast-conserving surgery is already standard practice. Therefore it is possible that the recommendations could lead to cost savings if radiotherapy is omitted in low risk patients (following a discussion with the patient).

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Review question 8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?

Introduction

Whole breast radiotherapy (WBRT) is the current standard adjuvant treatment option for most women with early invasive breast cancer after breast conserving surgery (BCS). Multiple retrospective studies and an overview of randomized trials have established the equivalence of this treatment approach compared with mastectomy in terms of both disease-free and overall survival.

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.

The aim of this review is to determine if there is a group of women in whom partial breast radiotherapy (PBR) would offer a better risk-benefit approach than whole breast radiotherapy.

PICO table

See Table 8 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 8: Summary of the protocol (PICO table)

Population	Women (18 or over) with invasive breast cancer (M0) who have undergone breast conserving surgery
Intervention	Partial breast radiotherapy
Comparison	Whole breast radiotherapy
Outcome	**Critical** • Local recurrence rate • Treatment-related morbidity • Health related Quality of Life (HRQoL) **Important** • Overall survival • Disease-free survival • Treatment-related mortality

HRQoL, health-related quality of lfie; M0, no distant metasases

For full details see review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

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.

Evidence from these are summarised in Table 9 and the clinical GRADE evidence profile in Table 10.

See also the study selection flow chart in appendix C, forest plots in appendix E and study evidence tables in appendix D.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 9: Summary of included studies

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
Ott 2016, Polgar 2017, Strnad 2016	GEC-ESTRO	**Inclusion criteria:** Women aged ≥ 40 years; histologically confirmed invasive breast cancer or ductal carcinoma in situ (DCIS) UICC stage 0–IIA, a maximum tumour diameter < 3 cm, complete resection with clear margins ≥2 mm (in case of invasive lobular cancer or pure DCISP5 mm), at least six negative axillary lymph nodes (pN0), or singular nodal micro-metastasis (pN1mi), or negative sentinel node biopsy (pN0sn), or a clinically negative axilla in case of DCIS (cN0), no distant metastasis or contralateral breast cancer. **Exclusion criteria:** Any signs of a multifocal growth pattern in mammography, had residual micro-calcifications post-operatively, an extensive intraductal component (EIC), vessel invasion (L1, V1), involved, close (<2 mm) or unknown margins (R1/Rx), or were pregnant.	1) APBI Interstitial brachytherapy; HDR 32 Gy/8 fractions or 30.3 Gy/7 fractions; PDR 50 Gy at 0.6-0.8 Gy/fractions given hourly. 2) External beam WBRT 50.0-50.4 Gy/1.8-2.0 Gy fractions (5-28) plus 10 Gy/5 fraction boost.

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
Coles 2017	IMPORT LOW	**Inclusion criteria:** Women ≥ 50 years undergoing breast conserving surgery for unifocal invasive ductal adenocarcinoma of any grade (1–3); pathological tumour size ≤ 3 cm (pT1–2), axillary node negative or one to three positive nodes (pN0–1), microscopic margins of non-cancerous tissue ≥ 2 mm. **Exclusion criteria:** Women < 50 years; Invasive carcinoma of classical lobular type; distant metastases; previous malignancy of any kind (unless non-melanomatous skin cancer); undergone a mastectomy; received neoadjuvant chemotherapy or concurrent adjuvant chemoradiotherapy.	• 1) Whole-breast radiotherapy received 40 Gy in 15 fractions to the whole breast. • 2) Reduced-dose group received 36 Gy in 15 fractions to the whole breast and 40 Gy in 15 fractions to the partial breast containing the tumour bed. • 3) Partial-breast group received 40 Gy in 15 fractions to the partial breast only.
Livi 2010, Livi 2015, Meattini 2017	Livi 2015	**Inclusion criteria:** Age at presentation >40 years; Tumour size ≤25 mm; Wide excision or quadrantectomy with clear margins (≤5 mm); Clips placed in tumour bed; Full informed consent from patient; Follow-up at the radiotherapy department of Florence University. **Exclusion criteria:** Women ≤ 40 years; Cardiac dysfunction (Left ventricular ejection fraction <50% as measured by echocardiography or history of active angina, myocardial infarction, or other cardiovascular disease); Forced expiratory volume <1 L/m; Extensive intraductal carcinoma; Multifocal cancer; Psychiatric problems; Follow-up at centre other than the radiotherapy department of Florence University.	1) Partial breast irradiation or accelerated partial breast irradiation using intensity-modulated radiotherapy (IMRT). 2) Whole breast radiotherapy (WBRT); used 50 Gy/25 fractions plus 10 Gy boost.
Lovey 2007, Polgar 2007, Polgar 2013	Polgar 2007	**Inclusion criteria:** Women > 40 years; Wide excision with microscopically negative surgical margins; unifocal tumour; primary tumour size ≤20 mm (pT1); cN0, pN0, or pN1mi (single nodal micro-metastasis >0.2mmand≤2.0 mm) axillary status; and histologic Grade 2 or less. **Exclusion criteria:** Women ≤ 40 years; bilateral breast carcinoma; prior uni- or contralateral breast cancer; concomitant or previous	1) PBI; 7 × 5.2GyHDRmulti-catheter brachytherapy (88/128 women). Those unsuitable for HDR (40/1280 women) had 50 Gy/25 fractions electron beam RT to partial breast. 2) Control arm: 50 Gy/25 fractions WBRT (130 women)

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
		other malignancies (except basal cell carcinoma of the skin); pure ductal or lobular carcinoma in situ (pTis); invasive lobular carcinoma; or the presence of an extensive intraductal component.	
Olivotto 2013	RAPID	**Inclusion criteria:** Women ≥ 40 years with invasive ductal carcinoma or ductal carcinoma in situ (DCIS) treated with BCS with microscopically clear margins and negative axillary nodes by sentinel node biopsy, or axillary dissection for those with invasive disease, or by clinical examination for those with DCIS alone. **Exclusion criteria:** Women < 40 years; combined tumour size (DCIS and/or invasive carcinoma)>3 cm, lobular carcinoma, > one primary tumour in different quadrants of the breast, or an RT plan that did not meet protocol-defined dose-volume constraints for APBI.	1) APBI using three-dimensional conformal radiotherapy (3D-CRT): 38.5 Gy in 10 fractions, bd over 5-8 days. 6-8 hour gap between doses. 2) WBRT; 42.5 Gy in 16 fractions daily over 22 days. Women with large breast size: 50 Gy in 25 fractions over 25 days. Boost 10 Gy in 4 or 5 fractions over 4-7 days was permitted women who were deemed at moderate to high risk of LR according to local cancer centre guidelines.
Rodriguez 2013	Rodriguez 2013	**Inclusion criteria:** Women age ≥60 years; invasive ductal carcinoma; unifocal tumour; primary tumour size ≤30 mm (pT2); cN0, pN0 axillary status; and histologic grade 2 or less. **Exclusion criteria:** Women age <60 years; Bilateral breast carcinoma; prior unilateral or contralateral breast cancer; concomitant or other previous malignancies; pure ductal or lobular carcinoma in situ (pTis); invasive lobular carcinoma; presence of an extensive intraductal component; excision with microscopically positive or close (3 mm) surgical margins; multicentric disease; nodepositive disease; concomitant or neoadjuvant chemotherapy; and postsurgical hematoma >2 cm, or seroma fluid that required multiple aspirations.	1) PBI/APBI delivered by 3D-CRT at 48Gy/24 fractions ± 10 Gy boost (according to risk factors for local recurrence) in 51 women. 2) Conventional WBRT at 48 Gy/24 fractions ± 10 Gy boost in 51 women.

3D-CRT: 3 dimensional conformal radiotherapy; APBI: Accelerated partial breast irradiation; BCS: breast conserving surgery; DCIS: ductal carcinoma in situ; EIC: extensive intraductal component; GEC-ESTRO: The Groupe Européen de Curiethérapie and the European SocieTy for Radiotherapy & Oncology; Gy: Gray; HDR: High dose rate; IMPORT: Intensity Modulated and Partial Organ Radiotherapy; IMRT: intensity modulated radiotherapy; PBI: Partial breast irradiation; PDR: Pulsed dose rate; RAPID: Randomized Trial of Accelerated Partial Breast Irradiation; UICC: Union for International Cancer Control; WBRT: Whole breast radiotherapy

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profile for this review question (partial-breast radiotherapy versus whole-breast radiotherapy after breast-conserving surgery) is presented in Table 10. The majority of the evidence is moderate or low quality. This is primarily due to small number of events of interest occurring.

Table 10: Summary clinical evidence profile: Comparison 1. Partial-breast radiotherapy versus whole-breast radiotherapy after breast-conserving surgery

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk: WBRT	Corresponding risk: PBI/APBI				
Local recurrence free survival: local recurrence in the ipsilateral breast as a discrete outcome Follow-up: 5 to 10 years[1]	14 per 1000	14 per 1000 (9 to 21)	HR 0.98 (0.63 to 1.52)	3407 (5 studies)	Low[1,2]	
Cosmesis, physician reported Assessed with four-point scales Follow-up: 3 to 5 years	153 per 1000	151 per 1000 (87 to 263)	RR 0.99 (0.57 to 1.72)	3764 (6 studies)	Very low[3,4,6]	Four-point scales were used to assess cosmesis as poor/worse, fair/normal, good, or excellent. These results represent those with poor/worse or fair/normal cosmesis.
Cosmesis, patient reported at 5 years follow-up Assessed with four-point scales Follow-up: mean 5 years	146 per 1000	147 per 1000 (98 to 220)	RR 1.01 (0.67 to 1.51)	1966 (4 studies)	Very low[3,5,6]	Four-point scales were used to assess cosmesis as poor, fair, good, or excellent. These results represent those with poor or fair cosmesis.
Cosmesis, nurse reported at 5 year follow-up Assessed with four-point scale Follow-up: mean 5 years	134 per 1000	327 per 1000 (211 to 511)	RR 2.44 (1.57 to 3.81)	335 (1 study)	Low[2,3]	Cosmesis characteristics were graded on a four-point scale: poor, fair, good, excellent. Results are for those with poor or fair cosmesis.
Acute radiotherapy (RT) skin toxicity Assessed with the Radiation Therapy Oncology Group Common Toxicity Criteria Follow-up: 0 to 90 days	752 per 1000	120 per 1000 (60 to 248)	RR 0.16 (0.08 to 0.33)	1790 (3 studies)	Low[4]	Treatment tolerance was assessed using the acute radiation morbidity scoring criteria.
Late RT skin toxicity Assessed with the Radiation Therapy Oncology Group Common (RTOG CTC) 5-point scale[10] Follow-up: 3 to 5 years	63 per 1000	61 per 1000 (19 to 190)	RR 0.97 (0.31 to 3.03)	3175 (5 studies)	Very low[4,6]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk: WBRT	Corresponding risk: PBI/APBI				
Breast Pain Self-reported Follow-up: 3 to 5 years	67 per 1000	61 per 1000 (45 to 81)	RR 0.9 (0.67 to 1.2)	2475 (3 studies)	Very low[2,7,8]	Self-reported using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-BR23 breast cancer module, and NCI CTC criteria.
Fat necrosis Assessed with EORTC and NCI 5-point scale Follow-up: 3 to 5 years	65 per 1000	89 per 1000 (64 to 122)	OR 1.4 (0.98 to 2)	1899 (3 studies)	Low[2,8]	Defined as grade 1 to 3 on EORTC and NCI CTC.
Health related quality of life Assessed using EORTC QLQ-C30 and BR23 module Follow-up: mean 2 years	-	The mean health related quality of life in the intervention groups was 16 higher (10.99 to 21.01 higher)	-	205 (1 study)	Low[2,9]	
Overall survival Follow-up: mean 5 years	53 per 1000	41 per 1000 (30 to 56)	HR 0.76 (0.55 to 1.06)	3047 (3 studies)	Moderate[2]	
Disease-free survival Follow-up: mean 5 years	31 per 1000	29 per 1000 (20 to 42)	HR 0.93 (0.63 to 1.37)	3305 (4 studies)	Moderate[2]	
Distant metastasis-free survival Follow-up: mean 5 years	22 per 1000	20 per 1000 (13 to 32)	HR 0.9 (0.56 to 1.46)	3305 (4 studies)	Moderate[2]	
Treatment-related mortality	No treatment related deaths	No treatment related deaths	Not estimable	1184 (1 study)	Moderate[2]	

APBI: accelerated partial breast irradiation; CI: Confidence interval; CTC, Common Toxicity Criteria; EORTC QLQ-30: European Organisation for Research and Treatment of Cancer Quality of Life Questionairre; HR: Hazard ratio; NCI, National Cancer Institute; PBI: partial breast irradiation; RR: Risk ratio; RT: radiotherapy; RTOG: Radiation Therapy Oncology Group; WBRT: whole breast radiotherapy

[1] Clinical heterogeneity was substantial relating to radiotherapy dose, technique and use of quality assurance procedures.

[2] < 300 events.

[3] Five of 6 studies were at high risk of bias for blinding of outcome assessors for subjective outcomes.

[4] Very serious heterogeneity (I2>80%); random effects model used, no subgroup analysis accounted for heterogeneity.

[5] Serious heterogeneity (I2>50% but <80%); random effects model used, no subgroup analysis accounted for heterogeneity.

[6] Effect estimate includes both default MID thresholds and the null effect (1).

[7] Blinding of participants to treatment group not possible for self-reported breast pain.

[8] Effect estimate includes one default MID threshold and the null effect (1).

[9] Blinding of outcome assessors was not reported.

See appendix F for full GRADE tables.

Economic evidence

Included studies

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).

Excluded studies

See supplement 1: Health economics for the list of excluded studies.

Summary of studies included in the economic evidence review

The base case results of Shah 2013 showed that all APBRT techniques were cost-effective and indeed dominant in comparison to whole beam intensity modulated radiotherapy (IMRT) techniques (i.e. less costly and more effective). In comparison to WBRT with 3D conformal radiotherapy (CRT), APBRT techniques with IMRT or 3DCRT were again found to be dominant. However, other forms of APBRT were found to be more costly and more effective with ICERs of $12,514, $67,329 and $557 per QALY for single lumen, multi lumen and interstitial APBRT techniques, respectively.

The analysis was deemed to be only partially applicable to the decision problem in the UK setting as it was conducted from the perspective of the US health care system. Furthermore, serious limitations were identified in the analysis. Most notably, uncertainty around the base case estimates was not assessed as no deterministic or probabilistic sensitivity analyses were conducted.

Overall, the analysis appears to suggest that accelerated partial breast radiotherapy may be cost-effective in comparison to whole beam radiotherapy. However, further research would be required before drawing decisive conclusions around the cost-effectiveness of accelerated partial breast radiotherapy in the UK context.

Evidence statements

Comparison 1. Partial breast radiotherapy versus whole breast radiotherapy

Critical outcomes

Local recurrence

- There is low quality evidence from 5 RCTs (N=3407) that there is no effect of a difference on local recurrence free survival at 5 to 10 years follow-up for women with invasive breast cancer when comparing partial breast radiotherapy with whole breast radiotherapy.

Treatment-related morbidity

- There is very low quality evidence from 6 RCTs (N=3764) that there is no clinically important difference in physician-reported cosmesis at 5 years follow-up between women with invasive breast cancer who received partial breast radiotherapy compared with those who received whole breast radiotherapy.
- There is very low quality evidence from 4 RCTs (N=1966) that there is no clinically important difference in patient-reported cosmesis at 5 years follow-up between women

with invasive breast cancer who received partial breast radiotherapy compared with those who received whole breast radiotherapy.

- There is low quality evidence from 1 RCT (N=335) that partial breast radiotherapy produces clinically meaningful reductions in nurse-reported cosmesis at 5 years follow-up compared with whole breast radiotherapy for women with invasive breast cancer.
- There is low quality evidence from 3 RCTs (N=1790) that partial breast radiotherapy produces clinically meaningful reductions in acute radiotherapy skin toxicity at 0 to 90 days follow-up compared with whole breast radiotherapy for women with invasive breast cancer.
- There is very low quality evidence from 5 RCTs (N=3175) that there is no clinically important difference in late radiotherapy skin toxicity at 3 to 5 years follow-up for women with invasive breast cancer when comparing partial breast radiotherapy with whole breast radiotherapy.
- There is very low quality evidence from 3 RCTs (N=2475) that there is no clinically important difference in breast pain at 3 to 5 years follow-up for women with invasive breast cancer when comparing partial breast radiotherapy with whole breast radiotherapy.
- There is low quality evidence from 3 RCTs (N=1899) that there is no clinically important difference in fat necrosis at 3 to 5 years follow-up for women with invasive breast cancer when comparing partial breast radiotherapy with whole breast radiotherapy.

Health-realted quality of life

- There is low quality evidence from 1 RCT (N=205) that that partial breast radiotherapy produces clinically important improvements in HRQoL, as measured using EORTC QLQ-C30 and BR23 module at 2 year follow-up, compared with whole breast radiotherapy for women with invasive breast cancer.

Important outcomes

Overall survival

- There is moderate quality evidence from 3 RCTs (N=3047) that there is no clinically important difference in overall survival at 5 years follow-up for women with invasive breast cancer when comparing partial breast radiotherapy with whole breast radiotherapy.

Disease-free survival

- There is moderate quality evidence from 4 RCTs (N=3305) that there is no clinically important difference in disease-free survival at 5 years follow-up for women with invasive breast cancer when comparing partial breast radiotherapy with whole breast radiotherapy.
- There is moderate quality evidence from 4 RCTs (N=3305) that there is no clinically important difference in distant metastasis-free survival at 5 years follow-up for women with invasive breast cancer when comparing partial breast radiotherapy with whole breast radiotherapy.

Treatment-related mortality

- There is moderate quality evidence from 1 RCT (N=1184) of no clinically important difference in treatment-related mortality at 5 year follow-up for women with invasive breast cancer, but no treatment related deaths were observed in this study.

Economic evidence statement

- 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

QALY for single lumen, multi lumen and interstitial APBRT techniques, respectively. The analysis was partially applicable with serious limitations.

Recommendations

H5. 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.

H6. When considering partial breast radiotherapy (see previous recommendation), 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.

H7. When delivering partial breast radiotherapy, consider:

- external beam radiotherapy to a dose of 40 Gy in 15 fractions **or**
- multicatheter interstitial brachytherapy.

Rationale and impact

Why the committee made the recommendations

Good evidence showed that partial breast radiotherapy led to similar results to whole breast radiotherapy after breast-conserving surgery in women with a low risk of local recurrence. In addition, it may have fewer treatment-related adverse effects.

Impact of the recommendations on practice

The committee was aware that current practice for external beam partial breast radiotherapy after breast conserving surgery is based on the Royal College of Radiologists' 2016 consensus statement, so there would be no change to recommended practice.

However, because multicatheter interstitial brachytherapy is not widely used in the UK, the committee agreed that this would involve a change in practice if centres decided to use this technique rather than external beam radiotherapy.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The critical outcomes were local recurrence, treatment-related morbidity and health related quality of life. This is because breast radiotherapy following surgery is done to reduce the risk of local recurrence and by irradiating less of the breast there is a potential impact on treatment-related morbidity and health related quality of life. Overall survival, disease-free survival and treatment related mortality were considered important outcomes, because the group offered partial breast radiotherapy are typically at low risk of disease recurrence and even lower risk of death from breast cancer.

The quality of the evidence

The evidence came from randomised trials and ranged from very low to high quality. The major issue was heterogeneity in treatment-related morbidity with some trials favouring partial breast RT but others favouring whole breast RT. This was most likely due to the different surgical and partial breast radiotherapy techniques used in the trials, for example the use of accelerated partial breast radiotherapy. For this reason the committee based their recommendations on the trials with surgical techniques, radiotherapy regimens and adjuvant endocrine therapy most applicable to the UK.

The evidence review aimed to identify a group with a particularly low absolute risk of local recurrence who would be best suited to partial breast radiotherapy. The inclusion criteria of the trials meant that only low risk patients were included and there were too few cases of local recurrence to define such a group. For this reason the committee used the trial entry criteria of the most relevant trial (IMPORT-LOW) in their recommendation: women aged 50 and over with tumours that are less than or equal to 3 cm, N0, oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative and grade 1 to 2.

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

Benefits and harms

The benefits of partial breast radiotherapy accrue from irradiating less tissue. This results in fewer acute adverse effects like skin toxicity and potentially fewer late adverse effects involving the heart and lungs. The potential harm of partial breast radiotherapy, as opposed to whole breast radiotherapy, is there may be an increased rate of local recurrence requiring further treatment. The evidence, however, suggests the absolute rates of local recurrence are very low in this selected patient group and are equivalent between partial breast and whole breast radiotherapy, at least up to five years.

The committee were also aware of the Royal College of Radiologists 2016 consensus statement on partial breast radiotherapy after breast-conserving surgery which recommended its use in women aged 50 and over with tumours that are less than or equal to 3 cm, N0, ER-positive, HER2-negative and grade 1 to 2.

Cost effectiveness and resource use

The committee considered the results of the cost-utility study (Shah 2013) identified in the literature review conducted for this topic. The analysis was thought to have demonstrated the potential cost-effectivenes 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 use of multi-catheter interstitial brachytherapy is not routine practice in the UK, although some centres may already undertake it. Therefore if centres decide to use this technique rather than external beam radiotherapy then there may be increased costs such as the cost of training and equipment aas well as increasing the planning time. However, when considering practice across the NHS, it was not thought that there would be a significant resource impact as many centres are still likely to choose to use external beam radiotherapy.

Other factors the committee took into account

The committee excluded those people with lobular carcinoma from the recommendation for partial breast radiotherapy due to the increased risk of multicentricity and therefore local recurrence in this group.

The committee were aware that NICE were in the process of developing separate guidance on the use of the intrabeam radiotherapy system in early breast cancer and so intrabeam radiotherapy was not considered in this review.

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

Introduction

Targeting clinically negative internal mammary nodes (IMN) with radiotherapy as part of the post-operative treatment of breast cancer is not commonly recommended in the UK. Notwithstanding the high rates of subclinical IMN involvement and a prior meta-analysis which demonstrated that regional node irradiation in conjunction with chest wall radiotherapy improved outcomes, there remains uncertainty about the benefits of this approach as isolated parasternal relapses are rare. Furthermore, until recently it has proven difficult to encompass the IMN using the available radiotherapy technologies whilst respecting safe dose limits to the heart and lungs.

The previous guideline CG80 (NICE 2009) recommended that radiotherapy to the IMN chain should not be offered after breast surgery. Recent randomised controlled trials (RCTs) and 1 large case controlled study have led to a reappraisal of this approach, and this review aims to revisit the potential indications for the inclusion of IMN in the radiation treatment volume

PICO table

See Table 11 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 11: Summary of the protocol (PICO table)

Population	Adults (18 or over) with invasive breast cancer but no distant metastases (M0) treated with breast conserving surgery or mastectomy (including modified radical mastectomy).
Intervention	Radiotherapy to internal mammary nodes (± other nodes)
Comparison	No internal mammary node radiotherapy (± other nodes)
Outcome	**Critical** • Locoregional recurrence rate • Disease-free survival • Treatment-related morbidity **Important** • Overall survival • HRQoL

HRQoL, health-related quality of lfie; M0, no distant metasases

For full details see review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

Six studies (n=10,981) were included in the review (Choi 2016; Hennequin 2013 ; Matzinger 2010; Poortmans 2015; Thorsen 2016; Whelan 2015), which report data from 5 trials: Danish Breast Cancer Group – Internal Mammary Node (DBCG-IMN) trial (k=1), European Organisation for Research and Treatment of Cancer (EORTC) trial 22922/10925 (k=2), Hennequin, Bossard 2013 (k=1), Korean Radiation Oncology Group (KROG) 08-06 trial (k=1), MA.20 trial (k=1).

The DBCG-IMN trial compared radiotherapy to the breast/chest wall, scar, and the supraclavicular, infraclavicular and axially lymph nodes with or without internal mammary (IM) lymph nodes, the EORTC trial 22922/10925 compared radiotherapy to the IM and medial supraclavicular (MS) lymph nodes with no radiation to the IM and MS lymph nodes, Hennequin 2013 compared radiotherapy to the chest wall, supraclavicular nodes, and apical axillary nodes (for pN+ cases) with or without radiotherapy to the IM lymph nodes, KROG-08-06 trial compared radiotherapy to the breast, IM and supraclavicular lymph nodes with radiotherapy to the breast and supraclavicular lymph nodes only, and MA.20 compared whole breast radiation with or without radiation to the IM, supraclavicular and axillary lymph nodes.

Only 2 studies (Poortmans 2015; Whelan 2015) reported data for critical outcomes by subgroups of interest: 0 lymph node metastases (k=2), 1-3 lymph node metastases (k=2), 4+ lymph node metastases (k=2), T stage 1 (k=1), T stage 2 (k=1), T stage 3 (k=1), medial tumour position (k=1), and lateral tumour position (k=1).

The clinical studies included in this evidence review are summarised in Table 12 and evidence from these are summarised in the clinical GRADE evidence profile below (Table 13). See also the study selection flow chart in appendix C, forest plots in appendix E, and study evidence tables in appendix D.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 12: Summary of included studies

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
Choi 2016	KROG 08-06	• Axillary node positive • No neoadjuvant systemic therapy • No previous history of cancer	• Intervention arm (IM RT+): Radiation once per day at a dose of 1.8–2 Gy, up to a total dose of 45–50.4 Gy. No strict guidelines on radiotherapy technique. Most common technique was partial wide tangent. • Control arm (IM RT-): Radiation once per day at a dose of 1.8–2 Gy, up to a total dose of 45–50.4 Gy. No strict guidelines on radiotherapy technique. Most common technique was standard tangent method.
Hennequin 2013	No trial name	• Aged <75 years	• Intervention arm (IM RT+): 50 Gy or equivalent. Ipsilateral parasternal area, including the internal

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
		• Stage I or II adenocarcinoma of the breast (tumour >1cm) • Undergoing modified radical mastectomy • Positive axillary nodes or medial/central tumour ± positive axillary nodes • 70% Karnofsky performance scale • No bilateral breast cancer, history of cancer, or severe comorbidity.	mammary chain, was treated using a combination of photons and electrons up to a total of 12.5 Gy, given in 5 fractions (2.5 Gy per fraction, 4 fractions per week) and 9-12 MeV electrons up to a total of 32.5 Gy, given in 13 fractions (2.5 Gy per fraction, 4 fractions per week) for a total treatment time of approximately 5 weeks. The lateral and superior edges of the IMN field were matched to the field irradiating the chest wall and the supraclavicular field. • Control arm (IM RT-): 50 Gy or equivalent. The internal border of the chest wall field was placed at the external border of a sham internal mammary node field and care was taken to avoid inclusion of the first intercostal spaces in the supraclavicular field.
Matzinger 2010	EORTC 22922/10925	• N0-N2 • Centrally or medially located tumours could be N- or N+. Externally located tumours had to be N+	• Intervention arm (IM RT+): Prescribed radiotherapy dose was 50 Gy in 25 fractions of 2 Gy - 26 Gy delivered with photons and 24 Gy delivered with electrons. One anterior field for the IM-MS radiation was recommended. • Control arm (IM RT-): no details reported.
Poortmans 2015	EORTC 22922/10925	• Centrally or medially located tumours could be N- or N+. Externally located tumours had to be N+	• Intervention arm (IM RT+): Regional nodal irradiation at a dose of 50 Gy in 25 fractions. No further information reported. • Control arm (IM RT-): No details reported.
Thorsen 2016	DBCG-IMN	• Node positive • <70 at age of operation • Excluded patients who experienced recurrence before radiotherapy, were unfit for standard radiotherapy, only had micrometastatic nodes, or had prior malignancy	• Intervention arm (IM RT+ [right sided cancers]): Radiotherapeutic dose to the breast/chest wall, scar, supraclavicular nodes, infraclavicular nodes, and axillary levels II to III was 48Gy in 24 fractions, administered in five fractions per week. The internal mammary nodes in intercostal spaces one to four were treated with anterior electron field or by inclusion in tangential photon fields. • Control arm: (IM RT- [left sided cancers]): Radiotherapeutic dose to the breast/chest wall, scar, supraclavicular nodes, infraclavicular nodes, and axillary levels II to III was 48Gy in 24 fractions, administered in five fractions per week.

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
Whelan 2015	MA.20	• Treated with breast conserving surgery and sentinel lymph node biopsy or axillary node dissection • Node positive or negative with high-risk features • Excluded if T stage 4, N2-3, serious non-malignant disease that would preclude radiotherapy, or had concurrent/previous malignancies, psychiatric or addictive disorders which precluded obtaining informed consent or adherence to protocol • Excluded if pregnant or lactating	• Intervention arm (IM RT+): The breast was treated with dose of 50Gy in 25 fractions. Radiation of the internal mammary nodes (50Gy in 25 fractions) was performed using a modified wide-tangent technique or separate internal mammary node field plus tangents. • Control arm (IM RT-): The breast was treated with dose of 50Gy in 25 fractions.

DBCG, Danish Breast Cancer Group; EORTC, European Organisation for Research and Treatment of Cancer; Gy, gray; IM, internal mammary; IMN, internal mammary nodes; KROG, Korean Radiation Oncology Group MeV, megaelectronvolt; MS, medial supraclavicular; RT, radiotherapy

Quality assessment of clinical studies included in the evidence review

The clinical evidence profile for this review is presented in Table 13. The majority of the evidence is moderate or low quality. This is primarily due to imprecision around the estimates due to a small number of events of interest and wide confidence intervals.

Table 13: Summary clinical evidence profile: Comparison 1. Radiotherapy to the internal mammary nodes versus no radiotherapy to the internal mammary nodes

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: IM RT-	Corresponding risk: IM RT+			
Overall survival (10 year follow-up)	8 yr OS 76%	8 yr OS 78% (77% to 80%)	HR 0.9 (0.83 to 0.97)	10259 (4 studies)	High
Treatment-related morbidity - acute radiation pneumonitis (within 3 to 6 months of completing radiotherapy)	11 per 1000	29 per 1000 (11 to 77)	RR 2.7 (1.03 to 7.08)	2542 (2 studies)	Moderate[1]
Disease-free survival - Whole sample (10 year follow-up)	10 yr DFS 67%	10 yr DFS 69% (67% to 71%)	HR 0.92 (0.85 to 1)	7170 (3 studies)	Moderate[2]
Disease-free survival - 0 positive lymph nodes (10 year follow-up)	10 yr DFS 73%	10 yr DFS 77% (73% to 80%)	HR 0.82 (0.69 to 0.98)	1955 (2 studies)	High
Disease-free survival - 1-3 positive lymph nodes (10 year follow-up)	10 yr DFS 73%	10 yr DFS 77% (74% to 80%)	HR 0.85 (0.74 to 0.98)	3283 (2 studies)	High
Disease-free survival - 4+ positive lymph nodes (10 year follow-up)	10 yr DFS 52%	10 yr DFS 56% (44% to 67%)	HR 0.89 (0.62 to 1.27)	596 (2 studies)	Moderate[1]
Disease-free survival - T stage: 1 (10 year follow-up)	10 yr DFS 74%	10 yr DFS 75% (72% to 78%)	HR 0.93 (0.8 to 1.09)	2408 (1 study)	High
Disease-free survival - T stage: 2 (10 year follow-up)	10 yr DFS 57%	10 yr DFS 63% (58% to 68%)	HR 0.83 (0.7 to 0.97)	1430 (1 study)	High

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: IM RT-	Corresponding risk: IM RT+			
Disease-free survival - T stage: 3 (10 year follow-up)	10 yr DFS 58%	10 yr DFS 61% (44% to 74%)	HR 0.9 (0.54 to 1.51)	141 (1 study)	Moderate[1]
Disease-free survival - Tumour position: medial (10 year follow-up)	10 yr DFS 75%	10 yr DFS 84% (74% to 90%)	HR 0.6 (0.35 to 1.04)	261 (1 study)	Moderate[1]
Disease-free survival - Tumour position: lateral (10 year follow-up)	10 yr DFS 79%	10 yr DFS 83% (79% to 87%)	HR 0.77 (0.59 to 1.01)	1142 (1 study)	Moderate[1]
Treatment-related morbidity - secondary cancer (potentially radiation-induced; 10 year follow-up)	110 per 1000	104 per 1000 (84 to 131)	RR 0.95 (0.77 to 1.19)	5686 (2 studies)	High
Locoregional recurrence (10 year follow-up)	10 yr free from LRR 92%	10 yr free from LRR 95% (93% to 97%)	HR 0.59 (0.39 to 0.89)	1832 (1 study)	Moderate[1]
Treatment-related morbidity - arm/shoulder function impairment (3 year follow-up)	4 per 1000	1 per 1000	RR 0.13 (0.02 to 1.01)	3866 (1 study)	Low[3]
Treatment-related morbidity – fatigue (3 month to 3 year follow-up)	66 per 1000	69 per 1000 (57 to 83)	RR 1.05 (0.87 to 1.26)	5686 (2 studies)	Moderate[4]
Treatment-related morbidity - Grade 2+ acute pain (site not specified; within 3 months of completing radiotherapy)	43 per 1000	60 per 1000 (40 to 88	RR 1.38 (0.92 to 2.05)	1820 (1 study)	Low[5]
Treatment-related morbidity - skin toxicity (3 month to 3 year follow-up)	215 per 1000	252 per 1000 (220 to 288)	RR 1.17 (1.02 to 1.34)	5686 (2 studies)	High
Treatment-related morbidity - lung toxicity (3 to 10 year follow-up)	13 per 1000	31 per 1000 (21 to 46)	RR 2.5 (1.7 to 3.67)	5686 (2 studies)	Moderate[1]
Treatment-related morbidity - cardiac toxicity (10 year follow-up)	35 per 1000	42 per 1000 (33 to 53)	RR 1.2 (0.95 to 1.52)	7020 (3 studies)	Low[5]
Treatment-related morbidity - Grade 2+ lymphoedema (10 year follow-up)	45 per 1000	84 per 1000 (58 to 121)	RR 1.85 (1.29 to 2.67)	1820 (1 study)	Moderate[1]
Treatment-related morbidity - Grade 3+ morbidity on SOMA-LENT scale (10 year follow-up)	23 per 1000	31 per 1000 (16 to 60)	RR 1.38 (0.72 to 2.65)	1334 (1 study)	Low[6]
Treatment-related morbidity - mastitis (3 year follow-up)	4 per 1000	3 per 1000 (1 to 9)	RR 0.87 (0.29 to 2.57)	3866 (1 study)	Moderate[8]
Treatment-related morbidity - breast infection (3 year follow-up)	2 per 1000	2 per 1000 (0 to 7)	RR 0.76 (0.17 to 3.38)	3866 (1 study)	Moderate[8]
Treatment-related morbidity - radionecrosis (3 year follow-up)	1 per 1000	1 per 1000 (0 to 6)	RR 0.51 (0.05 to 5.57)	3866 (1 study)	Moderate[8]
Treatment-related morbidity - osteonecrosis (3 year follow-up)	11 per 1000	14 per 1000 (8 to 25)	RR 1.24 (0.71 to 2.17)	3866 (1 study)	Low[6]
Treatment-related morbidity - oedema (3 year follow-up)	80 per 1000	79 per 1000 (63 to 97)	RR 0.99 (0.79 to 1.22)	3866 (1 study)	Moderate[7]
Treatment-related morbidity - breast/chest wall pain (3 year follow-up)	23 per 1000	18 per 1000 (12 to 28)	RR 0.79 (0.51 to 1.22)	3866 (1 study)	Low[3]
Treatment-related morbidity - retrosternal pain (3 year follow-up)	1 per 1000	1 per 1000 (0 to 11)	RR 2.02 (0.18 to 22.29)	3866 (1 study)	Moderate[8]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: IM RT-	Corresponding risk: IM RT+			
Treatment-related morbidity - dysphagia (3 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 9.1 (0.49 to 168.96)	3866 (1 study)	Moderate[8]

Rates of disease-free survival and locoregional recurrence in the control group correspond to the weighted average across included trials; rates of overall survival correspond to the trial with the shortest follow-up period (DBCG-IMN)
CI: Confidence interval; DFS: dsease-free survival; HR: hazard ratio; IM: internal mammary; OS: overall survival; RR: Risk ratio; RT: radiotherapy; SOMA-LENT: Subjective, Objective, Management, Analytic-Late Effects of Normal Tissues
[1] total events <300
[2] Significant heterogeneity (I2 = 73%) - not present in subsequent subgroup analysis
[3] total events <300 and 95% CI crosses both no effect (1) and minimally important difference based on GRADE default value (0.8)
[4] 95% CI crosses no effect (1) and minimally important difference based on GRADE default value (1.25)
[5] total events <300 and 95% CI crosses no effect (1) and minimally important difference based on GRADE default value (1.25)
[6] total events <300 and 95% CI crosses no effect (1) and minimally important differences based on GRADE default values (0.8 and 1.25)
[7] 95% CI crosses both no effect (1) and minimally important difference based on GRADE default value (0.8)
[8] total events<300; not downgraded based on 95% CI due to very small differences in absolute risk

See appendix F for full GRADE tables.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Evidence statements

Comparison 1. Radiotherapy to the internal mammary nodes versus no radiotherapy to the internal mammary nodes

Critical outcomes

Locoregional recurrence rate

- There is moderate quality evidence from 1 RCT (N=1832) that radiotherapy to the internal mammary nodes produces clinically meaningful reductions in locoregional recurrence following surgery for early invasive breast cancer compared with no radiotherapy to the internal mammary nodes at 10 year follow-up.

Disease-free survival

- There is moderate quality evidence from 3 RCTs (N=7170) that radiotherapy to the internal mammary nodes produces clinically meaningful increases in disease-free survival following surgery for early invasive breast cancer compared with no radiotherapy to the internal mammary nodes at 10 year follow-up.
- There is high quality evidence from 2 RCTs (N=1955) that radiotherapy to the internal mammary nodes produces clinically meaningful increases in disease-free survival following surgery for individuals with 0 positive lymph nodes compared with no radiotherapy to the internal mammary nodes at 10 year follow-up.
- There is high quality evidence from 2 RCTs (N=3283) that radiotherapy to the internal mammary nodes produces clinically meaningful increases in disease-free survival

following surgery for individuals with 1-3 positive lymph nodes compared with no radiotherapy to the internal mammary nodes at 10 year follow-up.

- There is moderate quality evidence from 2 RCTs (N=596) that there is no clinically important effect of radiotherapy to the internal mammary nodes on disease-free survival at 10 year follow-up for individuals with 4 or more positive lymph nodes.
- There is high quality evidence from 1 RCT (N=2408) that there is no clinically important effect of radiotherapy to the internal mammary nodes on disease-free survival at 10 year follow-up for individuals with T stage 1 invasive breast cancer.
- There is high quality evidence from 1 RCT (N=1430) that radiotherapy to the internal mammary nodes produces clinically significant increases in disease-free survival following surgery for individuals with T stage 2 invasive breast cancer compared with no radiotherapy to the internal mammary nodes at 10 year follow-up.
- There is low quality evidence from 1 RCT (N=141) that there is no clinically important effect of radiotherapy to the internal mammary nodes on disease-free survival at 10 year follow-up for individuals with T stage 3 invasive breast cancer.
- There is low quality evidence from 1 RCT (N=261) that there is no clinically important effect of radiotherapy to the internal mammary nodes on disease-free survival at 10 year follow-up for individuals with medially located invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=1142) that there is no clinically important effect of radiotherapy to the internal mammary nodes on disease-free survival at 10 year follow-up for individuals with laterally located invasive breast cancer.

Treatment-related morbidity

- There is moderate quality evidence from 2 RCTs (N=2542) that radiotherapy to the internal mammary nodes produces clinically meaningful increases in acute radiation pneumonitis (within 3 to 6 months of completing radiotherapy) for individuals with invasive breast cancer compared with no radiotherapy to the internal mammary nodes. However, this was not statistically significant.
- There is high quality evidence from 2 RCTs (N=5686) that there is no effect of radiotherapy to the internal mammary nodes on secondary cancer (potentially radiation-induced) at 10 year follow-up for individuals with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=3866) that radiotherapy to the internal mammary nodes produces clinically meaningful reductions in arm/shoulder function impairment at 3 year follow-up for individuals with invasive breast cancer compared with no radiotherapy to the internal mammary nodes. However, this was not statistically significant.
- There is moderate quality evidence from 2 RCTs (N=5686) that there is no effect of radiotherapy to the internal mammary nodes on fatigue at 3 month to 3 year follow-up for individuals with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=1820) that radiotherapy to the internal mammary nodes produces clinically meaningful increases in grade 2+ acute pain (site not specified; within 3 months of completing radiotherapy) for individuals with invasive breast cancer compared with no radiotherapy to the internal mammary nodes. However, this was not statistically significant.
- There is high quality evidence from 2 RCTs (N=5686) that there is no effect of radiotherapy to the internal mammary nodes on skin toxicity at 3 month to 3 year follow-up for individuals with invasive breast cancer.
- There is moderate quality evidence from 2 RCTs (N=5686) that radiotherapy to the internal mammary nodes produces clinically meaningful increases in lung toxicity at 3 to 10 year follow-up for individuals with invasive breast cancer compared with no radiotherapy to the internal mammary nodes.

- There is low quality evidence from 3 RCTs (N=7020) that there is no effect of radiotherapy to the internal mammary nodes on cardiac toxicity at 10 year follow-up for individuals with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=1820) that radiotherapy to the internal mammary nodes produces clinically meaningful increases in grade 2+ lymphoedema at 10 year follow-up for individuals with invasive breast cancer compared with no radiotherapy to the internal mammary nodes.
- There is low quality evidence from 1 RCT (N=1334) that radiotherapy to the internal mammary nodes produces clinically meaningful increases in grade 3+ morbidity as measured by the SOMA-LENT scale at 10 year follow-up for individuals with invasive breast cancer compared with no radiotherapy to the internal mammary nodes. However, this was not statistically significant.
- There is moderate quality evidence from 1 RCT (N=3866) that there is no effect of radiotherapy to the internal mammary nodes on mastitis at 3 year follow-up for individuals with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=3866) that radiotherapy to the internal mammary nodes produces clinically meaningful reductions in breast infection at 3 year follow-up for individuals with invasive breast cancer compared with no radiotherapy to the internal mammary nodes. However, this was not statistically significant.
- There is moderate quality evidence from 1 RCT (N=3866) that radiotherapy to the internal mammary nodes produces clinically meaningful reductions in radionecrosis at 3 year follow-up for individuals with invasive breast cancer compared with no radiotherapy to the internal mammary nodes. However, this was not statistically significant.
- There is low quality evidence from 1 RCT (N=3866) that there is no effect of radiotherapy to the internal mammary nodes on osteonecrosis at 3 year follow-up for individuals with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=3866) that there is no effect of radiotherapy to the internal mammary nodes on oedema at 3 year follow-up for individuals with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=3866) that radiotherapy to the internal mammary nodes produces clinically meaningful reductions in breast/chest wall pain at 3 year follow-up for individuals with invasive breast cancer compared with no radiotherapy to the internal mammary nodes. However, this was not statistically significant.
- There is moderate quality evidence from 1 RCT (N=3866) that radiotherapy to the internal mammary nodes produces clinically meaningful increases in retrosternal pain at 3 year follow-up for individuals with invasive breast cancer compared with no radiotherapy to the internal mammary nodes. However, this was not statistically significant.
- There is moderate quality evidence from 1 RCT (N=3866) that radiotherapy to the internal mammary nodes produces clinically meaningful increases in dysphagia at 3 year follow-up for individuals with invasive breast cancer compared with no radiotherapy to the internal mammary nodes. However, this was not statistically significant.

Important outcomes

Overall survival

- There is high quality evidence from 4 RCTs (N=10,259) that radiotherapy to the internal mammary nodes produces clinically meaningful increases in overall survival following surgery for individuals with invasive breast cancer compared with no radiotherapy to the internal mammary nodes at 10 year follow-up.

Health-related quality of life

- No evidence was found for this outcome.

Recommendations

H8. Consider including the internal mammary chain within the nodal radiotherapy target for people with node-positive (macrometastases) invasive breast cancer.

H9. Use a radiotherapy technique that minimises the dose to the lung and heart.

Rationale and impact

Why the committee made the recommendations

There was good evidence that radiotherapy to the internal mammary nodes reduced locoregional recurrence and improved survival. However, the committee took into account the potential for lung and heart toxicity, so recommended using a radiotherapy technique that minimises this risk.

Impact of the recommendations on practice

This recommendation is likely to require a change in practice for many centres. There will be some impact on resources in order to implement this recommendation because additional training will be needed and local protocols will need developing. However, the long-term impact on resources will be minimal: some additional planning time will be needed but there is no impact on the length or number of radiotherapy sessions.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee prioritised locoregional recurrence rate, disease-free survival and treatment-related morbidity as critical outcomes. Locoregional recurrence and disease-free survival were prioritised ahead of overall survival as the time taken for overall survival events to occur means there is less data available and it is less commonly examined by trials. Overall survival and health-related quality of life were selected as important outcomes.

There was no evidence available for health-related quality of life.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE. The evidence for locoregional recurrence was moderate quality. For disease-free survival the evidence was moderate quality for the sample as a whole, but the data for different subgroups ranged from low to high quality (with most of it being either moderate or high). The evidence for treatment related morbidity ranged from low to high quality with most of it being either low or moderate quality. Overall survival evidence was high quality.

It was noted that there were high rates of performance bias due to no blinding in studies. However it was agreed that this was unlikely to have a significant impact on the results due to the objective nature of the outcomes for which there was evidence available. It was also noted that there were high rates of imprecision for locoregional recurrence and treatment-related morbidities due to small number of events of interest and wide confidence intervals.

The committee noted that only two studies (Poortmans 2015; Whelan 2015) reported data for critical outcomes by the subgroups of interest. There was also no subgroup data based on laterality which could impact on toxicity.

The committee also noted that most of the studies had used internal mammary chain radiotherapy in conjunction with radiotherapy to the supraclavicular fossa. As a result it was difficult to determine the relative benefit of treatment solely to the internal mammary chain from these studies. Therefore the committee based their recommendations on the evidence from the one study that only irradiated the internal mammary nodes (rather than also irradiating the supraclavicular fossa). As this study reported overall survival, which was an important, not a critical outcome, the committee made a weaker recommendation.

Only one study included node negative patients and this gave radiotherapy to both trial arms. Therefore the committee agreed not to make any recommendations based on these data or for this group of people. The committee also noted the data on disease free survival for different T-stage had very wide confidence intervals and agreed not to make any recommendations based on this.

Benefits and harms

The evidence showed clinically meaningful reductions in locoregional recurrence and clinically meaningful increases in disease-free survival and overall survival with radiotherapy to the internal mammary nodes. The evidence also showed clinically meaningful increases in disease free survival for people with 0 and 1-3 positive lymph nodes. Whilst no clinically meaningful effect was found on this outcome for people with 4 or more positive nodes, the committee noted that the sample size was small and the magnitude of the effect was similar. They therefore agreed to recommend radiotherapy to the internal mammary chain for all node positive patients.

The committee noted that the evidence showed there was clinically meaningful increases in lung toxicity associated with radiotherapy to the internal mammary nodes. Therefore, based on their knowledge and experience, they recommended that a radiotherapy technique should be used that minimises the dose to the lung. Although the evidence review here did not demonstrate increased cardiac toxicity the committee were aware that radiotherapy to avoid cardiac toxicity was a separate question and that a heart-sparing technique should be used.

The committee noted that the potential benefits of giving radiotherapy to the internal mammary chain were likely to be reductions in locoregional recurrence and improvements in overall survival and disease-free survival. The potential harms would be increased treatment-related morbidity, but the committee noted that the evidence had not shown a clinically meaningful effect for anything except lung toxicity and grade 2+ lymphoedema. For lung toxicity a recommendation had been made to minimise the potential harm, but the risk of lymphoedema could not, unfortunately, be minimised.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee carefully considered the economic implications in this topic area as they were aware that including the internal mammary chain in the radiotherapy field may increase costs as it would increase planning time. It should be noted however that these potential cost increases cannot be captured when employing standard costing methodology for radiotherapy using NHS reference costs. This reflects the manner in which radiotherapy costs are estimated in NHS Reference costs whereby radiotherapy planning and delivery costs are stratified according to the type of radiotherapy delivered (and this category would not change when including the internal mammary chain). There is also no change in the overall dosage or number of fractions when including the internal mammary chain and so again there is no change in costs according to NHS Reference cost methodology.

While it is not possible to estimate the cost impact, the committee agreed that any increased cost would be minor as including the internal mammary chain does not impact delivery time

or the number of sessions required. Further, any expenditure was considered to be worthwhile because of a decrease in locoregional recurrence and improved disease-free survival.

Other factors the committee took into account

The committee discussed the fact that 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. There will be an increase to both the planning, dosimetry and treatment times to deliver this, and this will need to be done on a centre basis to ensure tolerance doses can be achieved, with respect to each centres specific equipment, set-up and imaging protocols.

With regard to nodal voluming, current guidelines recommend that if nodal volumes are to be treated, then these sites should be volumed to assist in field placement. If looking purely at the time it takes to volume the IMC, then the estimated additional time is approximately an extra 30 minutes per patient. Delineating the supraclavicular fossa (SCF) target volume may add a further 20-30 minutes. A number of patients may also require axillary radiotherapy as a treatment alternative to surgical clearance and this will have further voluming time increases of about 30 minutes.

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Appendices

Appendix A – Review protocols

Review protocol for 8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?

Field (based on PRISMA-P)	Content
Actual review question	What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?
Type of review question	Intervention review
Objective of the review	The objective of this review is to determine which heart-sparing breast radiotherapy techniques are effective without compromising the treatment of the whole breast volume. Recommendations will aim to cover which techniques should be offered to spare the heart during radiotherapy.
Eligibility criteria – population/disease/condition/issue/domain	Adults (18 or over) with invasive breast cancer (M0) and/or DCIS receiving whole breast radiotherapy
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Heart sparing techniques: • Deep inspiration breath-hold • Prone radiotherapy • Shielding • Proton beam radiotherapy
Eligibility criteria – comparator(s)/control or reference (gold) standard	• Heart sparing techniques • No heart sparing technique
Outcomes and prioritisation	Critical (up to 3 outcomes) • Mean heart dose (MID: GRADE default values) • Target coverage (MID: GRADE default values) Important but not critical • Local recurrence rate (MID: any statistically significant difference)

Field (based on PRISMA-P)	Content
	• Treatment-related morbidity (e.g., pulmonary toxicity [MID: any statistically significant difference], lung cancer [MID: any statistically significant difference]) • Treatment-related mortality (MID: any statistically significant difference) Immediate outcomes will be prioritised for mean heart dose and target coverage.
Eligibility criteria – study design	• Systematic reviews/meta-analyses of RCTs • RCTs • Controlled, non-randomised studies • Prospective cohort studies (minimum no. of participants 30)
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	N/A
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 be performed on at least 10% of records and where possible all records due to the inclusion of controlled non-RCTs and prospective cohort studies; 90% agreement is required and any discussions will be resolved through discussion and consultation with senior staff where necessary.
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 2008 onwards as it is an update from the previous version of this guideline. A general exclusions filter and methodological filters (RCT and systematic review) will also be used as it is an intervention question.
Identify if an update	N/A

Field (based on PRISMA-P)	Content
Author contacts	For details please see the guideline in development web site.
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.
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

DCIS, Ductal carcinoma in-situ; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MID, minimally important difference; N/A, not applicable; NGA, National Guideline Alliance; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; RCT, randomised controlled trial

Review protocol for 8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?

Field (based on PRISMA-P)	Content
Review question	Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?
Type of review question	Intervention review
Objective of the review	This review of evidence seeks to establish whether there is a subgroup of women with early breast cancer who are at such low risk of local recurrence after breast conserving surgery that the benefits of radiotherapy are unlikely to outweigh the risks. Recommendations will aim to cover groups of women where the option of omission of radiotherapy should be discussed as an alternative to whole breast radiotherapy.
Eligibility criteria – population/disease/condition/issue/domain	Women (18 or over) with invasive breast cancer (M0) who have undergone breast conserving surgery
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	No breast radiotherapy
Eligibility criteria – comparator(s)/control or reference (gold) standard	Whole breast radiotherapy
Outcomes and prioritisation	Critical (up to 3 outcomes) • Local recurrence rate (MID: any statistically significant difference) • Treatment-related morbidity (e.g., pulmonary toxicity [MID: GRADE default values], lung cancer [MID: any statistically significant difference]) any • HRQoL (MID: values from the literature where available, otherwise GRADE default values) Important but not critical • Overall survival (MID: any statistically significant difference) • Disease-free survival (MID: any statistically significant difference) • Treatment-related mortality (MID: any statistically significant difference) 10 year follow-up periods will be prioritised when multiple time points are reported. MID values from the literature: • HRQoL:

Field (based on PRISMA-P)	Content
	• 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
Eligibility criteria – study design	Systematic reviews/meta-analyses of RCTs RCTs
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: T Stage N stage Age (<65, 65 and over) Adjuvant systemic therapy (whether or not received therapy) Grade Margins (+/- note definitions in the studies) ER status HER-2 status
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 review question as it is a straightforward intervention review limited to RCTs.
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.

Field (based on PRISMA-P)	Content
	Searches will be undertaken from 2008 onwards as it is an update from the previous version of this guideline. A general exclusions filter and methodological filters (RCT and systematic review) will also be used as it is an intervention question.
Identify if an update	Previous question: What are the indications for radiotherapy after breast conserving surgery? Date of search: 28/02/2008 Relevant recommendation(s) from previous guideline: 1) Patients with early invasive breast cancer who have had breast conserving surgery with clear margins should have breast radiotherapy.
Author contacts	For details please see the guideline in development web site.
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

Field (based on PRISMA-P)	Content
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.
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;ER, oestrogen receptor; 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; HER2, human epidermal growth factor receptor 2; 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

Review protocol for 8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?

Field (based on PRISMA-P)	Content
Review question	Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?
Type of review question	Intervention review
Objective of the review	This review of evidence seeks to establish whether there is a subgroup of women with early breast cancer for whom partial breast radiotherapy is an equally effective treatment strategy, with less potential side effects, than whole breast radiotherapy. Recommendations will aim to cover which group of women should be offered partial breast radiotherapy.
Eligibility criteria – population/disease/condition/issue/domain	Women (18 or over) with HER2 - invasive breast cancer (M0) who have undergone breast conserving surgery (with clear margins) and are recommended radiotherapy
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Partial breast radiotherapy: Brachytherapy Intrabeam RT (removed as it is the subject of a separate NICE Technology Appraisal) 3D-Conformal RT Intensity modulated RT
Eligibility criteria – comparator(s)/control or reference (gold) standard	Whole breast radiotherapy
Outcomes and prioritisation	Critical (up to 3 outcomes) • Local recurrence rate (MID: any statistically significant difference) • Treatment-related morbidity(e.g., pulmonary toxicity [MID: any statistically significant difference], lung cancer [MID: any statistically significant difference]) • HRQoL(MID: values from the literature where available; GRADE default value for FACT-B endocrine scale) Important but not critical • Overall survival (MID: any statistically significant difference) • Disease-free survival (MID: any statistically significant difference) • Treatment-related mortality (MID: any statistically significant difference)

Field (based on PRISMA-P)	Content
	• Unplanned additional radiotherapy (Intrabeam only) 5 year follow-up periods will be prioritised when multiple time points are reported. MID values from the literature: HRQoL: • 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
Eligibility criteria – study design	• Systematic reviews/meta-analyses of RCTs • RCTs
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): • T Stage • N stage • Age (<50, >50, >60, >70) • Grade • ER status
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 not be performed for this review question as it is a straightforward intervention review.
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

Field (based on PRISMA-P)	Content
	OVID. Additionally Web of Science may be searched and consideration will be given to subject-specific databases and used as appropriate. The search will be undertaken from 1996 to capture studies using modern radiotherapy techniques. A general exclusions filter and methodological filters (RCT and systematic review) will also be used as it is an intervention question.
Identify if an update	N/A
Author contacts	For details please see the guideline in development web site.
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.

Field (based on PRISMA-P)	Content
	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.
Sources of funding/support	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
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; ER, oestrogen recptor; 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; HER2, human epidermal growth factor receptor 2; 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

1 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

Field (based on PRISMA-P)	Content
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.

Field (based on PRISMA-P)	Content
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

Appendix B – Literature search strategies

Literature search strategies for 8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?

Database: Medline & Embase (Multifile)

Last searched on **Embase** 1974 to 2017 July 10**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present.

Date of last search: 11 July 2017

#	Searches
1	exp breast cancer/ use oemezd
2	exp breast carcinoma/ use oemezd
3	exp medullary carcinoma/ use oemezd
4	exp intraductal carcinoma/ use oemezd
5	exp breast tumor/ use oemezd
6	exp Breast Neoplasms/ use prmz
7	exp "Neoplasms, Ductal, Lobular, and Medullary"/ use prmz
8	Carcinoma, Intraductal, Noninfiltrating/ use prmz
9	Carcinoma, Lobular/ use prmz
10	Carcinoma, Medullary/ use prmz
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp breast/ use oemezd
13	exp Breast/ use prmz
14	breast.tw.
15	12 or 13 or 14
16	(breast adj milk).tw.
17	(breast adj tender$).tw.
18	16 or 17
19	15 not 18
20	exp neoplasm/ use oemezd
21	exp Neoplasms/ use prmz
22	20 or 21
23	19 and 22
24	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
25	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
26	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz

#	Searches
27	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
28	exp Paget nipple disease/ use oemezd
29	Paget's Disease, Mammary/ use prmz
30	(paget$ and (breast$ or mammary or nipple$)).tw.
31	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	11 or 31
33	exp Radiotherapy/ use prmz
34	exp radiotherapy/ use oemezd
35	radiotherapy.fs.
36	(radiotherap$ or radiat$ or irradiat$ or brachytherap$ or tomotherap$).mp.
37	(fractionat$ or hyperfractionat$ or hypofractionat$).mp.
38	33 or 34 or 35 or 36 or 37
39	(deep adj3 (inspirat$ or inhal$) adj3 breath$).mp.
40	DIBH.mp.
41	(breath$ adj hold$).mp.
42	(deep adj (inspirat$ or inhal$)).mp.
43	((inspirat$ or inhal$) adj breath$).mp.
44	((respirat$ or inspirat$) adj3 (gated or gating)).mp.
45	((respirat$ or inspirat$) adj3 (manoeuv$ or motion$ or synchron$)).mp.
46	((free or active) adj3 breath$).mp.
47	Breath-Holding/ use prmz
48	breath-holding/ use oemezd
49	*Respiration/ use prmz
50	*breathing/ use oemezd
51	(prone adj4 (position$ or radiotherap$ or radiation$ or irradiation$ or planning or set-up or setup)).mp.
52	Prone Position/ use prmz
53	prone position/ use oemezd
54	shielding.mp.
55	Radiation Protection/ use prmz
56	radiation shield/ use oemezd
57	((proton$ or photon$) adj3 (therap$ or treatment$ or radiotherap$ or radiation$ or irradiation$ or RT or beam$ or field$)).tw.
58	Proton Therapy/ use prmz
59	proton therapy/ use oemezd
60	39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59
61	32 and 38 and 60
62	Heart/ use prmz
63	heart/ use oemezd
64	((heart$ or cardiac$ or cardio$) adj3 (morbidity or mortality or toxicity or event$ or effect$ or sequelae$)).mp.
65	62 or 63 or 64
66	32 and 38 and 65

#	Searches
67	Heart/re use prmz
68	((heart$ or cardiac$) adj3 (sparing or protect$ or avoid$ or displac$ or dose)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, ui, sy]
69	67 or 68
70	32 and 38 and 69
71	61 or 66 or 70
72	(left adj side$).ti.
73	32 and 38 and 72
74	71 or 73
75	limit 74 to yr="1996 -Current"
76	remove duplicates from 75 [Then general exclusions filter applied]

Database: Cochrane Library via Wiley Online

Date of last search: 11 July 2017

#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [Carcinoma, Medullary] this term only
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Breast] explode all trees
#8	breast:ti,ab,kw (Word variations have been searched)
#9	#7 or #8
#10	(breast next milk):ti,ab,kw (Word variations have been searched)
#11	(breast next tender*):ti,ab,kw (Word variations have been searched)
#12	#10 or #11
#13	#9 not #12
#14	MeSH descriptor: [Neoplasms] explode all trees
#15	#13 and #14
#16	(breast* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#18	MeSH descriptor: [Paget's Disease, Mammary] this term only
#19	(paget* and (breast* or mammary or nipple*)):ti,ab,kw (Word variations have been searched)
#20	#15 or #16 or #17 or #18 or #19
#21	#6 or #20
#22	(deep near/3 (inspirat* or inhal*) near/3 breath*):ti,ab,kw (Word variations have been searched)
#23	DIBH:ti,ab,kw (Word variations have been searched)
#24	(breath* next hold*):ti,ab,kw (Word variations have been searched)
#25	(deep next (inspirat* or inhal*)):ti,ab,kw (Word variations have been searched)

#	Searches
#26	((inspirat* or inhal*) next breath*):ti,ab,kw (Word variations have been searched)
#27	((respirat* or inspirat*) near/3 (gated or gating or manoeuv* or motion* or synchron*)):ti,ab,kw (Word variations have been searched)
#28	((free or active) near/3 breath*):ti,ab,kw (Word variations have been searched)
#29	MeSH descriptor: [Breath-Holding] explode all trees
#30	MeSH descriptor: [Respiration] this term only
#31	(prone near/4 (position* or radiotherap* or radiation* or irradiation* or planning or set-up or setup)):ti,ab,kw (Word variations have been searched)
#32	MeSH descriptor: [Prone Position] explode all trees
#33	shielding:ti,ab,kw (Word variations have been searched)
#34	MeSH descriptor: [Radiation Protection] explode all trees
#35	((proton* or photon*) near/3 (therap* or treatment* or radiotherap* or radiation* or irradiation* or RT or beam* or field*)):ti,ab,kw (Word variations have been searched)
#36	MeSH descriptor: [Proton Therapy] explode all trees
#37	#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36
#38	#21 and #37
#39	MeSH descriptor: [Radiotherapy] explode all trees
#40	(radiotherap* or radiat* or irradiat* or brachytherap* or tomotherap* or fractionat* or hyperfractionat* or hypofractionat*):ti,ab,kw (Word variations have been searched)
#41	#39 or #40
#42	MeSH descriptor: [Heart] explode all trees
#43	((heart* or cardiac* or cardio*) near/3 (morbidity or mortality or toxicity or event* or effect* or sequelae*)):ti,ab,kw (Word variations have been searched)
#44	#42 or #43
#45	#21 and #41 and #44
#46	MeSH descriptor: [Heart] explode all trees and with qualifier(s): [Radiation effects - RE]
#47	((heart* or cardiac*) near/3 (sparing or protect* or avoid* or displac* or dose)):ti,ab,kw (Word variations have been searched)
#48	#46 or #47
#49	#21 and #48
#50	#38 or #45 or #49
#51	(left next side*):ti,ab,kw (Word variations have been searched)
#52	#21 and #41 and #51
#53	#50 or #52 Publication Year from 1996 to 2017

Literature search strategies for 8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?

Database: Medline

Database: **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present.**

Date of last search: 18 November 2016

#	Searches
1	exp Breast Neoplasms/
2	exp "Neoplasms, Ductal, Lobular, and Medullary"/
3	Carcinoma, Intraductal, Noninfiltrating/
4	Carcinoma, Lobular/
5	Carcinoma, Medullary/
6	1 or 2 or 3 or 4 or 5
7	exp Breast/
8	breast.tw.
9	7 or 8
10	(breast adj milk).tw.
11	(breast adj tender$).tw.
12	10 or 11
13	9 not 12
14	exp Neoplasms/
15	13 and 14
16	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp.
17	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp.
18	Paget's Disease, Mammary/
19	(paget$ and (breast$ or mammary or nipple$)).tw.
20	15 or 16 or 17 or 18 or 19
21	6 or 20
22	Mastectomy, Segmental/
23	(segmentectom$ or post?segmentectom$).tw.
24	(lumpectom$ or post?lumpectom$).tw.
25	(quadrectom$ or post?quadrectom$).tw.
26	((local or limited) adj2 (excision or resection)).tw.
27	((partial or segment$) adj2 (mammectom$ or mastectomy$)).tw.
28	(breast adj conserv$).mp.
29	breast?conserv$.mp.
30	(conserv$ adj2 (surgery or therapy)).tw.
31	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	exp Radiotherapy/
33	radiotherapy.fs.

#	Searches
34	(radiotherap$ or radiat$ or irradiat$ or brachytherap$ or tomotherap$).mp.
35	(fractionat$ or hyperfractionat$ or hypofractionat$).mp.
36	32 or 33 or 34 or 35
37	21 and 31 and 36
38	limit 37 to yr="2008 -Current"
39	Limit 38 to RCTs and SRs, and general exclusions filter applied

Database: Embase

Database: **Embase Classic+Embase** 1947 to 2016 Week 45.

Date of last search: 18 November 2016

#	Searches
1	exp breast cancer/
2	exp breast carcinoma/
3	exp medullary carcinoma/
4	exp intraductal carcinoma/
5	exp breast tumor/
6	1 or 2 or 3 or 4 or 5
7	exp breast/
8	breast.tw.
9	7 or 8
10	(breast adj milk).tw.
11	(breast adj tender$).tw.
12	10 or 11
13	9 not 12
14	exp neoplasm/
15	13 and 14
16	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw.
17	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw.
18	exp Paget nipple disease/
19	(paget$ and (breast$ or mammary or nipple$)).tw.
20	15 or 16 or 17 or 18 or 19
21	6 or 20
22	partial mastectomy/
23	segmental mastectomy/
24	(segmentectom$ or post?segmentectom$).tw.
25	(lumpectom$ or post?lumpectom$).tw.
26	(quadrectom$ or post?quadrectom$).tw.
27	((local or limited) adj2 (excision or resection)).tw.
28	((partial or segment$) adj2 (mammectom$ or mastectomy$)).tw.
29	(breast adj conserv$).mp.

#	Searches
30	breast?conserv$.mp.
31	(conserv$ adj2 (surgery or therapy)).tw.
32	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33	exp radiotherapy/
34	radiotherapy.fs.
35	(radiotherap$ or radiat$ or irradiat$ or brachytherap$ or tomotherap$).mp.
36	(fractionat$ or hyperfractionat$ or hypofractionat$).mp.
37	33 or 34 or 35 or 36
38	21 and 32 and 37
39	limit 38 to yr="2008 -Current"
40	Limit 38 to RCTs and SRs, and general exclusions filter applied

Database: Cochrane Library via Wiley Online

Date of last search: 18 November 2016

#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [Carcinoma, Medullary] this term only
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Breast] explode all trees
#8	breast:ti,ab,kw (Word variations have been searched)
#9	#7 or #8
#10	(breast next milk):ti,ab,kw (Word variations have been searched)
#11	(breast next tender*):ti,ab,kw (Word variations have been searched)
#12	#10 or #11
#13	#9 not #12
#14	MeSH descriptor: [Neoplasms] explode all trees
#15	#13 and #14
#16	(breast* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#18	MeSH descriptor: [Paget's Disease, Mammary] this term only
#19	(paget* and (breast* or mammary or nipple*)):ti,ab,kw (Word variations have been searched)
#20	#15 or #16 or #17 or #18 or #19
#21	#6 or #20
#22	MeSH descriptor: [Mastectomy, Segmental] this term only
#23	(segmentectom* or post segmentectom* or post-segmentectom* or postsegmentectom*):ti,ab,kw (Word variations have been searched)
#24	(lumpectom* or post lumpectom* or post-lumpectom* or postlumpectom*):ti,ab,kw (Word variations have been searched)

#	Searches
#25	(quadrectom* or post quadrectom* or post-quadrectom* or postquadrectom*):ti,ab,kw (Word variations have been searched)
#26	((local or limited) near/2 (excision or resection)):ti,ab,kw (Word variations have been searched)
#27	((partial or segment*) near/2 (mammectom* or mastectomy*)):ti,ab,kw (Word variations have been searched)
#28	(breast next conserv*):ti,ab,kw (Word variations have been searched)
#29	(conserv* near/2 (surgery or therapy)):ti,ab,kw (Word variations have been searched)
#30	#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
#31	MeSH descriptor: [Radiotherapy] explode all trees
#32	(radiotherap* or radiat* or irradiat* or brachytherap* or tomotherap*):ti,ab,kw (Word variations have been searched)
#33	(fractionat* or hyperfractionat* or hypofractionat*):ti,ab,kw (Word variations have been searched)
#34	#31 or #32 or #33
#35	#21 and #30 and #34 Publication Year from 2008 to 2016

Literature search strategies for 8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?

Database: Medline & Embase (Multifile)

Database: Last searched on **Embase** 1974 to 2017 August 03, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present

Date of last search: 4 August 2017

#	Searches
1	exp breast cancer/ use oemezd
2	exp breast carcinoma/ use oemezd
3	exp medullary carcinoma/ use oemezd
4	exp intraductal carcinoma/ use oemezd
5	exp breast tumor/ use oemezd
6	exp Breast Neoplasms/ use prmz
7	exp "Neoplasms, Ductal, Lobular, and Medullary"/ use prmz
8	Carcinoma, Intraductal, Noninfiltrating/ use prmz
9	Carcinoma, Lobular/ use prmz
10	Carcinoma, Medullary/ use prmz
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp breast/ use oemezd
13	exp Breast/ use prmz
14	breast.tw.
15	12 or 13 or 14
16	(breast adj milk).tw.
17	(breast adj tender$).tw.
18	16 or 17
19	15 not 18
20	exp neoplasm/ use oemezd
21	exp Neoplasms/ use prmz
22	20 or 21
23	19 and 22
24	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
25	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
26	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
27	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
28	exp Paget nipple disease/ use oemezd
29	Paget's Disease, Mammary/ use prmz

#	Searches
30	(paget$ and (breast$ or mammary or nipple$)).tw.
31	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	11 or 31
33	Brachytherapy/ use prmz
34	*brachytherapy/ use oemezd
35	Radiotherapy, Conformal/ use prmz
36	conformal radiotherapy/ use oemezd
37	Radiotherapy, Intensity-Modulated/ use prmz
38	*intensity modulated radiation therapy/ use oemezd
39	((partial$ or whole$) adj breast$).tw.
40	((accelerat$ or target$) adj3 (radiat$ or irradiat$ or radiotherap$ or radiosurg$ or brachytherap$)).tw.
41	(APBI$ or PBI$ or WBI$).tw.
42	((intraoperativ$ or intra-operativ$) adj3 (radiat$ or irradiat$ or radiotherap$ or radiosurg$ or brachytherap$)).tw.
43	IORT$.tw.
44	mammosite.tw.
45	brachytherap$.tw.
46	(intensit$ adj modulat$).tw.
47	IMRT$.tw.
48	("3D conformal" or "3-D conformal").tw.
49	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50	32 and 49
51	limit 50 to yr="1996 -Current"
52	remove duplicates from 51
53	Limit 52 to RCTs and SRs, and general exclusions filter applied

Database: Cochrane Library via Wiley Online

Date of last search: 4 August 2017

#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [Carcinoma, Medullary] this term only
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Breast] explode all trees
#8	breast:ti,ab,kw (Word variations have been searched)
#9	#7 or #8
#10	(breast next milk):ti,ab,kw (Word variations have been searched)
#11	(breast next tender*):ti,ab,kw (Word variations have been searched)
#12	#10 or #11
#13	#9 not #12
#14	MeSH descriptor: [Neoplasms] explode all trees

#	Searches
#15	#13 and #14
#16	(breast* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#18	MeSH descriptor: [Paget's Disease, Mammary] this term only
#19	(paget* and (breast* or mammary or nipple*)):ti,ab,kw (Word variations have been searched)
#20	#15 or #16 or #17 or #18 or #19
#21	#6 or #20
#22	MeSH descriptor: [Brachytherapy] explode all trees
#23	MeSH descriptor: [Radiotherapy, Conformal] explode all trees
#24	MeSH descriptor: [Radiotherapy, Intensity-Modulated] explode all trees
#25	((partial* or whole*) next breast*):ti,ab,kw (Word variations have been searched)
#26	((accelerat* or target*) near/3 (radiat* or irradiat* or radiotherap* or radiosurg* or brachytherap*)):ti,ab,kw (Word variations have been searched)
#27	(APBI* or PBI* or WBI*):ti,ab,kw (Word variations have been searched)
#28	((intraoperativ* or intra-operativ*) near/3 (radiat* or irradiat* or radiotherap* or radiosurg* or brachytherap*)):ti,ab,kw (Word variations have been searched)
#29	IORT*:ti,ab,kw (Word variations have been searched)
#30	mammosite:ti,ab,kw (Word variations have been searched)
#31	brachytherap*:ti,ab,kw (Word variations have been searched)
#32	(intensit* next modulat*):ti,ab,kw (Word variations have been searched)
#33	IMRT$*:ti,ab,kw (Word variations have been searched)
#34	((3D* or 3-D*) next conformal):ti,ab,kw (Word variations have been searched)
#35	#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34
#36	#21 and #35

Literature search strategies for 8.4 What are the indications for radiotherapy to internal mammary nodes?

Database: Medline

Last searched on **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present**.**

Date of last search: 5 January 2017

#	Searches
1	exp Breast Neoplasms/
2	exp "Neoplasms, Ductal, Lobular, and Medullary"/
3	Carcinoma, Intraductal, Noninfiltrating/
4	Carcinoma, Lobular/
5	Carcinoma, Medullary/
6	1 or 2 or 3 or 4 or 5
7	exp Breast/
8	breast.tw.
9	7 or 8
10	(breast adj milk).tw.
11	(breast adj tender$).tw.
12	10 or 11
13	9 not 12
14	exp Neoplasms/
15	13 and 14
16	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp.
17	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp.
18	Paget's Disease, Mammary/
19	(paget$ and (breast$ or mammary or nipple$)).tw.
20	15 or 16 or 17 or 18 or 19
21	6 or 20
22	exp Radiotherapy/
23	radiotherapy.fs.
24	(radiotherap$ or radiat$ or irradiat$ or brachytherap$ or tomotherap$).mp.
25	(fractionat$ or hyperfractionat$ or hypofractionat$).mp.
26	22 or 23 or 24 or 25
27	21 and 26
28	Axilla/
29	Lymph Nodes/
30	Lymphatic Metastasis/
31	internal mammary.mp.
32	(supraclavicular or supraclavicule).mp.
33	28 or 29 or 30 or 31 or 32
34	27 and 33

#	Searches
35	((regional or node or nodal or lymph$ or axill$ or supraclavicul$ or internal mammary or IMN) adj3 (radiotherap$ or radiat$ or irradiat$ or RT or brachytherap$ or tomotherap$ or fractionat$ or hyperfractionat$ or hypofractionat$)).tw.
36	Lymphatic Metastasis/rt [Radiotherapy]
37	35 or 36
38	21 and 37
39	34 or 38
40	limit 39 to yr="2006 -Current"
41	Limit 40 to RCTs and SRs, and general exclusions filter applied

Database: Embase

Last searched on **Embase Classic+Embase** 1947 to 2017 January 04.

Date of last search: 5 January 2017

#	Searches
1	exp breast cancer/
2	exp breast carcinoma/
3	exp medullary carcinoma/
4	exp intraductal carcinoma/
5	exp breast tumor/
6	1 or 2 or 3 or 4 or 5
7	exp breast/
8	breast.tw.
9	7 or 8
10	(breast adj milk).tw.
11	(breast adj tender$).tw.
12	10 or 11
13	9 not 12
14	exp neoplasm/
15	13 and 14
16	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw.
17	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw.
18	exp Paget nipple disease/
19	(paget$ and (breast$ or mammary or nipple$)).tw.
20	15 or 16 or 17 or 18 or 19
21	6 or 20
22	exp radiotherapy/
23	radiotherapy.fs.
24	(radiotherap$ or radiat$ or irradiat$ or brachytherap$ or tomotherap$).mp.
25	(fractionat$ or hyperfractionat$ or hypofractionat$).mp.
26	22 or 23 or 24 or 25
27	21 and 26

#	Searches
28	axilla/
29	lymph node/
30	lymph node metastasis/
31	internal mammary.mp.
32	(supraclavicular or supraclavicule).mp.
33	28 or 29 or 30 or 31 or 32
34	27 and 33
35	((regional or node or nodal or lymph$ or axill$ or supraclavicul$ or internal mammary or IMN) adj3 (radiotherap$ or radiat$ or irradiat$ or RT or brachytherap$ or tomotherap$ or fractionat$ or hyperfractionat$ or hypofractionat$)).tw.
36	lymph node metastasis/rt [Radiotherapy]
37	35 or 36
38	21 and 37
39	34 or 38
40	limit 39 to yr="2006 -Current"
41	Limit 40 to RCTs and SRs, and general exclusions filter applied

Database: Cochrane Library via Wiley Online

Date of last search: 5 January 2017

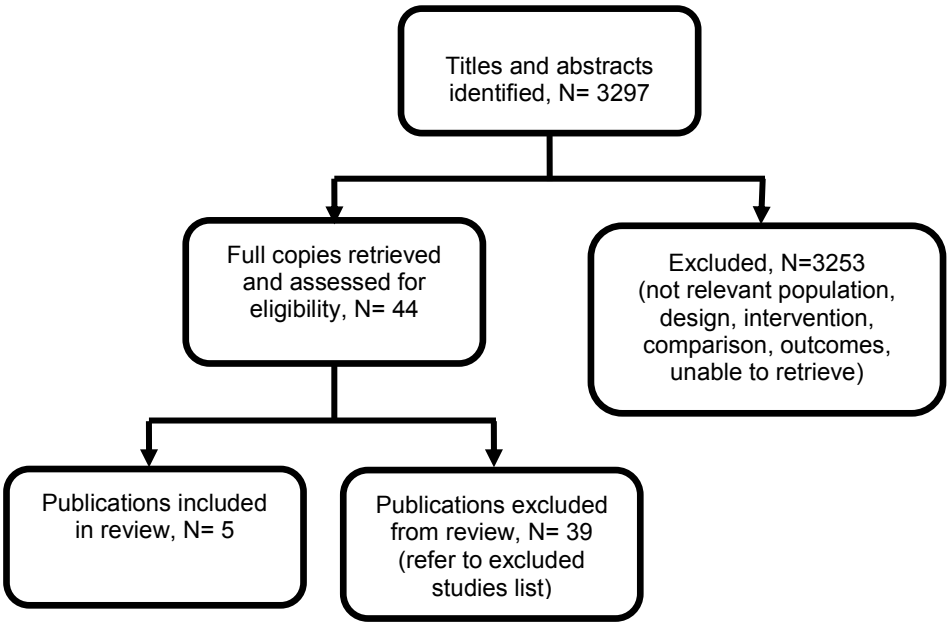
#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [Carcinoma, Medullary] this term only
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Breast] explode all trees
#8	breast:ti,ab,kw (Word variations have been searched)
#9	#7 or #8
#10	(breast next milk):ti,ab,kw (Word variations have been searched)
#11	(breast next tender*):ti,ab,kw (Word variations have been searched)
#12	#10 or #11
#13	#9 not #12
#14	MeSH descriptor: [Neoplasms] explode all trees
#15	#13 and #14
#16	(breast* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#18	MeSH descriptor: [Paget's Disease, Mammary] this term only
#19	(paget* and (breast* or mammary or nipple*)):ti,ab,kw (Word variations have been searched)
#20	#15 or #16 or #17 or #18 or #19
#21	#6 or #20

#	Searches
#22	MeSH descriptor: [Radiotherapy] explode all trees
#23	(radiotherap* or radiat* or irradiat* or brachytherap* or tomotherap*):ti,ab,kw (Word variations have been searched)
#24	(fractionat* or hyperfractionat* or hypofractionat*):ti,ab,kw (Word variations have been searched)
#25	#22 or #23 or #24
#26	#21 and #25
#27	MeSH descriptor: [Axilla] this term only
#28	MeSH descriptor: [Lymph Nodes] this term only
#29	MeSH descriptor: [Lymphatic Metastasis] this term only
#30	internal mammary:ti,ab,kw (Word variations have been searched)
#31	(supraclavicular or supraclavicule):ti,ab,kw (Word variations have been searched)
#32	#27 or #28 or #29 or #30 or #31
#33	#26 and #32
#34	((regional or node or nodal or lymph* or axill* or supraclavicul* or internal mammary or IMN) near/3 (radiotherap* or radiat* or irradiat* or RT or brachytherap* or tomotherap* or fractionat* or hyperfractionat* or hypofractionat*)):ti,ab,kw (Word variations have been searched)
#35	MeSH descriptor: [Lymphatic Metastasis] explode all trees and with qualifier(s): [Radiotherapy - RT]
#36	#34 or #35
#37	#21 and #36
#38	#33 or #37 Publication Year from 2006 to 2017

Appendix C – Clinical evidence study selection

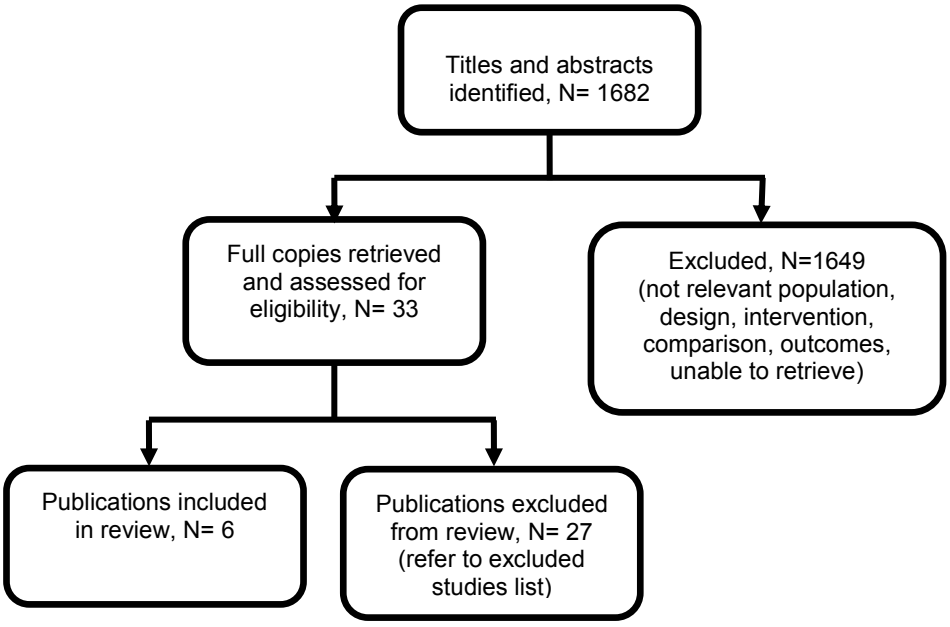
Clinical evidence study selection for 8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?

Figure 1: Flow diagram of clinical article selection for heart sparing radiotherapy review



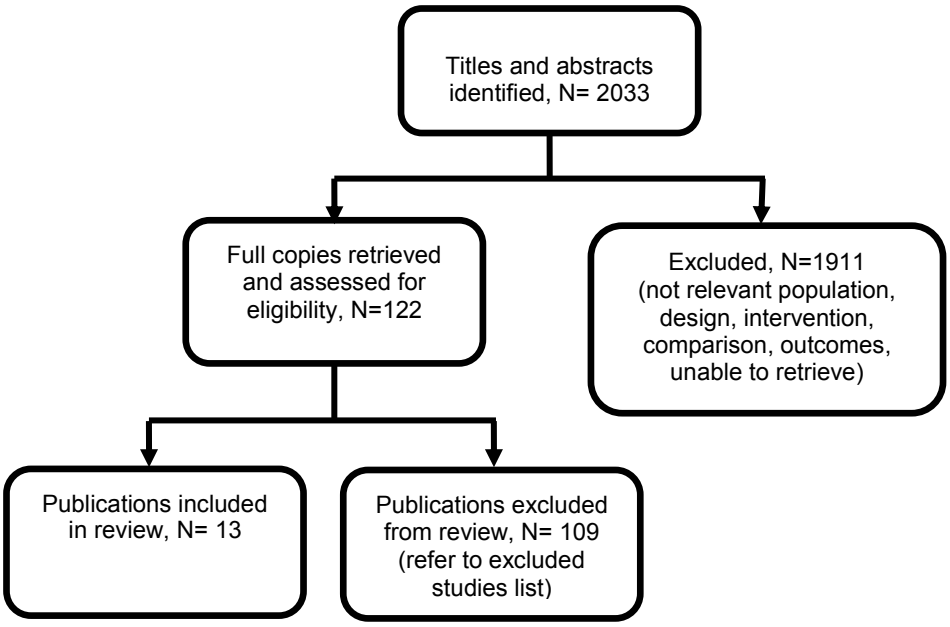
Clinical evidence study selection for 8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?

Figure 2: Flow diagram of clinical article selection for breast radiotherapy after breast-conserving surgery



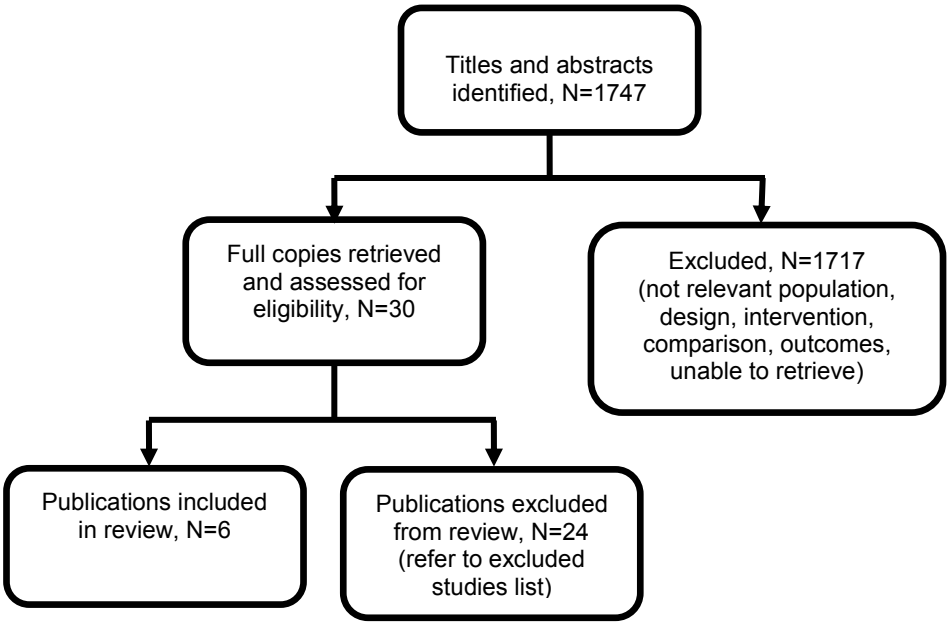
Clinical evidence study selection for 8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?

Figure 3: Flow diagram of clinical article selection for partial-breast radiotherapy versus whole-breast radiotherapy after breast-conserving surgery



Clinical evidence study selection for 8.4 What are the indications for radiotherapy to internal mammary nodes?

Figure 4: Flow diagram of clinical article selection for radiotherapy to the internal mammary nodes



Appendix D – Clinical evidence tables

Clinical evidence tables for 8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?

Table 14: Studies included in the evidence review for heart sparing radiotherapy

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Bartlett, F. R., Colgan, R. M., Donovan, E. M., McNair, H. A., Carr, K., Evans, P. M., Griffin, C., Locke, I., Haviland, J. S., Yarnold, J. R., Kirby, A. M., The UK HeartSpare Study (Stage IB): Randomised comparison of a voluntary breath-hold technique and prone radiotherapy after breast conserving surgery, Radiotherapy and Oncology, 114, 66-72, 2015 **Ref Id** 670601 **Country/ies where the study was carried out** United Kingdom **Study type**	**Sample size** 28 **Characteristics** Median age: 57 years(range 25-79 years) **Inclusion criteria** Women with left BC who had undergone breast-conserving surgery for invasive ductal or lobular carcinoma (pT1-3b,N0-1,M0), who required radiotherapy to the breast alone (± tumour bed boost) without nodal irradiation, and who had an estimated breast volume of >750 cm3 **Exclusion criteria** Not described	**Interventions** **Voluntary Breath Hold** The patients were asked to breathe in and out twice before taking a deep breath in and holding. The reference mark on the patient's skin should rise up to the level of the laser. They repeated the breath-hold procedure a couple of times to confirm reproducibility before proceeding with patient setup. Patients performed a breath-hold and the midline tattoo was aligned to the isocenter position superior/inferior and	**Details** Patients were randomised to receive one or other technique for fractions 1–7, before switching techniques for fractions 8–15.	**Results** Mean Heart Dose: VBH: 0.44(0.38-0.51)Gy Mean Heart Dose: Prone: 0.66(0.61-0.71)Gy Median target tissue coverage was≥95% for both techniques	**Limitations** Small sample size. Because of use of MLC/beam angle alterations to avoid cardiac tissue likely to result in lower coverage. **Other information** Selection Bias: Low risk Performance Bias: Low risk Detection Bias: Low risk

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Single centre randomized non blinded cross over study **Aim of the study** To compare mean heart and left anterior descending coronary artery (LAD) doses and positional reproducibility in larger-breasted women receiving left breast radiotherapy using supine voluntary deep-inspiratory breath-hold (VBH) and free-breathing prone techniques. **Study dates** January 2013 to April 2014 **Source of funding** National Institute of Health Research (NIHR)		set the focus-to-surface distance (FSD) at the midline. **Prone radiotherapy** Prone positioning was reproduced at treatment by aligning tattoos to lasers and using CT-planning photographs to check consistency.			(Objective Outcome) Attrition Bias:Low risk Reporting Bias: Low risk (Published protocol available) Indirectness: Only patients with breast volume >750 cm^3 were included
Full citation Bartlett, F. R., Donovan, E. M., McNair, H. A., Corsini, L. A., Colgan, R. M., Evans, P. M., Maynard, L., Griffin, C., Haviland, J. S., Yarnold, J. R., Kirby, A. M., The UK HeartSpare Study (Stage II): Multicentre Evaluation of a Voluntary Breath-hold	**Sample size** 93 from 10 UK centres **Characteristics** Median age: 56 years(27-78 yrs) 80(79%) Breast conserving surgery	**Interventions** **Voluntary Breath Hold** The patients were asked to breathe in and out twice before taking a deep breath in and holding. The reference mark on the patient's	**Details**	**Results** Mean Heart Dose: VBH: 1.04(0.97-1.12) Mean Heart Dose: Free breathing Prone: 1.79(1.66-1.91)Gy	**Limitations** Non randomized study **Other information** Selection

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Technique in Patients Receiving Breast Radiotherapy, Clinical Oncology, 29, e51-e56, 2017 **Ref Id** 670653 **Country/ies where the study was carried out** United Kingdom **Study type** Multicenter non randomised prospective study **Aim of the study** To evaluate the heart-sparing ability and feasibility of the VBH technique in a national multicentre setting **Study dates** Recruitment from January to October 2014 **Source of funding** National Institute of Health Research (NIHR)	11(11%): mastectomy±reconstruction 10(10%):Operation data missing: **Inclusion criteria** 1) underwent left breast conserving surgery or mastectomy for early stage invasive ductal or lobular carcinoma (pT1-3b N0-1 M0) or ductal carcinoma in situ 2) Recommended adjuvant radiotherapy to the whole breast or chest wall without nodal irradiation. 3)Women whose free-breathing planning computed tomography (CT) scan showed the presence of any heart tissue within tangential radiotherapy fields placed according to standard anatomical borders (i.e. any heart within the 50% isodose) **Exclusion criteria** Not separately described	skin should rise up to the level of the laser. They repeated the breath-hold procedure a couple of times to confirm reproducibility before proceeding with patient setup. Patients performed a breath-hold and the midline tattoo was aligned to the isocenter position superior/inferior and set the focus-to-surface distance (FSD) at the midline. **Free Breathing** Prone positioning was reproduced at treatment by aligning tattoos to lasers and using CT-planning photographs to check consistency.		Median target tissue coverage was≥95% for both techniques	Method of selection appropriate and likely to produce representative cohort Comparability: Comparable Outcome Outcome and follow-up adequate Indirectness Only women with larger breast volume included Other information
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Chi, F., Wu, S., Zhou, J., Li, F., Sun, J., Lin, Q., Lin, H., Guan, X., He, Z., Dosimetric comparison of moderate deep inspiration breath-hold and free-breathing intensity-modulated radiotherapy for left-sided breast cancer, Cancer/Radiotherapie, 19, 180-186, 2015 **Ref Id** 671586 **Country/ies where the study was carried out** China **Study type** Prospective **Aim of the study** This study determined the dosimetric comparison of moderate deep inspiration breath-holdusing active breathing control and free-breathing intensity-modulated radiotherapy (IMRT) after breast-conserving surgery for left-sided breast cancer. **Study dates** January 2008-July 2011	31 **Characteristics** Median age 39.5 yrs, Tumour stage T1 & T2 **Inclusion criteria** 1)female patient aged 18 years or older 2)Pathologically-confirmed breast cancer 3)axillary lymph node dissection or sentinel lymph node biopsy-confirmed pathology-negative lymph nodes 4)stage I or II (pT1N0M0, pT2N0M0) according to the 2009 7thedition of the American Joint Committee on Cancer (AJCC) TNMstaging 5) cardiac capacity and good cognitive ability based on active breathing control technology 6)informed consent **Exclusion criteria** Not described separately	Intervention: Two field-in-field-IMRT moderate deep inspiration breath-holding plans were compared in the dosimetry to target volume coverage of the glandular breast tissue and organs at risks for each patient. Control: Free breathing		There was no significant difference between the free-breathing and moderate deep inspiration breath-holding in the target volume coverage.The dose to ipsilateral lung, coronary artery and heartin the field-in-field-IMRT were significantly lower for the free-breathing plan than for the two moderate deep inspiration breath-holding plans (all $P < 0.05$)	Small sample size **Other information** Selection Method of selection appropriate and likely to produce representative cohort Comparability: Comparable Outcome Outcome and follow-up adequate

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding National NaturalScience Foundation of China (No. 81402527), the Sci-Tech Officeof Guangdong Province (No. 2013B021800157) and the EducationScientific Research Project of Young Teachers in Fujian Province(No. JB13131).					
Full citation Czeremszynska, B., Drozda, S., Gorzynski, M., Kepka, L., Selection of patients with left breast cancer for deep-inspiration breath-hold radiotherapy technique: Results of a prospective study, Reports of Practical Oncology and Radiotherapy, 22, 341-348, 2017 **Ref Id** 671669 **Country/ies where the study was carried out** Poland **Study type** Prospective study	**Sample size** 31 **Characteristics** Age: 24-70 yrs (Mean 55.5 yrs) **Inclusion criteria** 1)Early stage left breast cancer: Invasive ductal carcinoma in situ 2) Age 18-70 years 3) Informed consent **Exclusion criteria** 1) Did not agree to participate 2) Unable to cooperate in DIBH training	**Interventions** Prescribed radiation dose: 39.9 Gy Intervention: Align RT system used for alignment and coregistration, and breath hold during treatment. Control: Free breathing	**Details** Patients that had no sufficient improvement of treatment plan with DIBH, or those who were unable to breath hold steadily were given FB plan	**Results** Intervention(DIBH): Mean heart dose (Gy): 1.06(0.60 to 1.73) Control (Free breathing) Mean heart dose(Gy): 2.57(0.66 to 7.92)	**Limitations** Small sample size Selection Selection bias likely due to more chances of people with respirator fitness to be included Comparability: Comparable Outcome

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Aim of the study To assess prospectively which patients with left breast cancer have the dosimetric benefit from the use of deep-inspiration breath-hold radiotherapy (DIBH-RT). **Study dates** June 2014 to June 2015 **Source of funding** Not financially supported	3) Respiratory function impairment precluding them from deep inspiration maintenance				Outcome and follow-up adequate Indirectness Subjects with poor respiratory function were excluded **Other information**
Full citation Eldredge-Hindy, H., Lockamy, V., Crawford, A., Nettleton, V., Werner-Wasik, M., Siglin, J., Simone, N. L., Sidhu, K., Anne, P. R., Active Breathing Coordinator reduces radiation dose to the heart and preserves local control in patients with left breast cancer: Report of a prospective trial, Practical Radiation Oncology, 5, 4-10, 2015 **Ref Id**	**Sample size** 86 **Characteristics** Women with Stages 0-III left breast cancer Median age(Range): 52(25-80 years) **Inclusion criteria** 1) Adjuvant RT to the breast or chest wall 2) Could tolerate mDIBH	**Interventions** mDIBH with ABC device	**Details** ABC device (Elekta Oncology, Stockholm, Sweden) was used for intervention.	**Results** Absolute reduction in MHD : 1.7 Gy Relative reduction in MHD : 62%	**Limitations** Small sample size **Other information** Selection Method of selection appropriate and likely to produce representative cohort

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
671820 **Country/ies where the study was carried out** United States **Study type** Prospective trial **Aim of the study** To determine if radiotherapy with active breathing coordinator can reduce mean heart dose (MHD) by ≥20% and dose to the lung **Study dates** October 2002 to August 2011 **Source of funding** NCI Cancer Center Support Grant (P30 CA 56036)	3) Greater than 5 cc heart within the tangential field. **Exclusion criteria** 1) Unwilling to undergo device training 2) Unable to perform a breath hold for 20 seconds. 3) Patients who were non-English speaking or who had poor hearing				Comparability: Comparable Outcome Outcome and follow-up adequate Indirectness None

ABC: Active breathing coordinator; AJCC: American Joint committee on Cancer; BC: Breast cancer; CT: Computed tomography; DIBH: deep inspiration breath hold; FSD: Focus-to-surface distance; Gy: Gray; FB: Free breathing; IMRT: Intensity-modulated radiotherapy; LAD: Left anterior descending; mDIBH: Moderate deep inspiration breath hold; MHD: Mean heart dose; NCI: National Cancer Institute; NIHR: National Institute of Health Research; RT: Radiotherapy; VBH: Voluntary breath holding

Clinical evidence tables for 8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?

Table 15: studies included in the evidence review for breast radiotherapy after breast-conserving surgery

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Blamey, R, Bates, T, Chetty, U, Duffy, S, Ellis, I, George, D, Mallon, E, Mitchell, M, Monypenny, I, Morgan, D, Macmillan, R, Patnick, J, Pinder, S, Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial, European journal of cancer (Oxford, England : 1990), 49, 2294-302, 2013 **Ref Id** 552391 **Country/ies where the study was carried out** UK **Study type**	**Sample size** 1135 patients randomised - not interested in 20 patients that were only randomised based on Tamoxifen **Characteristics** Gender: 100% women Age: Mean 57; range 33-69 Ethnicity: NR **Inclusion criteria** Eligibility included women under 70 years of	**Interventions** **Intervention arm:** wide local excision (WLE) ± tamoxifen **Control arm:** WLE + whole breast radiotherapy ± tamoxifen	**Details** **Intervention arm (RT-):** WLE was defined in the trial protocol as surgical removal of the tumour mass with minimum width of 0.5–1.0 cm of surrounding uninvolved tissue confirmed by histological examination (if necessary, after a re-excision). Tamoxifen 20 mg daily for 5 years was prescribed to women randomised to tamoxifen and to those receiving tamoxifen by the elective choice of the Unit. **Control arm (RT+):** WLE was defined in the trial protocol as surgical removal of the tumour mass with minimum width of 0.5–1.0 cm of surrounding uninvolved tissue confirmed by histological examination (if necessary, after a re-excision). Tamoxifen 20 mg daily for 5 years was prescribed to women randomised to tamoxifen and to those receiving tamoxifen by the elective choice of the Unit. Whole breast irradiation was given with fractionation in the range between 40 Gy in 15 fractions and 50 Gy in 25 fractions. A boost to the tumour bed was recommended, but not obligatory.	**Results** **Local recurrence (Median follow-up 121 months):** O-E: 14.72; V: 14.82	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low **Attrition bias**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
RCT **Aim of the study** To identify a group in which the absolute risk of LR is low enough to omit treatment with RT, and to compare the effects on LR of adjuvant tamoxifen with RT **Study dates** Recruitment February 1992 - October 2000 **Source of funding** NHS Breast Screening Programme and Cancer Research UK	age with primary operable unilateral invasive breast cancer with no evidence of metastases. T he invasive carcinomas had to be of histological grade 1 or specific good prognosis special types (tubular, cribriform, tubular/cribrifor m, papillary or mucinous). Tumours had to be of maximum diameter 20 mm or less and have no evidence of lympho-vascular invasion (LVI). Histological examination of lymph nodes, excised by sampling or				Low **Selective reporting** Low **Indirectness** None **Limitations** No additional limitations **Other information** BASO II trial

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	dissection, had to be negative. **Exclusion criteria** Ineligible were patients with DCIS and microinvasive carcinoma alone, those with Paget's disease of the nipple, patients with synchronous bilateral breast cancer, those with a previous diagnosis of any cancer other than adequately treated basal cell carcinoma of the skin, and pregnant or lactating women. Also excluded were those women with evidence of distant metastases and those with				

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	other diseases that might preclude adequate surgery, adjuvant therapy or follow-up. Similarly those with planned receipt of any adjuvant therapy other than those within the trial were ineligible for trial entry. **Reported subgroups** All patients: T stage (1), N stage (0), Margins (negative)				
Full citation Holli, K, Hietanen, P, Saaristo, R, Huhtala, H, Hakama, M, Joensuu, H, Radiotherapy after segmental resection of breast cancer with	**Sample size** 264 randomised (1 subsequently refused RT)	**Interventions** **Intervention arm:** segmental breast resection (lumpectomy) and dissection of the ipsilateral axilla	**Details** **Intervention arm (RT-):** Surgery consisted of segmental breast resection (lumpectomy) and dissection of the ipsilateral axilla - the mammary gland was dissected free in the plane of Scapas fascia down to the pectoral muscle. The pectoral fascia was included in the specimen. Nonpalpable tumours were localized with wire-	**Results** **Local recurrence (Median follow-up 12.1 years):** O-E: 11.00; 11.08	**Selection bias: random sequence generation** Computer program–generated

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
favorable prognostic features: 12-year follow-up results of a randomized trial, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 27, 927-32, 2009 **Ref Id** 551555 **Country/ies where the study was carried out** Finland **Study type** RCT **Aim of the study** To compare breast-conserving surgery versus similar surgery followed by postoperative breast irradiation among women diagnosed with small size invasive breast cancer.	**Characteristics** Gender: 100% women Age: Median RT+ 56.3; Median RT- 55.6; range 37.4-85.2 Ethnicity: NR **Inclusion criteria** Age at random assignment had to be older than 40 years; the greatest tumour diameter measured microscopically had to be 20mm or less; histologic grade had to be either 1 (well differentiated) or 2 (moderately differentiated);	**Control arm:** segmental breast resection (lumpectomy) and dissection of the ipsilateral axilla + whole breast radiotherapy	hook marking. Levels I and II lymph node dissection were performed through a separate axillary incision. **Control arm (RT+):** Surgery consisted of segmental breast resection (lumpectomy) and dissection of the ipsilateral axilla - the mammary gland was dissected free in the plane of Scapas fascia down to the pectoral muscle. The pectoral fascia was included in the specimen. Nonpalpable tumours were localized with wire-hook marking. Levels I and II lymph node dissection were performed through a separate axillary incision. Postoperative radiation therapy was given by using a linear accelerator from two opposed tangential breast fields that provides approximately 5 MeV photon energy. A cumulative radiation dose of 50 Gy was administered within 5 weeks by using 2Gy daily fractions and wedge compensators to achieve a uniform dose. The planned target volume encompassed the entire ipsilateral breast and the lower ipsilateral axillary contents (levels I and II). No booster dose was given at the surgical bed. The ipsilateral supraclavicular lymph nodes were not included in the target volume.	**OS (Median follow-up 12.1 years):** O-E: 41.53; V: 89.55	random digits: Low **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low **Attrition bias** Low **Selective reporting** Low **Indirectness** None

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates Surgery occurred between May 1990 and September 1999 **Source of funding** Pirkanmaa Hospital District, Tampere University Hospital, the Finnish Breast Cancer Group, Cancer Society of Finland, the Academy of Finland, and Sigrid Juselius Foundation.	progesterone receptor (PR) status had to be positive (ie,10%of tumour cell nuclei stained positively in immunohistochemistry); the cell proliferation rate had to be low (i.e., either S phase fraction determined by DNA flow cytometry 7% or 10% of cancer cell nuclei stained for Ki-67 in immunohistochemistry); and the tumour had to be unifocal in a preoperative mammogram. The surgical resection margins had to be free of cancer with at least 1 cm of healthy breast				**Limitations** Rates of recurrence similar to previous trials where less emphasis was placed on entering patients with cancer with low biologic aggressiveness, which would suggest that the methods used to identify cancers with low biologic aggressiveness may not have worked as intended. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	tissue between the cancer and resection margin, as assessed by microscopy. If the tumour size was too small to allow sampling for DNA flow cytometry and hormone receptor analysis (i.e., patient cases with a primary tumour 5mm in diameter), histologic grade 1 or 2 together with small size were considered sufficient evidence of low biologic aggressivenes s. **Exclusion criteria** Patient cases with tumours				

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	that had an extensive intraductal component, axillary nodal metastases (pN), or distant metastases were excluded from the study. **Reported subgroups** All patients: T stage (1), N stage (0), Margins (negative)				
Full citation Hughes, K, Schnaper, L, Bellon, J, Cirrincione, C, Berry, D, McCormick, B, Muss, H, Smith, B, Hudis, C, Winer, E, Wood, W, Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of	**Sample size** 647 enrolled, 636 randomised **Characteristics** Gender: 100% women Age: ≥70 years (Mean/range NR)	**Intervention arm:** lumpectomy + tamoxifen **Control arm:** lumpectomy + tamoxifen + whole breast radiotherapy	**Details** **Intervention arm (RT-):** lumpectomy with a clear margin (absence of tumour at the inked margin). Axillary node dissection was allowed but not encouraged. 20mg tamoxifen per day for 5 years initiated during or after irradiation. Adjuvant hormonal treatment beyond 5 years was discretionary **Control arm: (RT+):** lumpectomy with a clear margin (absence of tumour at the inked margin). Axillary node dissection was allowed but not encouraged. 20mg tamoxifen per day for 5 years initiated during or after irradiation. Adjuvant hormonal treatment beyond 5 years	**Results** **Locoregional recurrence (10 year follow-up):** O-E: 8.15; V: 4.78 **OS (10 year follow-up):** O-E: 4.15; V: 85.12	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
CALGB 9343, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 31, 2382-7, 2013 **Ref Id** 552485 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To compare the efficacy of tamoxifen alone with tamoxifen plus radiotherapy in older women with ER-positive, clinical stage I breast cancer **Study dates** Recruited July 1994 - February 1999	Ethnicity: 90% Caucasian, 7% Black, 2% Hispanic <1% Asian **Inclusion criteria** Women age 70 years with clinical stage I, ER-positive breast cancer and no history of cancer other than in situ cervical or nonmelanoma skin cancer within 5 years were eligible. Initial eligibility criteria included breast cancers up to 4 cm regardless of oestrogen receptor status, but this was reduced in August 1996 to 2 cm (T1) with ER-		was discretionary. RT included tangential fields to the entire breast followed by an electron boost to the lumpectomy site.		**Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low **Attrition bias** Low **Selective reporting** Low **Indirectness** None **Limitations** No additional limitations

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding Not reported	positive or indeterminate receptor status. Patients were required to have clinically negative axillae. **Exclusion criteria** No additional criteria reported **Reported subgroups** All participants: N stage (0), Age (65+), Margins (negative)				**Other information** CALGB 9343 trial
Full citation Kunkler, I, Williams, L, Jack, W, Cameron, D, Dixon, J, Breast-conserving surgery with or without irradiation in women	**Sample size** 1326 randomised - 44 (5 in RT- and 39 in RT+) did not receive allocated	**Interventions** **Intervention arm:** BCS + no radiotherapy	**Details** **Intervention arm (RT-):** No details for breast conserving surgery procedures provided. Tamoxifen (20 mg daily for 5 years) as the standard adjuvant endocrine treatment, but we allowed other forms of adjuvant and neoadjuvant endocrine treatment.	**Results** **Local recurrence (median follow-up 5 years):** O-E: 6.89; V: 4.19	**Selection bias: random sequence generation** Permuted blocks: Low

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial, The Lancet. Oncology, 16, 266-73, 2015 **Ref Id** 553117 **Country/ies where the study was carried out** UK, Greece, Australia, Serbia **Study type** RCT **Aim of the study** To assess the effect of omission of whole-breast irradiation after breast-conserving surgery on local control. **Study dates** Recruited April 2003 - December 2009	treatment; 3 patients in RT- arm declined hormone treatment and 1 in each arm did not meet inclusion criteria. **Characteristics** Gender: 100% women Age: RT+ Median 70, IQR 67-74; RT- Median 69, IQR 67-73 Ethnicity: NR **Inclusion criteria** Women aged ≥65 years with breast cancer who had undergone breast-	**Control arm:** BCS + whole breast radiotherapy	**Control arm (RT+):** No details for breast conserving surgery procedures provided. Radiotherapy administered according to local practice in every centre. However, guideline was 40-50Gy (2.66-2.00Gy per fraction in 15-25 fractions) over 3-5 weeks at megavoltage irradiation to the breast. Breast boosts with electrons of 10–15 Gy at appropriate energy or an iridium implant (e.g., 20 Gy to 85% reference isodose) were permitted. Guidelines on radiotherapy included some form of immobilisation, a planned target volume of the whole breast (margin of 1 cm), and all patients being simulated to establish the volume of lung irradiated (maximum lung thickness no greater than 3 cm). We specified that the peripheral lymphatic system was not to be irradiated. Tamoxifen (20 mg daily for 5 years) as the standard adjuvant endocrine treatment, but we allowed other forms of adjuvant and neoadjuvant endocrine treatment.		**Selection bias: allocation concealment** Used independent randomisation service: Low **Selection bias: overall judgement** Low **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low **Attrition bias** Similar rates of loss to follow-up in both arms: Low **Selective reporting** Low **Indirectness**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding Chief Scientist Office of the Scottish Government and the Breast Cancer Institute at the Western General Hospital, Edinburgh	conserving surgery and pathological axillary staging. Cancer must be: T1-T2, N0, M0 hormone (ER/PR/both) receptor positive, excised with clear (≥1mm) margins, and receiving neoadjuvant hormonal treatment. **Exclusion criteria** Excluded patients if younger than 65 years or if they had a history of previous in-situ or invasive breast cancer of either breast. Also excluded women with current or				Population: not stated that it is limited to invasive breast cancer: serious **Limitations** Absence of detailed information on comorbidities and on adherence to endocrine treatment. Few patients were included with grade 3 tumours, therefore limited applicability in this groups. **Other information** PRIME II trial

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	previous malignant disease within the past year, other than non-melanomatous skin cancer or carcinoma in situ of the cervix. **Reported subgroups** All patients: N stage (0), Age (65+), Margins (negative)				
Full citation Wickberg, A, Holmberg, L, Adami, H, Magnuson, A, Villman, K, Liljegren, G, Sector resection with or without postoperative radiotherapy for stage I breast cancer: 20-year results of a randomized trial, Journal of clinical oncology : official journal of the American	**Sample size** 381 randomised **Characteristics** Gender: 100% women Age: Mean 60; SD 11.2 Ethnicity: NR	**Interventions** **Intervention arm:** sector resection and axilla dissected to levels I and II **Control arm:** sector resection and axilla dissected to levels I and II +	**Details** **Intervention arm (RT-):** sector resection and axilla dissected to levels I and II **Control arm (RT+):** sector resection and axilla dissected to levels I and II. Radiotherapy total dose of 54Gy in 27 fractions delivered to target volume, defined as breast parenchyma plus 1cm.	**Results** **OS (20 year follow-up):** O-E: 5.66; V: 59.99	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Unclear

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Society of Clinical Oncology, 32, 791-7, 2014 **Ref Id** 552969 **Country/ies where the study was carried out** Sweden **Study type** RCT **Aim of the study** To investigate how radiotherapy adds to tumour control using a standardised surgical technique with meticulous control of surgical margins. **Study dates** Recruited 1981 - 1988 **Source of funding**	**Inclusion criteria** Women ≤80 years old with a unifocal invasive breast cancer of histopathologic stage I **Exclusion criteria** No additional criteria reported **Reported subgroups** All patients: Adjuvant systemic therapy (none)	whole breast radiotherapy			**Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low **Attrition bias** Low **Selective reporting** Low **Indirectness** None **Limitations** Low statistical power

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Swedish Cancer Society; the Local Research Committee; University Hospital, Orebro; and the Regional Research Foundation, Uppsala/Orebro, Sweden.					**Other information** Uppsala/Orebro trial
Full citation Williams, L, Kunkler, I, King, C, Jack, W, Pol, M, A randomised controlled trial of post-operative radiotherapy following breast-conserving surgery in a minimum-risk population. Quality of life at 5 years in the PRIME trial, Health technology assessment (Winchester, England), 15, i-xi, 1-57, 2011 **Ref Id** 552070 **Country/ies where the study was carried out**	**Sample size** 255 randomised **Characteristics** Gender: 100% women Age: Mean 72.6; SD 5.1 Ethnicity: NR **Inclusion criteria** Age of ≥ 65 years, receiving	**Interventions** **Intervention arm:** breast-conserving surgery only **Control arm:** breast conserving surgery + post-operative radiotherapy	**Details** No further detail reported.	**Results** **OS (5 year follow-up):** O-E: 1.28; V: 7.71 **Treatment-related morbidity - fractures (5 year follow-up):** RT- 10/86; RT+ 9/85 **Treatment-related morbidity - congestive cardiac failure (5 year follow-up):** RT- 3/86; RT+ 3/85	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
UK **Study type** RCT **Aim of the study** To assess whether omission of post-operative radiotherapy in women with 'low-risk' early breast cancer treated by breast conserving surgery and adjuvant endocrine therapy improves quality of life and is more cost-effective **Study dates** Recruited 1999 - 2004 **Source of funding** Health Technology Assessment programme of the National Institute for Health Research	adjuvant endocrine therapy. Medically suitable to attend for all treatments and follow-up. Histologically confirmed unilateral breast cancer of TNM stages T0–2, N0 and M0. No axillary node involvement on histological assessment. Had breast-conserving surgery with complete excision on histological assessment. Able and willing to give informed consent. **Exclusion criteria** Past history of pure in situ			**Treatment-related morbidity - myocardial infarction (5 year follow-up):** RT- 5/86; RT+ 6/85 **Treatment-related morbidity - secondary cancer (5 year follow-up):** RT- 6/86; RT+ 0/85 **Treatment-related morbidity - score ≥10 on HADS anxiety sale (5 year follow-up):** RT- 12/101; 9/105 **Treatment-related morbidity - score ≥10 on HADS depression sale (5 year follow-up):** RT- 3/101; RT+ 1/105 **HRQoL - EQ5D score (5 year**	significant impact: Low **Detection bias** Low for recurrence and survival, High for all other outcomes **Attrition bias** Low **Selective reporting** Low **Indirectness** None **Limitations** Number of outcomes reported in insufficient detail. Relatively short follow-up period. **Other information** PRIME trial

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	carcinoma of either breast or previous or concurrent malignancy within the past 5 years other than non-melanomatous skin cancer or carcinoma in situ of cervix. Grade III cancer with lymphovascular invasion (LVI) (because of a higher risk of local recurrence). **Reported subgroups** All patients: N stage (0), Age (65+), Margins (negative)			**follow-up):** RT-N=83, M=0.77, SD=0.25; RT+ N=85, M=0.79, SD=0.28	

BASO, British Association of Surgical Oncologists; BCS, Breast conservation surgery; CALGB, Cancer and Leukemia Group B; DCIS, ductal carcinoma in situ; DNA, deoxyribonucleic acid; ER, oestrogen receptor; EQ5D, EuroQol Research Foundation measure of general health status; Gy, gray; HADS: Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; IQR, interquartile range; LR, local recurrence; LVI, lymphovascular invasion; NHS, National Health Service; NR, not reported; PR, progesterone receptor; PRIME, Postoperative Radiotherapy in Minimum-Risk Elderly; RCT, randomised controlled trial; RT, radiotherapy; SD, standard deviation; WLE, wide local excision

Clinical evidence tables for 8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?

Table 16: Studies included in the evidence review for partial breast radiotherapy

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Coles, Charlotte E., Griffin, Clare L., Kirby, Anna M., Titley, Jenny, Agrawal, Rajiv K., Alhasso, Abdulla, Bhattacharya, Indrani S., Brunt, Adrian M., Ciurlionis, Laura, Chan, Charlie, Donovan, Ellen M., Emson, Marie A., Harnett, Adrian N., Haviland, Joanne S., Hopwood, Penelope, Jefford, Monica L., Kaggwa, Ronald, Sawyer, Elinor J., Syndikus, Isabel, Tsang, Yat M., Wheatley, Duncan A., Wilcox, Maggie, Yarnold, John R., Bliss, Judith M., Al Sarakbi, Wail, Barber, Sarah, Barnett, Gillian, Bliss, Peter, Dewar, John, Eaton, David, Ebbs, Stephen, Ellis, Ian, Evans, Philip, Harris, Emma, James, Hayley, Kirwan, Cliona, Kirk, Julie, Mayles, Helen, McIntyre, Anne, Mills, Judith, Poynter, Andrew, Provenzano,	**Sample size** n=2018 randomised (two women withdrew consent for use of their data in the analysis). n=2016 available for analysis (n=674 whole-breast radiotherapy, n=673 reduced-dose group, and n=669 in the partial-breast group) **Characteristics** Whole-breast radiotherapy (n=674) vs Partial-breast group (n=669) Mean age (IQR range): 62 (57-67) vs 62 (57-67) Pathological tumour size (cm) (IQR range):1.2 (0.8-1.5) vs 1.2 (0.8-1.6) Tumour grade 1: 298/672 (44%) vs 284/668 (43%) Tumour grade 2: 310/672 (46%) vs 320/668 (48%) Tumour grade 3: 64/672 (10%) vs 63/668 (9%)	**Interventions** 1) Whole-breast radiotherapy received 40 Gy in 15 fractions to the whole breast. 2) Reduced-dose group received 36 Gy in 15 fractions to the whole breast and 40 Gy in 15 fractions to the partial breast containing the tumour bed. 3) Partial-breast group received 40 Gy in 15 fractions to the partial breast only.	**Details** Primary Outcomes: Local recurrence in the ipsilateral breast parenchyma or overlying skin. Secondary Outcomes: Location of local tumour relapse, time to regional relapse (axilla, supraclavicular fossa, and internal mammary chain), time to distant relapse, disease-free survival , overall survival, contralateral breast cancers, and other second primary cancers. Patient-reported outcomes substudy completed the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 core questionnaire, EORTC QLQ-BR23 breast cancer module, body-image scale, protocol-specific questions (has skin appearance changed, overall breast appearance changed, breast become smaller, breast become harder or firmer to touch, or is shoulder stiffness present?), Hospital Anxiety and Depression Scale, and the	**Results** **Comparison: Partial breast radiotherapy (PBI) vs. Whole breast radiotherapy (WBRT) at 5 years cumulative follow-up** Outcome: Local relapse PBI: 6/669 WBRT: 9/674 Outcome: Local regional relapse PBI: 8/669 WBRT: 9/674 Outcome: Distant relapse PBI: 12/669 WBRT: 13/674 Outcome: Any breast-cancer-related event PBI: 33/669 WBRT: 33/674 Outcome: All-cause mortality PBI: 37/669 WBRT: 40/674	**Limitations** **Cochrane risk of bias tool** Random sequence generation: Low risk. Women randomly assigned in a 1:1:1 ratio to the three arms using computer generated random permuted blocks (Mixed sizes of six and nine), stratified by treatment centre. Allocation concealment: Unclear risk. Unclear if research staff who telephoned treatment centres to obtain treatment allocation and trial ID number were blinded. Blinding of participants and personnel (Objective outcomes): High risk (patients and investigators were not blinded to treatment arm) Blinding of participants and personnel (Subjective outcomes): High risk

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Elena, Rawlings, Christine, Sculpher, Mark, Sumo, Georges, Sydenham, Mark, Tutt, Andrew, Twyman, Nicola, Venables, Karen, Winship, Anna, Winstanley, John, Wishart, Gordon, Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial, The Lancet, Online First - In Press, Corrected Proof, 2017 **Ref Id** 664212 **Country/ies where the study was carried out** United Kingdom **Study type** Multi-centre RCT **Aim of the study** To compare the safety and efficacy of standard whole-breast radiotherapy (control, whole-breast	**Inclusion criteria** Women ≥ 50 years undergoing breast conserving surgery for unifocal invasive ductal adenocarcinoma of any grade (1–3); pathological tumour size ≤ 3 cm (pT1–2), axillary node negative or one to three positive nodes (pN0–1), microscopic margins of non-cancerous tissue ≥ 2 mm. **Exclusion criteria** Invasive carcinoma of classical lobular type; distant metastases; previous malignancy of any kind (unless non-melanomatous skin cancer); undergone a mastectomy; received neoadjuvant chemotherapy or concurrent adjuvant chemoradiotherapy.		EuroQol EQ-5D-3L health status questionnaire (at baseline (before randomisation), 6 months, and 1, 2, and 5 years). Symptomatic rib fracture, symptomatic lung fibrosis, and ischaemic heart disease incidence (at 1, 2, 5, and 10-year follow-up).	Mild or marked changes in breast appearance at 2 years PBI: 31/333 WBRT: 37/332 Mild or marked changes in breast appearance at 5 years PBI: 50/279 WBRT: 60/262 Protocol specific items, cumulative number of adverse events 5 year cumulative incidence:- - Breast appearance changed PBI: 113/421 WBRT: 158/411 - Breast smaller PBI: 119/421 WBRT: 104/411 - Breast harder or firmer PBI: 58/421 WBRT: 115/411 - Shoulder stiffness PBI: 58/421 WBRT: 56/411 - Skin appearance changed	(patients and investigators were not blinded to treatment arm) Blinding of outcome assessment (Objective outcomes): High risk (clinicians and investigators were not blinded to treatment arm) Blinding of outcome assessment (Subjective outcomes): High risk (patients and investigators were not blinded to treatment arm) Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Low risk **Other information** The authors here report on IMPORT LOW. Two sub-studies investigating late adverse effects and patient reported outcomes, including the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 core questionnaire (EORTC QLQ-BR23), will be

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
group) with experimental schedules of radiotherapy to the whole breast and partial breast (reduced-dose group), and to the partial breast only in women at lower than average risk of local relapse. **Study dates** May 2007 - October 2010 **Source of funding** Cancer Research UK				PBI: 49/421 WBRT: 63/411 EORTC QLQ-BR23 related items, cumulative number of adverse events 5 year cumulative incidence: - - Arm or shoulder pain PBI: 97/421 WBRT: 98/411 - Swollen arm or hand PBI: 16/421 WBRT: 21/411 - Difficulty raising arm PBI: 47/421 WBRT: 42/411 - Breast pain PBI: 64/421 WBRT: 67/411 - Breast swollen PBI: 17/421 WBRT: 31/411 - Breast over sensitive PBI: 54/421 WBRT: 64/411	reported in additional papers.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				- Skin problems in breast PBI: 35/421 WBRT: 50/411	
Full citation Hickey, Brigid E, Lehman, Margot, Francis, Daniel P, See, Adrienne M, Partial breast irradiation for early breast cancer, Cochrane Database of Systematic Reviews, 2016 **Ref Id** 553396 **Country/ies where the study was carried out** **Study type** Cochrane Systematic Review **Aim of the study** To investigate whether partial breast irradiation (PBI) is equivalent to or better than conventional or hypofractionated whole breast radiotherapy (WRBT) following breast-	**Sample size** **Livi 2015 (Reported on by Livi 2010 and Livi 2015)** N=520 randomised **Polgár 2007 (Reported on by Lovey 2007, Polgár 2007, Polgár 2013)** N=258 randomised **RAPID (Reported on by Olivotto 2013)** N=2135 randomised **Rodriguez 2013** N=102 randomised **GEC-ESTRO (Reported by Ott 2016, Strnad 2016)** N=1184 randomised **Characteristics** **Livi 2015 (Reported on by Livi 2010 and Livi 2015)** Population: 520 women aged > 40 years	**Interventions** **Livi 2015 (Reported on by Livi 2010 and Livi 2015)** 1) Partial breast irradiation (PBI) or accelerated partial breast irradiation (APBI) using intensity-modulated radiotherapy (IMRT). 2) Whole breast radiotherapy (WBRT); used 50 Gy/25 fractions plus 10 Gy boost. **Polgár 2007 (Reported on by Lovey 2007, Polgár 2007, Polgár 2013)** 1) PBI; 7 × 5.2GyHDRmulti-catheter brachytherapy (88/128 women). Those unsuitable for HDR (40/1280 women) had 50 Gy/25 fractions electron beam RT to partial breast.	**Details** **Livi 2015 (Reported on by Livi 2010 and Livi 2015)** Design: RCT; Single centre. Outcomes: Not specified. **Polgár 2007 (Reported on by Lovey 2007, Polgár 2007, Polgár 2013)** Design: RCT; Single-centre trial. Primary Outcomes: Local recurrence in the ipsilateral breast at 5 years; Cosmetic outcome (using the Harvard cosmetic score) Secondary Outcomes: Overall survival; Toxicity; Cause-specific mortality (deaths due to breast cancer at 5 years); Distant metastasis-free survival at 5 years; Relapse-free survival at 5 years; Subsequent mastectomy (ipsilateral partial mastectomy, modified radical mastectomy or radical mastectomy);	**Results** **Comparison: PBI/APBI vs. WBRT** Outcome: Local recurrence-free survival (5 years follow up) **GEC-ESTRO (Reported by Ott 2016, Strnad 2016)** PBI/APBI: 9/633 WBRT: 5/551 **Livi 2015 (Reported on by Livi 2010 and Livi 2015)** PBI/APBI: 0/260 WBRT: 3/260 **Rodriguez 2013** PBI/APBI: 0/51 WBRT: 0/51 **Outcome: Local recurrence-free survival (10 years follow up)** **Polgár 2007 (Reported on by Lovey 2007, Polgár 2007, Polgár 2013)**	**Limitations** **Quality of the SR**: Assessed using AMSTAR checklist Total score: 11/11. **Quality of individual studies:** Extracte from the Cochrane SR (Cochrane risk of bias tool) **Livi 2015 (Reported on by Livi 2010 and Livi 2015)** Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel (Objective outcomes): Low risk Blinding of participants and personnel (Subjective outcomes): Low risk

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
conserving therapy for early stage breast cancer. **Study dates** Searches complete up to May 2015 **Source of funding** Internal sources No sources of support supplied. External sources Princess Alexandra Cancer Collaborative Group, Australia.	Setting: Italy, single institution trial from a cancer centre. **Polgár 2007 (Reported on by Lovey 2007, Polgár 2007, Polgár 2013)** Population: 258 randomised women aged < 40 years Setting: Hungary, single institution trial from a tertiary institution. **RAPID (Reported on by Olivotto 2013)** Population: 2135 women aged ≥ 40 years. Setting: Canada, Australia, New Zealand. Multicentered, international study. **Rodriguez 2013** Population: 102 women aged ≥ 60 years old. Setting: Spain, single institution trial from a tertiary institution. **GEC-ESTRO (Reported by Ott 2016, Strnad 2016)**	2) Control arm: 50 Gy/25 fractions WBRT (130 women) **RAPID (Reported on by Olivotto 2013)** 1) APBI using three-dimensional conformal radiotherapy (3D-CRT): 38.5 Gy in 10 fractions, bd over 5-8 days. 6-8 hour gap between doses. 2) WBRT; 42.5 Gy in 16 fractions daily over 22 days. Women with large breast size: 50 Gy in 25 fractions over 25 days. Boost 10 Gy in 4 or 5 fractions over 4-7 days was permitted women who were deemed at moderate to high risk of LR according to local cancer centre guidelines. **Rodriguez 2013** 1) PBI/APBI delivered by 3D-CRT at 48Gy/24 fractions ± 10 Gy boost (according to risk factors for local recurrence) in 51 women. 2) Conventional WBRT at 48 Gy/24 fractions ±	Compliance, defined as the number of women who commence treatment with PBI/APBI or conventional EBRT and complete the treatment course. **RAPID (Reported on by Olivotto 2013)** Design: Phase III RCT; stratified for age, tumour histology, tumour size, adjuvant hormonal therapy and clinical centre. Primary Outcomes: Ipsilateral breast tumour recurrence (defined as recurrent invasive or in situ cancer in the ipsilateral breast including the axillary tail), median follow-up 36 months. Secondary Outcomes: Adverse cosmetic outcome; Disease-free survival; Event-free survival; Overall survival; Radiation toxicity; Quality of life; Cost effectiveness. **Rodriguez 2013** Design: Phase III RCT (relative non-inferiority). Median follow-up time was 5 years. Outcomes: Local control; Dosimetry and toxicity (using RTOG CTC); Skin elasticity	PBI/APBI: 7/128 WBRT: 6/130 Outcome: Cosmesis, physician-reported **Livi 2015 (Reported on by Livi 2010 and Livi 2015)** PBI/APBI: 0/246 WBRT: 2/260 **Polgár 2007 (Reported on by Lovey 2007, Polgár 2007, Polgár 2013)** PBI/APBI: 24/125 WBRT: 43/116 **RAPID (Reported on by Olivotto 2013)** PBI/APBI: 140/399 WBRT: 61/367 **Rodriguez 2013** PBI/APBI: 12/51 WBRT: 8/51 Outcome: Overall survival **GEC-ESTRO (Reported by Ott 2016, Strnad 2016)** PBI/APBI: 27/633 WBRT: 32/551	Blinding of outcome assessment (Objective outcomes): Low risk Blinding of outcome assessment (Subjective outcomes): High risk (clinicians and investigators were not blinded to treatment arm) Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Low risk **Polgár 2007 (Reported on by Lovey 2007, Polgár 2007, Polgár 2013)** Random sequence generation: Low risk Allocation concealment: Unclear risk (description of allocation concealment incomplete) Blinding of participants and personnel (Objective outcomes): Low risk Blinding of participants and personnel (Subjective outcomes): Low risk

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	Population: 1184 women aged > 40 years Setting: Austria, Czech Republic, Germany, Hungary, Poland, Spain, and Switzerland. Multi-centered study in hospitals and medical centres. **Inclusion criteria** **Livi 2015 (Reported on by Livi 2010 and Livi 2015)** Wide local excision or quadrantectomy for invasive breast cancer, negative margins and tumour size 2.5 cm or less. **Polgár 2007 (Reported on by Lovey 2007, Polgár 2007, Polgár 2013)** Invasive breast cancer after wide local excision of tumour and negative pathological margins (unifocal tumours, tumour size less than 20 mm, clinically or pathologically N0, or single microscopic nodal metastasis (greater than 0.2 mm and less than 2.0 mm), that is, pT1N0-1miM0, Grade I or II; T1N0-N1miM0, Grade I or II. **RAPID (Reported on by Olivotto 2013)**	10 Gy boost in 51 women. **GEC-ESTRO (Reported by Ott 2016, Strnad 2016)** 1) APBI Interstitial brachytherapy; HDR 32 Gy/8 fractions or 30.3 Gy/7 fractions; PDR 50 Gy at 0.6-0.8 Gy/fractions given hourly. 2) External beam WBRT 50.0-50.4 Gy/1.8-2.0 Gy fractions (5-28) plus 10 Gy/5 fraction boost.	measured using a dedicated device. Median follow-up time was 5 years. **GEC-ESTRO (Reported by Ott 2016, Strnad 2016)** Design: Phase III RCT; Open-label trial. Primary Outcomes: Local recurrence, 5 year follow up. Secondary Outcomes: Incidence and severity of acute and late adverse effects; Differences in cosmetic results; Distant metastases disease-free survival; Survival rates (overall survival, disease-free survival); Contralateral breast cancer rate; Quality of life. Median follow up of 5 years.	**Livi 2015 (Reported on by Livi 2010 and Livi 2015)** PBI/APBI: 1/260 WBRT: 7/260 **Polgár 2007 (Reported on by Lovey 2007, Polgár 2007, Polgár 2013)** PBI/APBI: 25/128 WBRT: 23/130 Outcome: Acute radiotherapy (RT) skin toxicity. **Livi 2015 (Reported on by Livi 2010 and Livi 2015)** PBI/APBI: 5/246 WBRT: 98/260 **Rodriguez 2013** PBI/APBI: 9/51 WBRT: 38/51 Outcome: Outcome 5 Late RT skin toxicity. **Livi 2015 (Reported on by Livi 2010 and Livi 2015)** PBI/APBI: 0/246 WBRT: 2/260 **Rodriguez 2013** PBI/APBI: 0/51	Blinding of outcome assessment (Objective outcomes): Low risk Blinding of outcome assessment (Subjective outcomes): High risk (No mention of Participants, Physicians or Assessors being blinded) Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Low risk RAPID (Reported on by Olivotto 2013) Random sequence generation: Low risk Allocation concealment: Unclear risk (inadequate details of allocation concealment) Blinding of participants and personnel (Objective outcomes): Low risk Blinding of participants and personnel (Subjective outcomes): Low risk Blinding of outcome assessment (Objective outcomes): Low risk

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	Either invasive ductal carcinoma or ductal carcinoma in situ with tumours 3.3 cm or greater, with negative margins. **Rodriguez 2013** pT1-2pN0M0 invasive ductal carcinoma, with tumour size 3 cm or less, with negative margins and Grade I or II histology. **GEC-ESTRO (Reported by Ott 2016, Strnad 2016)** Small T1-2N0-miM0 (less than 3 cm) with negative margins and Tis. **Exclusion criteria** **Livi 2015 (Reported on by Livi 2010 and Livi 2015)** Not reported. **Polgár 2007 (Reported on by Lovey 2007, Polgár 2007, Polgár 2013)** Not reported. **RAPID (Reported on by Olivotto 2013)** No involved axillary nodes. **Rodriguez 2013** Not reported.			WBRT: 0/51 Outcome: Fat necrosis **Polgár 2007 (Reported on by Lovey 2007, Polgár 2007, Polgár 2013)** PBI/APBI: 26/127 WBRT: 26/129 **RAPID (Reported on by Olivotto 2013)** PBI/APBI: 12/399 WBRT: 4/367 Outcome: 'Elsewhere primary **GEC-ESTRO (Reported by Ott 2016, Strnad 2016)** PBI/APBI: 3/633 WBRT: 4/551 **Livi 2015 (Reported on by Livi 2010 and Livi 2015)** PBI/APBI: 3/260 WBRT: 0/260 Outcome: Case-specific survival **GEC-ESTRO (Reported by Ott 2016, Strnad 2016)** PBI/APBI: 4/633 WBRT: 4/551	Blinding of outcome assessment (Subjective outcomes): Low risk Incomplete outcome data: Unclear risk (exclusions and attrition not assessed) Selective reporting: Unclear risk (interim report) Other bias: Unclear risk (No other sources of bias noted) **Rodriguez 2013** Random sequence generation: Low risk Allocation concealment: Unclear risk (Not clearly described) Blinding of participants and personnel (Objective outcomes): Low risk Blinding of participants and personnel (Subjective outcomes): Low risk Blinding of outcome assessment (Objective outcomes): Low risk Blinding of outcome assessment (Subjective outcomes): High risk (Acute, late RT toxicity

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	GEC-ESTRO (Reported by Ott 2016, Strnad 2016) No lympho-vascular invasion (LVI) and women with multifocal tumours.			**Livi 2015 (Reported on by Livi 2010 and Livi 2015)** PBI/APBI: 1/260 WBRT: 3/260 **Polgár 2007 (Reported on by Lovey 2007, Polgár 2007, Polgár 2013)** PBI/APBI: 6/128 WBRT: 10/130 Outcome: Distant metastasis-free survival. **GEC-ESTRO (Reported by Ott 2016, Strnad 2016)** PBI/APBI: 5/633 WBRT: 5/551 **Livi 2015 (Reported on by Livi 2010 and Livi 2015)** PBI/APBI: 3/260 WBRT: 4/260 **Polgár 2007 (Reported on by Lovey 2007, Polgár 2007, Polgár 2013)** PBI/APBI: 11/128 WBRT: 14/130 Outcome: Relapse-free survival.	and cosmesis were evaluated by the treating physician and patients) Incomplete outcome data: Low risk Selective reporting: Low risk Other bias: Low risk **GEC-ESTRO (Reported by Ott 2016, Strnad 2016)** Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel (Objective outcomes): Low risk Blinding of participants and personnel (Subjective outcomes): Low risk Blinding of outcome assessment (Objective outcomes): Low risk Blinding of outcome assessment (Subjective outcomes): High risk (Blinding of outcome assessors was not mentioned) Incomplete outcome data: Low risk

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Polgár 2007 (Reported on by Lovey 2007, Polgár 2007, Polgár 2013) PBI/APBI: 19/128 WBRT: 20/130 **Rodriguez 2013** PBI/APBI: 0/51 WBRT: 0/51 Outcome: Locoregional recurrence-free survival **Rodriguez 2013** PBI/APBI: 0/51 WBRT: 0/51 Outcome: Masectomy **GEC-ESTRO (Reported by Ott 2016, Strnad 2016)** PBI/APBI: 1/633 WBRT: 0/551 **Polgár 2007 (Reported on by Lovey 2007, Polgár 2007, Polgár 2013)**	Selective reporting: Low risk Other bias: Low risk **Other information** Interim results from Livi 2015 on skin toxicity results are reported on in Livi 2010. Meattini 2017 present the early and 2-year follow-up health-related quality of life results from Livi 2015. Additional results from Polgár 2007 are reported in Lovey 2007,and Polgár 2013. Further results from GEC-ESTRO reported in Ott 2016.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				PBI/APBI: 0/128 WBRT: 2/130	
Full citation Livi, L., Buonamici, F. B., Simontacchi, G., Scotti, V., Fambrini, M., Compagnucci, A., Paiar, F., Scoccianti, S., Pallotta, S., Detti, B., Agresti, B., Talamonti, C., Mangoni, M., Bianchi, S., Cataliotti, L., Marrazzo, L., Bucciolini, M., Biti, G., Accelerated Partial Breast Irradiation With IMRT: New Technical Approach and Interim Analysis of Acute Toxicity in a Phase III Randomized Clinical Trial, International Journal of Radiation Oncology Biology Physics, 77, 509-515, 2010 **Ref Id** 664582 **Country/ies where the study was carried out** Italy **Study type**	**Sample size** n=259 women randomised. **Characteristics** APBI (131) vs. WBT (128) **Inclusion criteria** Age at presentation >40 years; Tumor size ≥25 mm; Wide excision or quadrantectomy with clear margins (≤5 mm); Clips placed in tumor bed; Full informed consent from patient; Follow-up at he radiotherapy department of Florence University. **Exclusion criteria** Cardiac dysfunction (Left ventricular ejection fraction <50% as measured by echocardiography or history of active angina, myocardial infarction, or other cardiovascular disease); Forced expiratory volume <1 L/m; Extensive intraductal carcinoma; Multifocal cancer; Psychiatric problems; Follow-up at center other than the radiotherapy department of Florence University.	**Interventions** Please see Hickey 2016 Cochrane systematic review.	**Details** Outcomes: Acute skin toxicity measured using the Radiation Therapy Oncology Group scale.	**Results** **Comparison: PBI/APBI vs. WBRT** Outcome: Grade 1 acute skin toxicity APBI: 5% of 131 WBRT: 22% of 128 Outcome: Grade 2 acute skin toxicity APBI: 0.8% of 131 WBRT: 19% of 128	**Limitations** Please see Hickey 2016 Cochrane systematic review. **Other information** Here the authors report on acute skin toxicity from September 2008 where the RCT had recruited 259 patients from a target of 520 patients. Livi 2015 provides skin toxicity results for the completed target of 520 patients.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
RCT **Aim of the study** To compare the use of accelerated partial breast irradiation (APBI) with external intensity-modulated radiotherapy (IMRT) to conventional fractionated whole breast treatment (WBT) in patients with early-stage breast cancer and to analyze the acute toxicity. **Study dates** March 2005 - September 2013 (As reported in Livi 2015). Here authors here present results from September 2008. **Source of funding** None disclosed.					
Full citation Livi, L., Meattini, I., Marrazzo, L., Simontacchi, G., Pallotta, S., Saieva, C., Paiar, F., Scotti, V., De Luca Cardillo, C.,	**Sample size** Please see Hickey 2016 Cochrane systematic review. **Characteristics**	**Interventions** Please see Hickey 2016 Cochrane systematic review.	**Details** Please see Hickey 2016 Cochrane systematic review.	**Results** Please see Hickey 2016 Cochrane systematic review.	**Limitations** Please see Hickey 2016 Cochrane systematic review.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Bastiani, P., Orzalesi, L., Casella, D., Sanchez, L., Nori, J., Fambrini, M., Bianchi, S., Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial, European Journal of Cancer, 51, 451-463, 2015 **Ref Id** 611859 **Country/ies where the study was carried out** Italy **Study type** RCT **Aim of the study** To compare the use of accelerated partial breast irradiation (APBI) with external intensity-modulated radiotherapy (IMRT) to conventional fractionated whole breast treatment (WBT) in patients with early-stage breast cancer and analyse local	Please see Hickey 2016 Cochrane systematic review. **Inclusion criteria** Age at presentation >40 years with early breast cancer (maximum diameter 2.5 cm); Tumor size ≥25 mm; Wide excision or quadrantectomy with clear margins (≤5 mm); Clips placed in tumor bed; Full informed consent from patient; Follow-up at the radiotherapy department of Florence University. **Exclusion criteria** Previously diagnosed solid tumours; left ventricular ejection fraction (LVEF) <50% as measured by echocardiography or a history of active angina, myocardial infarction, or other cardiovascular disease; forced expiratory volume in 1s (FEV1) <1 L/m; extensive intraductal carcinoma; multiple foci cancer; final surgical margins <5 mm; and the absence of surgical clips in tumour bed.				**Other information** Results for acute skin toxicity from September 2008 where the RCT had recruited 259 patients from a target of 520 patients are reported in Livi 2010.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
recurrence and survival rates. **Study dates** March 2005 - September 2013 **Source of funding** None disclosed.					
Full citation Lovey, K., Fodor, J., Major, T., Szabo, E., Orosz, Z., Sulyok, Z., Janvary, L., Frohlich, G., Kasler, M., Polgar, C., Fat Necrosis After Partial-Breast Irradiation With Brachytherapy or Electron Irradiation Versus Standard Whole-Breast Radiotherapy-4-Year Results of a Randomized Trial, International Journal of Radiation Oncology Biology Physics, 69, 724-731, 2007 **Ref Id** 538435 **Country/ies where the study was carried out**	**Sample size** Please see Hickey 2016 Cochrane systematic review. **Characteristics** Please see Hickey 2016 Cochrane systematic review. **Inclusion criteria** Women aged < 40 years with pT1 pN0-1mi, nonlobular breast cancer without the presence of extensive intraductal component, and resected with negative margins **Exclusion criteria** None reported.	**Interventions** Please see Hickey 2016 Cochrane systematic review.	**Details** Outcomes: Fat necrosis determined by an institutional scoring scheme to grade fat necroses.	**Results** **Comparison: PBI/APBI vs. WBRT** Outcome: Fat necrosis with a median follow-up of 4 years WBI: 32/129 HDR-BT: 7/87 ELE: 7/40	**Limitations** Please see Hickey 2016 Cochrane systematic review. **Other information** Further results from this RCT are presented in Polgár 2007 and Polgár 2013.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Hungary **Study type** RCT **Aim of the study** To investigate in patients with early-stage breast cancer the incidence and clinical relevance of fat necrosis after the use of accelerated partial-breast irradiation (APBI) using interstitial high-dose-rate brachytherapy (HDR-BT) in comparison with partial-breast electron irradiation (ELE) and whole-breast irradiation (WBI). **Study dates** July 1998 - May 2004 **Source of funding** None disclosed.					
Full citation Meattini, I., Saieva, C., Miccinesi, G., Desideri, I., Francolini, G., Scotti, V., Marrazzo, L., Pallotta, S., Meacci, F.,	**Sample size** Please see Livi 2015. **Characteristics** Please see Livi 2015.	**Interventions** Please see Livi 2015.	**Details** Outcomes: HRQoL (reported at short-term and 2-year follow-up)	**Results** **Comparison: Accelerated partial breast irradiation (APBI) vs. whole breast irradiation (WBI)**	**Limitations** Please see Livi 2015. **Other information** The 5-year results of this APBI-IMRT-Florence

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Muntoni, C., Bendinelli, B., Sanchez, L. J., Bernini, M., Orzalesi, L., Nori, J., Bianchi, S., Livi, L., Accelerated partial breast irradiation using intensity modulated radiotherapy versus whole breast irradiation: Health-related quality of life final analysis from the Florence phase 3 trial, European journal of cancer, 76, 17-26, 2017 **Ref Id** 664623 **Country/ies where the study was carried out** Italy **Study type** RCT **Aim of the study** To compare the use of accelerated partial breast irradiation (APBI) with external intensity-modulated radiotherapy (IMRT) to conventional fractionated whole breast treatment (WBT) in patients with early-stage breast cancer and analyse early and	**Inclusion criteria** Please see Livi 2015. **Exclusion criteria** Please see Livi 2015.			Mean values (and SD) of QLQ-C30 scores at 2 years follow up Outcome: Global health status APBI: 75.5 (13.3) WBI: 59.5 (22.0) Outcome: Physical functioning APBI: 90.9 (10.9) WBI: 79.9 (17.8) Outcome: Role functioning APBI: 91.3 (15.7) WBI: 80.2 (24.2) Outcome: Emotional functioning APBI: 85.0 (14.6) WBI: 69.8 (26.2) Outcome: Cognitive functioning APBI: 90.8 (10.3) WBI: 77.7 (20.3) Outcome: Social functioning APBI: 96.7 (7.8) WBI: 82.8 (18.6) Outcome: Fatigue APBI: 15.5 (16.0) WBI: 27.3 (23.7)	phase 3 randomised trial on disease failure, acute and early late toxicity are presented in Livi 2015.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
2-year follow-up health-related quality of life (HRQoL) results. **Study dates** March 2015 - June 2013 **Source of funding** None declared.				Outcome: Nausea-vomiting APBI: 1.0 (4.5) WBI: 8.3 (13.1) Outcome: Pain APBI: 7.3 (14.0) WBI: 21.8 (21.3) Outcome: Dyspnoea APBI: 13.0 (18.8) WBI: 18.3 (22.4) Outcome: Insomnia APBI: 10.5 (20.3) WBI: 28.3 (27.0) Outcome: Appetite loss APBI: 3.2 (13.5) WBI: 14.0 (22.8) Outcome: Constipation APBI: 13.3 (20.5) WBI: 16.0 (24.8) Outcome: Diarrhoea APBI: 2.9 (11.4) WBI: 6.3 (16.2) Outcome: Financial difficulties	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				APBI: 4.4 (18.5) WBI: 12.0 (22.0) Mean values of QLQ-BR23 scores Outcome: Body image APBI: 89.0 (13.2) WBI: 72.1 (26.6) Outcome: Sexual functioning APBI: 24.9 (30.4) WBI: 18.3 (19.9) Outcome: Sexual enjoyment APBI: 57.1 (18.0) WBI: 49.5 (21.7) Outcome: Future perspective APBI: 84.8 (23.1) WBI: 57.0 (28.5) Outcome: Systemic therapy side-effects APBI: 11.5 (9.8) WBI: 17.4 (13.3) Outcome: Breast symptoms APBI: 6.1 (6.6) WBI: 18.9 (18.2) Outcome: Arm symptoms	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				APBI: 11.7 (13.4) WBI: 19.6 (19.0) Outcome: Hair loss APBI: 31.8 (17.3) WBI: 36.3 (25.4)	
Full citation Olivotto, I. A., Whelan, T. J., Parpia, S., Kim, D. H., Berrang, T., Truong, P. T., Kong, I., Cochrane, B., Nichol, A., Roy, I., Germain, I., Akra, M., Reed, M., Fyles, A., Trotter, T., Perera, F., Beckham, W., Levine, M. N., Julian, J. A., Interim cosmetic and toxicity results from RAPID: A randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy, Journal of Clinical Oncology, 31, 4038-4045, 2013 **Ref Id** 552558	**Sample size** Please see Hickey 2016 Cochrane systematic review. **Characteristics** Please see Hickey 2016 Cochrane systematic review. **Inclusion criteria** Women ≥ 40 years with invasive ductal carcinoma or ductal carcinoma in situ (DCIS) treated with BCS with microscopically clear margins and negative axillary nodes by sentinel node biopsy, or axillary dissection for those with invasive disease, or by clinical examination for those with DCIS alone. **Exclusion criteria** Women < 40 years; combined tumor size (DCIS and/or invasive carcinoma)>3 cm,	**Interventions** Please see Hickey 2016 Cochrane systematic review.	**Details** Please see Hickey 2016 Cochrane systematic review. Outcomes: ipsilateral breast tumor recurrence (IBTR). Secondary outcomes: Cosmesis (adverse cosmesis defined scored as fair or poor using European Organisation for Research and Treatment of Cancer Cosmetic Rating System), toxicity.	**Results** Please see Hickey 2016 Cochrane systematic review. Outcome: Outcome: Physician reported cosmesis, 3 years PBI/APBI: 140/399 WBRT: 61/367 Outcome: Nurse reported cosmesis, 5 years PBI/APBI: 56/171 WBRT: 22/164 Outcome: Patient reported cosmesis, 5 years PBI/APBI: 55/170 WBRT: 34/258	**Limitations** Please see Hickey 2016 Cochrane systematic review. **Other information** This is an interim report as part of the RAPID (Randomized Trial of Accelerated Partial Breast Irradiation) trial.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out Canada, Australia, New Zealand. **Study type** Multi-centre RCT **Aim of the study** To compare the use of three-dimensional conformal RT (3D-CRT) with whole-breast irradiation (WBI) in patients with early-stage breast cancer and analyse the impact of cosmesis and normal tissue toxicity. **Study dates** February 2006 - July 2011 **Source of funding** Supported in part by Grants No. 78567 and 114947 from the Canadian Institutes for Health Research and No. 016421 from the Canadian Breast Cancer Research Alliance.	lobular carcinoma, > one primary tumor in different quadrants of the breast, or an RT plan that did not meet protocol-defined dose-volume constraints for APBI.				

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Ott, O. J., Strnad, V., Hildebrandt, G., Kauer-Dorner, D., Knauerhase, H., Major, T., Lyczek, J., Guinot, J. L., Dunst, J., Miguelez, C. G., Slampa, P., Allgauer, M., Lossl, K., Polat, B., Kovacs, G., Fischedick, A. R., Wendt, T. G., Fietkau, R., Kortmann, R. D., Resch, A., Kulik, A., Arribas, L., Niehoff, P., Guedea, F., Schlamann, A., Potter, R., Gall, C., Malzer, M., Uter, W., Polgar, C., GEC-ESTRO multicenter phase 3-trial: Accelerated partial breast irradiation with interstitial multicatheter brachytherapy versus external beam whole breast irradiation: Early toxicity and patient compliance, Radiotherapy and Oncology, 120, 119-123, 2016 **Ref Id** 553472 **Country/ies where the study was carried out**	**Sample size** Please see Hickey 2016 Cochrane systematic review. **Characteristics** Please see Hickey 2016 Cochrane systematic review. **Inclusion criteria** Women aged ≥ 40 years; histologically confirmed invasive breast cancer or ductal carcinoma in situ (DCIS) UICC stage 0–IIA, a maximum tumor diameter 6 3 cm, complete resection with clear marginsP2 mm (in case of invasive lobular cancer or pure DCISP5 mm), at least six negative axillary lymph nodes (pN0), or singular nodal micro-metastasis (pN1mi), or negative sentinel node biopsy (pN0sn), or a clinically negative axilla in case of DCIS (cN0), no distant metastasis or contralateral breast cancer. **Exclusion criteria** Any signs of a multifocal growth pattern in mammography, had residual micro-calcifications post-operatively, an extensive intraductal component (EIC), vessel invasion (L1, V1), involved, close (<2 mm) or	**Interventions** Please see Hickey 2016 Cochrane systematic review.	**Details** Outcomes: Early side effects (classified according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE; publish date: June 10, 2003)); late side effects (classified according to RTOG/EORTC criteria and Lent Soma Scores); Toxicity (defined as early if it occurred within the first 90 days from the start of radiotherapy).	**Results** **Comparison: APBI vs. WBI** Outcome: Early skin reaction (radiodermatitis) WBI: 513/552 APBI: 134/630 Outcome: Mild hematoma WBI: 10/553 APBI: 127/630 Outcome: Breast infection rate) WBI: 11/552 APBI: 32/630 Outcome: Low grade intraoperative breast injury WBI: 4/553 APBI: 31/630 Outcome: Breast Pain WBI: 161/553 APBI: 161/630	**Limitations** Please see Hickey 2016 Cochrane systematic review. **Other information** Long-term results from the Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO) multicentre, phase 3, randomised controlled trial are presented in Strnard 2016. Late side-effects and cosmesis for this trial are presented in Polgar 2017.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Austria, Czech Republic, Germany, Hungary, Poland, Spain, and Switzerland **Study type** Multi-centre RCT **Aim of the study** To compare accelerated partial breast irradiation (APBI) with multicatheter brachytherapy to external beam whole breast irradiation (WBI) in patients with early-stage breast cancer and analyse early side effects and patient compliance. **Study dates** April 2004 - July 2009 **Source of funding** German Cancer Aid (Deutsche Krebshilfe e.V.; Grant Number 106288)	unknown margins (R1/Rx), or were pregnant.				
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Polgar, C., Fodor, J., Major, T., Nemeth, G., Lovey, K., Orosz, Z.,	Please see Hickey 2016 Cochrane systematic review.	Please see Hickey 2016 Cochrane systematic review.	Outcomes: Local recurrence; 5-year probability; overall survival; cancer-specific	**Please see Hickey 2016 Cochrane systematic review.**	Please see Hickey 2016 Cochrane systematic review.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Sulyok, Z., Takacsi-Nagy, Z., Kasler, M., Breast-Conserving Treatment With Partial or Whole Breast Irradiation for Low-Risk Invasive Breast Carcinoma-5-Year Results of a Randomized Trial, International Journal of Radiation Oncology Biology Physics, 69, 694-702, 2007 **Ref Id** 580095 **Country/ies where the study was carried out** Hungary **Study type** RCT **Aim of the study** To compare partial breast irradiation (PBI) with conventional whole breast irradiation (WBI) in patients with early-stage breast cancer and analyse the 5-year results of survival and cosmetic results. **Study dates** July 1998 - May 2004	**Characteristics** Please see Hickey 2016 Cochrane systematic review. **Inclusion criteria** Women > 40 years; Wide excision with microscopically negative surgical margins; unifocal tumor; primary tumor size ≤20 mm (pT1); cN0, pN0, or pN1mi (single nodal micrometastasis >0.2mmand≤2.0 mm) axillary status; and histologic Grade 2 or less. **Exclusion criteria** Women ≤ 40 years; bilateral breast carcinoma; prior uni- or contralateral breast cancer; concomitant or previous other malignancies (except basal cell carcinoma of the skin); pure ductal or lobular carcinoma in situ (pTis); invasive lobular carcinoma; or the presence of an extensive intraductal component.		survival; disease-free survival	**Comparison: PBI vs. WBI** Outcome: Local recurrence at 5 years follow up WBI: 4/130 PBI: 6/128 Outcome: 5-year probability of overall survival WBI: 91.8% (95% CI, 86.3–97.4%) PBI: 94.6% (95% CI, 90.2–99.1%) Outcome: 5-year probability of cancer-specific survival WBI: 96.0% (95% CI, 92.4–99.6%) PBI: 98.3% (95% CI, 96.0–100%) Outcome: 5-year disease-free survival WBI: 90.3% (95% CI, 84.5–96.1%) PBI: 88.3% (95% CI, 81.3–95.2%)	**Other information** Polgar 2013 presents the 10 year follow-up results from the Polgar 2007 trial.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding None disclosed.					
Full citation Polgar, C., Fodor, J., Major, T., Sulyok, Z., Kasler, M., Breast-conserving therapy with partial or whole breast irradiation: Ten-year results of the Budapest randomized trial, Radiotherapy and Oncology, 108, 197-202, 2013 **Ref Id** 538607 **Country/ies where the study was carried out** Hungary **Study type** RCT **Aim of the study** To compare partial breast irradiation (PBI) with conventional whole breast irradiation (WBI) in patients with early-stage breast cancer and analyse	**Sample size** Please see Hickey 2016 Cochrane systematic review. **Characteristics** Please see Hickey 2016 Cochrane systematic review. **Inclusion criteria** Please see Polgar 2007. **Exclusion criteria** Please see Polgar 2007.	**Interventions** Please see Hickey 2016 Cochrane systematic review.	**Details** Please see Hickey 2016 Cochrane systematic review.	**Results** Please see Hickey 2016 Cochrane systematic review.	**Limitations** Please see Hickey 2016 Cochrane systematic review. **Other information** Polgar 2007 presents the 5 year results of this trial.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
the 10-year results of survival and cosmetic results. **Study dates** July 1998 - May 2004 **Source of funding** None disclosed.					
Full citation Polgar, C., Ott, O. J., Hildebrandt, G., Kauer-Dorner, D., Knauerhase, H., Major, T., Lyczek, J., Guinot, J. L., Dunst, J., Miguelez, C. G., Slampa, P., Allgauer, M., Lossl, K., Polat, B., Kovacs, G., Fischedick, A. R., Fietkau, R., Resch, A., Kulik, A., Arribas, L., Niehoff, P., Guedea, F., Schlamann, A., Potter, R., Gall, C., Uter, W., Strnad, V., Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of	**Sample size** Please see Hickey 2016 Cochrane systematic review. **Characteristics** Please see Hickey 2016 Cochrane systematic review. **Inclusion criteria** Women aged ≥ 40 years with ductal carcinoma in situ (pTis) or invasive breast carcinoma up to a diameter of 3 cm (pT1–2a), with pN0 or pN1mi axillary status (stage 0, I, and IIA) who had undergone local excision of the breast tumour with microscopically clear resection margins of at least 2 mm. **Exclusion criteria** Multiple tumour foci, lymphovascular invasion, an extensive intraductal	**Interventions** Please see Hickey 2016 Cochrane systematic review.	**Details** Please see Hickey 2016 Cochrane systematic review. Outcomes: late side-effects (occurring >3 months after radiotherapy) grade 2 or worse severity of any toxicity, any skin toxicity (including skin hyper pigmentation and skin telangiectasia), any subcutaneous tissue toxicity (including fibrosis and fat necrosis), arm lymphoedema, and breast pain.	**Results** **Comparison: APBI vs. WBRT** Outcome: Cosmesis 5 year follow up, physician-reported fair to poor APBI: 39/542 WBRT: 46/454 Outcome: Cosmesis 5 year follow up, patient-reported fair to poor APBI: 43/541 WBRT: 41/454 Outcome: Skin RTOG/EORTC	**Limitations** Please see Hickey 2016 Cochrane systematic review. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
a randomised, controlled, phase 3 trial, The Lancet Oncology., 2017 **Ref Id** 580945 **Country/ies where the study was carried out** Austria, Czech Republic, Germany, Hungary, Poland, Spain, and Switzerland **Study type** Multi-centre RCT **Aim of the study** To compare accelerated partial breast irradiation (APBI) with multicatheter brachytherapy to external beam whole breast irradiation (WBI) in patients with early-stage breast cancer and analyse late side-effects and cosmesis. **Study dates** April 2004 - July 2009 **Source of funding** German Cancer Aid.	component, Paget's disease or pathological skin involvement, synchronous or previous breast cancer, safety margins that could not be microscopically assessed, a history of other malignant disease, or were pregnant or breastfeeding.			APBI: 69/484 WBRT: 69/393 Outcome: Skin telangiectasia APBI: 49/483 WBRT: 40/392 Outcome: Skin hyperpigmentation APBI: 27/484 WBRT: 40/392 Outcome: Subcutaneous tissue RTOG/EORTC APBI: 204/485 WBRT: 145/393 Outcome: Fibrosis APBI: 187/484 WBRT: 138/392 Outcome: Fat necrosis APBI: 44/484 WBRT: 28/393 Outcome: Pain APBI: 105/484 WBRT: 84/393 Outcome: Arm lymphoedema	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				APBI: 11/483 WBRT: 16/393	
Full citation Rodriguez, N., Sanz, X., Dengra, J., Foro, P., Membrive, I., Reig, A., Quera, J., Fernandez-Velilla, E., Pera, O., Lio, J., Lozano, J., Algara, M., Five-year outcomes, cosmesis, and toxicity with 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation, International Journal of Radiation Oncology Biology Physics, 87, 1051-1057, 2013 **Ref Id** 614611 **Country/ies where the study was carried out** Spain **Study type** RCT	**Sample size** Please see Hickey 2016 Cochrane systematic review. **Characteristics** Please see Hickey 2016 Cochrane systematic review. **Inclusion criteria** Women age ≥60 years; invasive ductal carcinoma; unifocal tumor; primary tumor size ≤30 mm (pT2); cN0, pN0 axillary status; and histologic grade 2 or less. **Exclusion criteria** Bilateral breast carcinoma; prior unilateral or contralateral breast cancer; concomitant or other previous malignancies; pure ductal or lobular carcinoma in situ (pTis); invasive lobular carcinoma; presence of an extensive intraductal component; excision with microscopically positive or close (3 mm)	**Interventions** Please see Hickey 2016 Cochrane systematic review.	**Details** Please see Hickey 2016 Cochrane systematic review.	**Results** Please see Hickey 2016 Cochrane systematic review. Survival rates: The authors report no significant differences in survival rates were found. No data provided.	**Limitations** Please see Hickey 2016 Cochrane systematic review. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Aim of the study To compare accelerated partial breast irradiation (APBI) and whole breast irradiation (WBI) using 3-dimensional conformal external beam radiation therapy (3D-CRT) in patients with early-stage breast cancer and present the interim results analysing the efficacy, toxicity, and cosmesis of the breast-conserving treatments. **Study dates** Not reported. **Source of funding** None disclosed.	surgical margins; multicentric disease; nodepositive disease; concomitant or neoadjuvant chemotherapy; and postsurgical hematoma >2 cm, or seroma fluid that required multiple aspirations.				
Full citation Strnad, V., Ott, O. J., Hildebrandt, G., Kauer-Dorner, D., Knauerhase, H., Major, T., Lyczek, J., Guinot, J. L., Dunst, J., Miguelez, C. G., Slampa, P., Allgauer, M., Lossl, K., Polat, B., Kovacs, G., Fischedick, A. R., Wendt, T. G., Fietkau,	**Sample size** Please see Hickey 2016 Cochrane systematic review. **Characteristics** Please see Hickey 2016 Cochrane systematic review. **Inclusion criteria**	**Interventions** Please see Hickey 2016 Cochrane systematic review.	**Details** Please see Hickey 2016 Cochrane systematic review.	**Results** Please see Hickey 2016 Cochrane systematic review.	**Limitations** Please see Hickey 2016 Cochrane systematic review. **Other information** Early side effect results from the Groupe Européen de Curiethérapie of European Society

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
R., Hindemith, M., Resch, A., Kulik, A., Arribas, L., Niehoff, P., Guedea, F., Schlamann, A., Potter, R., Gall, C., Malzer, M., Uter, W., Polgar, C., 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: A randomised, phase 3, non-inferiority trial, The Lancet, 387, 229-238, 2016 **Ref Id** 553507 **Country/ies where the study was carried out** Austria, Czech Republic, Germany, Hungary, Poland, Spain, and Switzerland. **Study type** Multi-centre RCT **Aim of the study**	Women ≥ aged 40 years; pTis or pT1–2a (lesions of ≤3 cm diameter), pN0/pNmi, and M0 breast cancer (stage 0, I, and IIA), undergone local excision of the breast tumour with microscopically clear resection margins of at least 2 mm in any direction; no lymph or blood-vessel invasion (L0, V0); DCIS lesions classified as low or intermediate risk (Van Nuys prognostic index <8); axillary dissection with minimum of six nodes in the specimen or a negative sentinel node was required in patients with invasive carcinoma; axillary staging in case of pure DCIS. **Exclusion criteria** Women aged < 40 years; multiple tumour foci or an extensive intraductal component; Paget's disease or pathological skin involvement; synchronous or previous breast cancer; history of other malignant disease; pregnant or lactating.				for Radiotherapy and Oncology (GEC-ESTRO) multicentre, phase 3, randomised controlled trial are presented in Ott 2016. Late side-effects and cosmesis for this trial are presented in Polgar 2017.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
To compare accelerated partial breast irradiation (APBI) and whole-breast irradiation in patients with stage 0, I, and IIA breast cancer. **Study dates** April 2004 -July 2009 **Source of funding** German Cancer Aid and consultation fees from Nucletron Operations BV, an Elekta Company.					

3D-CRT: 3 dimensional conformal radiotherapy; APBI: Accelerated partial breast irradiation; BCS: breast conserving surgery; CTC, Common Toxicity Criteria; DCIS: ductal carcinoma in situ; EIC: extensive intraductal component; EORTC QLQ-30: European Organisation for Research and Treatment of Cancer Quality of Life Questionairre; EQ5D: EuroQol Research Foundation measure of general health status; GEC-ESTRO: The Groupe Européen de Curiethérapie and the European SocieTy for Radiotherapy & Oncology; Gy: Gray; HDR: High dose rate; HRQoL: health-related quality of life; IMPORT: Intensity Modulated and Partial Organ Radiotherapy; IMRT: intensity modulated radiotherapy; IQR: interquartile range; LVI: lymphovascular invasion; NCI, National Cancer Institute; PBI: Partial breast irradiation; PDR: Pulsed dose rate; RAPID: Randomized Trial of Accelerated Partial Breast Irradiation; RCT: randomised controlled trial; RT: radiotherapy; RTOG: Radiation Therapy Oncology Group; SD: standard deviation; SOMA-LENT: SOMA-LENT: Subjective, Objective, Management, Analytic-Late Effects of Normal Tissues; SR: systematic review; UICC: Union for International Cancer Control; WBRT: Whole breast radiotherapy

Clinical evidence tables for 8.4 What are the indications for radiotherapy to internal mammary nodes?

Table 17: Studies included in the evidence review for radiotherapy to the internal mammary nodes

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Matzinger, O., Heimsoth, I., Poortmans, P., Collette, L., Struikmans, H., Van Den Bogaert, W., Fourquet, A., Bartelink, H., Ataman, F., Gulyban, A., Pierart, M., Van Tienhoven, G., Eortc Radiation Oncology, Breast Cancer, Groups, Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer (EORTC trial 22922/10925), Acta oncologica, 49, 24-34, 2010 **Ref Id** 565843 **Country/ies where the study was carried out** Belgium, Netherlands, France, Germany, Switzerland, Poland, United Kingdom, Bosnia and Herzegovina, Italy, Portugal, Chile, Israel, Spain **Study type** RCT **Aim of the study**	**Sample size** 4004 patients randomised **Characteristics** Gender: 100% women Age: Median 54; range 19-75 Ethnicity: NR **Inclusion criteria** Unilateral, histologically confirmed adenocarcinoma (TX-T3, N0-N2, M0). Undergone mastectomy or breast-conserving treatment and axillary dissection. Centrally or medially located tumours could be N- or N+. Externally located tumours had to be N+ **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest	**Interventions** **Intervention arm:** radiation to internal mammary (IM) and medial supraclavicular (MS) lymph nodes **Control arm:** no radiation to IM and MS lymph nodes	**Details** **Intervention arm (IM RT+):** Prescribed radiotherapy dose was 50 Gy in 25 fractions of 2 Gy - 26 Gy delivered with photons and 24 Gy delivered with electrons. One anterior field for the IM-MS radiation was recommended. **Control arm (IM RT-):** no details reported.	**Results** **Treatment-related morbidity - lung toxicity (3 year follow-up):** IM RT+ 83/1922; IM RT- 26/1944 **Treatment-related morbidity - breast skin toxicity (3 year follow-up)** IM RT+ 262/1922; IM RT- 246/1944 **Treatment-related morbidity - mastitis (3 year follow-up)** IM RT+ 6/1922; IM RT- 7/1944 **Treatment-related morbidity - breast infection (3 year follow-up)** IM RT+ 3/1922; IM RT- 4/1944 **Treatment-related morbidity - radionecrosis (3 year follow-up)** IM RT+ 1/1922; IM RT- 2/1944	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low **Attrition bias** Complete follow-up data available for 95.3% of patients but unclear what percentage available in each arm: Unclear **Selective reporting** Low **Indirectness**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Trial aim: to investigated the potential survival benefit and toxicity of elective irradiation of the internal mammary and medial supraclavicular (IM-MS) nodes. Study aim: to examine toxicity up to three years after treatment. **Study dates** Recruited July 1996 to January 2004 **Source of funding** National Cancer Institute (Bethesda, Maryland, USA)				**Treatment-related morbidity - osteonecrosis (3 year follow-up)** IM RT+ 27/1922; IM RT- 22/1944 **Treatment-related morbidity - oedema (3 year follow-up)** IM RT+ 151/1922; IM RT- 155/1944 **Treatment-related morbidity - breast/chest wall pain (3 year follow-up)** IM RT+ 35/1922; IM RT- 45/1944 **Treatment-related morbidity - retrosternal pain (3 year follow-up)** IM RT+ 2/1922; IM RT- 1/1944 **Treatment-related morbidity - Dysphagia (3 year follow-up)** IM RT+ 4/1922; IM RT- 0/1944 **Treatment-related morbidity - Fatigue (3 year follow-up)** IM RT+ 22/1922; IM RT- 20/1944	None **Limitations** The protocol contained no guidelines which patients were to receive adjuvant treatment (hormonotherapy, chemotherapy). Unclear if rates were equivalent across arms. **Other information** EORTC trial 22922/10925

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Treatment-related morbidity - arm/shoulder function impairment (3 year follow-up) IM RT+ 1/1922; IM RT- 8/1944	
Full citation Hennequin, C., Bossard, N., Servagi-Vernat, S., Maingon, P., Dubois, J. B., Datchary, J., Carrie, C., Roullet, B., Suchaud, J. P., Teissier, E., Lucardi, A., Gerard, J. P., Belot, A., Iwaz, J., Ecochard, R., Romestaing, P., Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy.[Erratum appears in Int J Radiat Oncol Biol Phys. 2014 Aug 1;89(5):1145], International journal of radiation oncology, biology, physics, 86, 860-6, 2013 **Ref Id** 566242 **Country/ies where the study was carried out** France **Study type** RCT	**Sample size** 1407 patients randomised, 73 lost to follow-up at the beginning of the study, leaving 1334 for analysis. **Characteristics** Gender: 100% women Age: NR Ethnicity: NR **Inclusion criteria** Patients (aged <75) with stage I or II adenocarcinoma of the breast (tumour >1cm) that were undergoing modified radical mastectomy. Must have had positive axillary nodes or a medial/central tumour with or without axillary node involvement. 70% Karnofsky performance scale. **Exclusion criteria**	**Interventions** **Intervention arm:** radiotherapy to chest wall, supraclavicular nodes, apical axillary nodes for pN+ cases, and the internal mammary chain. **Control arm:** radiotherapy to the chest wall, supraclavicular nodes and apical axillary nodes for pN+ cases. No radiotherapy to internal mammary chain.	**Details** **Intervention arm (IM RT+):** Supraclavicular and apical axillary nodes were treated usually with a single-field dose calculated at a 3-cm depth. A posterior axillary field was used to obtain the reference dose at mid-depth. The prescribed dose to the target volume was 50 Gy or equivalent. All patients were treated in the supine position, with addition of wedges when necessary. The ipsilateral parasternal area, including the internal mammary chain, was treated using a combination of photons and electrons up to a total of 12.5 Gy, given in 5 fractions (2.5 Gy per fraction, 4 fractions per week), at a 3-cm depth, and 9-12 MeV electrons up to a total of 32.5 Gy, given in 13 fractions (2.5 Gy per fraction, 4 fractions per week) for a total treatment time of approximately 5	**Results** **DFS (10 year follow-up):** O-E: 12.25; V: 171.69 **OS (10 year follow-up):** O-E: 3.61; V: 203.07 **Treatment-related morbidity - GRADE 3+ on SOMA-LENT scale (10 year follow-up):** IM RT+ 21/672, IM RT- 15/662 **Treatment-related morbidity - cardiac events (10 year follow-up):** IM RT+ 15/672, IM RT- 11/662	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Assigned by coordinating centre: Low **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low **Attrition bias** 73 lost to follow-up but treatment arm not reported so unclear if this differed between groups: Unclear

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Aim of the study To compare 10 year overall survival of patients who received IMN radiation after postmastectomy with that of patients who did not **Study dates** Recruited January 1991 to December 1997 **Source of funding** Ligue Nationale contre le Cancer and PARCC-ARA	Bilateral breast cancer, history of cancer or severe comorbidity or metastatic disease. **Reported subgroups** None of interest		weeks. The medial border was set on the midline and the lateral border was laid 6-cm lateral from the midline. The field was approximately 14 cm high in order to include the first 5 intercostal spaces. The lateral and superior edges of the IMN field were matched to the field irradiating the chest wall and the supraclavicular field. **Control arm (IM RT-):** Supraclavicular and apical axillary nodes were treated usually with a single-field dose calculated at a 3-cm depth. A posterior axillary field was used to obtain the reference dose at mid-depth. The prescribed dose to the target volume was 50 Gy or equivalent. All patients were treated in the supine position, with addition of wedges when necessary. The internal border of the chest wall field was placed at the external border of a sham internal mammary node field and care was taken to avoid inclusion of the first intercostal spaces in the supraclavicular field.		**Selective reporting** Low **Indirectness** None **Limitations** Risk of IMN involvement overestimated - probably decreased power. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Poortmans, P. M., Collette, S., Kirkove, C., Van Limbergen, E., Budach, V., Struikmans, H., Collette, L., Fourquet, A., Maingon, P., Valli, M., De Winter, K., Marnitz, S., Barillot, I., Scandolaro, L., Vonk, E., Rodenhuis, C., Marsiglia, H., Weidner, N., van Tienhoven, G., Glanzmann, C., Kuten, A., Arriagada, R., Bartelink, H., Van den Bogaert, W., Eortc Radiation Oncology, Breast Cancer, Groups, Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer, New England Journal of MedicineN Engl J Med, 373, 317-27, 2015 **Ref Id** 566650 **Country/ies where the study was carried out** Belgium, Netherlands, France, Germany, Switzerland, Poland, United Kingdom, Bosnia and Herzegovina, Italy, Portugal, Chile, Israel, Spain **Study type** RCT **Aim of the study** To investigate the effect of elective internal mammary and	**Sample size** 4004 randomised **Characteristics** Gender: 100% women Age: Median 54, range 19-75 Ethnicity: NR **Inclusion criteria** Unilateral histologically confirmed breast adenocarcinoma of stage I, II, or III with a centrally or medially located primary tumour, irrespective of axillary involvement, or an externally located tumour with axillary involvement. Eligible patients had undergone mastectomy or breast conserving surgery and axillary dissection. **Exclusion criteria** No additional criteria reported **Reported subgroups** Extent of lymph node metastases (0 [N0], 1-3 [N1], 4+[N2/3]; T stage (1,2,3)	**Interventions** **Intervention arm:** whole breast/thoracic-wall radiation + radiation to internal mammary and medial supraclavicular lymph nodes **Control arm:** whole breast/thoracic-wall radiation only	**Details** **Intervention arm (IM RT+):** Regional nodal irradiation at a dose of 50 Gy in 25 fractions. No further information reported. **Control arm (IM RT-):** No details reported.	**Results** **Whole sample:** **DFS (10 year follow-up):** O-E: -35.96; V: 308.59 **Treatment-related morbidity - pulmonary fibrosis (10 year follow-up):** IM RT+ 85/1922; IM RT- 33/1944 **Treatment-related morbidity - cardiac fibrosis (10 year follow-up):** IM RT+ 23/1922; IM RT- 12/1944 **Treatment-related morbidity - cardiac disease (10 year follow-up):** IM RT+ 125/1922; IM RT- 109/1944 **Treatment-related morbidity - secondary cancer (10 year follow-up):** IM RT+ 191/1922; IM RT- 222/1944	**Selection bias: random sequence generation** Minimisation algorithm: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have significant impact: Low **Detection bias** Low **Attrition bias** 45 and 69 did not receive treatment per protocol in the IM RT- and IM RT+ arms, respectively: Unclear **Selective reporting** Low **Indirectness** None **Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
medial supraclavicular lymph-node irradiation (here termed regional nodal irradiation) on overall survival. **Study dates** Recruited July 1996 to January 2004 **Source of funding** Fonds Cancer				**OS (10 year follow-up):** O-E: -28.41; V: 204.02 **Extent of lymph node metastases: 0** **DFS (10 year follow-up):** O-E: -19.3; V: 115.1 **Extent of lymph node metastases: 1-3** **DFS (10 year follow-up):** O-E: -15.9; V: 135.2 **Extent of lymph node metastases: 4+** **DFS (10 year follow-up):** O-E: -1.17; V: 22.87 **T stage: 1** **DFS (10 year follow-up):** O-E: -10.5; V: 153.7	EORTC trial 22922/10925

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				T stage: 2 **DFS (10 year follow-up):** O-E: 27.3; V: 143 **T stage: 3** **DFS (10 year follow-up):** O-E: -1.5; V: 14.5	
Full citation Whelan, T. J., Olivotto, I. A., Parulekar, W. R., Ackerman, I., Chua, B. H., Nabid, A., Vallis, K. A., White, J. R., Rousseau, P., Fortin, A., Pierce, L. J., Manchul, L., Chafe, S., Nolan, M. C., Craighead, P., Bowen, J., McCready, D. R., Pritchard, K. I., Gelmon, K., Murray, Y., Chapman, J. A., Chen, B. E., Levine, M. N., M. A. Study Investigators, Regional Nodal Irradiation in Early-Stage Breast Cancer, New England Journal of MedicineN Engl J Med, 373, 307-16, 2015 **Ref Id** 566692	**Sample size** 1832 recruited **Characteristics** Gender: 100% women Age: RT+ Median 54, range 29-84; RT- Median 53, range 26-84 Ethnicity: NR **Inclusion criteria** Women with invasive carcinoma of the breast who were treated with breast-conserving surgery and sentinel lymph node biopsy or axillary node dissection and had positive axillary lymph nodes or negative axillary lymph nodes with	**Interventions** **Intervention arm:** whole breast radiation + radiation to ipsilateral internal mammary, supraclavicular and axillary lymph nodes. **Control arm:** whole breast radiation only	**Details** **Intervention arm (IM RT+):** The breast was treated with a pair of opposed fields tangentially arranged across the chest - dose of 50Gy in 25 fractions. Radiation of the internal mammary nodes (50Gy in 25 fractions) was performed using a modified wide-tangent technique (upper tangents widened to include internal mammary nodes and narrowed inferiorly to reduce dose to heart and lung) or separate internal mammary node field plus tangents (mixed electron and photon field angled to match tangent fields). CT planning was recommended with internal mammary node defined as	**Results** **Whole sample:** **Locoregional recurrence (10 year follow-up):** O-E: -12.24; V: 23.20 **DFS (10 year follow-up):** O-E: -22.55; V: 82.18 **Treatment related morbidity - Grade 2+ fatigue (National Cancer Institute Common Toxicity Criteria; occurring within 3 months following completion of radiation):**	**Selection bias: random sequence generation** Centralized minimization procedure: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out Canada, USA, Australia **Study type** RCT **Aim of the study** Whether the addition of regional nodal irradiation to whole-breast irradiation following breast-conserving surgery improved outcomes (primarily overall survival) **Study dates** Recruited March 2000 to February 2007 **Source of funding** Canadian Cancer Society Research Institute to the NCIC Clinical Trials Group (021039 and 015469), the Canadian Breast Cancer Research Initiative (010415), the U.S. National Cancer Institute (CA077202, CA32102, and CA27057) and the Cancer Council of Victoria, New South Wales, Queensland, and South Australia (288720).	high-risk features (tumour ≥5cm or ≥2cm with fewer than 10 axillary lymph nodes removed and at least one of the following: grade 3, ER-, or lymphovascular invasion). Level I or II axillary dissection was required for patients with positive SLNB. All patients received adjuvant systemic therapy (chemotherapy and/or endocrine therapy). **Exclusion criteria** Patients were excluded if they had T4 tumours (clinical evidence of direct extension to chest wall or skin) or N2–3 nodes (involvement of axillary nodes that are fixed or of internal mammary nodes), distant metastasis, or serious nonmalignant disease (e.g., cardiovascular or pulmonary) that would preclude definitive radiation therapy. Also excluded if currently pregnant or lactating, had concurrent or previous malignancies, psychiatric or addictive disorders which precluded obtaining informed consent or adherence to protocol, or inability to receive radiotherapy within 8 weeks of completing adjuvant chemotherapy or within 16		1cm around internal mammary vessels in the first three intercostal spaces to be covered by at least the 80% isodose. Supraclavicular and level III axillary nodes (extended to include level I and II nodes for patients who had fewer than 10 axillary nodes removed or more than 3 positive axillary nodes) were treated with a non-divergent anterior field to include the head of the clavicle medially and the coracoid process laterally (50 Gy in 25 fractions as depth of 3cm). For patients who were treated with anterior and posterior fields, a dose of 45Gy in 25 fractions was prescribed at midseparation at the centre of the fields. **Control arm (IM RT-):** the breast was treated with a pair of opposed fields tangentially arranged across the chest - dose of 50Gy in 25 fractions.	IM RT+ 170/893; IM RT- 169/927 **Treatment related morbidity - Grade 2+ pain (National Cancer Institute Common Toxicity Criteria; occurring within 3 months following completion of radiation):** IM RT+ 53/893; IM RT- 40/927 **Treatment related morbidity - Grade 2+ pneumonitis (National Cancer Institute Common Toxicity Criteria; occurring within 3 months following completion of radiation):** IM RT+ 11/893; IM RT- 2/927 **Treatment related morbidity - Grade 2+ radiation dermatitis (National Cancer Institute Common Toxicity Criteria; occurring within 3 months following completion of radiation):**	**Attrition bias** RT+ arm: loss to follow-up 21, withdrew consent 17; RT- arm: loss to follow-up 16, withdrew consent 18: Low **Selective reporting** Low **Indirectness** None **Limitations** Most of the included patients had no more than 3 positive lymph nodes. It is likely that patients with more than three nodes were routinely treated off trial with regional nodal irradiation, which would potentially decrease the probability of detecting a significant effect on overall survival in this trial. Also, since most patients were treated with multiagent chemotherapy containing anthracyclines or taxanes and endocrine therapy, the baseline risk of death and the power to detect a between-group improvement in overall survival were probably further reduced. **Other information** MA.20 trial

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	weeks after the last surgical breast procedure for patients receiving endocrine therapy only. **Reported subgroups** Extent of lymph node metastases (0, 1-3, 4+); tumour position (medial, lateral)			IM RT+ 442/893; IM RT- 372/927 **Treatment related morbidity - Grade 2+ cardiac events (National Cancer Institute Common Toxicity Criteria; occurring greater than 3 months following completion of radiation):** IM RT+ 8/893; IM RT- 4/927 **Treatment related morbidity - Grade 2+ lymphoedema (National Cancer Institute Common Toxicity Criteria; occurring greater than 3 months following completion of radiation):** IM RT+ 75/893; IM RT- 42/927 **Treatment related morbidity - Grade 2+ pneumonitis or fibrosis (National Cancer Institute Common Toxicity Criteria; occurring greater than 3 months following completion of radiation):** IM RT+ 4/893; IM RT- 3/927	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Treatment related morbidity - secondary cancer (National Cancer Institute Common Toxicity Criteria; occurring greater than 3 months following completion of radiation): IM RT+ 98/893; IM RT- 93/927 **OS (10 year follow-up):** O-E: -7.13; V: 75.64 **Extent of lymph node metastases: 0** **DFS (10 year follow-up):** O-E: -4.97; V: 8.32 **Extent of lymph node metastases: 1-3** **DFS (10 year follow-up):** O-E: -16.26; V: 68.98 **Extent of lymph node metastases: 4+**	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				DFS (10 year follow-up): O-E: -2.43; V: 7.10**-O** **Tumour location: medial** **DFS (10 year follow-up):** O-E: -6.50; V: 12.73 **Tumour location: lateral** **DFS (10 year follow-up):** O-E: -13.90; 53.17	
Full citation Choi, J., Kim, Y. B., Shin, K. H., Ahn, S. J., Lee, H. S., Park, W., Kim, S. S., Kim, J. H., Lee, K. C., Kim, D. W., Suh, H. S., Park, K. R., Shin, H. S., Suh, C. O., 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 CancerJ, 19, 275-282, 2016 **Ref Id** 566731	**Sample size** 747 recruited. 25 patients (3.3%) who had not undergone chest X-ray within 6 months of radiotherapy completion were excluded from the analysis, leaving 722 analysable patients. **Characteristics** Gender: NR Age: Median 48, range 28-77	**Interventions** **Intervention arm:** breast radiotherapy + supraclavicular and internal mammary lymph nodes **Control arm:** breast radiotherapy + supraclavicular lymph nodes	**Details** **Intervention arm (IM RT+):** Radiation was administered once per day at a dose of 1.8–2 Gy, up to a total dose of 45–50.4 Gy. The protocol contained no strict guidelines on radiotherapy technique - techniques determined at discretion of physician. Most common technique was partial wide tangent. **Control arm (IM RT-):** Radiation was administered once per day at a dose of	**Results** **Treatment-related morbidity - radiation pneumonitis within 6 months of completing radiotherapy:** RT+ 23/356; RT- 12/366	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out Korea **Study type** RCT **Aim of the study** To investigate the effect of internal mammary node irradiation on disease-free survival and toxicity in breast cancer patients. **Study dates** Recruited November 2008 to February 2013 **Source of funding** National R&D Program for Cancer Control, Ministry for Health, Welfare, and Family Affairs, Republic of Korea (0820010)	Ethnicity: NR **Inclusion criteria** Eligible patients were pathologically confirmed to have axillary node-positive breast cancer after surgery (either modified radical mastectomy or breast-conserving surgery). All patients underwent axillary dissection in which eight or more lymph nodes were identified. **Exclusion criteria** Patients who received neoadjuvant systemic therapy or had a previous history of cancer or distant metastasis were excluded. **Reported subgroups** None of interest		1.8–2 Gy, up to a total dose of 45–50.4 Gy. The protocol contained no strict guidelines on radiotherapy technique - techniques determined at discretion of physician. Most common technique was standard tangent method.		**Detection bias** Low **Attrition bias** Not reported: Unclear **Selective reporting** Disease free survival not reported: Unclear **Indirectness** None **Limitations** One drawback of this study is that the chest X-ray follow-up visit could occur at any time within 6 months after RT. Considering that most radiologic changes in this study were found at 2 or 3 months after RT, the heterogeneity of the follow-up time among patients may have caused an underestimation of asymptomatic grade 1 RP. **Other information** KROG 08-06 trial
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Selection:**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Thorsen, L. B., Offersen, B. V., Dano, H., Berg, M., Jensen, I., Pedersen, A. N., Zimmermann, S. J., Brodersen, H. J., Overgaard, M., Overgaard, J., DBCG-IMN: A Population-Based Cohort Study on the Effect of Internal Mammary Node Irradiation in Early Node-Positive Breast Cancer, Journal of clinical oncology, 34, 314-20, 2016 **Ref Id** 566840 **Country/ies where the study was carried out** Denmark, Germany **Study type** Prospective, population-based, cohort study **Aim of the study** To investigate the effect of internal mammary node irradiation (IMNI) in patients with early stage node-positive breast cancer **Study dates**	3377 assessed for eligibility, 3089 patients included **Characteristics** Gender: NR Age: RT+ median 56, range 22-70; RT- median 56, range 27-70 Ethnicity: NR **Inclusion criteria** Patients treated with radiotherapy after surgery (mastectomy or breast-conserving surgery - including axillary lymph node dissection of axillary level I and part of level II) for unilateral, node-positive breast cancer. **Exclusion criteria** Patients who experienced recurrence before radiotherapy, were unfit for standard radiotherapy, only had micro-metastatic nodes, were older than 70 years of age at operation, or had prior malignancy were excluded. **Reported subgroups** None of interest	**Intervention arm:** radiotherapy to the breast/chest wall, scar, supraclavicular and infraclavicular nodes and axillary + internal mammary nodes **Control arm:** radiotherapy to the breast/chest wall, scar, supraclavicular and infraclavicular nodes and axillary.	**Intervention arm (IM RT+ [right sided cancers]):** Radiotherapeutic dose to the breast/chest wall, scar, supraclavicular nodes, infraclavicular nodes, and axillary levels II to III was 48Gy in 24 fractions, administered in five fractions per week. If six or more axillary nodes contained macromtastases. axillary level I was treated. In patients with right-sided breast cancer, the internal mammary nodes in intercostal spaces one to four were treated with anterior electron field or by inclusion in tangential photon fields. **Control arm: (IM RT- [left sided cancers]):** Radiotherapeutic dose to the breast/chest wall, scar, supraclavicular nodes, infraclavicular nodes, and axillary levels II to III was 48Gy in 24 fractions, administered in five fractions per week. If six or more axillary nodes contained macro-mestases. axillary level I was treated.	**OS (8 year follow-up):** O-E: -42.89; V: 216.14	Method of selection appropriate and likely to produce cohort representative of the time. May not be representative of current practice as inclusion stopped with introduction of taxanes. **Comparability:** Differences between groups were adjusted for in analysis. However, groups differed with respect to laterality. **Outcome:** Assessment of outcomes and follow-up were adequate **Indirectness** None **Limitations** Exclusion of patients unfit to receive standard radiotherapy may have led to an overestimation of the treatment effect. Also, there was a lack of radiation-induced morbidity that did not result in death. Further, because IM radiation was avoided in left-side breast cancer, can make no conclusion about cardiotoxicity of radiotherapy in these patients. Due to

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Recruited January 2003 to December 2007 **Source of funding** Danish Cancer Society; the Breast Friends breast cancer campaign; and the Lundbeck Foundation Center for Interventional Research in Radiation Oncology, Max and Inger Wørzners Memorial Foundation					advances in surgery and systemic treatment of early-stage breast cancer, results of this study may not readily apply to current breast cancer patient populations. **Other information** DBCG-IMN trial

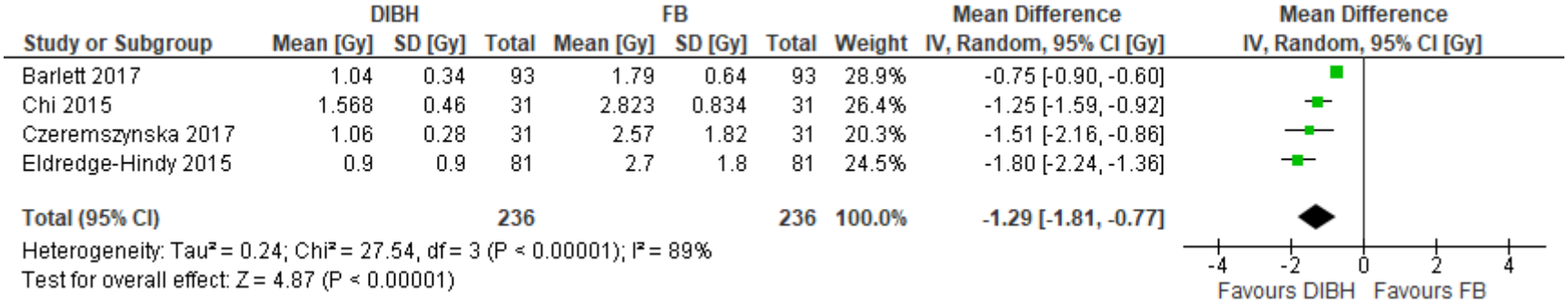
DBCG, Danish Breast Cancer Group; EORTC, European Organisation for Research and Treatment of Cancer; Gy, gray; IM, internal mammary; IMN, internal mammary nodes; KROG, Korean Radiation Oncology Group MeV, megaelectronvolt; MS, medial supraclavicular; NR, not reported; RT, radiotherapy; SLNB, sentinel lymph node biopsy

Appendix E – Forest plots

Forest plots for 8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?

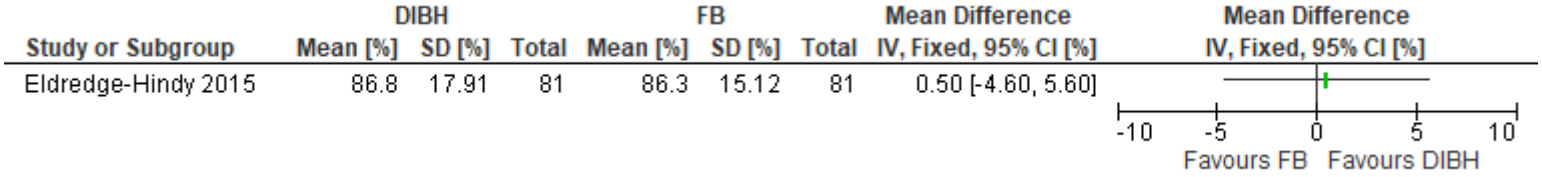
Comparison 1. Deep inspiration breat-hold versus free breathing

Figure 5: Mean heart dose



CI: Confidence Interval; DIBH: Deep inhalation breath-hold; FB: Free breathing; Gy: Gray

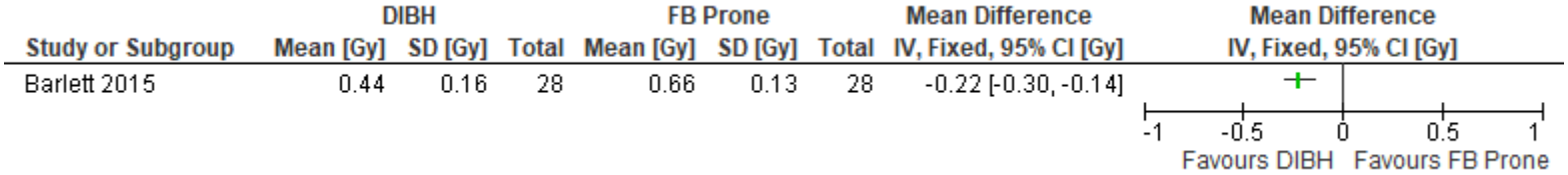
Figure 6: Target coverage



CI: Confidence Interval; DIBH: Deep inhalation breath-hold; FB: Free breathing; Gy: Gray

Comparison 2. Deep inspiration breath-hold versus prone radiotherapy

Figure 7: Mean heart dose



CI: Confidence Interval; DIBH: Deep inhalation breath-hold; FB: Free breathing; Gy: Gray

Forest plots for 8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?

Comparison 1. No whole breast radiotherapy versus whole breast radiotherapy

Figure 8: Local recurrence at 5 to 12 year follow-up

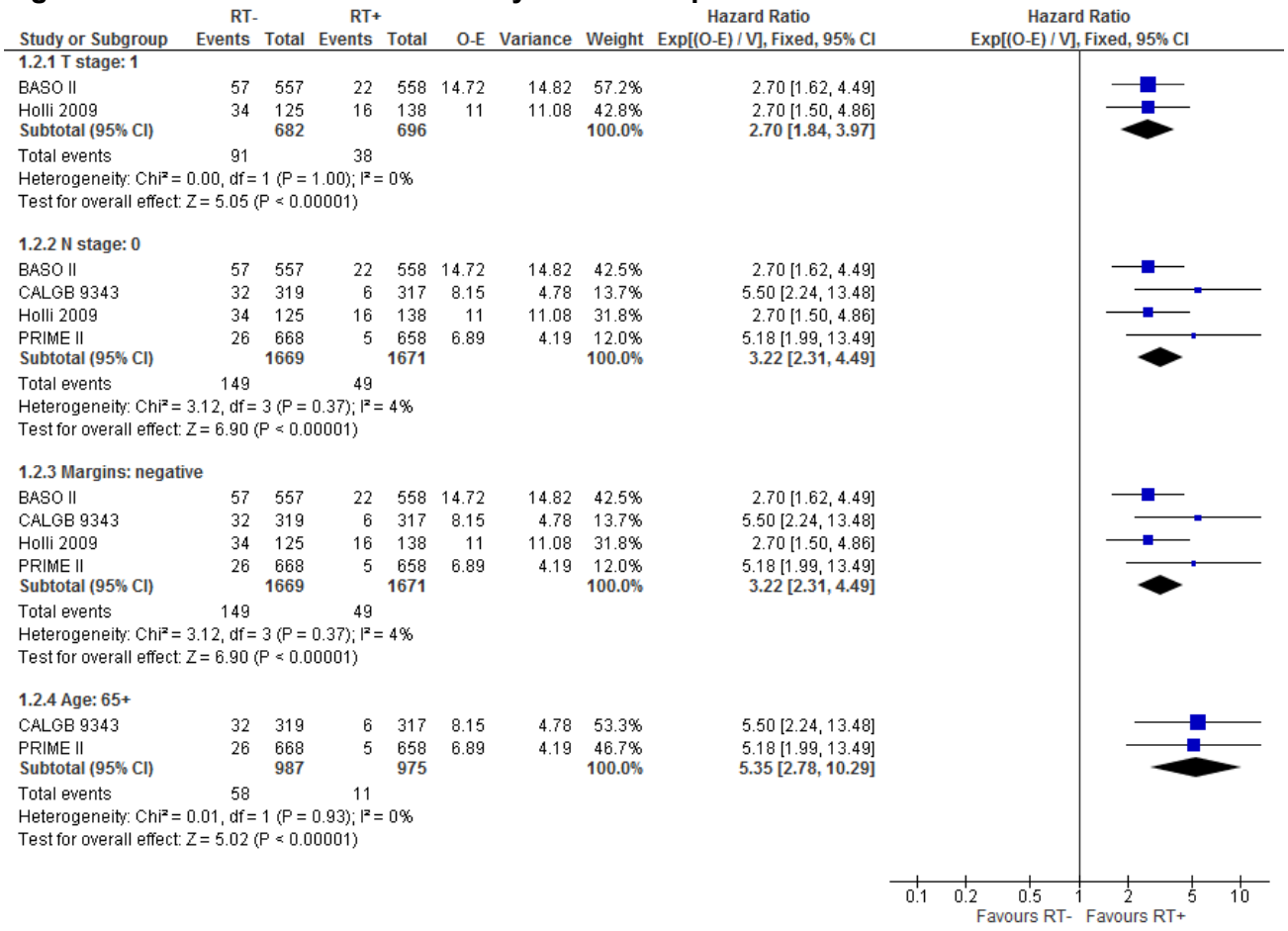


Figure 9: Treatment-related morbidity: fractures (cause unspecified) at 5 year follow-up (all patients N stage 0, 65+, negative margins)

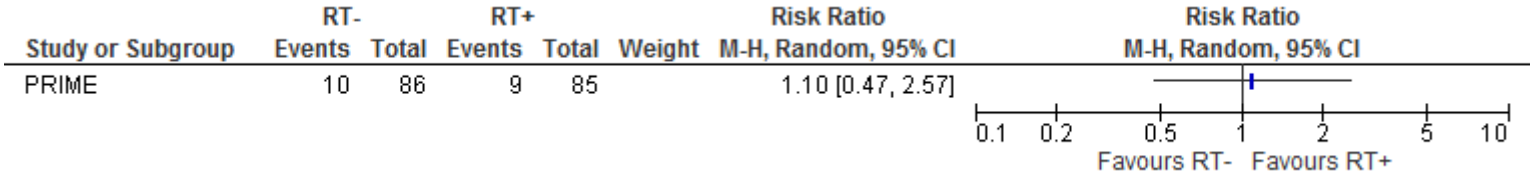


Figure 10: Treatment-related morbidity: congestive cardiac failure at 5 year follow-up (all patients N stage 0, 65+, negative margins)

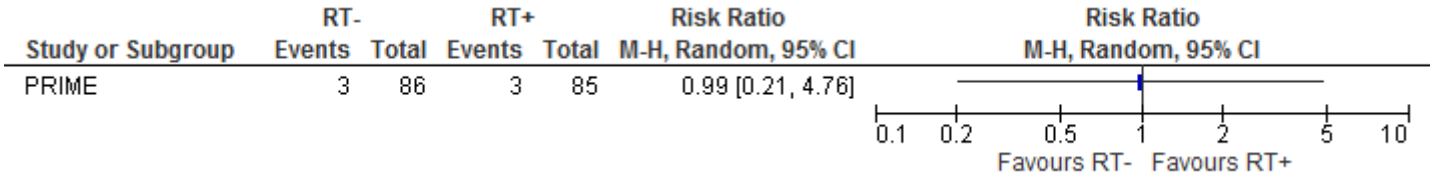


Figure 11: Treatment-related morbidity: myocardial infarction at 5 year follow-up (all patients N stage 0, 65+, negative margins)

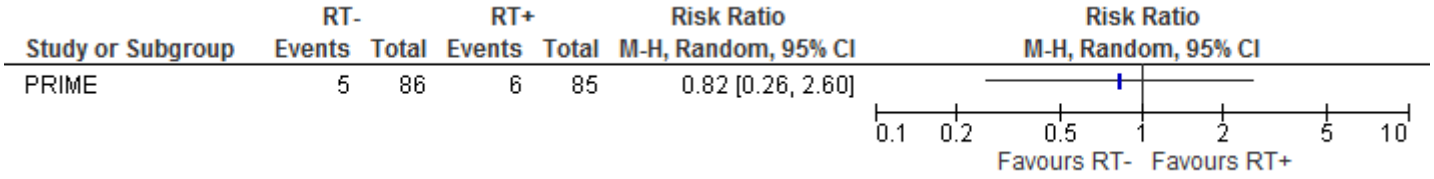


Figure 12: Treatment-related morbidity: secondary cancer (cause unspecified) at 5 year follow-up (all patients N stage 0, 65+, negative margins)

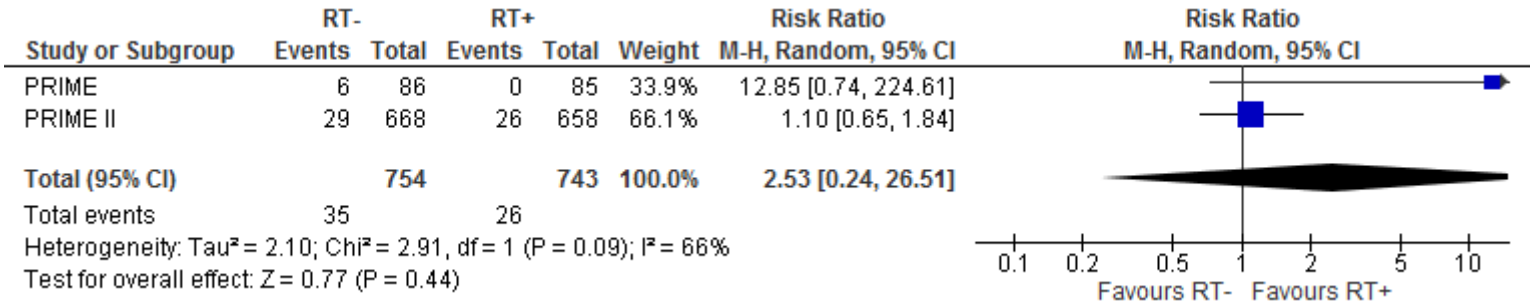


Figure 13: Treatment-related morbidity: score 10+ on HADS anxiety scale at 5 year follow-up (all patients N stage 0, 65+, negative margins)

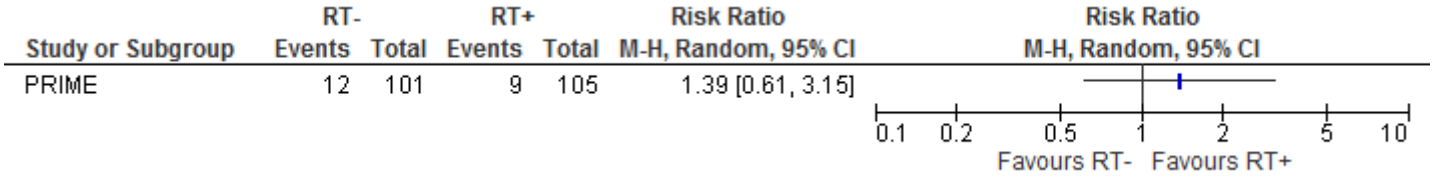


Figure 14: Treatment-related morbidity: score 10+ on HADS depression scale at 5 year follow-up (all patients N stage 0, 65+, negative margins)

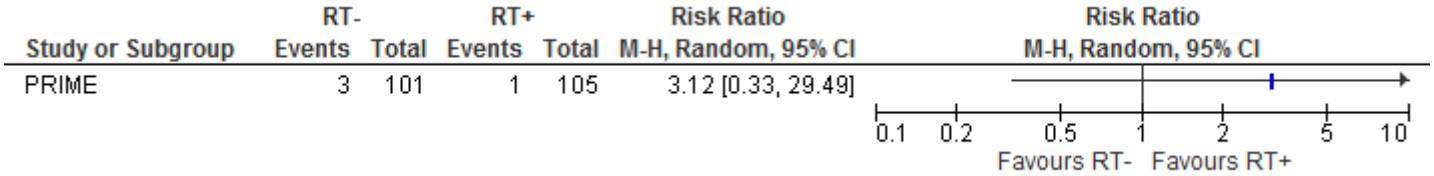


Figure 15: HRQoL: EQ5D scores at 5 year follow-up (all patients N stage 0, 65+, negative margins)

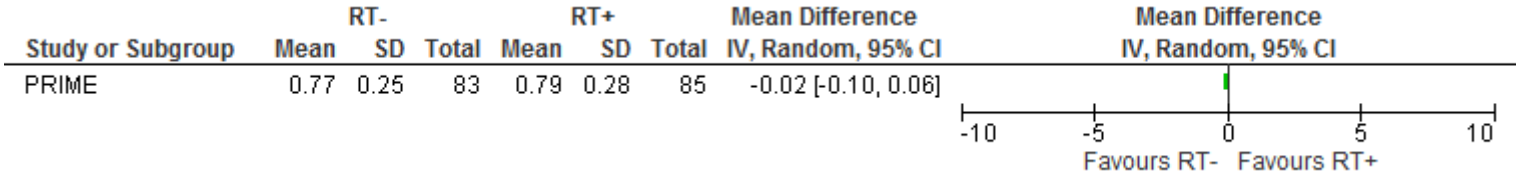


Figure 16: HRQoL: reduction in scores on Breast Cancer Chemotherapy Questionnaire at 2 month follow-up (all patients N stage 0, negative margins)

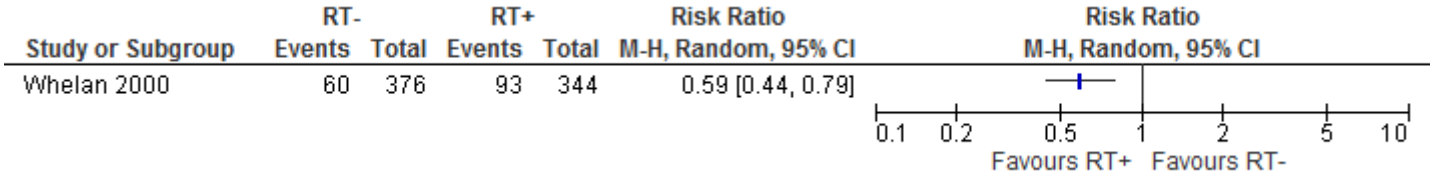
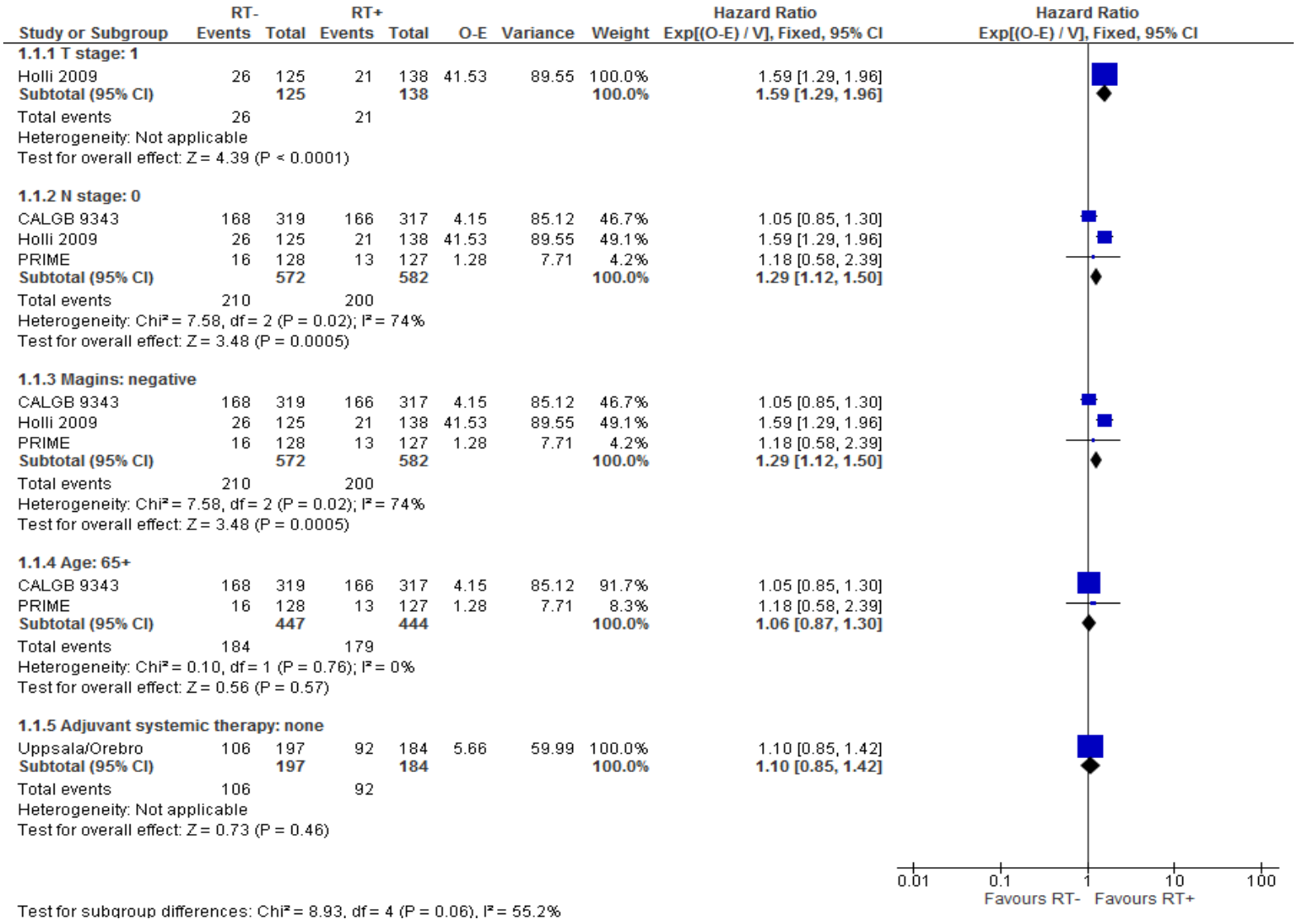


Figure 17: Overall survival at 5 to 20 year follow-up



Forest plots for 8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?

Comparison 1. Whole breast radiotherapy versus partial breast radiotherapy

Figure 18: Local recurrence free survival at 5 to 10 year follow-up

	PBI/APBI		WBRT					Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI
GEC-ESTRO	9	633	5	551	1.45	3.21	15.9%	1.57 [0.53, 4.69]
IMPORT LOW	6	669	9	674	-1.53	3.6	17.8%	0.65 [0.23, 1.84]
Livi 2015	0	260	3	260	-1.38	0.75	3.7%	0.16 [0.02, 1.53]
Polgar 2007	7	128	6	130	1.09	12.61	62.5%	1.09 [0.63, 1.89]
Rodriguez 2013	0	51	0	51	1	0		Not estimable
Total (95% CI)		**1741**		**1666**			**100.0%**	**0.98 [0.63, 1.52]**
Total events	22		23					

Heterogeneity: Chi² = 3.93, df = 3 (P = 0.27); I² = 24%
Test for overall effect: Z = 0.08 (P = 0.93)

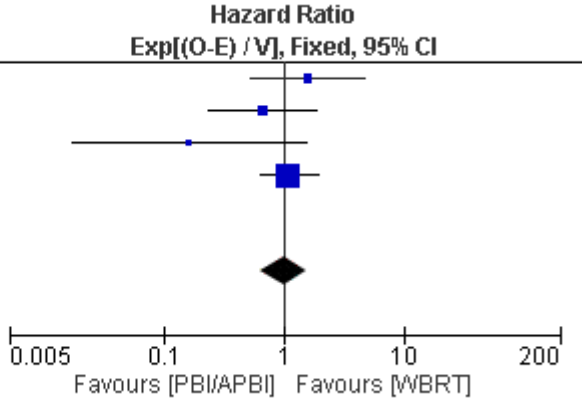


Figure 19: Cosmesis, physician reported at 3 to 5 year follow-up

Study or Subgroup	PBI/APBI Events	PBI/APBI Total	WBRT Events	WBRT Total	Weight	Risk Ratio M-H, Random, 95% CI
GEC-ESTRO	39	352	46	454	19.9%	1.09 [0.73, 1.64]
IMPORT LOW	94	669	134	674	21.3%	0.71 [0.56, 0.90]
Livi 2015	0	246	2	260	2.9%	0.21 [0.01, 4.38]
Polgar 2007	24	125	43	116	19.6%	0.52 [0.34, 0.80]
RAPID	140	399	61	367	21.1%	2.11 [1.62, 2.75]
Rodriguez 2013	12	51	8	51	15.1%	1.50 [0.67, 3.36]
Total (95% CI)		**1842**		**1922**	**100.0%**	**0.99 [0.57, 1.72]**
Total events	309		294			

Heterogeneity: Tau² = 0.36; Chi² = 49.22, df = 5 (P < 0.00001); I² = 90%
Test for overall effect: Z = 0.04 (P = 0.97)

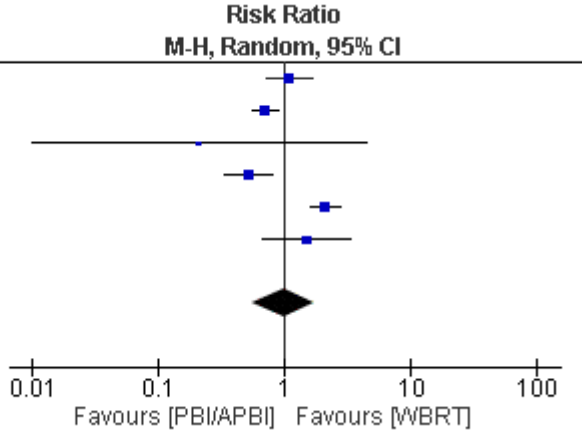


Figure 20: Cosmesis, patient reported at 3 to 5 year follow-up

Study or Subgroup	PBI/APBI Events	PBI/APBI Total	WBRT Events	WBRT Total	Weight	Risk Ratio M-H, Random, 95% CI
GEC-ESTRO	43	541	41	454	31.4%	0.88 [0.58, 1.33]
IMPORT LOW	50	279	60	262	35.1%	0.78 [0.56, 1.09]
RAPID	55	170	34	158	33.4%	1.50 [1.04, 2.17]
Rodriguez 2013	0	51	0	51		Not estimable
Total (95% CI)		**1041**		**925**	**100.0%**	**1.01 [0.67, 1.51]**
Total events	148		135			

Heterogeneity: Tau² = 0.09; Chi² = 7.14, df = 2 (P = 0.03); I² = 72%
Test for overall effect: Z = 0.05 (P = 0.96)

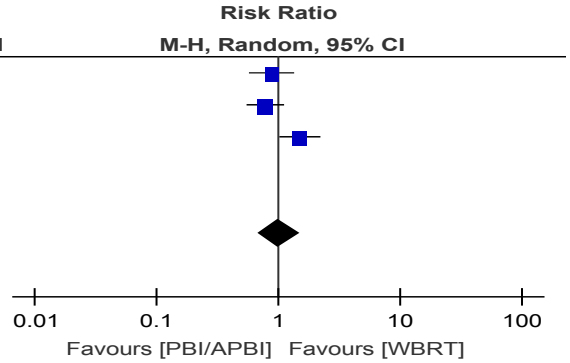


Figure 21: Cosmesis, nurse reported at 5 year follow-up

Study or Subgroup	PBI/APBI Events	PBI/APBI Total	WBRT Events	WBRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RAPID	56	171	22	164	100.0%	2.44 [1.57, 3.81]
Total (95% CI)		**171**		**164**	**100.0%**	**2.44 [1.57, 3.81]**
Total events	56		22			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.94 (P < 0.0001)

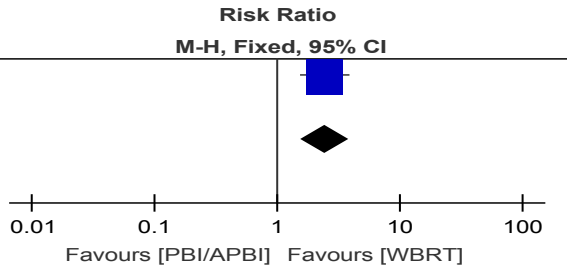


Figure 22: Acute radiotherapy skin toxicity

Study or Subgroup	PBI/APBI Events	PBI/APBI Total	WBRT Events	WBRT Total	Weight	Risk Ratio M-H, Random, 95% CI
GEC-ESTRO	134	630	513	552	41.6%	0.23 [0.20, 0.27]
Livi 2015	5	246	98	260	26.0%	0.05 [0.02, 0.13]
Rodriguez 2013	9	51	38	51	32.4%	0.24 [0.13, 0.44]
Total (95% CI)		**927**		**863**	**100.0%**	**0.16 [0.08, 0.33]**
Total events	148		649			

Heterogeneity: Tau² = 0.32; Chi² = 11.07, df = 2 (P = 0.004); I² = 82%
Test for overall effect: Z = 4.99 (P < 0.00001)

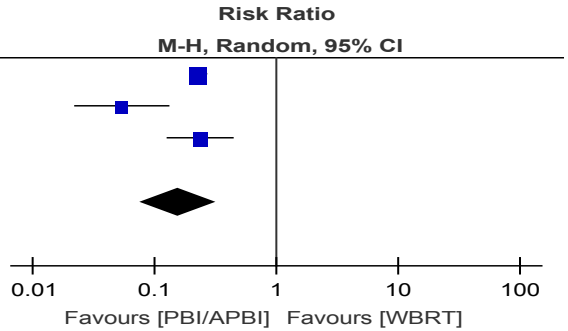


Figure 23: Late radiotherapy skin toxicity (3 to 5 years)

Study or Subgroup	PBI/APBI Events	PBI/APBI Total	WBRT Events	WBRT Total	Weight	Risk Ratio M-H, Random, 95% CI
GEC-ESTRO	17	527	25	442	29.3%	0.57 [0.31, 1.04]
IMPORT LOW	35	421	50	411	30.7%	0.68 [0.45, 1.03]
Livi 2015	0	246	2	260	9.8%	0.21 [0.01, 4.38]
RAPID	79	399	19	367	30.2%	3.82 [2.37, 6.18]
Rodriguez 2013	0	51	0	51		Not estimable
Total (95% CI)		**1644**		**1531**	**100.0%**	**0.97 [0.31, 3.03]**
Total events	131		96			

Heterogeneity: Tau² = 1.05; Chi² = 37.07, df = 3 (P < 0.00001); I² = 92%

Test for overall effect: Z = 0.05 (P = 0.96)

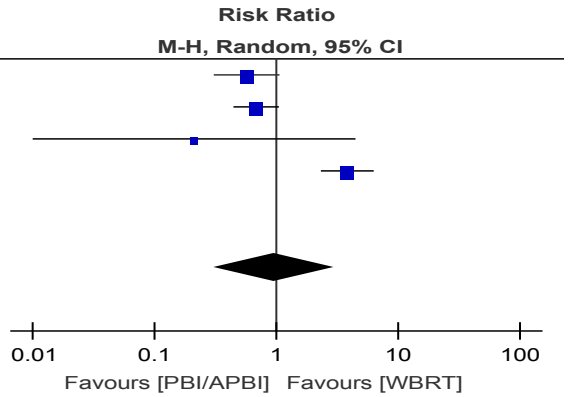


Figure 24: Breast pain (3 to 5 years)

Study or Subgroup	PBI/APBI Events	PBI/APBI Total	WBRT Events	WBRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GEC-ESTRO	3	484	9	393	12.3%	0.27 [0.07, 0.99]
IMPORT LOW	64	421	67	411	83.9%	0.93 [0.68, 1.28]
RAPID	7	399	3	367	3.9%	2.15 [0.56, 8.24]
Total (95% CI)		**1304**		**1171**	**100.0%**	**0.90 [0.67, 1.20]**
Total events	74		79			

Heterogeneity: Chi² = 4.94, df = 2 (P = 0.08); I² = 59%

Test for overall effect: Z = 0.72 (P = 0.47)

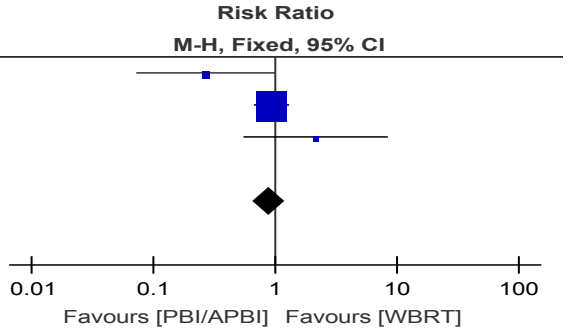


Figure 25: Fat necrosis (3 to 5 years)

Study or Subgroup	PBI/APBI Events	PBI/APBI Total	WBRT Events	WBRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GEC-ESTRO	44	484	27	393	49.0%	1.32 [0.84, 2.10]
Polgar 2007	26	127	26	129	42.4%	1.02 [0.63, 1.65]
RAPID	17	399	5	367	8.6%	3.13 [1.17, 8.39]
Total (95% CI)		**1010**		**889**	**100.0%**	**1.35 [0.98, 1.84]**
Total events	87		58			

Heterogeneity: Chi² = 4.10, df = 2 (P = 0.13); I² = 51%

Test for overall effect: Z = 1.86 (P = 0.06)

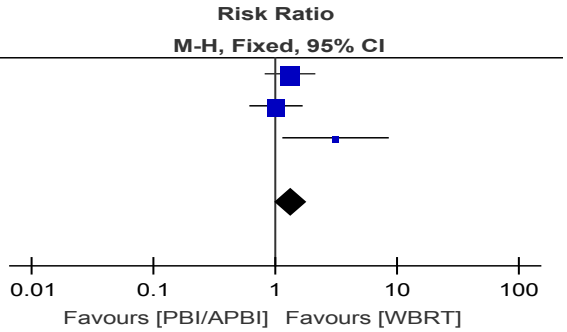


Figure 26: Health-related quality of life, QLQ-C30 scores at 2 years follow up

Study or Subgroup	PBI/APBI Mean	PBI/APBI SD	PBI/APBI Total	WBRT Mean	WBRT SD	WBRT Total	Weight	Mean Difference IV, Fixed, 95% CI
Livi 2015	75.5	13.3	105	59.5	22	100	100.0%	16.00 [10.99, 21.01]
Total (95% CI)			**105**			**100**	**100.0%**	**16.00 [10.99, 21.01]**

Heterogeneity: Not applicable
Test for overall effect: Z = 6.26 (P < 0.00001)

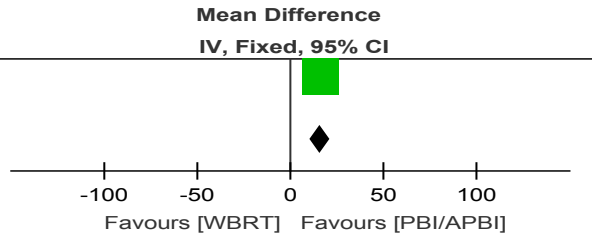


Figure 27: Overall survival

Study or Subgroup	PBI/APBI Events	PBI/APBI Total	WBRT Events	WBRT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
GEC-ESTRO	27	633	32	551	-6.12	14.64	42.1%	0.66 [0.39, 1.10]
IMPORT LOW	37	669	40	674	-1.82	19.25	55.4%	0.91 [0.58, 1.42]
Livi 2015	1	260	7	260	-1.55	0.88	2.5%	0.17 [0.02, 1.39]
Total (95% CI)		**1562**		**1485**			**100.0%**	**0.76 [0.55, 1.06]**
Total events	65		79					

Heterogeneity: Chi² = 2.87, df = 2 (P = 0.24); I² = 30%
Test for overall effect: Z = 1.61 (P = 0.11)

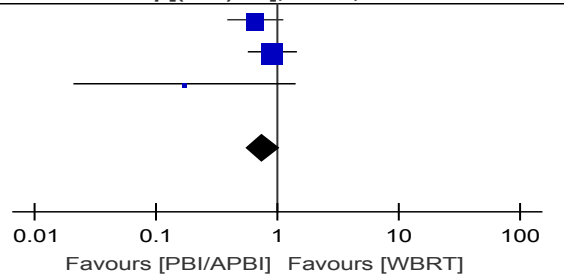


Figure 28: Disease-free survival

Study or Subgroup	PBI/APBI Events	PBI/APBI Total	WBRT Events	WBRT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
GEC-ESTRO	4	633	4	551	-0.29	2	8.0%	0.87 [0.22, 3.46]
IMPORT LOW	33	669	33	674	0	16.5	65.6%	1.00 [0.62, 1.62]
Livi 2015	1	260	3	260	-0.73	2.9	11.5%	0.78 [0.25, 2.46]
Polgar 2007	6	128	10	130	-0.93	3.75	14.9%	0.78 [0.28, 2.15]
Total (95% CI)		**1690**		**1615**			**100.0%**	**0.93 [0.63, 1.37]**
Total events	44		50					

Heterogeneity: Chi² = 0.31, df = 3 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.70)

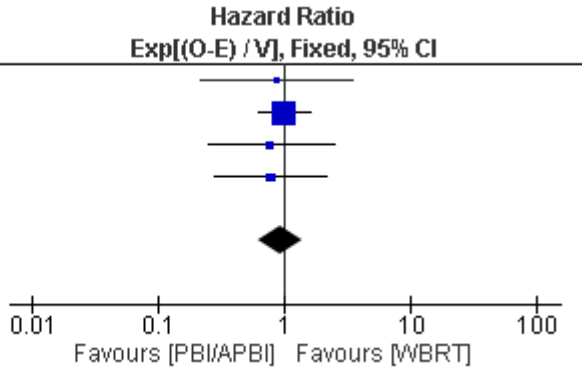


Figure 29: Distant metastasis-free survival

Study or Subgroup	PBI/APBI Events	PBI/APBI Total	WBRT Events	WBRT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
GEC-ESTRO	5	633	5	551	-0.38	2.5	15.1%	0.86 [0.25, 2.97]
IMPORT LOW	12	669	13	674	-0.51	6.24	37.6%	0.92 [0.42, 2.02]
Livi 2015	3	260	4	260	-0.21	1.71	10.3%	0.88 [0.20, 3.96]
Polgar 2007	11	128	14	130	-0.65	6.16	37.1%	0.90 [0.41, 1.98]
Total (95% CI)		**1690**		**1615**			**100.0%**	**0.90 [0.56, 1.46]**
Total events	31		36					

Heterogeneity: Chi² = 0.01, df = 3 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)

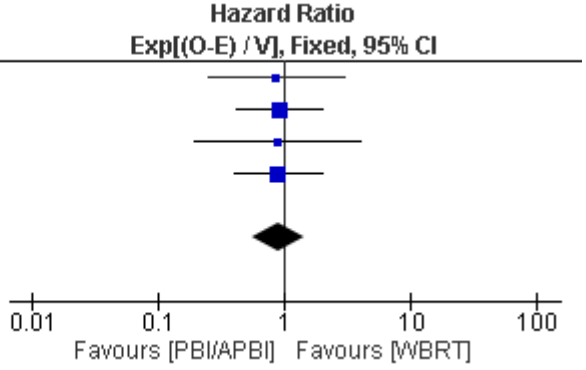
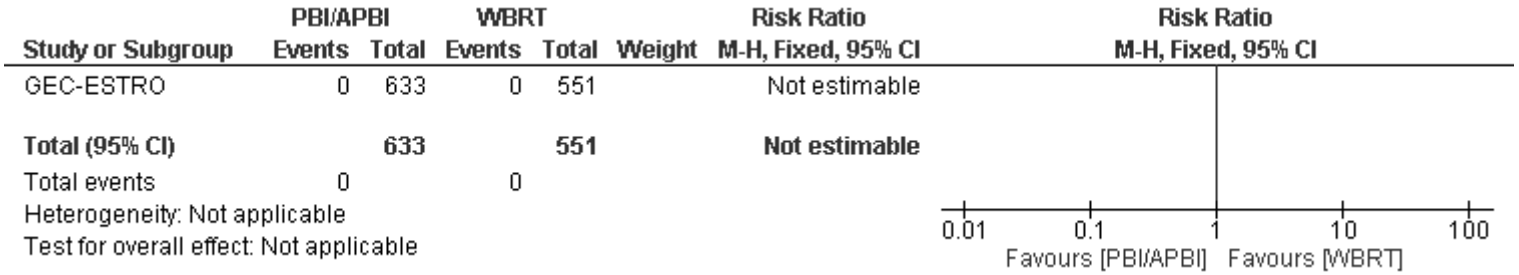


Figure 30: Treatment-related mortality



Forest plots for 8.4 What are the indications for radiotherapy to internal mammary nodes?

Comparison 1. Radiotherapy to the internal mammary nodes versus no radiotherapy to the internal mammary nodes

Figure 31: Locoregional recurrence at 10 year follow-up

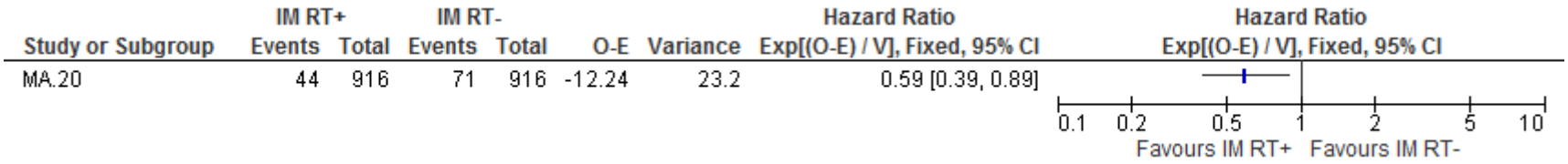


Figure 32: Disease-free survival at 10 year follow-up

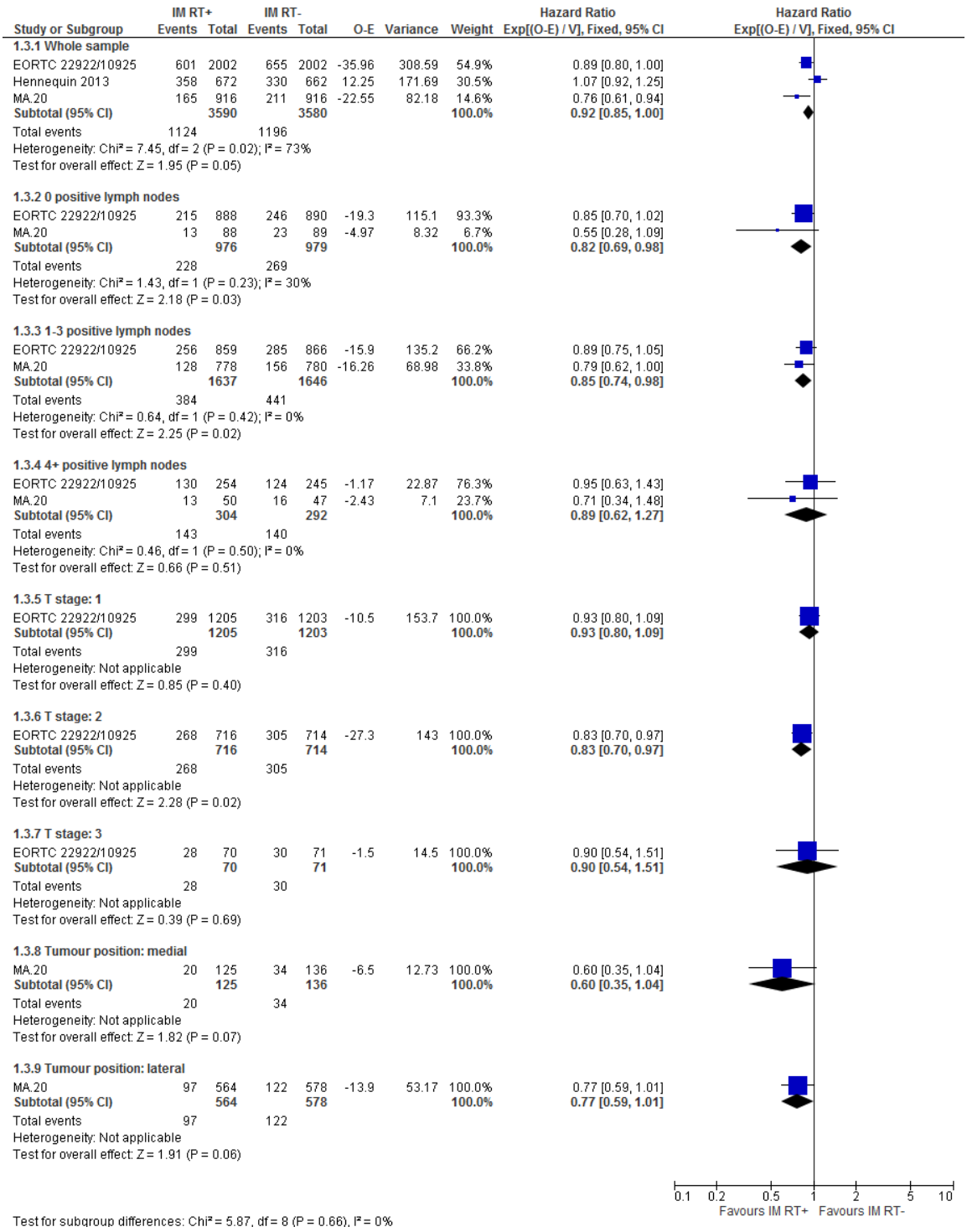


Figure 33: Treatment related morbidity: secondary cancer (potentially radiation-induced) at 10 year follow-up

Study or Subgroup	IM RT+ Events	IM RT+ Total	IM RT- Events	IM RT- Total	Weight	Risk Ratio M-H, Random, 95% CI
EORTC 22922/10925	191	1922	222	1944	59.6%	0.87 [0.72, 1.04]
MA.20	98	893	93	927	40.4%	1.09 [0.84, 1.43]
Total (95% CI)		**2815**		**2871**	**100.0%**	**0.95 [0.77, 1.19]**
Total events	289		315			

Heterogeneity: Tau² = 0.01; Chi² = 1.91, df = 1 (P = 0.17); I² = 48%
Test for overall effect: Z = 0.42 (P = 0.68)

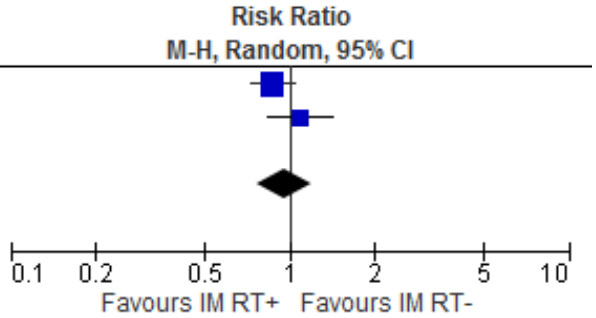


Figure 34: Treatment related morbidity: lung toxicity at 3 to 10 year follow-up

Study or Subgroup	IM RT+ Events	IM RT+ Total	IM RT- Events	IM RT- Total	Weight	Risk Ratio M-H, Random, 95% CI
EORTC 22922/10925	85	1922	33	1944	93.4%	2.61 [1.75, 3.88]
MA.20	4	893	3	927	6.6%	1.38 [0.31, 6.17]
Total (95% CI)		**2815**		**2871**	**100.0%**	**2.50 [1.70, 3.67]**
Total events	89		36			

Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 4.68 (P < 0.00001)

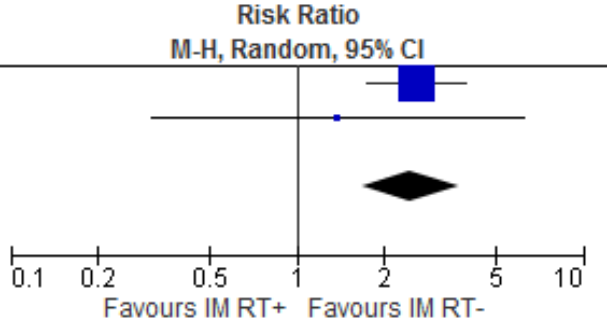


Figure 35: Treatment related morbidity: cardiac toxicity at 10 year follow-up

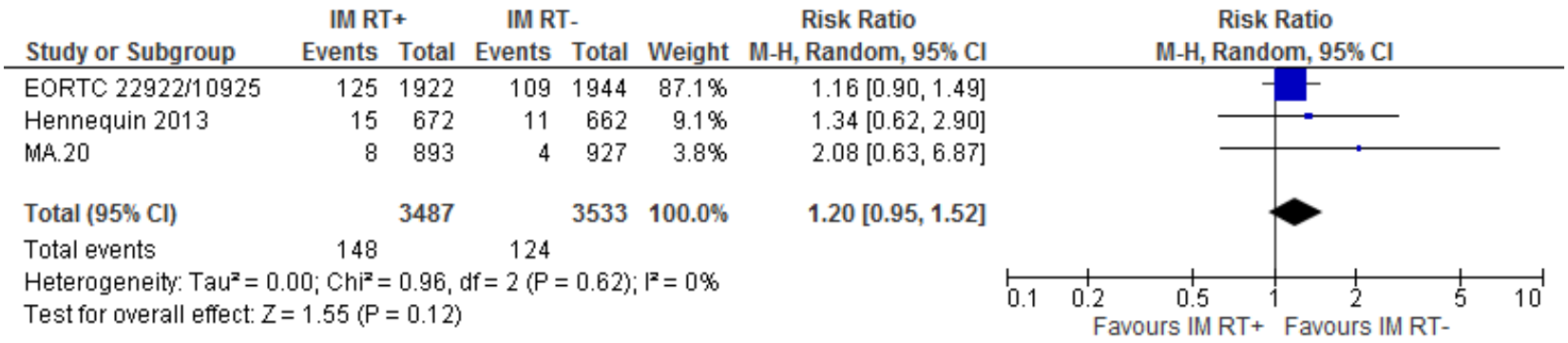


Figure 36: Treatment related morbidity: Grade 2+ lymphoedema at 10 year follow-up

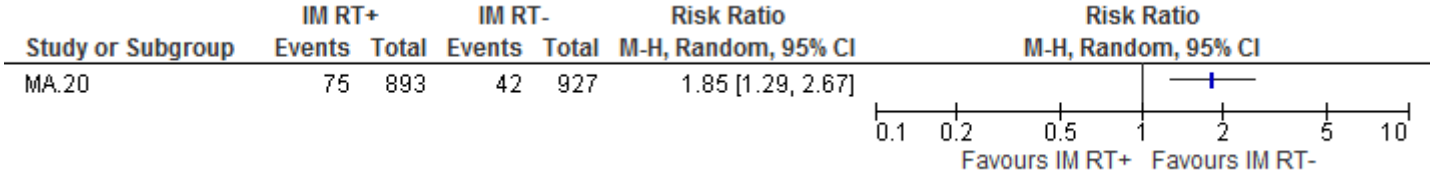


Figure 37: Treatment-related morbidity: arm/shoulder function impairment at 3 year follow-up

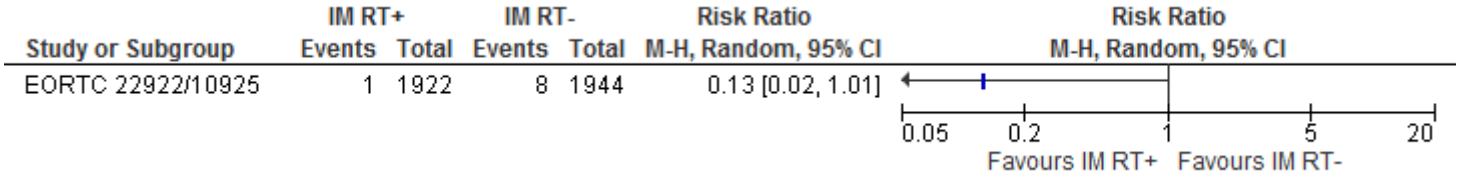


Figure 38: Treatment-related morbidity: fatigue at 3 month to 3 year follow-up

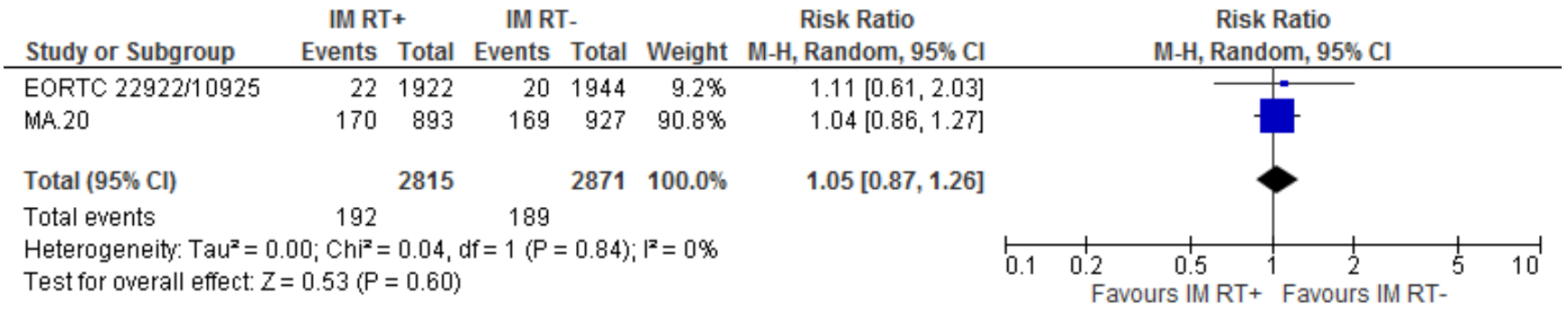


Figure 39: Treatment related morbidity: skin toxicity at 3 month to 3 year follow-up

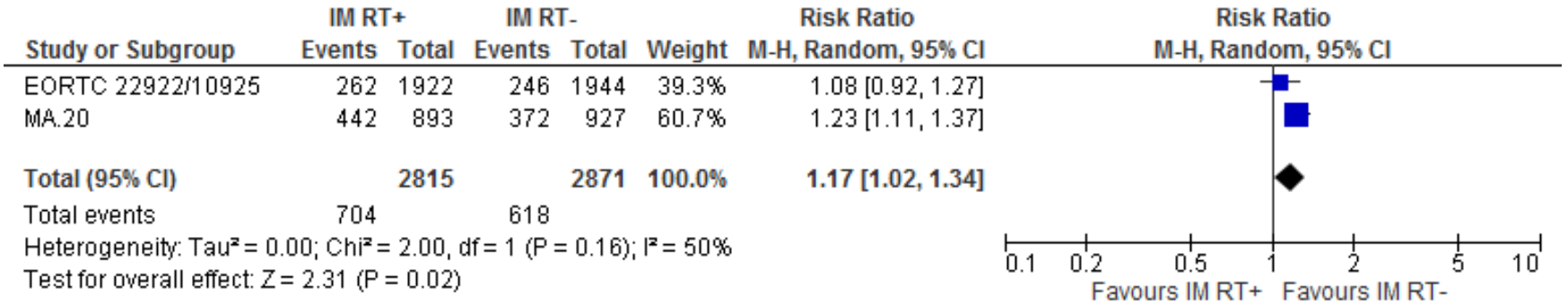


Figure 40: Treatment related morbidity: mastitis at 3 year follow-up

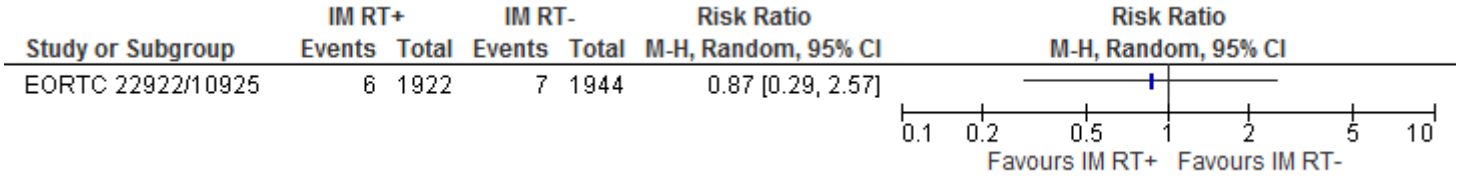


Figure 41: Treatment related morbidity: breast infection at 3 year follow-up

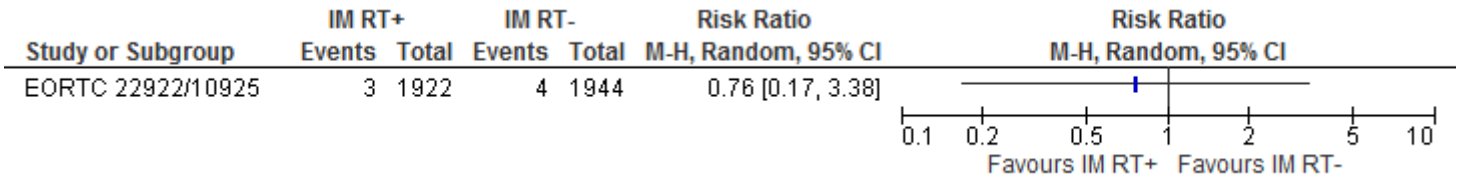


Figure 42: Treatment related morbidity: radionecrosis at 3 year follow-up

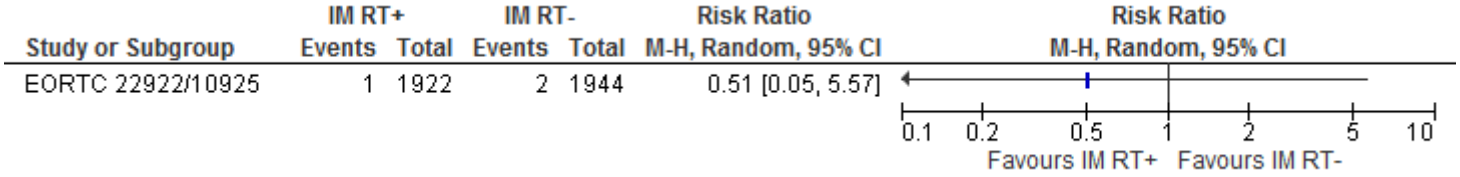


Figure 43: Treatment related morbidity: oedema at 3 year follow-up

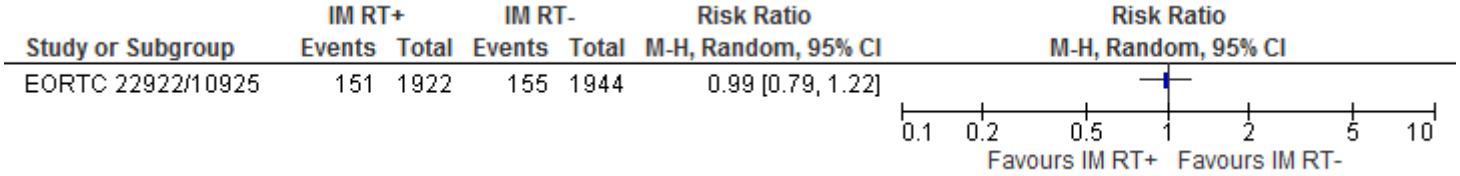


Figure 44: Treatment related morbidity: breast/chest wall pain at 3 year follow-up

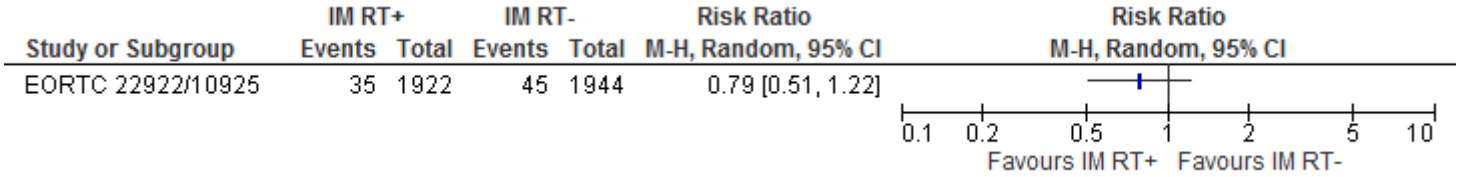


Figure 45: Treatment related morbidity: retrosternal pain at 3 year follow-up

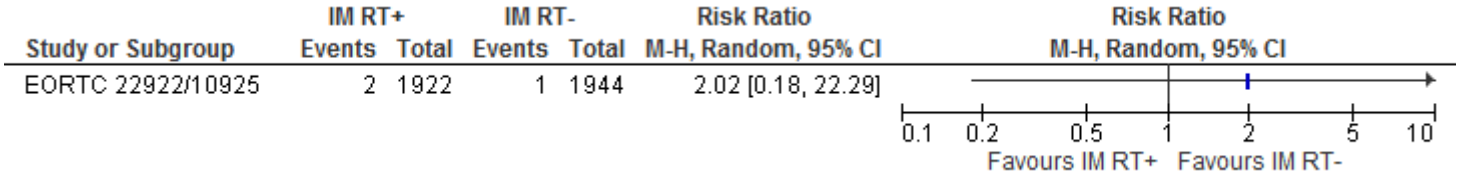


Figure 46: Treatment related morbidity: dysphagia at 3 year follow-up

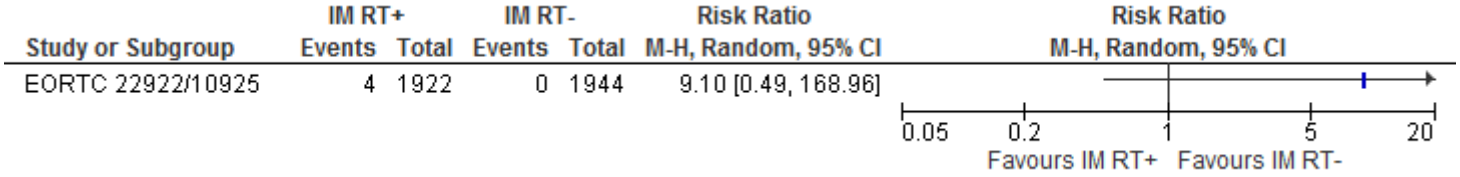


Figure 47: Treatment related morbidity: osteonecrosis

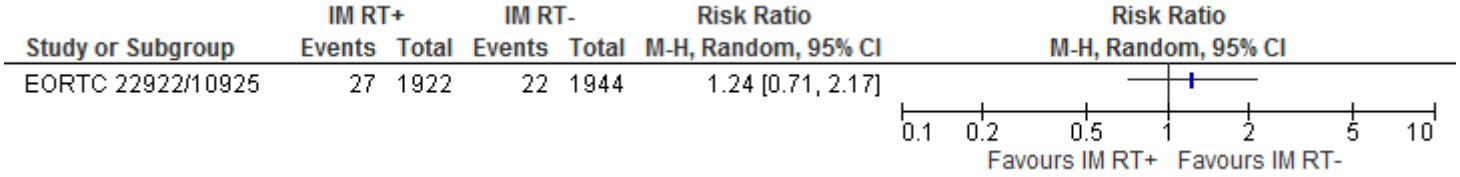


Figure 48: Treatment related morbidity: Grade 2+ acute (within 3 months of the completion of treatment) pain (site not specified)

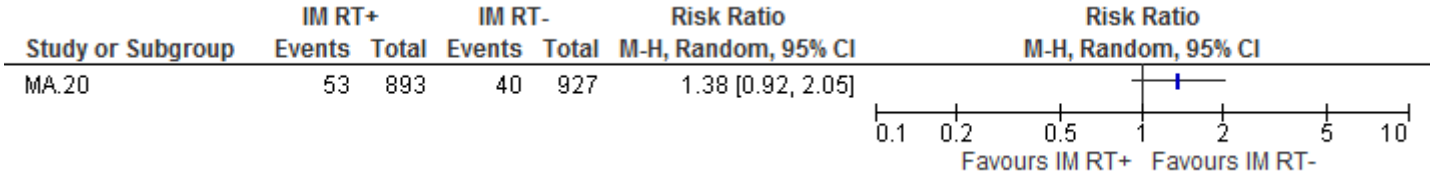


Figure 49: Treatment related morbidity: acute (within 3 to 6 months of the completion of treatment) radiation pneumonitis

Study or Subgroup	IM RT+ Events	IM RT+ Total	IM RT- Events	IM RT- Total	Weight	Risk Ratio M-H, Random, 95% CI
KROG 08-06	23	356	12	366	70.2%	1.97 [1.00, 3.90]
MA.20	11	893	2	927	29.8%	5.71 [1.27, 25.69]
Total (95% CI)		**1249**		**1293**	**100.0%**	**2.70 [1.03, 7.08]**
Total events	34		14			

Heterogeneity: Tau² = 0.22; Chi² = 1.63, df = 1 (P = 0.20); I² = 39%
Test for overall effect: Z = 2.02 (P = 0.04)

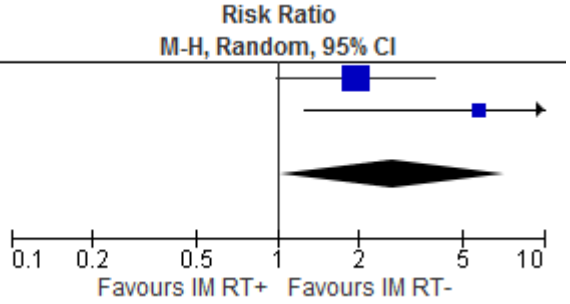


Figure 50: Treatment related morbidity: Grade 3+ morbidity on SOMA-LENT scale at 10 year follow-up

Study or Subgroup	IM RT+ Events	IM RT+ Total	IM RT- Events	IM RT- Total	Risk Ratio M-H, Random, 95% CI
Hennequin 2013	21	672	15	662	1.38 [0.72, 2.65]

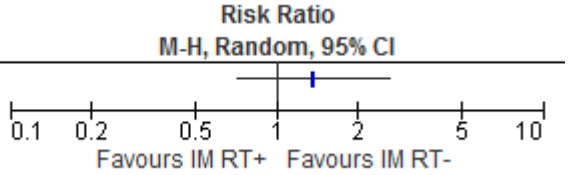
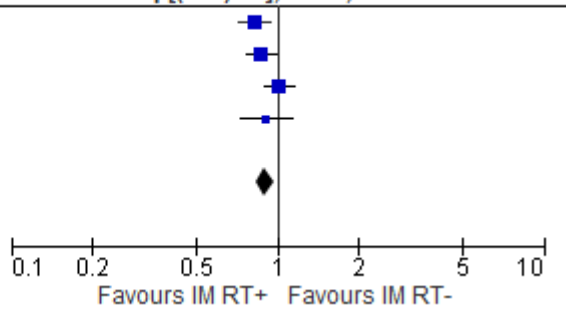


Figure 51: Overall survival at 8 to 10 year follow-up

Study or Subgroup	IM RT+ Events	IM RT+ Total	IM RT- Events	IM RT- Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
DBCG-IMN	360	1492	444	1597	-42.89	216.14	30.9%	0.82 [0.72, 0.94]
EORTC 22922/10925	382	2002	429	2002	-28.41	204.02	29.2%	0.87 [0.76, 1.00]
Hennequin 2013	421	672	393	662	3.61	203.07	29.1%	1.02 [0.89, 1.17]
MA.20	155	916	168	916	-7.13	75.64	10.8%	0.91 [0.73, 1.14]
Total (95% CI)		**5082**		**5177**			**100.0%**	**0.90 [0.83, 0.97]**
Total events	1318		1434					

Heterogeneity: Chi² = 5.19, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 2.83 (P = 0.005)



Appendix F – GRADE tables

GRADE tables for 8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?

Table 5: Clinical evidence profile: Comparison 1. Deep inspiration breath-hold versus free breathing

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deep Inspiration Breath-Hold	Free Breathing(Supine)	Relative (95% CI)	Absolute	Quality	Importance
Mean Heart Dose at RT (measured with: Gy; Better indicated by lower values)												
4[1,2,3,4]	Observational studies	No serious risk of bias	Very serious[5]	Serious[6]	Serious[7]	None	236	236	-	MD 1.29 lower (1.81 to 0.77 lower)	VERY LOW	CRITICAL
Target Coverage at RT (range of scores: 0-100; Better indicated by higher values)												
1[1]	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[5]	None	81	81	-	MD 0.5 higher (4.6 lower to 5.6 higher)	VERY LOW	CRITICAL

CI: Confidence interval; DCIS: Ductal carcinoma in situ; Gy: Gray; MD: Mean difference; RT: Radiotherapy
[1] Eldredge-Hindy 2015
[2] Chi 2015
[3] Czeremszynska 2017
[4] Barlett 2017
[5] Downgraded by 2 levels for very serious inconsistency as I square=89%
[6] Downgraded by 1 level for indirectness due to inclusion of women with only larger breast volumes (estimated volume>750cm^3)
7 Downgraded by 1 level for serious imprecision, as number of events <400

Table 6: Clinical evidence profile: Comparison 2. Deep inspiration breath-hold versus prone radiotherapy

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Deep Inspiration Breath-Hold	Free breathing Prone RT	Relative (95% CI)	Absolute	Quality	Importance
Mean Heart Dose at RT (measured with: Gy; Better indicated by lower values)												
1[1]	Randomized controlled trials	No serious risk of bias	No serious inconsistency	Serious[2]	Serious[3]	None	28	28	-	MD 0.22 lower (0.30 to 0.14 lower)	LOW	CRITICAL

CI: Confidence interval; Gy: Gray; MD:Mean difference; RT: Radiotherapy
[1] Barlett 2015
[2] Downgraded by 1 level for serious indirectness as only women with larger breasts included
[3] Downgraded by 1 level for serious imprecision, as small sample size<400

GRADE tables for 8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?

Table 18: Clinical evidence profile: Comparison 1. No whole breast radiotherapy versus whole breast radiotherapy

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT-	RT+	Relative (95% CI)	Absolute	Quality	Importance
Overall survival - T stage: 1 (12 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	26/125 (20.8%)	21/138 (15.2%)	HR 1.59 (1.29 to 1.96)	79 more per 1000 (from 40 more to 124 more)	MODERATE	IMPORTANT
Overall survival - N stage: 0 (5 to 12 year follow-up)												
3	Randomised trials	No serious risk of bias	Serious[2]	No serious indirectness	No serious imprecision	None	210/572 (36.7%)	200/582 (34.4%)	HR 1.29 (1.12 to 1.5)	75 more per 1000 (from 32 more to 125 more)	MODERATE	IMPORTANT
Overall survival - Margins: negative (5 to 12 year follow-up)												
3	Randomised trials	No serious risk of bias	Serious[2]	No serious indirectness	No serious imprecision	None	210/572 (36.7%)	200/582 (34.4%)	HR 1.29 (1.12 to 1.5)	75 more per 1000 (from 32 more to 125 more)	MODERATE	IMPORTANT
Overall survival - Age: 65+ (5 to 10 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	184/447 (41.2%)	179/444 (40.3%)	HR 1.06 (0.87 to 1.3)	18 more per 1000 (from 41 fewer to 86 more)	HIGH	IMPORTANT
Overall survival - Adjuvant systemic therapy: none (20 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RT-**	**RT+**	**Relative (95% CI)**	**Absolute**		
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	106/197 (53.8%)	92/184 (50%)	HR 1.1 (0.85 to 1.42)	33 more per 1000 (from 55 fewer to 126 more)	MODERATE	IMPORTANT
Local recurrence - T stage: 1 (10 to 12 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	91/682 (13.3%)	38/696 (5.5%)	HR 2.7 (1.84 to 3.97)	86 more per 1000 (from 44 more to 145 more)	MODERATE	CRITICAL
Local recurrence - N stage: 0 (5 to 12 year follow-up)												
4	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	149/1669 (8.9%)	49/1671 (2.9%)	HR 3.22 (2.31 to 4.49)	62 more per 1000 (from 37 more to 96 more)	MODERATE	CRITICAL
Local recurrence - Margins: negative (5 to 12 year follow-up)												
4	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	149/1669 (8.9%)	49/1671 (2.9%)	HR 3.22 (2.31 to 4.49)	62 more per 1000 (from 37 more to 96 more)	MODERATE	CRITICAL
Local recurrence - Age: 65+ (5 to 10 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	58/987 (5.9%)	11/975 (1.1%)	HR 5.35 (2.78 to 10.29)	48 more per 1000 (from 20 more to 99 more)	LOW	CRITICAL
Treatment-related morbidity – fractures (cause unspecified; all patients N stage 0, 65+, negative margins; 5 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT-	RT+	Relative (95% CI)	Absolute		
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	10/86 (11.6%)	9/85 (10.6%)	RR 1.10 (0.47 to 2.57)	11 more per 1000 (from 56 fewer to 166 more)	LOW	CRITICAL
Treatment-related morbidity - congestive cardiac failure (all patients N stage 0, 65+, negative margins; 5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[8]	None	3/86 (3.5%)	3/85 (3.5%)	RR 0.99 (0.21 to 4.76)	0 fewer per 1000 (from 28 fewer to 133 more)	MODERATE	CRITICAL
Treatment-related morbidity - myocardial infarction (all patients N stage 0, 65+, negative margins; 5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	5/86 (5.8%)	6/85 (7.1%)	RR 0.82 (0.26 to 2.6)	13 fewer per 1000 (from 52 fewer to 113 more)	LOW	CRITICAL
Treatment-related morbidity - secondary cancer (cause unspecified; all patients N stage 0, 65+, negative margins; 5 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	35/754 (4.6%)	26/743 (3.5%)	RR 2.53 (0.24 to 26.51)	-	LOW	CRITICAL
Treatment-related morbidity - score 10+ on HADS depression scale (all patients N stage 0, 65+, negative margins; 5 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RT-**	**RT+**	**Relative (95% CI)**	**Absolute**		
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	3/101 (3%)	1/105 (1%)	RR 3.12 (0.33 to 29.49)	20 more per 1000 (from 6 fewer to 271 more)	LOW	CRITICAL
Treatment-related morbidity - score 10+ on HADS anxiety scale (all patients N stage 0, 65+, negative margins; 5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	12/101 (11.9%)	9/105 (8.6%)	RR 1.39 (0.61 to 3.15)	33 more per 1000 (from 33 fewer to 184 more)	LOW	CRITICAL
HRQoL - EQ5D scale (all patients N stage 0, 65+, negative margins; 5 year follow-up) (Better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	83	85	-	MD 0.02 lower (0.1 lower to 0.06 higher)	LOW	CRITICAL
HRQoL - reduction in scores on Breast Cancer Chemotherapy Questionnaire (all patients N stage 0, negative margins; 2 month follow-up)												
1	Randomised trials	[6]	No serious inconsistency	7	Serious3	None	60/376 (16%)	93/344 (27%)	RR 0.59 (0.44 to 0.79)	111 fewer per 1000 (from 57 fewer to 151 fewer)		CRITICAL

CI: Confidence interval; EQ5D, EuroQol Research Foundation measure of general health status; HADS: Hospital Anxiety and Depression Scale; HR: Hazard ratio; HRQoL: Health related quality of life; RR: Risk ratio;

[1] <300 events

[2] Random effects model with significant heterogeneity - I squared value 74% - not possible to investigate heterogeneity as additional subgroups of interest identified by the GC were not reported for the trials that contributed to this estimate. All estimated effects were in the same direction

[3] *Total events <300*
[4] *<300 events and 95% CI crosses both thresholds for minimally important difference based on GRADE default values (0.80 and 1.25)*
[5] *N<400*
[6] *Insufficient evidence available to rate risk of bias*
[7] *Insufficient information available to judge whether evidence is indirect*
[8] *total events<300; not downgraded based on 95% CI due to very small differences in absolute risk*

GRADE tables for 8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?

Table 19: Clinical evidence profile: Comparison 1. Partial-breast radiotherapy versus whole-breast radiotherapy after breast-conserving surgery

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT-	RT+	Relative (95% CI)	Absolute	Quality	Importance
Local recurrence free survival (follow-up 5 to 10 years; assessed with: Local recurrence in the ipsilateral breast as a discrete outcome)												
5	Randomised trials	No serious risk of bias	Serious inconsistency[1]	No serious indirectness	Serious[2]	None	22/1741 (1.3%)	23/1666 (1.4%)	HR 0.98 (0.63 to 1.52)	0 fewer per 1000 (from 5 fewer to 7 more)	LOW	CRITICAL
Cosmesis, physician reported (follow-up 3 to 5 years; assessed with: global cosmetic scores, a cosmetic rating system for breast cancer, as well as digital photos)												
6	Randomised trials	Serious[3]	Very serious[4]	No serious indirectness	Very serious[6]	None	309/1842 (16.8%)	294/1922 (15.3%)	RR 0.99 (0.57 to 1.72)	2 fewer per 1000 (from 66 fewer to 110 more)	VERY LOW	CRITICAL
Cosmesis, patient reported at 5 years follow-up (follow-up mean 5 years; assessed with: four-point scales)												
4	Randomised trials	Serious[3]	Serious[5]	No serious indirectness	Very serious[6]	None	148/1041 (14.2%)	135/925 (14.6%)	RR 1.01 (0.67 to 1.51)	1 more per 1000 (from 48 fewer to 74 more)	VERY LOW	CRITICAL
Cosmesis, nurse reported at 5 year follow-up (follow-up mean 5 years; assessed with: four-point scale)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[2]	None	56/171 (32.7%)	22/164 (13.4%)	RR 2.44 (1.57 to 3.81)	193 more per 1000 (from 76 more to 377 more)	LOW	CRITICAL
Acute radiotherapy (RT) skin toxicity (follow-up 0 to 90 days; assessed with: Radiation Therapy Oncology Group Common Toxicity Criteria (RTOG CTC) grade 2 or more)												
3	Randomised trials	No serious risk of bias	Very serious[4]	No serious indirectness	No serious imprecision	None	148/927 (16%)	649/863 (75.2%)	RR 0.16 (0.08 to 0.33)	632 fewer per 1000 (from 504 fewer to 692 fewer)	LOW	CRITICAL
Late RT skin toxicity (follow-up 3 to 5 years; assessed with: Radiation Therapy Oncology Group Common (RTOG CTC) 5-point scale grade 2 or more)												
5	Randomised trials	No serious risk of bias	Very serious[4]	No serious indirectness	Very serious[6]	None	131/1644 (8%)	96/1531 (6.3%)	RR 0.97 (0.31 to 3.03)	2 fewer per 1000 (from 43 fewer to 127 more)	VERY LOW	CRITICAL
Breast Pain (follow-up 3 to 5 years; assessed with: Self-reported)												
3	Randomised trials	Serious[7]	No serious inconsistency	No serious indirectness	Very serious[2,8]	None	74/1304 (5.7%)	79/1171 (6.7%)	RR 0.9 (0.67 to 1.2)	7 fewer per 1000 (from 22 fewer to 13 more)	VERY LOW	CRITICAL
Fat necrosis (follow-up 3 to 5 years; assessed with: Assessed with EORTC and NCI 5-point scale)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT-	RT+	Relative (95% CI)	Absolute	Quality	Importance
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2,8]	None	87/1010 (8.6%)	58/889 (6.5%)	RR 1.4 (0.98 to 2)	24 more per 1000 (from 1 fewer to 57 more)	LOW	CRITICAL
Health related quality of life (follow-up mean 2 years; measured with: Assessed using EORTC QLQ-C30 and BR23 module; Better indicated by lower values)												
1	Randomised trials	Serious[9]	No serious inconsistency	No serious indirectness	Serious[2]	None	105	100	-	MD 16 higher (10.99 to 21.01 higher)	LOW	CRITICAL
Overall survival (follow-up mean 5 years)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	65/1562 (4.2%)	79/1485 (5.3%)	HR 0.76 (0.55 to 1.06)	13 fewer per 1000 (from 24 fewer to 3 more)	MODERATE	IMPORTANT
Disease-free survival (follow-up mean 5 years)												
4	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	44/1690 (2.6%)	50/1615 (3.1%)	HR 0.93 (0.63 to 1.37)	2 fewer per 1000 (from 11 fewer to 11 more)	MODERATE	IMPORTANT
Distant metastasis-free survival (follow-up mean 5 years)												
4	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	31/1690 (1.8%)	36/1615 (2.2%)	HR 0.9 (0.56 to 1.46)	2 fewer per 1000 (from 10 fewer to 10 more)	MODERATE	IMPORTANT
Treatment-related mortality												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	0/633 (0%)	0/551 (0%)	-	-	MODERATE	IMPORTANT

CI: Confidence interval; CTC, Common Toxicity Criteria; EORTC QLQ-30: European Organisation for Research and Treatment of Cancer Quality of Life Questionairre; HR: Hazard ratio; NCI, National Cancer Institute; PBI: partial breast irradiation; RR: Risk ratio; RT: radiotherapy; RTOG: Radiation Therapy Oncology Group; WBRT: whole breast radiotherapy

[1] Clinical heterogeneity was substantial relating to radiotherapy dose, technique and use of quality assurance procedures.

[2] < 300 events.

[3] Five of six studies were at high risk of bias for blinding of outcome assessors for subjective outcomes.

[4] Very serious heterogeneity (I^2>80%); random effects model used, no subgroup analysis accounted for heterogeneity.

[5] Serious heterogeneity (I^2>50% but <80%); random effects model used, no subgroup analysis accounted for heterogeneity.

[6] Effect estimate includes both default MID thresholds.

[7] Blinding of participants to treatment group not possible for self-reported breast pain.

[8] Effect estimate includes one default MID threshold.

[9] Blinding of outcome assessors was not reported.

GRADE tables for 8.4 What are the indications for radiotherapy to internal mammary nodes?

Table 20: Clinical evidence profile: Comparison 1. Radiotherapy to the internal mammary nodes versus no radiotherapy to the internal mammary nodes

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IM RT+	IM RT-	Relative (95% CI)	Absolute	Quality	Importance
Overall survival (10 year follow-up)												
4	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1318/5082 (25.9%)	1434/5177 (27.7%)	HR 0.9 (0.83 to 0.97)	21 fewer per 1000 (from 6 fewer to 36 fewer)	HIGH	IMPORTANT
Treatment-related morbidity - acute radiation pneumonitis (within 3 to 6 months of completing radiotherapy)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	34/1249 (2.7%)	14/1293 (1.1%)	RR 2.7 (1.03 to 7.08)	18 more per 1000 (from 0 more to 66 more)	MODERATE	CRITICIAL
Disease-free survival - Whole sample (10 year follow-up)												
3	Randomised trials	No serious risk of bias	Serious[2]	No serious indirectness	No serious imprecision	None	1124/3590 (31.3%)	1196/3580 (33.4%)	HR 0.92 (0.85 to 1)	18 fewer per 1000 (from 35 fewer to 0 more)	MODERATE	CRITICIAL
Disease-free survival - 0 positive lymph nodes (10 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	228/976 (23.4%)	269/979 (27.5%)	HR 0.82 (0.69 to 0.98)	38 fewer per 1000 (from 4 fewer to 68 fewer)	HIGH	CRITICIAL
Disease-free survival - 1-3 positive lymph nodes (10 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	384/1637 (23.5%)	441/1646 (26.8%)	HR 0.85 (0.74 to 0.98)	31 fewer per 1000 (from 4 fewer to 55 fewer)	HIGH	CRITICIAL
Disease-free survival - 4+ positive lymph nodes (10 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IM RT+	IM RT-	Relative (95% CI)	Absolute		
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	143/304 (47%)	140/292 (47.9%)	HR 0.89 (0.62 to 1.27)	29 fewer per 1000 (from 116 fewer to 60 more)	MODERATE	CRITICIAL
Disease-free survival - T stage: 1 (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	299/1205 (24.8%)	316/1203 (26.3%)	HR 0.93 (0.8 to 1.09)	14 fewer per 1000 (from 41 fewer to 17 more)	HIGH	CRITICIAL
Disease-free survival - T stage: 2 (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	268/716 (37.4%)	305/714 (42.7%)	HR 0.83 (0.7 to 0.97)	45 fewer per 1000 (from 7 fewer to 84 fewer)	HIGH	CRITICIAL
Disease-free survival - T stage: 3 (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	28/70 (40%)	30/71 (42.3%)	HR 0.9 (0.54 to 1.51)	25 fewer per 1000 (from 139 fewer to 102 more)	MODERATE	CRITICAL
Disease-free survival - Tumour position: medial (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	20/125 (16%)	34/136 (25%)	HR 0.6 (0.35 to 1.04)	83 fewer per 1000 (from 146 fewer to 7 more)	MODERATE	CRITICAL
Disease-free survival - Tumour position: lateral (10 year follow-up)												
1	Randomised trials	No serious	No serious inconsistency	No serious indirectness	Serious[1]	None	97/564 (17.2%)	122/578 (21.1%)	HR 0.77 (0.59 to 1.01)	40 fewer per 1000 (from 75	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IM RT+	IM RT-	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias								fewer to 2 more)		
Treatment-related morbidity - secondary cancer (potentially radiation-induced; 10 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	289/2815 (10.3%)	315/2871 (11%)	RR 0.95 (0.77 to 1.19)	5 fewer per 1000 (from 25 fewer to 21 more)	HIGH	CRITICAL
Locoregional recurrence (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	44/916 (4.8%)	71/916 (7.8%)	HR 0.59 (0.39 to 0.89)	30 fewer per 1000 (from 8 fewer to 46 fewer)	MODERATE	CRITICAL
Treatment-related morbidity - arm/shoulder function impairment (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	1/1922 (0.1%)	8/1944 (0.4%)	RR 0.13 (0.02 to 1.01)	4 fewer per 1000 (from 4 fewer to 0 more)	LOW	CRITICAL
Treatment-related morbidity – fatigue (3 month to 3 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[4]	None	192/2815 (6.8%)	189/2871 (6.6%)	RR 1.05 (0.87 to 1.26)	3 more per 1000 (from 9 fewer to 17 more)	MODERATE	CRITICAL
Treatment-related morbidity - Grade 2+ acute pain (site not specified; within 3 months of completing radiotherapy)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	53/893 (5.9%)	40/927 (4.3%)	RR 1.38 (0.92 to 2.05)	16 more per 1000 (from 3 fewer to 45 more)	LOW	CRITICAL
Treatment-related morbidity - skin toxicity (3 month to 3 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	704/2815 (25%)	618/2871 (21.5%)	RR 1.17 (1.02 to 1.34)	37 more per 1000 (from 4	HIGH	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IM RT+	IM RT-	Relative (95% CI)	Absolute	Quality	Importance
										more to 73 more)		
Treatment-related morbidity - lung toxicity (3 to 10 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	89/2815 (3.2%)	36/2871 (1.3%)	RR 2.5 (1.7 to 3.67)	19 more per 1000 (from 9 more to 33 more)	MODERATE	CRITICAL
Treatment-related morbidity - cardiac toxicity (10 year follow-up)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	148/3487 (4.2%)	124/3533 (3.5%)	RR 1.2 (0.95 to 1.52)	7 more per 1000 (from 2 fewer to 18 more)	LOW	CRITICAL
Treatment-related morbidity - Grade 2+ lymphoedema (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	75/893 (8.4%)	42/927 (4.5%)	RR 1.85 (1.29 to 2.67)	39 more per 1000 (from 13 more to 76 more)	MODERATE	CRITICAL
Treatment-related morbidity - Grade 3+ morbidity on SOMA-LENT scale (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[6]	None	21/672 (3.1%)	15/662 (2.3%)	RR 1.38 (0.72 to 2.65)	9 more per 1000 (from 6 fewer to 37 more)	LOW	CRITICAL
Treatment-related morbidity – mastitis (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[8]	None	6/1922 (0.3%)	7/1944 (0.4%)	RR 0.87 (0.29 to 2.57)	0 fewer per 1000 (from 3 fewer to 6 more)	MODERATE	CRITICAL
Treatment-related morbidity - breast infection (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[8]	None	3/1922 (0.2%)	4/1944 (0.2%)	RR 0.76 (0.17 to 3.38)	0 fewer per 1000 (from 2	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IM RT+	IM RT-	Relative (95% CI)	Absolute		
										fewer to 5 more)		
Treatment-related morbidity – radionecrosis (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[8]	None	1/1922 (0.1%)	2/1944 (0.1%)	RR 0.51 (0.05 to 5.57)	1 fewer per 1000 (from 1 fewer to 5 more)	MODERATE	CRITICAL
Treatment-related morbidity – osteonecrosis (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[6]	None	27/1922 (1.4%)	22/1944 (1.1%)	RR 1.24 (0.71 to 2.17)	3 more per 1000 (from 3 fewer to 13 more)	LOW	CRITICAL
Treatment-related morbidity – oedema (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[7]	None	151/1922 (7.9%)	155/1944 (8%)	RR 0.99 (0.79 to 1.22)	1 fewer per 1000 (from 17 fewer to 18 more)	MODERATE	CRITICAL
Treatment-related morbidity - breast/chest wall pain (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	35/1922 (1.8%)	45/1944 (2.3%)	RR 0.79 (0.51 to 1.22)	5 fewer per 1000 (from 11 fewer to 5 more)	LOW	CRITICAL
Treatment-related morbidity - retrosternal pain (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[8]	None	2/1922 (0.1%)	1/1944 (0.1%)	RR 2.02 (0.18 to 22.29)	1 more per 1000 (from 0 fewer to 11 more)	MODERATE	CRITICAL
Treatment-related morbidity – dysphagia (3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[8]	None	4/1922 (0.2%)	0/1944 (0%)	RR 9.1 (0.49 to 168.96)	-	MODERATE	CRITICAL

CI: Confidence interval; HR: hazard ratio; IM: internal mammary; RR: Risk ratio; RT: radiotherapy; SOMA-LENT: Subjective, Objective, Management, Analytic-Late Effects of Normal Tissues

[1] total events <300

[2] Significant heterogeneity (I2 = 73%) - not present in subsequent subgroup analysis

[3] total events <300 and 95% CI crosses both no effect (1) and minimally important difference based on GRADE default value (0.8)

[4] 95% CI crosses no effect (1) and minimally important difference based on GRADE default value (1.25)

[5] total events <300 and 95% CI crosses no effect (1) and minimally important difference based on GRADE default value (1.25)

[6] total events <300 and 95% CI crosses no effect (1) and minimally important differences based on GRADE default values (0.8 and 1.25)

[7] 95% CI crosses both no effect (1) and minimally important difference based on GRADE default value (0.8)

[8] total events <300; not downgraded based on 95% CI due to very small differences in absolute risk

Appendix G – Economic evidence study selection

Economic evidence study selection for 8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?

See Supplement 1: Health economics literature review for details of economic study selection.

Economic evidence study selection for 8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?

See Supplement 1: Health economics literature review for details of economic study selection.

Economic evidence study selection for 8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?

See Supplement 1: Health economics literature review for details of economic study selection.

Economic evidence study selection for 8.4 What are the indications for radiotherapy to internal mammary nodes?

See Supplement 1: Health economics literature review for details of economic study selection.

Appendix H – Economic evidence tables

Economic evidence tables for 8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?

No economic evidence was identified for this review question.

Economic evidence tables for 8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?

No economic evidence was identified for this review question.

Economic evidence tables for 8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?

Table 21: Economic evidence table showing the included health economic evidence for the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
Author & year: Shah et al. 2013 **Country:** United States (US) **Type of economic analysis:** Cost-utility analysis **Source of funding:** Not reported.	Accelerated partial breast radiotherapy (APBRT) techniques were compared against whole beam radiotherapy (WBRT) techniques. Various APBRT and WBRT techniques were considered: APBRT techniques • 3D Conformal radiotherapy (CT) • Intensity modulated radiotherapy (IMRT) • Single lumen (SL) • Multi lumen (ML) • Interstitial WBRT techniques • 3D Conformal radiotherapy (CT) • Intensity modulated radiotherapy (IMRT)	**Population characteristics:** Women with invasive early stage (breast cancer. **Modelling approach:** Cost-efficacy analysis and cost-utility analysis (results reported here reflect cost-utility analysis). **Source of base-line and effectiveness data:** Matched pair analyses of cohort data for patients treated with APBI and WBI was used to inform analysis. It was assumed that WBI and APBI effectiveness was the same regardless of technique. WBI effectiveness was based on data from traditional techniques (2D and 3D CRT) and this was extended to newer techniques (IMRT). APBI effectiveness was based on data from interstitial technique and it was assumed to be equivalent to all other APBI techniques (based on a trail which found no difference in outcome between techniques). **Source of cost data:** Costs were based on reimbursement costs from Medicare schedules for each treatment technique. Costs associated with recurrence and distant disease were	***APBRT techniques compared against WBRT – 3D CRT*** **Mean (and incremental) cost per patient** • WBRT – 3D CRT: $11,726 • APBRT – 3DCRT: $6,578 (-$5,148) • APBRT –IMRT: $10,547 (-$1,179) • APBRT –SL: $12,602 ($876) • APBRT –ML: $16,439 ($4,713) • APBRT –Interstitial: $11,765 ($39) - **Mean (and incremental) QALYs per patient:** • WBRT – 3D CRT: 10.84 QALYs • APBRT – 3DCRT: 10.91 QALYs (0.07 QALYs) • APBRT –IMRT: 10.91 QALYs (0.07 QALYs) • APBRT –SL: 10.91 QALYs (0.07 QALYs) • APBRT –ML: 10.91 QALYs (0.07 QALYs) • APBRT –Interstitial: 10.91 QALYs (0.07 QALYs) **ICERs:** • APBRT – 3DCRT: Dominant • APBRT –IMRT: Dominant • APBRT –SL: $12,514 per QALY • APBRT –ML: $67,329 per QALY • APBRT –Interstitial: $557 per QALY	**Perspective:** Multiple perspectives were considered as various costs were included. Results reported here focus on reimbursement costs and therefore reflect the US health care payer perspective. **Currency:** US dollars ($) **Cost year:** 2011. **Time horizon:** Not reported **Discounting:** Not reported. **Applicability:** The analysis was only partially applicable to the UK context since it considered the US health care system. **Limitations:**

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
		sourced from a published cost analysis. Follow-up costs were not considered in the analysis because of the similarity in follow-up between treatment strategies. In some scenarios, non-medical costs were incorporated based on costs from a previous analysis. **Source of QoL data:** QoL values were sourced from a previous cost-effectiveness analysis. QoL values were applied for three health states (no recurrence, recurrence and distant metastases).	***APBRT techniques compared against WBRT – IMRT*** **Mean (and incremental) cost per patient** • WBRT – IMRT: $20,637 • APBRT – 3DCRT: $6,578 (-$14,059) • APBRT –IMRT: $10,547 (-$10,090) • APBRT –SL: $12,602 (-$8,035) • APBRT –ML: $16,439 (-$4,198) • APBRT –Interstitial: $11,765 (-$8,872) - **Mean (and incremental) QALYs per patient:** • WBRT – IMRT: 10.84 QALYs • APBRT – 3DCRT: 10.91 QALYs (0.07 QALYs) • APBRT –IMRT: 10.91 QALYs (0.07 QALYs) • APBRT –SL: 10.91 QALYs (0.07 QALYs) • APBRT –ML: 10.91 QALYs (0.07 QALYs) • APBRT –Interstitial: 10.91 QALYs (0.07 QALYs) **ICERs:** • APBRT – 3DCRT: Dominant • APBRT –IMRT: Dominant • APBRT –SL: Dominant • APBRT –ML: Dominant • APBRT –Interstitial: Dominant **Subgroup analysis:** Not conducted. **Sensitivity analysis:** No deterministic or probabilistic sensitivity analyses were conducted.	Serious limitations were identified in the analysis. Most notably, uncertainty around the base case estimates was not assessed as no deterministic or probabilistic sensitivity analyses were conducted. Also the modelled time horizon was not clear and the discount rate was not reported (possible that no discount rates were used). **Other comments:** Incremental costs and QALYs were not reported in the study. Incremental values above have therefore been estimated as the difference between the absolute values reported in the study. Note also that the study presents costs under numerous scenarios. The costs presented above are for reimbursement costs only as it was thought to best reflect the third party perspective (other scenarios reported in the analysis included 'non-medical' costs which possibly include costs

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
				more applicable to the societal perspective).

Economic evidence tables for 8.4 What are the indications for radiotherapy to internal mammary nodes?

No economic evidence was identified for this review question.

Appendix I – Health economic evidence profiles

Health economic evidence profiles for 8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?

No economic evidence was identified for this review question.

Health economic evidence profiles for 8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?

No economic evidence was identified for this review question.

Health economic evidence profiles for 8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?

Table 22: Summary table showing the included health economic evidence for the cost-effectiveness of partial breast radiotherapy after breast-conserving surgery

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Shah et al. 2013	Patients with invasive early stage breast cancer.	APBRT techniques compared against WBRT - 3D CRT						No deterministic or probabilistic sensitivity analyses were conducted.	The analysis was only partially applicable to the UK context since it considered the US health care system. Serious limitations were identified in the analysis. Most notably, uncertainty around the base case estimates was not assessed as no deterministic or probabilistic sensitivity analyses were conducted.
		WBRT - 3D CRT	$11,726	10.84	Reference				
		APBRT - 3D CRT	$6,578	10.91	-$5,148	0.07	Dominant		
		APBRT - IMRT	$10,547	10.91	-$1,179	0.07	Dominant		
		APBRT - SL	$12,602	10.91	$876	0.07	$12,514 per QALY		
		APBRT - ML	$16,439	10.91	$4,713	0.07	$67,329 per QALY		
		APBRT - Interstitial	$11,765	10.91	$39	0.07	$557 per QALY		
		APBI techniques compared against WBRT - IMRT							
		WBRT - IMRT	$20,637	10.84	Reference				
		APBRT - 3D CRT	$6,578	10.91	-$14,059	0.07	Dominant		
		APBRT - IMRT	$10,547	10.91	-$10,090	0.07	Dominant		
		APBRT - SL	$12,602	10.91	-$8,035	0.07	Dominant		
		APBRT - ML	$16,439	10.91	-$4,198	0.07	Dominant		
		APBRT - Interstitial	$11,765	10.91	-$8,872	0.07	Dominant		
	Comments: Incremental costs and QALYs were not reported in the study. Incremental values above have therefore been estimated as the difference between the absolute values reported in the study.								

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
	Note also that the study presents costs under numerous scenarios. The costs presented above are for reimbursement costs only as it was thought to best reflect the third party perspective (other scenarios reported in the analysis included 'non-medical' costs which possibly include costs more applicable to the societal perspective).								

Health economic evidence profiles for 8.4 What are the indications for radiotherapy to internal mammary nodes?

No economic evidence was identified for this review question.

Appendix J – Health economic analysis

Health economic analysis for 8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?

No health economic analysis was conducted for this review question.

Health economic analysis for 8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?

No health economic analysis was conducted for this review question.

Health economic analysis for 8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?

No health economic analysis was conducted for this review question.

Health economic analysis for 8.4 What are the indications for radiotherapy to internal mammary nodes?

No health economic analysis was conducted for this review question

Appendix K – Excluded studies

Excluded studies for 8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?

Clinical studies

Excluded studies--8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?	
Study	**Reason for exclusion**
Bartlett, F. R., Colgan, R. M., Carr, K., Donovan, E. M., McNair, H. A., Locke, I., Evans, P. M., Haviland, J. S., Yarnold, J. R., Kirby, A. M., The UK HeartSpare Study: randomised evaluation of voluntary deep-inspiratory breath-hold in women undergoing breast radiotherapy, Radiotherapy & OncologyRadiother Oncol, 108, 242-7, 2013	Other published article of this study has been included
Bartlett, F. R., Colgan, R. M., Donovan, E. M., Carr, K., Landeg, S., Clements, N., McNair, H. A., Locke, I., Evans, P. M., Haviland, J. S., Yarnold, J. R., Kirby, A. M., Voluntary breath-hold technique for reducing heart dose in left breast radiotherapy, Journal of Visualized ExperimentsJ, 89, 03, 2014	Does not report primary study data
Bartlett, F. R., Yarnold, J. R., Donovan, E. M., Evans, P. M., Locke, I., Kirby, A. M., Multileaf collimation cardiac shielding in breast radiotherapy: Cardiac doses are reduced, but at what cost?, Clinical Oncology, 25, 690-696, 2013	Retrospective study
Becker-Schiebe, M., Stockhammer, M., Hoffmann, W., Wetzel, F., Franz, H., Does mean heart dose sufficiently reflect coronary artery exposure in left-sided breast cancer radiotherapy?: Influence of respiratory gating, Strahlentherapie und Onkologie, 192, 624-631, 2016	Retrospective study, not meeting inclusion criteria
Bergom, C., Kelly, T., Bedi, M., Saeed, H., Prior, P., Rein, L. E., Szabo, A., Wilson, J. F., Currey, A. D., White, J., Association of Locoregional Control With High Body Mass Index in Women Undergoing Breast Conservation Therapy for Early-Stage Breast Cancer, International Journal of Radiation Oncology Biology Physics, 96, 65-71, 2016	Outcomes related to cardiac sparing not reported

Excluded studies--8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?	
Study	**Reason for exclusion**
Bergom, C., Kelly, T., Morrow, N., Wilson, J. F., Walker, A., Xiang, Q., Ahn, K. W., White, J., Prone whole-breast irradiation using three-dimensional conformal radiotherapy in women undergoing breast conservation for early disease yields high rates of excellent to good cosmetic outcomes in patients with large and/or pendulous breasts, International Journal of Radiation Oncology Biology Physics, 83, 821-828, 2012	Exclusion by Outcomes: Cardiac sparing outcomes not reported.
Bergom, C., Prior, P., Kainz, K., Morrow, N. V., Ahunbay, E. E., Walker, A., Allen Li, X., White, J., A phase I/II study piloting accelerated partial breast irradiation using CT-guided intensity modulated radiation therapy in the prone position, Radiotherapy & Oncology, 108, 215-9, 2013	Exclusion by Outcome: Cardiac sparing outcomes not reported
Brouwers, P. J. A. M., Lustberg, T., Borger, J. H., van Baardwijk, A. A. W., Jager, J. J., Murrer, L. H. P., Nijsten, S. M. J. J. G., Reymen, B. H., van Loon, J. G. M., Boersma, L. J., Set-up verification and 2-dimensional electronic portal imaging device dosimetry during breath-hold compared with free breathing in breast cancer radiation therapy, Practical Radiation Oncology, 5, e135-e141, 2015	Exclusion by outcome: Outcomes of interest not reported
Bush, D. A., Slater, J. D., Garberoglio, C., Yuh, G., Hocko, J. M., Slater, J. M., A technique of partial breast irradiation utilizing proton beam radiotherapy: comparison with conformal x-ray therapy, Cancer JournalCancer J, 13, 114-8, 2007	Partial breast irradiation
Cahlon, O., MacDonald, S., Increased cardio and cerebrovascular mortality in breast cancer patients treated with postmastectomy radiotherapy - 25 year follow-up of a randomised trial from the South Sweden Breast Cancer Group: Killander F, Anderson H, Kjellen E, et al (Skane Univ Hosp, Lund, Sweden; Lund Univ, Sweden) Eur J Cancer 50:2201-2210, 2014, Breast Diseases, 26, 74-76, 2015	Does not report on cardiac sparing
Chiu, G., Fung, W. W. K., Wu, V. W. C., Geometric and actual dose delivery accuracy in supine and prone position of breast tomotherapy, Radiotherapy and Oncology, 115, S596-S597, 2015	Abstract

Excluded studies--8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?	
Study	**Reason for exclusion**
Conway, J. L., Conroy, L., Harper, L., Scheifele, M., Li, H., Smith, W. L., Graham, T., Phan, T., Olivotto, I. A., Deep inspiration breath-hold produces a clinically meaningful reduction in ipsilateral lung dose during locoregional radiation therapy for some women with right-sided breast cancer, Practical Radiation Oncology, 7, 147-153, 2017	Related to reducing doses to lung in right sided breast cancer patients
Cozzi, L., Fogliata, A., Nicolini, G., Rancati, T., Bernier, J., Breast irradiation with three conformal photon fields for patients with high lung involvement, Acta Oncologica, 43, 558-566, 2004	Outcomes related to lung. No comparison
Darapu, A., Balakrishnan, R., Sebastian, P., Kather Hussain, M. R., Ravindran, P., John, S., Is the Deep Inspiration Breath-Hold Technique Superior to the Free Breathing Technique in Cardiac and Lung Sparing while Treating both Left-Sided Post-Mastectomy Chest Wall and Supraclavicular Regions, Case Reports in Oncology, 10, 37-51, 2017	Prospective study with less than 30 patients
de Almeida, C. E., Fournier-Bidoz, N., Massabeau, C., Mazal, A., Canary, P. C., Kuroki, I. R., Campana, F., Fourquet, A., Kirova, Y. M., Potential benefits of using cardiac gated images to reduce the dose to the left anterior descending coronary during radiotherapy of left breast and internal mammary nodes, Cancer RadiotherapieCancer Radiother, 16, 44-51, 2012	Case report
De Puysseleyr, A., De Neve, W., De Wagter, C., A patient immobilization device for prone breast radiotherapy: Dosimetric effects and inclusion in the treatment planning system, Physica Medica, 32, 758-66, 2016	No patient specific data
De Puysseleyr, A., Mulliez, T., Gulyban, A., Bogaert, E., Vercauteren, T., Van Hoof, T., Van de Velde, J., Van Den Broecke, R., De Wagter, C., De Neve, W., Improved cone-beam computed tomography in supine and prone breast radiotherapy. Surface reconstruction, radiation exposure, and clinical workflow, Strahlentherapie und Onkologie, 189, 945-50, 2013	Cadaveric study
De Puysseleyr, A., Veldeman, L., Bogaert, E., De Wagter, C., De Neve, W., Optimizing image acquisition settings for cone-beam computed tomography in supine and prone breast radiotherapy, Radiotherapy and Oncology, 100, 227-230, 2011	Phantom study

Excluded studies--8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?	
Study	**Reason for exclusion**
Eldredge-Hindy, H. B., Duffy, D., Yamoah, K., Simone, N. L., Skowronski, J., Dicker, A. P., Anne, P. R., Modeled risk of ischemic heart disease following left breast irradiation with deep inspiration breath-hold, Practical Radiation Oncology, 5, 162-168, 2015	Research Question does not relate to cardiac sparing intervention
Fung, E., Hendry, J., External beam radiotherapy (EBRT) techniques used in breast cancer treatment to reduce cardiac exposure, Radiography, 19, 73-78, 2013	Review article
Hayden, A. J., Rains, M., Tiver, K., Deep inspiration breath-hold technique reduces heart dose from radiotherapy for left-sided breast cancer, Journal of Medical Imaging and Radiation Oncology, 56, 464-472, 2012	Not enough data for extracting data for comparison
Lee, H. Y., Chang, J. S., Lee, I. J., Park, K., Kim, Y. B., Suh, C. O., Kim, J. W., Keum, K. C., The deep inspiration breath-hold technique using Abches reduces cardiac dose in patients undergoing left-sided breast irradiation, Radiation Oncology Journal, 31, 239-246, 2013	Prospective study with less than 30 patients
Lin, A., Sharieff, W., Juhasz, J., Whelan, T., Kim, D. H., The benefit of deep inspiration breath-hold: evaluating cardiac radiation exposure in patients after mastectomy and after breast-conserving surgery, Breast Cancer, 24, 86-91, 2017	There are two subgroups reported separately. Each less than 30 in sample size
Lomax, A. J., Cella, L., Weber, D., Kurtz, J. M., Miralbell, R., Potential role of intensity-modulated photons and protons in the treatment of the breast and regional nodes, International journal of radiation oncology, biology, physics, 55, 785-92, 2003	Plans based on data of one patient
Merino Lara, T. R., Fleury, E., Mashouf, S., Helou, J., McCann, C., Ruschin, M., Kim, A., Makhani, N., Ravi, A., Pignol, J. P., Measurement of mean cardiac dose for various breast irradiation techniques and corresponding risk of major cardiovascular event, Frontiers in Oncology, 4, 284, 2014	Phantom study
Mowery, Y. M., Blitzblau, R. C., The UK HeartSpare Study (Stage IB): Randomised comparison of a voluntary breath-hold technique and prone	Same as Barlett 2015

Excluded studies--8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?	
Study	**Reason for exclusion**
radiotherapy after breast conserving surgery, Breast Diseases, 26, 237-239, 2015	
Mulliez, T., Speleers, B., Mahjoubi, K., Remouchamps, V., Gilsoul, M., Veldeman, L., Van den Broecke, R., De Neve, W., Prone left-sided whole-breast irradiation: Significant heart dose reduction using end-inspiratory versus end-expiratory gating, Cancer/Radiotherapie, 18, 672-677, 2014	Less than 30 patients. Does not meet inclusion criteria
Nilsson, G., Blomqvist, C., Breast cancer radiotherapy and coronary artery disease: Hazards and protection of organs at risk, Breast Cancer Management, 1, 13-16, 2012	Editorial
Osa, E. O. O., Dewyngaert, K., Roses, D., Speyer, J., Guth, A., Axelrod, D., Fenton Kerimian, M., Goldberg, J. D., Formenti, S. C., Prone breast intensity modulated radiation therapy: 5-year results, International Journal of Radiation Oncology Biology Physics, 89, 899-906, 2014	5 year follow up study. Critical outcomes not reported
Osa, E. O., Huppert, N., Fenton-Kerimian, M., Goldberg, J. D., Jozsef, G., DeWyngaert, K., Formenti, S. C., Prospective randomized trial of prone accelerated whole breast radiation therapy with a concurrent daily versus weekly boost to the tumor bed: Acute toxicity, International Journal of Radiation Oncology Biology Physics, 84, S84-S85, 2012	Comparison here is concurrent versus weekly boost
Sayan, M., Hopkins, W. E., Heimann, R., Deep inspiration breath-hold (DIBH) technique to reduce cardiac radiation dose in the management of breast cancer, Anti-Inflammatory and Anti-Allergy Agents in Medicinal Chemistry, 15,e2-14, 2016	Review article
Scull, A., Irradiation of pendulous breasts: Prone vs supine, a systematic review, Journal of medical imaging and radiation oncology, 58, 158, 2014	Conference Abstract.
Sixel, K. E., Aznar, M. C., Ung, Y. C., Deep inspiration breath-hold to reduce irradiated heart volume in breast cancer patients, International Journal of Radiation Oncology Biology Physics, 49, 199-204, 2001	Study includes 5 participants

Excluded studies--8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?	
Study	**Reason for exclusion**
Smyth, L. M., Knight, K. A., Aarons, Y. K., Wasiak, J., The cardiac dose-sparing benefits of deep inspiration breath-hold in left breast irradiation: A systematic review, Journal of Medical Radiation Sciences, 62, 66-73, 2015	Systematic review with no additional studies
Stick, L. B., Yu, J., Maraldo, M. V., Aznar, M. C., Pedersen, A. N., Bentzen, S. M., Vogelius, I. R., Joint Estimation of Cardiac Toxicity and Recurrence Risks After Comprehensive Nodal Photon Versus Proton Therapy for Breast Cancer, International Journal of Radiation Oncology Biology Physics, 97, 754-761, 2017	Critical outcomes not reported
Swanson, T., Grills, I. S., Ye, H., Entwistle, A., Teahan, M., Letts, N., Yan, D., Duquette, J., Vicini, F. A., Six-year experience routinely using moderate deep inspiration breath-hold for the reduction of cardiac dose in left-sided breast irradiation for patients with early-stage or locally advanced breast cancer, American Journal of Clinical Oncology: Cancer Clinical Trials, 36, 24-30, 2013	Not enough data in outcome measures for comparison
Tanguturi, S. K., Lyatskaya, Y., Chen, Y., Catalano, P. J., Chen, M. H., Yeo, W. P., Marques, A., Truong, L., Yeh, M., Orlina, L., Wong, J. S., Punglia, R. S., Bellon, J. R., Prospective assessment of deep inspiration breath-hold using 3-dimensional surface tracking for irradiation of left-sided breast cancer, Practical Radiation Oncology, 5, 358-365, 2015	Conference Abstract available. Full text not available.
Trela, K., Eberhardt, B., Bereza, I., Misztal, L., Gabrys, D., Prone versus supine breast irradiation in early stage breast cancer patients, 69, 2009	Conference Abstract
Verhoeven, K., Sweldens, C., Petillion, S., Laenen, A., Peeters, S., Janssen, H., Van Limbergen, E., Weltens, C., Breathing adapted radiation therapy in comparison with prone position to reduce the doses to the heart, left anterior descending coronary artery, and contralateral breast in whole breast radiation therapy, Practical Radiation Oncology, 4, 123-129, 2014	Each comparison less than 30 sample size

Economic studies

See Supplement 1: Health economics literature review for list of excluded economic studies.

Excluded studies for 8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?

Clinical studies

Excluded studies - RQ8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
Early Breast Cancer Trialists' Collaborative, Group, Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials, Lancet (London, England), 378, 1707-16, 2011	More recent results available for some included studies
Fyles, A, Breast-conservative surgery with and without radiotherapy in patients aged 55-75 years with early-stage breast cancer: A prospective, randomized, multicenter trial analysis after 108 months of median follow-up, Breast Diseases, 25, 347-8, 2015	Review of article
Gatzemeier, W, Andreoli, C, Costa, A, Gentilini, Ma, Tinterri, C, Zanini, V, Regolo, L, Pedrazzoli, C, Rondini, E, Amanti, C, Gentile, G, Taffurelli, M, Fenaroli, P, Tondini, C, Sacchetto, G, Sismondi, P, Murgo, R, Orlandi, M, Cianchetti, E, Multi-centre prospective randomised trial on breast conservative surgery (BCS) with and without whole breast irradiation (WBI) in postmenopausal women aged 55-75 and low in-breast-recurrence (IBR) risk: Analysis after 9 years medium follow-up - RT 55-75 Study Group, European Journal of Cancer, 49, S449, 2013	Conference abstract
Henson, Katherine E., Jagsi, Reshma, Cutter, David, McGale, Paul, Taylor, Carolyn, Darby, Sarah C., Inferring the Effects of Cancer Treatment: Divergent Results From Early Breast Cancer Trialists' Collaborative Group Meta-Analyses of Randomized Trials and Observational Data From SEER Registries, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 34, 803-9, 2016	Article retracted
Housri, N., Haffty, B. G., Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10 801 women in 17 randomised trials, Breast Diseases, 23, 266-267, 2012	Overview - full text already identified
Hughes, K. S., Schnaper, L. A., Cirrincione, C., Berry, D. A., McCormick, B., Muss, H. B., Shank, B., Hudis, C., Winer, E. P., Smith, B. L., Lumpectomy plus tamoxifen with or without irradiation in women age 70 or older with early breast cancer, Journal of Clinical Oncology, 28, no pagination, 2010	Conference abstract

Excluded studies - RQ8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
Killander, F, Karlsson, P, Anderson, H, Mattsson, J, Holmberg, E, Lundstedt, D, Holmberg, L, Malmstrom, P, No breast cancer subgroup can be spared postoperative radiotherapy after breast-conserving surgery. Fifteen-year results from the Swedish Breast Cancer Group randomised trial, SweBCG 91 RT, European Journal of Cancer, 67, 57-65, 2016	Insufficient presentation of results
Kunkler, I, Williams, L, King, C, Prescott, R, Dixon, M, Pol, M, The PRIME (Post-Operative Radiotherapy in Minimum-Risk Elderly) Breast Cancer Trial of Adjuvant Radiotherapy after Breast Conserving Surgery: Impact on Quality of Life and Cost-Effectiveness at Three Years, 69, 2010	Conference abstract
Kunkler, I., The role of postoperative radiotherapy in the older patient: Impact on local control and quality of life, Radiotherapy and Oncology, 115, S104-S105, 2015	Conference abstract
Kunkler, I. H., Williams, L. J., Prescott, R. J., King, C. C., Jack, W., Dixon, J. M., Van Der Pol, M., Goh, T. T., Lindley, R., Cairns, J., The post-operative radiotherapy in minimum-risk elderly (Prime) randomised trial of adjuvant radiotherapy after breast conserving surgery: Impact on quality of life and cost-effectiveness at 5 years, European Journal of Cancer, Supplement, 8, 18, 2010	Abstract only
Kunkler, Ih, Williams, Lw, Jack, W, Canney, P, Prescott, Rj, Dixon, Mj, The PRIME II trial: Wide local excision and adjuvant hormonal therapy +/- postoperative whole breast irradiation in women > 65 years with early breast cancer managed by breast conservation, Cancer Research, 73, 2013	Conference abstract
Lundstedt, D, Gustafsson, M, Malmstrom, P, Johansson, K-A, Alsadius, D, Sundberg, A, Wilderang, U, Holmberg, E, Anderson, H, Steineck, G, Karlsson, P, Symptoms 10-17 years after breast cancer radiotherapy data from the randomised SWEBCG91-RT trial, Radiotherapy and Oncology, 97, 281-7, 2010	Outcomes within scope not presented in sufficient detail
Marta, G. N., Hanna, S. A., Martella, E., da Silva, J. L. F., Carvalho, H. A., Early stage breast cancer and radiotherapy: Update, Revista da Associacao Medica Brasileira, 57, 459-464, 2011	Narrative review
Matuschek, C., Boelke, E., Kammers, K., Budach, W., The Benefit of Adjuvant Radiation Therapy After Breast-Conserving Surgery in Older Patients With Low-Risk Breast Cancer: A Meta-Analysis of Randomized Trials, International journal of radiation oncology, biology, physics, 96, E6, 2016	Abstract only
Matuschek, C., Boelke, E., Kammers, K., Budach, W., Do patients with low-risk (T1-2 [<3 cm] N0, HR+) breast cancer and antihormone treatment need adjuvant radiation therapy? A meta-analysis of randomized trials, Journal of Clinical Oncology, 34, no pagination, 2016	Conference abstract

Excluded studies - RQ8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
Matuschek, C., Boelke, E., Kammers, K., Budach, W., Patients with low-risk breast cancer and tamoxifen - Do they need adjuvant radiation therapy-A meta-analysis, Radiotherapy and Oncology, 120, S45, 2016	Conference abstract
Matuschek, C., Bolke, E., Orth, K., Zwiefel, K., Nestle-Kramling, C., Budach, W., Irradiation of the breast after breast conserving surgery: Current medical practice, Onkologe, 19, 471-480, 2013	Non-English language
Recht, A, Sector resection with or without postoperative radiotherapy for stage i breast cancer: 20-year results of a randomized trial: Wickberg A, Holmberg L, Adami HO, et al (Orebro Univ Hosp, Sweden; Karolinska Institutet, Stockholm, Sweden; King's College, London, UK) J Clin Oncol 32:791-797, 2014, Breast Diseases, 26, 79-82, 2015	Overview
Sautter-Bihl, M. L., Sedlmayer, F., Budach, W., Dunst, J., Feyer, P., Fietkau, R., Haase, W., Harms, W., Rodel, C., Souchon, R., Wenz, F., Sauer, R., When are breast cancer patients old enough for the quitclaim of local control?, Strahlentherapie und Onkologie : Organ der Deutschen Röntgengesellschaft ... [et al], 188, 1069-73, 2012	Narrative review
Simmons, R, Long-term results of phase II ablation after breast lumpectomy added to extend intraoperative margins (ABLATE I) trial, Breast Diseases, 25, 331-2, 2015	Intervention outside scope
Skandarajah, Anita R., Mann, G. Bruce, Do all patients require radiotherapy after breast-conserving surgery?, Cancers, 2, 740-51, 2010	Narrative review
Tinterri, C, Costa, A, Andreoli, C, Valagussa, P, Gatzemeier, W, Breast conservative surgery with and without radiotherapy in patients aged 55-75 with early-stage breast cancer: A prospective randomized multicenter trial analysis after 90 months of medium follow-up, Annals of Surgical Oncology, 20, 3-4, 2013	Same as Tinterri 2014 but shorter follow-up period
Tinterri, C, Gatzemeier, W, Costa, A, Gentilini, Ma, Zanini, V, Regolo, L, Pedrazzoli, C, Rondini, E, Amanti, C, Gentile, G, Taffurelli, M, Fenaroli, P, Tondini, C, Sacchetto, G, Sismondi, P, Murgo, R, Orlandi, M, Cianchetti, E, Andreoli, C, Breast-conservative surgery with and without radiotherapy in patients aged 55-75 years with early-stage breast cancer: a prospective, randomized, multicenter trial analysis after 108 months of median follow-up, Annals of Surgical Oncology, 21, 408-15, 2014	Insufficient presentation of results
Tinterri, C, Gatzemeier, W, Zanini, V, Regolo, L, Pedrazzoli, C, Rondini, E, Amanti, C, Gentile, G, Taffurelli, M, Fenaroli, P, Tondini, C, Sacchetto, G, Sismondi, P, Murgo, R, Orlandi, M, Cianchetti, E, Andreoli, C, Conservative surgery with and without radiotherapy in elderly patients with early-stage	Same outcomes as Tinterri 2014 but with shorter follow-up periods

Excluded studies - RQ8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
breast cancer: a prospective randomised multicentre trial, Breast (Edinburgh, Scotland), 18, 373-7, 2009	
van de Water, Willemien, Bastiaannet, Esther, Scholten, Astrid N., Kiderlen, Mandy, de Craen, Anton J. M., Westendorp, Rudi G. J., van de Velde, Cornelis J. H., Liefers, Gerrit-Jan, Breast-conserving surgery with or without radiotherapy in older breast patients with early stage breast cancer: a systematic review and meta-analysis, Annals of Surgical Oncology, 21, 786-94, 2014	Insufficient presentation of results
Winzer, Kj, Sauerbrei, W, Braun, M, Liersch, T, Dunst, J, Guski, H, Schumacher, M, Radiation therapy and tamoxifen after breast-conserving surgery: updated results of a 2 x 2 randomised clinical trial in patients with low risk of recurrence, European journal of cancer (Oxford, England : 1990), 46, 95-101, 2010	Insufficient presentation of results
Zeng, S., Zhang, X., Yang, D., Wang, X., Ren, G., Effects of adjuvant radiotherapy on borderline and malignant phyllodes tumors: A systematic review and meta-analysis, Molecular and Clinical Oncology, 3, 663-671, 2015	Observational studies only

Economic studies

See Supplement 1: Health economics literature review for list of excluded economic studies.

Excluded studies for 8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?

Clinical studies

Excluded studies -8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
TARGIT-B:An international randomised controlled trial to compare targeted intra-operative radiotherapy boost with conventional external beam radiotherapy boost after lumpectomy for breast cancer in women with a high risk of local recurrence (Project record), Health Technology Assessment Database, 2013	Intrabeam has not been included in this review, as there is a NICE TA in development
Abo-Madyan, Y., Welzel, G., Sperk, E., Neumaier, C., Keller, A., Ehmann, M., Wenz, F., Intraoperative (IORT) versus whole breast radiotherapy (WBRT) for early breast cancer: Single centre results from the randomized phase III trial TARGIT-A, Strahlentherapie und Onkologie, 192 (1 Supplement 1), 18-19, 2016	Intrabeam has not been included in this review, as there is a NICE TA in development
Alvarado, M., Gallant, E., Rice, J. S., Grobmyer, S. R., Harris, E. E., Holmes, D., Pavord, D., Small, W., TARGIT-U.S.: A registry trial of targeted intraoperative radiation therapy following breast-conserving surgery, Journal of Clinical Oncology, 33, no pagination, 2015	Intrabeam has not been included in this review, as there is a NICE TA in development
Andersen, K. G., Gartner, R., Kroman, N., Flyger, H., Kehlet, H., Persistent pain after targeted intraoperative radiotherapy (TARGIT) or external breast radiotherapy for breast cancer: a randomized trial, Breast, 21, 46-9, 2012	Intrabeam has not been included in this review, as there is a NICE TA in development
Anonymous, Vaidya et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 2014. (2), International Journal of Radiation Oncology Biology Physics, 89, 497-498, 2014	Intrabeam has not been included in this review, as there is a NICE TA in development
Baum, M., The targeted intraoperative radiotherapy (TARGIT) trial for breast cancer: A review after the first 10 years of clinical application, European Journal of Cancer, Supplement, 8, 129-130, 2010	Intrabeam has not been included in this review, as there is a NICE TA in development
Baum, M., Targit-a trial (targeted intraoperative radiotherapy): Updated analysis of local recurrence, Breast, 22, S95, 2013	Intrabeam has not been included in this review, as there is a NICE TA in development
Baum, M., Joseph, D. J., Tobias, J. S., Wenz, F. K., Keshtgar, M. R., Alvarado, M., Bulsara, M., Eiermann, W., Williams, N. R., Vaidya, J. S., Safety and efficacy of targeted intraoperative radiotherapy (TARGIT) for early breast cancer: First report of a randomized controlled trial at 10-years maximum follow-up, Journal of Clinical Oncology, 28, no pagination, 2010	Intrabeam has not been included in this review, as there is a NICE TA in development

Excluded studies -8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
Baum, M., Vaidya, J. S., Targeted intra-operative radiotherapy-TARGIT for early breast cancer, Annals of the new york academy of sciences, 1138, 132-5, 2008	Intrabeam has not been included in this review, as there is a NICE TA in development
Baum, M., Vaidya, J. S., Bulsara, M. K., Wenz, F., Tobias, J. S., Eiermann, W., Joseph, D., Insights into the natural history of subclinical breast cancer: A biological fall out from the TARGIT-a trial, Annals of Oncology, 23, ix3, 2012	Intrabeam has not been included in this review, as there is a NICE TA in development
Baum, M., Vaidya, J. S., Tobias, J. S., Keshtgar, M., Williams, N. R., Wenz, F., Bulsara, M., Saunders, C., Joseph, D., Targit (targeted intra-operative radiotherapy for early stage breast cancer): Results from the targit a randomized controlled trial, European Journal of Cancer, Supplement, 8, 19, 2010	Intrabeam has not been included in this review, as there is a NICE TA in development
Coles, C, Donovan, E, Venables, K, Rowlings, C, Maylex, H, Bentzen, S, Sydenham, M, Bliss, J, Yarnold, J, Randomised trial testing intensity modulated radiotherapy and partial organ radiotherapy in early breast cancer (import trial), British journal of cancer, 91, S80, 2004	Abstract
Coles, C., Agrawal, R., Ah-See, M. L., Algurafi, H., Alhasso, A., Brunt, A. M., Chan, C., Griffin, C., Harnett, A., Hopwood, P., Kirby, A., Sawyer, E., Syndikus, I., Titley, J., Tsang, Y., Wheatley, D., Wilcox, M., Yarnold, J., Bliss, J. M., Partial breast radiotherapy for women with early breast cancer: First results of local recurrence data for IMPORT LOW (CRUK/06/003), European Journal of Cancer, 57, S4, 2016	Abstract.
Coles, C., Griffin, C., Kirby, A., Titley, J., Tsang, Y., Harnett, A., Chan, H., Sawyer, E., Bliss, J., Yarnold, J., Partial breast radiotherapy for women with early breast cancer: First analysis of late cosmesis adverse events from IMPORT LOW (CRUK/06/003), European Journal of Cancer, 50, S103, 2014	Abstract.
Corica, T., Nowak, A. K., Saunders, C. M., Bulsara, M., Taylor, M., Vaidya, J. S., Baum, M., Joseph, D. J., Cosmesis and Breast-Related Quality of Life Outcomes After Intraoperative Radiation Therapy for Early Breast Cancer: A Substudy of the TARGIT-A Trial, International Journal of Radiation Oncology Biology Physics, 96, 55-64, 2016	Intrabeam has not been included in this review, as there is a NICE TA in development
Dodwell, D. J., Dyker, K., Brown, J., Hawkins, K., Cohen, D., Stead, M., Ash, D., A randomised study of whole-breast vs tumour-bed irradiation after local excision and axillary dissection for early breast cancer, Clinical Oncology, 17, 618-622, 2005	Intervention does not fit inclusion criteria.
Engel, D., Schnitzer, A., Brade, J., Blank, E., Wenz, F., Suetterlin, M., Schoenberg, S., Wasser, K., Are mammographic changes in the tumour bed more pronounced after intraoperative radiotherapy for breast cancer? Subgroup analysis from a randomized trial (TARGIT-A), Breast Journal, 19, 92-95, 2013	Intrabeam has not been included in this review, as there is a NICE TA in development

Excluded studies -8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
Hanna, Samir A, Marta, Gustavo N, Riera, Rachel, da, Silva Joao Lf, de, Andrade Carvalho Heloisa, De, Barros Alfredo Carlos Sd, Intensity-modulated versus conventional radiotherapy for breast cancer, Cochrane Database of Systematic Reviews, 2013	Systematic Review Protocol.
Holmes, D. R., Baum, M., Joseph, D., The TARGIT trial: targeted intraoperative radiation therapy versus conventional postoperative whole-breast radiotherapy after breast-conserving surgery for the management of early-stage invasive breast cancer (a trial update), American journal of surgery, 194, 507-510, 2007	Intrabeam has not been included in this review, as there is a NICE TA in development
Jain, A. K., Vallow, L. A., Gale, A. A., Buskirk, S. J., Does Three-Dimensional External Beam Partial Breast Irradiation Spare Lung Tissue Compared With Standard Whole Breast Irradiation?, International Journal of Radiation Oncology Biology Physics, 75, 82-88, 2009	Non-RCT.
Joseph, D. J., Targit, Radiotherapy and Oncology, 103, S4, 2012	Intrabeam has not been included in this review, as there is a NICE TA in development
Julian, T. B., Costantino, J. P., Vicini, F. A., White, J. R., Cecchini, R. S., Winter, K. A., Arthur, D. W., Kuske, R., Rabinovitch, R., Parda, D. S., Mamounas, E. P., Curran Jr, W. J., Wolmark, N., A randomized phase III study of conventional whole breast irradiation (WBI) vs partial breast irradiation (PBI) for women with stage 0, 1, or 2 breast cancer: NSABP B-39/RTOG 0413, Cancer Research, 71, no pagination, 2011	Abstract.
Keshtgara, M., Vaidyab, J., Tobiasc, J., Williamsd, N., Baumdon, M., TARGIT (Targeted intra-operative radiotherapy for early stage breast cancer): Early results from the multi-centre randomized controlled trial, European Journal of Surgical Oncology, 36, 1098, 2010	Intrabeam has not been included in this review, as there is a NICE TA in development
Livi, L., Meattini, I., Marrazzo, L., Pallotta, S., Simontacchi, G., Saieva, C., Scotti, V., De Luca Cardillo, C., Bastiani, P., Nori, J., Orzalesi, L., Bianchi, S., Accelerated partial breast irradiation using intensity modulated radiotherapy versus whole breast irradiation: 5-year survival results of a phase 3 randomized trial, Cancer Research, 75, no pagination, 2015	Abstract
Livi, L., Meattini, I., Saieva, C., Franceschini, D., Meacci, F., Franzese, F., Scotti, V., De Luca Cardillo, C., Greto, D., Biti, G., Accelerated partial breast irradiation with IMRT: 3-years interim analysis of a Phase III randomized clinical trial, Radiotherapy and Oncology, 103, S51, 2012	Abstract.
Livi, L., Meattini, I., Saieva, C., Scotti, V., De Luca Cardillo, C., Meacci, F., Nori, J., Bianchi, S., Orzalesi, L., Biti, G., Accelerated partial breast irradiation with intensity-modulated radiotherapy (IMRT): The florence phase III randomized clinical trial at 3 years median follow-up, European Journal of Cancer, 48, S183, 2012	Abstract.

Excluded studies -8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
Livi, L., Saieva, C., Borghesi, S., Paoletti, L., Meattini, I., Rampini, A., Petrucci, A., Scoccianti, S., Paiar, F., Cataliotti, L., Leonulli, B. G., Bianchi, S., Biti, G. P., Concurrent Cyclophosphamide, Methotrexate, and 5-Fluorouracil Chemotherapy and Radiotherapy for Early Breast Carcinoma, International Journal of Radiation Oncology Biology Physics, 71, 705-709, 2008	Not a RCT.
Livi, L., Scotti, V., Saieva, C., Meattini, I., Detti, B., Simontacchi, G., Cardillo, C. D., Paiar, F., Mangoni, M., Marrazzo, L., Agresti, B., Cataliotti, L., Bianchi, S., Biti, G., Outcome after conservative surgery and breast irradiation in 5,717 patients with breast cancer: implications for supraclavicular nodal irradiation, International journal of radiation oncology, biology, physics, 76, 978-83, 2010	Intervention does not fit the inclusion criteria.
Marta, G. N., Macedo, C. R., Carvalho, H. D. A., Hanna, S. A., Da Silva, J. L. F., Riera, R., Accelerated partial irradiation for breast cancer: Systematic review and meta-analysis of 8653 women in eight randomized trials, Radiotherapy and Oncology, 114, 42-49, 2015	All studies included in the Hickey (2016) Cochrane systematic review.
Marta, G. N., Macedo, C. R., De Andrade Carvalho, H., Hanna, S. A., Da Silva, J. L. F., Riera, R., Erratum: Accelerated partial irradiation for breast cancer: Systematic review and meta-analysis of 8653 women in eight randomized trials (Radiotherapy and Oncology (2015) 114 (42-49)), Radiotherapy and Oncology, 115, 436-437, 2015	All studies included in the Hickey (2016) Cochrane systematic review.
McCormick, B., Partial breast radiation for early-stage breast cancer, Current Opinion in Obstetrics and Gynecology, 24, 31-37, 2012	Non-RCT.
Meattini, I., Marrazzo, L., Saieva, C., Pallotta, S., Simontacchi, G., Scotti, V., Furfaro, I., Meacci, F., Orzalesi, L., Livi, L., APBI versus whole breast irradiation in women age 70 years or older: A subgroup analysis of a phase 3 randomised trial, Radiotherapy and Oncology, 115, S20, 2015	Abstract.
Meattini, I., Saieva, C., Desideri, I., De Luca Cardillo, C., Scotti, V., Miccinesi, G., Bonomo, P., Orzalesi, L., Bernini, M., Casella, D., Sanchez, L. J., Nori, J., Bianchi, S., Livi, L., Accelerated partial breast irradiation versus whole breast radiotherapy: Quality of Life results from a phase 3 randomized trial and focus on patients aged 70 years or older, European Journal of Cancer, 57, S47, 2016	Abstract.
Meattini, I., Saieva, C., Desideri, I., Miccinesi, G., Francolini, G., Meacci, F., Muntoni, C., Scotti, V., De Luca Cardillo, C., Marrazzo, L., Simontacchi, G., Pallotta, S., Sanchez, L., Casella, D., Bernini, M., Orzalesi, L., Nori, J., Bianchi, S., Livi, L., Accelerated partial breast irradiation versus whole breast irradiation: Health-related quality of life analysis from a phase 3 trial, Cancer Research. Conference: 39th Annual CTRC AACR San Antonio Breast Cancer Symposium. United States, 77, 2017	Abstract.

Excluded studies -8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
Meattini, I., Saieva, C., Desideri, I., Simontacchi, G., Marrazzo, L., Scoccianti, S., De Luca Cardillo, C., Scotti, V., Bonomo, P., Mangoni, M., Rossi, F., Nori, J., Casella, D., Bernini, M., Sanchez, L., Orzalesi, L., Pallotta, S., Bianchi, S., Livi, L., Accelerated partial breast irradiation for Luminal-A breast cancer: Analysis from a phase 3 trial, Radiotherapy and Oncology, 119, S242, 2016	Abstract.
Meattini, I., Saieva, C., Marrazzo, L., Di Brina, L., Pallotta, S., Mangoni, M., Meacci, F., Bendinelli, B., Francolini, G., Desideri, I., De Luca Cardillo, C., Scotti, V., Furfaro, I. F., Rossi, F., Greto, D., Bonomo, P., Casella, D., Bernini, M., Sanchez, L., Orzalesi, L., Simoncini, R., Nori, J., Bianchi, S., Livi, L., Accelerated partial breast irradiation using intensity-modulated radiotherapy technique compared to whole breast irradiation for patients aged 70 years or older: subgroup analysis from a randomized phase 3 trial, Breast Cancer Research & TreatmentBreast Cancer Res Treat, 153, 539-47, 2015	Abstract.
Murawa, D., Rutten, H., Maluta, S., Electron IORT APBI: What does the data tell us at 5 years?, European journal of surgical oncology, 42 (9), S137, 2016	Abstract.
Olivotto, I., What have we learned from the randomized trials of partial breast RT?, Cancer Research, 75, no pagination, 2015	Abstract.
Ott, O. J., Hildebrandt, G., Potter, R., Hammer, J., Hindemith, M., Resch, A., Spiegl, K., Lotter, M., Uter, W., Kortmann, R. D., Schrauder, M., Beckmann, M. W., Fietkau, R., Strnad, V., Accelerated partial breast irradiation with interstitial implants: risk factors associated with increased local recurrence, International Journal of Radiation Oncology, Biology, Physics, 80, 1458-63, 2011	Control/Comparator of interest does not fit inclusion criteria.
Ott, O. J., Hildebrandt, G., Potter, R., Hammer, J., Lotter, M., Resch, A., Sauer, R., Strnad, V., Accelerated partial breast irradiation with multi-catheter brachytherapy: Local control, side effects and cosmetic outcome for 274 patients. Results of the German-Austrian multi-centre trial, Radiotherapy & Oncology, 82, 281-6, 2007	Control/Comparator of interest does not fit inclusion criteria.
Ott, O. J., Lotter, M., Fietkau, R., Strnad, V., Accelerated partial-breast irradiation with interstitial implants. Analysis of factors affecting cosmetic outcome, Strahlentherapie und Onkologie, 185, 170-6, 2009	Outcomes of interest does not fit inclusion criteria.
Ott, O. J., Lotter, M., Sauer, R., Strnad, V., Accelerated partial-breast irradiation with interstitial implants: the clinical relevance of the calculation of skin doses, Strahlentherapie und Onkologie, 183, 426-31, 2007	Control/Comparator of interest does not fit inclusion criteria.
Ott, O. J., Potter, R., Hildebrandt, G., Hammer, J., Lotter, M., Beckmann, M. W., Sauer, R., Strnad, V., [Partial breast irradiation for early breast cancer with favorable prognostic factors: 3-year results of the German-Austrian phase II-trial], Rofo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der NuklearmedizinROFO Fortschr Geb Rontgenstr Nuklearmed, 177, 962-7, 2005	Not in English language.

Excluded studies -8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
Ott, O. J., Schulz-Wendtland, R., Uter, W., Pfahlberg, A., Beckmann, M. W., Sauer, R., Strnad, V., Fat necrosis after conserving surgery and interstitial brachytherapy and/or external-beam irradiation in women with breast cancer, Strahlentherapie und Onkologie, 181, 638-44, 2005	Non-RCT.
Ott, O. J., Strnad, V., Stillkrieg, W., Uter, W., Beckmann, M. W., Fietkau, R., Accelerated partial breast irradiation with external beam radiotherapy : First results of the German phase 2 trial, Strahlentherapie und Onkologie, 193, 55-61, 2017	Non-RCT.
Pan, X. B., Huang, S. T., Jiang, Y. M., Ma, J. L., Zhu, X. D., Secondary malignancies after partial versus whole breast irradiation: A systematic review and meta-analysis, Oncotarget, 7, 71951-71959, 2016	All studies included in the Hickey (2016) Cochrane systematic review.
Picot, J., Copley, V., Colquitt, J. L., Kalita, N., Hartwell, D., Bryant, J., The INTRABEAM photon radiotherapy system for the adjuvant treatment of early breast cancer: A systematic review and economic evaluation, Health Technology Assessment, 19, 1-190, 2015	All studies included in the Hickey (2016) Cochrane systematic review.
Polgar, C., Fodor, J., Orosz, Z., Major, T., Takacsi-Nagy, Z., Csaba Mangel, L., Sulyok, Z., Somogyi, A., Kasler, M., Nemeth, G., Electron and high-dose-rate brachytherapy boost in the conservative treatment of stage I-II breast cancer: First results of the randomized Budapest boost trial, Strahlentherapie und Onkologie, 178, 615-623, 2002	Intervention does not fit the inclusion criteria.
Polgar, C., Kahan, Z., Orosz, Z., Gabor, G., Hadijev, J., Cserni, G., Kulka, J., Jani, N., Sulyok, Z., Lazar, G., Boross, G., Diczhazi, C., Szabo, E., Laszlo, Z., Pentek, Z., Major, T., Fodor, J., The role of radiotherapy in the conservative treatment of ductal carcinoma in situ of the breast, Pathology Oncology ResearchPathol Oncol Res, 14, 179-92, 2008	Systematic review with non-RCTs.
Polgar, C., Limbergen, E. V., Potter, R., Kovacs, G., Polo, A., Lyczek, J., Hildebrandt, G., Niehoff, P., Guinot, J. L., Guedea, F., Johansson, B., Ott, O. J., Major, T., Strnad, V., Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: Recommendations of the Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009), Radiotherapy and Oncology, 94, 264-273, 2010	Abstract.
Polgar, C., Major, T., Fodor, J., [Modern radiotherapy after breast-conserving surgery], Orvosi HetilapOrv Hetil, 153, 45-55, 2012	Not in English language.
Polgar, C., Major, T., Fodor, J., Sulyok, Z., Takacsi-Nagy, Z., Nemeth, G., Kasler, M., Breast-conserving therapy with partial or whole breast RT: 10-year results of the Budapest randomized trial, Radiotherapy and Oncology, 103, S35, 2012	Abstract.
Polgar, C., Major, T., Somogyi, A., Fodor, J., Toth, J., Sulyok, Z., Forrai, G., Takacsi-Nagy, Z., Mangel, L. C., Nemeth, G., Sole brachytherapy of the tumour bed after breast conserving surgery: A new radiotherapeutic strategy for patients at low risk of local relapse, Neoplasma, 46, 182-189, 1999	Non-RCT.

Excluded studies -8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
Polgar, C., Major, T., Sulyok, Z., Takacsi-Nagy, Z., Fodor, J., Long-term toxicity and cosmetic results of partial versus whole breast irradiation: 10-year results of a phase iii APBI trial, International Journal of Radiation Oncology Biology Physics, 90, S133-S134, 2014	Abstract.
Polgar, C., Major, T., Sulyok, Z., Takacsi-Nagy, Z., Fodor, J., Toxicity and cosmetic results of partial vs whole breast irradiation: 10-year results of a randomized trial, Radiotherapy and Oncology, 111, S60, 2014	Abstract.
Polgar, C., Orosz, Z., Kahan, Z., Gabor, G., Jani, N., Cserni, G., Hadijev, J., Kulka, J., Sulyok, Z., Boross, G., Lazar, G., Laszlo, Z., Diczhazi, C., Udvarhelyi, N., Szabo, E., Pentek, Z., Major, T., Fodor, J., Combined surgery and radiotherapy in the treatment of ductal carcinoma in situ of the breast: preliminary results of the Hungarian multicentre prospective randomised study. [Hungarian], Magyar onkologia, 52, 269-277, 2008	Not in English language.
Polgar, C., Strnad, V., Kovacs, G., Partial-breast irradiation or whole-breast radiotherapy for early breast cancer: a meta-analysis of randomized trials, Strahlentherapie und Onkologie, 186, 113-4, 2010	Not a systematic review.
Polgar, C., Strnad, V., Major, T., Brachytherapy for partial breast irradiation: the European experience, Seminars in Radiation Oncology, 15, 116-22, 2005	Not a systematic review.
Polgar, C., Strnad, V., Ott, O., Hildebrandt, G., Kauer-Dorner, D., Knauerhase, H., Major, T., Lyczek, J., Guinot, J., Dunst, J., Gutierrez Miguelez, C., Slampa, P., Allgauer, M., Lossl, K., Polat, B., Kovacs, G., Fischedick, A., Wendt, T., Hindemith, M., Resch, A., Niehoff, P., Guedea, F., Potter, R., Gall, C., Uter, W., Late toxicity and cosmesis after APBI with brachytherapy vs WBI: 5-year results of a phase III trial, Radiotherapy and Oncology, 119, S230-S231, 2016	Abstract.
Polgar, C., Van Limbergen, E., Potter, R., Kovacs, G., Polo Rubio, J. A., Lyczek, J., Hildebrandt, G., Niehoff, P., Guinot, J. L., Guedea, F., Johansson, B., Ott, O. J., Major, T., Strnad, V., Selection criteria for brachytherapy in partial breast irradiation - Recommendations of the GEC-ESTRO Breast Cancer Working Group, Radiotherapy and Oncology, 96, S134, 2010	Abstract.
Polgar, C., Van Limbergen, E., Potter, R., Kovacs, G., Polo, A., Lyczek, J., Hildebrandt, G., Niehoff, P., Major, T., Strnad, V., Patient selection for accelerated partial breast irradiation after breast-conserving surgery: Recommendations of the groupe europeen de curietherapie-european society for therapeutic radiology and oncology (GEC-ESTRO) breast cancer working group, International Journal of Radiation Oncology Biology Physics, 78, S243, 2010	Systematic review includes non-RCTs.
Rodriguez De Dios, N., Sanz, X., Dengra, J., Foro, P., Reig, A., Membrive, I., Lozano, J., Fernandez-Velilla, E., Iglesias, P., Algara, M., Interim cosmetic results and toxicity using 3d conformal external beam radiation therapy to deliver accelerated partial breast irradiation in patients with early-stage breast cancer, International Journal of Radiation Oncology Biology Physics, 84, S87, 2012	Abstract.

Excluded studies -8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
Rodriguez, N., Sanz, X., Dengra, J., Foro, P., Perez, P., Fernandez-velilla, E., Membrive, I., Reig, A., Quera, J., Lio, J., Pera, O., Algara, M., Long-term toxicity and cosmetic results using 3D-CRT to deliver accelerated partial breast irradiation in earlystage breast cancer, Reports of Practical Oncology and Radiotherapy, 18, S60-S61, 2013	Abstract.
Rodriguez, N., Sanz, X., Foro, P., Reig, A., Membrive, I., Lozano, J., Fernandez-Velilla, E., Quera, J., Pera, O., Algara, M., Phase III study comparing accelerated partial breast irradiation vs whole breast radiation therapy using 3D-CRT, Radiotherapy and Oncology, 103, S400, 2012	Abstract.
Silverstein, M. J., Fastner, G., Maluta, S., Reitsamer, R., Goer, D. A., Vicini, F., Wazer, D., Intraoperative Radiation Therapy: A Critical Analysis of the ELIOT and TARGIT Trials. Part 2-TARGIT, Annals of surgical oncology, 21, 3793-3799, 2014	Intrabeam has not been included in this review, as there is a NICE TA in development
Silverstein, M. J., Fastner, G., Maluta, S., Reitsamer, R., Goer, D. A., Vicini, F., Wazer, D., Intraoperative Radiation Therapy: A Critical Analysis of the ELIOT and TARGIT Trials. Part 1-ELIOT, Annals of surgical oncology, 21, 3787-3792, 2014	Intrabeam has not been included in this review, as there is a NICE TA in development
Smith, B. D., Arthur, D. W., Buchholz, T. A., Haffty, B. G., Hahn, C. A., Hardenbergh, P. H., Julian, T. B., Marks, L. B., Todor, D. A., Vicini, F. A., Whelan, T. J., White, J., Wo, J. Y., Harris, J. R., Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO), International Journal of Radiation Oncology, Biology, Physics, 74, 987-1001, 2009	Systematic review with non-RCTs.
Sperk, E., Vaidya, J., Bulsara, M., Sutterlin, M., Ataseven, B., Pigorsch, S., Feyer, P., Blohmer, J. U., Kaufmann, M., Rodel, C., Friese, K., Belka, C., Solomayer, E. F., Fleckenstein, J., Park-Simon, T. W., Bremer, M., Joseph, D., Tobias, J., Baum, M., Wenz, F., Updates from the TARGIT A trial for the German centers: Local recurrence and survival, Oncology Research and Treatment, 37, 16-17, 2014	Intrabeam has not been included in this review, as there is a NICE TA in development
Sperk, E., Welzel, G., Keller, A., Kraus-Tiefenbacher, U., Gerhardt, A., Sutterlin, M., Wenz, F., Late radiation toxicity after intraoperative radiotherapy (IORT) for breast cancer: Results from the randomized phase III trial TARGIT A, Breast Cancer Research and Treatment, 135, 253-260, 2012	Intrabeam has not been included in this review, as there is a NICE TA in development
Strnad, V., Multicatheter brachytherapy is the best for APBI, Radiotherapy and Oncology, 119, S141, 2016	Abstract.
Strnad, V., Hildebrandt, G., Potter, R., Hammer, J., Hindemith, M., Resch, A., Spiegl, K., Lotter, M., Uter, W., Bani, M., Kortmann, R. D., Beckmann, M. W., Fietkau, R., Ott, O. J., Accelerated partial breast irradiation: 5-year results of the German-Austrian multicentre phase II trial using interstitial multicatheter brachytherapy alone after breast-conserving surgery, International Journal of Radiation Oncology Biology Physics, 80, 17-24, 2011	Control/Comparator of interest does not fit inclusion criteria.

Excluded studies -8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
Strnad, V., Ott, O. J., Hildebrandt, G., Potter, R., Fietkau, R., Lyczek, J., Uter, W., Major, T., Lotter, M., Polgar, C., First clinical results of the GEC-ESTRO breast WG phase III multicentric APBI trial, Radiotherapy and Oncology, 103, S35-S36, 2012	Abstract.
Tobias, J. S., Vaidya, J. S., Keshtgar, M., Douek, D., Metaxas, M., Stacey, C., Sainsbury, R., D'Souza, D., Baum, M., Breast-conserving surgery with intra-operative radiotherapy: The right approach for the 21st century?, Clinical Oncology, 18, 220-228, 2006	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, A., Vaidya, P., Both, B., Brew-Graves, C., Vaidya, J., Cost effectiveness analysis of targeted intraoperative radiotherapy alone (TARGIT-A) in early breast cancer patients, Value in Health, 17, A640, 2014	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J. S., Baum, M., Tobias, J. S., D'Souza, D. P., Naidu, S. V., Morgan, S., Metaxas, M., Harte, K. J., Sliski, A. P., Thomson, E., Targeted intra-operative radiotherapy (Targit): An innovative method of treatment for early breast cancer, Annals of oncology, 12, 1075-1080, 2001	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J. S., Baum, M., Tobias, J. S., Massarut, S., Wenz, F., Murphy, O., Hilaris, B., Houghton, J., Saunders, C., Corica, T., Roncadin, M., Kraus-Tiefenbacher, U., Melchaert, F., Keshtgar, M., Sainsbury, R., Douek, M., Harrison, E., Thompson, A., Joseph, D., Targeted intraoperative radiotherapy (TARGIT) yields very low recurrence rates when given as a boost, International Journal of Radiation Oncology Biology Physics, 66, 1335-1338, 2006	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J. S., Baum, M., Tobias, J. S., Morgan, S., D'Souza, D., The novel technique of delivering targeted intraoperative radiotherapy (Targit) for early breast cancer, European journal of surgical oncology, 28, 447-454, 2002	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J. S., Baum, M., Tobias, J. S., Wenz, F., Massarut, S., Keshtgar, M., Hilaris, B., Saunders, C., Williams, N. R., Brew-Graves, C., Corica, T., Roncadin, M., Kraus-Tiefenbacher, U., Sutterlin, M., Bulsara, M., Joseph, D., Long-term results of TARGeted Intraoperative radioTherapy (Targit) boost during breast-conserving surgery, International Journal of Radiation Oncology Biology Physics, 81, 1091-1097, 2011	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J. S., Baum, M., Wenz, F., Bulsara, M., Tobias, J., Alvarodo, M., Saunders, C., Williams, N., Joseph, D., The TARGIT-a trial update confirms no increase in local recurrence, Cancer Research. Conference: 34th Annual CTRC AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Publication:, 71, 2011	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J. S., Bulsara, M., Wenz, F., Coombs, N., Singer, J., Ebbs, S., Massarut, S., Saunders, C., Douek, M., Williams, N. R., Joseph, D., Tobias, J. S., Baum, M., Reduced Mortality With Partial-Breast Irradiation for Early Breast Cancer: A Meta-Analysis of Randomized Trials, International Journal of Radiation Oncology Biology Physics, 96, 259-265, 2016	All studies included in the Hickey (2016) Cochrane systematic review.

Excluded studies -8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
Vaidya, J. S., Bulsara, M., Wenz, F., Massarut, S., Joseph, D., Tobias, J., Williams, N. R., Baum, M., Fewer non-breast cancer deaths in targit-a trial: Systemic benefit of targit or lack of EBRT toxicity, Breast, 22, S97, 2013	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J. S., Bulsara, M., Wenz, F., Massarut, S., Joseph, D., Tobias, J., Williams, N. R., Baum, M., Omitting whole breast radiotherapy does not increase axillary recurrence-data from targit-a trial, Breast, 22, S96, 2013	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J. S., Bulsara, M., Wenz, F., Massarut, S., Joseph, D., Tobias, J., Williams, N., Baum, M., The lower non-breast cancer mortality with targit in the targita trial could be a systemic effect of targit on tumour microenvironment, International Journal of Radiation Oncology Biology Physics, 87, S240, 2013	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J. S., Joseph, D. J., Tobias, J. S., Bulsara, M., Wenz, F., Saunders, C., Alvarado, M., Flyger, H. L., Massarut, S., Eiermann, W., Keshtgar, M., Dewar, J., Kraus-Tiefenbacher, U., Sutterlin, M., Esserman, L., Holtveg, H. M. R., Roncadin, M., Pigorsch, S., Metaxas, M., Falzon, M., Matthews, A., Corica, T., Williams, N. R., Baum, M., Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): An international, prospective, randomised, non-inferiority phase 3 trial, The Lancet, 376, 91-102, 2010	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J. S., Joseph, D., Tobias, J. S., Wenz, F., Keshtgar, M., Bulsara, M., Saunders, C., Williams, N., Baum, M., Single dose targeted intra-operative radiotherapy (TARGIT) for early breast cancer compared with external beam radiotherapy - First report of a randomized controlled trial (TARGIT-A) at 10 years maximum follow up, European Journal of Surgical Oncology, 36, 829-830, 2010	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J. S., Massarut, S., Tobias, J. S., Wenz, F., Bulsara, M., Keshtgar, M., Saunders, C., Alavarado, M., Williams, N., Joseph, D., Baum, M., Targeted intra-operative radiotherapy boost-TARGIT-B trial: A randomized trial for young and high risk patients including those after post-neoadjuvant systemic therapy lumpectomy, European Journal of Surgical Oncology, 36, 820, 2010	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J. S., Tobias, J. S., Baum, M., Wenz, F., Kraus-Tiefenbacher, U., D'Souza, D., Keshtgar, M., Massarut, S., Hilaris, B., Saunders, C., Joseph, D., TARGeted Intraoperative radiotherapy (TARGIT): An innovative approach to partial-breast irradiation, Seminars in Radiation Oncology, 15, 84-91, 2005	Not an RCT.
Vaidya, J. S., Walton, L., Dewar, J., Single dose targeted intraoperative radiotherapy (TARGIT) for breast cancer can be delivered as a second procedure under local anaesthetic, World Journal of Surgical Oncology, 4, 2, 2006	Not an RCT.

Excluded studies -8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
Vaidya, J. S., Wenz, F., Bulsara, M., Erratum: Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial (Lancet (2014) 383 (603-613)), The Lancet, 383, 602, 2014	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J. S., Wenz, F., Bulsara, M., Joseph, D., Tobias, J. S., Keshtgar, M., Flyger, H., Massarut, S., Alvarado, M., Saunders, C., Eiermann, W., Metaxas, M., Sperk, E., Sutterlin, M., Brown, D., Esserman, L., Roncadin, M., Thompson, A., Dewar, J. A., Holtveg, H., Pigorsch, S., Falzon, M., Harris, E., Matthews, A., Brew-Graves, C., Potyka, I., Corica, T., Williams, N. R., Baum, M., Targeted intraoperative radiotherapy for early breast cancer: TARGIT-A trial-updated analysis of local recurrence and first analysis of survival, Cancer Research, 72, no pagination, 2012	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J. S., Wenz, F., Bulsara, M., Tobias, J. S., Joseph, D. J., Keshtgar, M., Flyger, H. L., Massarut, S., Alvarado, M., Saunders, C., Eiermann, W., Metaxas, M., Sperk, E., Sutterlin, M., Brown, D., Esserman, L., Roncadin, M., Thompson, A., Dewar, J. A., Holtveg, H. M. R., Pigorsch, S., Falzon, M., Harris, E., Matthews, A., Brew-Graves, C., Potyka, I., Corica, T., Williams, N. R., Baum, M., Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer:5-year results for local control and overall survival from the TARGIT-A randomised trial, The Lancet, 383, 603-613, 2014	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J. S., Wenz, F., Bulsara, M., Tobias, J. S., Joseph, D. J., Saunders, C., Brew-Graves, C., Potyka, I., Morris, S., Vaidya, H. J., Williams, N. R., Baum, M., An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial), Health Technology Assessment, 20, vii-188, 2016	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J. S., Wenz, F., Bulsara, M., Tobias, J. S., Massarut, S., Joseph, D., Baum, M., Case selection for targeted intraoperative radiotherapy (TARGIT), European Journal of Cancer, 49, S451, 2013	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, J., Bulsara, M., Wenz, F., Tobias, J. S., Joseph, D. J., Massarut, S., Flyger, H., Eiermann, W., Saunders, C., Alvarado, M., Brew-Graves, C., Potyka, I., Williams, N. R., Baum, M., Whole breast radiotherapy does not affect growth of cancer foci in other quadrants: Results from the TARGIT A trial, Radiotherapy and Oncology, 115, S232-S233, 2015	Intrabeam has not been included in this review, as there is a NICE TA in development
Vaidya, Js, Baum, M, Tobias, Js, Houghton, J, Keshtgar, M, Sainsbury, R, Taylor, I, Morgan, S, Metaxas, M, D'Souza, D, Targeted intraoperative radiotherapy for breast cancer-a randomised trial, Breast Cancer Research and Treatment, 69, 228, 2001	Intrabeam has not been included in this review, as there is a NICE TA in development

Excluded studies -8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
Vaidya, Js, Joseph, Dj, Tobias, Js, Wenz, Fk, Bulsara, M, Alvarado, M, Abstract PD06-01: A Single Treatment with Targeted Intraoperative Radiotherapy (TARGIT) Is Similar to Several Weeks of External Beam Radiotherapy (EBRT) with Respect to Efficacy and Safety, and Has Obvious Advantages to the Patient and the Economy, 70, 2010	Intrabeam has not been included in this review, as there is a NICE TA in development
Valachis, A., Mauri, D., Polyzos, N. P., Mavroudis, D., Georgoulias, V., Casazza, G., Partial breast irradiation or whole breast radiotherapy for early breast cancer: A meta-analysis of randomized controlled trials, Journal of clinical oncology, 27, CRA532, 2009	All studies included in the Hickey (2016) Cochrane systematic review.
Valachis, A., Mauri, D., Polyzos, N. P., Mavroudis, D., Georgoulias, V., Casazza, G., Partial breast irradiation or whole breast radiotherapy for early breast cancer: a meta-analysis of randomized controlled trials, Breast Journal, 16, 245-51, 2010	All studies included in the Hickey (2016) Cochrane systematic review.
Veronesi, U., Orecchia, R., Maisonneuve, P., Viale, G., Rotmensz, N., Sangalli, C., Luini, A., Veronesi, P., Galimberti, V., Zurrida, S., Leonardi, M. C., Lazzari, R., Cattani, F., Gentilini, O., Intra, M., Caldarella, P., Ballardini, B., Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial, Lancet OncologyLancet Oncol, 14, 1269-77, 2013	Intrabeam has not been included in this review, as there is a NICE TA in development
Welzel, G., Boch, A., Blank, E., Kraus-Tiefenbacher, U., Keller, A., Hermann, B., Sutterlin, M., Wenz, F., Radiation-related quality of life parameters after targeted intraoperative radiotherapy vs. Whole breast radiotherapy in patients with breast cancer: Results from the randomized phase iii trial TARGIT-A, International Journal of Radiation Oncology Biology Physics, 81, S206-S207, 2011	Intrabeam has not been included in this review, as there is a NICE TA in development
Welzel, G., Boch, A., Blank, E., Kraus-Tiefenbacher, U., Keller, A., Hermann, B., Sutterlin, M., Wenz, F., Radiation-related quality of life parameters after targeted intraoperative radiotherapy versus whole breast radiotherapy in patients with breast cancer: Results from the randomized phase III trial TARGIT-A, Journal of cancer research and clinical oncology, 138, 82, 2012	Intrabeam has not been included in this review, as there is a NICE TA in development
Welzel, G., Boch, A., Sperk, E., Hofmann, F., Kraus-Tiefenbacher, U., Gerhardt, A., Suetterlin, M., Wenz, F., Radiation-related quality of life parameters after targeted intraoperative radiotherapy versus whole breast radiotherapy in patients with breast cancer: results from the randomized phase III trial TARGIT-A, Radiation Oncology, 8, 9, 2013	Intrabeam has not been included in this review, as there is a NICE TA in development
Wenz, F., TARGIT E(lderly) - Prospective phase II study of Intraoperative Radiotherapy (IORT) in elderly patients with small breast cancer, Strahlentherapie und Onkologie, 192 (1 Supplement 1), 17-18, 2016	Intrabeam has not been included in this review, as there is a NICE TA in development

Excluded studies -8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?	
Study	**Reason for exclusion**
Wenz, F. K., TARGIT E(lderly): Prospective phase II study of intraoperative radiotherapy (IORT) in elderly patients with small breast cancer, Journal of Clinical Oncology, 34, no pagination, 2016	Intrabeam has not been included in this review, as there is a NICE TA in development
Wenz, F. K., Vaidya, J. S., Bulsara, M., Suetterlin, M., Sperk, E., Ataseven, B., Pigorsch, S., Feyer, P. C., Blohmer, J. U., Kaufmann, M., Roedel, C., Friese, K., Belka, C., Solomayer, E., Fleckenstein, J., Park-Simon, T. W., Bremer, M., Joseph, D. J., Tobias, J. S., Baum, M., TARGIT-A trial: Updated results for local recurrence and survival for the German centers, Journal of Clinical Oncology, 31, no pagination, 2013	Intrabeam has not been included in this review, as there is a NICE TA in development
Wenz, F., Vaidya, J. S., Pigorsch, S., Feyer, P., Roedel, C., Belka, C., Fleckenstein, J., Bremer, M., Joseph, D., Baum, M., Local recurrence and survival for the german centers in the targit-a (targeted intraoperative radiation therapy-alone) trial, International Journal of Radiation Oncology Biology Physics, 87, S241, 2013	Intrabeam has not been included in this review, as there is a NICE TA in development
Williams, N. R., Keshtgar, M., Corica, T., Saunders, C., Joseph, D., Bulsara, M. K., Early breast cancer and cosmetic outcome one, two, three and four years after intra-operative radiotherapy compared with external beam radiotherapy: An objective assessment of patients from a randomised controlled trial (on behalf of the targit trialists' group), European Journal of Cancer, 47, S365, 2011	Intrabeam has not been included in this review, as there is a NICE TA in development
Zhang, L., Zhou, Z., Mei, X., Yang, Z., Ma, J., Chen, X., Wang, J., Liu, G., Yu, X., Guo, X., Intraoperative radiotherapy versus whole-breast external beam radiotherapy in early-stage breast cancer, Medicine (United States), 94, e1143, 2015	All studies included in the Hickey (2016) Cochrane systematic review.
Zhang, L., Zhou, Z., Yu, X., Mei, X., Yang, Z., Chen, X., Guo, X., Intraoperative radiation therapy versus whole-breast external beam radiation therapy in early-stage breast cancer: A systematic review and meta-analysis, International Journal of Radiation Oncology Biology Physics, 93, E10, 2015	All studies included in the Hickey (2016) Cochrane systematic review.

NICE, National Institute of Health and Care Excellence; RCT, randomised controlled trial; TA, technology appraisal

Economic studies

See Supplement 1: Health economics literature review for list of excluded economic studies.

Excluded studies for 8.4 What are the indications for radiotherapy to internal mammary nodes?

Clinical studies

Excluded studies - 8.4 What are the indications for radiotherapy to internal mammary nodes?	
Study	**Reason for exclusion**
Boelke, E., Matuschek, C., Kammers, K., Budach, W., Adjuvant radiotherapy of regional lymph nodes in breast cancer-a meta-analysis of randomized trials, International Journal of Gynecological Cancer, 24, 8-9, 2014	Abstract
Brower, V., Nodal radiation in breast cancer does not improve survival, Lancet OncologyLancet Oncol, 16, e430, 2015	Brief narrative review
Budach, W., Bolke, E., Kammers, K., Gerber, P. A., Nestle-Kramling, C., Matuschek, C., Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update, Radiation OncologyRadiat, 10, 258, 2015	Insufficient information to judge study quality
Chen, R. C., Lin, N. U., Golshan, M., Harris, J. R., Bellon, J. R., Internal mammary nodes in breast cancer: diagnosis and implications for patient management -- a systematic review, Journal of clinical oncology, 26, 4981-9, 2008	Contains interventions outside scope
Haffty, B. G., Regional Nodal Irradiation in Breast Cancer, Breast Diseases, 27, 16-19, 2016	Expert review
Matuschek, C., Kammers, K., Boelke, E., Budach, W., Adjuvant radiotherapy of regional lymph nodes in breast cancer-a meta-analysis of randomized trials, Radiotherapy and Oncology, 111, S57, 2014	Conference abstract
Mei, X., Guo, X. M., Zhang, Z., Chen, J. Y., Postmastectomy radiation in supraclavicular and internal mammary regions of patients with breast cancer of stage II/III, Chinese Medical JournalChin Med J, 122, 103-5, 2009	Non RCT N<2000
Moreno, A. C., Lin, H., Bedrosian, I., Smith, B. D., Babiera, G., Stauder, M. C., Buchholz, T. A., Woodward, W. A., Shen, Y., Shaitelman, S. F., Effect of Regional Nodal Irradiation on Overall Survival in Patients With High-risk Invasive Breast Cancer: A National Cancer Data Base Analysis, International journal of radiation oncology, biology, physics, 96, E50-E51, 2016	Conference abstract
Nilsson, G., Holmberg, L., Garmo, H., Terent, A., Blomqvist, C., Radiation to supraclavicular and internal mammary lymph nodes in breast cancer increases the risk of stroke, British Journal of Cancer, 100, 811-816, 2009	Non-RCT N<2000
Olson, R. A., Maas, B., Gondara, L., Woods, R., Speers, C., Truong, P., Lo, A. C., Olivotto, I., Tyldesley, S., Nichol, A., Weir, L., Impact of Internal Mammary Node Radiation on Survival of Patients With Breast Cancer: Extended Follow-Up of a Population-Based Analysis, International journal of radiation oncology, biology, physics, 96, E54-E55, 2016	Conference abstract

Excluded studies - 8.4 What are the indications for radiotherapy to internal mammary nodes?	
Study	**Reason for exclusion**
Olson, R. A., Woods, R., Lau, J., Speers, C., Lo, A., Tyldesley, S., Weir, L., Impact of internal mammary node inclusion in the radiation treatment volume on the outcomes of patients with breast cancer treated with locoregional radiation after six years of follow-up, Journal of clinical oncology, 29, 81, 2011	Conference abstract
Olson, R. A., Woods, R., Speers, C., Lau, J., Lo, A., Truong, P. T., Tyldesley, S., Olivotto, I. A., Weir, L., Does the intent to irradiate the internal mammary nodes impact survival in women with breast cancer? A population-based analysis in British Columbia, International journal of radiation oncology, biology, physics, 83, e35-41, 2012	Retrospective cohort study
Osman, M. A. M., Elkady, M. S., Nasr, K. E., For stage II node-positive breast cancer, is it worthwhile to consider adjuvant radiotherapy following mastectomy?, Frontiers in Oncology, 4 (NOV) (no pagination), 2014	No RT to IMN
Poortmans, P., Fourquet, A., Collette, L., Struikmans, H., Bartelink, H., Kirkove, C., Budach, V., Maingon, P., Valli, M. C., Van Den Bogaert, W., Irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer: State of the day of EORTC phase III trial 22922/10925 with 4004 patients, European Journal of Cancer, Supplement, 8, 54, 2010	Conference abstract
Poortmans, P., Struikmans, H., Collette, S., Kirkove, C., Budach, V., Maingon, P., Valli, M. C., Fourquet, A., Van Den Bogaert, W., Bartelink, H., Lymph node RT improves survival in breast cancer: 10 years results of the EORTC ROG and BCG phase III trial 22922/10925, Radiotherapy and Oncology, 111, S206, 2014	Conference abstract
Poortmans, P., Struikmans, H., Kirkove, C., Budach, V., Maingon, P., Valli, M. C., Collette, S., Fourquet, A., Bartelink, H., Van Den Bogaert, W., Irradiation of the internal mammary and medial supraclavicular lymph nodes in stage I to III breast cancer: 10 years results of the EORTC Radiation Oncology and Breast Cancer Groups phase III trial 22922/10925, European Journal of Cancer, 49, S1-S2, 2013	Conference abstract
Shah, C., Vicini, F. A., Regional Nodal Irradiation: Moving Beyond Overall Survival, International journal of radiation oncology, biology, physics, 94, 208-9, 2016	Opinion paper
Stokes, E. L., Tyldesley, S., Woods, R., Wai, E., Olivotto, I. A., Effect of nodal irradiation and fraction size on cardiac and cerebrovascular mortality in women with breast cancer treated with local and locoregional radiotherapy, International journal of radiation oncology, biology, physics, 80, 403-9, 2011	Retrospective cohort study
Struikmans, H., Collette, S., Van Den Bogaert, W., Kirkove, C., Budach, V., Maingon, P., Valli, M. C., Fourquet, A., Bartelink, H., Poortmans, P., The benefit of regional irradiation in stage I-III breast cancer: 10 years results of the EORTC ROG and BCG phase III trial 22922/10925, European Journal of Cancer, 50, S3, 2014	Abstract
Thorsen, L. B. J., Berg, M., Brodersen, H. J., Dano, H., Jensen, I., Overgaard, J., Overgaard, M., Pedersen, A. N., Zimmermann, S. J., Offersen, B. V., Improved survival with internal mammary node irradiation: A prospective study on 3,072 breast cancer patients, Radiotherapy and Oncology, 111, S57, 2014	Conference abstract

Excluded studies - 8.4 What are the indications for radiotherapy to internal mammary nodes?	
Study	**Reason for exclusion**
Verma, V., Vicini, F., Tendulkar, R. D., Khan, A. J., Wobb, J., Edwards-Bennett, S., Desai, A., Shah, C., 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, 617-31, 2016	Contains comparisons outside scope
Vu, C. C., Sura, K., Chen, P. Y., Dilworth, J. T., Regional Nodal Irradiation in Breast Cancer Patients With Clinical N1 and Pathologic N0 Disease After Neoadjuvant Chemotherapy: An Analysis of the National Cancer Data Base, International journal of radiation oncology, biology, physics, 96, E4-E5, 2016	Conference abstract
Wendling, P., Regional nodal irradiation combats disease recurrence, Oncology Report, 7, 2011	Narrative review
Wolstenholme, V., Ross, G., Current indications for post-mastectomy radiotherapy, Advances in Breast Cancer, 4, 4-7, 2007	Narrative review

IMN, internal mammary node; RCT, randomised controlled trial; RT, radiotherapy

Economic studies

See Supplement 1: Health economics literature review for list of excluded economic studies.

Appendix L – Research recommendations

Research recommendations for 8.1 What radiotherapy techniques are effective for excluding the heart from the radiation field without compromising coverage of the whole breast target volume for people with early or locally advanced breast cancer?

No research recommendations were made for this review question.

Research recommendations for 8.2 Is there a subgroup of people with early invasive breast cancer who do not need breast radiotherapy after breast-conserving surgery?

No research recommendations were made for this review question.

Research recommendations for 8.3 Is there a subgroup of women with early invasive breast cancer for whom partial breast radiotherapy is an equally effective alternative to whole breast radiotherapy after breast-conserving surgery?

No research recommendations were made for this review question.

Research recommendations for 8.4 What are the indications for radiotherapy to internal mammary nodes?

No research recommendations were made for this review question.