National Institute for Health and Care Excellence

Draft for Consultation

Early and locally advanced breast cancer: diagnosis and management

[I] Evidence reviews for postmastectomy 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

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN:

Contents

Postmastectomy radiotherapy

This evidence report contains information on 2 reviews relating to postmastectomy radiotherapy.

- Review question 9.1 What are the indications for postmastectomy radiotherapy for people with early and locally advanced breast cancer?
- Review question 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?

Review question 9.1 What are the indications for postmastectomy radiotherapy for people with early and locally advanced breast cancer?

Introduction

Although many people with early breast cancer are suitable for breast conserving surgery a significant number undergo mastectomy. Local chest wall recurrence can occur many years later, which may cause increased psychological morbidity and affect breast cancer mortality. Postmastectomy radiotherapy is effective in reducing the risk of recurrence and consequently reduces mortality. However, the risk of local recurrence varies between people, and is related to factors such as tumour size, axillary nodal involvement, extensive lympho-vascular involvement and positive resection margins.

This evidence review will seek to define the indications for postmastectomy radiotherapy after primary surgery and will aim to determine which groups should be offered such treatment.

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 who have undergone primary mastectomy.
Intervention	• Radiotherapy to the chest wall • Radiotherapy to the chest wall plus nodes
Comparison	• Radiotherapy to the chest wall • Radiotherapy to the chest wall plus nodes • No radiotherapy
Outcome	**Critical** • Locoregional recurrence • Treatment-related morbidity • Overall survival **Important** • Disease-free survival • Treatment-related mortality • HRQoL

DCIS: ductal carcinoma in situ; HRQoL, health-related quality of life; M0, no distant metastases

For full details see the 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

One meta-analysis of individual patient data was included in the review (Early Breast Cancer Trialists' Collaborative Group [EBCTCG] 2014). This meta-analysis included 26 relevant studies. Four additional studies were identified for inclusion (Hojris 1999, Hojris 2000, Killander 2014, Poortmans 2015).

No studies reported on quality of life.

The clinical studies included in this evidence review are summarised in Table 2 and evidence from these are summarised in the clinical GRADE evidence profiles below (Table 3 to 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 included in CG80 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.

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: Summary of included studies

Study details	Trial	Interventions	Outcomes
Systematic reviews			
EBCTCG 2014	22 trials (multinational)	Intervention Chest wall RT Comparison: No RT	• 10-year risk of locoregional recurrence • 20-year risk of all-cause mortality • 20-year breast cancer mortality rate (Data was extracted from EBCTCG 2014 Suppl.)
RCTs included in EBCTCG meta-analysis			
Andersson 1999	DBCG 82b	Intervention Chest wall RT Comparison: No RT	No additional outcomes reported in the study.
De Oliveira 1984	Coimbra	Intervention Chest wall RT Comparison: No RT	The paper could not be checked for additional outcomes as it was unavailable

Study details	Trial	Interventions	Outcomes
Deutsch 2008	NSABP B-04	Intervention Chest wall RT Comparison: No RT	Additional outcome reported in the paper: • Arm oedema (total women with oedema on final measurement, follow-up 2 to 5 years)
Faber 1979	Dusseldorf U	Intervention Chest wall RT Comparison: No RT	No additional outcomes were reported in the paper
Fisher 1980	NSABP B-04	Intervention Chest wall RT Comparison: No RT	No additional outcomes reported in the paper
Gyenes 1998	Stockholm A	Intervention Chest wall RT Comparison: No RT	Additional outcomes reported in the trial: • Myocardial infarction, at median 20 years • Death due to cardiovascular disease, at median 20 years • Death due to ischaemic heart disease, at median 20 years • Death due to myocardial infarction, at median 20 years
Host 1986	Oslo X-ray	Intervention Chest wall RT Comparison: No RT	No additional outcomes reported in the trial
Houghton 1994	CRC, UK	Intervention Chest wall RT Comparison: No RT	Other outcomes reported in the study • Cardiac deaths
Katz 2000	MD Ander 7730 B	Intervention Chest wall RT Comparison: No RT	No additional outcomes reported in the paper.
Killander 2007	Swedish BCG	Intervention Chest wall RT Comparison: No RT	No additional outcomes were reported

Study details	Trial	Interventions	Outcomes
Kyndi 2009	DBCG 82b&c	Intervention Chest wall RT Comparison: No RT	No additional outcomes reported.
Lythgoe 1982	Manchester RBS1	Intervention Chest wall RT Comparison: No RT	No additional outcomes reported in the study
McArdle 2010	Glasgow trial	Intervention Chest wall RT Comparison: No RT	No additional outcomes were reported in the study.
Muss 1991	Piedmont AO	Intervention Chest wall RT Comparison: No RT	No other outcomes reported.
Olson 1997	ECOG EST3181	Intervention Chest wall RT Comparison: No RT	No additional outcomes reported.
Overgaard 2007	DBCG 82 b&c	Intervention Chest wall RT Comparison: No RT	No additional outcomes reported.
Overgaard 1999	DBCG 82c	Intervention Chest wall RT Comparison: No RT	No additional outcomes reported.
Papaioannou 1985	Metaxas Athens	Intervention Chest wall RT Comparison: No RT	No additional outcomes reported in the study.
Ragaz 1997	BCCA Vancouver	Intervention Chest wall RT Comparison: No RT	Additional outcomes reported in the paper: • Adverse events: arm oedema requiring intervention • Adverse events: congestive heart failure • Adverse events: pneumonitis

Study details	Trial	Interventions	Outcomes
Saarto 1997	Helsinki trial	Intervention Chest wall RT Comparison: No RT	No additional outcomes reported in the paper
Schmoor 2002	GBSG03	Intervention Chest wall RT Comparison: No RT	No additional outcomes reported in the study
Shapiro 1998	DFCI Boston	Intervention Chest wall RT Comparison: No RT	Additional results reported in the study: • Cardiac events (defined as congestive heart failure or myocardial infarction), at median 6 years follow-up
1994	Edinburgh I	Intervention Chest wall RT Comparison: No RT	No additional outcomes reported.
Stewart 2001	Scottish D	Intervention Chest wall RT Comparison: No RT	No additional outcomes reported.
Turnbull 1978	Southampton UK trial	Intervention Chest wall RT Comparison: No RT	No additional outcomes are reported
Velez-Garcia 19952	SECSG 1	Intervention Chest wall RT Comparison: No RT	No additional outcomes reported.
Additional primary studies (RCTs)			
Hojris 2000	DBCG 82b and 82c	Intervention: Chest wall and regional lymph nodes RT + Adjuvant systemic therapy was also administered (CMF, tamoxifen or CMF + tamoxifen) Comparison: No RT (Adjuvant treatment alone)	Treatment related morbidity at median 9 years • Lymphedema, • Cardiac morbidity • Lung morbidity •
Hojris 1999	DBCG 82b and 82c	Premenopausal and menopausal women: • RT + chemotherapy • Chemotherapy	• Ischaemic heart disease morbidity • Death from ischaemic heart disease

Study details	Trial	Interventions	Outcomes
		• Postmenopausal women: • RT + Tamoxifen • Tamoxifen alone	• Acute myocardial infarction morbidity • Death from acute myocardial infarction
Killander 2014	S. Sweden	Premenopausal patients were randomised to: • RT • RT + oral cyclophosphamide for one year • cyclophosphamide only Postmenopausal patients were randomised to: • RT • RT +Tamoxifen for one year • Tamoxifen only	• Number of deaths from heart disease, at 25 years follow-up (heart disease including ischaemic heart disease, congestive heart failure, dysrhythmias and non-rheumatic valvular and pericardial disease) • Number of deaths from lung disease, at 25 years follow-up (lung disease, excluding pneumothorax and pleurisy)
Poortmans 2015	No trial name	Intervention: Regional nodal irradiation Dose of 50 Gy in 25 fractions Comparison: No regional nodal irradiation.	• Death, any cause at median 10 years

BCCA, British Columbia Cancer Agency; CMF, cyclophosphamide, methotrexate, fluorouracil; DBCG, Danish Breast Cancer Cooperative Group; DFCI, Dana-Farber Cancer Institute; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; ECOG, Eastern Cooperative Oncology Group; Gy, Gray; NSABP, National Surgical Adjuvant Breast and Bowel Project; RT: radiotherapy; SECSG, Southeastern Cancer Study Group

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review question (postmastectomy radiotherapy) are presented in Table 3 to Table 7.

Comparison 1. Radiotherapy to the chest wall versus no radiotherapy

No studies were identified for this comparison.

Table 3: Summary clinical evidence profile: Comparison 2. Radiotherapy to the chest wall plus nodes versus no radiotherapy – all women

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk: No radiotherapy	Corresponding risk: Radiotherapy to the chest wall + nodes				
Treatment-related morbidity at 9 years - lymphedema: >6	48 per 1000	24 per 1000 (2 to 253)	RR 0.5 (0.05 to 5.31)	84 (1 study[4])	Very low[1,2]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk: No radiotherapy	Corresponding risk: Radiotherapy to the chest wall + nodes				
cm increase in arm circumference						
Treatment-related morbidity at 9 years - cardiac morbidity: irreversible clinical heart failure	-	See comment[3]	Not estimable[3]	84 (1 study[4])	Moderate	0 events in both groups
Treatment-related morbidity at 9 years - cardiac morbidity: myocardial infarction	-	Not calculable[5]	RR 3 (0.13 to 71.61)	84 (1 study[4])	Very low[1,2]	1 event in intervention group, and 0 events in control group
Treatment-related morbidity at 9 years - lung morbidity: dense fibrosis, severe scarring & major retraction of normal lung	-	See comment[t3]	Not estimable[3]	84 (1 study[4])	Moderate	0 events in both groups
Treatment-related morbidity at 9 years - lung morbidity: refractory chest pain/ discomfort	-	See comment[t3]	Not estimable[3]	84 (1 study[4])	Moderate	0 events in both groups

CI: Confidence interval; RR: Risk ratio

[1] Downgraded by 1 level due to unclear randomization and allocation concealment. Blinding was unclear, but it was not downgraded further as it is unlikely to affect the outcomes.

[2] Downgraded by 2 levels as the CI crossed 2 default MIDs (0.8 and 1.25) and <300 events

[3] Not calculable, as there were 0 event in each group

[4] Hojiris 2000 (DBCG 82b&c)

[5] Not calculable, as there were 0 events in 1 group

Table 4: Summary clinical evidence profile: Comparison 2.1. Radiotherapy to the chest wall + nodes versus no radiotherapy following mastectomy without axillary surgery in women with invasive breast cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No radiotherapy	Radiotherapy to the chest wall + nodes				
First locoregional recurrence during years 0-9 *[women with clinically node-negative disease]*	306 per 1000	116 per 1000 (98 to 138)	Rate ratio 0.38 (0.32 to 0.45)	2896 (3 studies[1])	Low[2,3]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No radiotherapy	Radiotherapy to the chest wall + nodes				
First locoregional recurrence during years 0-9 *[women with clinically node-positive disease]*	393 per 1000	137 per 1000 (110 to 165)	Rate ratio 0.35 (0.28 to 0.42)	1481 (3 studies[4])	Moderate[5]	
20-year all-cause mortality *[women with clinically node-negative disease]*	717 per 1000	760 per 1000 (695 to 831)	Rate ratio 1.06 (0.97 to 1.16)	2896 (3 studies[1])	Moderate[2]	
20-year all-cause mortality *[women with clinically node-positive disease]*	818 per 1000	744 per 1000 (662 to 834)	Rate ratio 0.91 (0.81 to 1.02)	1481 (3 studies[4])	Moderate[5]	
20-year breast cancer mortality *[women with clinically node-negative disease]*	535 per 1000	525 per 1000 (482 to 573)	Rate ratio 0.98 (0.9 to 1.07)	2896 (3 studies[1])	Moderate[2]	
20-year breast cancer mortality *[women with clinically node-positive disease]*	640 per 1000	550 per 1000 (480 to 627)	Rate ratio 0.86 (0.75 to 0.98)	1481 (3 studies[4])	Moderate[5]	
Treatment related morbidity: women with arm oedema on final measurement at 2 to 5 years follow-up	253 per 1000	147 per 1000 (119 to 185)	RR 0.58 (0.47 to 0.73)	1457 (1 study[7])	Low[8]	
Treatment related mortality: cardiac deaths at 5 years *[all participants]*	See comment	See comment	RR 1.52 (1.01 to 2.29)	2800 (1 study[9])	Low[10]	Number of events per group not reported
Treatment related mortality: cardiac deaths at 5 years *[left breast]*	See comment	See comment	RR 1.92 (1.09 to 3.38)	2800 (1 study[9])	Low[10]	Number of events per group not reported
Treatment related mortality: cardiac deaths at 5 years *[right breast]*	See comment	See comment	RR 1.19 (0.66 to 2.15)	2800 (1 study[9])	Very low[10,11]	Number of events per group not reported

CI: Confidence interval; RR: Risk ratio

[1] EBCTCG 2014 meta-analysis with 3 RCTs: Fisher 1990 & Deutsch 2008 (NSABP-04); Houghton 1994 (Kings/ Cambridge); & Stewart 2001 (Scottish D)

[2] Downgraded by 1 level due to unclear randomization and allocation concealment in the 3 trials. Blinding was

also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[3] Downgraded by 1 level due to serious inconsistency (I2=85%). It was not downgraded by 2 because all studies showed a similar direction of effect. Heterogeneity could not be explored as subgroup data was not available. Random effect could not be performed in Revman as this option is not available.
[4] EBCTCG 2014 meta-analysis with 3 RCTs: Houghton 1984 (Kings/ Cambridge); Lythgoe 1982 (Manchester RBS1) & Stewart 2001 (Scottish D)
[5] Downgraded by 1 level due to unclear randomization and allocation concealment in the 3 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[7] Fisher 1990 & Deutsch 2008 (NSABP B-04)
[8] Downgraded by 2 levels due to unclear randomization, allocation concealment, and blinding of participants, personnel and outcome assessors
[9] Houghton 1994 (Kings/ Cambridge)
[10] Downgraded by 2 level due to unclear randomization and allocation concealment. Outcome poorly reported, as number of events in not available per group. Blinding was also unclear but it is not likely to impact objective outcomes
[11] Downgraded by 2 level as the 95% CI crosses the line of null effect, and both minimally important differences (0.8 and 1.25) based on GRADE default values

Table 5: Summary clinical evidence profile: Comparison 2.2. Radiotherapy to the chest wall + nodes versus no radiotherapy following mastectomy with axillary surgery in women with invasive breast cancer and node-negative disease

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No radiotherapy	Radiotherapy to the chest wall + nodes			
First locoregional recurrence during years 0-9 *[Mastectomy + axillary dissection]*	14 per 1000	26 per 1000 (9 to 76)	Rate ratio 1.85 (0.64 to 5.37)	698 (8 studies[1])	Low[2,3]
First locoregional recurrence during years 0-9 *[Mastectomy + axillary sampling]*	162 per 1000	40 per 1000 (26 to 63)	Rate ratio 0.25 (0.16 to 0.39)	870 (5 studies[4])	Low[3,5]
20-year all-cause mortality *[Mastectomy + axillary dissection]*	674 per 1000	829 per 1000 (688 to 1000)	Rate ratio 1.23 (1.02 to 1.49)	700 (9 studies[6])	Moderate[6]
20-year all-cause mortality *[Mastectomy + axillary sampling]*	667 per 1000	667 per 1000 (561 to 788)	Rate ratio 1 (0.84 to 1.18)	870 (5 studies[4])	Moderate[5]
20-year breast cancer mortality *[Mastectomy + axillary dissection]*	300 per 1000	354 per 1000 (267 to 465)	Rate ratio 1.18 (0.89 to 1.55)	700 (9 studies[6])	Low[6,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No radiotherapy	Radiotherapy to the chest wall + nodes			
20-year breast cancer mortality *[Mastectomy + axillary sampling]*	384 per 1000	373 per 1000 (296 to 469)	Rate ratio 0.97 (0.77 to 1.22)	870 (5 studies[4])	Moderate[5]

CI: Confidence interval
[1] EBCTCG 2014 MA with 8 RCTs: Anderson 1999 & Kyndi 2009 (DBCG 82b); Host 1986 (Oslo X-ray); Killander 2007 (Sweden); McArdle 2010 (Glasgow); Olson 1997 (ECOG EST3181); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Papaionnou 1985 (Metaxas Athens) and Saphiro 1998 (DFCI Boston)
[2] Downgraded by 1 level due to unclear randomization and allocation concealment in the 8 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[3] Downgraded by 1 level as <300 events (OIS for dichotomous outcomes = 300)
[4] EBCTCG 2014 MA with 5 RCTs: Andersson 1999 & Kyndi 2009 (DBCG 82b); Gyenes 1988 (Stockholm A); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Stewart 1994 (Edinburgh I) and Turnbull (DBCI Boston)
[5] Downgraded by 1 level due to unclear randomization and allocation concealment in the 5 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[6] EBCTCG 2014 MA with 9 RCTs: Anderson 1999 & Kyndi 2009 (DBCG 82b); Host 1986 (Oslo X-ray); Katz 2000 (MD Ander); Killander 2007 (Sweden); McArdle 2010 (Glasgow); Olson 1997 (ECOG EST3181); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Papaionnou 1985 (Metaxas Athens) and Saphiro 1998 (DFCI Boston)
[7] Downgraded by 1 level due to unclear randomization and allocation concealment in the 9 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes

Table 6: Summary clinical evidence profile: Comparison 2.3. Radiotherapy to the chest wall + nodes versus no radiotherapy following mastectomy with axillary surgery in women with invasive breast cancer and node-positive disease

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No radiotherapy	Radiotherapy to the chest wall + nodes				
First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes *[Mastectomy + axillary dissection]*	167 per 1000	40 per 1000 (28 to 57)	Rate ratio 0.24 (0.17 to 0.34)	1294 (11 studies[1])	Low[2,3]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No radiotherapy	Radiotherapy to the chest wall + nodes				
First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes *[Mastectomy + axillary sampling]*	235 per 1000	49 per 1000 (38 to 66)	Rate ratio 0.21 (0.16 to 0.28)	1412 (5 studies[4])	Low[3,5]	
First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes *[subgroup analysis: tumour grade - low grade]*	146 per 1000	47 per 1000 (13 to 175)	Rate ratio 0.32 (0.09 to 1.2)	112 (1 study[6])	Low[7,9]	Inconsistency could not be assessed, as only pooled data was available
First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes *[subgroup analysis: tumour grade - intermediate grade]*	221 per 1000	57 per 1000 (24 to 130)	Rate ratio 0.26 (0.11 to 0.59)	176 (1 study[6])	Low[3,7]	Inconsistency could not be assessed, as only pooled data was available
First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes *[subgroup analysis: tumour grade - high grade]*	158 per 1000	43 per 1000 (11 to 156)	Rate ratio 0.27 (0.07 to 0.99)	107 (1 study[6])	Low[3,7]	Inconsistency could not be assessed, as only pooled data was available

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No radiotherapy	Radiotherapy to the chest wall + nodes				
First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes *[subgroup analysis: tumour size - 0-19 mm.]*	176 per 1000	40 per 1000 (19 to 83)	Rate ratio 0.23 (0.11 to 0.47)	286 (1 study[6])	Low[3,7]	Inconsistency could not be assessed, as only pooled data was available
First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes *[subgroup analysis: tumour size - 20 to 49 mm.]*	198 per 1000	47 per 1000 (26 to 91)	Rate ratio 0.24 (0.13 to 0.46)	335 (1 study[6])	Low[3,7]	Inconsistency could not be assessed, as only pooled data was available
First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes *[subgroup analysis: tumour size - 50+ mm.]*	179 per 1000	43 per 1000 (25 to 75)	Rate ratio 0.24 (0.14 to 0.42)	60 (1 study[6])	Low[3,7]	Inconsistency could not be assessed, as only pooled data was available
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[Mastectomy + axillary dissection]*	203 per 1000	79 per 1000 (61 to 101)	Rate ratio 0.39 (0.3 to 0.5)	1718 (13 studies[7])	Low[3,8]	Inconsistency could not be assessed, as only pooled data was available

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No radiotherapy	Radiotherapy to the chest wall + nodes				
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[Mastectomy + axillary sampling]*	338 per 1000	64 per 1000 (47 to 91)	Rate ratio 0.19 (0.14 to 0.27)	694 (4 studies[9])	Very low[3,10,11]	
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[subgroup analysis: tumour grade - low grade]*	216 per 1000	76 per 1000 (19 to 303)	Rate ratio 0.35 (0.09 to 1.4)	73 (1 study[6])	Low[7,9]	Inconsistency could not be assessed, as only pooled data was available
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[subgroup analysis: tumour grade - intermediate grade]*	330 per 1000	46 per 1000 (23 to 89)	Rate ratio 0.14 (0.07 to 0.27)	207 (1 study[6])	Low[3,7]	Inconsistency could not be assessed, as only pooled data was available
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[subgroup analysis: tumour grade - high grade]*	300 per 1000	99 per 1000 (48 to 210)	Rate ratio 0.33 (0.16 to 0.7)	163 (1 study[6])	Low[3,7]	Inconsistency could not be assessed, as only pooled data was available

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No radiotherapy	Radiotherapy to the chest wall + nodes				
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[subgroup analysis: tumour size - 0-19 mm.]*	218 per 1000	63 per 1000 (28 to 135)	Rate ratio 0.29 (0.13 to 0.62)	194 (1 study[6])	Low[3,7]	Inconsistency could not be assessed, as only pooled data was available
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[subgroup analysis: tumour size - 20-49 mm.]*	276 per 1000	72 per 1000 (44 to 116)	Rate ratio 0.26 (0.16 to 0.42)	426 (1 study[6])	Low[3,7]	Inconsistency could not be assessed, as only pooled data was available
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[subgroup analysis: tumour size - 50+ mm.]*	237 per 1000	69 per 1000 (33 to 142)	Rate ratio 0.29 (0.14 to 0.6)	249 (1 study[6])	Low[3,7]	Inconsistency could not be assessed, as only pooled data was available
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[subgroup analysis: number of positive nodes - 4-9 positive nodes]*	244 per 1000	68 per 1000 (44 to 107)	Rate ratio 0.28 (0.18 to 0.44)	513 (1 study[6])	Low[3,7]	Inconsistency could not be assessed, as only pooled data was available

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No radiotherapy	Radiotherapy to the chest wall + nodes				
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[subgroup analysis: number of positive nodes - 10+ positive nodes]*	254 per 1000	76 per 1000 (46 to 127)	Rate ratio 0.30 (0.18 to 0.5)	406 (1 study[6])	Low[3,7]	Inconsistency could not be assessed, as only pooled data was available
20-year all-cause mortality in women with 1-3 pathologically positive nodes *[Mastectomy + axillary dissection]*	597 per 1000	531 per 1000 (460 to 621)	Rate ratio 0.89 (0.77 to 1.04)	1314 (12 studies[12])	Moderate[13],	
20-year all-cause mortality in women with 1-3 pathologically positive nodes *[Mastectomy + axillary sampling]*	644 per 1000	528 per 1000 (457 to 605)	Rate ratio 0.82 (0.71 to 0.94)	1420 (6 studies[14])	Moderate[15]	
20-year all-cause mortality in women with 4+ pathologically positive nodes *[Mastectomy + axillary dissection]*	745 per 1000	663 per 1000 (581 to 745)	Rate ratio 0.89 (0.78 to 1)	1772 (14 studies[16])	Low[17,18]	
20-year all-cause mortality in women with 4+ pathologically positive nodes *[Mastectomy + axillary sampling]*	870 per 1000	678 per 1000 (565 to 809)	Rate ratio 0.78 (0.65 to 0.93)	703 (5 studies[19])	Low[20,21]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No radiotherapy	Radiotherapy to the chest wall + nodes				
20-year breast cancer mortality in women with 1-3 pathologically positive nodes – *[Mastectomy + axillary dissection]*	477 per 1000	381 per 1000 (319 to 453)	Rate ratio 0.8 (0.67 to 0.95)	1314 (12 studies[12])	Low[13,22]	
20-year breast cancer mortality in women with 1-3 pathologically positive nodes – *[Mastectomy + axillary sampling*]	568 per 1000	431 per 1000 (369 to 500)	Rate ratio 0.76 (0.65 to 0.88)	1420 (6 studies[14])	Moderate[15]	
20-year breast cancer mortality in women with 4+ pathologically positive nodes *[Mastectomy + axillary dissection]*	688 per 1000	606 per 1000 (530 to 681)	Rate ratio 0.88 (0.77 to 0.99)	1772 (14 studies[23])	Low[24,25]	
20-year breast cancer mortality in women with 4+ pathologically positive nodes *[Mastectomy + axillary sampling]*	812 per 1000	625 per 1000 (519 to 763)	Rate ratio 0.77 (0.64 to 0.94)	703 (5 studies[26])	Low[27]	
Treatment-related morbidity in women with node positive disease - ischaemic heart disease morbidity at 10 years	See comment	See comment	HR 0.86 (0.57 to 1.3)	3046 (1 study[29])	Low[31,31]	Number of events not reported

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No radiotherapy	Radiotherapy to the chest wall + nodes				
Treatment-related morbidity in women with node-positive disease - acute myocardial infarction morbidity at 10 years	See comment	See comment	HR 1.1 (0.62 to 1.95)	3046 (1 study[29])	Low[30,31]	Number of events not reported
Treatment-related morbidity in women with node-positive disease - arm oedema requiring intervention, at 15 years	6 per 1000	37 per 1000 (4 to 300)	RR 5.63 (0.69 to 46.27)	318 (1 study[32])	Low[30,33]	
Treatment-related morbidity in women with node-positive disease - pneumonitis, at 15 years	See comment	See comment	RR 2.82 (0.12 to 68.66)	318 (1 study[32])	Low[30,33]	1 event in intervention group, and 0 events in control group
Treatment-related morbidity in women with node-positive disease - cardiac events (congestive heart failure or myocardial infarction), at 6 years *[low RT vs no RT]*	84 per 1000	22 per 1000 (3 to 165)	RR 0.26 (0.04 to 1.96)	199 (1 study[34])	Low[30,33]	
Treatment-related morbidity in women with node-positive disease - cardiac events (congestive heart failure or myocardial infarction), at 6 years	84 per 1000	84 per 1000 (29 to 244)	RR 0.99 (0.34 to 2.89)	202 (1 study[34])	Low[30,33]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No radiotherapy	Radiotherapy to the chest wall + nodes				
[moderate RT vs no RT]						
Treatment-related morbidity in women with node-positive disease - cardiac events (congestive heart failure or myocardial infarction), at 6 years *[high RT vs no RT]*	84 per 1000	138 per 1000 (48 to 393)	RR 1.63 (0.57 to 4.66)	183 (1 study[34])	Low[30,33]	
Treatment-related morbidity in women with node-positive disease - congestive heart failure, at 15 years	See comment	See comment	RR 2.82 (0.12 to 68.66)	318 (1 study[32])	Low[30,33]	1 event in intervention group, and 0 events in control group
Treatment-related morbidity in women with node-positive disease - myocardial infarction, at 20 years	65 per 1000	52 per 1000 (28 to 98)	RR 0.8 (0.43 to 1.5)	644 (1 study[35])	Low[3,30]	
Treatment-related mortality in women with node-positive disease- death from ischaemic heart disease at 10 years	See comment	See comment	HR 0.84 (0.38 to 1.86)	3046 (1 study[29])	Low[30,31]	Number of events not reported
Treatment-related mortality in women with node-positive disease - death from acute myocardial infarction at 10 years	See comment	See comment	HR 0.5 (0.17 to 1.47)	3046 (1 study[29])	Low[30,31]	Number of events not reported
Treatment-related mortality	53 per 1000	85 per 1000 (46 to 160)	RR 1.61	544 (1 study[35])	Low[30,33]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No radiotherapy	Radiotherapy to the chest wall + nodes				
in women with node-positive disease - death from cardiovascular disease, at 20 years			(0.86 to 3.03)			
Treatment-related mortality in women with node-positive disease - death from ischemic heart disease, at 20 years	31 per 1000	54 per 1000 (24 to 122)	RR 1.73 (0.76 to 3.93)	544 (1 study[35])	Low[30,33]	
Treatment-related mortality in women with node-positive disease - death from myocardial infarction, at 20 years	31 per 1000	31 per 1000 (12 to 81)	RR 1.01 (0.39 to 2.61)	544 (1 study[35])	Low[30,33]	

CI: Confidence interval; HR: Hazard ratio; RR: Risk ratio; RT, radiotherapy

[1] EBCTCG 2014 MA with 11 RCTs: Anderson 1999 & Kyndi 2009 (DBCG 82b); Host 1986 (Oslo X-ray); Killander 2007 (Sweden); McArdle 2010 (Glasgow); Olson 1997 (ECOG EST3181); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Papaionnou 1985 (Metaxas Athens), Ragaz 1997 (BCCA Vancouver); Saarto 1997 (Helsinki); Saphiro 1998 (DFCI Boston) and Velez-Garcia (SECSG 1)

[2] Downgraded by 1 level due to unclear randomization and allocation concealment in the 11 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes

[3] Downgraded by 1 level as <300 event (OIS for dichotomous outcomes = 300)

[4] EBCTCG 2014 MA with 5 RCTs: Andersson 1999 & Kyndi 2009 (DBCG 82b); De Oliveira 1984 (Coimbra); Gyenes 1988 (Stockholm A); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Schoomor 2002 (GB03 Germany)

[5] Downgraded by 1 level due to unclear randomization and allocation concealment in the 5 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes

[6] EBCTCG 2014 MA: unknown number of trials, pooled result only

[7] EBCTCG 2014 MA with 13 RCTs: Anderson 1999 & Kyndi 2009 (DBCG 82b); Faber 1979 (Dusseldorf U); Host 1986 (Oslo X-ray); Killander 2007 (Sweden); McArdle 2010 (Glasgow); Muss 1991 (Piedmont OA); Olson 1997 (ECOG EST3181); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Papaionnou 1985 (Metaxas Athens), Ragaz 1997 (BCCA Vancouver); Saarto 1997 (Helsinki); Saphiro 1998 (DFCI Boston) and Velez-Garcia (SECSG 1)

[8] Downgraded by 1 level due to unclear randomization and allocation concealment in the 13 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes

[9] EBCTCG 2014 MA with 4 RCTs: Andersson 1999 & Kyndi 2009 (DBCG 82b); De Oliveira 1984 (Coimbra); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Schoomor 2002 (GB03 Germany)

[10] Downgraded by 1 level due to unclear randomization and allocation concealment in the 4 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes

[11] Downgraded by 1 level due to serious inconsistency (I2=64%). Heterogeneity could not be explored as data for subgroup analysis was not available. Random model could not be conduted in Revman.

[12] EBCTCG 2014 MA with 12 RCTs: Anderson 1999 & Kyndi 2009 (DBCG 82b); Katz 2000 (MD Ander); Killander 2007 (Sweden); McArdle 2010 (Glasgow); Olson 1997 (ECOG EST3181); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Papaionnou 1985 (Metaxas Athens), Ragaz 1997 (BCCA Vancouver); Saarto 1997 (Helsinki); Saphiro 1998 (DFCI Boston) and Velez-Garcia (SECSG 1)

[13] Downgraded by 1 level due to unclear randomization and allocation concealment in the 12 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes

[14] *EBCTCG 2014 MA with 6 RCTs: Andersson 1999 & Kyndi 2009 (DBCG 82b); De Oliveira 1984 (Coimbra); Gyenes 1988 (Stockholm A); Katz 2000 (MD Ander); Overgaard 1999 & Kyndi 2009 (DBCG 82c) and Schoomor 2002 (GB03 Germany)*
[15] *Downgraded by 1 level due to unclear randomization and allocation concealment in the 6 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes*
[16] *EBCTCG 2014 MA with 14 RCTs: Anderson 1999 & Kyndi 2009 (DBCG 82b); Faber 1979 (Dusseldorf U); Host 1986 (Oslo X-ray); Katz 2000 (MD Ander); Killander 2007 (Sweden); McArdle 2010 (Glasgow); Muss 1991 (Piedmont OA); Olson 1997 (ECOG EST3181); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Papaionnou 1985 (Metaxas Athens), Ragaz 1997 (BCCA Vancouver); Saarto 1997 (Helsinki); Saphiro 1998 (DFCI Boston) and Velez-Garcia (SECSG 1)*
[17] *Downgraded by 1 level due to unclear randomization and allocation concealment in the 14 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes*
[18] *Downgraded by 1 level due to moderate inconsistency (I2=46%). Heterogeneity could not be explored further as data for subgroup analysis was not available. A random model could not be performed in Revman*
[19] *EBCTCG 2014 MA with 5 RCTs: Andersson 1999 & Kyndi 2009 (DBCG 82b); De Oliveira 1984 (Coimbra); Katz 2000 (MD Ander); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Schoomor 2002 (GB03 Germany)*
[20] *Downgraded by 1 level due to unclear randomization and allocation concealment in the 5 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes*
[21] *Downgraded by 1 level due to moderate inconsistency (I2=58%). Heterogeneity could not be explored further as data for subgroup analysis was not available. A random model could not be performed in Revman*
[22] *Downgraded by 1 level due to moderate inconsistency (I2=27%). Heterogeneity could not be explored further as data for subgroup analysis was not available. A random model could not be performed in Revman*
[23] *EBCTCG 2014 MA with 14 RCTs: Anderson 1999 & Kyndi 2009 (DBCG 82b); Host 1986 (Oslo X-ray); Katz 2000 (MD Ander); Killander 2007 (Sweden); McArdle 2010 (Glasgow); Olson 1997 (ECOG EST3181); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Papaionnou 1985 (Metaxas Athens), Ragaz 1997 (BCCA Vancouver); Saarto 1997 (Helsinki); Saphiro 1998 (DFCI Boston) and Velez-Garcia (SECSG 1)*
[24] *Downgraded by 1 level due to unclear randomization and allocation concealment in the 14 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes*
[25] *Downgraded by 1 level due to moderate inconsistency (I2=54%). Heterogeneity could not be explored further as data for subgroup analysis was not available. A random model could not be performed in Revman*
[26] *EBCTCG 2014 MA with 5 trials: Anderson 1999 & Kyndi 2009 (DBCG 82b); De Oliverira 1984 (Coimbra); Katz 2000 (MD Ander); Overgaard 1999 & Kyndi 1999 (DBCG 82c) and Schomoor (GBSG 03 Germany)*
[27] *Downgraded by 1 level due to unclear randomization and allocation concealment in the 5 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes*
[28] *Downgraded by 1 level due to moderate to high inconsistency (I2=59%). The 2 largest trials showed inconsistent results. Heterogeneity could not be explored further as data for subgroup analysis was not available. A random model could not be performed in Revman*
[29] *Hojiris 1999 (DBCG 82b&c)*
[30] *Downgraded by 1 level due to unclear randomization and allocation concealment. Blinding was unclear, but it was not downgraded further as it is unlikely to affect the outcomes.*
[31] *Downgraded by 1 level as the 95% CI crossed the line of null effect and minimally important difference (0.8) based on GRAE default value*
[32] *Ragaz 1997 (BCCA Vancouver)*
[33] *Downgraded by 1 level as the 95% CI crosses the line of null effect and <300 events (OIS for dichotomous outcomes = 300)*
[34] *Shapiro 1998 (DFCI Boston)*
[35] *Gyenes 1998 (Stockholm A)*

Table 7: Summary clinical evidence profile: Comparison 3. Radiotherapy to the chest wall plus versus radiotherapy to the chest wall plus alone in women with invasive breast cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Radiotherapy to the chest wall alone	Radiotherapy to the chest wall + nodes				
Overall survival at 10 years	313 per 1000	290 per 1000 (237 to 351)	HR 0.91 (0.72 to 1.15)	955 (1 study[1])	Moderate[2,3]	

CI: Confidence interval; HR: Hazard ratio
[1] *Poortrmans 2014*
[2] *Unclear whether blinding was performed, but the evidence was not downgraded as blinding is unlikely to affect*

objective outcomes
[3] Downgraded by 1 level as <300 events (OIS for dichotomous outcomes = 300)

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

Women with ductal carcinoma in situ (DCIS)

- No evidence was found for this population.

Women with invasive breast cancer

Comparison 1. Radiotherapy to the chest wall versus no radiotherapy

- No studies were identified for this comparison.

Comparison 2. Radiotherapy to the chest wall plus nodes versus no radiotherapy

Critical outcomes

Locoregional recurrence

- See comparisons 2.1, 2.2 and 2.3 for subgroup results.

Treatment-related morbidity

- There is very low quality evidence from 1 RCT (number of participants, N=84) that there is no clinically important effect of postmastectomy radiotherapy on the occurrence of lymphoedema (defined as >6 cm increase in arm circumference) and myocardial infarction for women with invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=84) that there is no clinically important effect of postmastectomy radiotherapy on irreversible clinical heart failure, and severe lung morbidity (defined as dense fibrosis, severe scarring and major retraction of normal lung, or refractory chest pain) for women with invasive breast cancer; however, there were no events of interest in either group.

Overall survival

- See comparisons 2.1, 2.2 and 2.3 for subgroup results.

Important outcomes

Disease-free survival

- See comparisons 2.1, 2.2 and 2.3 for subgroup results.

Treatment-related mortality

- See comparisons 2.1 and 2.3 for subgroup results.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 2.1. Radiotherapy to the chest wall plus nodes versus no radiotherapy following mastectomy without axillary surgery in women with invasive breast cancer

Critical outcomes

Locoregional recurrence

Subgroup analysis: nodal status

- There is low quality evidence from 1 systematic review (*N*=2,896) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with node-negative invasive breast cancer.
- There is moderate quality evidence from 1 systematic review (N=1,481) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with node-positive invasive breast cancer.

Treatment-related morbidity

- There is low quality evidence from 1 RCT (N=1,457) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in arm oedema (as reported in last measurement, at 2 to 5 years) compared with no radiotherapy for women with invasive breast cancer.

Overall survival

Subgroup analysis: nodal status

- There is moderate quality evidence from 1 systematic review (N=2,896) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on overall survival at 20 year follow-up for women with node-negative invasive breast cancer.
- There is moderate quality evidence from 1 systematic review (N=1,481) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on overall survival at 20 year follow-up for women with node-positive invasive breast cancer.

Important outcomes

Disease-free survival

Subgroup analysis: nodal status

- There is moderate quality evidence from 1 systematic review (N=2,896) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on breast-cancer mortality at 20 year follow-up for women with node-negative invasive breast cancer.
- There is moderate quality evidence from 1 systematic review (N=1,481) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically meaningful reductions in breast-cancer mortality at 20 year follow-up compared with no radiotherapy for women with node-positive invasive breast cancer.

Treatment-related mortality

- There is low to very low quality evidence from 1 RCT (N=2,800) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically higher rates of cardiac deaths at 5 year follow-up compared with no radiotherapy for women with invasive breast cancer. When left-sided and right-sided disease where looked at separately, this difference only remained clinically important for the left-sided tumours.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 2.2. Radiotherapy to the chest wall plus nodes versus no radiotherapy following mastectomy with axillary surgery in women with invasive breast cancer and node-negative disease

Critical outcomes

Locoregional recurrence

Subgroup analysis: axillary surgery

- There is low quality evidence from 1 systematic review (N=698) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on locoregional recurrence at 10 year follow-up for women with node-negative invasive breast cancer following axillary dissection.
- There is moderate quality evidence from 1 systematic review (N=870) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with node-negative invasive breast cancer following axillary sampling.

Treatment-related morbidity

- No evidence was found for this outcome.

Overall survival

Subgroup analysis: axillary surgery

- There is moderate quality evidence from 1 systematic review (N=700) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important increases in overall survival at 20 year follow-up compared with no radiotherapy for women with node-negative invasive breast cancer following axillary dissection.
- There is moderate quality evidence from 1 systematic review (N=870) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on overall survival at 20 year follow-up for women with node-negative invasive breast cancer following axillary sampling.

Important outcomes

Disease-free survival

Subgroup analysis: axillary surgery

- There is low quality evidence from 1 systematic review (N=700) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on breast-cancer mortality at 20 year follow-up for women with node-negative invasive breast cancer following axillary dissection.

- There is moderate quality evidence from 1 systematic review (N=870) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on breast-cancer mortality at 20 year follow-up for women with node-negative invasive breast cancer following axillary sampling.

Treatment-related mortality

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 2.3. Radiotherapy to the chest wall plus nodes versus no radiotherapy following mastectomy with axillary surgery in women with invasive breast cancer and node-positive disease

Critical outcomes

Locoregional recurrence

Women with 1-3 pathologically positive nodes

Subgroup analysis: axillary surgery

- There is low quality evidence from 1 systematic review (N=1,294) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with invasive breast cancer and 1-3 positive nodes following axillary dissection.
- There is low quality evidence from 1 systematic review (N=1,412) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with invasive breast cancer and 1-3 positive nodes following axillary sampling.

Subgroup analysis: tumour grade

- There is low quality evidence from 1 systematic review (N=112) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on locoregional recurrence at 10 year follow-up for women with low grade invasive breast cancer and 1-3 positive nodes.
- There is low quality evidence from 1 systematic review (N=176) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with intermediate grade invasive breast cancer and 1-3 positive nodes.
- There is low quality evidence from 1 systematic review (N=107) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with high grade invasive breast cancer and 1-3 positive nodes.

Subgroup analysis: tumour size

- There is low quality evidence from 1 systematic review (N=286) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with invasive breast cancer, tumour size 0-19 mm and 1-3 positive nodes.
- There is low quality evidence from 1 systematic review (N=335) that that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with invasive breast cancer, tumour size 20-49 mm and 1-3 positive nodes.

- There is low quality evidence from 1 systematic review (N=360) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with invasive breast cancer, tumour size greater than or equal to 50 mm and 1-3 positive nodes.

Women with 4 or more pathologically positive nodes

Subgroup analysis: axillary surgery

- There is low quality evidence from 1 systematic review (N=1,718) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with invasive breast cancer and 4 or more positive nodes positive nodes following axillary dissection.
- There is very low quality evidence from 1 systematic review (N=694) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with invasive breast cancer and 4 or more positive nodes positive nodes following axillary sampling.

Subgroup analysis: tumour grade

- There is low quality evidence from 1 systematic review (N=73) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on locoregional recurrence at 10 year follow-up for women with low grade invasive breast cancer and 4 or more positive nodes.
- There is low quality evidence from 1 systematic review (N=207) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with intermediate grade invasive breast cancer and 4 or more positive nodes.
- There is low quality evidence from 1 systematic review (N=163) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with high grade invasive breast cancer and 4 or more positive nodes.

Subgroup analysis: tumour size

- There is low quality evidence from 1 systematic review (N=194) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with invasive breast cancer, tumour size 0-19 mm and 4 or more positive nodes.
- There is low quality evidence from 1 systematic review (N=426) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with invasive breast cancer, tumour size 20-49 mm and 4 or more positive nodes.
- There is low quality evidence from 1 systematic review (N=249) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with invasive breast cancer, tumour size greater than or equal to 50 mm and 4 or more positive nodes.

Subgroup analysis: number of positive nodes

- There is low quality evidence from 1 systematic review (N=513) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with invasive breast cancer and 4-9 positive nodes.

- There is low quality evidence from 1 systematic review (N=406) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in locoregional recurrence at 10 year follow-up compared with no radiotherapy for women with invasive breast cancer and 10 or more positive nodes.

Treatment-related morbidity

Cardiac morbidity

- There is low quality evidence from 1 RCT that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on cardiac events (including heart failure and myocardial infarction) at 6 year follow-up for women with invasive breast cancer receiving radiotherapy at low, moderate or high intensity(N=199, 202 and 183 respectively).
- There is low quality evidence from 1 RCT (N=3046) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on cardiac morbidity (including ischaemic heart disease and myocardial infarction) at 10 year follow-up for women with invasive breast cancer.
- There is low quality evidence from 1 RCT (N=318) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on cardiac congestive failure at 15 year follow-up for women with node-positive invasive breast cancer.
- There is low quality evidence from 1 RCT (N=644) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on myocardial infarction at 20 year follow-up for women with node-positive invasive breast cancer.

Lymphoedema

- There is low quality evidence from 1 RCT (N=318) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on arm oedema requiring intervention at 15 year follow-up for women with node-positive invasive breast cancer.

Lung morbidity

- There is low quality evidence from 1 RCT (N=318) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on pneumonitis at 15 year follow-up for women with node-positive invasive breast cancer.

Overall survival

Women with 1-3 pathologically positive nodes

Subgroup analysis: axillary surgery

- There is moderate quality evidence from 1 systematic review (N=1,314) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on overall survival at 20 year follow-up for women with invasive breast cancer and 1-3 positive nodes following axillary dissection.
- There is moderate quality evidence from 1 systematic review (N=1,420) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important increases in overall survival at 20 year follow-up compared with no radiotherapy for women with invasive breast cancer and 1-3 positive nodes following axillary sampling.

Women with 4 or more pathologically positive nodes

Subgroup analysis: axillary surgery

- There is low quality evidence from 1 systematic review (N=1,772) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important increases in

overall survival at 20 year follow-up compared with no radiotherapy for women with invasive breast cancer and 4 or more positive nodes following axillary dissection.

- There is low quality evidence form 1 systematic review (N=703) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important increases in overall survival at 20 year follow-up compared with no radiotherapy for women with invasive breast cancer and 4 or more positive nodes following axillary sampling.

Important outcomes

Disease-free survival

Women with 1-3 pathologically positive nodes

Subgroup analysis: axillary surgery

- There is low quality evidence from 1 systematic review (N=1,314) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in breast-cancer mortality at 20 year follow-up compared with no radiotherapy for women with invasive breast cancer and 1-3 positive nodes following axillary dissection.
- There is moderate quality evidence from 1 systematic review (N=1,420) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in breast-cancer mortality at 20 year follow-up compared with no radiotherapy for women with invasive breast cancer and 1-3 positive nodes following axillary sampling.

Women with 4 or more pathologically positive nodes

Subgroup analysis: axillary surgery

- There is low quality evidence from 1 systematic review (N=1,772) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in breast-cancer mortality at 20 year follow-up compared with no radiotherapy for women with invasive breast cancer and 4 or more positive nodes following axillary dissection.
- There is very low quality evidence from 1 systematic review (N=703) that postmastectomy radiotherapy to the chest wall and lymph nodes produced clinically important reductions in breast-cancer mortality at 20 year follow-up compared with no radiotherapy for women with invasive breast cancer and 4 or more positive nodes following axillary sampling.

Treatment-related mortality

Cardiac mortality

- There is low quality evidence from 1 RCT (N=3,046) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on cardiac mortality (including ischaemic heart disease and myocardial infarction) at 10 year follow-up for women with node-positive invasive breast cancer.
- There is low quality evidence from 1 RCT (N=544) that there is no clinically important effect of postmastectomy radiotherapy to the chest wall and lymph nodes on cardiac mortality (including cardiovascular disease, ischaemic heart disease and myocardial infarction) at 20 year follow-up for women with node-positive invasive breast cancer.

Health-related quality of life

- No evidence was found for this outcome.

Comparison 3. Radiotherapy to the chest wall plus nodes versus radiotherapy to the chest wall alone

Critical outcomes

Locoregional recurrence

- No evidence was found for this outcome.

Treatment-related morbidity

- No evidence was found for this outcome.

Overall survival

- There is moderate quality evidence from 1 RCT (N=995) that there is no clinically important effect of postmastectomy radiotherapy to the lymph nodes on overall survival at 10 year follow-up for women with invasive breast cancer.

Important outcomes

Disease-free survival

- No evidence was found for this outcome.

Treatment-related mortality

- No evidence was found for this outcome.

Health-related quality of life

- No evidence was found for this outcome.

Recommendations

I1. Offer adjuvant postmastectomy radiotherapy to people with node-positive (macrometastases) invasive breast cancer or involved resection margins.

I2. Consider adjuvant postmastectomy radiotherapy for people with node-negative T3 or T4 invasive breast cancer.

I3. Do not offer radiotherapy following mastectomy to people with invasive breast cancer who are at low risk[a] of local recurrence (for example, most people who have lymph node-negative breast cancer).

Rationale and impact

Why the committee made the recommendations

The committee agreed that adjuvant postmastectomy radiotherapy should be offered to people who have macroscopically node-positive invasive breast cancer or have involved resection margins. This is because the evidence showed a beneficial effect on survival and local recurrence. Although the evidence was limited and the committee acknowledged that radiotherapy is associated with lung and cardiac morbidity, they concluded that for this group of women, the benefits of radiotherapy outweigh the harms.

There was evidence of a beneficial effect of postmastectomy radiotherapy on local recurrence and overall survival for people with node-negative invasive breast cancer.

a Risk can be estimated using a range of standardised tools and clinical expertise.

However, the committee agreed that there was a risk of over-treatment if all people with node-negative invasive breast cancer received postmastectomy radiotherapy. Therefore, the committee recommended that adjuvant postmastectomy radiotherapy should be considered for people with node-negative T3 or T4 invasive breast cancer. There was no evidence for this specific subgroup but they would be considered at increased risk of recurrence and mortality relative to smaller, node-negative invasive breast cancers due to the size of the tumour.

The committee agreed that radiotherapy after mastectomy should not be offered to women with early invasive breast cancer who are at low risk of local recurrence (for example, most women who are lymph node-negative) because the evidence showed limited benefit in survival and local recurrence.

Impact of the recommendations on practice

The committee agreed that the recommendations will reinforce current practice, so there would be little change in practice.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of this review was to define the indications for postmastectomy radiotherapy after primary surgery.

The committee chose locoregional recurrence, overall survival and treatment-related morbidity as critical outcomes for decision making, as the aim of adjuvant radiotherapy is to prevent disease recurrence and improve survival. It was also noted that side-effects need to be weighed against the potential benefits of treatment. Disease-free survival, treatment-related mortality and health related quality of life were selected as important outcomes.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE and was found to be of very low to low quality.

The main reason for downgrading the quality of the evidence was the risk of bias. All the trials included in the EBCTCG (2014) meta-analysis were rated as having unclear randomisation and allocation concealment. Blinding was not reported in any of the trials, but the quality of the evidence was not downgraded for objective outcomes (such as mortality, recurrence, or objective adverse events of treatment). The additional trials identified also showed similar methodological limitations.

Heterogeneity was also observed in a number of comparisons. Since the data was retrieved from a meta-analysis it was not possible to conduct subgroup analysis. The plots were examined visually to judge whether imprecision should be downgraded by 1 or 2 levels.

Another reason for downgrading the quality of the evidence was imprecision, due to a small number of events and wide confidence intervals.

No issues were identified regarding the directness of the population.

Benefits and harms

All the evidence found was on women with invasive breast cancer. The committee were not surprised about this, as postmastectomy radiotherapy is not used in women with DCIS who have undergone mastectomy.

For the comparison of chest wall radiotherapy versus no radiotherapy, no evidence was found. Again, the committee were not surprised about this, as usually the nodes are irradiated as well as the chest wall.

For the comparison chest wall radiotherapy plus nodes versus no radiotherapy, we identified a large meta-analysis of individual patient data. An additional 4 studies reported on treatment-related morbidity or mortality. Results were presented and discussed based on type of surgery and nodal status.

The committee noted that in women who had mastectomy without axillary surgery, postmastectomy radiotherapy reduced local recurrence (in both clinically node-negative and node-positive disease). It also improved disease-free survival at 20 years in women with clinically node-positive disease. However radiotherapy did not improve overall survival at 20 years in in both clinically node-negative and node-positive disease or disease-free survival at 20 years. The risk of arm oedema was higher in women who did not have radiotherapy. Regarding treatment-related mortality, there was an increased risk of cardiac deaths at 5 years in the group of women receiving radiotherapy, but this risk only remained significant in women with left-sided tumours.

In women who had mastectomy with axillary surgery and had node-negative disease, no differences were found regarding disease-free survival at 20 years. There was improved overall survival at 20 years in women who received adjuvant radiotherapy following axillary dissection, but not in women who had axillary sampling. The rate of locoregional recurrence at 10 years was lower in women who received adjuvant radiotherapy following axillary sampling, but not in women who had axillary dissection.

The committee also discussed the evidence for women who received radiotherapy following mastectomy with axillary surgery and had node-positive disease. The evidence showed that in women with 1-3 positive nodes, adjuvant radiotherapy reduced locoregional recurrence at 10 years. This reduction was shown on all tumour sizes, and in women with intermediate and high grade tumours (but not in low grade tumours). Postmastectomy radiotherapy also seemed to improve disease-free survival at 20 years (independent of the type of surgery), and overall survival at 20 years in women who had axillary sampling.

The evidence also showed that in women with 4+ positive nodes, postmastectomy radiotherapy reduced locoregional recurrence at 10 years. This reduction was shown on all tumour sizes, and in women with intermediate and high grade tumours (but not in low grade tumours). Adjuvant radiotherapy also improved disease-free survival and overall survival at 20 years.

Regarding treatment-related morbidity, no differences were found in arm oedema, and in cardiac and lung morbidity. Likewise, no differences were found in cardiac related mortality between the people who received adjuvant postmastectomy radiotherapy and those who did not at 10 and at 20 years follow-up. The committee still emphasised their concern regarding the adverse events associated with radiotherapy, and they noted that the evidence was of very low to low quality, and that many trials were underpowered to detect differences in treatment-related mortality.

Finally, for the comparison chest wall radiotherapy plus nodes versus chest wall radiotherapy alone, only 1 trial was identified. This trial only reported on overall survival at 10 years, and did not find differences between the 2 groups.

The committee concluded that the trade-off benefits and harms depends on the absolute risk, and based on the evidence and their clinical experience, they agreed that adjuvant radiotherapy should be offered to women at high risk of local recurrence (for example those with triple negative disease, high grade or large tumours, or with lymphovascular invasion), as in this group of women the benefits are likely to outweigh the risk. On the contrary, they agreed that postmastectomy radiotherapy should not be offered to women at low risk of local

recurrence (for example women with node negative disease and small tumours), as potential benefits do not compensate the harms. This is consistent with current clinical practice.

Uncertainty still exists regarding the benefit of treatment in women at intermediate risk (for example women with 1-2 positive lymph nodes, oestrogen receptor [ER] positive and human epidermal growth factor receptor 2 [HER2] negative, T2, grade 2 tumours, women with node-negative disease and large tumours). The committee agreed adjuvant radiotherapy could be considered for some of these women, weighing the individual potential benefits and harms. There is, however, a risk of overtreatment in people with intermediate risk disease.

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 considered the potential cost-effectiveness of radiotherapy interventions and agreed that it was likely to be cost-effective when used in patients with a high absolute risk of recurrence. In such patients, the upfront costs of radiotherapy would be balanced against more substantial benefits (in quality adjusted life years [QALY] terms) and potential cost savings downstream (through reductions in recurrence).

The committee discussed the potential cost impact of the recommendations and agreed that there would not be any substantial change in resources required to implement the recommendations as they reflect current practice.

Other factors the committee took into account

The committee noted that postmastectomy adjuvant radiotherapy may have an adverse effect on reconstruction, for example a detrimental effect on cosmesis, volume asymmetry, and by increasing the risk of implant complications, including an increased rates of capsular contracture and implant loss.

The committee agreed not to write a research recommendation for this topic. They acknowledged there is still uncertainty with regards to the benefit of offering postmastectomy radiotherapy to women at intermediate risk of recurrence, but they noted that the ongoing Selective Use of Postoperative Radiotherapy aftEr MastectOmy (SUPREMO) trial will address this, and that the results may affect future guidance.

References

Andersson 1999

Andersson,M., Kamby,C., Jensen,M.B., Mouridsen,H., Ejlertsen,B., Dombernowsky,P., Rose,C., Cold,S., Overgaard,M., Andersen,J., Kjaer,M. (1999) Tamoxifen in high-risk premenopausal women with primary breast cancer receiving adjuvant chemotherapy. Report from the Danish Breast Cancer co-operative Group DBCG 82B Trial. European Journal of Cancer, 35, 1659-1666.

De Oliveira 1984

De Oliveira, CF., Gervasio, H., Alves, R., Silva, A., Pedro, L. (1984) Adjuvant chemotherapy versus radiotherapy and chemotherapy in operable breast cancer. A randomized trial. Preliminary results.

Deutsch 2008

Deutsch, M., Land, S., Begovic, M., Sharif, S. (2008) The incidence of arm edema in women with breast cancer randomized on the National Surgical Adjuvant Breast and Bowel Project

study B-04 to radical mastectomy versus total mastectomy and radiotherapy versus total mastectomy alone. International journal of radiation oncology, biology, physics, 70, 1020-4.

EBCTCG 2014

EBCTCG, McGale, P., Taylor, C., Correa, C., Cutter, D., Duane, F., Ewertz, M., Gray, R., Mannu, G., Peto, R., Whelan, T., Wang, Y., Wang, Z., Darby, S. (2014) Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. [Erratum appears in Lancet. 2014 Nov 22;384: 9957):1848]. Lancet, 383, 2127-35.

Faber & Jesdinsky 1979

Faber, P., Jesdinsky, H. (1979) Adjuvant chemotherapy in breast cancer--a multicenter trial. Cancer Treatment Reviews, 6 Suppl, 75-8.

Fisher 1980

Fisher, B., Montague, E., Redmond, C., Deutsch, M., Brown, G. R., Zauber, A., Hanson, W. F., Wong, A. (1980) Findings from NSABP Protocol No. B-04-comparison of radical mastectomy with alternative treatments for primary breast cancer. I. Radiation compliance and its relation to treatment outcome. Cancer, 46, 1-13.

Gyenes 1998

Gyenes, G., Rutqvist, L. E., Liedberg, A., Fornander, T. (1998) Long-term cardiac morbidity and mortality in a randomized trial of pre- and postoperative radiation therapy versus surgery alone in primary breast cancer. Radiotherapy and Oncology, 48, 185-190.

Hojris 1999

Hojris, I., Overgaard, M., Christensen, J. J., Overgaard, J. (1999) Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. Radiotherapy committee of the Danish Breast Cancer Cooperative Group. Lancet, 354, 1425-30.

Hojris 2000

Hojris, I., Andersen, J., Overgaard, M., Overgaard, J. (2000) Late treatment-related morbidity in breast cancer patients randomized to postmastectomy radiotherapy and systemic treatment versus systemic treatment alone. Acta Oncologica, 39, 355-372.

Host 1986

Host, H., Brennhovd, I. O., Loeb, M. (1986) Postoperative radiotherapy in breast cancer--long-term results from the Oslo study. International journal of radiation oncology, biology, physics, 12, 727-32.

Houghton 1994

Houghton, J., Baum, M., Haybittle, J. L. (1994) Role of radiotherapy following total mastectomy in patients with early breast cancer. World Journal of Surgery, 18, 117-122.

Katz 2000

Katz, A., Strom, E. A., Buchholz, T. A., Thames, H. D., Smith, C. D., Jhingran, A., Hortobagyi, G., Buzdar, A. U., Theriault, R., Singletary, S. E., McNeese, M. D. (2000) Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: Implications for postoperative irradiation. Journal of Clinical Oncology, 18, 2817-2827.

Killander 2007

Killander, F., Anderson, H., Ryden, S., Moller, T., Aspegren, K., Ceberg, J., Danewid, C., Malmstrom, P. (2007) Radiotherapy and tamoxifen after mastectomy in postmenopausal women - 20 year follow-up of the South Sweden Breast Cancer group randomised trial SSBCG II:I. European Journal of Cancer, 43, 2100-2108.

Killander 2014

Killander, F., Anderson, H., Kjellen, E., Malmstrom, P. (2014) 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. European journal of cancer, 50, 2201-2210.

Kyndi 2009

Kyndi,M., Overgaard,M., Nielsen,H.M., Sorensen,F.B., Knudsen,H., Overgaard,J. (2009) High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: A subgroup analysis of DBCG 82b&c. Radiotherapy and Oncology, 90, 74-79.

Lythgoe & Palmer 1982

Lythgoe, J. P., Palmer, M. K. (1982) Manchester regional breast study--5 and 10 year results. British journal of surgery, 69, 693-6.

McArdle 2010

McArdle, C. S., McMillan, D. C., Greenlaw, N., Morrison, D. S. (2010) Adjuvant radiotherapy and chemotherapy in breast cancer: 30 year follow-up of survival. BMC cancer, 10 (no pagination).

Muss 1991

Muss, H. B., Cooper, M. R., Brockschmidt, J. K., Ferree, C., Richards, Ii F., White, D. R., Jackson, D. V., Spurr, C. L. (1991) A randomized trial of chemotherapy (L-PAM vs CMF) and irradiation for node positive breast cancer. Eleven year follow-up of a Piedmont Oncology Association trial. Breast Cancer Research and Treatment, 19, 77-84.

NICE 2009

National Institute for Health and Clinical Excellence. (2009) Early and locally advanced breast cancer: diagnosis and treatment. NICE guideline (CG80).

Olson 1997

Olson, J. E., Neuberg, D., Pandya, K. J., Richter, M. P., Solin, L. J., Gilchrist, K. W., Tormey, D. C., Veeder, M., Falkson, G. (1997) The role of radiotherapy in the management of operable locally advanced breast carcinoma: Results of a randomized trial by the Eastern Cooperative Oncology Group. Cancer, 79, 1138-1149.

Overgaard 1999

Overgaard,M., Jensen,M.B., Overgaard,J., Hansen,P.S., Rose,C., Andersson,M., Kamby,C., Kjaer,M., Gadeberg,C.C., Rasmussen,B.B., Blichert-Toft,M., Mouridsen,H.T. (1999) Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet, 353, 1641-1648.

Overgaard 2007

Overgaard, M., Nielsen, H. M., Overgaard, J. (2007) Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiotherapy & Oncology, 82, 247-53.

Papaionnaou 1985

Papaioannou, A. N. (1985). Preoperative chemotherapy: advantages and clinical application in stage III breast cancer. Recent Results in Cancer Research, 98, 65-90.

Poortmans 2015a

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. (2015) Internal mammary and medial supraclavicular irradiation in breast cancer. New England Journal of Medicine, 373, 317-327.

Ragaz 1997

Ragaz, J., Jackson, S. M., Le, N., Plenderleith, I. H., Spinelli, J. J., Basco, V. E., Wilson, K. S., Knowling, M. A., Coppin, C. M. L., Paradis, M., Coldman, A. J., Olivotto, I. A. (1997) Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer, New England Journal of Medicine, 337, 956-962.

Saarto 1997

Saarto, T., Blomqvist, C., Rissanen, P., Auvinen, A., Elomaa, I. (1997) Haematological toxicity: a marker of adjuvant chemotherapy efficacy in stage II and III breast cancer. British Journal of Cancer, 75, 301-5.

Schmoor 2002

Schmoor, C., Olschewski, M., Sauerbrei, W., Schumacher, M. (2002) Long-term follow-up of patients in four prospective studies of the German Breast Cancer Study Group (GBSG): A summary of key results. Onkologie, 25, 143-150.

Shapiro 1998

Shapiro, C. L., Hardenbergh, P. H., Gelman, R., Blanks, D., Hauptman, P., Recht, A., Hayes, D. F., Harris, J., Henderson, I. C. (1998) Cardiac effects of adjuvant doxorubicin and radiation therapy in breast cancer patients. Journal of Clinical Oncology, 16, 3493-3501.

Stewart 1994

Stewart, H. J., Jack, W. J. L., Everington, D., Forrest, A. P. M., Rodger, A., McDonald, C. C., Prescott, R. J., Langlands, A. O. (1994) South east Scottish trial of local therapy in node negative breast cancer. Breast, 3, 31-39.

Stewart 2001a

Stewart, H. J., Prescott, R. J., Forrest, A. P. M. (2001) Scottish adjuvant tamoxifen trial: A randomized study updated to 15 years. Journal of the National Cancer Institute, 93, 456-462.

Turnbull 1978

Turnbull, A. R., Turner, D. T., Chant, A. D., Shepherd, J. M., Buchanan, R. B., Fraser, J. D. (1978) Treatment of early breast cancer, Lancet, 2, 7-9.

Velez-Garcia 1992

1 Velez-Garcia, E., Carpenter Jr, J. T., Moore, M., Vogel, C. L., Marcial, V., Ketcham, A.,
2 Singh, K. P., Bass, D., Bartolucci, A. A., Smalley, R. (1992) Postsurgical adjuvant
3 chemotherapy with or without radiotherapy in women with breast cancer and positive axillary
4 nodes: A South-Eastern Cancer Study Group (SEG) trial. European Journal of Cancer Part
5 A: General Topics, 28, 1833-1837.
6

Review question 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?

Introduction

Postmastectomy breast reconstruction improves the quality of life after mastectomy and, as recommended in the previous guideline CG80 (NICE 2009), should be offered to those undergoing mastectomy. Reconstruction can be performed at the time of mastectomy (immediate breast reconstruction) or planned as a later procedure (delayed reconstruction). Immediate breast reconstruction at the time of mastectomy has been shown to reduce psychological morbidity, decrease costs, reduce the total number of operations needed to complete breast reconstruction and has a cosmetic benefit.

Some women are treated with postmastectomy chest wall radiotherapy to reduce the risk of disease recurrence. It is known that radiotherapy can alter the outcomes after breast reconstruction including impairing cosmetic outcomes and increasing rates of re-operation and complications. Despite this however many women remain satisfied with the results of immediate breast reconstruction after radiotherapy, and it is also known that a proportion of women who plan a delayed reconstruction (after completion of treatments) do not complete surgical breast reconstruction

The effects of radiotherapy on breast reconstruction can be unpredictable and it is not always possible to predict who will be recommended radiotherapy until surgery (mastectomy and axillary staging) has been completed. This had led to uncertainty whether immediate breast reconstruction or delayed breast reconstruction is optimal in those who may need postmastectomy radiotherapy. The aim of this review is to determine whether immediate breast reconstruction is clinically and cost effective in women who may need postmastectomy 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	Adults (18 or over) with invasive breast cancer (M0) who undergo total breast reconstruction following mastectomy
Intervention	Immediate (same time as mastectomy) total breast reconstruction ± radiotherapy
Comparison	Delayed (after mastectomy – additional procedure) total breast reconstruction ± radiotherapy
Outcome	**Critical** • Patient satisfaction • Delay in adjuvant therapy • Complication rates **Important** • Local recurrence rate • Cosmetic result • HRQoL

HRQoL, health-related quality of life; M0, no distant metastases

For full details see the 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

Twenty-two articles reporting data from 23 cohort studies (N=29,710) were included in the review (Adesiyun 2011; Alderman 2010; Atisha 2008; Baltaci Goktas 2011; Carlson 2008; Christante 2010; Fernandez-Delgado, at al., 2008; Hughes 2012; Jeevan 2014; Kim 2012; Lee 2010; Leone 2011; Major 2016; McKeown 2009; Reintgen 2016; Sanati-Mehrizy 2015; Scuderi 2011; Sullivan 2008; Terao 2017; Tsai 2016; Zahra 2014; Zhong 2016).

All included studies compared immediate reconstruction against delayed reconstruction. Thirteen studies reported data for subgroups of interest: radiotherapy following mastectomy, (number of publications, k=6), no radiotherapy following mastectomy (k=3), reconstruction with implants (k=6) and autologous reconstruction (k=9).

The clinical studies included in this evidence review are summarised in Table 9 and evidence from these is summarised in the clinical GRADE evidence profile below (Table 10). 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 that 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, the 6 articles included in the previous guideline were not incorporated into the current results as they did not meet inclusion criteria outlined in the review protocol.

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	Additional inclusion/exclusion criteria	Interventions/comparison
Adesiyun 2011	• Mastectomy followed by reconstruction and radiotherapy • Exclusion: previous radiotherapy for treatment of Hodgkin disease, lymphoma, or failed breast-conserving surgery; immediate reconstruction with a tissue expander	• Intervention arm (immediate): No information about mastectomy or reconstruction. Mean interval between reconstruction and radiotherapy 5.2 months (1-15.5 months). Median radiotherapy dose 50Gy. • Control arm (delayed): No information about mastectomy or reconstruction. Median radiotherapy dose 50Gy; mean interval between radiotherapy and reconstruction 8.2 months (2.7-80.9 months).

Study	Additional inclusion/exclusion criteria	Interventions/comparison
Alderman 2010	• Stage I-III unilateral breast cancer; recommended adjuvant chemotherapy • Exclude: Received neoadjuvant systemic/radiation therapy	• Intervention arm (immediate): no information about mastectomy - reconstruction methods: implant, pedicle transverse rectus abdominus myocutaneous flap [TRAM], free TRAM requiring microvascular surgery, other rotational flap, and other free flap. Immediate reconstruction defined as reconstruction started or completed on same day as mastectomy. • Control arm (delayed): no information about mastectomy - reconstruction methods: implant, pedicle transverse rectus abdominus myocutaneous flap [TRAM], free TRAM requiring microvascular surgery, other rotational flap, and other free flap.
Atisha 2008	• Reconstruction with expander/implant, pedicle TRAM flap or free TRAM flap	• Intervention arm (immediate): No information reported about mastectomy. Reconstruction methods: 47% pedicle TRAM flap, 22% free TRAM flap, 30% expander/implant • Control arm (delayed): No information reported about mastectomy. Reconstruction methods: 63% pedicle TRAM flap, 25% free TRAM flap, 12% expander/implant
Baltaci Goktas 2011	• No additional criteria	• Intervention arm (immediate): 71% underwent simple mastectomy (SM), 29% modified radical mastectomy (MRM). 71% reconstruction with implant, 29% autologous. • Control arm (delayed): 35% SM, 65% MRM. 52% reconstruction with implant, 48% autologous.
Carlson 2008	• Reconstruction with pedicled TRAM flap	• No detailed information about interventions. Outcome data obtained through personal communication, physical examination and chart and photographic review.
Christante 2010	• Excluded: bilateral breast cancer and reconstruction	• No detailed information about interventions.
Fernandez-Delgado 2008	• No additional criteria	• No information reported about mastectomy. Implants were used in the majority of reconstructions (direct submuscular prostheses in immediate reconstructions and tissue expanders in delayed reconstructions. Autologous tissues were only used in small number of patients.
Hughes 2012	• Reconstruction with permanent tissue expanders	• Conventional or skin-sparing mastectomy followed by immediate reconstruction with Mentor or Inamed/Allergan tissue expanders
Jeevan 2014	• Women aged ≥16 years; invasive breast cancer and/or DCIS; unilateral mastectomy ± reconstruction	• Intervention arm (immediate): No information reported about type of mastectomy. Majority of patients had reconstruction with an implant (± flap) • Control arm (delayed): No information reported about type of mastectomy. Majority of patients had autologous reconstruction

Study	Additional inclusion/exclusion criteria	Interventions/comparison
Kim 2012	• Patients who had mastectomy, reconstruction and postmastectomy radiotherapy for breast cancer.	• Intervention arm (immediate): mean time between reconstruction and radiotherapy 1.2 months; mean radiation dose 5632.3cGy. No further details reported • Control arm (delayed): mean time between radiotherapy and reconstruction 7.1 months; mean radiation dose 5837.5cGy. No further details reported
Lee 2010	• Women who underwent simple or modified radical mastectomy and breast reconstruction • Exclude: Partial, subtotal or radical salvage mastectomy; reconstruction for micromastia or Poland syndrome; previous radiotherapy for failed breast conserving therapy, Hodgkin disease or lymphoma; planned delayed-immediate reconstruction; revision of reconstruction	• No detailed information about interventions.
Leone 2011	• Unilateral breast reconstruction	• No detailed information about interventions.
Major 2016	• Diabetic women undergoing mastectomy and breast reconstruction	• NSQIP: • Intervention arm (immediate): no further information about mastectomy. 84% had reconstructions with implants and 16% autologous reconstructions. • Control arm (delayed): no further information about mastectomy. 74% had reconstructions with implants and 26% autologous reconstructions. • JHH: • No detailed information about interventions.
McKeown 2009	• Autologous latissimus dorsi flap reconstruction and had a complete set of pre- and post-operative photographs	• Intervention arm (immediate): no details about mastectomy. Breast was reconstructed immediately with autologous latissimus dorsi flap and followed by radiotherapy - 25 fractions of 2Gy radiotherapy delivered to the chest wall and axilla. • Control arm (delayed): no details about mastectomy. Breast was reconstructed with autologous latissimus dorsi flap 4 to 71 months (median 38) after mastecomy; 45% had radiotherapy prior to reconstruction - 25 fractions of 2Gy radiotherapy delivered to the chest wall and axilla.
Reintgen 2016	• No additional criteria	• No detailed information about interventions
Sanati-Mehrizy 2015	• No additional criteria	• No detailed information about interventions

Study	Additional inclusion/exclusion criteria	Interventions/comparison
Scuderi 2011	• Reconstruction with an anatomical Becker-type implant in the sub-muscular position	• Intervention arm (immediate): no details about mastectomy. After the breast had been removed, the free lateral border of the pectoralis major muscle was split and raised to create cleavage and the serratus anterior was raised laterally to provide lateral implant cover. The inferior pectoralis major muscle was detached from the ribs and raised with the abdominal fascia, or the deep subcutaneous layer above it, to provide complete coverage of the implant. The partially filled implant was then placed in the subcutaneous pocket. The inferior mastectomy skin flap was stretched over the lower part of the anatomical expander implant to accentuate the lower pole of the reconstructed breast. Two or three drains were placed; one in the submuscular plane, one in the subcutaneous plane and, if required, in the axilla. After insertion, the implant was filled with further saline to fill the pocket as much as possible; final fill was performed on an outpatient basis. • Control arm (delayed): no details about mastectomy. For the delayed reconstruction, the mastectomy incision was reopened, the sub-muscular pocket was dissected, and the partially filled implant was inserted; one drain was placed. After insertion, the implant was filled with further saline to fill the pocket as much as possible; final fill was performed on an outpatient basis.
Sullivan 2008	• No additional criteria	• Intervention arm (immediate): no information about mastectomy. Immediate reconstruction was only offered to those who had not had prior chest wall irradiation, were not actively smoking or morbidly obese, and had stage I or II disease. 53% had reconstruction with tissue expander/implant and 47% were reconstructed with autologous tissue. • Control arm (delayed): no information about mastectomy. 32% had reconstruction with tissue expander/implant and 68% had reconstruction with autologous tissue.
Terao 2017	• All patients underwent autologous reconstruction with a flap and postmastectomy radiotherapy	• Intervention arm (immediate): no information about mastectomy. Underwent immediate reconstruction with a free rectus abdominis musculocutaneious (TRAM) flap (40%), a pedicled TRAM flap (55%), or a latissimus dorsi musculocutaneous (LD) flap (5%). Mean time to initiation of postmastectomy radiotherapy was 9.1 weeks (range 7 to 18) for those that received neoadjuvant chemotherapy and 35.4 weeks (range 22 to 48) for those that received adjuvant chemotherapy.

Study	Additional inclusion/exclusion criteria	Interventions/comparison
		• Control arm (delayed): no information about mastectomy. Underwent delayed reconstruction with a free rectus abdominis musculocutaneious (TRAM) flap (70%), a pedicled TRAM flap (15%), or a latissimus dorsi musculocutaneous (LD) flap (15%). Mean time to reconstruction after postmastectomy radiotherapy was 51 months (range 15 to 120).
Tsai 2016	• No additional criteria	• No detailed information about interventions
Zahra 2014	• No additional criteria	• Intervention arm (immediate): subcutaneous mastectomy followed by immediate reconstruction with extended latissimus dorsi myocutaneous (EDLM) flap. • Control arm (delayed): no details about mastectomy. Delayed reconstruction with LD flap or implant (33%), EDLM flap (33%) and TRAM flap (33%). All patients received radiotherapy and/or chemotherapy between mastectomy and reconstruction (minimum of 6 months between adjuvant therapy and reconstruction)
Zhong 2016	• Autologous reconstruction	• Intervention arm (immediate): no information about mastectomy and limited information about reconstruction. Immediate reconstruction was normally offered to women with in situ breast cancer or stage I/II cancer with no lymph node involvement where postmastectomy radiotherapy was not anticipated • Control arm (delayed): no information about mastectomy or reconstruction. Mean time between mastectomy and reconstruction 2.8 years (range 5 months to 18 years)

cGy, centigray; DCIS, ductal carcinoma in situ; EDLM, extended latissimus dorsi myocutaneous; Gy, gray; JHH, John Hopkins Hospital; LD, latissimus dorsi musculocutaneous; MRM, modified radical mastectomy; NSQIP, National Surgical Quality and Improvement Program; SM, simple mastectomy; TRAM, transverse rectus abdominus myocutaneous

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 (immediate versus delayed reconstruction) is presented in Table 10. All of the included evidence was of very low quality. The main reasons for downgrading evidence were imprecision around the estimates due to a small number of events of interest and wide confidence intervals, and risk of bias due to lack of comparability between groups at baseline.

Table 10: Summary clinical evidence profile: Comparison 1. Immediate reconstruction versus delayed reconstruction

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Delayed reconstruction	Corresponding risk: Immediate reconstruction			
Patient satisfaction - aesthetic - Mixed PMRT; mixed reconstruction type (6 month follow-up)	564 per 1000	688 per 1000 (564 to 834)	RR 1.22 (1 to 1.48)	263 (1 study)	Very low[1,2]
Patient satisfaction - aesthetic - PMRT+; mixed reconstruction type (3.9 year follow-up)	500 per 1000	620 per 1000 (415 to 925)	RR 1.24 (0.83 to 1.85)	77 (1 study)	Very low[3,4]
Patient satisfaction - aesthetic - PMRT+; implant (2.3 to 5.4 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 1.87 (0.32 to 11.11)	15 (2 studies)	Very low[3,5]
Patient satisfaction - aesthetic - PMRT+; autologous (2.3 to 5.4 year follow-up)	589 per 1000	666 per 1000 (495 to 896)	RR 1.13 (0.84 to 1.52)	104 (2 studies)	Very low[3,4]
Patient satisfaction - aesthetic - Mixed PMRT; mixed reconstruction type (6 month follow-up)		The mean patient satisfaction - aesthetic - mixed PMRT; mixed reconstruction type in the intervention groups was 0.45 standard deviations higher (0.07 lower to 0.96 higher)		60 (1 study)	Very low[6,7]
Patient satisfaction - aesthetic - Mixed PMRT; autologous (6 month follow-up)		The mean patient satisfaction - aesthetic - mixed PMRT; autologous in the intervention groups was 0 standard deviations higher (0.57 lower to 0.57 higher)		50 (1 study)	Very low[6,7]
Patient satisfaction - aesthetic - PMRT+; mixed reconstruction type		The mean patient satisfaction - aesthetic - PMRT+; mixed reconstruction		21 (1 study)	Very low[3,8]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Delayed reconstruction	Corresponding risk: Immediate reconstruction			
(follow-up not reported)		type in the intervention groups was 1.52 standard deviations higher (0.5 to 2.53 higher)			
Patient satisfaction - general - PMRT+; implant (2.3 to 5.4 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 1.43 (0.11 to 19.2)	7 (1 study)	Very low[3,5]
Patient satisfaction - general - PMRT+; autologous (2.3 to 5.4 year follow-up)	741 per 1000	748 per 1000 (541 to 1000)	RR 1.01 (0.73 to 1.4)	51 (1 study)	Very low[3,5]
Patient satisfaction - general - Mixed PMRT; mixed reconstruction type (6 month follow-up)		The mean patient satisfaction - general - mixed PMRT; mixed reconstruction type in the intervention groups was 0.09 standard deviations higher (0.41 lower to 0.6 higher)		60 (1 study)	Very low[6,7]
Patient satisfaction - general - Mixed PMRT; autologous (6 to 12 month follow-up)		The mean patient satisfaction - general - mixed PMRT; autologous in the intervention groups was 0.4 standard deviations lower (0.93 lower to 0.13 higher)		156 (2 studies)	Very low[7,9,10]
Patient satisfaction - general - PMRT+; mixed reconstruction type (follow-up not reported)		The mean patient satisfaction - general - PMRT+; mixed reconstruction type in the intervention groups was 0.08 standard deviations higher		21 (1 study)	Very low[3,7]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Delayed reconstruction	Corresponding risk: Immediate reconstruction			
		(0.8 lower to 0.96 higher)			
Delay in adjuvant therapy - Chemotherapy initiated >= 8 weeks after definitive surgery	30 per 1000	89 per 1000 (28 to 279)	RR 2.96 (0.94 to 9.3)	696 (1 study)	Very low[1,4]
Delay in adjuvant therapy - Chemotherapy not administered	100 per 1000	163 per 1000 (88 to 301)	RR 1.63 (0.88 to 3.01)	696 (1 study)	Very low[1,4]
Complication rates - any - Mixed PMRT; mixed reconstruction type (3.2 year follow-up)	375 per 1000	334 per 1000 (180 to 619)	RR 0.89 (0.48 to 1.65)	90 (1 study)	Very low[3,5]
Complication rates - any - PMRT+; mixed reconstruction type (3.9 year follow-up)	500 per 1000	620 per 1000 (415 to 925)	RR 1.24 (0.83 to 1.85)	77 (1 study)	Very low[3,4]
Complication rates - any - PMRT+; autologous; early complications (within 3 months of reconstruction)	209 per 1000	84 per 1000 (25 to 285)	RR 0.4 (0.12 to 1.36)	79 (1 study)	Very low[3,5]
Complication rates - any - PMRT+; autologous; late complications (3.9 year follow-up)	116 per 1000	194 per 1000 (67 to 560)	RR 1.67 (0.58 to 4.82)	79 (1 study)	Very low[3,5]
Complication rates - any - PMRT+; implant; early complications (within 3 months of reconstruction)	0 per 1000	0 per 1000 (0 to 0)	RR 0.71 (0.05 to 10.11)	14 (1 study)	Very low[3,5]
Complication rates - any - PMRT+; implant; late complications (3.9 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 2.43 (0.21 to 27.78)	14 (1 study)	Very low[3,5]
Complication rates - any surgical - Mixed PMRT; mixed reconstruction type (11 to 12 month follow-up)	174 per 1000	71 per 1000 (14 to 357)	RR 0.41 (0.08 to 2.05)	51 (1 study)	Very low[3,5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Delayed reconstruction	Corresponding risk: Immediate reconstruction			
Complication rates - any surgical - Mixed PMRT; autologous (follow-up not reported)	101 per 1000	60 per 1000 (47 to 77)	RR 0.59 (0.46 to 0.76)	3664 (1 study)	Very low[2,11]
Complication rates - any surgical - Mixed PMRT; implant (follow-up not reported)	66 per 1000	41 per 1000 (34 to 49)	RR 0.62 (0.52 to 0.74)	15560 (1 study)	Very low[11]
Complication rates - any donor site (17 to 18 month follow-up)	65 per 1000	81 per 1000 (60 to 108)	RR 1.24 (0.92 to 1.65)	2437 (2 studies)	Very low[4,12,13]
Complication rates - any mastectomy site - Mixed PMRT; autologous (18 month follow-up)	61 per 1000	79 per 1000 (58 to 108)	RR 1.3 (0.96 to 1.77)	2362 (1 study)	Very low[3,4,13]
Complication rates - any mastectomy site - Mixed PMRT; implant (18 month follow-up)	29 per 1000	92 per 1000 (45 to 186)	RR 3.22 (1.59 to 6.52)	1487 (1 study)	Very low[2,3,13]
Complication rates - any implant related (18 month follow-up)	21 per 1000	8 per 1000 (3 to 22)	RR 0.39 (0.14 to 1.05)	1487 (1 study)	Very low[3,13,14]
Complication rates - any flap related (18 month follow-up)	87 per 1000	44 per 1000 (32 to 61)	RR 0.51 (0.37 to 0.7)	2362 (1 study)	Very low[2,3,13]
Complication rates - flap/prosthesis failure - Mixed PMRT; mixed reconstruction type (1 to 17 month follow-up)	2 per 1000	22 per 1000 (4 to 115)	RR 10.90 (2.12 to 55.97)	1483 (2 studies)	Very low[2,3,15]
Complication rates - flap/prosthesis failure - Mixed PMRT; autologous (follow-up not reported)	14 per 1000	29 per 1000 (15 to 54)	RR 2.12 (1.13 to 3.95)	3664 (1 study)	Very low[2,3]
Complication rates - flap/prosthesis failure - Mixed PMRT; implant (follow-up not reported)	5 per 1000	7 per 1000 (4 to 14)	RR 1.51 (0.79 to 2.9)	15560 (1 study)	Very low[3,5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Delayed reconstruction	Corresponding risk: Immediate reconstruction			
Complication rates - any radiological (follow-up not reported)	59 per 1000	750 per 1000 (103 to 1000)	RR 12.75 (1.75 to 92.7)	21 (1 study)	Very low[2,3]
Complication rates – lymphoedema (11 to 12 month follow-up)	391 per 1000	145 per 1000 (51 to 403)	RR 0.37 (0.13 to 1.03)	51 (1 study)	Very low[3,14]
Complication rates - heart attack (1 to 18 month follow-up)	3 per 1000	2 per 1000 (1 to 8)	RR 0.72 (0.22 to 2.41)	3728 (3 studies)	Very low[3,5,13]
Complication rates - capsular contracture (cosmetic) - Mixed PMRT; mixed reconstruction type (6 month to 4 year follow-up)	54 per 1000	67 per 1000 (3 to 1000)	RR 1.23 (0.06 to 23.51)	409 (2 studies)	Very low[3,5]
Complication rates - capsular contracture (cosmetic) - Mixed PMRT; implant (12 to 36 month follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 3.29 (0.2 to 54.7)	227 (1 study)	Very low[1,5]
Complication rates - capsular contracture (cosmetic) - PMRT+; mixed reconstruction type (3.9 year follow-up)	15 per 1000	101 per 1000 (19 to 544)	RR 6.54 (1.21 to 35.36)	135 (2 studies)	Very low[2,3]
Complication rates - capsular contracture (cosmetic) - PMRT-; implant (1 year follow-up)	33 per 1000	28 per 1000 (5 to 149)	RR 0.85 (0.16 to 4.54)	204 (1 study)	Very low[1,5]
Complication rates - implant malposition (cosmetic) - Mixed PMRT; mixed reconstruction type (6 month to 4 year follow-up)	6 per 1000	18 per 1000 (2 to 171)	RR 3 (0.32 to 28.55)	334 (1 study)	Very low[3,5]
Complication rates - implant malposition (cosmetic) - PMRT+; mixed reconstruction type (3.9 year follow-up)	18 per 1000	35 per 1000 (3 to 376)	RR 2 (0.19 to 21.44)	114 (1 study)	Very low[3,5]
Complication rates - implant malposition (cosmetic) - PMRT-; implant (1 year follow-up)	197 per 1000	153 per 1000 (81 to 291)	RR 0.78 (0.41 to 1.48)	204 (1 study)	Very low[1,5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Delayed reconstruction	Corresponding risk: Immediate reconstruction			
Complication rates - implant rupture/extrusion (implant loss) - Mixed PMRT; mixed reconstruction type (6 month to 4 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 5 (0.24 to 103.36)	334 (1 study)	Very low[3,5]
Complication rates - implant rupture/extrusion (implant loss) - PMRT+; mixed reconstruction type (3.9 year follow-up)	18 per 1000	35 per 1000 (3 to 376)	RR 2 (0.19 to 21.44)	114 (1 study)	Very low[3,5]
Complication rates - implant rupture/extrusion (implant loss) - PMRT-; implant (1 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 1.29 (0.05 to 31.27)	204 (1 study)	Very low[1,5]
Complication rates - implant deflation (implant loss) (6 month to 4 year follow-up)	30 per 1000	24 per 1000 (7 to 88)	RR 0.8 (0.22 to 2.93)	334 (1 study)	Very low[3,5]
Complication rates - implant removed due to dissatisfaction/pain; PMRT+; mixed reconstruction type (implant loss) (3.9 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 3 (0.12 to 72.13)	114 (1 study)	Very low[3,5]
Complication rates - flap loss (flap loss) - Mixed PMRT; mixed reconstruction type; total flap loss (6 month to 4 year follow-up)	30 per 1000	24 per 1000 (7 to 88)	RR 0.8 (0.22 to 2.93)	334 (1 study)	Very low[3,5]
Complication rates - flap loss (flap loss) - Mixed PMRT; mixed reconstruction type; partial flap loss (6 month to 4 year follow-up)	24 per 1000	18 per 1000 (4 to 79)	RR 0.75 (0.17 to 3.3)	334 (1 study)	Very low[3,5]
Complication rates - flap loss (flap loss) - PMRT+; mixed reconstruction type (3.9 year follow-up)	31 per 1000	25 per 1000 (2 to 386)	RR 0.82 (0.05 to 12.54)	135 (2 studies)	Very low[3,5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Delayed reconstruction	Corresponding risk: Immediate reconstruction			
Complication rates - flap loss (flap loss) - PMRT+; autologous (follow-up not reported)	0 per 1000	0 per 1000 (0 to 0)	RR 1.62 (0.07 to 37.94)	58 (1 study)	Very low[3,5]
Complication rates - major fat necrosis (flap loss) - Mixed PMRT; mixed reconstruction type (6 month to 4 year follow-up)	77 per 1000	56 per 1000 (41 to 76)	RR 0.72 (0.53 to 0.98)	2654 (3 studies)	Very low[2,3,13]
Complication rates - major fat necrosis (flap loss) - Mixed PMRT; autologous (4.25 year follow-up)	91 per 1000	154 per 1000 (16 to 1000)	RR 1.69 (0.18 to 16.25)	24 (1 study)	Very low[3,5]
Complication rates - major fat necrosis (flap loss) - PMRT+; mixed reconstruction type (3.9 year follow-up)	77 per 1000	35 per 1000 (4 to 307)	RR 0.46 (0.05 to 3.99)	135 (2 studies)	Very low[3,5]
Complication rates - major fat necrosis (flap loss) - PMRT+; autologous (follow-up not reported)	133 per 1000	320 per 1000 (79 to 1000)	RR 2.4 (0.59 to 9.84)	40 (1 study)	Very low[5,6]
Complication rates - major fat necrosis (flap loss) - PMRT-; autologous (follow-up not reported)	36 per 1000	154 per 1000 (22 to 1000)	RR 4.32 (0.61 to 30.71)	177 (1 study)	Very low[5,6]
Complication rates - valve obstruction; PMRT-; implant (flap loss) (1 year follow-up)	33 per 1000	7 per 1000 (1 to 76)	RR 0.21 (0.02 to 2.31)	204 (1 study)	Very low[3,5]
Complication rates - valve displacement; PMRT-; implant (flap loss) (1 year follow-up)	49 per 1000	14 per 1000 (2 to 82)	RR 0.28 (0.05 to 1.66)	204 (1 study)	Very low[3,5]
Complication rates - hematoma (bleeding) - mixed PMRT; mixed reconstruction type (6 month to 4 year follow-up)	6 per 1000	36 per 1000 (4 to 295)	RR 6 (0.73 to 49.3)	334 (1 study)	Very low[3,5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Delayed reconstruction	Corresponding risk: Immediate reconstruction			
Complication rates - hematoma (bleeding) - PMRT+; mixed reconstruction type (follow-up not reported)	125 per 1000	26 per 1000 (1 to 589)	RR 0.21 (0.01 to 4.71)	21 (1 study)	Very low[3,5]
Complication rates - hematoma (bleeding) - PMRT+; mixed reconstruction type; donor site hematoma (3.9 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 5 (0.25 to 101.89)	114 (1 study)	Very low[3,5]
Complication rates - hematoma (bleeding) - PMRT+; mixed reconstruction type; recipient site hematoma (3.9 year follow-up)	53 per 1000	35 per 1000 (6 to 202)	RR 0.67 (0.12 to 3.84)	114 (1 study)	Very low[3,5]
Complication rates - hematoma (bleeding) - PMRT+; autologous (follow-up not reported)			Not estimable	40 (1 study)	Very low[6,16]
Complication rates - hematoma (bleeding) - PMRT-; autologous (follow-up not reported)	0 per 1000	0 per 1000 (0 to 0)	RR 1.35 (0.07 to 25.51)	177 (1 study)	Very low[5,6]
Complication rates - bleeding requiring transfusion/surgery; mixed PMRT; mixed reconstruction type (bleeding) (18 month follow-up)	19 per 1000	17 per 1000 (9 to 32)	RR 0.89 (0.46 to 1.72)	2245 (1 study)	Very low[3,5,13]
Complication rates - bleeding; PMRT-; implant (bleeding) (1 year follow-up)	82 per 1000	63 per 1000 (22 to 180)	RR 0.77 (0.27 to 2.2)	204 (1 study)	Very low[3,5]
Complication rates - hernia/fascial defect (flap donor site) - Mixed PMRT; mixed reconstruction type (18 month follow-up)	39 per 1000	45 per 1000 (29 to 69)	RR 1.16 (0.75 to 1.78)	2245 (1 study)	Very low[3,5,13]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Delayed reconstruction	Corresponding risk: Immediate reconstruction			
Complication rates - hernia/fascial defect (flap donor site) - PMRT+; mixed reconstruction type (3.9 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 3 (0.12 to 72.13)	114 (1 study)	Very low[3,5]
Complication rates - infection (wound) - Flap donor site; PMRT+; mixed reconstruction type (3.9 year follow-up)	35 per 1000	7 per 1000 (0 to 143)	RR 0.2 (0.01 to 4.08)	114 (1 study)	Very low[3,5]
Complication rates - infection (wound) - Recipient site; PMRT+; mixed reconstruction type (3.9 year follow-up)	35 per 1000	35 per 1000 (5 to 241)	RR 1 (0.15 to 6.86)	114 (1 study)	Very low[3,5]
Complication rates - infection (wound) - Site not reported; mixed PMRT; mixed reconstruction (1 month to 4 year follow-up)	152 per 1000	141 per 1000 (121 to 162)	RR 0.93 (0.8 to 1.07)	4062 (4 studies)	Very low[3,13]
Complication rates - infection (wound) - Site not reported; PMRT+; autologous (follow-up not reported)			Not estimable	40 (1 study)	Very low[6,16]
Complication rates - infection (wound) - Site not reported; PMRT-; autologous (follow-up not reported)	0 per 1000	0 per 1000 (0 to 0)	RR 0.58 (0.02 to 13.89)	177 (1 study)	Very low[5,6]
Complication rates - infection (wound) - Site not reported; PMRT-; implant (1 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 2.15 (0.1 to 44.19)	204 (1 study)	Very low[3,5]
Complication rates - wound dehiscence (wound) - Mixed PMRT; mixed reconstruction type (1 to 17 month follow-up)	19 per 1000	12 per 1000 (1 to 119)	RR 0.66 (0.07 to 6.42)	1483 (2 studies)	Very low[3,5,15]
Complication rates - wound dehiscence (wound) - PMRT+; mixed	53 per 1000	35 per 1000 (6 to 202)	RR 0.67 (0.12 to 3.84)	114 (1 study)	Very low[3,5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Delayed reconstruction	Corresponding risk: Immediate reconstruction			
reconstruction type (3.9 year follow-up)					
Complication rates - wound dehiscence (wound) - PMRT-; implant (1 year follow-up)	16 per 1000	49 per 1000 (6 to 389)	RR 2.99 (0.38 to 23.75)	204 (1 study)	Very low[3,5]
Complication rates - delayed wound healing (wound) (6 month to 4 year follow-up)	36 per 1000	18 per 1000 (5 to 71)	RR 0.5 (0.13 to 1.97)	334 (1 study)	Very low[3,5]
Complication rates - skin flap necrosis (mastectomy skin flaps) - Mixed PMRT; mixed reconstruction type (2 month to 4 year follow-up)	57 per 1000	162 per 1000 (34 to 768)	RR 2.82 (0.59 to 13.4)	2893 (4 studies)	Very low[3,5,13,17]
Complication rates - skin flap necrosis (mastectomy skin flaps) - PMRT+; autologous (follow-up not reported)	67 per 1000	120 per 1000 (14 to 1000)	RR 1.8 (0.21 to 15.78)	40 (1 study)	Very low[5,6]
Complication rates - skin flap necrosis (mastectomy skin flaps) - PMRT-; autologous (follow-up not reported)	0 per 1000	0 per 1000 (0 to 0)	RR 9.47 (0.59 to 151.42)	177 (1 study)	Very low[5,6]
Complication rates - skin loss; PMRT+; mixed reconstruction type (mastectomy skin flaps) (3.9 year follow-up)	53 per 1000	7 per 1000 (1 to 142)	RR 0.14 (0.01 to 2.7)	114 (1 study)	Very low[3,5]
Complication rates - additional surgery - Reason not reported; mixed PMRT; mixed reconstruction type (1 month to 18 month follow-up)	104 per 1000	119 per 1000 (58 to 246)	RR 1.15 (0.56 to 2.38)	3728 (3 studies)	Very low[3,13,18,19]
Complication rates - additional surgery - Reason not reported; mixed PMRT; autologous	131 per 1000	105 per 1000 (85 to 128)	RR 0.8 (0.65 to 0.98)	3664 (1 study)	Very low[11]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Delayed reconstruction	Corresponding risk: Immediate reconstruction			
(follow-up not reported)					
Complication rates - additional surgery - Reason not reported; mixed PMRT; implant (12 to 36 month follow-up)	85 per 1000	38 per 1000 (9 to 169)	RR 0.45 (0.1 to 1.98)	15787 (2 studies)	Very low[11,19,20]
Complication rates - additional surgery - Reason not reported; PMRT+; mixed reconstruction type (2.6 year follow-up)	222 per 1000	424 per 1000 (118 to 1000)	RR 1.91 (0.53 to 6.9)	42 (1 study)	Very low[1,5]
Complication rates - additional surgery - Reason not reported; PMRT+; autologous (follow-up not reported)	0 per 1000	0 per 1000 (0 to 0)	RR 4.31 (0.24 to 78.05)	40 (1 study)	Very low[5,6]
Complication rates - additional surgery - Reason not reported; PMRT-; mixed reconstruction type (2.6 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 4.33 (0.28 to 68.02)	110 (1 study)	Very low[1,5]
Complication rates - additional surgery - Reason not reported; PMRT-; autologous (follow-up not reported)	125 per 1000	188 per 1000 (49 to 720)	RR 1.5 (0.39 to 5.76)	144 (1 study)	Very low[5,6]
Complication rates - additional surgery - Wound opening; mixed PMRT; mixed reconstruction type (18 month follow-up)	61 per 1000	51 per 1000 (35 to 73)	RR 0.84 (0.58 to 1.21)	2245 (1 study)	Very low[3,5,13]
Complication rates - additional surgery - Flap removal; mixed PMRT; mixed reconstruction type (18 month follow-up)	49 per 1000	31 per 1000 (20 to 48)	RR 0.63 (0.41 to 0.97)	2245 (1 study)	Very low[2,3,13]
Complication rates - additional surgery - Flap reposition; mixed PMRT;	91 per 1000	26 per 1000 (1 to 580)	RR 0.29 (0.01 to 6.38)	24 (1 study)	Very low[3,5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Delayed reconstruction	Corresponding risk: Immediate reconstruction			
autologous (4.25 year follow-up)					
Complication rates - additional surgery - Symmetrisation; mixed PMRT; mixed reconstruction type (3 year follow-up)	430 per 1000	116 per 1000 (77 to 185)	RR 0.27 (0.18 to 0.43)	586 (1 study)	Very low[1,2]
Complication rates - additional surgery - Symmetrisation: mixed PMRT; autologous (4.25 year follow-up)	182 per 1000	155 per 1000 (25 to 920)	RR 0.85 (0.14 to 5.06)	24 (1 study)	Very low[3,5]
Complication rates - additional surgery - Symmetrisation; PMRT-; implant (1 year follow-up)	131 per 1000	84 per 1000 (37 to 195)	RR 0.64 (0.28 to 1.49)	204 (1 study)	Very low[1,5]
Complication rates - pneumothorax; PMRT-; implant (1 year follow-up)	16 per 1000	2 per 1000 (0 to 57)	RR 0.14 (0.01 to 3.47)	204 (1 study)	Very low[1,5]
Cosmetic result; mixed PMRT; mixed reconstruction type - Excellent (as measured by the Christie scale) (6 month follow-up)	367 per 1000	700 per 1000 (414 to 1000)	RR 1.91 (1.13 to 3.23)	60 (1 study)	Very low[2,6]
Cosmetic result; mixed PMRT; mixed reconstruction type - Good (as measured by the Christie scale) (6 month follow-up)	400 per 1000	200 per 1000 (88 to 464)	RR 0.5 (0.22 to 1.16)	60 (1 study)	Very low[5,6]
Cosmetic result; mixed PMRT; mixed reconstruction type - Fair (as measured by the Christie scale) (6 month follow-up)	133 per 1000	100 per 1000 (24 to 409)	RR 0.75 (0.18 to 3.07)	60 (1 study)	Very low[5,6]
Cosmetic result; mixed PMRT; mixed reconstruction type - Poor (as measured by the Christie scale) (6 month follow-up)	100 per 1000	14 per 1000 (1 to 265)	RR 0.14 (0.01 to 2.65)	60 (1 study)	Very low[5,6]
Health-related quality of life -		The mean health-related		111 (2 studies)	Very low[6,8,21]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Delayed reconstruction	Corresponding risk: Immediate reconstruction			
general - Mixed PMRT; mixed reconstruction type (6 to 11 month follow-up)		quality of life - general - mixed PMRT; mixed reconstruction type in the intervention groups was 1.43 standard deviations higher (0.17 to 2.69 higher)			
Health-related quality of life - general - Mixed PMRT; autologous (6 month follow-up)		The mean health-related quality of life - general - mixed PMRT; autologous in the intervention groups was 2.17 standard deviations higher (1.45 to 2.88 higher)		50 (1 study)	Very low[6,8]
Health-related quality of life - social; mixed PMRT; mixed reconstruction type (11 to 12 month follow-up)		The mean health-related quality of life - social; mixed PMRT; mixed reconstruction type in the intervention groups was 0.28 standard deviations higher (0.05 lower to 0.62 higher)		157 (2 studies)	Very low[3,7,10]
Health-related quality of life - social (change from pre- to post-reconstruction FACT-B social wellbeing scale); mixed PMRT; mixed reconstruction type (2 year follow-up)		The mean health-related quality of life - social (change from pre- to post-reconstruction FACT-B social wellbeing scale); mixed PMRT; mixed reconstruction type in the intervention groups was 0.65 lower		169 (1 study)	Very low[6,7]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Delayed reconstruction	Corresponding risk: Immediate reconstruction			
		(2.04 lower to 0.74 higher)			
Health-related quality of life - physical - General (measured by EORTC QLQ-30); mixed PMRT; mixed reconstruction type (11 to 12 month follow-up)		The mean health-related quality of life - physical - general (measured by EORTC QLQ-30); mixed PMRT; mixed reconstruction type in the intervention groups was 0.89 standard deviations higher (0.31 to 1.47 higher)		51 (1 study)	Very low[3,8]
Health-related quality of life - physical - Chest (measured by BREAST-Q): mixed PMRT; autologous (12 month follow-up)		The mean health-related quality of life - physical - chest (measured by BREAST-Q): mixed PMRT; autologous in the intervention groups was 0.04 standard deviations lower (0.46 lower to 0.39 higher)		106 (1 study)	Very low[3,8,10]
Health-related quality of life - physical - Abdomen (measured by BREAST-Q): mixed PMRT; autologous (12 month follow-up)		The mean health-related quality of life - physical - abdomen (measured by BREAST-Q): mixed PMRT; autologous in the intervention groups was 0.05 standard deviations higher (0.37 lower to 0.47 higher)		106 (1 study)	Very low[3,8,10]
Health-related quality of life - sexual (measured by BREAST-Q); mixed PMRT;		The mean health-related quality of life - sexual (measured by		106 (1 study)	Very low[3,8]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Delayed reconstruction	Corresponding risk: Immediate reconstruction			
autologous (12 month follow-up)		BREAST-Q); mixed PMRT; autologous in the intervention groups was 5.4 higher (5.13 lower to 15.93 higher)			
Health-related quality of life - role functioning (measured by EORTC QLQ-30); mixed PMRT; mixed reconstruction type (11 to 12 month follow-up)		The mean health-related quality of life - role functioning (measured by EORTC QLQ-30); mixed PMRT; mixed reconstruction type in the intervention groups was 1.35 lower (10.07 lower to 7.37 higher)		51 (1 study)	Very low[3,7]
Health-related quality of life - emotional functioning (measured by EORTC QLQ-30); mixed PMRT; mixed reconstruction type (11 to 12 month follow-up)		The mean health-related quality of life - emotional functioning (measured by EORTC QLQ-30); mixed PMRT; mixed reconstruction type in the intervention groups was 9.22 higher (0.27 lower to 18.71 higher)		51 (1 study)	Very low[3,7]
Health-related quality of life - cognitive functioning (measured by EORTC QLQ-30); mixed PMRT; mixed reconstruction type (11 to 12 month follow-up)		The mean health-related quality of life - cognitive functioning (measured by EORTC QLQ-30); mixed PMRT; mixed reconstruction type in the intervention groups was 0.26 higher (10.05 lower to 10.57 higher)		51 (1 study)	Very low[3,7]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Delayed reconstruction	Corresponding risk: Immediate reconstruction			
Health-related quality of life - functional (change from pre- to post-reconstruction FACT-B functional wellbeing scale); mixed PMRT; mixed reconstruction type (2 year follow-up)		The mean health-related quality of life - functional (change from pre- to post-reconstruction FACT-B functional wellbeing scale); mixed PMRT; mixed reconstruction type in the intervention groups was 2.06 higher (0.51 to 3.61 higher)		171 (1 study)	Very low[6,8]

CI: Confidence interval; EORTC QLQ-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-B; Functional assessment of cancer therapy – Breast cancer; HR: Hazards ratio; PMRT: postmastectomy radiotherapy; RR: Risk ratio;

[1] Unclear if groups were comparable at baseline

[2] <300 events

[3] Groups not comparable at baseline

[4] <300 events; 95% confidence interval crosses both boundary for no effect (1) and minimally important difference (1.25) based on GRADE default values

[5] <300 events; 95% confidence interval crosses boundary for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values

[6] Insufficient information about method of selection and groups not comparable at baseline

[7] sample size <400; 95% confidence interval crosses both boundary of no effect (0) and minimally important difference (0.5 times SD) based on GRADE default values

[8] sample size <400

[9] Insufficient information about method of selection for Zahra 2014 and groups not comparable at baseline

[10] 25% of Zhong 2016 had in situ breast cancer

[11] Groups not comparable at baseline and follow-up limited

[12] Groups not comparable at baseline for Jeevan 2014 which has 99% of weight in analysis

[13] 29% of Jeevan 2014 had in situ breast cancer

[14] <300 events; 95% confidence interval crosses both no effect (1) and minimally important difference (0.80) based on GRADE default values

[15] Unclear what proportion of patients had delayed-immediate reconstruction

[16] No events

[17] I2 64% - significant unexplained heterogeneity; no further subgroups of interest identified by guideline committee

[18] I2 79% - significant unexplained heterogeneity; no further subgroups of interest identified by guideline committee

[19] 95% confidence interval crosses both boundary for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values

[20] I2 95% - significant unexplained heterogeneity; no further subgroups of interest identified by guideline committee

[21] I2 88% - significant unexplained heterogeneity; no further subgroups of interest identified by guideline committee

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. Immediate reconstruction versus delayed reconstruction

Critical outcomes

Patient satisfaction: aesthetic

- There is very low quality evidence from 2 cohort studies (N=373) that there is no clinically important effect of reconstruction timing on patients' aesthetic satisfaction at 6 month follow-up for women with unspecified reconstruction methods and autologous reconstructions following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=77) that there is no clinically important effect of reconstruction timing on patients' aesthetic satisfaction at 3.9 year follow-up for women with unspecified reconstruction methods following mastectomy and radiotherapy when measured dichotomously. However, there is very low quality evidence from 1 study (N=21) that patients' aesthetic satisfaction is clinically higher following immediate reconstruction compared with delayed reconstruction for women with unspecified reconstruction methods following mastectomy and radiotherapy when measured continuously.
- There is very low quality evidence from 2 cohort studies (N=104) that patients' aesthetic satisfaction at 2.3 to 5.4 year follow-up is clinically higher following immediate reconstruction compared with delayed reconstruction for women with autologous reconstructions following mastectomy and radiotherapy; however, the effect was not statistically significant.
- There is very low quality evidence from 2 cohort studies (N=15) that patients' aesthetic satisfaction at 2.3 to 5.4 year follow-up is clinically higher following immediate reconstruction compared with delayed reconstruction for women with implant reconstructions following mastectomy and radiotherapy; however, the effect was not statistically significant.

Patient satisfaction: general

- There is very low quality evidence from 2 cohort studies (N=216) that there is no clinically important effect of reconstruction timing on patients' general satisfaction at 6 to 12 month follow-up for women with unspecified reconstruction methods and autologous reconstructions following mastectomy (± radiotherapy).
- There is very low quality evidence from 2 cohort studies (N=72) that there is no clinically important effect of reconstruction timing on patients' general satisfaction at 2.3 to 5.4 year follow-up for women with unspecified reconstruction methods and autologous reconstructions following mastectomy and radiotherapy.
- There is very low quality evidence from 1 cohort study (N=7) that patients' general satisfaction at 2.3 to 5.4 year follow-up is clinically higher following immediate reconstruction compared with delayed reconstruction for women with implant reconstructions following mastectomy and radiotherapy; however, the effect was not statistically significant.

Delay in adjuvant therapy

- There is very low quality evidence from 1 cohort study (N=696) that immediate reconstruction produced clinically meaningful increases in the number of individuals that commenced adjuvant chemotherapy ≥8 weeks after surgery compared with delayed

reconstruction for women with unspecified reconstruction methods following mastectomy (± radiotherapy); however, the effect was not statistically significant.

- There is very low quality evidence from 1 cohort study (N=696) that immediate reconstruction produced clinically meaningful increases in the number of individuals that did not receive recommended adjuvant chemotherapy compared with delayed reconstruction for women with unspecified reconstruction methods following mastectomy (± radiotherapy); however, the effect was not statistically significant.

Complication rates: non-specific

- There is very low quality evidence from 2 cohort studies (N=167) that there is no clinically important effect of reconstruction timing on any complications at 3.2 to 3.9 year follow-up for women with unspecified reconstruction methods following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=77) that there is no clinically important effect of reconstruction timing on any complications at 3.9 year follow-up for women with unspecified reconstruction methods following mastectomy and radiotherapy.
- There is very low quality evidence from 1 cohort study (N=93) that immediate reconstructions produced clinically lower rates of any early complications (within 3 months of reconstruction) compared with delayed reconstructions for women with autologous and implant reconstructions following mastectomy and radiotherapy; however, the effects were not statistically significant.
- There is very low quality evidence from 1 cohort study (N=93) that immediate reconstructions produced clinically higher rates of any late complications (at 3.9 year follow-up) compared with delayed reconstructions for women with autologous and implant reconstructions following mastectomy and radiotherapy; however, the effects were not statistically significant.
- There is very low quality evidence from 1 cohort study (N=51) that immediate reconstructions produced clinically lower rates of any surgical complications at 11 to 12 month follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy (± radiotherapy); however, the effect was not statistically significant.
- There is very low quality evidence from 1 cohort study (N=19,224) that immediate reconstructions produced clinically lower rates of any surgical complications (follow-up not reported) compared with delayed reconstructions for women with autologous and implant reconstructions following mastectomy (± radiotherapy).
- There is very low quality evidence from 2 cohort studies (N=2437) that there is no clinically important effect of reconstruction timing on any donor site complications at 17 to 18 month follow-up for women with unspecified reconstruction methods following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=2362) that immediate reconstructions produced clinically higher rates of any mastectomy site complications at 18 month follow-up compared with delayed reconstructions for women with autologous reconstructions following mastectomy (± radiotherapy); however, the effect was not statistically significant.
- There is very low quality evidence from 1 cohort study (N=1487) that immediate reconstructions produced clinically higher rates of any mastectomy site complications at 18 month follow-up compared with delayed reconstructions for women with implant reconstructions following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=1487) that immediate reconstructions produced clinically lower rates of any implant related complications at 18 month follow-up compared with delayed reconstructions following mastectomy (± radiotherapy); however, the effect was not statistically significant.

- There is very low quality evidence from 1 cohort study (N=2362) that immediate reconstructions produced clinically lower rates of any flap related complications at 18 month follow-up compared with delayed reconstructions following mastectomy (± radiotherapy).
- There is very low quality evidence from 3 cohort studies (N=5146) that immediate reconstructions produced clinically higher rates of flap or prosthesis failure at 1 to 17 month follow-up compared with delayed reconstructions for women with unspecified reconstruction methods and autologous reconstructions following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=15,560) that immediate reconstructions produced clinically higher rates of flap or prosthesis failure (follow-up not reported) compared with delayed reconstructions for women with implant reconstructions following mastectomy (± radiotherapy); however, the effect was not statistically significant.

Complication rates: cosmetic

- There is very low quality evidence from 2 cohort studies (N=409) that there is no clinically important effect of reconstruction timing on capsular contracture at 6 month to 4 year follow-up for women with unspecified reconstruction methods following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=227) that immediate reconstructions produced clinically higher rates of capsular contracture at 12 to 36 month follow-up compared with delayed reconstructions for women with implant reconstructions following mastectomy (± radiotherapy); however, the effect was no statistically significant.
- There is very low quality evidence from 2 cohort studies (N=135) that immediate reconstructions produced clinically higher rates of capsular contracture at 3.9 year follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy and radiotherapy.
- There is very low quality evidence from 1 cohort study (N=204) that there is no clinically important effect of reconstruction timing on capsular contracture at 1 year follow-up for women with implant reconstructions following mastectomy and no radiotherapy.
- There is very low quality evidence from 2 cohort studies (N=448) that immediate reconstructions produced clinically higher rates of implant malposition at 6 month to 4 year follow-up compared with delayed reconstructions following mastectomy and radiotherapy, or unspecific radiotherapy; however, the effects were not statistically significant.
- There is very low quality evidence from 1 cohort study (N=204) that immediate reconstructions produced clinically lower rates of implant malposition at 1 year follow-up compared with delayed reconstructions following mastectomy and no radiotherapy; however the effect was not statistically significant.

Complication rates: implant loss

- There is very low quality evidence from 3 cohort studies (N=652) that immediate reconstructions produced clinically higher rates of implant rupture/extrusion at 6 month to 4 year follow-up compared with delayed reconstructions following mastectomy irrespective of receipt of radiotherapy; however, the effects were not statistically significant.
- There is very low quality evidence from 1 cohort study (N=334) that there is no clinically important effect of reconstruction timing on implant deflation at 6 month to 4 year follow-up following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=114) that immediate reconstructions produced clinically higher rates of implant removal due to dissatisfaction and/or pain at 3.9 year follow-up compared with delayed reconstructions following mastectomy and radiotherapy; however, the effect was not statistically significant.

Complication rates: flap loss

- There is very low quality evidence from 1 cohort study (N=334) that there is no clinically important effect of reconstruction timing on total flap loss at 6 month to 4 year follow-up for women with unspecified reconstruction methods following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=334) that immediate reconstructions produced clinically lower rates of partial flap loss at 6 month to 4 year follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy (± radiotherapy); however, the effect was not statistically significant.
- There is very low quality evidence from 2 cohort studies (N=135) that there is no clinically important effect of reconstruction timing on flap loss at 3.9 year follow-up for women with unspecified reconstruction methods following mastectomy and radiotherapy.
- There is very low quality evidence from 1 cohort study (N=58) that immediate reconstructions produced clinically higher rates of flap loss (follow-up not reported) compared with delayed reconstructions for women with autologous reconstructions following mastectomy and radiotherapy; however, the effect was not statistically significant.
- There is very low quality evidence from 3 cohort studies (N=2654) that immediate reconstructions produced clinically lower rates of major fat necrosis compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy (± radiotherapy).
- There is very low quality evidence from 2 cohort studies (N=135) that immediate reconstructions produced clinically lower rates of major fat necrosis at 6 month to 4 year follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy and radiotherapy; however, the effect was not statistically significant.
- There is very low quality evidence from 2 cohort studies (N=241) that immediate reconstructions produced clinically higher rates of major fat necrosis (follow-up not reported) compared with delayed reconstructions for women with autologous reconstructions following mastectomy irrespective of receipt of radiotherapy; however, the effects were not statistically significant.
- There is very low quality evidence from 1 cohort study (N=204) that immediate reconstructions produced clinically lower rates of valve obstruction at 1 year follow-up compared with delayed reconstructions for women with implant reconstructions following mastectomy and no radiotherapy; however, the effect was not statistically significant.
- There is very low quality evidence from 1 cohort study (N=204) that immediate reconstructions produced clinically lower rates of valve displacement at 1 year follow-up compared with delayed reconstructions for women with implant reconstructions following mastectomy and no radiotherapy; however, the effect was not statistically significant.

Complication rates: bleeding

- There is very low quality evidence from 1 cohort study (N=334) that immediate reconstructions produced clinically higher rates of unspecified hematomas at 6 month to 4 year follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy (± radiotherapy); however, the effect was not statistically significant.
- There is very low quality evidence from 1 cohort study (N=21) that immediate reconstructions produced clinically lower rates of unspecified hematomas (follow-up not reported) compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy and radiotherapy; however, the effect was not statistically significant.

- There is very low quality evidence from 1 cohort study (N=114) that immediate reconstructions produced clinically higher rates of donor site hematomas at 3.9 year follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy and radiotherapy; however, the effect was not statistically significant.
- There is very low quality evidence from 1 cohort study (N=114) that immediate reconstructions produced clinically lower rates of recipient site hematomas at 3.9 year follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy and radiotherapy; however, the effect was not statistically significant.
- It was not possible to estimate the clinical effect of reconstruction timing on unspecified hematomas (follow-up not reported) for women with autologous reconstructions following mastectomy and radiotherapy as no events of interest occurred in either arm (1 study; N=40).
- There is very low quality evidence from 1 cohort study (N=177) that immediate reconstructions produced clinically higher rates of unspecified hematomas (follow-up not reported) compared with delayed reconstructions for women with autologous reconstruction methods following mastectomy and no radiotherapy; however, the effect was not statistically significant.
- There is very low quality evidence from 1 cohort study (N=2245) that there is no clinically important effect of reconstruction timing on bleeding requiring transfusion or surgery at 18 month follow-up for women with unspecified reconstruction methods following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=204) that immediate reconstructions produced clinically lower rates of unspecified bleeding at 1 year follow-up compared with delayed reconstructions for women with implant reconstructions following mastectomy and no radiotherapy; however, the effect was not statistically significant.

Complication rates: flap donor site

- There is very low quality evidence from 1 cohort study (N=2245) that there is no clinically important effect of reconstruction timing on hernias/fascial defects at 18 month follow-up for women with unspecified reconstruction methods following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=114) that immediate reconstructions produced clinically higher rates of hernias/fascial defects at 3.9 year follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy and radiotherapy; however, the effect was not statistically significant.

Complication rates: wound

- There is very low quality evidence from 1 cohort study (N=114) that immediate reconstructions produced clinically lower rates of donor site infections at 3.9 year follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy and radiotherapy; however, the effect was not statistically significant.
- There is very low quality evidence from 1 cohort study (N=114) that there is no clinically important effect of reconstruction timing on recipient site infections at 3.9 year follow-up for women with unspecified reconstruction methods following mastectomy and radiotherapy.
- There is very low quality evidence from 4 cohort studies (N=4062) that there is no clinically important effect of reconstruction timing on unspecified infections at 1 month to 4 year follow-up for women with unspecified reconstruction methods following mastectomy (±radiotherapy).

- It was not possible to estimate the clinical effect of reconstruction timing on unspecified infections (follow-up not reported) for women with autologous reconstructions following mastectomy and radiotherapy as no events of interest occurred in either arm (1 study; N=40).
- There is very low quality evidence from 1 cohort study (N=177) that immediate reconstructions produced clinically lower rates of unspecified infections (follow-up not reported) compared with delayed reconstructions for women with autologous reconstructions following mastectomy and no radiotherapy; however, the effect was not statistically significant.
- There is very low quality evidence from 1 cohort study (N=204) that immediate reconstructions produced clinically higher rates of unspecified infections at 1 year follow-up compared with delayed reconstructions for women with implant reconstructions following mastectomy and no radiotherapy; however, the effect was not statistically significant.
- There is very low quality evidence from 3 cohort studies (N=1597) that immediate reconstructions produced clinically lower rates of wound dehiscence at 1 month to 3.9 year follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy (± radiotherapy); however, the effects were not statistically significant.
- There is very low quality evidence from 1 cohort study (N=204) that immediate reconstructions produced clinically higher rates of wound dehiscence at 1 year follow-up compared with delayed reconstructions for women with implant reconstructions following mastectomy and no radiotherapy; however, the effect was not statistically significant.
- There is very low quality evidence from 1 cohort study (N=334) that immediate reconstructions produced clinically lower rates of delayed wound healing at 6 month to 4 year follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy (± radiotherapy); however, the effect was not statistically significant.

Complication rates: mastectomy skin flaps

- There is very low quality evidence from 4 cohort studies (N=2893) that immediate reconstructions produced clinically higher rates of skin flap necrosis at 2 month to 4 year follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy (± radiotherapy); however, the effect was not statistically significant.
- There is very low quality evidence from 1 cohort study (N=217) that immediate reconstructions produced clinically higher rates of skin flap necrosis (follow-up not reported) compared with delayed reconstructions for women with autologous reconstructions following mastectomy irrespective of receipt of radiotherapy; however, the effects were not statistically significant.
- There is very low quality evidence from 1 cohort study (N=114) that immediate reconstructions produced clinically lower rates of skin loss at 3.9 year follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy and radiotherapy; however, the effect was not statistically significant.

Complication rates: additional surgery

- There is very low quality evidence from 4 cohort studies (N=7392) that there is no clinically important effect of reconstruction timing on unspecified additional surgeries at 1 to 18 month follow-up for women with unspecified reconstruction methods and autologous reconstructions following mastectomy (± radiotherapy).
- There is very low quality evidence from 2 cohort studies (N=15,787) that immediate reconstructions produced clinically lower rates of unspecified additional surgeries at 12 to 36 month follow-up compared with delayed reconstructions for women with implant

reconstructions following mastectomy (± radiotherapy); however, the effect was not statistically significant.

- There is very low quality evidence from 2 cohort studies (N=82) that immediate reconstructions produced clinically higher rates of unspecified additional surgeries at 2.6 year follow-up compared with delayed reconstructions for women with unspecified reconstruction methods and autologous reconstructions following mastectomy and radiotherapy; however, the effects were not statistically significant.
- There is very low quality evidence from 2 cohort studies (N=254) that immediate reconstructions produced clinically higher rates of unspecified additional surgeries at 2.6 year follow-up compared with delayed reconstructions for women with unspecified reconstruction methods and autologous reconstructions following mastectomy and no radiotherapy; however, the effects were not statistically significant.
- There is very low quality evidence from 1 cohort study (N=2245) that there is no clinically important effect of reconstruction timing on additional surgeries required for wound opening at 18 month follow-up for women with unspecified reconstruction methods and autologous reconstructions following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=2245) that immediate reconstructions produced clinically lower rates of additional surgeries required for flap removal at 18 month follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 study (N=24) that immediate reconstructions produced clinically lower rates of additional surgeries required for flap reposition at 4.25 year follow-up compared with delayed reconstructions for women with autologous reconstructions following mastectomy (± radiotherapy); however, the effect was not statistically significant.
- There is very low quality evidence from 1 cohort study (N=586) that immediate reconstructions produced clinically lower rates of additional surgeries required for symmetrisation at 3 year follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=24) that there is no clinically important effect of reconstruction timing on additional surgeries required for symmetrisation at 4.25 year follow-up for women with autologous reconstructions following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=204) that immediate reconstructions produced clinically lower rates of additional surgeries required for symmetrisation at 1 year follow-up compared with delayed reconstructions for women with implant reconstructions following mastectomy and no radiotherapy; however, the effect was not statistically significant.

Complication rates: other

- There is very low quality evidence from 1 cohort study (N=21) that immediate reconstructions produced clinically higher rates of radiological complications (follow-up not reported) compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=51) that immediate reconstructions produced clinically lower rates of lymphoedema at 11 to 12 month follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy (± radiotherapy); however, the effect was not statistically significant.
- There is very low quality evidence from 3 cohort studies (N=3728) that immediate reconstructions produced clinically lower rates of heart attacks at 1 to 18 month follow-up compared with delayed reconstructions for women with unspecified reconstruction

methods following mastectomy (± radiotherapy); however, the effect was not statistically significant.

- There is very low quality evidence from 1 cohort study (N=204) that immediate reconstructions produced clinically lower rates of pneumothorax at 1 year follow-up compared with delayed reconstructions for women with implant reconstructions following mastectomy and no radiotherapy; however, the effect was not statistically significant.

Important outcomes

Cosmetic result

- There is very low quality evidence from 1 cohort study (N=60) that immediate reconstructions produced clinically higher rates of excellent cosmetic results at 6 month follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=60) that immediate reconstructions produced clinically lower rates of good, fair and poor cosmetic results at 6 month follow-up compared with delayed reconstructions for women with unspecified reconstruction methods following mastectomy (± radiotherapy); however, the effects were not statistically significant.

Health-related quality of life

- There is very low quality evidence from 2 cohort studies (N=111) that immediate reconstructions produced clinically higher general health-related quality of life at 6 to 11 month follow-up compared with delayed reconstruction for women with unspecified reconstruction methods following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=50) that immediate reconstructions produced clinically higher general health-related quality of life at 6 month follow-up compared with delayed reconstruction for women with autologous reconstructions following mastectomy (± radiotherapy).
- There is very low quality evidence from 2 cohort studies (N=157) that immediate reconstructions produced clinically higher social health-related quality of life at 11 to 12 month follow-up compared with delayed reconstruction for women with unspecified reconstruction methods following mastectomy (± radiotherapy); however, the effect was not statistically significant.
- There is very low quality evidence from 1 cohort study (N=169) that immediate reconstructions produced greater negative change from pre-reconstruction to post-reconstruction social health-related quality of life at 2 year follow-up compared with delayed reconstruction for women with unspecified reconstruction methods following mastectomy (± radiotherapy); however, the effect was not statistically significant.
- There is very low quality evidence from 1 cohort study (N=51) that immediate reconstructions produced clinically higher physical health-related quality of life at 11 to 12 month follow-up compared with delayed reconstruction for women with unspecified reconstruction methods following mastectomy (± radiotherapy).
- There is very low quality evidence from 1 cohort study (N=106) that there is no clinically important effect of reconstruction timing on chest- or abdomen-related health-related quality of life at 12 month follow-up for women with autologous reconstructions following mastectomy (± radiotherapy); however, the effects were not statistically significant.
- There is very low quality evidence from 1 cohort study (N=106) that immediate reconstructions produced clinically higher sexual health-related quality of life at 12 month follow-up compared with delayed reconstruction for women with autologous reconstructions following mastectomy (± radiotherapy); however, the effect was not statistically significant.

- There is very low quality evidence from 1 cohort study (N=51) that immediate reconstructions produced clinically lower role functioning at 11 to 12 month follow-up compared with delayed reconstruction for women with unspecified reconstruction methods following mastectomy (± radiotherapy); however, the effect was not statistically significant.
- There is very low quality evidence from 1 cohort study (N=51) that immediate reconstructions produced clinically higher emotional and cognitive functioning at 11 to 12 month follow-up compared with delayed reconstruction for women with unspecified reconstruction methods following mastectomy (± radiotherapy); however, the effects were not statistically significant.
- There is very low quality evidence from 1 cohort study (N=171) that immediate reconstructions produced greater positive change from pre-reconstruction to post-reconstruction functioning at 2 year follow-up compared with delayed reconstruction for women with unspecified reconstruction methods following mastectomy (± radiotherapy).

Recommendations

I4. Offer immediate breast reconstruction to women who have been advised to have a mastectomy, including those who may need radiotherapy, unless they have significant comorbidities that rule out reconstructive surgery.

I5.Discuss the benefits and risks of breast reconstruction with women. Topics to discuss include:

- the timing of breast reconstruction surgery (at the same time as mastectomy or later)
- different breast reconstruction surgery options and what they involve
- how the timing of breast reconstruction surgery affects the options available
- the uncertainty over long-term outcomes in women having radiotherapy.

I6. Offer all appropriate breast reconstruction options, whether or not they are all available locally.

Research recommendation

What are the long-term outcomes for breast reconstruction in women having radiotherapy to the chest wall?

Rationale and impact

Why the committee made the recommendations

The committee agreed that the main benefits of immediate breast reconstruction compared with delayed reconstruction are improved aesthetic satisfaction, improved health-related quality of life, lower rates of complications and a reduced need for further surgery. In addition, although radiotherapy can impact on outcomes after breast reconstruction, there was no consistent evidence of a difference in outcomes between radiotherapy delivered after immediate reconstructions compared with delayed reconstructions. Therefore, the committee agreed that the benefits outweighed potential risks sufficiently to offer immediate reconstruction to all women, despite the lack of good evidence.

Impact of the recommendations on practice

The recommendations may result in a substantial change in practice because many centres do not routinely offer immediate breast reconstruction to all women (including those who have been advised to have radiotherapy). The impact will depend on how many immediate reconstructions are already carried out. In addition, the uptake of immediate breast reconstruction will also depend on women's preferences. There may be cost savings

associated with immediate reconstructions because fewer surgical procedures are needed (reconstruction is done at the same time as mastectomy and there are lower rates of additional symmetrisation surgery).

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Patient satisfaction was prioritised as a critical outcome as mastectomy can have a substantial impact on psychological morbidity and satisfaction with the breast reconstruction provided and its success is likely to have an important role in ameliorating or aggravating this.

Complication rates were also prioritised as critical outcomes as they will likely affect satisfaction, health-related quality of life (HRQoL), health and can be financially costly.

Overall survival was not selected as an outcome for this question as reconstruction timing does not usually have a direct impact on survival. It is possible there may be an indirect effect on survival if the type of breast reconstruction offered or chosen by the patient leads to delays to recommended adjuvant therapy, However, the impact of this is likely to affect local recurrence (and over a shorter follow-up period). For this reason delay to adjuvant therapy was selected as critical outcome and local recurrence was chosen as an important outcome.

Cosmetic result (measured objectively) and HRQoL were selected as important outcomes. The committee recognised that HRQoL is likely to be affected by both patient satisfaction and complication rates.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE, and evidence for all outcomes was very low quality as it was taken from cohort studies. The evidence was also down-graded due to high rates of imprecision, due to a small number of events of interest and wide confidence intervals. There were also issues with a lack of comparability between groups at baseline.

The committee also noted that the evidence may be confounded by the fact that those women who were offered immediate reconstructions probably had a more favourable reconstruction prognosis as they were less likely to have diabetes, to smoke or to be obese.

Benefits and harms

The committee agreed that the main benefits of immediate breast reconstruction were improved aesthetic satisfaction, a better objective cosmetic result, and improved general and functional HRQoL compared with delayed reconstruction. There was also evidence that early reconstruction led to lower rates of surgical complications, major fat necrosis, and surgery required for flap removal or symmetrisation.

Specifically, immediate reconstruction was associated with a 3% decrease in major fat necrosis (number needed to treat [NNT] 33), a 2% decrease in surgery needed for flap removal (NNT 50) and 31% decrease in symmetrisation procedures (NNT 3) for populations with unspecific reconstruction methods and mixed postmastectomy radiotherapy (PMRT). The committee also agreed that offering immediate reconstruction led to an additional benefit of increased patient choice.

The harms seen with immediate reconstruction included higher rates of mastectomy site complications, flap or prosthesis failure and capsular contracture compared with delayed reconstruction.

Specifically, autologous and implant reconstructions were associated with a 2% increase and a 6% increase in mastectomy site complications respectively (NNTs 50 and 17). There was also a 2.6% increase in flap/prosthesis failure for populations with unspecific reconstruction methods and mixed PMRT (NNT 39) and 15% increase in capsular contracture following PMRT (NNT 7).

There was no clear evidence that there is a greater detrimental effect of radiotherapy on reconstruction following immediate compared with delayed reconstructions or that adjuvant therapy is delayed following immediate reconstructions. The committee therefore recommended that immediate reconstruction be offered to all women following mastectomy, including those who might need radiotherapy, with the exception of those where immediate reconstruction is precluded by significant co-morbidity.

The committee agreed that due to the potential adverse effects seen with immediate reconstruction it is important to discuss the risks and benefits of both the method and timing of reconstruction with the woman so she can make an informed decision. Although there is uncertainty over the long-term outcomes of radiotherapy, there is some evidence that immediate implant reconstructions may be more affected by radiotherapy than immediate autologous reconstructions, so the women's decision may involve weighing up what type of reconstruction (implant or autologous) she would prefer, and the psychological and HRQoL impact of delayed reconstruction.

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.

This topic was considered to be of much more importance clinically rather than economically since it is concerned with the timing of interventions rather than differences in the interventions themselves. However, there may be cost savings associated with immediate reconstructions as fewer surgical procedures are required because reconstruction is done at the same time as mastectomy. The rates of additional surgeries required for symmetrisation are also much lower with immediate reconstruction. The change in practice is therefore likely to be either be cost-neutral, or potentially cost saving.

Other factors the committee took into account

The committee were aware that the data available was from cohort studies and was of low quality but noted that randomised controlled trials had been attempted and recruitment had always been unsuccessful. The committee were also aware of results from the implant breast reconstruction evaluation (IBRA)-2 cohort study (Potter, 2017) that showed no difference in time to administration of adjuvant therapy between women who did and did not have immediate breast reconstruction following mastectomy; this is in contrast with the very low quality evidence identified in the current review which showed a potential delay to adjuvant chemotherapy but supports the recommendations made by the committee. This evidence was only available as a conference presentation at the time of this guideline.

The committee were aware that at the moment there is great variation in the availability of reconstruction methods, and that this varies based on geographical location, local protocols, and surgical expertise. The committee agreed that their recommendation would counteract this inequality by ensuring people are offered, and have access to, all appropriate options

References

Adesiyun 2011

Adesiyun, T. A., Lee, B. T., Yueh, J. H., Chen, C., Colakoglu, S., Anderson, K. E. M., Nguyen, M. D. T., Recht, A. (2011) Impact of sequencing of postmastectomy radiotherapy and breast reconstruction on timing and rate of complications and patient satisfaction. International Journal of Radiation Oncology Biology Physics, 80, 392-397.

Alderman 2010

Alderman, A. K., Collins, E. D., Schott, A., Hughes, M. E., Ottesen, R. A., Theriault, R. L., Wong, Y. N., Weeks, J. C., Niland, J. C., Edge, S. B. (2010) The impact of breast reconstruction on the delivery of chemotherapy. Cancer, 116, 1791-1800.

Atisha 2008

Atisha, D., Alderman, A. K., Lowery, J. C., Kuhn, L. E., Davis, J., Wilkins, E. G. (2008) Prospective analysis of long-term psychosocial outcomes in breast reconstruction: two-year postoperative results from the Michigan Breast Reconstruction Outcomes Study. Annals of Surgery, 247, 1019-28.

Baltaci Goktas 2011

Baltaci Goktas, S., Gulluoglu, B. M., Selimen, D. (2011) Immediate or delayed breast reconstruction after radical mastectomy in breast cancer patients: Does it make a difference in the quality of life. Turkiye Klinikleri Journal of Medical Sciences, 31, 664-673.

Carlson 2008

Carlson, G. W., Page, A. L., Peters, K., Ashinoff, R., Schaefer, T., Losken, A. (2008) Effects of radiation therapy on pedicled transverse rectus abdominis myocutaneous flap breast reconstruction. Annals of plastic surgery, 60, 568-572.

Christante 2010

Christante, D., Pommier, S. J., Diggs, B. S., Samuelson, B. T., Truong, A., Marquez, C., Hansen, J., Naik, A. M., Vetto, J. T., Pommier, R. F. (2010) Using complications associated with postmastectomy radiation and immediate breast reconstruction to improve surgical decision making. Archives of Surgery, 145, 873-878.

Fernandez-Delgado 2008

Fernandez-Delgado, J., Lopez-Pedraza, M. J., Blasco, J. A., Andradas-Aragones, E., Sanchez-Mendez, J. I., Sordo-Miralles, G., Reza, M. M. (2008) Satisfaction with and psychological impact of immediate and deferred breast reconstruction. Annals of Oncology, 19, 1430-1434.

Hughes 2012

Hughes, K., Brown, C., Perez, V., Ting, J. W. C., Rozen, W. M., Whitaker, I. S., Korentager, R. (2012) The effect of radiotherapy on implant-based breast reconstruction in the setting of skin-sparing mastectomy: Clinical series and review of complications. Anticancer research, 32, 553-557.

Jeevan 2014

Jeevan, R., Cromwell, D. A., Browne, J. P., Caddy, C. M., Pereira, J., Sheppard, C., Greenaway, K., van der Meulen, J. H. (2014) Findings of a national comparative audit of mastectomy and breast reconstruction surgery in England. Journal of Plastic, Reconstructive & Aesthetic Surgery, 67, 1333-44.

Kim 2012

Kim, S. H., Kim, J. M., Park, S. H., Lee, S. Y. (2012) Analysis of the effects of breast reconstruction in breast cancer patients receiving radiotherapy after mastectomy. Archives of Plastic Surgery, 39, 222-226.

Lee 2010

Lee, B. T., A. Adesiyun T, Colakoglu, S., Curtis, M. S., Yueh, J. H., E. Anderson K, Tobias, A. M., Recht, A. (2010) Postmastectomy radiation therapy and breast reconstruction: an analysis of complications and patient satisfaction. Annals of plastic surgery, 64, 679-683.

Leone 2011

Leone, M. S., Priano, V., Franchelli, S., Puggioni, V., Merlo, D. F., Mannucci, M., Santi, P. L. (2011) Factors affecting symmetrization of the contralateral breast: a 7-year unilateral postmastectomy breast reconstruction experience. Aesthetic Plastic Surgery, 35, 446-451.

Major 2016

Major, M., Devulapalli, C., Bello, R. J., Baltodano, P. A., Reinhardt, M. E., Manahan, M. A., Cooney, C. M., Rosson, G. D. (2016) The Effect of Timing on Breast Reconstruction Outcomes in Diabetic Women. Plastic and Reconstructive Surgery - Global Open, 4, e1090.

McKeown 2009

McKeown, D. J., Hogg, F. J., Brown, I. M., Walker, M. J., Scott, J. R., Weiler-Mithoff, E. M. (2009) The timing of autologous latissimus dorsi breast reconstruction and effect of radiotherapy on outcome. Journal of Plastic, Reconstructive and Aesthetic Surgery, 62, 488-493.

NICE 2009

National Institute for Health and Clinical Excellence. (2009) Early and locally advanced breast cancer: diagnosis and treatment. NICE guideline (CG80).

Potter 2017 (On behalf of the Breast Reconstruction Research Collaborative)

Potter, S. (2017). The IBRA-2 study: does immediate breast reconstruction delay the delivery of adjuvant therapy. Oncoplastic & Reconstructive Breast Surgery Meeting (September, 2017); Nottingham, UK.

Reintgen 2016

Reintgen, C., Leavitt, A., Pace, E., Molas-Pierson, J., Mast, B. A. (2016) Risk Factor Analysis for Mastectomy Skin Flap Necrosis: Implications for Intraoperative Vascular Analysis. Annals of plastic surgery, 76 Suppl 4, S336-9.

Sanati-Mehrizy 2015

Sanati-Mehrizy, P., Massenburg, B. B., Rozehnal, J. M., Gupta, N., Rosa, J. H., Ingargiola, M. J., Taub, P. J. (2015) A Comparison of Postoperative Outcomes in Immediate Versus Delayed Reconstruction After Mastectomy. Eplasty [Electronic Resource], 15, e44.

Scuderi 2011

Scuderi, N., Alfano, C., Campus, G. V., Rubino, C., Chiummariello, S., Puddu, A., Mazzocchi, M. (2011) Multicenter study on breast reconstruction outcome using Becker implants. Aesthetic Plastic Surgery, 35, 66-72.

Sullivan 2008

Sullivan, S. R., Fletcher, D. R. D., Isom, C. D., Isik, F. F. (2008) True incidence of all complications following immediate and delayed breast reconstruction. Plastic and Reconstructive Surgery, 122, 19-28.

Terao 2017

Terao, Y., Taniguchi, K., Fujii, M., Moriyama, S. (2017) Postmastectomy radiation therapy and breast reconstruction with autologous tissue. Breast Cancer, 1-6.

Tsai 2016

Tsai, Y. J., Lin, P. Y., Chiang, Y. C., Chen, Y. C., Kuo, P. J., Kuo, Y. R. (2016) Breast reconstruction modality and outcomes after mastectomy. Formosan Journal of Surgery, 49, 9-14.

Zahra 2014

Zahra, T., El-Din, A. B., Shouman, O., Ismail, H. E. D. A., Rifaat, M. A. (2014) Assessment of aesthetic results and quality of life following different procedures of breast reconstruction. Journal of Plastic Dermatology, 10, 105-110.

Zhong 2016

Zhong, T., Hu, J., Bagher, S., Vo, A., O'Neill, A. C., Butler, K., Novak, C. B., Hofer, S. O., Metcalfe, K. A. (2016) A Comparison of Psychological Response, Body Image, Sexuality, and Quality of Life between Immediate and Delayed Autologous Tissue Breast Reconstruction: A Prospective Long-Term Outcome Study. Plastic & Reconstructive Surgery, 138, 772-80.

Appendices

Appendix A – Review protocols

Review protocol for 9.1 What are the indications for postmastectomy radiotherapy for people with early and locally advanced breast cancer?

Field (based on PRISMA-P)	Content
Review question	9.1. What are the indications for postmastectomy radiotherapy for people with early and locally advanced breast cancer?
Type of review question	Intervention review
Objective of the review	This evidence based review will seek to define the indications for postmastectomy radiotherapy after primary surgery. Recommendations will aim to cover which groups should be offered such treatment.
Eligibility criteria – population/disease/condition/issue/domain	Adults (18 or over) with invasive breast cancer (M0) and/or DCIS who have undergone primary mastectomy. Studies with indirect populations will not be considered.
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Radiotherapy to the chest wall • Radiotherapy to the chest wall plus nodes
Eligibility criteria – comparator(s)/control or reference (gold) standard	• Radiotherapy to the chest wall • Radiotherapy to the chest wall plus nodes • No radiotherapy
Outcomes and prioritisation	Critical (up to 3 outcomes) • Locoregional recurrence rate (MID: any statistically significant difference) • Treatment-related morbidity (e.g., pulmonary toxicity [MID: GRADE default values], lung cancer [MID: any statically sufficient difference]) • Overall survival (MID: any statistically significant difference) Important but not critical • Disease-free survival (MID: any statistically significant difference)

Field (based on PRISMA-P)	Content
	• Treatment-related mortality (MID: any statistically significant difference) • HRQoL (MID: values from the literature) 10 year follow-up periods will be prioritised if 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
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):
	• DCIS
	• Invasive
	  ○ Nodal status (N0, N1-3, N4+)
	  ○ T stage
	  ○ Grade
	  ○ Margins (positive/negative)
	  ○ Lymphovascular invasion (present or not)
	  ○ ER status
	  ○ HER-2 status
	  ○ Axillary surgery (> or less than 10 nodes removed)
	• Consider composite groups if possible.

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.

Field (based on PRISMA-P)	Content
	Dual sifting will not be performed for this 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. 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: Which groups of patients should receive chest wall radiotherapy after mastectomy? Date of search: 28/02/2008 Relevant recommendation(s) from previous guideline: 1) Offer adjuvant chest wall radiotherapy to patients with early invasive breast cancer who have had a mastectomy and are at a high risk of local recurrence. Patients at a high risk of local recurrence include those with four or more positive axillary lymph nodes or involved resection margins. 2) Consider entering patients who have had a mastectomy for early invasive breast cancer and who are at an intermediate risk of local recurrence, into the current UK trial (SUPREMO) assessing the value of postoperative radiotherapy. Patients at an intermediate risk of local recurrence include those with one to three lymph nodes involved, lympho-vascular invasion, histological grade 3 tumours, ER-negative tumours, and those aged under 40 years. 3) Do not offer radiotherapy following mastectomy to patients with early invasive breast cancer who are at low risk of local recurrence (for example, most patients who are lymph node negative).
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

Field (based on PRISMA-P)	Content
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/ Please document any deviations/alternative approach when GRADE isn't used or if a modified GRADE approach has been used for non-intervention or non-comparative studies.
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	Not applicable.

BCS, breast cancer subscale; DCIS, ductal carcinoma in situ; 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; TOI, Trial outcome index; WHOQOL, World Health Organization quality of life

1 Review protocol for 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?

Field (based on PRISMA-P)	Content
Review question	Should the potential need for radiotherapy preclude immediate breast reconstruction?
Type of review question	Intervention review
Objective of the review	The aim of this review is to determine whether immediate breast reconstruction is clinically and cost effective in women who may need postmastectomy radiotherapy. Recommendations will aim to cover the appropriate timing of breast reconstruction in women who will or may need radiotherapy after mastectomy.
Eligibility criteria – population/disease/condition/issue/domain	Adults (18 or over) with invasive breast cancer (M0) who undergo total breast reconstruction following mastectomy
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Immediate (same time as mastectomy) total breast reconstruction ± radiotherapy
Eligibility criteria – comparator(s)/control or reference (gold) standard	Delayed (after mastectomy –additional procedure) total breast reconstruction ± radiotherapy
Outcomes and prioritisation	Critical (up to 3 outcomes) • Patient satisfaction (MID: GRADE default values) • Delay in adjuvant therapy (MID: GRADE default values) • Complication rates (Need for unplanned additional surgery i.e., no of operations [MID: GRADE default values], implant loss rate [MID: GRADE default values]) Important but not critical • Local recurrence rate (MID: any statistically significant difference) • Cosmetic result – e.g., Breast-Q (MID: GRADE default values) • HRQoL (MID: values from the literature where available, otherwise GRADE default values) Longest follow-up periods will be prioritised where 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

Field (based on PRISMA-P)	Content
	• WHOQOL-100: 1 point
Eligibility criteria – study design	Systematic reviews/meta-analyses of RCTs RCTs Non-randomised controlled studies (n>50) Cohort studies (n>50) Non-comparative studies (e.g., case series - only if insufficient comparative evidence; n>50)
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 (for critical outcomes only): • Implant • Autologous • Radiotherapy following mastectomy (yes/no)
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 as there was some difficulty in agreeing this PICO; 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.
Identify if an update	Previous question: When is it appropriate to perform immediate breast reconstructive surgery? Date of search: 28/02/2008 Relevant recommendation(s) from previous guideline: Discuss immediate breast reconstruction with all patients who are being advised to have a mastectomy, and offer it except where significant

Field (based on PRISMA-P)	Content
	comorbidity or (the need for) adjuvant therapy may preclude this option. All appropriate breast reconstruction options should be offered and discussed with patients, irrespective of whether they are all available locally.
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; 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; TOI, Trial outcome index; WHOQOL, World Health Organization quality of life

Appendix B – Literature search strategies

Literature search strategies for 9.1 What are the indications for postmastectomy radiotherapy for people with early and locally advanced breast cancer?

Database: Medline & Embase (Multifile)

Last searched on **Embase** 1974 to 2017 March 01**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present.

Date of final search: 2 March 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$).mp.
38	33 or 34 or 35 or 36 or 37
39	exp Mastectomy/ use prmz
40	exp mastectomy/ use oemezd
41	(mastectom$ or post?mastectom$ or post-mastectom$ or postmastectom$).mp.
42	(mammectom$ or post?mammectom$ or post-mammectom$ or postmammectom$).mp.
43	39 or 40 or 41 or 42
44	32 and 38 and 43
45	limit 44 to yr="1990 -Current"
46	remove duplicates from 45
47	Limit 46 to RCTs and SRs, and general exclusions filter applied

Database: Cochrane Library via Wiley Online

Date of last search: 2 March 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

#	Searches
#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: [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	MeSH descriptor: [Mastectomy] explode all trees
#27	(mastectom* or post?mastectom* or post-mastectom* or postmastectom*):ti,ab,kw (Word variations have been searched)
#28	(mammectom* or post?mammectom* or post-mammectom* or postmammectom*):ti,ab,kw (Word variations have been searched)
#29	#26 or #27 or #28
#30	#21 and #25 and #29 Publication Year from 1990 to 2017

Literature search strategies for 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?

Database: Medline & Embase (Multifile)

Last searched on **Embase** 1974 to 2017 March 08**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present.

Date of last search: 9 March 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

#	Searches
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$).mp.
38	33 or 34 or 35 or 36 or 37
39	exp Mammaplasty/ use prmz
40	exp breast reconstruction/ use oemezd
41	exp breast endoprosthesis/ use oemezd
42	exp Reconstructive Surgical Procedures/ use prmz
43	exp Surgery, Plastic/ use prmz
44	plastic surgery/ use oemezd
45	exp Breast Implants/ use prmz
46	exp breast implant/ use oemezd
47	exp "Prostheses and Implants"/ use prmz
48	exp "prostheses and orthoses"/ use oemezd
49	exp Surgical Flaps/ use prmz
50	exp surgical flaps/ use oemezd
51	(mammoplast$ or mammaplast*).tw.
52	(breast adj6 reconstruct$).tw.
53	((immediat$ or delay$) adj6 reconstruct$).tw.
54	or/39-53
55	32 and 38 and 54
56	(immediate$ adj3 breast adj3 reconstruct$).tw.
57	(delay$ adj3 breast adj3 reconstruct$).tw.
58	55 or 56 or 57
59	limit 58 to yr="2008 -Current"
60	remove duplicates from 59 [Then general exclusions filter applied]

Database: Cochrane Library via Wiley Online

Date of last search: 9 March 2017

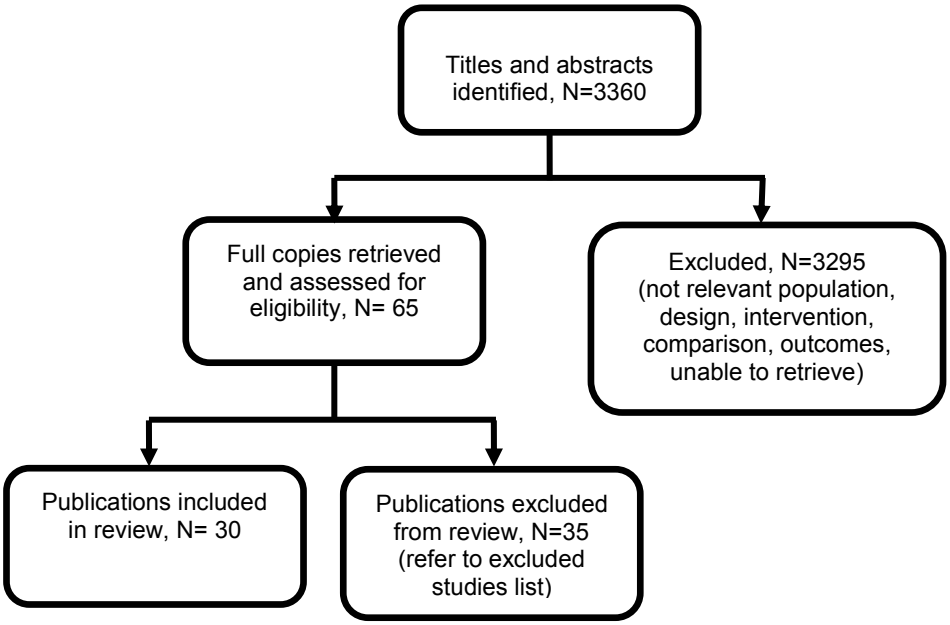
#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [Carcinoma, Medullary] this term only

#	Searches
#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: [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	MeSH descriptor: [Mammaplasty] explode all trees
#27	MeSH descriptor: [Reconstructive Surgical Procedures] explode all trees
#28	MeSH descriptor: [Surgery, Plastic] explode all trees
#29	MeSH descriptor: [Breast Implants] explode all trees
#30	MeSH descriptor: [Prostheses and Implants] explode all trees
#31	MeSH descriptor: [Surgical Flaps] explode all trees
#32	(mammoplast* or mammaplast*):ti,ab,kw (Word variations have been searched)
#33	(breast near/6 reconstruct*):ti,ab,kw (Word variations have been searched)
#34	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
#35	#21 and #25 and #34
#36	(immediate* near/6 breast near/6 reconstruct*):ti,ab,kw (Word variations have been searched)
#37	(delay* near/6 breast near/6 reconstruct*):ti,ab,kw (Word variations have been searched)
#38	((immediat* or delay*) near/6 reconstruct*):ti,ab,kw (Word variations have been searched)
#39	#21 and #38
#40	#36 or #37 or #39
#41	#35 or #40 Publication Year from 2008 to 2017

Appendix C – Clinical evidence study selection

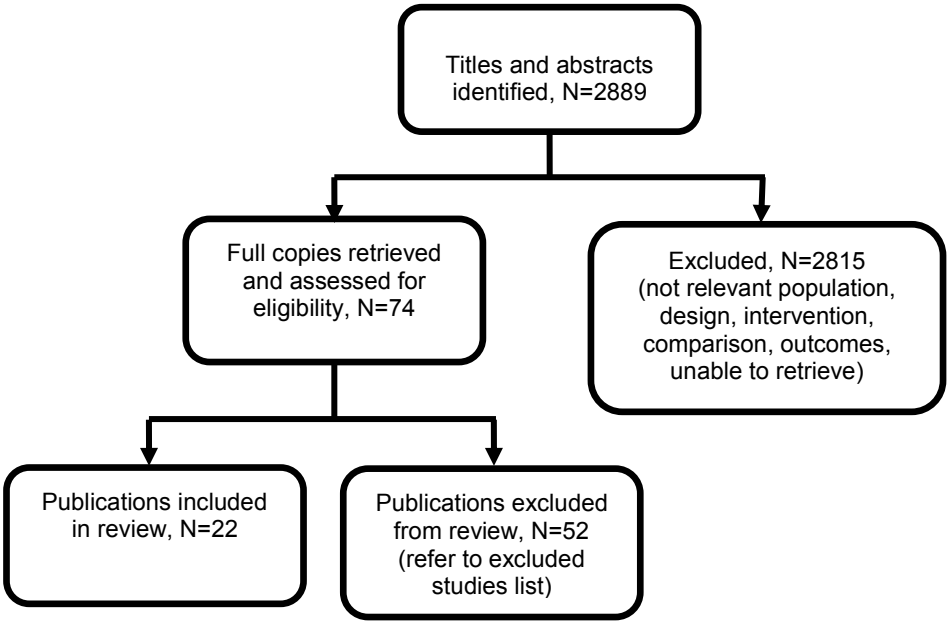
Clinical evidence study selection for 9.1 What are the indications for postmastectomy radiotherapy for people with early and locally advanced breast cancer?

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



Clinical evidence study selection for 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?

Figure 2: Flow diagram of clinical article selection for postmastectomy radiotherapy



Appendix D – Clinical evidence tables

Clinical evidence tables for 9.1 What are the indications for postmastectomy radiotherapy for people with early and locally advanced breast cancer?

Table 11: Clinical evidence summaries for 9.1 Indications for postmastectomy radiotherapy

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Deutsch, M., Land, S., Begovic, M., Sharif, S., The incidence of arm edema in women with breast cancer randomized on the National Surgical Adjuvant Breast and Bowel Project study B-04 to radical mastectomy versus total mastectomy and radiotherapy versus total mastectomy alone, International journal of radiation oncology, biology, physics, 70, 1020-4, 2008 **Ref Id** 565638 **Country/ies where the study was carried out** USA **Study type**	**Sample size** See EBCTCG 2014 (NSABP B-04 trial) **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014 (NSABP B-04 trial)	**Details** -	**Results** See EBCTCG 2014 (NSABP B-04 trial) Additional outcome reported in the paper **Arm oedema (total women with oedema on final measurement, follow-up 2 to 5 years)** RT arm: 84/568 Non RT arm: 225/889 (includes both radical mastectomy and total mastectomy)	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: Low risk (Low loss of follow-up was <20%) and ITT analysis used) Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
RCT **Aim of the study** - **Study dates** - **Source of funding** -					Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** This study (NSABP B-04 trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation Kyndi,M., Overgaard,M., Nielsen,H.M., Sorensen,F.B., Knudsen,H., Overgaard,J., High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: A subgroup analysis of DBCG 82 b&c, Radiotherapy and Oncology, 90, 74-79, 2009 **Ref Id**	**Sample size** See EBCTCG 2014 (Danish BCG 82b&c). **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014 (Danish BCG 82b&c).	**Details** -	**Results** See EBCTCG 2014 (Danish BCG 82b&c). No additional outcomes reported.	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** (Overgaard 1997 was also checked as details are also reported in that study) Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
300654 **Country/ies where the study was carried out** **Study type** RCT - Included in EBCTCG 2014. **Aim of the study** - **Study dates** - **Source of funding** -					Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: unclear (this is a subgroup analysis, no details reported) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** This study (Danish BCG 82b&c) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation EBCTCG, McGale, P., Taylor, C., Correa, C., Cutter, D., Duane, F., Ewertz, M., Gray, R.,	**Sample size** N=8135 women from 22 trials. **Characteristics**	**Interventions** Data was extracted from EBCTCG 2010 Suppl.	**Details** The process of trial identification and data handling was previously described	**Results** Data was extracted from EBCTCG 2014 Suppl.	**Limitations** **The quality of the systematic review was assessed using the ROBIS tool.** Phase 1: Assessing relevance

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Mannu, G., Peto, R., Whelan, T., Wang, Y., Wang, Z., Darby, S., Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials.[Erratum appears in Lancet. 2014 Nov 22;384(9957):1848], Lancet, 383, 2127-35, 2014 **Ref Id** 566382 **Country/ies where the study was carried out** Multinational **Study type** Systematic review of RCTs. **Aim of the study** To evaluate the effectiveness of radiotherapy in women with breast cancer after mastectomy. **Study dates**	Follow-up (median): 9·4 years per woman (IQR 3·7–17·3) 5424 (67%) women (67%) were known to have died Type of axillary surgery: known for 98% of women Nodal status: 1594 (20%) women had pathologically node-negative disease, 5821 (72%) had pathologically node-positive disease, and for 720 pathological nodal status was unknown. **Inclusion criteria** RCTs beginning before 2000 evaluating the use of adjuvant radiotherapy versus no radiotherapy but the same surgery after mastectomy for invasive cancer. **Exclusion criteria**	Andersson 1999 (Danish BCG 82b pre) N=1804 Type of breast surgery: simple (total) mastectomy Axillary surgery: axillary dissection (n=418) or axillary sampling (n=1386) Chest wall RT: 36-50 Gy (1.8-2.2 Gy/f) o or e Supraclavicular (SC) and axillary fossa (AF) RT: 36-50 Gy (1.8-2.2 Gy/f) o or m Other adjuvant therapy: cyclophosphamide, methotrexate and fluorouracil De Oliveira 1984 (Coimbra) N=124 Type of breast surgery: not reported Axillary surgery: axillary sampling	(Clarke 2005, EBCTCG). Information was sought for every individual woman for: patient characteristics, tumour characteristics, treatment, time to first recurrence, whether the first recurrence was locoregional or distant, and date last known alive or date and underlying cause of death. If recurrence was not reported before breast cancer death, distant recurrence was assumed to have just preceded it. Women were classified as having axillary dissection if they were in a trial in which the protocol required removal of axillary lymph nodes in at least levels I and II. When the extent of axillary dissection was not described in terms of levels, women were classified as having axillary dissection if the trial protocol or publications indicated	**Locoregional recurrence (critical)** ***10-year risk of locoregional recurrence*** Comparison. CWRT + lymph nodes vs no RT following mastectomy w/o axillary surgery in women with clinically node-negative disease Ratio of annual event rates, results reported as deaths/ women Houghton 1994 (Kings/ Cambridge): 153/996 vs 348/1049; O-E: -100.0 (119.7) Fisher 1980 (NSABP B-04): 16/386 vs 92/384; O-E: -40.1 (24.4) Stewart 2001 (Scottish D): 6/42 vs 11/39; O-E: -2.9 (3.8) Comparison. CWRT + lymph nodes vs no RT following mastectomy w/o axillary surgery in women with clinically node-positive disease Ratio of annual event rates, results reported as events/ women Lythgoe 1982 (Manchester RBS1): 49/355 vs 120/359; O-E: -39.7 (39.5) Houghton 1994 (Kings/ Cambridge): 66/380 vs 168/375: O-E: -58.5 (53.4)	Does the question addressed by the review match the target question? YES Phase 2: Identifying concerns with the review process Concerns regarding specification of study eligibility criteria: LOW Concerns regarding methods used to identify and/or select studies: LOW Concerns regarding methods used to collect data and appraise studies: LOW for data extraction; NA for appraisal Concerns regarding the synthesis and findings: LOW Phase 3. Judging risk of bias Did the interpretation of findings address all of the concerns identified in Domains 1 to 4? probably yes Was the relevance of identified studies to the review's research question appropriately considered? yes Did the reviewers avoid emphasizing results on the basis of their statistical significance? Probably yes Risk of bias in the review: LOW **Other information** Conflict of interest: none

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Search dates not reported. **Source of funding** Cancer Research UK, the British Heart Foundation, and the UK Medical Research Council.	Not reported	Chest wall RT: 36 Gy (3 Gy/f) o or m Supraclavicular (SC) and axillary fossa (AF) RT: 39-45 Gy (3.3-3.8 Gy/f) m Other adjuvant therapy: doxorubicin and cyclophosphamide Faber 1979 (Dusseldorf U) N=88 Type of breast surgery: Patey mastectomy Axillary surgery: axillary dissection Chest wall RT: 40 Gy (2 Gy/f) c Supraclavicular (SC) and axillary fossa (AF) RT: 40 Gy (2 Gy/f) c Other adjuvant therapy: LMF Fisher 1980 and Deutsch 2008 (NSABP B-04) N=770	that the median number of resected nodes was ≥10. Women with less extensive axillary surgery were classified as having axillary sampling.	Stewart 2001 (Scottish D): 1/5 vs 3/7; O-E not reported Comparison. CWRT + lymph nodes vs no RT following mastectomy + axillary dissection or axillary sampling in women with node-negative disease (N=1594) Ratio of annual event rates, results reported as events/ women *[Subgroup: Axillary dissection]* Host 1986 (Oslo X-ray): 57/175 vs 62/174; O-E: 0.0 (1.0) Shapiro 1998 (DFCI Boston): 1/8 vs 1/2; O-E: not reported McArdle 2010 (Glasgow): 0/1 vs 0/1; O-E: not reported Killander 2007 (S. Sweden): 6/134 vs 3/144; O-E: 1.7 (2.2) Papaioannou 1985 (Metaxas Athens): 0/5 vs 0/5; O-E: not reported Andersson 1999 (DBCG 82b): 1/8 vs 0/10; O-E: 0.4 (0.2) Overgaard 1999 (DBCG 82c): 0/6 vs 0/12; O-E: not reported Olson 1997 (ECOG EST3181): 0/9 vs 0/4; O-E: not reported *[Subgroup: Axillary sampling]*	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
		Type of breast surgery: simple (total) mastectomy Axillary surgery: axillary sampling Chest wall RT: 50 Gy (2 Gy/f) s Supraclavicular (SC) and axillary fossa (AF) RT: 45-50 Gy de (1.8-2.0 Gy/f) s Other adjuvant therapy: none Gyenes 1998 (Stockholm A) N=644 Type of breast surgery: modified radical mastectomy Axillary surgery: axillary sampling Chest wall RT: 45 Gy (1.8 Gy/f) e Supraclavicular (SC) and axillary fossa (AF) RT: 45 Gy de (1.8 Gy/f) c Other adjuvant therapy: none		Gyenes 1998 (Stockholm A): 4/203 vs 30/196; O-E: -13.2 (8.2) Turnbull 1978 (Southamptom UK): 3/23 vs 4/29: O-E: 0.5 (1.4) Stewart 1994 (Edinburgh I): 5/114 vs 24/114; O-E: -9.6 (6.9) Andersson 1999 (DBCG 82b): 0/36 vs 4/53; O-E: -1.6 (0.9) Overgaard 1999 (DBCG 82c): 2/49 vs 10/53; O-E: -3.5 (2.5) Comparison. CWRT + lymph nodes vs no RT following mastectomy + axillary dissection in women with 1-3 pathologically positive nodes (N=1314; RT n=632; no RT n=682) *[sub-group analysis: tumour grade]* Low grade: 4/64 vs 7/48; O-E: -2.5 (2.2) Intermediate grade: 4/81 vs 21/95; O-E: -7.5 (5.5.) High grade: 1/50 vs 9/57; O-E: -3.0 (2.3) *[Sub-group analysis: tumour size]* 1 to 19 mm: 4/138 vs 26/148; O-E: -10.4 (7.0) 20 to 49 mm: 5/148 vs 37/187; O-E: -13.6 (9.6)	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
		Host 1986 (Oslo X-ray) N=552 Type of breast surgery: radical mastectomy Axillary surgery: axillary dissection Chest wall RT: 25-41 Gy (1.3-2.1 Gy/f) o Supraclavicular (SC) and axillary fossa (AF) RT: 36 Gy (1.8 Gy/f) o, SC; 18 Gy (u Gy/f) o, AF Other adjuvant therapy: ovarian RT Houghton 1994 (Kings/ Cambridge) N=2800 Type of breast surgery: simple (total) mastectomy Axillary surgery: axillary sampling Chest wall RT: 28.5-46 Gy (1.5-3.2 Gy/f) o or s Supraclavicular (SC) and axillary fossa		50+ mm: 2/32 vs 5/28; O-E: -2.1 (1.1) Comparison. CWRT + lymph nodes vs no RT following mastectomy + axillary dissection or axillary sampling in women with 1-3 pathologically positive nodes (N=2801) Ratio of annual event rates, results reported as events/ women *[Subgroup: Axillary dissection]* Host 1986 (Oslo X-ray): 0/80 vs 6/73; O-E: -3.1 (1.5) Shapiro 1998 (DFCI Boston): 1/37 vs 3/41; O-E:-0.9 (1.0) Velez-Garcia 1992 (SECSG 1): 0/1 vs 0/00; O-E: not reported McArdle 2010 (Glasgow): 3/70 vs 19/69; O-E: -8.1 (5.2) Killander 2007 (S. Sweden): 41/140 vs 25/155; O-E: -10.6 (6.9) Ragaz 1997 (BCCA Vancouver): 7/91 vs 14/92; O-E: -3.6 (5.0) Papaioannou 1985 (Metaxas Athens): 0/7 vs 1/11: O-E:-0.5 (0.2) Saarto 1997 (Helsinki): 1/29 vs 10/38; O-E: -3.6 (2.6) Andersson 1999 (DBCG 82b): 1/83 vs 13/79; O-E: -6.3 (3.1)	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
		(AF) RT: 28.5-46 Gy (1.5-3.2 Gy/f) o or s Other adjuvant therapy: none Katz 2000 (MD Ander, 7730 B) N=97 Type of breast surgery: modified radical mastectomy or simple (total) mastectomy Axillary surgery: axillary dissection (n=80) or axillary sampling (n=17) Chest wall RT: 45-50 Gy (1.8-2.0 Gy/f) c Supraclavicular (SC) and axillary fossa (AF) RT: 45-50 Gy (1.8-2.0 Gy/f) c Other adjuvant therapy: bCG+FAC or FAC Killander2007 (S Swedish BCG) N=771		Overgaard 1999 (DBCG 82c): 1/53 vs 19/75; O-E: -7.3 (4.7) Olson 1997 (ECOG EST3181): 1/34 vs 2/36; O-E:-0.6 (0.7) *[Subgroup: Axillary sampling]* Gyenes 1998 (Stockholm A): 5/43 vs 12/42; O-E: -3.7 (3.8) De Oliveira 1984 (Coimbra): 1/28 vs 4/29; O-E: -1.4 (1.2) Andersson 1999 (DBCG 82b): 12/344 vs 82/322; O-E: -38.3 (24.4) Overgaard 1999 (DBCG 82c): 11/245 vs 59/240; O-E: -25.6 (16.9) Schmoor 2002 (GBSG 03 Germany): 1/62 vs 5/57; O-E: -2.3 (1.5) Comparison. CWRT + lymph nodes vs no RT following mastectomy + axillary dissection in women with 4+ pathologically positive nodes (N=1772; RT n=893; no RT n=879) *[sub-group analysis: tumour grade]* Low grade: 3/36 vs 8/37; O-E: -2.1 (2.0) Intermediate grade: 4/104 vs 34/103; O-E: -16.4 (8.3) High grade: 7/83 vs 24/80; O-E: -7.8 (7.1)	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
		Type of breast surgery: modified radical mastectomy Axillary surgery: axillary dissection Chest wall RT: 38 Gy (1.9 Gy/f) e,o,m or c Supraclavicular (SC) and axillary fossa (AF) RT: 48-60 Gy (2.4 Gy/f) c or m Other adjuvant therapy: Premenopausal: cyclophosphamide,; Postmenopausal: tamoxifen Lythgoe 1982 (Manchester RBS1) N=714 Type of breast surgery: simple (total) mastectomy Axillary surgery: axillary sampling Chest wall RT: 30-37 Gy (2-2.5 Gy/f) o Supraclavicular (SC) and axillary fossa		*[Sub-group analysis: tumour size]* 1 to 19 mm: 6/93 vs 22/101; O-E: -8.1 (6.5) 20 to 49 mm: 19/227 vs 55/199; O-E: -22.1 (16.3) 50+ mm.: 7/118 vs 31/131; O-E: -9.2 (7.5) *[Sub-group analysis: number of positive nodes]* 4 to 9: 20/267 vs 60/246; O-E: -22.8 (17.9) 10+: 15/201 vs 52/205; O-E: -18.4 (15.3) Comparison. CWRT + lymph nodes vs no RT following mastectomy + axillary dissection or axillary sampling in women with 4+ pathologically positive nodes (N=2557) Ratio of annual event rates, results reported as events/ women *[Subgroup: Axillary dissection]* Host 1986 (Oslo X-ray): 0/30 vs 4/20; O-E: -2.2 (0.9) Shapiro 1998 (DFCI Boston): 5/55 vs 14/56; O-E: -4.0 (4.2) Muss 1991 (Piedmont): 6/65 vs 9/55; O-E: -16 (2.9)	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
		(AF) RT: 37-40 Gy (2.5-2.7 Gy/f) o or m Other adjuvant therapy: ovarian ablation McArdle 2010 (Glasgow) N=219 Type of breast surgery: simple (total) mastectomy Axillary surgery: axillary dissection Chest wall RT: 37.8 Gy (2.5 Gy/f) o Supraclavicular (SC) and axillary fossa (AF) RT: 37.8 Gy (2.5 Gy/f) o Other adjuvant therapy: cyclophosphamide, methotrexate and fluorouracil Muss 1991 (Piedmont OA) N=120 Type of breast surgery: modified radical mastectomy or radical mastectomy		Velez-Garcia 1992 (SECSG 1): 12/125 vs 18/129; O-E: -3.5 (7.1) McArdle 2010 (Glasgow): 11/40 vs 10/31; O-E: -0.8 (4.6) Killander 2007 (S. Sweden): 5/85 vs 11/73; O-E: -4.2 (3.7) Ragaz 1997 (BCCA Vancouver): 8/60 vs 17/54; O-E: -6.1 (5.7) Faber 1979 (Dusseldorf U.): 0/34 vs 1/54; O-E: -0.4 (0.2) Papaioannou 1985 (Metaxas Athens): 4/18 vs 3/25; O-E: 0.5 (1.7) Saarto 1997 (Helsinki): 3/16 vs 2/9; O-E: -0.3 (0.7) Andersson 1999 (DBCG 82b): 8/110 vs 29/128; O-E: -10.8 (8.4) Overgaard 1999 (DBCG 82c): 5/104 vs 27/94; O-E: -12.3 (7.4) Olson 1997 (ECOG EST3181): 11/127 vs 27/121; O-E: -8.3 (8.8) *[Subgroup: Axillary sampling]* De Oliveira 1984 (Coimbra): 5/32 vs 4/29; O-E: 0.5 (1.8) Andersson 1999 (DBCG 82b): 10/146 vs 50/143; O-E: -22.4 (13.6) Overgaard 1999 (DBCG 82c): 6/127 vs 60/140; O-E: -28.8 (15.0)	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
		Axillary surgery: axillary dissection Chest wall RT: 50 Gy (1.5-1.8 Gy/f) c or m Supraclavicular (SC) and axillary fossa (AF) RT: 45-50 Gy (1.5-2.8 Gy/f) c or m Other adjuvant therapy: melphalan or cyclophosphamide, methotrexate and fluorouracil Olson 1997 (ECOG EST3181) N=332 Type of breast surgery: modified radical mastec tomy or radical mastectomy Axillary surgery: axillary dissection Chest wall RT: 46 Gy (2 Gy/f) c or m Supraclavicular (SC) and axillary fossa (AF) RT: 46-50 Gy (2 Gy/f) c or m Other adjuvant therapy: doxorubicin,		Schmoor 2002 (GBSG 03 Germany): 1/34 vs 6/43; O-E: -1.9 (1.7) **Treatment-related morbidity (critical)** Not reported **Overall survival (%) (critical)** ***20-year risk of all-cause mortality*** Comparison. CWRT + lymph nodes vs no RT following mastectomy w/o axillary surgery in women with clinically node-negative disease (N=2904) Ratio of annual death rates, results reported as deaths/ women Houghton 1994 (Kings/ Cambridge): 740/996 vs 762/1049; O-E: 15.3 (355.4) Fisher 1980 (NSABP B-04): 279/386 vs 266/384; O-E:11.9 (124.1) Stewart 2001 (Scottish D): 24/42 vs 27/39; O-E:1.0 (10.2) Comparison. CWRT + lymph nodes vs no RT following mastectomy w/o axillary surgery in women with clinically node-positive disease	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
		cyclophosphamide and fluorouracil, & halotestin, and tamoxifen Overgaard 1999 (Danish BCG 82c post) N=1463 Type of breast surgery: simple (total) mastectomy Axillary surgery: axillary dissection (n=344) or axillary sampling (n=1119) Chest wall RT: 36-50 Gy (1.8-2.2 Gy/f) o or e Supraclavicular (SC) and axillary fossa (AF) RT: 36-50 Gy (1.8-2.2 Gy/f) o or m Other adjuvant therapy: tamoxifen Papaioannou 1985 (Metaxas Athens) N=71 Type of breast surgery: modified radical mastectomy, Patey		Ratio of annual deaths, results reported as deaths/ women Lythgoe 1982 (Manchester RBS1): 274/355 vs 286/359; O-E:-11.9 (130.0) Houghton 1994 (Kings/ Cambridge): 303/380 vs 316/375; O-E: -14.4 (140.5) Stewart 2001 (Scottish D): 5/5 vs 4/7; O-E:0.5 (0.2) Comparison. CWRT + lymph nodes vs no RT following mastectomy + axillary dissection or axillary sampling in women with node-negative disease (N=1594) Ratio of annual death rates, results reported as deaths/ women *[Subgroup: Axillary dissection]* Host 1986 (Oslo X-ray): 148/175 vs 150/174; O-E: 11.3 (64.7) Shapiro 1998 (DFCI Boston): 1/8 vs 1/2; O-E:-0.3 (0.2) McArdle 2010 (Glasgow): 1/1 vs 1/1; O-E:0.5 (0.2) Katz 2000 (MD Ander): 0/1 vs 0/1; O-E: not reported Killander 2007 (S. Sweden): 78/134 vs 73/144; O-E: 8.7 (35.2)	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
		mastectomy or radical mastectomy Axillary surgery: axillary dissection Chest wall RT: 45-60 Gy (2 Gy/f) m Supraclavicular (SC) and axillary fossa (AF) RT: 45-60 Gy (2 Gy/f) m Other adjuvant therapy: cyclophospha mide, doxorrubicin, methotrexate and fluorouracil & tam Premen: ovarian RT Ragaz 1997 (BCCA Vancouver) N=318 Type of breast surgery: modified radical mastectomy Axillary surgery: axillary dissection Chest wall RT: 37.5-40 Gy (2.3 Gy/f) c or m Supraclavicular (SC) and axillary fossa (AF) RT: 37.5 Gy de (2.2 Gy/f) c or m		Papaioannou 1985 (Metaxas Athens): 2/5 vs 1/5; O-E: 0.3 (0.2) Andersson 1999 (DBCG 82b): 3/8 vs 4/10; O-E: -0.2 (1.3) Overgaard 1999 (DBCG 82c): 6/6 vs 7/12; O-E:1.8 (2.6) Olson 1997 (ECOG EST3181): 3/9 vs 1/4; O-E:-0.2 (0.7) *[Subgroup: Axillary sampling]* Gyenes 1998 (Stockholm A): 153/203 vs 145/196; O-E:-0.6 (68.3) Turnbull 1978 (Southamptom UK): 16/23 vs 20/29; O-E:1.7 (6.8) Stewart 1994 (Edinburgh I): 87/114 vs 83/114; O-E:2.8 (38.0) Andersson 1999 (DBCG 82b): 11/36 vs 19/53; O-E:-2.9 (6.4) Overgaard 1999 (DBCG 82c): 31/49 vs 30/53; O-E:-1.3 (14.1) Comparison. CWRT + lymph nodes vs no RT following mastectomy + axillary dissection or axillary sampling in women with 1-3 pathologically positive nodes (N=2801) Ratio of annual death rates, results reported as deaths/ women *[Subgroup: Axillary dissection]*	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
		Other adjuvant therapy: cyclophosphamide, methotrexate, fluorouracil and prednisone +ovarian RT or cyclophosphamide, methotrexate and fluorouracil Saarto 1997 (Helsinki) N=99 Type of breast surgery: radical mastec tomy Axillary surgery: axillary dissection Chest wall RT: 45 Gy (3 Gy/f) c Supraclavicular (SC) and axillary fossa (AF) RT: 45 Gy (3 Gy/f) c, SC; 45 Gy (3 Gy/f) c, AF Other adjuvant therapy: doxorubicin, cyclophosphamide and Ftorafur Schmoor 2002 (GBSG03 Germany)		Host 1986 (Oslo X-ray): 71/80 vs 65/73; O-E: 1.4 (29.6) Shapiro 1998 (DFCI Boston): 14/37 vs 12/41; O-E: 2.0 (5.4) Velez-Garcia 1992 (SECSG 1): 0/1 vs 0/0; O-E: not reported McArdle 2010 (Glasgow): 45/70 vs 52/69; O-E:-3.2 (20.6) Katz 2000 (MD Ander): 5/7 vs 7/13; O-E:0.6 (1.3) Killander 2007 (S. Sweden): 80/140 vs 99/155; O-E:-11.2 (40.1) Ragaz 1997 (BCCA Vancouver): 41/91 vs 49/92; O-E:-6.4 (21.4) Papaioannou 1985 (Metaxas Athens): 3/7 vs 6/11; O-E:-1.1 (1.2) Saarto 1997 (Helsinki): 10/29 vs 20/38; O-E:-0.6 (5.9) Andersson 1999 (DBCG 82b): 26/83 vs 36/79; O-E:-7.8 (13.9) Overgaard 1999 (DBCG 82c): 33/53 vs 45/75; O-E:0.5 (17.8) Olson 1997 (ECOG EST3181): 24/34 vs 16/36; O-E:7.1 (8.8) *[Subgroup: Axillary sampling]* Gyenes 1998 (Stockholm A): 32/43 vs 35/42; O-E:-0.9 (15.1) Katz 2000 (MD Ander): 4/4 vs 3/4; O-E:0.0. (0.5)	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
		N=199 Type of breast surgery: Patey mastectomy Axillary surgery: axillary sampling Chest wall RT: 50 Gy (2 Gy/f) c or m Supraclavicular (SC) and axillary fossa (AF) RT: 50 Gy (2 Gy/f) c or m Other adjuvant therapy: cyclophosphamide, methotrexate and fluorouracil Shapiro 1998 (DFCI Boston) N=218 Type of breast surgery: modified radical mastectomy or radical mastectomy Axillary surgery: axillary dissection Chest wall RT: 45 Gy (2.3 Gy/f) c or m Supraclavicular (SC) and axillary fossa (AF) RT: 45 Gy (2.3 Gy/f) c or m		De Oliveira 1984 (Coimbra): 15/28 vs 18/29; O-E: -1.0 (7.1) Andersson 1999 (DBCG 82b): 175/344 vs 199/322; O-E:-23.2 (85.2) Overgaard 1999 (DBCG 82c): 165/245 vs 176/240; O-E:-14.5 (77.9) Schmoor 2002 (GBSG 03 Germany): 22/62 vs 21/57; O-E:0.4 (9.4) Comparison. CWRT + lymph nodes vs no RT following mastectomy + axillary dissection or axillary sampling in women with 4+ pathologically positive nodes (N=2557) Ratio of annual death rates, results reported as deaths/ women *[Subgroup: Axillary dissection]* Host 1986 (Oslo X-ray): 30/30 vs 20/20; O-E:-6.6 (6.3) Shapiro 1998 (DFCI Boston): 35/55 vs 39/56; O-E: 0.9 (16.0) Muss 1991 (Piedmont): 41/65 vs 41/55; O-E: -1.6 (15.2) Velez-Garcia 1992 (SECSG 1): 60/125 vs 69/129; O-E: -3.2 (26.9) McArdle 2010 (Glasgow): 32/40 vs 29/31; O-E: -4.2 (10.8)	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
		Other adjuvant therapy: 5 or 10 cycles of doxorubicin and cyclophosphamide; or cyclophosphamide, methotrexate and fluorouracil or methotrexate and fluorouracil Stewart 1994 (Edinburgh I) N=348 Type of breast surgery: simple (total) mastectomy Axillary surgery: axillary sampling Chest wall RT: 42.5-45.0 Gy (4.25-4.5 Gy/f) m Supraclavicular (SC) and axillary fossa (AF) RT: 42.5-45.0 Gy (4.25-4.5 Gy/f) m Other adjuvant therapy: fluorouracil Stewart 2001 (Scottish D) N=93		Katz 2000 (MD Ander): 19/24 vs 17/30; O-E: 5.9 (5.9) Killander 2007 (S. Sweden): 69/85 vs 62/73; O-E: -5.0 (27.4) Ragaz 1997 (BCCA Vancouver): 40/60 vs 46/54; O-E: -7.9 (18.6) Faber 1979 (Dusseldorf U.): 17/34 vs 24/54; O-E: 3.3 (7.8) Papaioannou 1985 (Metaxas Athens): 8/18 vs 15/25; O-E: -2.4 (4.7) Saarto 1997 (Helsinki): 12/16 vs 3/9; O-E: 3.0 (2.6) Andersson 1999 (DBCG 82b): 85/110 vs 108/128; O-E: -9.2 (40.8) Overgaard 1999 (DBCG 82c): 89/104 vs 86/94; O-E: -1.6 (36.3) Olson 1997 (ECOG EST3181): 94/127 vs 96/121; O-E: -2.9 (41.3) *[Subgroup: Axillary sampling]* Katz 2000 (MD Ander): 1/3 vs 3/6; O-E: not reported De Oliveira 1984 (Coimbra): 24/32 vs 21/29; O-E: 3.2 (7.5) Andersson 1999 (DBCG 82b): 109/146 vs 132/143; O-E: -23.2 (48.7) Overgaard 1999 (DBCG 82c): 107/127 vs 131/140; O-E: -10.2 (49.3)	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
		Type of breast surgery: simple (total) mastectomy Axillary surgery: axillary sampling Chest wall RT: 37-45 Gy (2.3-3.7 Gy/f) o or m Supraclavicular (SC) and axillary fossa (AF) RT: 38.4-45.9 Gy (2.3-3.8 Gy/f) o or m Other adjuvant therapy: tamoxifen or none Turnbull 1978 (Southampton UK) N=151 Type of breast surgery: simple (total) mastectomy Axillary surgery: axillary sampling Chest wall RT: 46 Gy (2.3 Gy/f) c Supraclavicular (SC) and axillary fossa (AF) RT: 55 Gy (2.5 Gy/f) c & b Other adjuvant therapy: none		Schmoor 2002 (GBSG 03 Germany): 23/34 vs 27/43; O-E: 0.9 (10.5) **Disease-free survival (important)** ***20-year breast cancer mortality rate*** Comparison. CWRT + lymph nodes vs no RT following mastectomy w/o axillary surgery in women with clinically node-negative disease (N=2904) Ratio of annual death rates, results reported as deaths/ women Houghton 1994 (Kings/ Cambridge): 523/996 vs 590/1049; O-E: -3.7 (270.0) Fisher 1980 (NSABP B-04): 169/386 vs 181/384; O-E: -6.5 (81.3) Stewart 2001 (Scottish D): 18/42 vs 17/39; O-E: -0.2 (7.6) Comparison. CWRT + lymph nodes vs no RT following mastectomy w/o axillary surgery in women with clinically node-positive disease Ratio of annual deaths, results reported as deaths/ women	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
		Velez-Garcia 1992 (SECSG 1) N=257 Type of breast surgery: modified radical mastectomy or radical mastectomy Axillary surgery: axillary dissection Chest wall RT: 50 Gy (2 Gy/f) u Supraclavicular (SC) and axillary fossa (AF) RT: 50 Gy (2 Gy/f) u Other adjuvant therapy: cyclophosphamide, methotrexate and fluorouracil		Lythgoe 1982 (Manchester RBS1): 178/355 vs 215/359; O-E: -14.5 993.7) Houghton 1994 (Kings/ Cambridge): 235/380 vs 255/375; O-E: -17.3 (114.6) Stewart 2001 (Scottish D): 3/5 vs 4/7; O-E: 0.5 (0.2) Comparison. CWRT + lymph nodes vs no RT following mastectomy + axillary dissection or axillary sampling in women with node-negative disease (N=1594) Ratio of annual death rates, results reported as deaths/ women *[Subgroup: Axillary dissection]* Host 1986 (Oslo X-ray): 57/175 vs 62/174; O-E:-2.0 (27.3) Shapiro 1998 (DFCI Boston): 1/8 vs 1/2; O-E: -0.3 (0.2) McArdle 2010 (Glasgow): 1/1 vs 0/1; O-E: 0.5 (0.2) Katz 2000 (MD Ander): 0/1 vs 0/1; O-E: not reported Killander 2007 (S. Sweden): 42/134 vs 34/144; O-E: 8.5 (18.2) Papaioannou 1985 (Metaxas Athens): 1/5 vs 1/5; O-E: 0.3 (0.2)	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Andersson 1999 (DBCG 82b): 3/8 vs 3/10; O-E: -0.2 (1.3) Overgaard 1999 (DBCG 82c): 4/6 vs 4/12; O-E: 1.6 (1.5) Olson 1997 (ECOG EST3181): 2/9 vs 1/4; O-E: -0.4 (0.5) *[Subgroup: Axillary sampling]* Gyenes 1998 (Stockholm A): 77/203 vs 75/196; O-E: 2.5 (35.7) Turnbull 1978 (Southamptom UK): 8/23 vs 13/29; O-E: -0.6 (4.0) Stewart 1994 (Edinburgh I): 44/114 vs 50/114; O-E: -1.5 (20.7) Andersson 1999 (DBCG 82b): 6/36 vs 14/53; O-E: -3.3 (4.2) Overgaard 1999 (DBCG 82c): 19/49 vs 19/53; O-E: 0.6 (8.9) Comparison. CWRT + lymph nodes vs no RT following mastectomy + axillary dissection or axillary sampling in women with 1-3 pathologically positive nodes (N=2801) Ratio of annual death rates, results reported as deaths/ women *[Subgroup: Axillary dissection]* Host 1986 (Oslo X-ray): 41/80 vs 45/73; O-E: -2.0 (19.5)	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Shapiro 1998 (DFCI Boston): 9/37 vs 12/41; O-E: 0.2 (4.6) Velz-Garcia 1992 (SECSG 1): 0/1 vs 0/0; O-E: not reported McArdle 2010 (Glasgow): 33/70 vs 42/69; O-E: -4.1 (15.8) Katz 2000 (MD Ander): 5/7 vs 7/13; O-E: 0.6 (1.3) Killander 2007 (S. Sweden): 48/140 vs 75/155; O-E: -14.0 (27.3) Ragaz 1997 (BCCA Vancouver): 34/91 vs 45/92; O-E: -6.8 (19.0) Papaioannou 1985 (Metaxas Athens): 3/7 vs 6/11; O-E: -1.1 (1.2) Saarto 1997 (Helsinki): 9/29 vs 16/38; O-E: -1.1 (5.4) Andersson 1999 (DBCG 82b): 25/83 vs 31/79; O-E: -5.3 (12.5) Overgaard 1999 (DBCG 82c): 22/53 vs 35/75; O-E: -0.6 (12.7) Olson 1997 (ECOG EST3181): 19/34 vs 11/36; O-E: 5.8 (6.7) *[Subgroup: Axillary sampling]* Gyenes 1998 (Stockholm A): 23/43 vs 32/42; O-E: -1.6 (12.8) Katz 2000 (MD Ander): 4/4 vs 3/4; O-E: 0.0. (0.5) De Oliveira 1984 (Coimbra):8/28 vs 13/29; O-E: -1.7 (4.5)	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Andersson 1999 (DBCG 82b): 153/344 vs 188/322; O-E: -28.6 (78.4) Overgaard 1999 (DBCG 82c): 126/245 vs 138/240; O-E: -12.1 (59.6) Schmoor 2002 (GBSG 03 Germany): 16/62 vs 20/57; O-E: -1.6 (7.8) Comparison. CWRT + lymph nodes vs no RT following mastectomy + axillary dissection or axillary sampling in women with 4+ pathologically positive nodes (N=2557) Ratio of annual death rates, results reported as deaths/ women *[Subgroup: Axillary dissection]* Host 1986 (Oslo X-ray): 27/30 vs 18/20; O-E: -5.9 (5.6) Shapiro 1998 (DFCI Boston): 30/55 vs 37/56; O-E: -0.2 (14.6) Muss 1991 (Piedmont): 36/65 vs 40/55; O-E: -3.5 (14.3) Velez-Garcia 1992 (SECSG 1): 54/125 vs 65/129; O-E: -3.7 (24.7) McArdle 2010 (Glasgow): 30/40 vs 27/31; O-E: -3.9 (9.8) Katz 2000 (MD Ander): 18/24 vs 17/30; O-E: 5.4 (5.7)	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Killander 2007 (S. Sweden): 58/85 vs 56/73; O-E: -4.6 (23.9) Ragaz 1997 (BCCA Vancouver): 37/60 vs 46/54; O-E: -8.8 (18.0) Faber 1979 (Dusseldorf U.): 14/34 vs 14/54; O-E: 4.9 (5.1) Papaioannou 1985 (Metaxas Athens): 8/18 vs 15/25; O-E: -2.4 (4.7) Saarto 1997 (Helsinki): 11/16 vs 2/9; O-E: 2.8 (2.1) Andersson 1999 (DBCG 82b): 79/110 vs 107/128; O-E: -11.5 (39.1) Overgaard 1999 (DBCG 82c): 81/104 vs 81/94; O-E: -0.4 (33.9) Olson 1997 (ECOG EST3181): 84/127 vs 80/121; O-E: 0.1 (35.7) *[Subgroup: Axillary sampling]* Katz 2000 (MD Ander): 1/3 vs 3/6; O-E: 2.1 (6.7) De Oliveira 1984 (Coimbra): 21/32 vs 20/2; O-E -24.8 (46.4) Andersson 1999 (DBCG 82b): 101/146 vs 130/143; O-E: -4.1 (44.7) Overgaard 1999 (DBCG 82c): 98/127 vs 116/140; O-E: -0.3 (8.5)	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Schmoor 2002 (GBSG 03 Germany): 18/34 vs 24/43; O-E: not reported **Treatment–related mortality (important)** Not reported **Health related quality of life (important)** Not reported	
Full citation Killander, F., Anderson, H., Kjellen, E., Malmstrom, P., 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, European journal of	**Sample size** N=1119 pre- and post-menopausal women with breast cancer **Characteristics** Pre-menopausal women who received RT only median age: 47 years	**Interventions** Patients were randomised to one of 6 options, based on menopausal status. Pre-menopausal patients were randomised to: radiotherapy RT RT + oral cyclophosphamide for one year	**Details** Sample selection and data collection: In 2003 all patients' hospital records were monitored for treatment details. In 2010 an update of mortality, cause of death and morbidity was made using the unique national personal identification numbers and the following registries.	**Results** Treatment related mortality: number of deaths from heart disease, at 25 years follow-up (heart disease including ischaemic heart disease, congestive heart failure, dysrhythmias and non-rheumatic valvular and pericardial disease) pre-menopausal: RT: 11/ 243 no RT: 0/122	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
cancer, 50, 2201-2210, 2014 **Ref Id** 566414 **Country/ies where the study was carried out** Sweden **Study type** Follow-up of an RCT (South Sweden Breast Cancer group) **Aim of the study** To evaluate long-term morbidity and mortality in people treated with postmastectomy radiotherapy. **Study dates** 1978 to 1985 **Source of funding** Swedish cancer society , Skane university Hospital Research Foundation, Goverment, and the Swedish Breast Cancer Association	median tumour size: 25 mm pN0: 33% pN1-3: 46% pN≥4: 19% Pre-menopausal women who received RT + chemotherapy median age: 47 years median tumour size: 25 mm pN0: 33% pN1-3: 46% pN≥4: 20% Pre-menopausal women who received chemotherapy only median age: 46 years median tumour size: 26 mm pN0: 34%	or cyclophosphamide only Post-menopausal patients were randomised to: RT RT +Tamoxifen for one year Tamoxifen only RT: The radiotherapy technique consisesd in specified absorbed target doses were 38 Gy to the chest wall, 48 Gy to the axilla and parasternal lymph nodes and 45 Gy to the supra- and infraclavicular fossae. All fields were treated in 20 fractions. The treatment was given concomitantly with radiotherapy to those patients allocated combined treatment. Chemotherapy was given in 12 courses of oral cyclophosphamide (Sendoxan®) 130 mg/m^2 days 1–14 in 28 day cycles.	All diagnoses were classified according to ICD-8,9,10 for the following: (1) breast cancer (2) heart disease including ischaemic heart disease, congestive heart failure, dysrhythmias and non-rheumatic valvular and pericardial disease (3) cerebrovascular disease including intra-cerebral bleeding, emboli, thrombosis but excluding spontaneous subarachnoidal bleeding or traumatic bleeding since we do not consider them to be side-effects of radiotherapy (4) lung disease, excluding pneumothorax and pleurisy (5) heart surgery (coronary by-pass and valvular surgery) and invasive diagnostic procedures e.g. coronary angiography and pacemaker implantation. Statistical analysis	post-menopausal: RT: 79/439 no RT: 26/240 Treatment related mortality: number of deaths from lung disease, at 25 years follow-up (lung disease, excluding pneumothorax and pleurisy) pre-menopausal: RT: 2/ 243 no RT: 1/122 post-menopausal: RT: 6/439 no RT: 2/240	Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: low risk (<20% loss to follow-up; per protocol analysis was used for side effects) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** Conflict of interest: none

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	pN1-3: 40% pN≥4: 21% Post-menopausal who received RT only median age: 63 years median tumour size: 25 mm pN0: 41% pN1-3: 41% pN≥4: 16% Post-menopausal who received RT + tamoxifen median age: 63 years median tumour size: 22 mm pN0: 40% pN1-3: 37% pN≥4: 21% **Inclusion criteria**	Tamoxifen was given in doses of 10 mg tamoxifen (Nolvadex®) orally three times daily for one year.	Logrank tests were used to compare overall mortality, cause specific mortality and first admission to hospital due to different diseases. To evaluate the effect of RT, the RT + C arm was compared with the C arm and the RT + Tam arm was compared with the Tam arm, in the pre and post-menopausal patients, respectively. Death due to heart disease was also studied by comparing RT for left and right sided breast cancer using logrank tests stratified by, respectively, +/− C and +/− Tam. ITT was used to report overall mortality and breast cancer mortality; whereas per protocol analysis was used for side-effects. Per-protocol population = 1044.		

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
	Invasive mammary adenocarcinoma T1N+ or T2N0/N+ **Exclusion criteria** Not reported				
Full citation Muss, H. B., Cooper, M. R., Brockschmidt, J. K., Ferree, C., Richards, Ii F., White, D. R., Jackson, D. V., Spurr, C. L., A randomized trial of chemotherapy (L-PAM vs CMF) and irradiation for node positive breast cancer. Eleven year follow-up of a Piedmont Oncology Association trial, Breast Cancer Research and Treatment, 19, 77-84, 1991 **Ref Id** 669762 **Country/ies where the study was carried out** USA **Study type**	**Sample size** See EBCTCG 2014 (Piedmont AO trial). **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014 (Piedmont AO trial).	**Details** -	**Results** See EBCTCG 2014 (Piedmont AO trial). No other outcomes reported.	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: unclear (not reported) Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
RCT - Included in EBCTCG 2014. **Aim of the study** - **Study dates** - **Source of funding** -					Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** This study (Piedmont OA) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation Velez-Garcia, E., Carpenter Jr, J. T., Moore, M., Vogel, C. L., Marcial, V., Ketcham, A., Singh, K. P., Bass, D., Bartolucci, A. A., Smalley, R., Postsurgical adjuvant chemotherapy with or without radiotherapy in women with breast cancer and positive axillary nodes: A South-Eastern Cancer Study Group (SEG) trial, European Journal of Cancer Part A: General Topics, 28, 1833-1837, 1992	**Sample size** See EBCTCG 2014 (SECSG 1 trial). **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014 (SECSG 1 trial).	**Details** -	**Results** See EBCTCG 2014 (SECSG 1 trial). No additional outcomes reported.	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: low risk (randomisation was done by telephone to the SEG statistical centre. Treatment was assigned from computer-generated lists) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Ref Id 669799 **Country/ies where the study was carried out** Puerto Rico **Study type** RCT - Included in EBCTCG 2014. **Aim of the study** - **Study dates** - **Source of funding** -					Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: Low risk (Low loss of follow-up was <20%, the study did not report if ITT analysis used) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** This study (SECSG 1 trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation Houghton, J., Baum, M., Haybittle, J. L., Role of radiotherapy following total mastectomy in patients with early breast cancer, World Journal of Surgery, 18, 117-122, 1994	**Sample size** See EBCTCG 2014 (CRC, UK trial) **Characteristics** - **Inclusion criteria**	**Interventions** See EBCTCG 2014 (CRC, UK trial)	**Details** -	**Results** See EBCTCG 2014 (CRC, UK trial) Other outcomes reported in the study Treatment related mortality: cardiac deaths	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: high risk (there were concerns regarding the randomization of 390 out of 2800 patients, as the validity of the randomization

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Ref Id 669843 **Country/ies where the study was carried out** UK **Study type** RCT - Included in EBCTCG 2014. **Aim of the study** - **Study dates** - **Source of funding** -	- **Exclusion criteria** -			Results are presented RT vs no RT All patients: RR 1.52 (1.01 to 2.29) Left: RR 1.92 (1.09 to 3.39) Right: RR 1.19 (0.66 to 2.14)	procedure had been questioned. However this 490 patients are included in the analysis, as their characteristics do not differ between groups) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: unclear (not reported, unclear if IIT analysis was used) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** This study (CRC, UK trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Stewart, H. J., Jack, W. J. L., Everington, D., Forrest, A. P. M., Rodger, A., McDonald, C. C., Prescott, R. J., Langlands, A. O., South east Scottish trial of local therapy in node negative breast cancer, Breast, 3, 31-39, 1994 **Ref Id** 669862 **Country/ies where the study was carried out** UK **Study type** RCT - Included in EBCTCG 2014. **Aim of the study** - **Study dates** - **Source of funding** -	**Sample size** See EBCTCG 2014 (Edinburgh I trial). **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014 (Edinburgh I trial).	**Details** -	**Results** See EBCTCG 2014 (Edinburgh I trial). No additional outcomes reported.	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: low risk (stratification into 12 groups, randomization with a series of sealed envelopes held centrally) Allocation concealment: low risk (sealed envelopes) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: Low risk (Low loss of follow-up was <20%) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					This study (Edinburgh I trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation Olson, J. E., Neuberg, D., Pandya, K. J., Richter, M. P., Solin, L. J., Gilchrist, K. W., Tormey, D. C., Veeder, M., Falkson, G., The role of radiotherapy in the management of operable locally advanced breast carcinoma: Results of a randomized trial by the Eastern Cooperative Oncology Group, Cancer, 79, 1138-1149, 1997 **Ref Id** 669959 **Country/ies where the study was carried out** USA **Study type** RCT	**Sample size** See EBCTCG 2014 (ECOG EST3181 trial) **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014 (ECOG EST3181 trial)	**Details** -	**Results** See EBCTCG 2014 (ECOG EST3181 trial) No additional outcomes reported (the trial only reports toxicity in 1 arm)	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: unclear Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Aim of the study - **Study dates** - **Source of funding** -					Selective reporting: Low risk (All outcomes reported, however high risk for toxicity, as only reported in RT arm) Other bias Other sources of bias: none **Other information** This study (ECOG EST3181 trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation Papaioannou, A. N. Preoperative chemotherapy: advantages and clinical application in stage III breast cancer. Recent Results in Cancer Research, 98, 65-90. 1985 **Ref Id** 675418 **Country/ies where the study was carried out** USA **Study type**	**Sample size** See EBCTCG 2014 **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014	**Details** -	**Results** See EBCTCG 2014 No additional outcomes reported (the trial only reports toxicity in 1 arm)	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
RCT - Included in EBCTCG 2014. **Aim of the study** - **Study dates** - **Source of funding**					Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: unclear Reporting bias Selective reporting: Low risk Other bias Other sources of bias: none **Other information** This study was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation Ragaz, J., Jackson, S. M., Le, N., Plenderleith, I. H., Spinelli, J. J., Basco, V. E., Wilson, K. S., Knowling, M. A., Coppin, C. M. L., Paradis, M., Coldman, A. J., Olivotto, I. A., Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer, New England Journal of	**Sample size** See EBCTCG 2014 (BCCA Vancouver trial). **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014 (BCCA Vancouver trial).	**Details** -	**Results** See EBCTCG 2014 (BCCA Vancouver trial). Additional outcomes reported in the paper Adverse events: arm oedema requiring intervention RT: 6/164 no RT: 1/154	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Medicine, 337, 956-962, 1997 **Ref Id** 669962 **Country/ies where the study was carried out** USA **Study type** RCT - Included in EBCTCG 2014. **Aim of the study** - **Study dates** - **Source of funding** -				Adverse events: congestive heart failure RT: 1/164 no RT: 0/154 Adverse events: pneumonitis RT: 1/164 no RT: 0/154	Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: Low risk (Low loss of follow-up was <20% and ITT analysis used) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** This study (BCCA Vancouver trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation Hojris, I., Overgaard, M., Christensen, J. J., Overgaard, J., Morbidity	**Sample size** N=3083 women at high risk of breast	**Interventions** Premenopausal and menopausal women were randomly	**Details** Sample selection	**Results** **Comparison: chest wall RT vs no RT**	**Limitations** **The quality of this study was assessed using the Cochrane risk of bias tool.**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. Radiotherapy committee of the Danish Breast Cancer Cooperative Group, Lancet, 354, 1425-30, 1999 **Ref Id** 670008 **Country/ies where the study was carried out** Denmark **Study type** Analysis of 2 RCTs DBCG 82b and 82c) **Aim of the study** To assess morbidity and mortality from ischaemic heart disease following postmastectomy radiotherapy. **Study dates** 1982 to 1990	cancer following mastectomy **Characteristics** Not reported **Inclusion criteria** Age <70 years Mastectomy, including partial axillary dissection No evidence of metastatic disease No history of cancer Unilateral breast cancer High risk of breast-cancer recurrence because of 1 or more of positive lymph nodes, tumour size >5 cm, or invasion of the skin or pectoral fascia. **Exclusion criteria** Not reported	assigned, after mastectomy, 8cycles of cyclophosphamide 600 mg/m2, methotrexate 40 mg/m2, and fluorouracil 600 mg/m2, + radiotherapy, or 9 cycles of the same chemotherapy regimen alone. Postmenopausal women were randomly assigned, after mastectomy, to tamoxifen 30 mg daily + radiotherapy for 1 year, or tamoxifen alone. In all women, RT was delivered to the chest wall, including the surgical scar and regional lymph nodes (ie, supraclavicular, infraclavicular, axillary, and ipsilateral internal mammary nodes in the four upper intercostal spaces). Adherence to radiotherapy was high (96%).	The DBCG conducted 2 RTCs between 1982 and 1990 (DBCG b and c) with women at high risk of breast-cancer recurrence Data collection The study reported ischaemic heart disease morbidity and mortality. Morbidity was defined as hospital admission for any diagnosis of ischaemic heart disease according to ICD10; mortality was defined as primary cause of death. Relevant case records were checked for accuracy. The median potential follow-up time (time from entry date until the date of assessment) was 122 months (range 81–171), and the date for the assessment of ischaemic heart disease, recurrence, and	**Outcome: Ischaemic heart disease morbidity** All patients 46/1525 vs 49/1521; HR 0.86 (0.57–1.29) Left breast 22/755 vs 27/784; HR 0.78 (0.44–1.38) Right breast 24/770 vs 22/737; HR 0.96 (0.54–1.71) **Outcome: Death from ischaemic heart disease** All patients 12/1525 vs 13/1521; HR 0.84 (0.38–1.83) Left breast 5/755 vs 6/784; HR 0.81 (0.25–2.67) Right breast 7/770 vs 7/737; HR 0.85 (0.30–2.42) **Outcome: Acute myocardial infarction morbidity** All patients 26/1525 vs 22/152; HR 1.10 (0.62–1.94) Left breast 14/755 vs 13/784; HR 1.05 (0.49–2.23) Right breast 12/770 vs 9/737; HR 1.19 (0.50–2.83) **Outcome: Death from acute myocardial infarction** All patients 5/1525 vs 9/1521; HR 0.50 (0.17–1.50) Left breast 4/755 vs 5/784; HR 0.78 (0.21–2.91) Right breast 1/770 vs 4/737; HR 0.21 (0.02–1.89)	Selection bias - random sequence generation: low (as described in full publication Overgaard 1997 and Andersen 1988) Selection bias - allocation concealment: Reporting bias - performance bias: No blinding but unlikely to have a significant impact: Low Detection bias Low Attrition bias High: 122 deviated from treatment in TAM+OFS arm compared with 22 in TAM arm Selective reporting Low **Indirectness** The study includes direct population. **Other information** Conflict of interest: not reported

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding Danish Cancer Society			survival was Dec 31, 1996. Data analysis Morbidity and mortality of ischaemic heart disease was estimated using the Kaplan-Meier method. The authors used the relative hazard among women who had received RT compared with those who had not received RT to describe the relative risk of morbidity and mortality at the time of assessment (HR > 1 indicate an increased risk of morbidity or mortality among patients who received radiotherapy). Intention to treat analysis was used. SPSS v8.0 was used to conduct statistical analyses		

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Overgaard,M., Jensen,M.B., Overgaard,J., Hansen,P.S., Rose,C., Andersson,M., Kamby,C., Kjaer,M., Gadeberg,C.C., Rasmussen,B.B., Blichert-Toft,M., Mouridsen,H.T., Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial, Lancet, 353, 1641-1648, 1999 **Ref Id** 268073 **Country/ies where the study was carried out** **Study type** RCT - Included in EBCTCG 2014. **Aim of the study** - **Study dates**	**Sample size** See EBCTCG 2014 (Danish BCG 82c trial) **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014 (Danish BCG 82c trial)	**Details** -	**Results** See EBCTCG 2014 (Danish BCG 82c trial) No additional outcomes reported.	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: low risk (participants were randomly allocated to treatment options by a closed-envelope system) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: Low risk (Low loss of follow-up was <20% and ITT analysis used) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
- **Source of funding** -					**Other information** This study (Danish BCG 82c trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation Hojris, I., Andersen, J., Overgaard, M., Overgaard, J., Late treatment-related morbidity in breast cancer patients randomized to postmastectomy radiotherapy and systemic treatment versus systemic treatment alone, Acta Oncologica, 39, 355-372, 2000 **Ref Id** 670066 **Country/ies where the study was carried out** Denmark **Study type**	**Sample size** Number of patients = 84 of 118 eligible patients. Systemic treatment plus radiotherapy (RT-group) n= 42 Systemic treatment alone (no RT-group) n=42 **Characteristics** Median age at mastectomy = 50 years (range 35–69 years) **Inclusion criteria** Mastectomy and axillary dissection, no evidence of metastatic disease,	**Interventions** The primary surgical treatment included total mastectomy and axillary node dissection involving level I and partly level II (Waat-Boolsen et al 1988).The pectoral fascia was stripped and neither the major, nor the minor pectoral muscles were removed. All patients were treated on a linear accelerator in one institution. The target volume included the chest wall and regional lymph nodes, i.e. supraclavicular, infraclavicular, axillary and ipsilateral internal mammary nodes in the four upper intercostal	**Details** Follow up: 81% of invited participants took part in the follow-up study (95/118 eligible patients). Patients were followed for a median of 9 years (range 6–13 years).	**Results** **Treatment related morbidity at median 9 years** Treatment related morbidity: lymphedema >6 cm increase in arm circumference RT: 1/42 no RT: 2/42 Treatment related morbidity: cardiac morbidity Irreversible clinical heart failure RT: 0/42 no RT: 0/42 Acute myocardial infarction RT: 1/42 no RT: 0/42	**Limitations** Critical appraisal was conducted using the Cochrane Risk of Bias tool Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: Low risk (Low loss of follow-up was <20%) Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
RCT (subgroup analysis) **Aim of the study** The aim of the study was to evaluate late treatment-related morbidity in the DBCG 82b and c trials by assessing the morbidity in survivors living in the county of Aarhus. **Study dates** **Source of funding** Danish Cancer Society	no previous history of cancer, no bilateral breast cancer, age less than 70 years, high risk (defined as node positive and/or tumour size > 5cm and/or invasion to skin or fascia). **Exclusion criteria** Patients without previously treated local recurrence.	spaces. The median dose was 50 Gy in 25 fractions, 5 fractions per week, with a dose variation of less than 10%. The lung and heart cauda to the first rib was protected by individually shaped blocks, and the chest wall covering this part was treated through two anterior shaped electron fields. Chest wall thickness- the distance from the skin surface to the pleural surface- was measured with ultrasound, and the electron energy was chosen to include the clinical target volume within the 85% isodose curve. Adjuvant systemic therapy was also administered (CMF, tamoxifen or CMF + tamoxifen).		Treatment related morbidity: lung morbidity Dense fibrosis, severe scarring & major retraction of normal lung RT: 0/42 no RT: 0/42 Refractory chest pain/ discomfort RT: 0/42 no RT: 0/42	Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** Included in the old guideline (where possible, data was extracted from the previous guideline, the individual study was retrieved for additional outcomes and risk of bias assessment).
Full citation Katz, A., Strom, E. A., Buchholz, T. A., Thames, H. D., Smith, C. D., Jhingran, A., Hortobagyi, G., Buzdar, A. U., Theriault, R., Singletary, S. E.,	**Sample size** See EBCTCG 2014 (MD Ander 7730 B trial) **Characteristics** -	**Interventions** See EBCTCG 2014 (MD Ander 7730 B trial)	**Details** -	**Results** See EBCTCG 2014 (MD Ander 7730 B trial) No additional outcomes reported in the paper.	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported)

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
McNeese, M. D., Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: Implications for postoperative irradiation, Journal of Clinical Oncology, 18, 2817-2827, 2000 **Ref Id** 611709 **Country/ies where the study was carried out** USA **Study type** RCT - Included in EBCTCG 2014. **Aim of the study** - **Study dates** - **Source of funding** -	**Inclusion criteria** - **Exclusion criteria** -				Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: unclear (not reported) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** This study (MD Ander 7730 B trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Stewart, H. J., Prescott, R. J., Forrest, A. P. M., Scottish adjuvant tamoxifen trial: A randomized study updated to 15 years, Journal of the National Cancer Institute, 93, 456-462, 2001 **Ref Id** 670130 **Country/ies where the study was carried out** UK **Study type** RCT - included in EBCTCG 2014 **Aim of the study** - **Study dates** - **Source of funding** -	Included in EBCTCG 2014. **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	See EBCTCG 2014 (Scottish D trial)	-	See EBCTCG 2014 (Scottish D trial) No additional outcomes reported.	**Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: Low risk (Low loss of follow-up was <20%) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** This study (Scottish D trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation Schmoor, C., Olschewski, M., Sauerbrei, W., Schumacher, M., Long-term follow-up of patients in four prospective studies of the German Breast Cancer Study Group (GBSG): A summary of key results, Onkologie, 25, 143-150, 2002 **Ref Id** 572419 **Country/ies where the study was carried out** Germany **Study type** RCT - Included in EBCTCG 2014. **Aim of the study** - **Study dates**	**Sample size** See EBCTCG 2014 (GBSG03 Germany trial) **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014 (GBSG03 Germany)	**Details** -	**Results** See EBCTCG 2014 (GBSG03 Germany trial) No additional outcomes reported in the study	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (the data sent to EBCTCG group was that of randomized patients, but no details are provided regarding randomization) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: unclear (cannot be assessed with the information available in the study) Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
- **Source of funding** -					Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** This study (GBSG03 Germany trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation Killander, F., Anderson, H., Ryden, S., Moller, T., Aspegren, K., Ceberg, J., Danewid, C., Malmstrom, P., Radiotherapy and tamoxifen after mastectomy in postmenopausal women - 20 year follow-up of the South Sweden Breast Cancer group randomised trial SSBCG II:I, European Journal of Cancer, 43, 2100-2108, 2007 **Ref Id** 649491	**Sample size** See EBCTCG 2014 (Swedish BCG) **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014 (Swedish BCG)	**Details** -	**Results** See EBCTCG 2014 (Swedish BCG) No additional outcomes were reported	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported) Detection bias Blinding of outcome assessment: unclear (not reported)

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out **Study type** RCT - Included in EBCTCG 2014. **Aim of the study** - **Study dates** - **Source of funding** -					Attrition bias Incomplete outcome data: unclear (protocol stated 6 years follow-up, but most patients were followed longer than that. All 15 participant hospitals were visited. Women who moved from the catchment region were censored from the analysis) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** This study (Swedish BCG) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation Overgaard, M., Nielsen, H. M., Overgaard, J., Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in	**Sample size** See EBCTCG 2014 (Danish BCG82b and Danish BCG82b trials) **Characteristics**	**Interventions** See EBCTCG 2014 (Danish BCG82b and Danish BCG82b trials)	**Details** -	**Results** See EBCTCG 2014 (Danish BCG82b and Danish BCG82b trials) No additional outcomes reported.	**Limitations** See Overgaard 1997 and Overgaard 1999. This is a sub-group analysis of the trials above. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials, Radiotherapy & OncologyRadiother Oncol, 82, 247-53, 2007 **Ref Id** 565603 **Country/ies where the study was carried out** Denmark **Study type** Subgroup analysis of RCT **Aim of the study** - **Study dates** - **Source of funding** -	- **Inclusion criteria** - **Exclusion criteria** -				This study (Danish BCG82b and Danish BCG82b trials) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation Poortmans, P. M., Collette, S., Kirkove, C., Van Limbergen, E., Budach, V., Struikmans, H., Collette, L.,	**Sample size** N=4004 n=955 had a mastectomy (only results relevant to	**Interventions** Intervention: Regional nodal irradiation	**Details** Sample selection and randomization Randomization was performed centrally at	**Results** **Comparison: Chest wall RT + nodes vs chest wall RT alone**	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: low risk

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
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., Internal mammary and medial supraclavicular irradiation in breast cancer, New England journal of medicine, 373, 317-327, 2015 **Ref Id** 664746 **Country/ies where the study was carried out** **Study type** RCT **Aim of the study** To evaluate the effect of internal mammary and medial supraclavicular lymph-node irradiation (regional nodal irradiation) in addition to chest wall RT after surgery on survival among women with early-stage breast cancer.	this group are reported here) **Characteristics** Characteristics are reported for the total population, and are not available for women who had a mastectomy. **Inclusion criteria** Unilateral histologically confirmed breast adenocarcinoma of stage I, II, or III with a centrally or medially located primary tumour. All women had undergone mastectomy or breast conserving surgery and axillary dissection. **Exclusion criteria** Not reported.	Dose of 50 Gy in 25 fractions Comparison: No regional nodal irradiation.	the EORTC headquarters. A minimization algorithm for randomization in a 1:1 ratio was used to stratify group assignments according to institution, menopausal status, tumor site within the breast, type of breast surgery, type of axillary dissection, pathological tumor stage, and pathological nodal stage. Data collection The primary end point was overall survival. This was calculated from the date of randomization to the date of death from any cause. Secondary end points were the rates of disease-free survival, and death from breast cancer. However these results are not reported here as they are not disaggregated by type of surgery.	Death, any cause at median 10 years 139/476 vs 150/479; O-E -6.8 (72.2); HR 0.91 (0.72 to 1.15)	Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported, but unlikely given the nature of the intervention) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: unclear (ITT analysis used, but loss to follow-up is not disaggregated by type of surgery) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** Conflict of interest: No commercial support was provided (full forms available at BMJ) Other outcomes could not be reported, as they were not provided by type of surgery (mastectomy, breast conserving surgery).

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates 1996 to 2004 **Source of funding** Fonds Cancer			Participants were seen annually for the first 5 years and then every 2 years. Statistical analysis The trial was powered to detect a difference of 4 percentage points in 10-year overall survival. Time-to-event curves were estimated by the Kaplan–Meier method and compared with the use of a two-sided log-rank test. The cumulative incidences of death were compared by means of the Fine–Gray test. Intention to treat analysis was used. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute).		
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Faber, P., Jesdinsky, H., Adjuvant chemotherapy in breast cancer--a multicenter trial, 6 Suppl, 75-8, 1979 **Ref Id** 675415 **Country/ies where the study was carried out** Germany **Study type** RCT - included in See EBCTCG 2014 **Aim of the study** - **Study dates** - **Source of funding**	See EBCTCG 2014 (Dusseldorf U trial) **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	See EBCTCG 2014 (Dusseldorf U trial)	-	See EBCTCG 2014 (Dusseldorf U trial)	**Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: unclear (not reported) Reporting bias Selective reporting: unclear (not reported) Other bias Other sources of bias: none **Other information** This study (Dusseldorf U trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					by the NGA technical team as it was not included in the EBCTCG review.
Full citation McArdle, C. S., McMillan, D. C., Greenlaw, N., Morrison, D. S., Adjuvant radiotherapy and chemotherapy in breast cancer: 30 year follow-up of survival, BMC cancer, 10 (no pagination), 2010 **Ref Id** 565844 **Country/ies where the study was carried out** UK **Study type** RCT **Aim of the study** - **Study dates** - **Source of funding** -	**Sample size** See EBCTCG2014 (Glasgow trial) **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG2014 (Glasgow trial)	**Details** -	**Results** See EBCTCG2014 (Glasgow trial) No additional outcomes were reported in the study.	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: Low risk (Low loss of follow-up not reported. ITT analysis used) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					This study was included in EBCTCG 2014 (Glasgow trial). The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review. Methods described in McArdle 1986.
Full citation Shapiro, C. L., Hardenbergh, P. H., Gelman, R., Blanks, D., Hauptman, P., Recht, A., Hayes, D. F., Harris, J., Henderson, I. C., Cardiac effects of adjuvant doxorubicin and radiation therapy in breast cancer patients, Journal of Clinical Oncology, 16, 3493-3501, 1998 **Ref Id** 673128 **Country/ies where the study was carried out** USA **Study type** RCT - included in EBCTCG 2014	**Sample size** See EBCTCG 2014 (DFCI Boston trial) **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014 (DFCI Boston trial)	**Details** -	**Results** See EBCTCG 2014 (DFCI Boston trial) Additional results reported in the study Cardiac events (defined as congestive heart failure or myocardial infarction), at median 6 years follow-up no RT: 13/154 low risk RT (txt of right sided breast cancers with tangential fields): 1/45 moderate risk RT (txt of left sided breast cancer with tangential fields): 4/48 high risk RT (txt of right or left sided breast cancer with tangential fields and of separate anterior field of the internal mammary node): 4/29	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: low risk (a cardiologist blindly reviewed all the records) Attrition bias Incomplete outcome data: unclear (Low loss of follow-up ≅ 20%)

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Aim of the study - **Study dates** - **Source of funding** -				*All participants also received 5 or 10 cycles of chemotherapy*	Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** This study (DFCI Boston trial)) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation Saarto, T., Blomqvist, C., Rissanen, P., Auvinen, A., Elomaa, I., Haematological toxicity: a marker of adjuvant chemotherapy efficacy in stage II and III breast cancer, British Journal of CancerBr J Cancer, 75, 301-5, 1997 **Ref Id** 675416 **Country/ies where the study was carried out**	**Sample size** See EBCTCG 2014 (Helsinki trial) **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014 (Helsinki trial)	**Details** -	**Results** See EBCTCG 2014 (Helsinki trial) No additional outcomes reported in the paper (toxicity related outcomes were related to chemotherapy)	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Finland **Study type** RCT - included in EBCTCG 2014 **Aim of the study** - **Study dates** - **Source of funding** -					Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: Low risk (Low loss of follow-up was <20% Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** This study (Helsinki trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation Gyenes, G., Rutqvist, L. E., Liedberg, A., Fornander, T., Long-term cardiac morbidity and mortality in a randomized trial of pre- and postoperative radiation therapy versus surgery alone in primary breast cancer,	**Sample size** See EBCTCG 2014 (Stockholm A trial) **Characteristics** - **Inclusion criteria**	**Interventions** See EBCTCG 2014 (Stockholm A trial)	**Details** -	**Results** See EBCTCG 2014 (Stockholm A trial) Additional outcomes reported in the trial Txt related morbidity: myocardial infarction, at median 20 years	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported)

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Radiotherapy and Oncology, 48, 185-190, 1998 **Ref Id** 672072 **Country/ies where the study was carried out** Sweden **Study type** RCT - included in EBCTCG 2014 **Aim of the study** - **Study dates** - **Source of funding** -	- **Exclusion criteria** -			RT: 17/323 no RT: 21/321 Txt related mortality: Death due to cardiovascular disease, at median 20 years RT: 13/323 no RT: 17/321 Txt related mortality: Death due to ischaemic heart disease, at median 20 years RT: 12/323 no RT: 10/321 Txt related mortality: Death due to myocardial infarction, at median 20 years RT: 7/323 no RT: 10/321	Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: Low risk (Low loss of follow-up was <20%) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** This study (Stockholm A trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Host, H., Brennhovd, I. O., Loeb, M.,		See EBCTCG 2014 (Oslo X-ray trial)	-	See EBCTCG 2014 (Oslo X-ray trial)	**Critical appraisal was conducted using the Cochrane Risk of Bias tool**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Postoperative radiotherapy in breast cancer--long-term results from the Oslo study, 12, 727-32, 1986 **Ref Id** 675417 **Country/ies where the study was carried out** Norway **Study type** RCT - included in EBCTCG 2014 **Aim of the study** - **Study dates** - **Source of funding** -	See EBCTCG 2014 (Oslo X-ray trial) **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -			No additional outcomes reported in the trial	Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: Low risk (Low loss of follow-up was <20%) but per protocol analysis used) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** This study (Oslo X-ray trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
					by the NGA technical team as it was not included in the EBCTCG review.
Full citation Andersson,M., Kamby,C., Jensen,M.B., Mouridsen,H., Ejlertsen,B., Dombernowsky,P., Rose,C., Cold,S., Overgaard,M., Andersen,J., Kjaer,M., Tamoxifen in high-risk premenopausal women with primary breast cancer receiving adjuvant chemotherapy. Report from the Danish Breast Cancer co-operative Group DBCG 82B Trial, European Journal of Cancer, 35, 1659-1666, 1999 **Ref Id** 98396 **Country/ies where the study was carried out** Denmark **Study type** RCT - included in EBCTCG 2014 **Aim of the study**	**Sample size** See EBCTCG 2014 (Danish BCG 82b) **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014 (Danish BCG 82b trial)	**Details** -	**Results** See EBCTCG 2014 (Danish BCG 82b trial) No additional outcomes reported in the study.	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (closed envelope system?) Allocation concealment: unclear (closed envelope system?) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: Low risk (Low loss of follow-up was <20% and ITT analysis used) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
- **Study dates** - **Source of funding** -					**Other information** This study (Danish BCG 82b trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation Turnbull, A. R., Turner, D. T., Chant, A. D., Shepherd, J. M., Buchanan, R. B., Fraser, J. D., Treatment of early breast cancer, Lancet, 2, 7-9, 1978 **Ref Id** 675419 **Country/ies where the study was carried out** UK **Study type** RCT - included in EBCTCG 2014 **Aim of the study** - **Study dates**	**Sample size** See EBCTCG 2014 (Southampton UK) **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014 (Southampton UK)	**Details** -	**Results** See EBCTCG 2014 (Southampton UK trial) No additional outcomes are reported	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: unclear (not reported)

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
- **Source of funding** -					Reporting bias Selective reporting: unclear (not reported) Other bias Other sources of bias: none **Other information** This study (Southampton UK trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation De Oliveira, CF., Gervasio, H., Alves, R., Silva, A., Pedro, L., Adjuvant chemotherapy versus radiotherapy and chemotherapy in operable breast cancer. A randomized trial. Preliminary results. , 1984 **Ref Id** 675615 **Country/ies where the study was carried out** -	**Sample size** See EBCTCG 2014 (Coimbra trial) **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014 (Coimbra trial).	**Details** -	**Results** See EBCTCG 2014 (Coimbra trial) The paper could not be checked for additional outcomes as it was unavailable	**Limitations** The paper could not be assessed as it is not available **Other information** This study (Coimbra trial) was included in EBCTCG 2014. The individual paper could not retrieved.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study type RCT - included in EBCTCG 2014 **Aim of the study** - **Study dates** - **Source of funding** -					
Full citation Fisher, B., Montague, E., Redmond, C., Deutsch, M., Brown, G. R., Zauber, A., Hanson, W. F., Wong, A., Findings from NSABP Protocol No. B-04-comparison of radical mastectomy with alternative treatments for primary breast cancer. I. Radiation compliance and its relation to treatment outcome, CancerCancer, 46, 1-13, 1980 **Ref Id** 688359	**Sample size** See EBCTCG 2014 (NSABP B-04 trial) **Characteristics** - **Inclusion criteria** - **Exclusion criteria** -	**Interventions** See EBCTCG 2014 (NSABP B-04 trial)	**Details** -	**Results** See EBCTCG 2014 (NSABP B-04 trial) No additional outcomes reported in the paper	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported) Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported)

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out USA **Study type** RCT - included in EBCTCG 2014 **Aim of the study** - **Study dates** - **Source of funding** -					Attrition bias Incomplete outcome data: unclear (unknown loses to follow-up, it is suggested that per protocol analysis was used) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** This study (NSABP B-04 trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.
Full citation Lythgoe, J. P., Palmer, M. K., Manchester regional breast study--5 and 10 year results, Br J SurgThe British journal of surgery, 69, 693-6, 1982 **Ref Id** 688360	**Sample size** See EBCTCG 2014 (Manchester RBS1 trial) **Characteristics** - **Inclusion criteria** -	**Interventions** See EBCTCG 2014 (Manchester RBS1 trial)	**Details** -	**Results** See EBCTCG 2014 (Manchester RBS1 trial) No additional outcomes reported in the study	**Limitations** **Critical appraisal was conducted using the Cochrane Risk of Bias tool** Selection bias Random sequence generation: unclear (not reported) Allocation concealment: unclear (not reported)

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out UK **Study type** RCT - included in EBCTCG 2014 **Aim of the study** - **Study dates** - **Source of funding** -	**Exclusion criteria** -				Performance bias Blinding of participants and personnel: unclear (not reported - unlikely to affect objective outcomes) Detection bias Blinding of outcome assessment: unclear (not reported) Attrition bias Incomplete outcome data: Low risk (Low loss of follow-up was <20% and ITT analysis used) Reporting bias Selective reporting: Low risk (All outcomes reported) Other bias Other sources of bias: none **Other information** This study (Manchester RBS1 trial) was included in EBCTCG 2014. The individual paper was retrieved for accuracy but full data extraction was not done. Additional outcomes reported in the original paper were extracted. Risk of bias was also done by the NGA technical team as it was not included in the EBCTCG review.

AF, axillary fossa; BCCA, British Columbia Cancer Agency; C, cyclophosphamide; CMF, cyclophosphamide, methotrexate, fluorouracil; CWRT, chest wall radiotherapy; DBCG, Danish Breast Cancer Cooperative Group; DFCI, Dana-Farber Cancer Institute; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; ECOG, Eastern Cooperative Oncology Group; Gy, Gray; HR, hazard ratio; ICD, International Classification of Diseases; IQR, interquartile range; ITT, intention to treat; NGA, National Guideline Alliance; NSABP, National Surgical Adjuvant Breast and Bowel Project; RCT, randomised controlled trial; ROBIS, Risk of Bias in Systematic Reviews; RR, risk ratio; RT: radiotherapy; SC, supraclavicular; SECSG, Southeastern Cancer Study Group

Clinical evidence tables for 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?

Table 12: Studies included in the evidence review for immediate versus delayed breast reconstruction

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Adesiyun, T. A., Lee, B. T., Yueh, J. H., Chen, C., Colakoglu, S., Anderson, K. E. M., Nguyen, M. D. T., Recht, A., Impact of sequencing of postmastectomy radiotherapy and breast reconstruction on timing and rate of complications and patient satisfaction, International Journal of Radiation Oncology Biology Physics, 80, 392-397, 2011 **Ref Id** 612722 **Country/ies where the study was carried out** USA **Study type**	**Sample size** 114 **Characteristics** Gender: 100% female Age: immediate mean 45.4, range 31.9-69.6; delayed mean 46.1, range 34.3-62.9 Ethnicity: NR **Inclusion criteria** Women who had mastectomy, breast reconstruction and postmastectomy radiotherapy. **Exclusion criteria** People who had previously received radiotherapy for treatment of Hodgkin disease, lymphoma, or failed breast-conserving surgery; immediate reconstruction with a tissue expander **Reported subgroups**	**Interventions** **Intervention arm:** mastectomy and immediate breast reconstruction followed by radiotherapy **Control arm:** mastectomy followed by radiotherapy and delayed breast reconstruction	**Details** **Intervention arm (immediate):** Mean interval between reconstruction and radiotherapy 5.2 months (1-15.5 months). Median radiotherapy dose 50Gy. **Control arm (delayed):** Median radiotherapy dose 50Gy; mean interval between radiotherapy and reconstruction 8.2 months (2.7-80.9 months). Reconstructions: pedicled transverse rectus abdominis muscle (TRAM) flap (31%), muscle-sparing free flap (25%), latissimus dorsi muscle flap plus a prosthesis (18%), permanent prosthesis or initial tissue expander and then prosthesis (12%), latissimus flap without a	**Results** **Postmastectomy radiotherapy:** **Patient satisfaction - aesthetic satisfaction rate:** immediate 23/37; delayed 20/40 **Complication rates - any:** immediate 25/57; delayed 18/57 **Complication rates - capsular contracture (cosmetic):** immediate 11/57; delayed 1/57 **Complication rates - implant malposition (cosmetic):** immediate 2/57; delayed 1/57	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** Groups not comparable at baseline; higher rates of stage III disease in the intervention arm - not controlled for in analysis **Outcome** Outcome and follow-up assessment adequate **Indirectness** None **Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Retrospective cohort study **Aim of the study** To examine how the sequencing of reconstruction and postmastectomy radiotherapy affect patient satisfaction and development of complications **Study dates** Underwent reconstruction January 1999 to December 2006 **Source of funding** None reported	All patients radiotherapy following mastectomy; autologous; implant		prosthesis (8%), a free TRAM flap (5%), and free TRAM flap plus implant (1%).	**Complication rates - implant rupture/extrusion (implant loss):** immediate 2/57; delayed 1/57 **Complication rates - implant removed due to dissatisfaction/pain (implant loss):** immediate 1/57; delayed 0/57 **Complication rates - flap loss (flap loss):** immediate 0/57; delayed 2/57 **Complication rates - major fat necrosis (flap loss):** immediate 1/57; delayed 5/57 **Complication rates - hematoma at donor site (bleeding):** immediate 2/57; delayed 0/57 **Complication rates - hematoma at recipient**	Same sample as Lee 2010

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				site (bleeding): immediate 2/57; delayed 3/57 **Complication rates - hernia or fascial defect (flap donor site):** immediate 1/57; delayed 0/57 **Complication rates - infection at donor site (flap donor site):** immediate 0/57; delayed 2/57 **Complication rates - bulge or fascial laxity (flap donor site):** immediate 2/57; delayed 1/57 **Complication rates - infection at recipient site (wound):** immediate 2/57; delayed 2/57 **Complication rates - open wound (wound):** immediate 2/57; delayed 3/57	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Complication rates - mastectomy skin loss (mastectomy skin flap): immediate 0/57; delayed 3/57 **Autologous reconstruction (PMRT+):** **Patient satisfaction - aesthethic satisfaction rate:** immediate 16/24; delayed 17/29 **Complication rates - any early:** immediate 3/36; delayed 9/43 **Complication rates - any late:** immediate 7/36; delayed 5/43 **Implant (PMRT+):**	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Patient satisfaction - aesthetic satisfaction rate: immediate 3/7; delayed 0/1 **Complication rates - any early:** immediate 2/13; delayed 0/1 **Complication rates - any late:** immediate 8/13; delayed 0/1	
Full citation Alderman, A. K., Collins, E. D., Schott, A., Hughes, M. E., Ottesen, R. A., Theriault, R. L., Wong, Y. N., Weeks, J. C., Niland, J. C., Edge, S. B., The impact of breast reconstruction on the delivery of chemotherapy, Cancer, 116, 1791-1800, 2010	**Sample size** Total 3643 - only interested in those that received mastectomy and reconstruction (696) **Characteristics** Gender: 100% female Age: NR Ethnicity: 84% Caucasian, 7% African-American, 5% Hispanic **Inclusion criteria**	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction **Control arm:** mastectomy + delayed reconstruction	**Details** **Intervention arm (immediate):** no information about mastectomy - reconstruction methods: implant, pedicle transverse rectus abdominus myocutaneous flap [TRAM], free TRAM requiring microvascular surgery, other rotational flap, and other free flap. Immediate reconstruction defined as reconstruction started or completed on same day as mastectomy.	**Results** **Delay in adjuvant therapy - chemotherapy initiated ≥ 8 weeks after definitive surgery:** Immediate 53/596; delayed 3/100 **Delay in adjuvant therapy - chemotherapy not administered:** Immediate 97/596; delayed 10/100	**Selection** Method of selection appropriate and likely to produce representative cohort. **Comparability** Unclear whether groups are comparable - not reported. **Outcome** Outcome assessment and follow-up adequate

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Ref Id 612763 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To identify factors associated with delay or omission of adjuvant chemotherapy **Study dates** Treated July 1997 to December 2003 **Source of funding** Robert Wood Johnson Foundation, National Cancer Institute to Dana-Farber Cancer Institute	Women with stage I-III unilateral breast cancer who received surgery at a participating NCCN institution, received care there for at least a year, and NCCN guidelines recommended adjuvant chemotherapy. **Exclusion criteria** Received neoadjuvant systemic/radiation therapy **Reported subgroups** None of interest		**Control arm (delayed):** no information about mastectomy - reconstruction methods: implant, pedicle transverse rectus abdominus myocutaneous flap [TRAM], free TRAM requiring microvascular surgery, other rotational flap, and other free flap.		**Indirectness** None **Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Baltaci Goktas, S., Gulluoglu, B. M., Selimen, D., Immediate or delayed breast reconstruction after radical mastectomy in breast cancer patients: Does it make a difference in the quality of life, Turkiye Klinikleri Journal of Medical Sciences, 31, 664-673, 2011 **Ref Id** 612848 **Country/ies where the study was carried out** Turkey **Study type** Retrospective cohort study **Aim of the study**	**Sample size** 51 **Characteristics** Gender: NR Age: immediate median 48, range 30-61; delayed median 50, range 34-63 Ethnicity: NR **Inclusion criteria** Patients with breast cancer who had undergone reconstruction at Marmara University Hospital, Istanbul. **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction **Control arm:** mastectomy + delayed reconstruction	**Details** **Intervention arm (immediate):** 71% underwent simple mastectomy (SM), 29% modified radical mastectomy (MRM). 71% reconstruction with implant, 29% autologous. **Control arm (delayed):** 35% SM, 65% MRM. 52% reconstruction with implant, 48% autologous.	**Results** **Complication rates - surgical:** immediate 2/28; delayed 4/23 **Complication rates - lymphedema:** immediate 4/28; delayed 9/23 **Health-related quality of life - EORTC QLQ-30 Global Health Status:** immediate N=28, M=29.16, SD=15.30; delayed N=23, M=15.94, SD=17.57 **Health-related quality of life - EORTC QLQ-30 Physical Functioning:** immediate N=28, M=88.70.16, SD=8.15; delayed N=23, M=80.95, SD=9.02	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** Groups differed in terms of stage (more advanced in delayed group), and time of mastectomy performed (more MRM in delayed group) **Outcome** Outcome and follow-up adequate **Indirectness** None **Limitations** Small sample size **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
To investigate effect of delayed and immediate reconstruction on quality of life **Study dates** January 2002 to December 2006 **Source of funding** No sources reported				**Health-related quality of life - EORTC QLQ-30 Role Functioning:** immediate N=28, M=89.13, SD=16.37; delayed N=23, M=90.48, SD=15.33 **Health-related quality of life - EORTC QLQ-30 Emotional Functioning:** immediate N=28, M=88.68, SD=19.44; delayed N=23, M=79.46, SD=15.13 **Health-related quality of life - EORTC QLQ-30 Cognitive Functioning:** immediate N=28, M=84.78, SD=15.82; delayed N=23, M=84.52, SD=20.75 **Health-related quality of life - EORTC QLQ-30 Social Functioning:** immediate N=28, M=91.07, SD=18.47; delayed N=23, M=85.51, SD=20.90	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Complication rates - radiotherapy: immediate 3/4; delayed 1/17	
Full citation Carlson, G. W., Page, A. L., Peters, K., Ashinoff, R., Schaefer, T., Losken, A., Effects of radiation therapy on pedicled transverse rectus abdominis myocutaneous flap breast reconstruction, Annals of plastic surgery, 60, 568-572, 2008 **Ref Id** 613002 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study	**Sample size** Total 199 - not interested in immediate reconstruction and preoperative radiotherapy group (n=15) **Characteristics** Gender: NR Age: mean 48.6, range NR Ethnicity: NR **Inclusion criteria** No criteria reported - all patients had pedicled TRAM flap reconstructions **Exclusion criteria** No additional criteria reported **Reported subgroups** All patients autologous reconstruction; radiotherapy	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction **Control arm:** mastectomy + delayed reconstruction	**Details** No further information about interventions. Outcome data obtained through personal communication, physical examination and chart and photographic review. Fat necrosis was defined a firm area of the TRAM flap and was usually confirmed by needle aspiration. Remedial surgery was defined as secondary procedures performed to improve breast shape. Complication rates reported for number of reconstructions (232) rather than number of patients (199)	**Results** **No radiotherapy following mastectomy (autologous reconstruction):** **Complication rates - hematoma:** immediate 3/149; delayed 0/28 **Complication rates - infection:** immediate 1/149; delayed 0/28 **Complication rates - skin flap necrosis (mastectomy skin flap):** immediate 24/149; delayed 0/28 **Complication rates - fat necrosis (mastectomy**	**Selection** Insufficient information about selection methods **Comparability** Groups not compared at baseline **Outcome** Outcome assessment and follow-up adequate **Indirectness** None **Limitations** Very small sample sizes with exception of those that had immediate reconstruction and no radiotherapy. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Aim of the study To examine the effect of radiation on pedicled TRAM flaps. **Study dates** Not reported **Source of funding** No sources reported	following mastectomy, no radiotherapy following mastectomy			**skin flap):** immediate 23/149; delayed 1/28 **Complication rates - remedial surgery:** immediate 24/128; delayed 2/16 **Radiotherapy following mastectomy (autologous reconstruction):** **Complication rates - hematoma:** immediate 0/25; delayed 0/15 **Complication rates - infection:** immediate 0/25; delayed 0/15 **Complication rates - skin flap necrosis (mastectomy skin flap):** immediate 3/25; delayed 1/15	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Complication rates - fat necrosis (mastectomy skin flap): immediate 8/25; delayed 2/15 **Complication rates - remedial surgery:** immediate 3/25; delayed 0/15	
Full citation Christante, D., Pommier, S. J., Diggs, B. S., Samuelson, B. T., Truong, A., Marquez, C., Hansen, J., Naik, A. M., Vetto, J. T., Pommier, R. F., Using complications associated with postmastectomy radiation and immediate breast reconstruction to improve surgical decision making,	**Sample size** Total 302 - only interested in those that had reconstruction (n=152) **Characteristics** Gender: 100% female Age: NR Ethnicity: NR **Inclusion criteria** Women with primary non-metastatic breast cancer who underwent mastectomy	**Intervention arm:** mastectomy + immediate reconstruction **Control arm:** mastectomy + delayed reconstruction	**Details** No further details reported	**Results** **Radiotherapy following mastectomy:** **Complication rates - surgical complications requiring additional operation:** immediate 14/33; delayed 2/9 **No radiotherapy following mastectomy:**	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** Groups not compared at baseline **Outcome** Outcome assessment and follow-up adequate **Indirectness**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Archives of Surgery, 145, 873-878, 2010 **Ref Id** 613102 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To examine factors associated with surgical complications following mastectomy and reconstruction **Study dates** Treated 2000 to 2008 **Source of funding** No sources reported	**Exclusion criteria** Bilateral breast cancer **Reported subgroups** Radiotherapy following mastectomy; no radiotherapy following mastectomy			**Complication rates - surgical complications requiring additional operation:** immediate 16/98; delayed 0/12	None **Limitations** Small number of people receive delayed reconstruction **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Selection**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Fernandez-Delgado, J., Lopez-Pedraza, M. J., Blasco, J. A., Andradas-Aragones, E., Sanchez-Mendez, J. I., Sordo-Miralles, G., Reza, M. M., Satisfaction with and psychological impact of immediate and deferred breast reconstruction, Annals of Oncology, 19, 1430-1434, 2008 **Ref Id** 613379 **Country/ies where the study was carried out** Spain **Study type** Retrospective cohort study **Aim of the study** To assess psychology impact of, and satisfaction with, breast reconstruction.	526 **Characteristics** Gender: 100% female Age: mean 55.3; SD 12.4 Ethnicity: NR **Inclusion criteria** Inclusion criteria not reported. All patients underwent surgery at the Immediate Breast Reconstruction Unit, Hospital Universitario de la Paz, Madrid, Spain, between 2002 and 2006 **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest	**Intervention arm:** mastectomy + immediate reconstruction **Control arm:** mastectomy + delayed reconstruction	**Intervention arm (immediate):** No information reported about mastectomy. Implants were used in the majority of reconstructions (direct submuscular prostheses in immediate reconstructions and tissue expanders in delayed reconstructions. Autologous tissues were only used in small number of patients. **Control arm (delayed):** No information reported about mastectomy. Implants were used in the majority of reconstructions (direct submuscular prostheses in immediate reconstructions and tissue expanders in delayed reconstructions. Autologous tissues were only used in small number of patients. Patients were contacted (up to 15 attempts made) 6 months after reconstruction	**Patient satisfaction - satisfied with aesthetic results:** immediate 105/153; delayed 62/110	Method of selection appropriate and likely to present a representative cohort **Comparability** Unclear if groups are comparable - not reported but author states there were 'probably differences (p. 1433) **Outcome** Outcome assessment and follow-up adequate **Indirectness** None **Limitations** 28% did not respond to telephone questionnaires; 48% of these could not be found, 20% had died, and 15% did not want to take part - not reported whether rates were equivalent between arms. Did not account for whether women were undergoing radiotherapy or chemotherapy at time of telephone interview

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates Underwent surgery 2002 to 2006 **Source of funding** None reported					which may have affected satisfaction. **Other information**
Full citation Hughes, K., Brown, C., Perez, V., Ting, J. W. C., Rozen, W. M., Whitaker, I. S., Korentager, R., The effect of radiotherapy on implant-based breast reconstruction in the setting of skin-sparing mastectomy: Clinical series and review of complications, Anticancer research, 32, 553-557, 2012 **Ref Id** 613674 **Country/ies where the study was carried out**	**Sample size** 132 **Characteristics** Gender: NR Age: mean 52 Ethnicity: 84% White, 5% African-American, 5% Hispanic **Inclusion criteria** None reported - all patients had breast reconstruction using permanent tissue expanders. **Exclusion criteria** None reported **Reported subgroups**	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction **Control arm:** mastectomy + delayed reconstruction	**Details** **Intervention arm (immediate):** conventional or skin-sparing mastectomy followed by immediate reconstruction with Mentor or Inamed/Allergan tissue expanders **Control arm (delayed):** conventional or skin-sparing mastectomy followed by delayed reconstruction with Mentor or Inamed/Allergan tissue expanders	**Results** **Complication rates - reoperation:** immediate 16/197; delayed 12/30 **Complication rates - capsular contraction (cosmetic):** immediate 10/197; delayed 0/30	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** Unclear: groups not compared at baseline **Outcome** Outcome assessment and follow-up adequate **Indirectness** None **Limitations** Small number of patients in control arm **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
USA **Study type** Retrospective cohort study **Aim of the study** To investigate the effect of radiation on implant based reconstruction following mastectomy **Study dates** Treated 2006 to 2009 **Source of funding** No sources reported	All implant reconstruction				
Full citation Jeevan, R., Cromwell, D. A., Browne, J. P., Caddy, C. M., Pereira, J., Sheppard, C., Greenaway, K., van der Meulen, J. H., Findings of a national comparative audit of mastectomy and breast reconstruction	**Sample size** Total 19,336 - only interested in those with reconstructions (n=5120) **Characteristics** Gender: 100% women Age: mean/range NR; 87% 40-69 Ethnicity: 95% White (based on whole sample)	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction **Control arm:** mastectomy + delayed reconstruction	**Details** **Intervention arm (immediate):** No information reported about type of mastectomy. Majority of patients had reconstruction with an implant (± flap) **Control arm (delayed):** No information reported about type of mastectomy. Majority	**Results** **Whole sample:** **Complication rates - further unplanned treatment/surgery:** immediate 245/1553; delayed 96/692	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** Groups not compared statistically but higher rates of invasive disease and positive lymph nodes in delayed arm

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
surgery in England, Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS, 67, 1333-44, 2014 **Ref Id** 613729 **Country/ies where the study was carried out** UK **Study type** Prospective cohort study (national audit) **Aim of the study** To examine outcomes of mastectomy and reconstruction **Study dates** Underwent mastectomy/primary reconstruction January 2008 to March 2009 **Source of funding** No sources reported	**Inclusion criteria** Women aged ≥16 years with invasive breast cancer and/or DCIS who had unilateral mastectomy ± reconstruction **Exclusion criteria** No additional criteria reported **Reported subgroups** Implant; autologous		of patients had autologous reconstruction	**Complication rates - bleeding requiring transfusion/surgery (bleeding):** immediate 26/1553; delayed 13/692 **Complication rates - wound opening requiring surgery (wound):** immediate 79/1553; delayed 42/692 **Complication rates - wound infection requiring antibiotics (wound):** immediate 374/1553; delayed 185/692 **Complication rates - breast skin necrosis (mastectomy skin flap):** immediate 95/1553; delayed 53/692 **Complication rates - heart attack:** immediate 5/1553; delayed 3/692	**Outcome** Outcome assessment and follow-up adequate **Indirectness** Population: only 71% had invasive cancer: serious **Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Complication rates - flap necrosis (flap loss): immediate 61/1553; delayed 43/692 **Complication rates - surgery to remove some or all of flap (flap loss):** immediate 48/1553; delayed 34/692 **Complication rates - hernia at donor site (flap donor site):** immediate 70/1553; delayed 27/692 **Implant:** **Complication rates - mastectomy site:** immediate 111/1207; delayed 8/280 **Complication rates - implant related:** immediate 10/1207; delayed 6/280	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Autologous: **Complication rates - mastectomy site:** immediate 109/1375; delayed 60/987 **Complication rates - flap related:** immediate 61/1375; delayed 86/987 **Complication rates - donor site :** immediate 114/1375; delayed 66/987	
Full citation Kim, S. H., Kim, J. M., Park, S. H., Lee, S. Y., Analysis of the effects of breast reconstruction in breast cancer patients receiving radiotherapy after mastectomy, Archives of Plastic Surgery, 39, 222-226, 2012 **Ref Id**	**Sample size** 21 **Characteristics** Gender: NR Age: immediate mean 36.3; delayed mean 48.0 Ethnicity: NR **Inclusion criteria** Patients who had mastectomy, reconstruction	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction followed by radiotherapy **Control arm:** mastectomy followed by radiotherapy +	**Details** **Intervention arm (immediate):** mean time between reconstruction and radiotherapy 1.2 months; mean radiation dose 5632.3cGy. No further details reported **Control arm (delayed):** mean time between radiotherapy and reconstruction 7.1 months;	**Results** **Patient satisfaction - general:** immediate N=13, M=22.3 SD=1.2; delayed N=8, M=22.2, SD=1.2 **Patient satisfaction - aesthetic:** immediate N=13, M=8.3, SD=0.7; delayed N=8, M=7.0; SD=1.0	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** Groups not compared statistically but control arm was older and had lower rates of hormone therapy and chemotherapy, and a shorted hospital stay

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
613847 **Country/ies where the study was carried out** Korea **Study type** Retrospective cohort study **Aim of the study** To investigate the effect of timing of breast reconstruction on complications, overall health and aesthetic satisfaction **Study dates** November 2004 to November 2010 **Source of funding** No sources reported	and postmastectomy radiotherapy for breast cancer. **Exclusion criteria** No additional criteria reported **Reported subgroups** All patients has radiotherapy following mastectomy	delayed reconstruction	mean radiation dose 5837.5cGy. No further details reported	**Complication rates - hematoma (bleeding):** immediate 0/13; delayed 1/8 **Complication rates - capsular contracture (cosmetic):** immediate 1/13; delayed 0/8 **Complication rates - fat necrosis (flap loss):** immediate 1/13; delayed 0/8 **Complication rates - flap loss (flap loss):** immediate 2/13; delayed 0/8	**Outcome** Outcome assessment and follow-up adequate **Indirectness** None **Limitations** Very small sample size **Other information**
Full citation Lee, B. T., A. Adesiyun T, Colakoglu, S., Curtis, M. S., Yueh, J. H., E.	**Sample size** Total 707 - only interested in those that received PMRT (n=116) as results not presented separately for	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction	**Details** No further details reported	**Results** **Implant (PMRT+):**	**Selection** Method of selection appropriate and likely to produce representative cohort

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Anderson K, Tobias, A. M., Recht, A., Postmastectomy radiation therapy and breast reconstruction: an analysis of complications and patient satisfaction, Annals of plastic surgery, 64, 679-683, 2010 **Ref Id** 613961 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To investigate the effect of post mastectomy radiotherapy on complication rates and patient satisfaction **Study dates**	immediate and delayed reconstruction for those that did not have PMRT **Characteristics** Gender: 100% female Age: mean/range NR; 48% 40-49, 25% 50-59; 20% <40, 7% ≥60 Ethnicity: NR **Inclusion criteria** Women who underwent simple or modified radical mastectomy and breast reconstruction **Exclusion criteria** Partial, subtotal or radical salvage mastectomy; reconstruction for micromastia or Poland syndrome; previous radiotherapy for failed breast conserving therapy, Hodgkin disease or lymphoma; planned delayed-immediate reconstruction; revision of reconstruction **Reported subgroups** All patients radiotherapy following mastectomy; implant; autologous	followed by radiotherapy **Control arm:** mastectomy followed by radiotherapy + delayed reconstruction		**Patient satisfaction - general (scored 4 or 5 on MBROS questionnaire):** immediate 2/6; delayed 0/1 **Patient satisfaction - aesthetic (scored 4 or 5 on MBROS questionnaire):** immediate 3/6; delayed 0/1 **Autologous (PMRT+):** **Patient satisfaction - general (scored 4 or 5 on MBROS questionnaire):** immediate 18/24; delayed 20/27 **Patient satisfaction - aesthetic (scored 4 or 5 on MBROS questionnaire):** immediate 16/24; delayed 16/27	**Comparability** Immediate reconstruction arm younger **Outcome** Outcome assessment and follow-up adequate **Indirectness** None **Limitations** Small sample sizes (particularly delayed implant reconstruction) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Underwent reconstruction January 1999 to December 2006 **Source of funding** No sources reported					
Full citation Leone, M. S., Priano, V., Franchelli, S., Puggioni, V., Merlo, D. F., Mannucci, M., Santi, P. L., Factors affecting symmetrization of the contralateral breast: a 7-year unilateral postmastectomy breast reconstruction experience, Aesthetic Plastic Surgery, 35, 446-451, 2011 **Ref Id** 614006 **Country/ies where the study was carried out** Italy **Study type**	**Sample size** 606 **Characteristics** Gender: 100% women Age: NR Ethnicity: NR **Inclusion criteria** Not reported - all women underwent unilateral breast reconstructions **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction **Control arm:** mastectomy + delayed reconstruction	**Details** No further details reported	**Results** **Complication rates - symmetrisation procedure required:** immediate 18/153; delayed 186/433	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** Groups not compared at baseline **Outcome** Outcome assessment and follow-up adequate **Indirectness** None **Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Retrospective cohort study **Aim of the study** To determine optimal surgical procedures to achieve best aesthetic outcome with fewest surgical procedures **Study dates** Underwent reconstruction September 2001 to April 2008 **Source of funding** No sources identified					
Full citation Major, M., Devulapalli, C., Bello, R. J., Baltodano, P. A., Reinhardt, M. E., Manahan, M. A., Cooney, C. M., Rosson, G. D., The Effect of Timing on Breast Reconstruction Outcomes in Diabetic	**Sample size** **NSQIP:** 1408 **JHH:** 52 **Characteristics** **NSQIP:** Gender: 100% female Age: mean 58.3, SD 9.4	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction **Control arm:** mastectomy + delayed reconstruction	**Details** **NSQIP:** **Intervention arm (immediate):** no further information about mastectomy. 84% had reconstructions with implants and 16% autologous reconstructions.	**Results** **NSQIP:** **Complication rates - superficial infection (wound):** immediate 30/958; delayed 12/450	**Selection** Methods of selection appropriate and likely to produce representative cohorts **Comparability** NSQIP: longer operation time and greater number of inpatients in immediate cohort. JHH: groups comparable at baseline

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Women, Plastic and Reconstructive Surgery - Global Open, 4, e1090, 2016 **Ref Id** 614091 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To determine effect of breast reconstruction timing on post-operative morbidity **Study dates** **NSQIP:** January 2005 to December 2012 **JHH:** January 2005 to July 2014 **Source of funding**	Ethnicity: 58% White, 14.1% African-American, 8.5% Latino, 2.7% Asian or Pacific Islander **JHH:** Gender: 100% female Age: mean 53.9, SD 9.3 Ethnicity: 52% White, 40% African-American, 2% Asian or Pacific Islander **Inclusion criteria** Diabetic women undergoing mastectomy and breast reconstruction **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest		**Control arm (delayed):** no further information about mastectomy. 74% had reconstructions with implants and 26% autologous reconstructions. **JHH:** no further details reported	**Complication rates - wound dehiscence (wound):** immediate 19/958; 6/450 **Complication rates - flap/prosthesis failure:** immediate 15/958; delayed 1/450 **Complication rates - myocardial infarction:** immediate 0/958; delayed 1/450 **Complication rates - reoperation:** immediate 35/958; delayed 25/450 **JHH (long-term morbidity):** **Complication rates - superficial infection (wound):** immediate 3/39; delayed 3/36	**Outcome** NSQIP: outcome assessment adequate, follow-up time limited (only 30 days). JHH: outcome assessment and follow-up adequate **Indirectness** NSQIP: intervention/comparison: unclear what proportion had delayed-immediate reconstruction: serious. JHH: intervention/comparison: majority (number NR) had delayed-immediate reconstructions: very serious **Limitations** Could not distinguish delayed immediate reconstructions in the NSQIP database. Therefore, delayed-immediate reconstructions performed at JHH were included in both arms to aid comparability **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
No sources reported				**Complication rates - flap/prosthesis failure:** immediate 13/39; delayed 0/36 **Complication rates - wound dehiscence (wound):** immediate 0/39; delayed 3/36 **Complication rates - fat necrosis (flap loss):** immediate 4/39; delayed 3/36 **Complication rates - skin necrosis (mastectomy skin flap):** immediate 5/39; delayed 1/36 **Complication rates - capsular contracture (cosmetic):** immediate 0/39; delayed 2/36 **Complication rates - myocardial infarction:**	Study 1: retrospective analysis of The American College of Surgeons National Surgical Quality and Improvement Program (NSQIP) database Study 2: retrospective analysis of patients from John Hopkins Hospital

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				immediate 1/39; delayed 0/36 **Complication rates - donor site morbidity:** immediate 1/39; delayed 1/36 **Complication rates - reoperation:** immediate 12/39; delayed 1/36	
Full citation McKeown, D. J., Hogg, F. J., Brown, I. M., Walker, M. J., Scott, J. R., Weiler-Mithoff, E. M., The timing of autologous latissimus dorsi breast reconstruction and effect of radiotherapy on outcome, Journal of Plastic, Reconstructive and Aesthetic Surgery, 62, 488-493, 2009 **Ref Id** 614159	**Sample size** 24 **Characteristics** Gender: NR Age: immediate mean 45.2, delayed mean 50.5, range 36-72 Ethnicity: NR **Inclusion criteria** Patients who underwent autologous latissimus dorsi flap reconstruction and had a complete set of pre- and post-operative photographs	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction followed by radiotherapy **Control arm:** mastectomy + delayed reconstruction	**Details** **Intervention arm (immediate):** no details about mastectomy. Breast was reconstructed immediately with autologous latissimus dorsi flap and followed by radiotherapy - 25 fractions of 2Gy radiotherapy delivered to the chest wall and axilla. **Control arm (delayed):** no details about mastectomy. Breast was reconstructed	**Results** **Complication rates - fat necrosis (flap loss):** immediate 2/13; delayed 1/11 **Complication rates - surgery to reposition flap:** immediate 0/13; delayed 1/11 **Complication rates - symmetrisation procedure:** immediate 2/13; delayed 2/11	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** Groups not compared statistically but delayed arm older and had higher rates of chemotherapy; rates of radiotherapy higher in immediate arm **Outcome** Outcome assessment and follow-up adequate **Indirectness**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out UK **Study type** Retrospective cohort study **Aim of the study** To compare cosmetic outcome and patient satisfaction following immediate and delayed breast reconstruction **Study dates** Underwent reconstruction 1997 to 2000 **Source of funding** No sources reported	**Exclusion criteria** No additional criteria reported **Reported subgroups** All patients had autologous reconstruction		with autologous latissimus dorsi flap 4 to 71 months (median 38) after mastectomy; 45% had radiotherapy prior to reconstruction - 25 fractions of 2Gy radiotherapy delivered to the chest wall and axilla.		None **Limitations** Very small sample size **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Selection**
Reintgen, C., Leavitt, A., Pace, E., Molas-Pierson, J., Mast, B.	Total 581 but only interested in those that had reconstruction (n=239)	**Intervention arm:** mastectomy	No further details reported regarding mastectomy,	**Complication rates - skin flap necrosis (mastectomy skin flap):**	Method of selection appropriate and likely to

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
A., Risk Factor Analysis for Mastectomy Skin Flap Necrosis: Implications for Intraoperative Vascular Analysis, Annals of plastic surgery, 76 Suppl 4, S336-9, 2016 **Ref Id** 614573 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To identify incidence and risk factors for mastectomy skin flap necrosis **Study dates** Underwent mastectomy 2007 to 2013 **Source of funding**	**Characteristics** Gender: NR Age: NR Ethnicity: NR **Inclusion criteria** All patients who underwent mastectomy at University of Florida between 2007 and 2013 - only interested in those that had reconstruction for current review **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest	+ immediate reconstruction **Control arm:** mastectomy + delayed reconstruction	reconstruction or radiotherapy	immediate 14/192; delayed 0/47	produce representative cohort **Comparability** Groups not compared at baseline **Outcome** Outcome assessment and follow-up adequate **Indirectness** None **Limitations** Limited information available about groups as focus of study was not comparison of immediate vs. delayed reconstruction **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
No sources of funding reported					
Full citation Sanati-Mehrizy, P., Massenburg, B. B., Rozehnal, J. M., Gupta, N., Rosa, J. H., Ingargiola, M. J., Taub, P. J., A Comparison of Postoperative Outcomes in Immediate Versus Delayed Reconstruction After Mastectomy, Eplasty [Electronic Resource], 15, e44, 2015 **Ref Id** 614686 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study	**Sample size** Total 49,450 - only interested in those that had reconstruction (n=19,224) **Characteristics** Gender: NR Age: mean 50.1, SD 10.5 Ethnicity: 80% White, 8% Black, 3% Asian, 1% Hispanic **Inclusion criteria** All patients in the NSQIP database who underwent mastectomy for breast cancer between 2005 and 2012 **Exclusion criteria** No additional criteria reported **Reported subgroups** implant; autologous	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction **Control arm:** mastectomy + delayed reconstruction	**Details** No further details reported	**Results** **Implant:** **Complication rates - surgical:** immediate 553/13,513; delayed 135/2047 **Complication rates - graft failure:** immediate 100/13,513; delayed 10/2047 **Complication rates - reoperation:** immediate 1004/13,513; delayed 165/2047 **Autologous:**	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** Implant: delayed cohort older, higher rates of hypertension, fewer Asian patients. Autologous: delayed cohort older, higher BMI, more diabetes, higher American Society of Anaesthesiologists score **Outcome** Outcome assessment adequate. Follow-up limited (30 days) **Indirectness** None **Limitations** **Other information** NSQIP database

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Aim of the study To examine the frequency of postoperative complications in patients undergoing immediate and delayed breast reconstruction following mastectomy for breast cancer **Study dates** Underwent mastectomy 2005 to 2012 **Source of funding** No sources reported				**Complication rates - surgical:** immediate 171/2854; delayed 82/810 **Complication rates - graft failure:** immediate 82/2854; delayed 11/810 **Complication rates - reoperation:** immediate 298/2854; delayed 106/810	
Full citation Scuderi, N., Alfano, C., Campus, G. V., Rubino, C., Chiummariello, S., Puddu, A., Mazzocchi, M., Multicenter study on breast reconstruction outcome using Becker implants, Aesthetic Plastic	**Sample size** 204 **Characteristics** Gender: 100% women Age: median 47.5, range 26-66 Ethnicity: NR **Inclusion criteria**	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction **Control arm:** mastectomy + delayed reconstruction	**Details** **Intervention arm (immediate):** no details about mastectomy. After the breast had been removed, the free lateral border of the pectoralis major muscle was split and raised to create cleavage and the serratus anterior was raised laterally to provide lateral implant cover. The inferior pectoralis	**Results** **Complication rates - symmetrisation procedure:** immediate 12/143; delayed 8/61 **Complication rates - pneumothorax:** immediate 0/143; delayed 1/61	**Selection** Method of selection appropriate and likely to produce a representative cohort **Comparability** Groups not compared at baseline **Outcome**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Surgery, 35, 66-72, 2011 **Ref Id** 614740 **Country/ies where the study was carried out** Italy **Study type** Retrospective cohort study **Aim of the study** To examine rates of complications and reoperation in people having immediate or delayed breast reconstruction with Becker implants **Study dates** November 2004 to December 2006 **Source of funding** No sources reported	Women who had breast reconstruction at La Sapienza University of Rome, the University of Sassari or the University of Perugia with an anatomical Becker-type implant in the sub-muscular position **Exclusion criteria** No additional criteria reported **Reported subgroups** All had reconstruction with implants and did not have radiotherapy		major muscle was detached from the ribs and raised with the abdominal fascia, or the deep subcutaneous layer above it, to provide complete coverage of the implant. The partially filled implant was then placed in the subcutaneous pocket. The inferior mastectomy skin flap was stretched over the lower part of the anatomical expander implant to accentuate the lower pole of the reconstructed breast. Two or three drains were placed; one in the submuscular plane, one in the subcutaneous plane and, if required, in the axilla. After insertion, the implant was filled with further saline to fill the pocket as much as possible; final fill was performed on an outpatient basis. **Control arm (delayed):** no details about mastectomy. For the delayed reconstruction, the mastectomy incision was reopened, the sub-muscular pocket was dissected, and the partially filled implant was inserted; one drain was	**Complication rates - bleeding (bleeding):** immediate 9/143; delayed 5/61 **Complication rates - wound dehiscence (wound):** immediate 7/143; 1/61 **Complication rates - infection:** immediate 2/143; delayed 0/61 **Complication rates - valve obstruction (flap loss):** immediate 1/143; delayed 2/61 **Complication rates - valve displacement (flap loss):** immediate 2/143; delayed 3/61 **Complication rates - implant rupture (implant**	Outcome assessment adequate and follow-up adequate **Indirectness** None **Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
			placed. After insertion, the implant was filled with further saline to fill the pocket as much as possible; final fill was performed on an outpatient basis.	**loss):** immediate 1/143; delayed 0/61 **Complication rates - implant malposition (cosmetic):** immediate 22/143; delayed 12/61 **Complication rates - capsular contracture (cosmetic):** immediate 4/143; delayed 2/61	
Full citation Sullivan, S. R., Fletcher, D. R. D., Isom, C. D., Isik, F. F., True incidence of all complications following immediate and delayed breast reconstruction, Plastic and Reconstructive Surgery, 122, 19-28, 2008 **Ref Id** 614891	**Sample size** 240 **Characteristics** Gender: 100% female Age: mean 47.2, SD 9.1 Ethnicity: NR **Inclusion criteria** Women who underwent unilateral or bilateral breast reconstruction at the University of Washington Medical Center **Exclusion criteria**	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction **Control arm:** mastectomy + delayed reconstruction	**Details** **Intervention arm (immediate):** no information about mastectomy. Immediate reconstruction was only offered to those who had not had prior chest wall irradiation, were not actively smoking or morbidly obese, and had stage I or II disease. 53% had reconstruction with tissue expander/implant and 47% were reconstructed with autologous tissue.	**Results** **Complication rates - total flap loss (flap loss):** immediate 4/167; delayed 5/167 **Complication rates - partial flap loss (flap loss):** immediate 3/167; delayed 4/167 **Complication rates - fat necrosis (flap loss):** immediate 20/167; delayed 23/167	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** Delayed cohort had significantly higher rates of radiotherapy and lower rates of previous lumpectomy **Outcome** Outcome assessment and follow-up adequate **Indirectness**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out USA **Study type** Retrospective cohort study **Aim of the study** To examine frequency and patterns of reconstruction, clinical characteristics associated with complications and refine criteria for performing reconstructions **Study dates** Underwent reconstruction 2002 to 2006 **Source of funding** No sources reported	No additional criteria reported **Reported subgroups** None of interest		**Control arm (delayed):** no information about mastectomy. 32% had reconstruction with tissue expander/implant and 68% had reconstruction with autologous tissue.	**Complication rates - infection:** immediate 9/167; delayed 4/167 **Complication rates - skin flap necrosis (mastectomy skin flaps):** immediate 5/167; delayed 0/167 **Complication rates - delayed wound healing (wound):** immediate 3/167; delayed 6/167 **Complication rates - hematoma (bleeding):** immediate 6/167; delayed 1/167 **Complication rates - capsular contracture (cosmetic):** immediate 36/167; delayed 9/167 **Complication rates - implant malposition**	None **Limitations** Unit of analysis was breast (some women had bilateral reconstruction) rather than patient - likelihood of complication in each breast may not be independent. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				(cosmetic): immediate 3/167; delayed 1/167 **Complication rates - implant exposure (implant loss):** immediate 2/167; delayed 0/167 **Complication rates - implant deflation (implant loss):** immediate 4/167; delayed 5/167	
Full citation Terao, Y., Taniguchi, K., Fujii, M., Moriyama, S., Postmastectomy radiation therapy and breast reconstruction with autologous tissue, Breast Cancer, 1-6, 2017 **Ref Id** 614940 **Country/ies where the study was carried out** Japan	**Sample size** 58 **Characteristics** Gender: NR Age: immediate mean 53, delayed mean 49, range 35-77 Ethnicity: NR **Inclusion criteria** None reported - all patients underwent autologous reconstruction with a flap and postmastectomy radiotherapy	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction followed by radiotherapy **Control arm:** mastectomy followed by radiotherapy + delayed reconstruction	**Details** **Intervention arm (immediate):** no information about mastectomy. Underwent immediate reconstruction with a free transverse rectus abdominus myocutaneous (TRAM) flap (40%), a pedicled TRAM flap (55%), or a latissimus dorsi musculocutaneous (LD) flap (5%). Mean time to initiation of postmastectomy radiotherapy was 9.1 weeks (range 7 to 18) for those that received neoadjuvant chemotherapy and 35.4 weeks (range 22 to 48) for	**Results** **Complication rates - total flap loss (flap loss):** immediate 1/38; delayed 0/20	**Selection** Insufficient information reported; unclear if all eligible patients were included **Comparability** 53% of immediate cohort received neoadjuvant chemotherapy whereas none of the delayed cohort did. Immediate cohort older than delayed cohort (not compared statistically) **Outcome**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study type Retrospective cohort study **Aim of the study** To investigate the timing of postmastectomy radiotherapy, prognosis, and cosmetic results of patients undergoing breast reconstruction **Study dates** Underwent reconstruction 2006 to 2015 **Source of funding** No sources reported	**Exclusion criteria** Delayed reconstruction after breast conserving surgery **Reported subgroups** All patients autologous reconstruction and had radiotherapy after mastectomy		those that received adjuvant chemotherapy. **Control arm (delayed):** no information about mastectomy. Underwent delayed reconstruction with a free rectus abdominis musculocutaneious (TRAM) flap (70%), a pedicled TRAM flap (15%), or a latissimus dorsi musculocutaneous (LD) flap (15%). Mean time to reconstruction after postmastectomy radiotherapy was 51 months (range 15 to 120).		Insufficient information about outcome assessment or length of follow-up **Indirectness** None **Limitations** Small sample size; limited comparison of immediate and delayed cohorts as this was not primary aim of study **Other information**
Full citation Tsai, Y. J., Lin, P. Y., Chiang, Y. C., Chen, Y. C., Kuo, P. J., Kuo, Y. R., Breast reconstruction modality and outcomes after mastectomy, Formosan Journal of	**Sample size** 90 **Characteristics** Gender: NR Age: mean 44.8, range 28-61	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction **Control arm:** mastectomy	**Details** No further details reported	**Results** **Complication rates - any:** immediate 22/66; delayed 9/24	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** Groups not compared at baseline

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Surgery, 49, 9-14, 2016 **Ref Id** 614988 **Country/ies where the study was carried out** Taiwan **Study type** Retrospective cohort study **Aim of the study** To examine complication rates following different modalities for breast reconstruction **Study dates** Underwent reconstruction during past 5 years; estimated as 2009 to 2014 as paper first received by journal October 2014 **Source of funding** No sources reported	Ethnicity: NR **Inclusion criteria** All patients who underwent breast reconstruction at Kaohsiung Medical University Hospital during the past 5 years **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest	+ delayed reconstruction			**Outcome** Outcome assessment and follow-up adequate **Indirectness** None **Limitations** Small sample size; limited comparison between immediate and delayed reconstruction as not primary aim of study **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Zahra, T., El-Din, A. B., Shouman, O., Ismail, H. E. D. A., Rifaat, M. A., Assessment of aesthetic results and quality of life following different procedures of breast reconstruction, Journal of Plastic Dermatology, 10, 105-110, 2014 **Ref Id** 615222 **Country/ies where the study was carried out** Egypt **Study type** Prospective cohort study **Aim of the study** To examine the effect of different breast reconstruction procedures on	**Sample size** 60 **Characteristics** Gender: NR Age: NR Ethnicity: NR **Inclusion criteria** Not reported - patients who were operated on at Mansoura University and Cairo University between 2011 and 2013 **Exclusion criteria** No additional criteria reported **Reported subgroups** Autologous reconstruction	**Interventions** **Intervention arm:** mastectomy +immediate reconstruction **Control arm:** mastectomy + delayed reconstruction	**Details** **Intervention arm (immediate):** subcutaneous mastectomy followed by immediate reconstruction with extended latissimus dorsi myocutaneous (EDLM) flap. **Control arm (delayed):** no details about mastectomy. Delayed reconstruction with LD flap or implant (33%), EDLM flap (33%) and TRAM flap (33%). All patients received radiotherapy and/or chemotherapy between mastectomy and reconstruction (minimum of 6 months between adjuvant therapy and reconstruction)	**Results** **Whole sample:** **Patient satisfaction - general satisfaction measured by MBROS-S questionnaire:** immediate N=30, M=4.1, SD=1.03; delayed N=30, M=4.0, SD=1.11 **Patient satisfaction - aesthetic satisfaction measured by MBROS-S questionnaire:** immediate N=30, M=1.7, SD=0.06; delayed N=30, M=1.4, SD=0.72 **Health-related quality of life - BREAST-Q score:** immediate N=30, M=90.39, SD=4.48; delayed N=30, M=75.39, SD=9.01 **Cosmetic result - excellent result**	**Selection** Insufficient information about selection methods; unclear if all eligible were included. **Comparability** Groups not compared at baseline **Outcome** Outcome assessment and follow-up adequate **Indirectness** None **Limitations** Small sample size **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
aesthetic results and quality of life **Study dates** Underwent reconstruction 2011 to 2013 **Source of funding** No sources reported				**measured by the Christie Scale:** immediate 21/30; delayed 11/30 **Cosmetic result - good result measured by the Christie Scale:** immediate 6/30; delayed 12/30 **Cosmetic result - fair result measured by the Christie Scale:** immediate 3/30; delayed 4/30 **Cosmetic result - poor result measured by the Christie Scale:** immediate 0/30; delayed 3/30 **Autologous reconstruction:** **Patient satisfaction - general satisfaction measured by MBROS-S questionnaire:** immediate N=30, M=4.1, SD=1.03; delayed N=20, M=4.2, SD=1.06	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Patient satisfaction - aesthetic satisfaction measured by MBROS-S questionnaire: immediate N=30, M=1.7, SD=0.06; delayed N=20, M=1.7, SD=0.07 **Health-related quality of life - BREAST-Q score:** immediate N=30, M=90.39, SD=4.48; delayed N=20, M=80.25, SD=4.8	
Full citation Zhong, T., Hu, J., Bagher, S., Vo, A., O'Neill, A. C., Butler, K., Novak, C. B., Hofer, S. O., Metcalfe, K. A., A Comparison of Psychological Response, Body Image, Sexuality, and Quality of Life between Immediate and Delayed	**Sample size** 106 **Characteristics** Gender: 100% female Age: mean/range NR; 68% ≤49 years, 28% 50-59 years, 13% ≥60 years Ethnicity: NR	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction **Control arm:** mastectomy + delayed reconstruction	**Details** **Intervention arm (immediate):** no information about mastectomy and limited information about reconstruction. Immediate reconstruction was normally offered to women with in situ breast cancer or stage I/II cancer with no lymph node involvement where postmastectomy radiotherapy was not anticipated	**Results** **Patient satisfaction - measured by BREAST-Q:** immediate N=30, M=60.8, SD=13.2; delayed N=76, M=70.6, SD=15.9 **Health-related quality of life - psychosocial wellbeing measured by BREAST Q:** immediate N=30, M=79.7, SD=21.3;	**Selection** Method of selection appropriate and likely to produce representative cohort **Comparability** Higher rates of in situ breast cancer in immediate cohort; higher rates of previous chemotherapy and

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Autologous Tissue Breast Reconstruction: A Prospective Long-Term Outcome Study, Plastic & Reconstructive Surgery, 138, 772-80, 2016 **Ref Id** 615247 **Country/ies where the study was carried out** Canada **Study type** Prospective cohort study **Aim of the study** To evaluate psychological response and health-related quality of life in immediate reconstruction compared with delayed reconstruction **Study dates**	**Inclusion criteria** Adult women with in situ or invasive breast cancer undergoing autologous reconstruction (and able to read and write English) **Exclusion criteria** No additional criteria reported **Reported subgroups** All autologous reconstructions		**Control arm (delayed):** no information about mastectomy or reconstruction. Mean time between mastectomy and reconstruction 2.8 years (range 5 months to 18 years)	delayed N=76, M=74, SD=19.2 **Health-related quality of life - sexual wellbeing measured by BREAST Q:** immediate N=30, M=62.7, SD=25.5; delayed N=76, M=57.3, SD=23.4 **Health-related quality of life - physical wellbeing (chest) measured by BREAST Q:** immediate N=30, M=79.9, SD=15.3; delayed N=76, M=80.4, SD=13.3 **Health-related quality of life - physical wellbeing (abdomen) measured by BREAST Q:** immediate N=30, M=77.6, SD=18.7; delayed N=76, M=76.7, SD=17.1	current endocrine therapy in delayed cohort **Outcome** Outcome assessment and follow-up adequate **Indirectness** Population: 25% had in situ breast cancer: serious **Limitations** Small sample size, particularly in immediate cohort **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Underwent reconstruction June 2009 to December 2010 **Source of funding** Canadian Breast Cancer Foundation; Canadian Institutes of Health Research					
Full citation Atisha, D., Alderman, A. K., Lowery, J. C., Kuhn, L. E., Davis, J., Wilkins, E. G., Prospective analysis of long-term psychosocial outcomes in breast reconstruction: two-year postoperative results from the Michigan Breast Reconstruction Outcomes Study, 247, 1019-28, 2008 **Ref Id** 669728	**Sample size** 287 **Characteristics** Gender: 100% female Age: NR Ethnicity: NR **Inclusion criteria** Women undergoing postmastectomy breast reconstruction with expander/implant, pedicle TRAM flap or free TRAM flap **Exclusion criteria**	**Interventions** **Intervention arm:** mastectomy + immediate reconstruction **Control arm:** mastectomy + delayed reconstruction	**Details** **Intervention arm (immediate):** No information reported about mastectomy. Reconstruction methods: 47% pedicle TRAM flap, 22% free TRAM flap, 30% expander/implant **Control arm (delayed):** No information reported about mastectomy. Reconstruction methods: 63% pedicle TRAM flap, 25% free TRAM flap, 12% expander/implant	**Results** **Health-related quality of life - change from pre- to post-reconstruction FACT-B functional wellbeing scale:** immediate N=116; M=2.51, SD=5.37; delayed N=55, M=0.45, SD=4.54 **Health-related quality of life - change from pre- to post-reconstruction FACT-B social wellbeing scale:** immediate N=115; M=-0.95, SD=3.90; delayed N=54, M=-0.30, SD=4.46	**Selection** Insufficient information about method of selection; patients contributed to study by their plastic surgeon - unclear if entire cohort was approached **Comparability** Unclear if groups are comparable at baseline; focus of study was not to compare immediate and delayed reconstruction **Outcome** Outcome assessment and follow-up adequate **Indirectness**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out USA **Study type** Prospective cohort study **Aim of the study** To evaluate the impact of postmastectomy reconstruction on psychosocial outcomes and body image **Study dates** 1994 to 1999 **Source of funding** No sources reported	Reconstruction with latissimus dorsi flaps **Reported subgroups** None of interest				None **Limitations** **Other information**

cGy, centigray; DCIS, ductal carcinoma in situ; EDLM, extended latissimus dorsi myocutaneous; EORTC QLQ-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-B; Functional assessment of cancer therapy – Breast cancer; Gy, gray; JHH, John Hopkins Hospital; LD, latissimus dorsi musculocutaneous; MBROS, Michigan Breast Reconstruction Outcomes Study; MRM, modified radical mastectomy; NCCN, National Comprehensive Cancer Network; NR, not reported; NSQIP, National Surgical Quality and Improvement Program; SD, standard deviation; SM, simple mastectomy; TRAM, transverse rectus abdominus myocutaneous

Appendix E – Forest plots

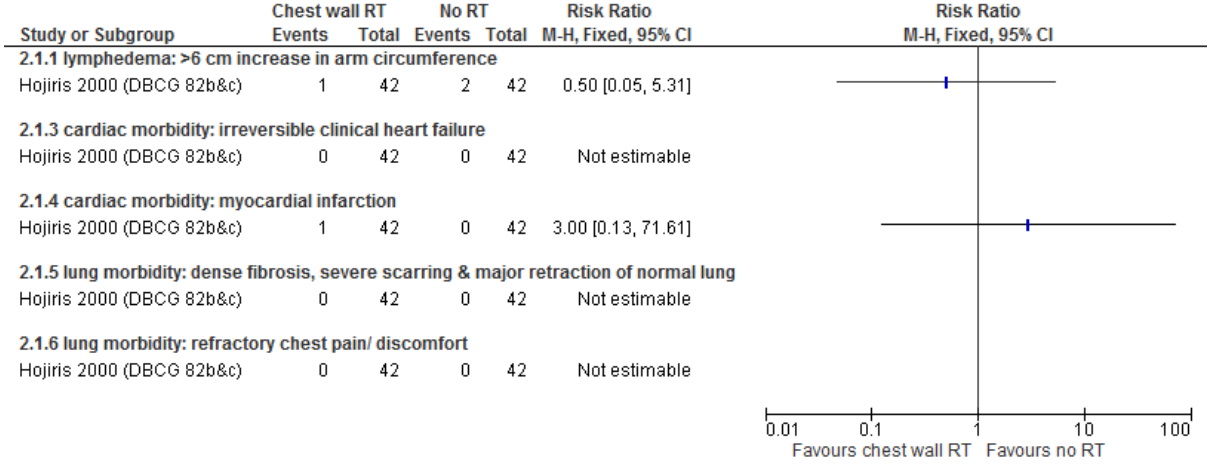
Forest plots for 9.1 What are the indications for postmastectomy radiotherapy for people with early and locally advanced breast cancer?

Comparison 1. Radiotherapy to the chest wall versus no radiotherapy

No studies were identified for this comparison.

Comparison 2. Radiotherapy to the chest wall plus nodes versus no radiotherapy

Figure 3: Treatment-related morbidity at median 9 years



Comparison 2.1. Radiotherapy to the chest wall + nodes versus no radiotherapy following mastectomy without axillary surgery in women with invasive breast cancer

Figure 4: First locoregional recurrence during years 0-9

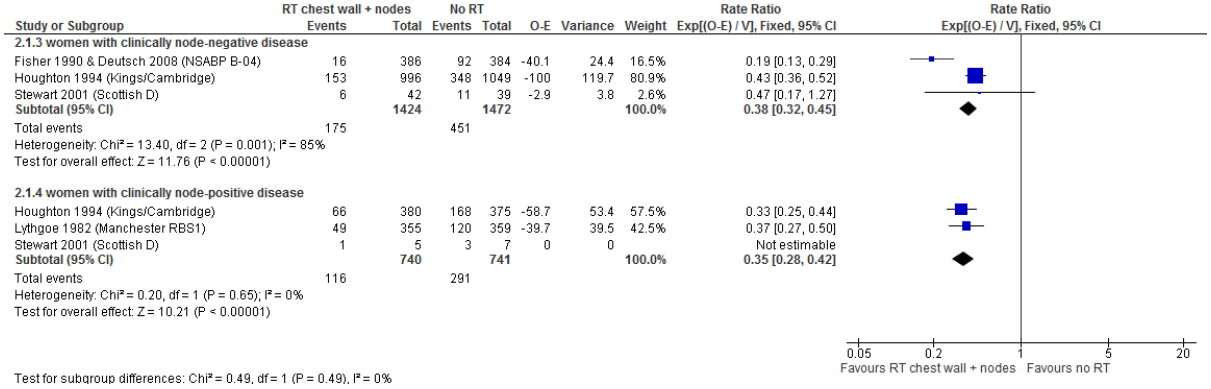


Figure 5: 20-year all-cause mortality

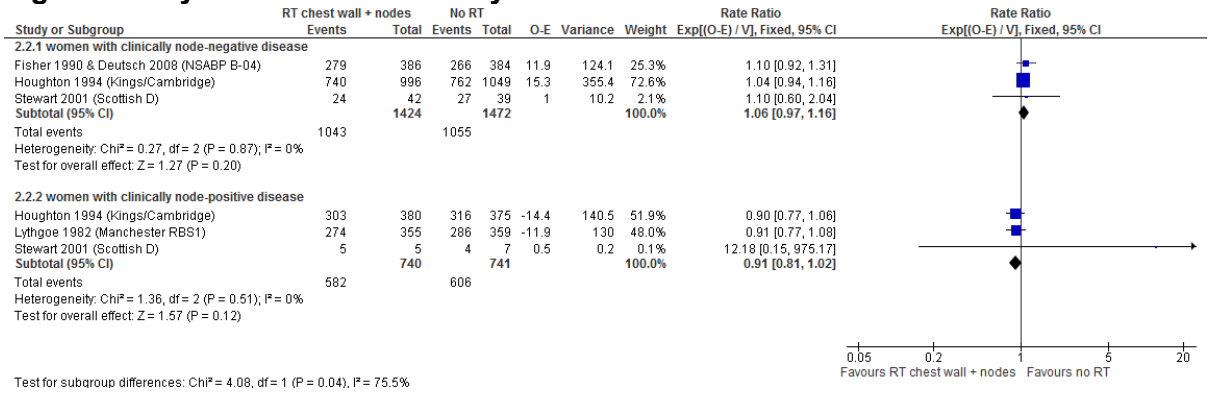


Figure 6: 20-year breast cancer mortality

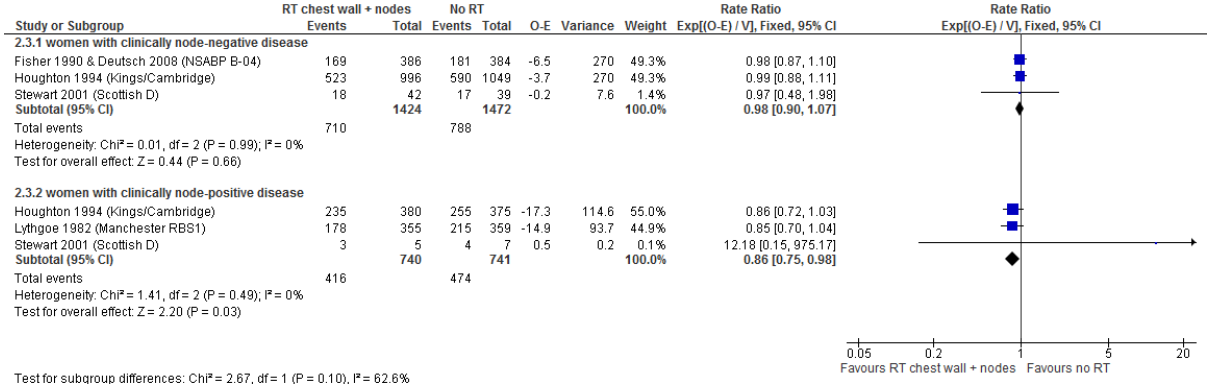


Figure 7: Treatment-related morbidity: arm oedema at 2 to 5 years follow-up

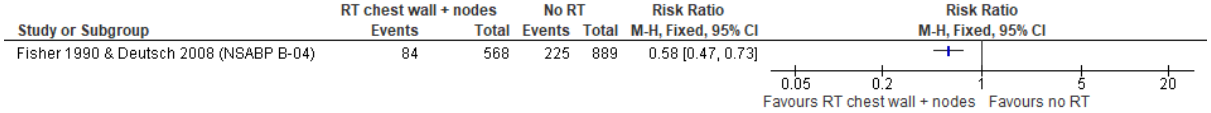
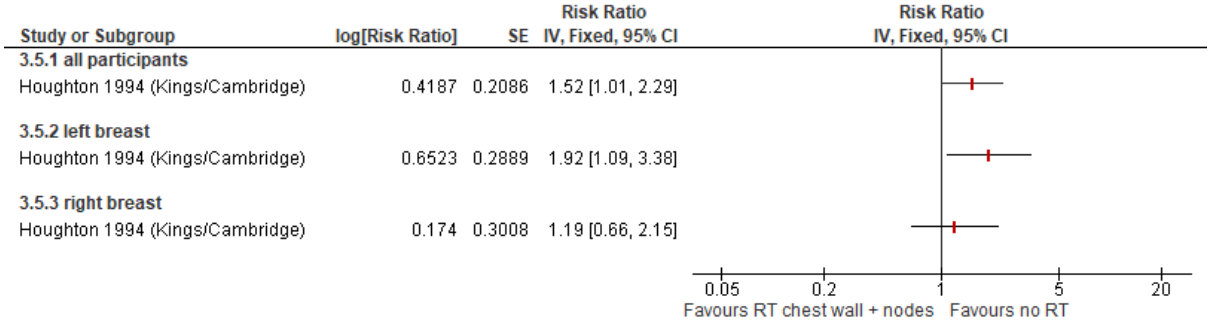


Figure 8: Treatment-related mortality: cardiac death at 5 years follow-up



Comparison 2.2. Radiotherapy to the chest wall + nodes versus no radiotherapy following mastectomy with axillary surgery in women with invasive breast cancer and node-negative disease

Figure 9: First locoregional recurrence during years 0-9

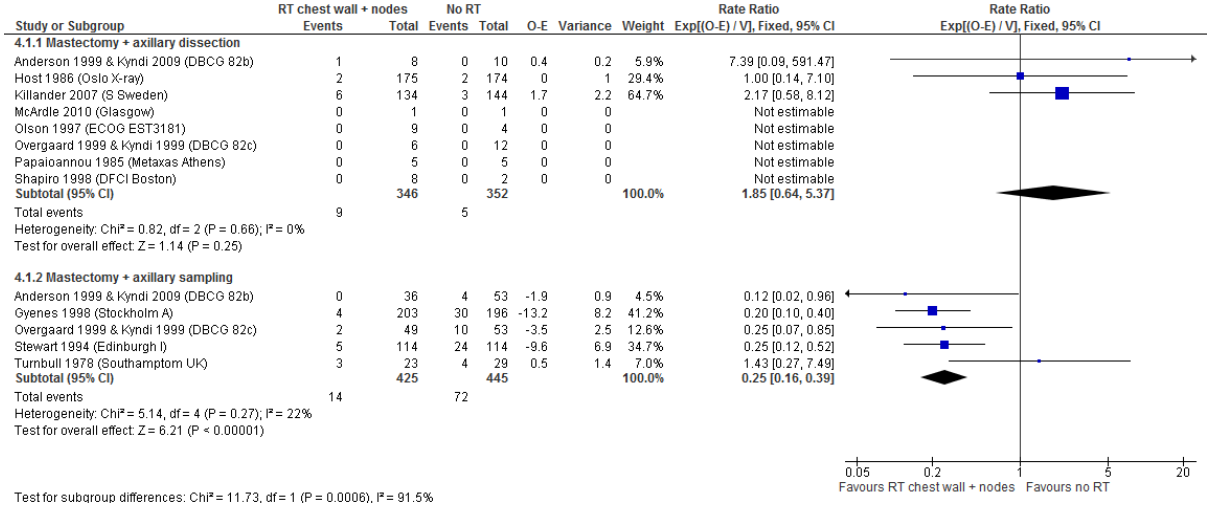


Figure 10: 20-year all-cause mortality

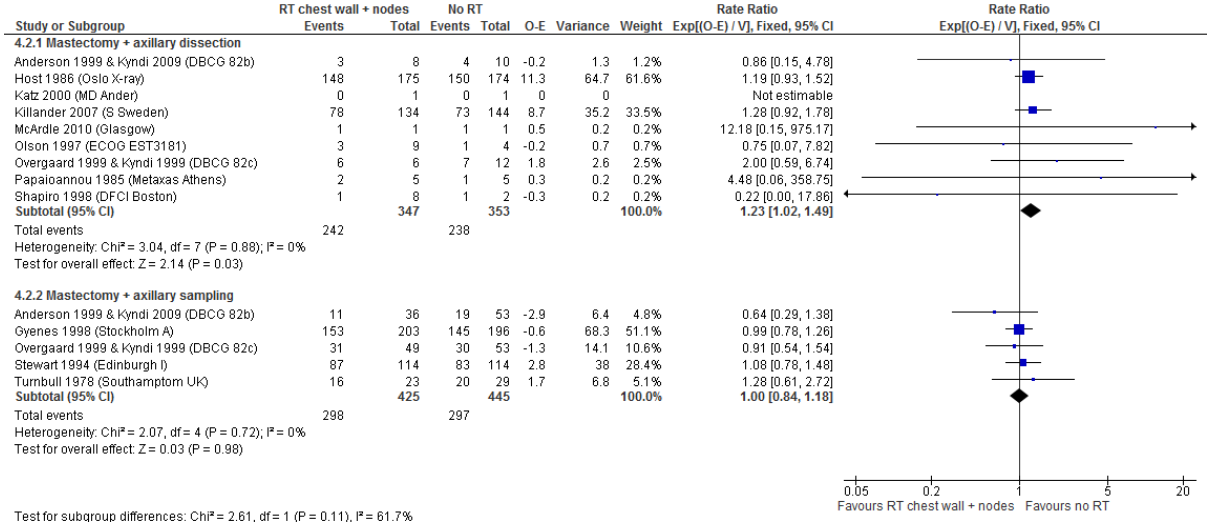
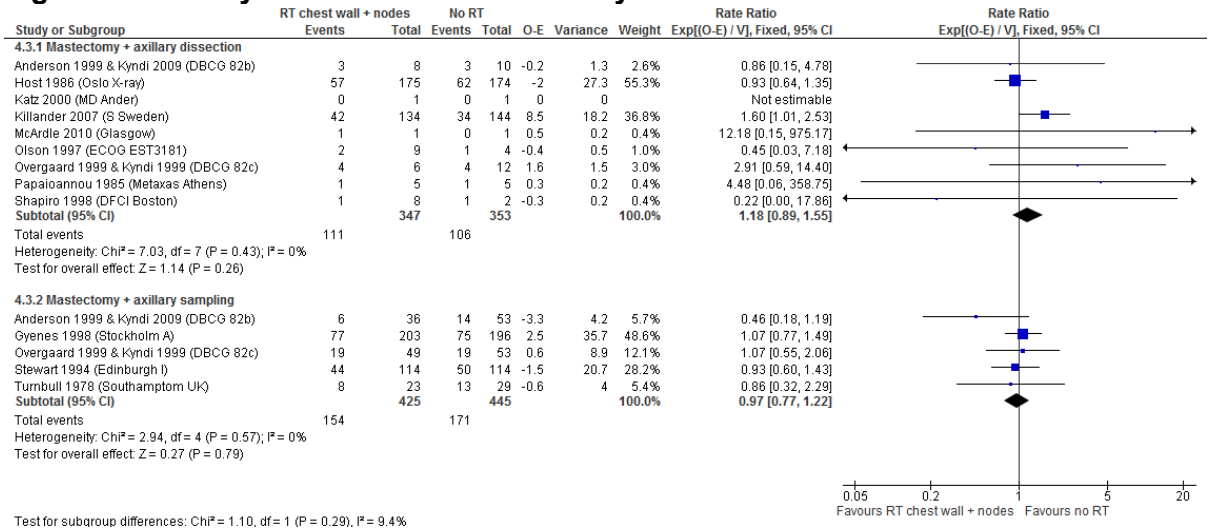


Figure 11: 20-year breast cancer mortality



Comparison 2.3. Radiotherapy to the chest wall + nodes versus no radiotherapy following mastectomy with axillary surgery in women with invasive breast cancer and node-positive disease

Figure 12: First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes

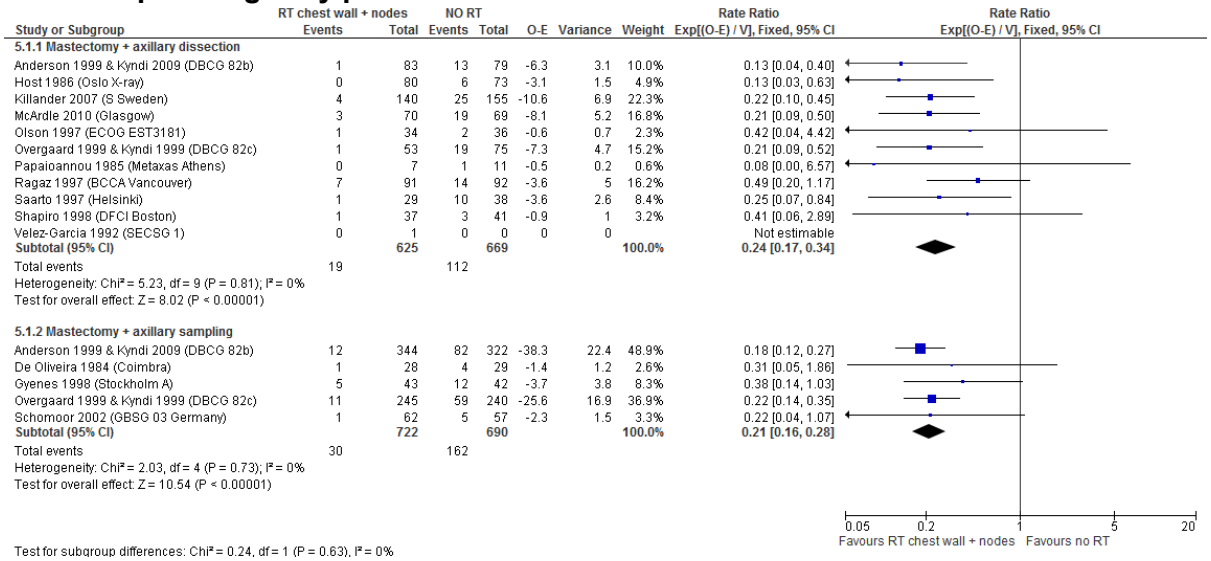


Figure 13: First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes [subgroup analysis: tumour grade]

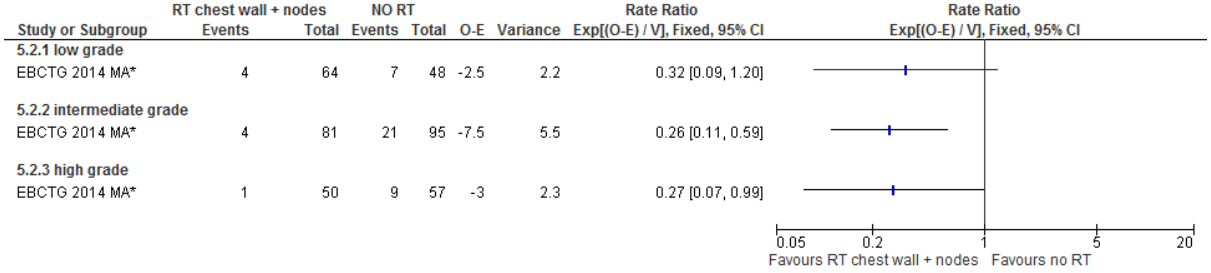


Figure 14: First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes [subgroup analysis: tumour size]

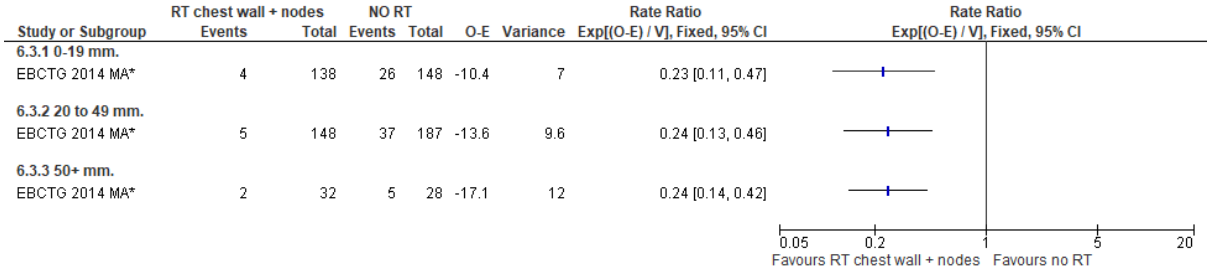


Figure 15: First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes

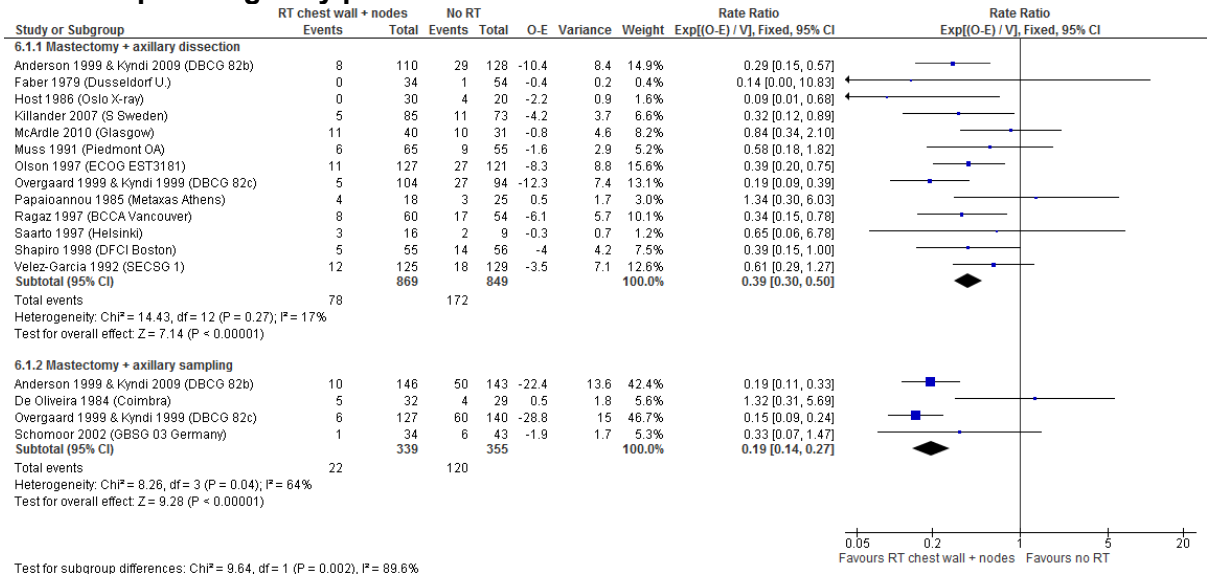


Figure 16: First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes [subgroup analysis: tumour grade]

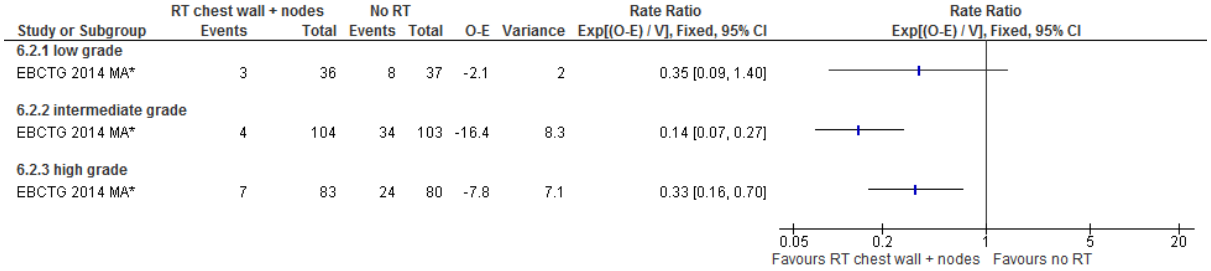


Figure 17: First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes [subgroup analysis: tumour size]

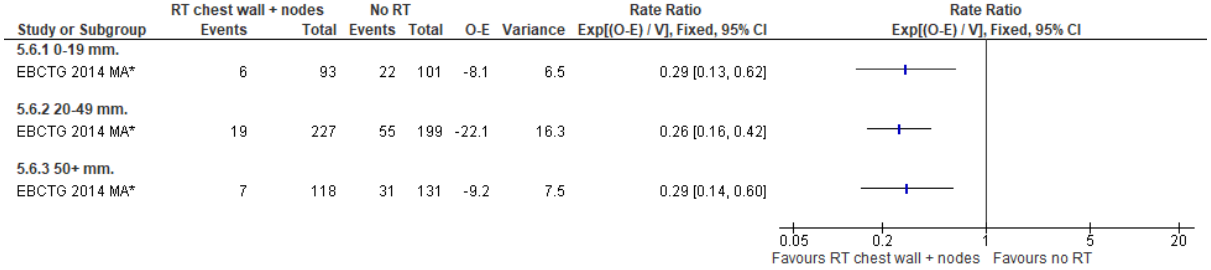


Figure 18: First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes [subgroup analysis: number of positive nodes]

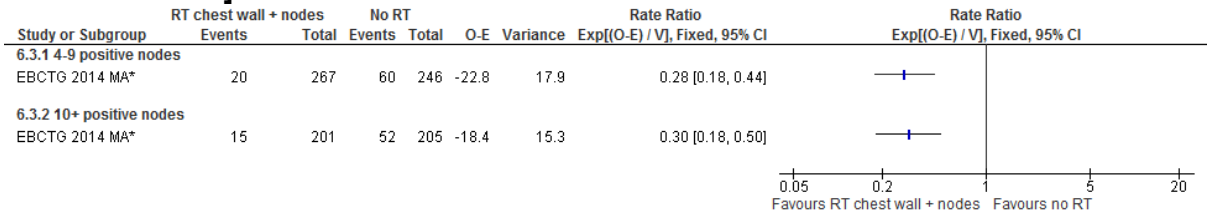


Figure 19: 20-year all-cause mortality in women with 1-3 pathologically positive nodes

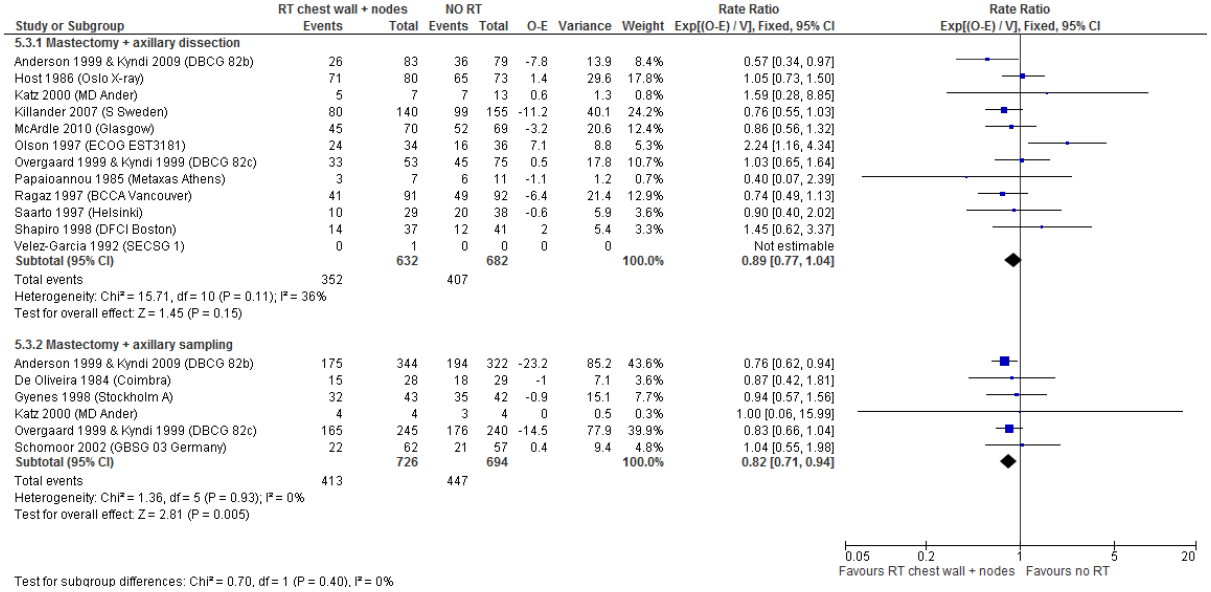


Figure 20: 20-year all-cause mortality in women with 4+ pathologically positive nodes

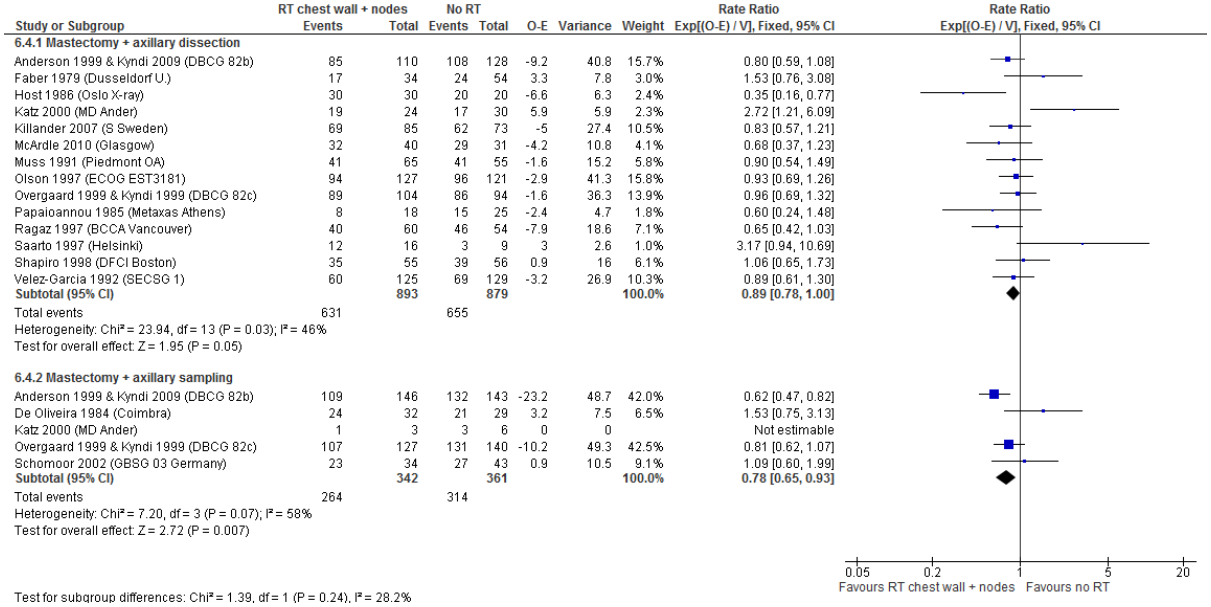


Figure 21: 20-year breast cancer mortality in women with 1-3 pathologically positive nodes

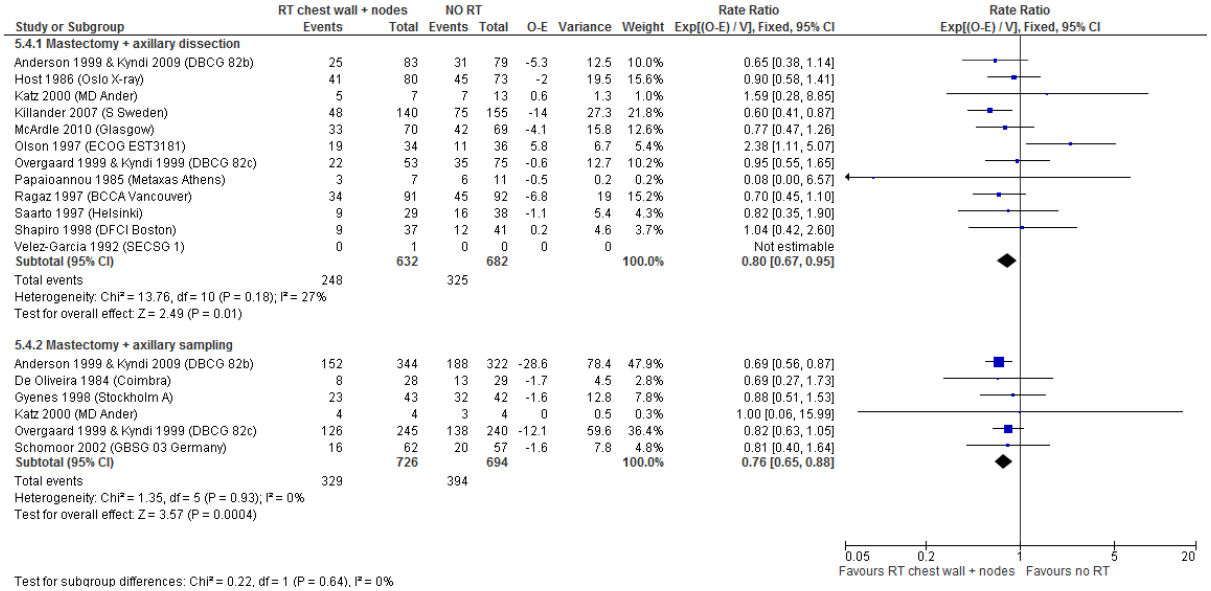


Figure 22: 20-year breast cancer mortality in women with 4+ pathologically positive nodes

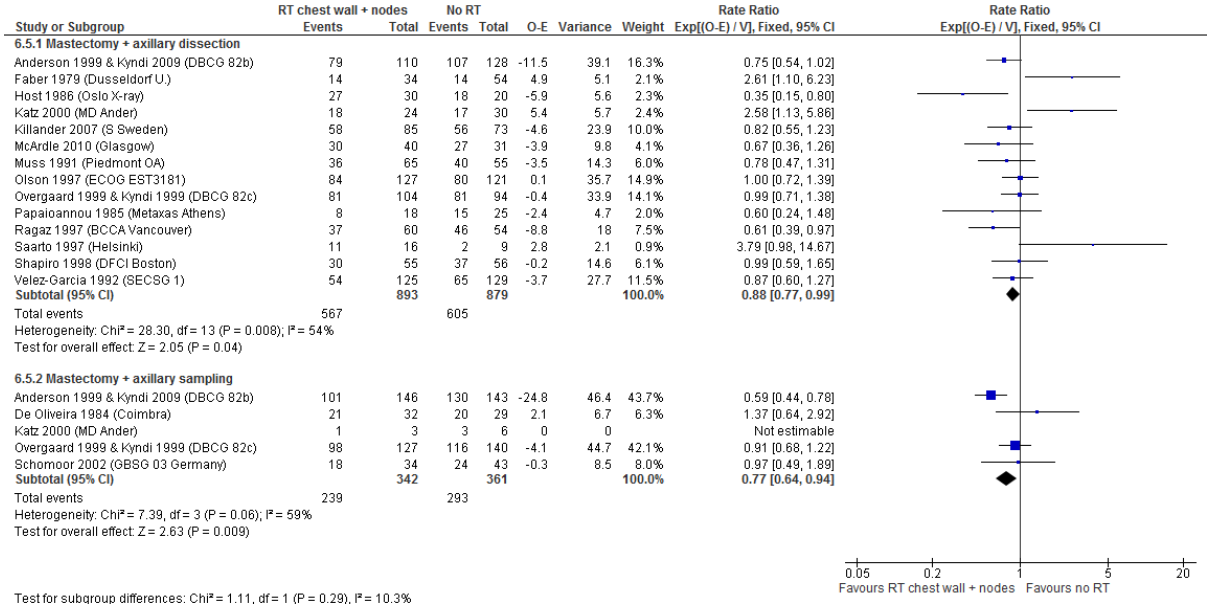


Figure 23: Treatment related morbidity in women with node-positive disease

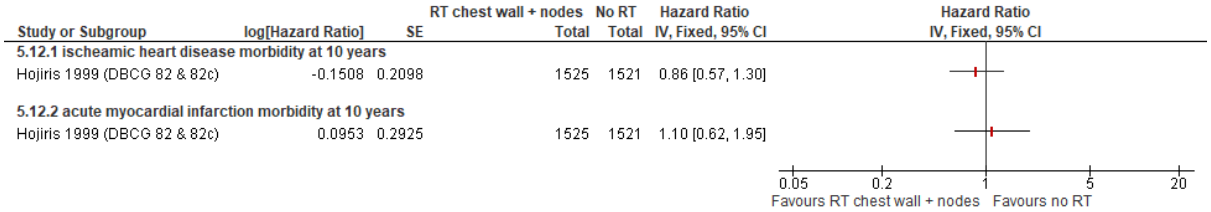


Figure 24: Treatment related morbidity in women with node-positive disease

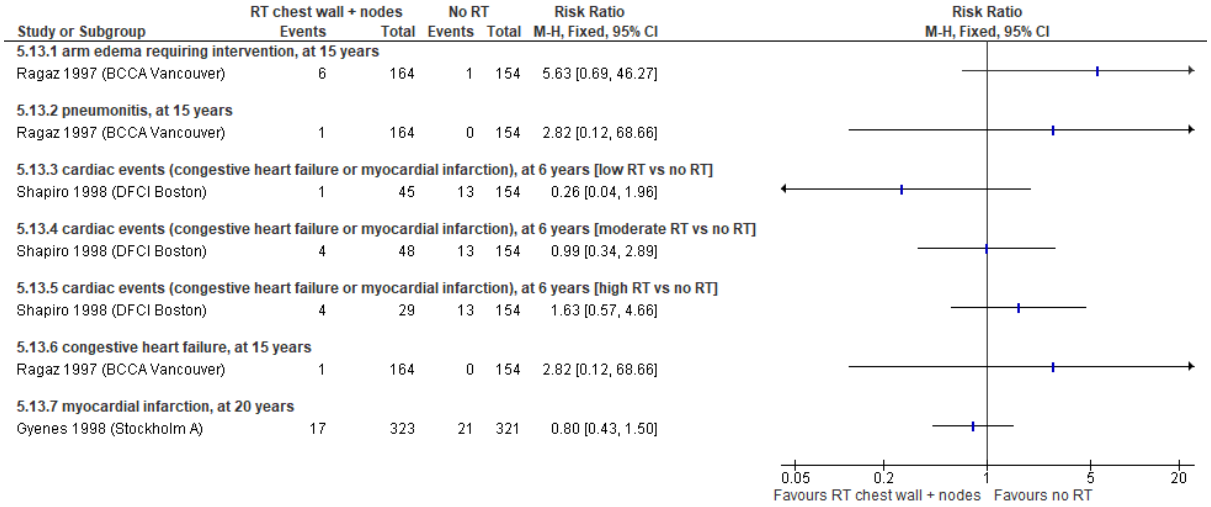


Figure 25: Treatment related mortality in women with node-positive disease

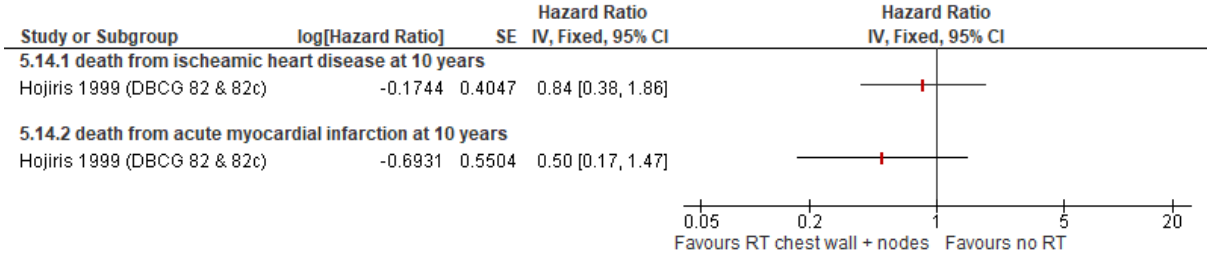
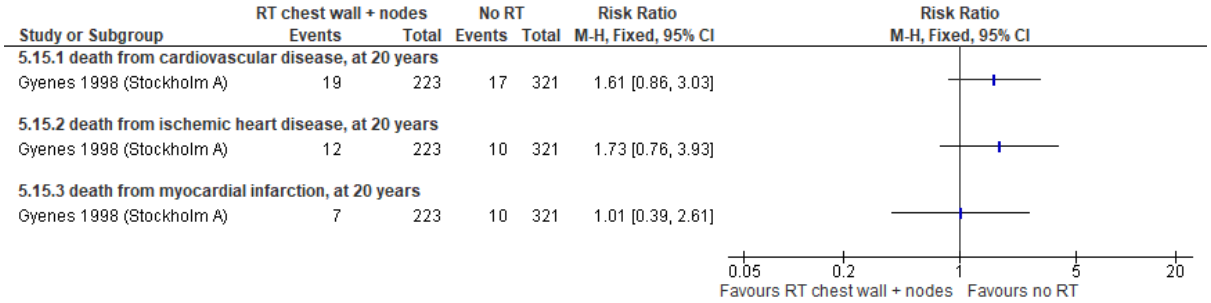
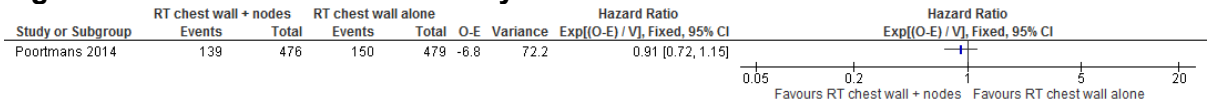


Figure 26: Treatment related mortality in women with node-positive disease



Comparison 3. Radiotherapy to the chest wall plus nodes versus radiotherapy to the chest wall alone

Figure 27: Overall survival at 10 years



Forest plots for 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?

Comparison 1. Immediate reconstruction versus delayed reconstruction

Figure 28: Patient satisfaction: aesthetic (dichotomous) at 6 month to 5.4 year follow-up

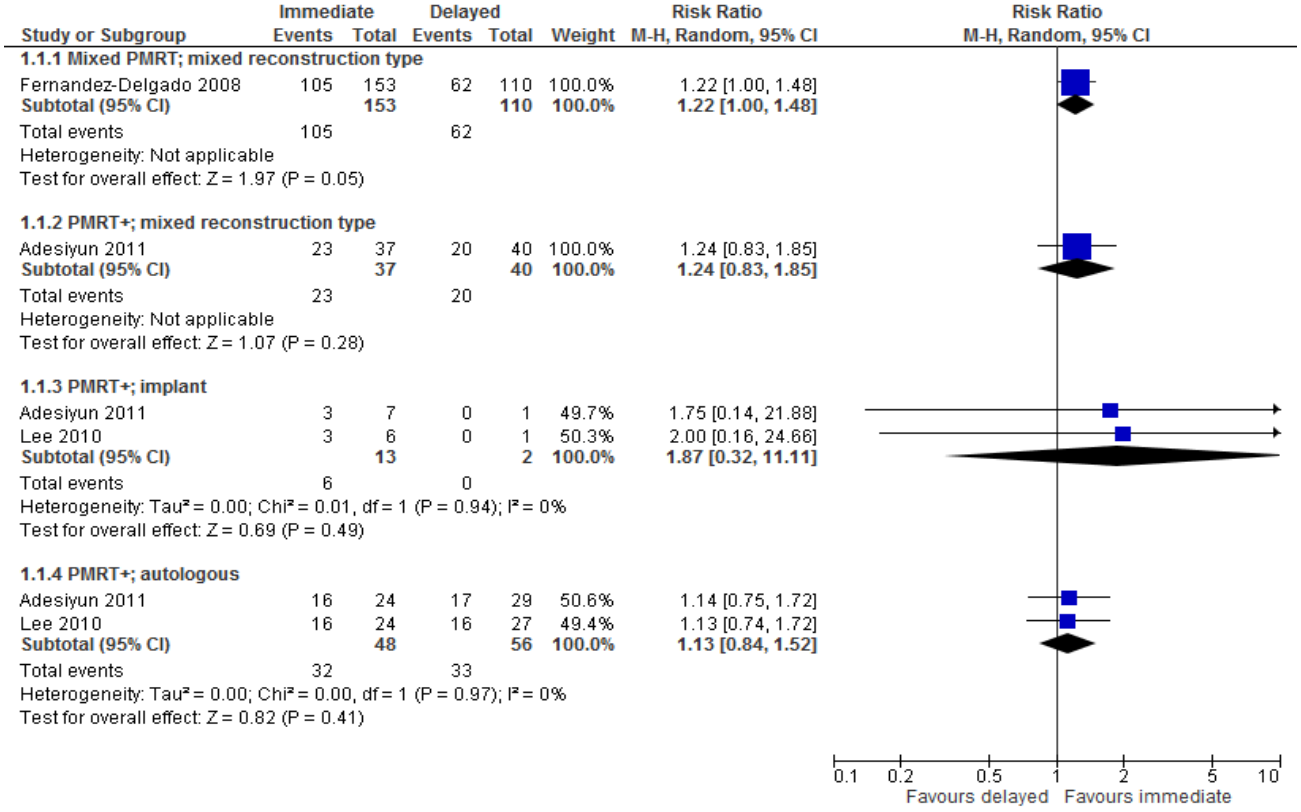


Figure 29: Patient satisfaction: aesthetic (continuous; follow-up not reported)

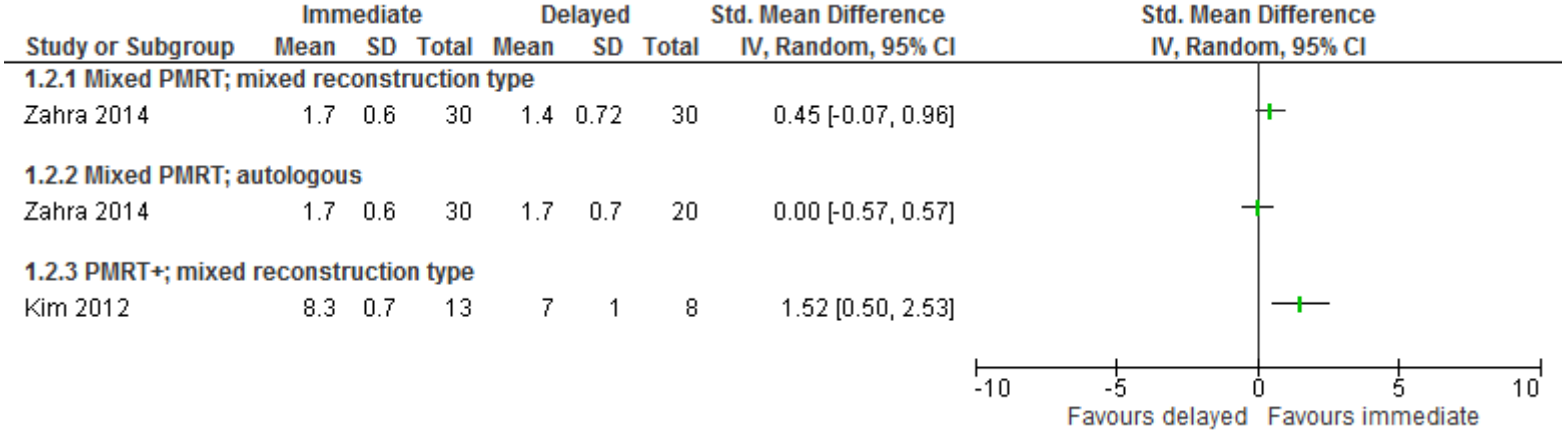


Figure 30: Patient satisfaction: general (dichotomous) at 2.3 to 5.4 year follow-up

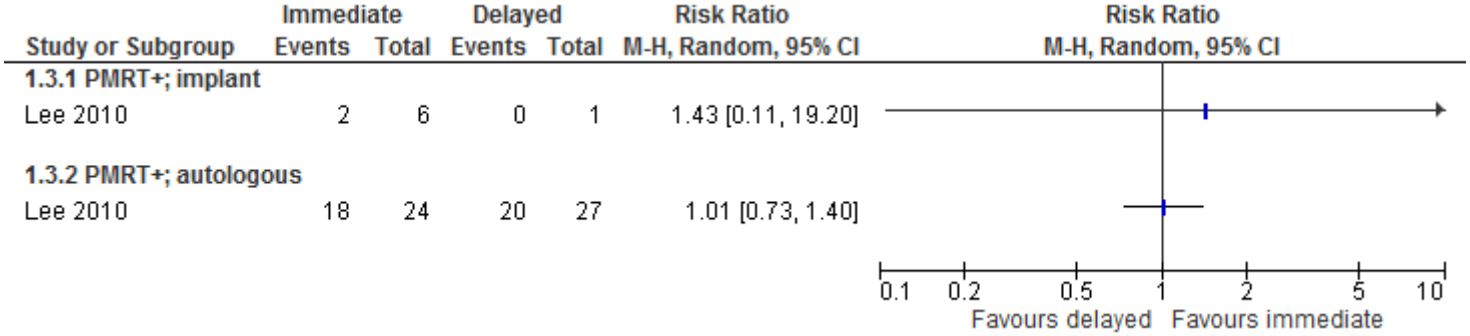


Figure 31: Patient satisfaction: general (continuous) at 6 month follow-up

Study or Subgroup	Immediate Mean	SD	Total	Delayed Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.4.1 Mixed PMRT; mixed reconstruction type								
Zahra 2014	4.1	1.03	30	4	1.11	30	100.0%	0.09 [-0.41, 0.60]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**0.09 [-0.41, 0.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.36 (P = 0.72)								
1.4.2 Mixed PMRT; autologous								
Zahra 2014	4.1	1.03	30	4.2	1.06	20	44.1%	-0.09 [-0.66, 0.47]
Zhong 2016	60.8	13.2	30	70.6	15.9	76	55.9%	-0.64 [-1.07, -0.21]
Subtotal (95% CI)			**60**			**96**	**100.0%**	**-0.40 [-0.93, 0.13]**
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 2.26$, df = 1 (P = 0.13); $I^2 = 56\%$								
Test for overall effect: Z = 1.47 (P = 0.14)								
1.4.3 PMRT+; mixed reconstruction type								
Kim 2012	22.3	1.2	13	22.2	1.2	8	100.0%	0.08 [-0.80, 0.96]
Subtotal (95% CI)			**13**			**8**	**100.0%**	**0.08 [-0.80, 0.96]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.18 (P = 0.86)								

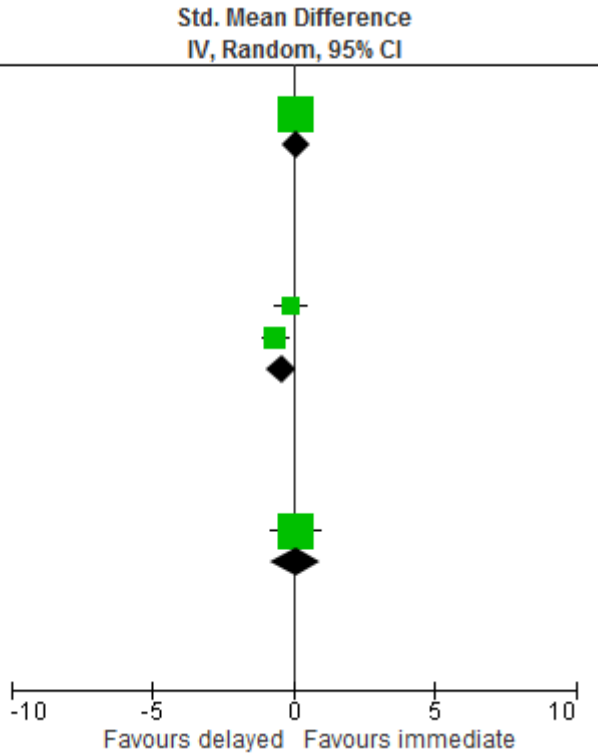


Figure 32: Delay in adjuvant chemotherapy: mixed PMRT; mixed reconstruction type

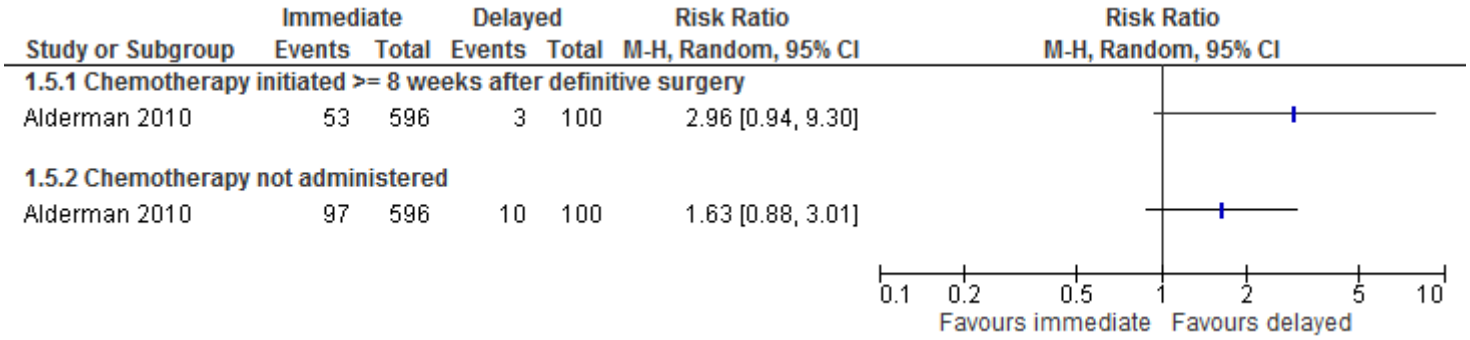


Figure 33: Complication rates: any at 3.2 to 3.9 year follow-up (early occurring within 3 months of reconstruction)

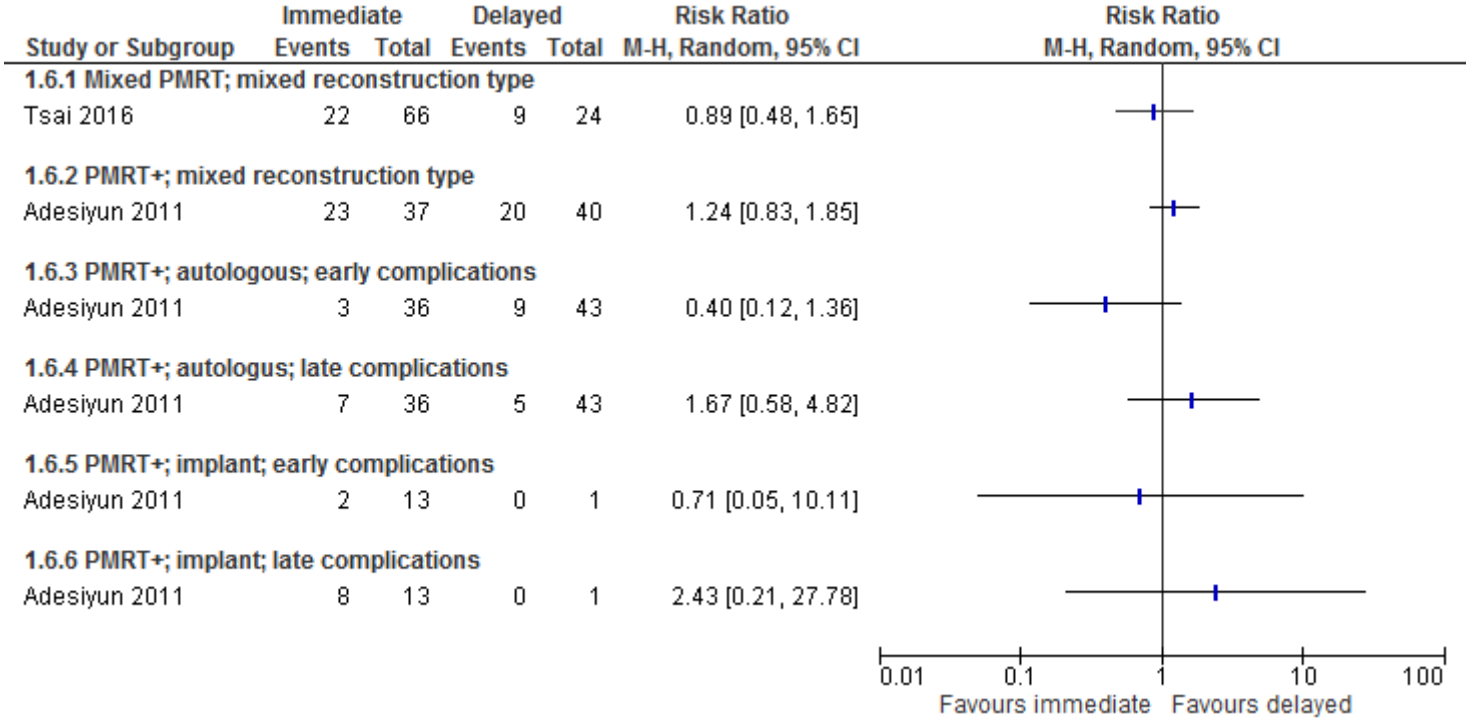


Figure 34: Complication rates: any surgical at 111 to 12 month follow-up

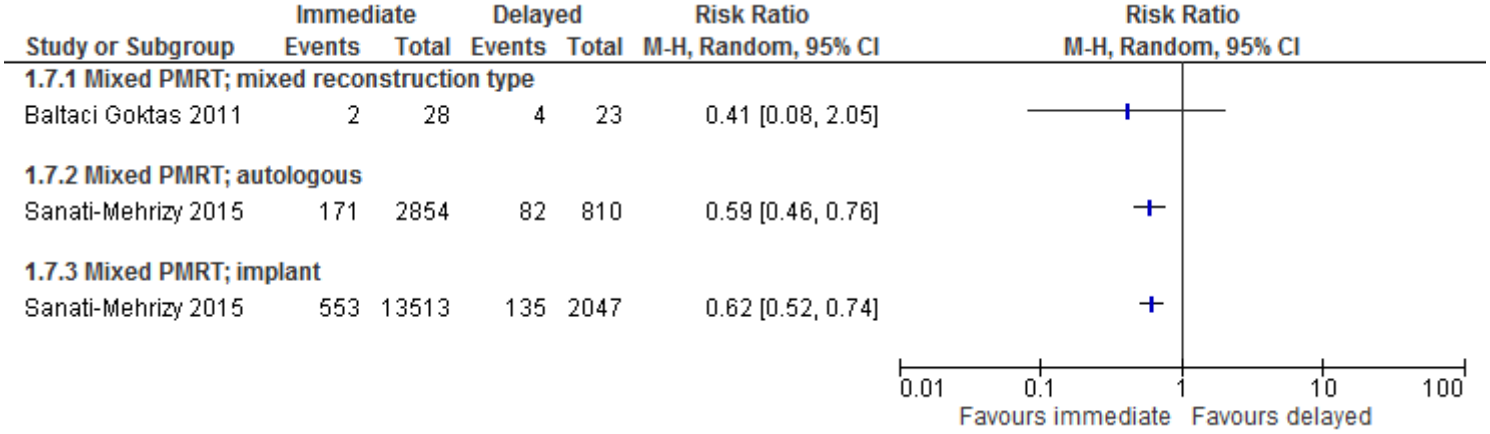


Figure 35: Complication rates: any donor site: mixed PMRT; mixed reconstruction type at 17 to 18 month follow-up

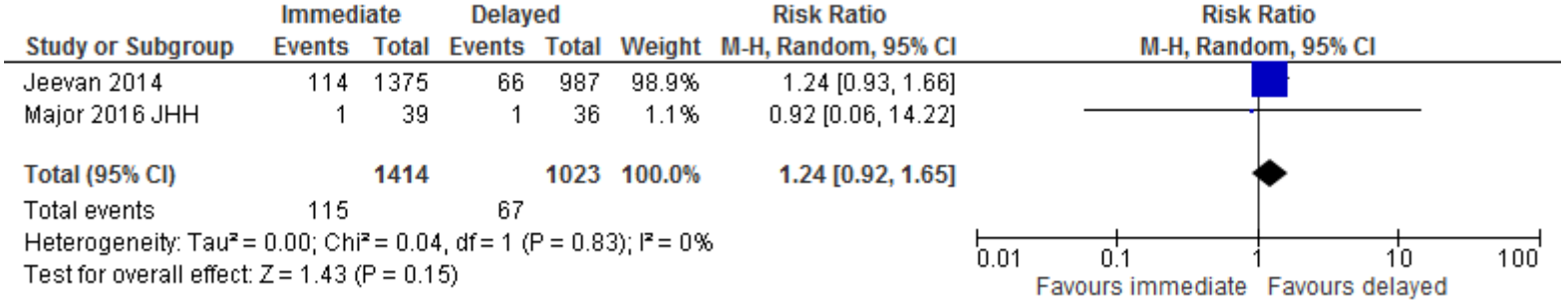


Figure 36: Complication rates: any mastectomy site at 18 month follow-up

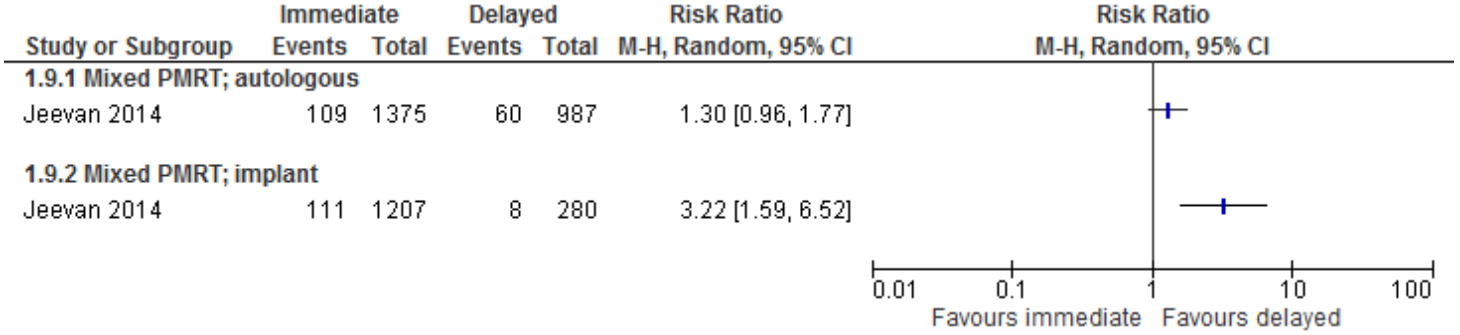


Figure 37: Complication rates: any implant related: mixed PMRT at 18 month follow-up

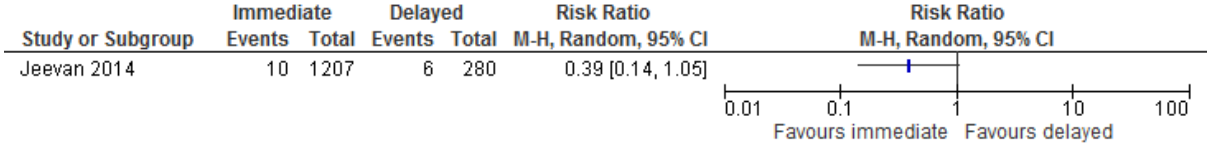


Figure 38: Complication rates: any flap related: mixed PMRT at 18 month follow-up

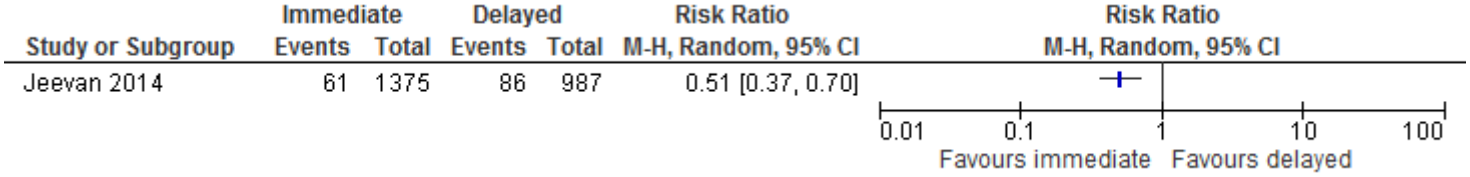


Figure 39: Complication rates: flap/prosthesis failure at 1 to 17 month follow-up

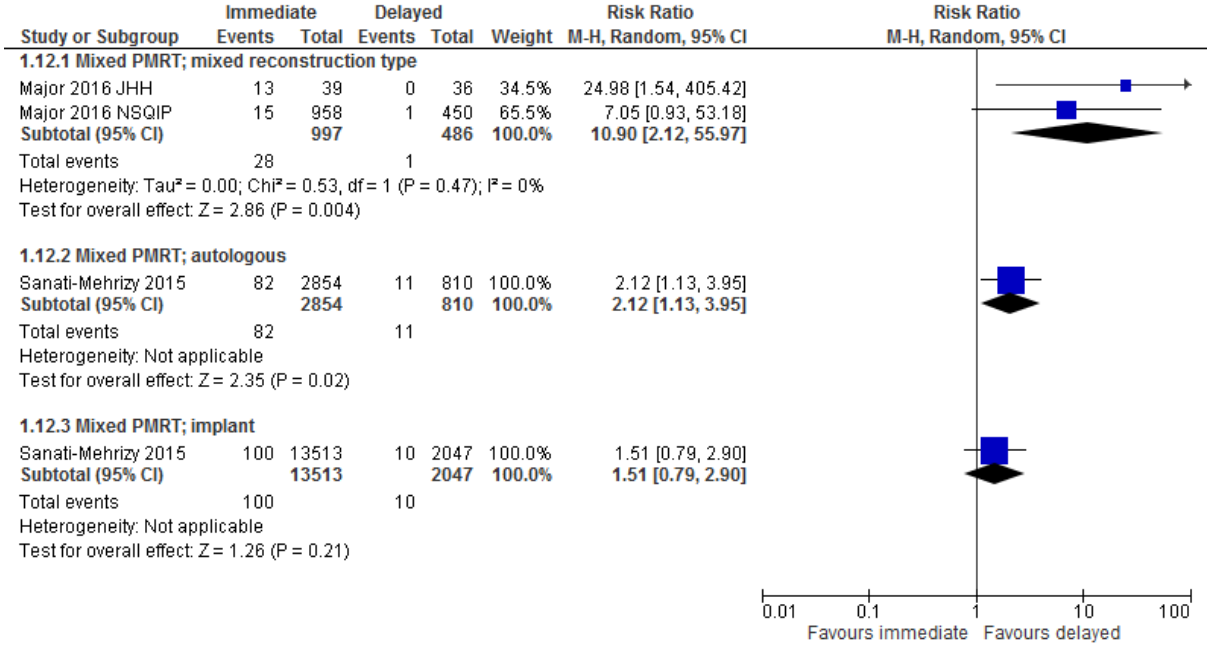


Figure 40: Complication rates: any radiological: mixed PMRT; mixed reconstruction type

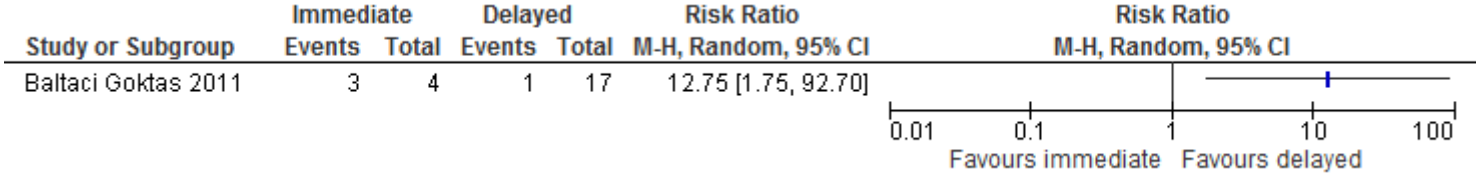


Figure 41: Complication rates: lymphoedema: mixed PMRT; mixed reconstruction type at 11 to 12 month follow-up

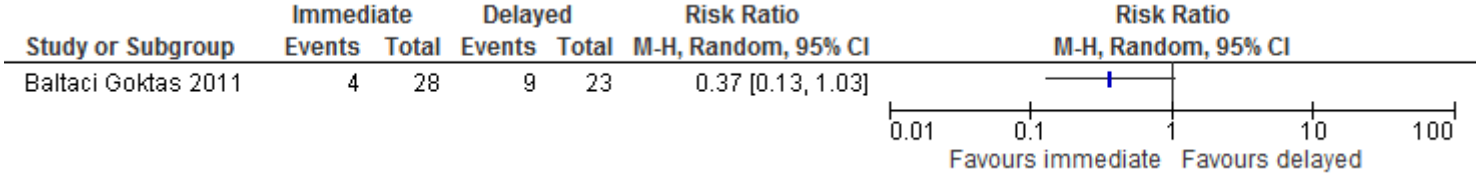


Figure 42: Complication rates: heart attack: mixed PMRT; mixed reconstruction type at 1 to 18 month follow-up

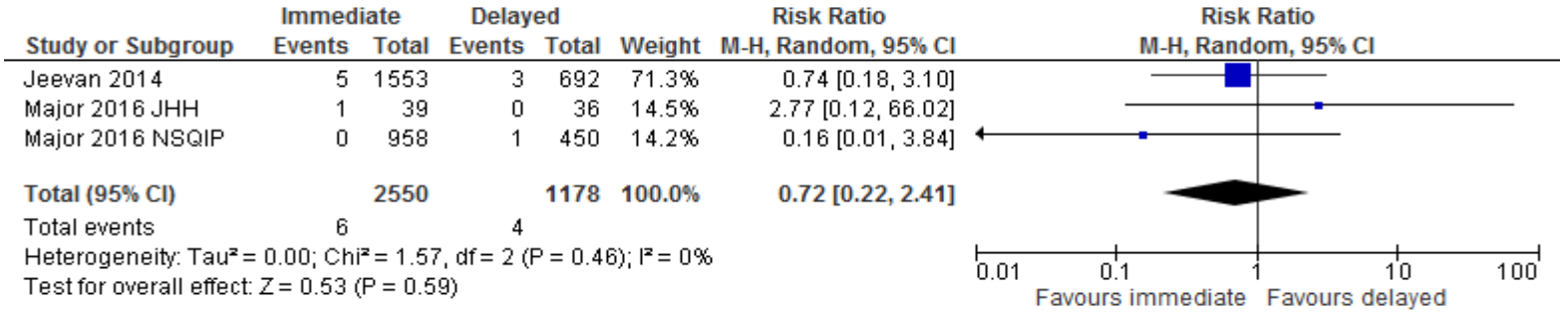


Figure 43: Complication rates: capsular contracture (cosmetic) at 6 month to 4 year follow-up

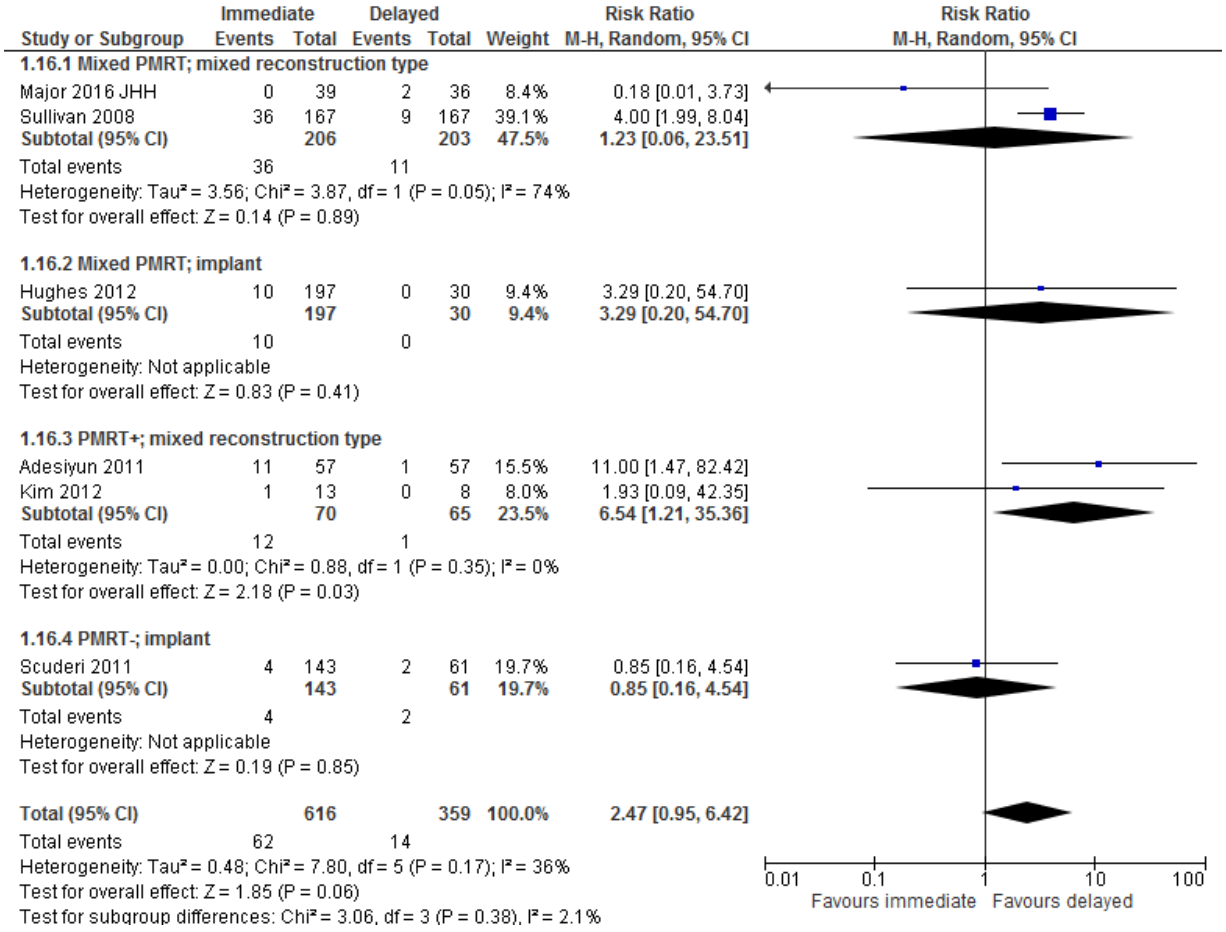


Figure 44: Complication rates: implant malposition (cosmetic) at 6 month to 4 year follow-up

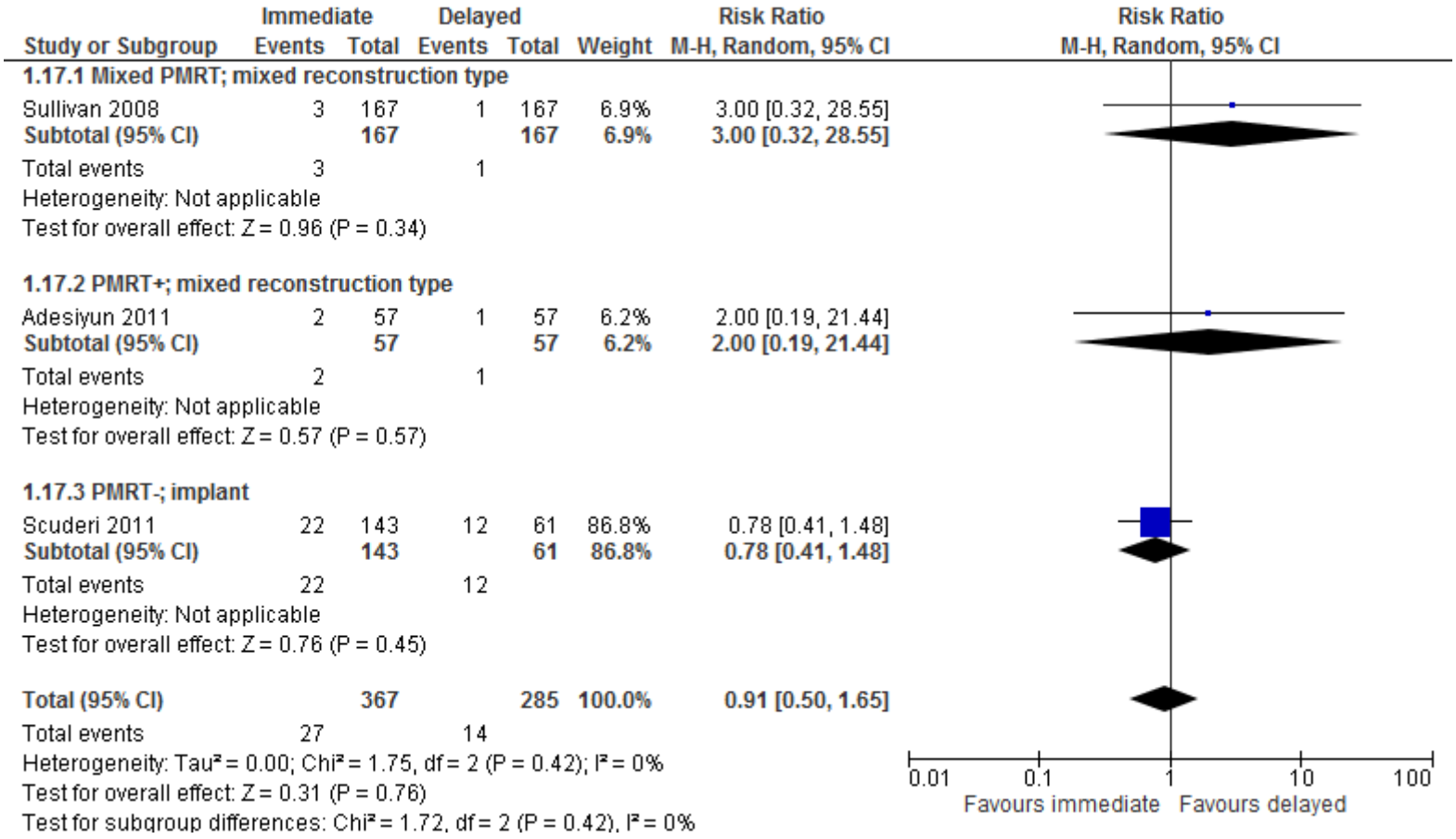


Figure 45: Complication rates: implant rupture/extrusion (implant loss) at 6 month to 4 year follow-up

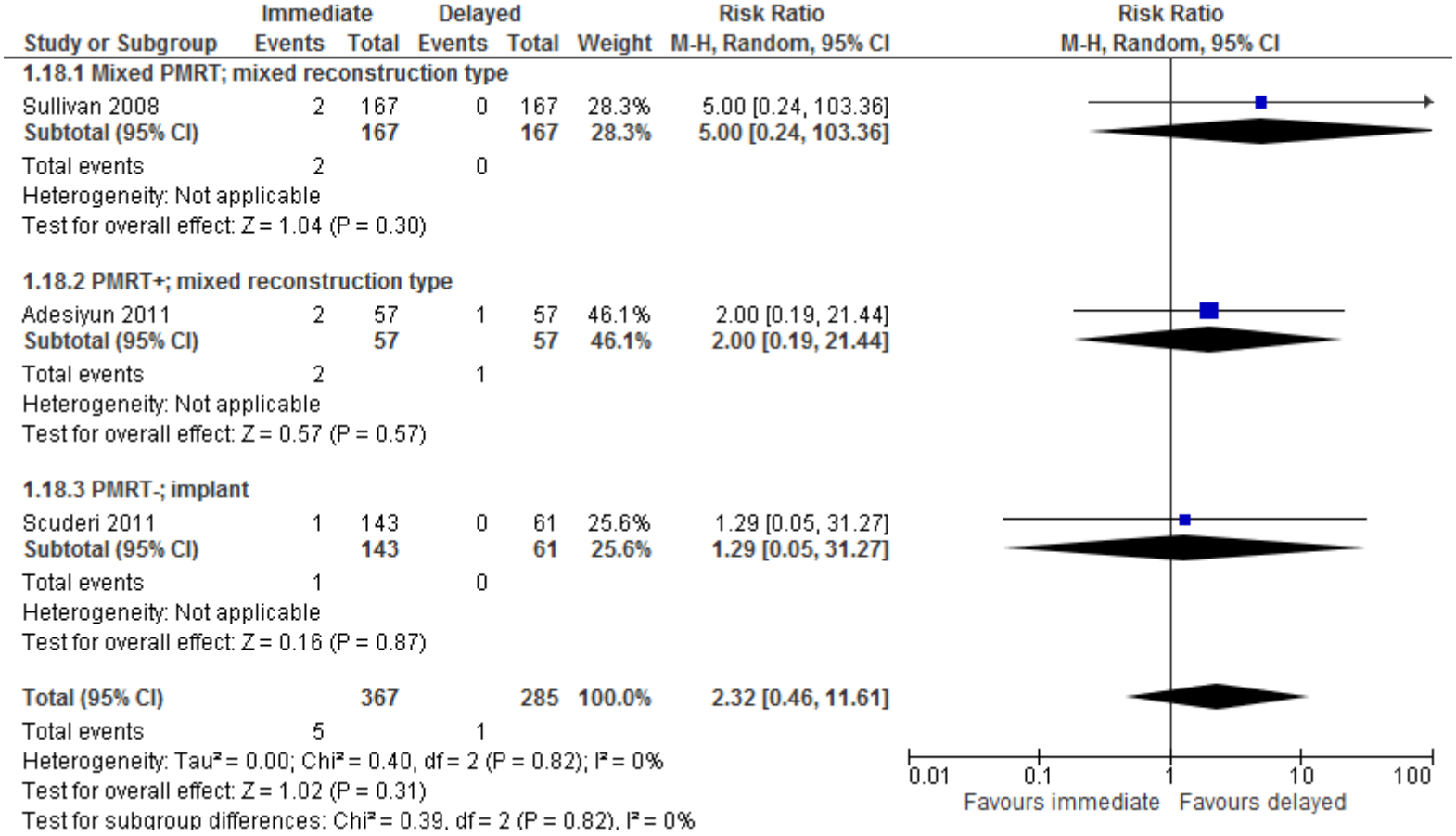


Figure 46: Complication rates: implant deflation (implant loss): mixed PMRT at 6 month to 4 year follow-up

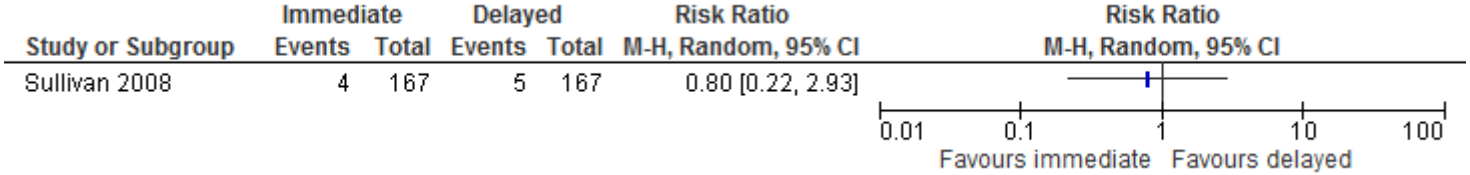


Figure 47: Complication rates: implant removed due to dissatisfaction/pain (implant loss) + at 3.9 year follow-up: PMRT

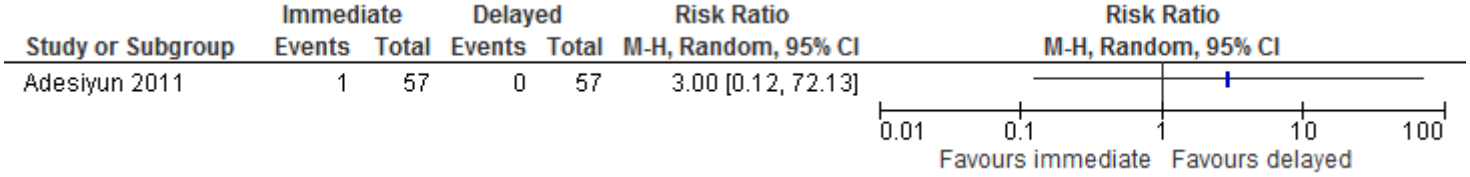


Figure 48: Complication rates: flap loss (flap loss) at 6 month to 4 year follow-up

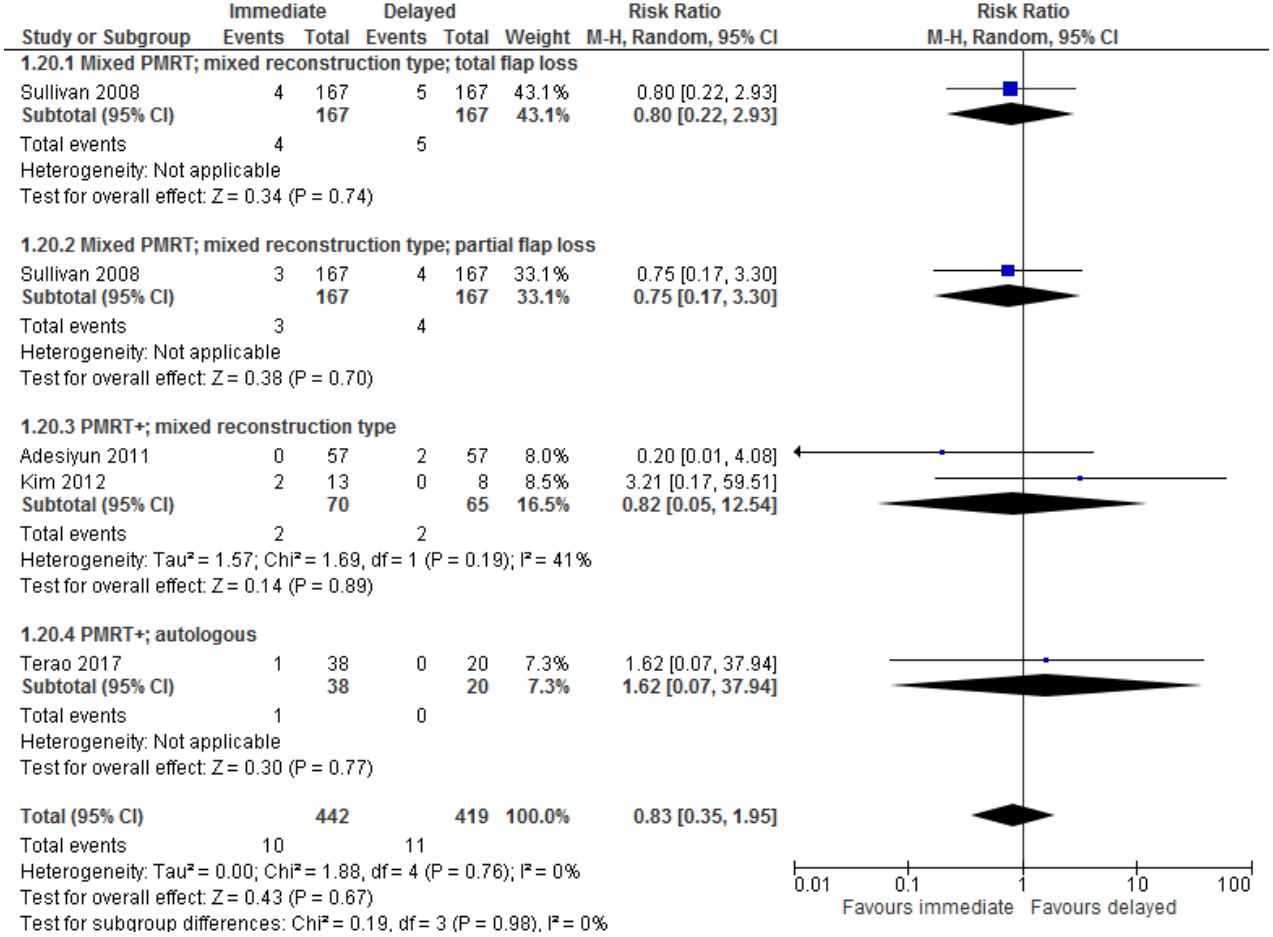


Figure 49: Complication rates: major fat necrosis (flap loss) at 6 month to 4 year follow-up

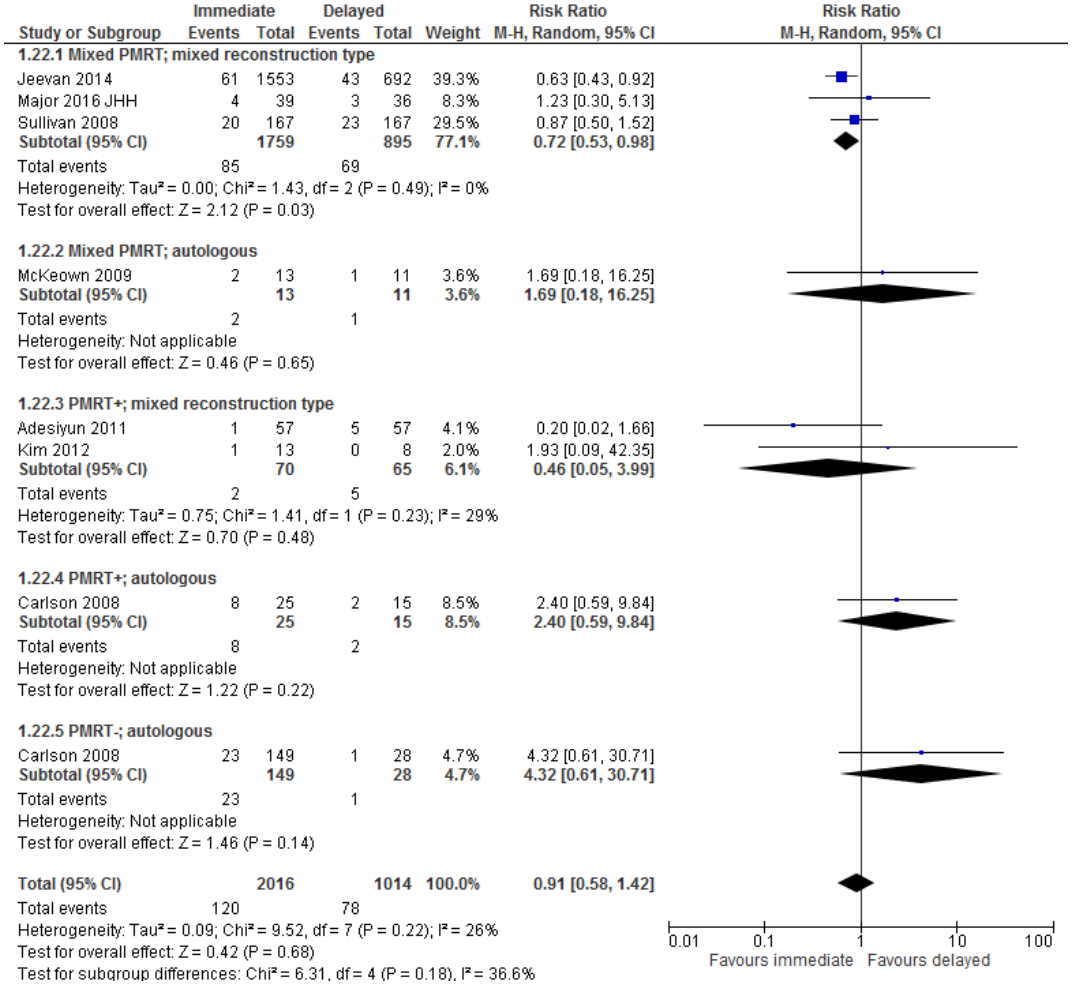


Figure 50: Complication rates: valve obstruction (flap loss) at 1 year follow-up: PMRT-; implant

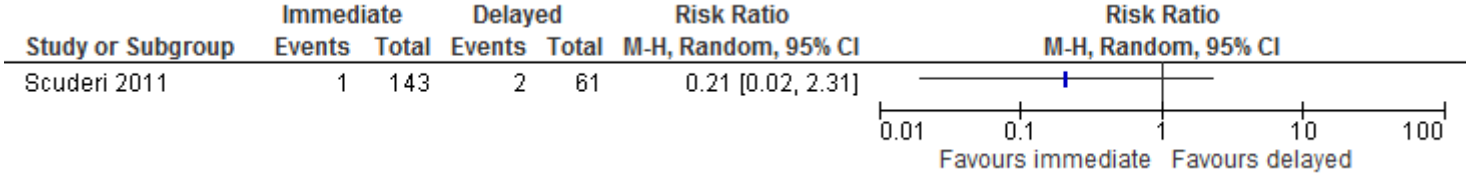


Figure 51: Complication rates: valve displacement (flap loss) at 1 year follow-up: PMRT-; implant

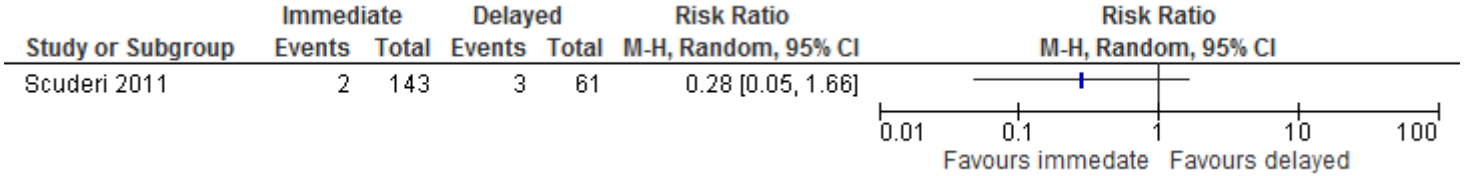


Figure 52: Complication rates: hematoma (bleeding) at 6 month to 4 year follow-up

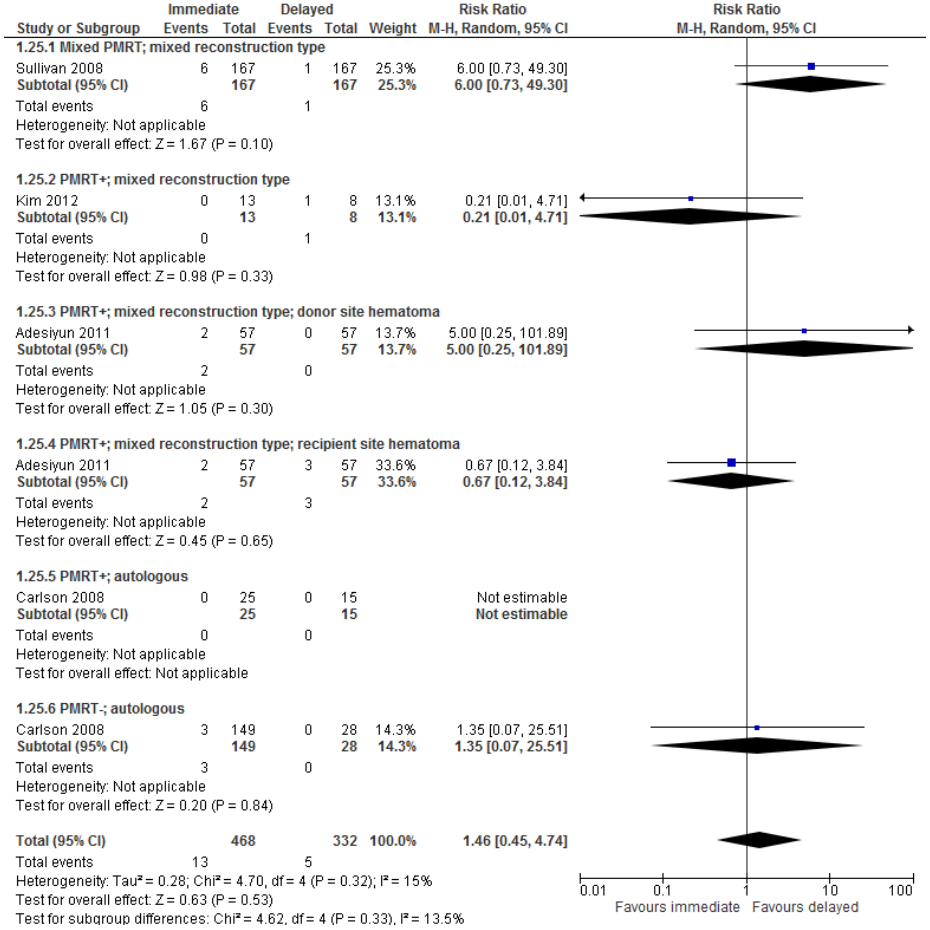


Figure 53: Complication rates: bleeding requiring transfusion/surgery (bleeding) at 18 month follow-up: mixed PMRT; mixed reconstruction typ

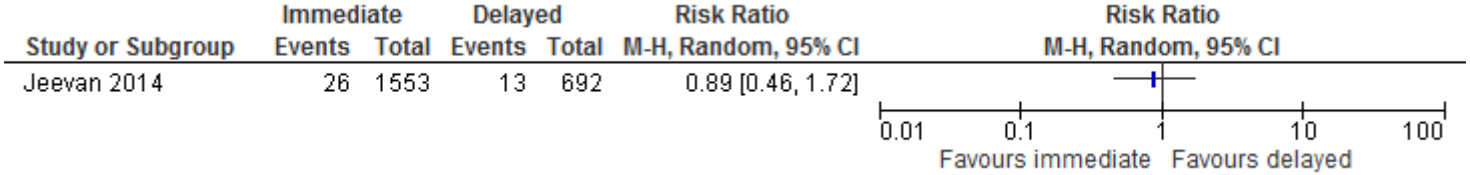


Figure 54: Complication rates: bleeding (bleeding) at 1 year follow-up: PMRT-; implant

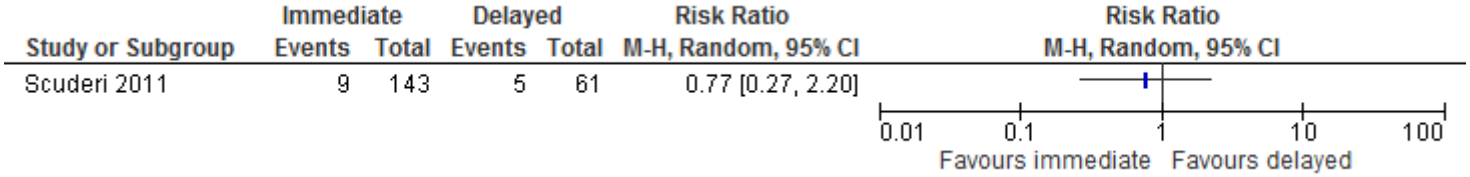


Figure 55: Complication rates: hernia/fascial defect (flap donor site) at 18 month to 3.9 year follow-up

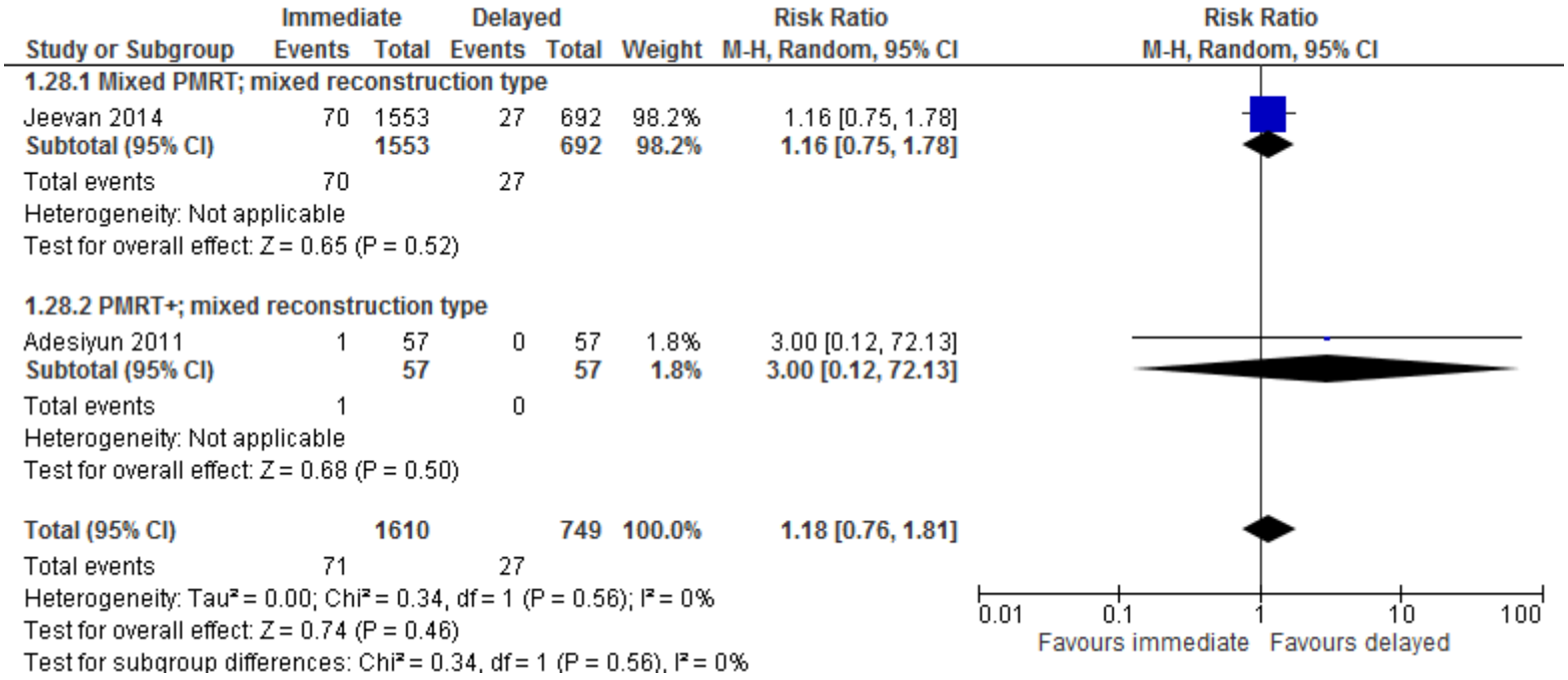


Figure 56: Complication rates: infection (wound) at 1 month to 4 year follow-up

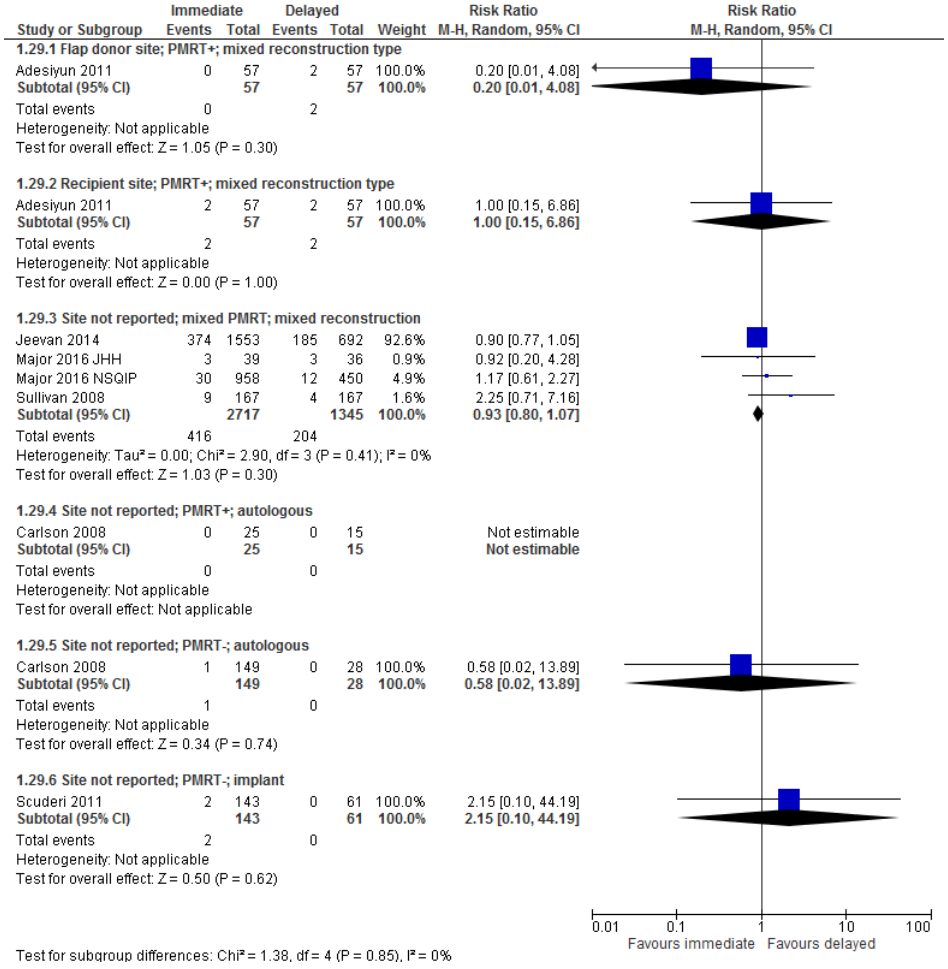


Figure 57: Complication rates: wound dehiscence (wound) at 1 year follow-up

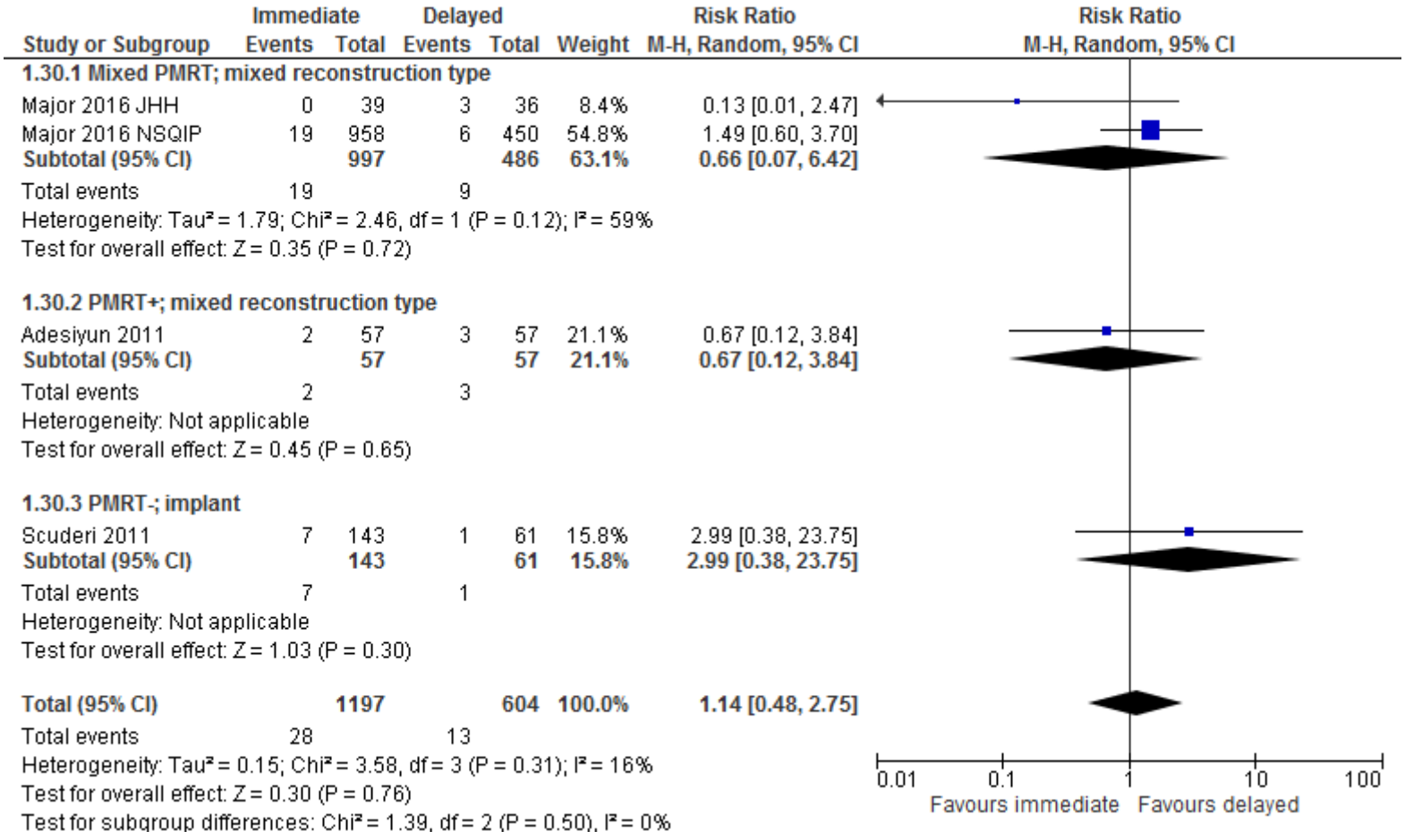


Figure 58: Complication rates: delayed wound healing (wound) at 6 month to 4 year follow-up: mixed PMRT; mixed reconstruction type

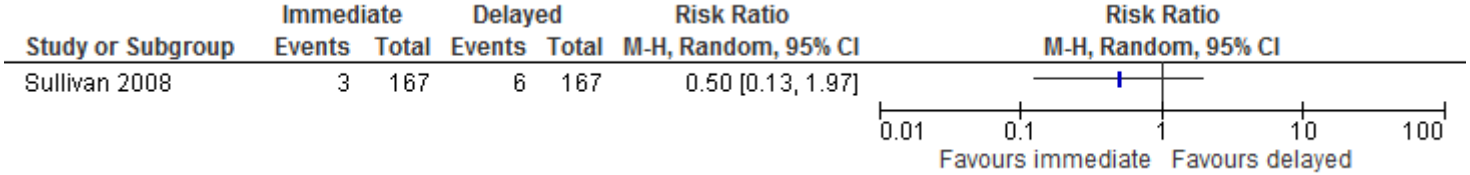


Figure 59: Complication rates: skin flap necrosis (mastectomy skin flaps) at 2 month to 4 year follow-up

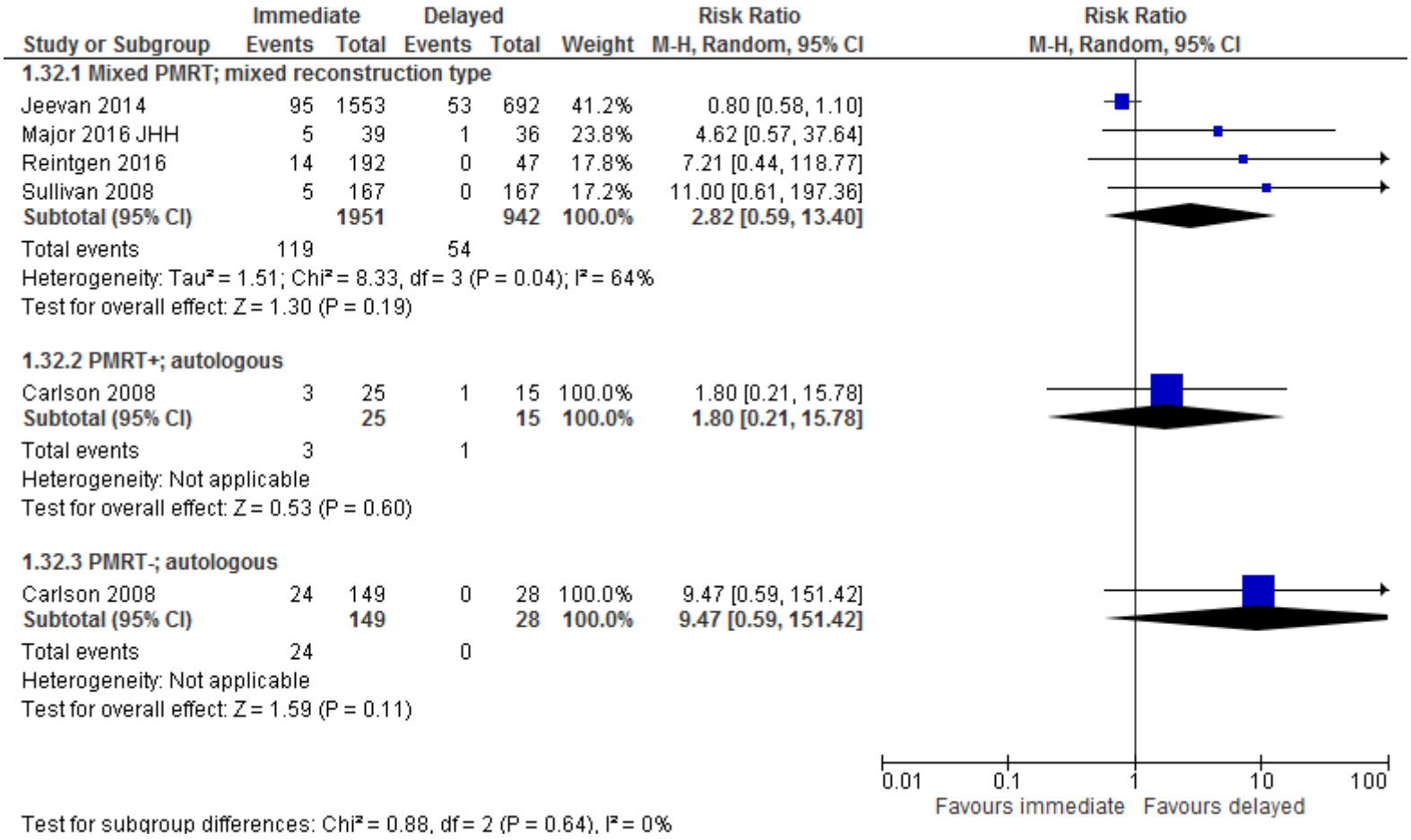


Figure 60: Complication rates: skin loss (mastectomy skin flaps) at 3.9 year follow-up: PMRT+; mixed reconstruction type

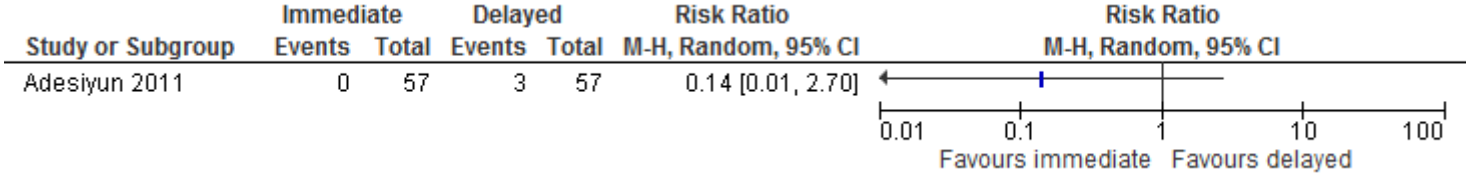


Figure 61: Complication rates: additional surgery at 1 month to 4.25 year follow-up

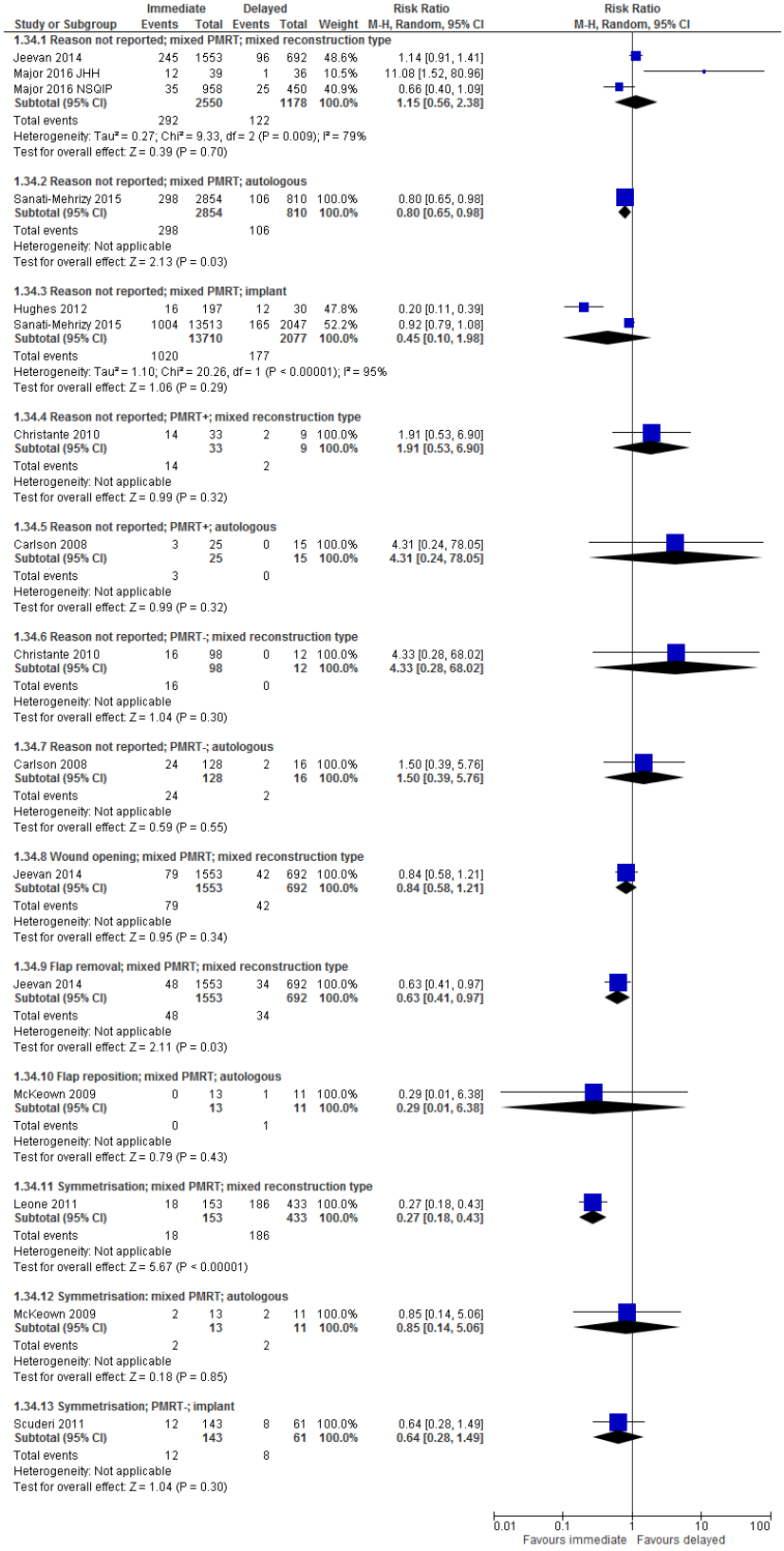


Figure 62: Complication rates: pneumothorax at 1 year follow-up: PMRT-; implant

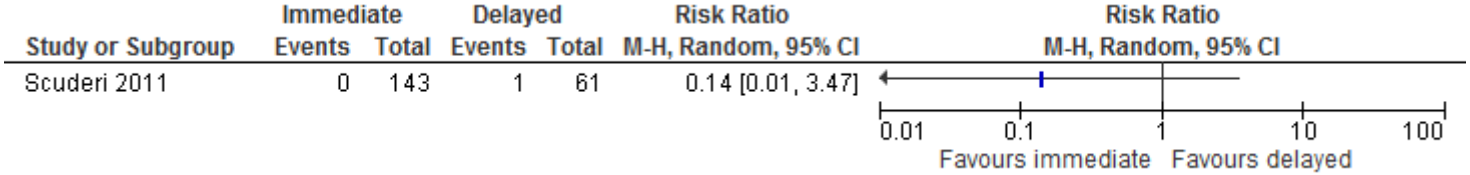


Figure 63: Cosmetic result at 6 month follow-up: mixed PMRT; mixed reconstruction type

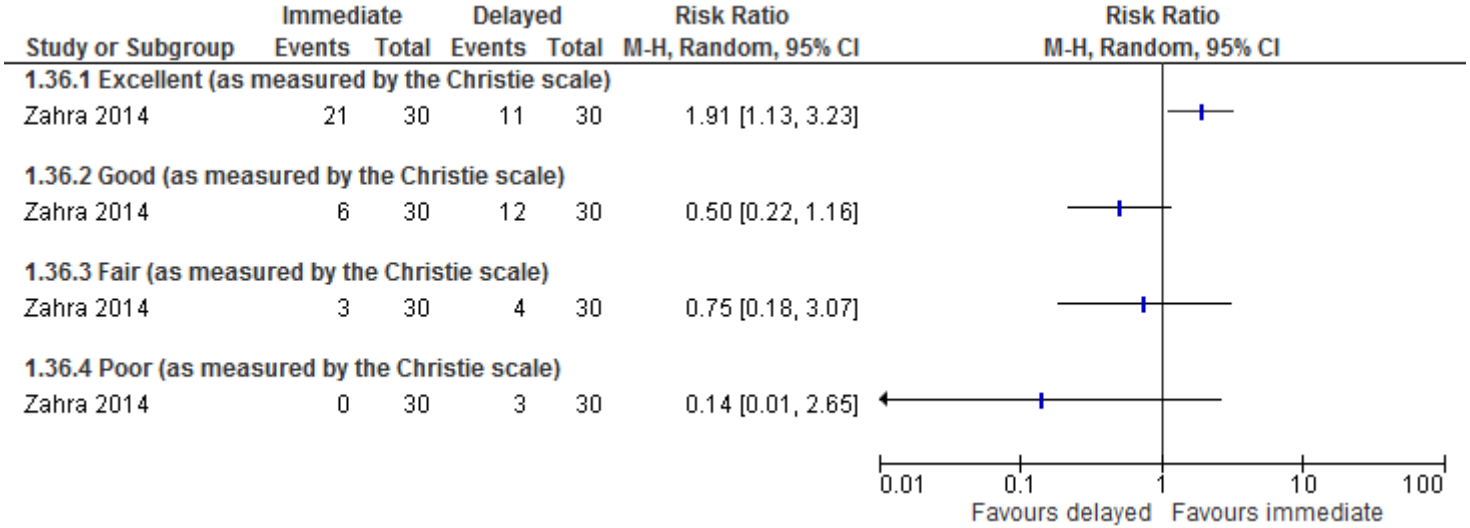


Figure 64: Health-related quality of life: general at 6 to 11 month follow-up

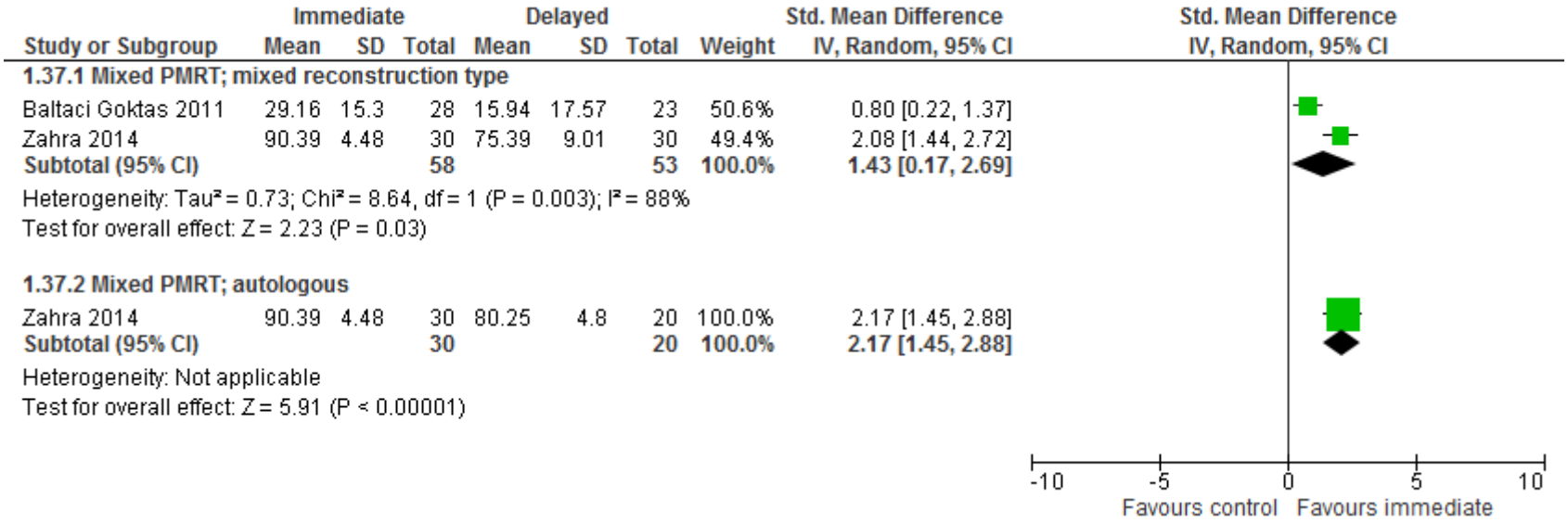


Figure 65: Health-related quality of life: social at 11 to 12 month follow-up: mixed PMRT; mixed reconstruction type

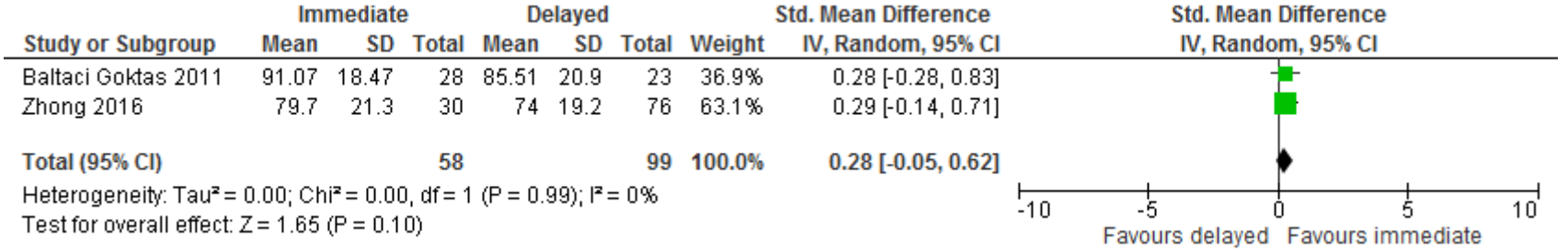


Figure 66: Health-related quality of life: social (change from pre- to post-reconstruction FACT-B social wellbeing scale) at 2 year follow-up: mixed PMRT; mixed reconstruction type

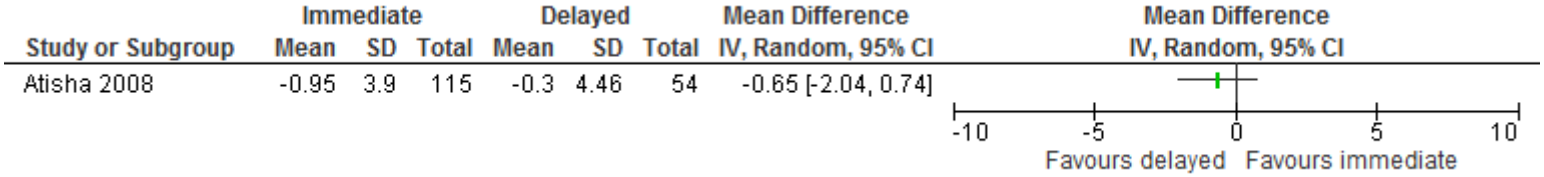


Figure 67: Health-related quality of life: physical at 11 to 12 month follow-up

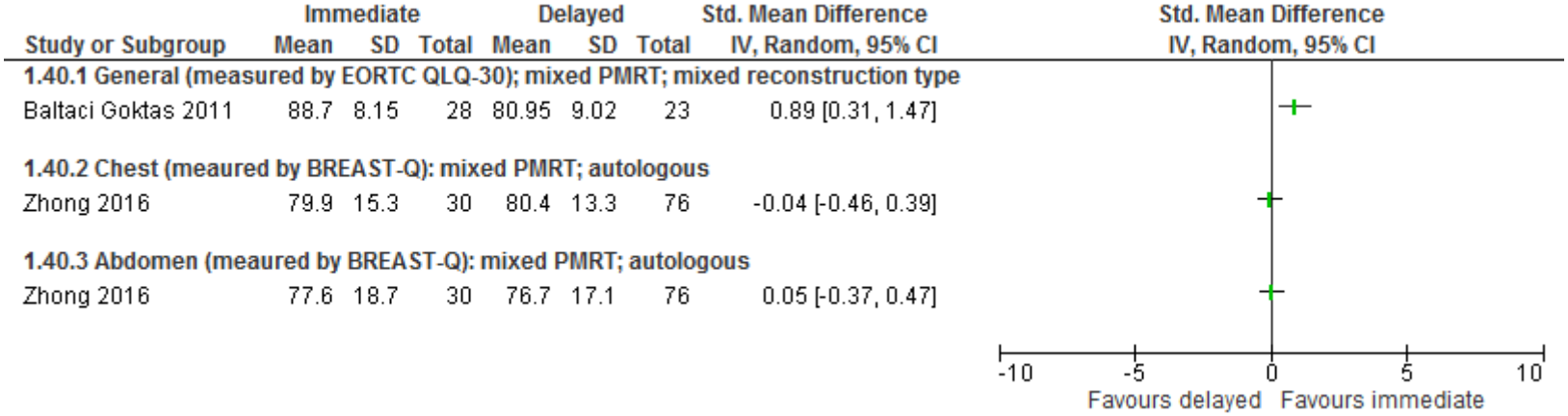


Figure 68: Health-related quality of life: sexual (measured by BREAST-Q) at 12 month follow-up; mixed PMRT; autologous

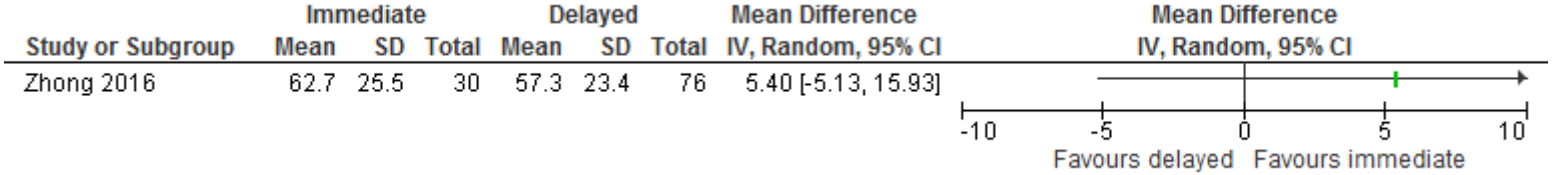


Figure 69: Health-related quality of life: role functioning (measured by EORTC QLQ-30) at 11 to 12 month follow-up; mixed PMRT; mixed reconstruction type

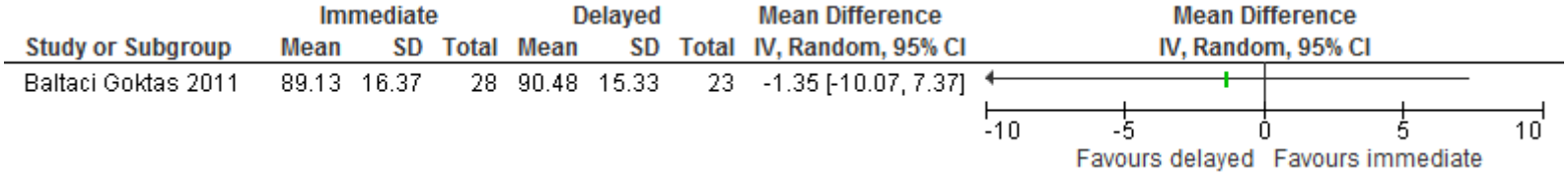


Figure 70: Health-related quality of life: emotional functioning (measured by EORTC QLQ-30) at 11 to 12 month follow-up; mixed PMRT; mixed reconstruction type

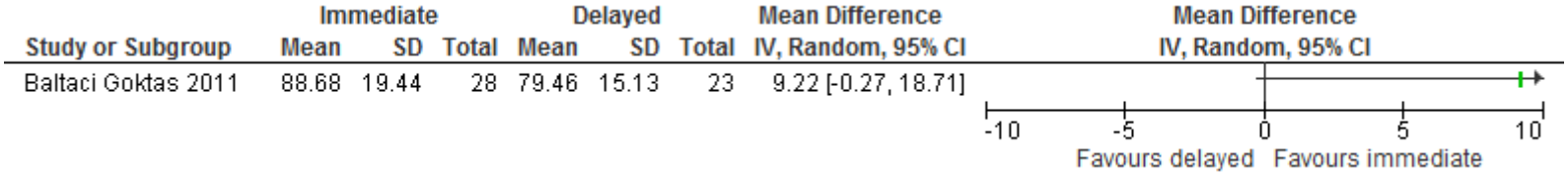


Figure 71: Health-related quality of life: cognitive functioning (measured by EORTC QLQ-30) at 11 to 12 month follow-up; mixed PMRT; mixed reconstruction type

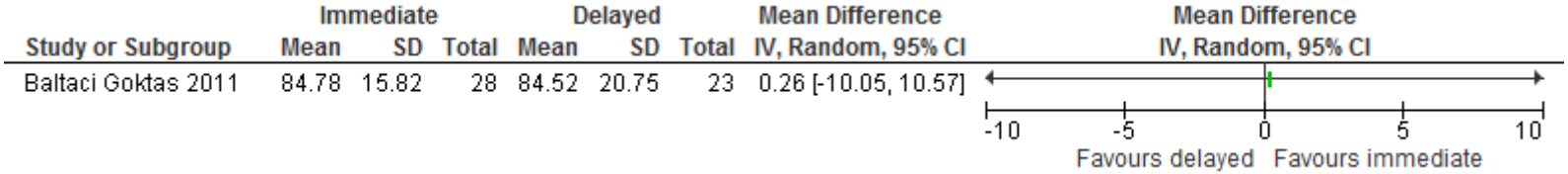
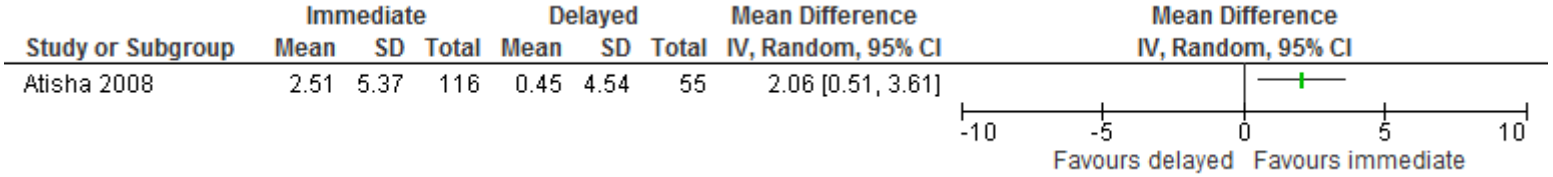


Figure 72: Health-related quality of life: functional (change from pre- to post-reconstruction FACT-B functional wellbeing scale) at 2 year follow-up; mixed PMRT; mixed reconstruction type



Appendix F – GRADE tables

GRADE tables for 9.1 What are the indications for postmastectomy radiotherapy for people with early and locally advanced breast cancer?

Comparison 1. Radiotherapy to the chest wall versus no radiotherapy

No studies were identified for this comparison.

Comparison 2. Radiotherapy to the chest wall plus nodes versus no radiotherapy

Table 13: GRADE evidence profile: Comparison 2. Radiotherapy to the chest wall plus nodes versus no radiotherapy – all women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute		
Treatment-related morbidity at 9 years - lymphedema: >6 cm increase in arm circumference												
1[3]	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/42 (2.4%)	2/42 (4.8%)	RR 0.5 (0.05 to 5.31)	24 fewer per 1000 (from 45 fewer to 205 more)	VERY LOW	CRITICAL
Treatment-related morbidity at 9 years - cardiac morbidity: irreversible clinical heart failure												
1[3]	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Not calculable[4]	None	0/42 (0%)	0/42 (0%)	Not calculable[5]	-	MODERATE	CRITICAL
Treatment-related morbidity at 9 years - cardiac morbidity: myocardial infarction												
1[3]	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/42 (2.4%)	0/42 (0%)	RR 3 (0.13 to 71.61)	-	VERY LOW	CRITICAL
Treatment-related morbidity at 9 years - lung morbidity: dense fibrosis, severe scarring & major retraction of normal lung												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute	Quality	Importance
1[3]	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Not calculable[5]	None	0/42 (0%)	0/42 (0%)	Not calculable[5]	-	MODERATE	CRITICAL
Treatment-related morbidity at 9 years - lung morbidity: refractory chest pain/ discomfort												
1[3]	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Not calculable[5]	None	0/42 (0%)	0/42 (0%)	Not calculable[5]	-	MODERATE	CRITICAL

CI, confidence interval; RR, risk ratio
[1] Downgraded by 1 level due to unclear randomization and allocation concealment. Blinding was unclear, but it was not downgraded further as it is unlikely to affect the outcomes.
[2] Downgraded by 2 levels as the CI crossed 2 default MIDs (0.8 and 1.25) and <300 events
[3] Hojiris 2000 (DBCG 82b&c)
[4] Imprecision was not calculable, as there were 0 events in each group
[5] Not calculable, as there were 0 event in each group
[6] Not calculable, as there were 0 events in 1 group

Table 14: GRADE evidence profile: Comparison 2.1. Radiotherapy to the chest wall + nodes versus no radiotherapy following mastectomy without axillary surgery in women with invasive breast cancer

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute	Quality	Importance
First locoregional recurrence during years 0-9 *[women with clinically node-negative disease]*												
3[1]	Randomised trials	Serious[2]	Serious[3]	No serious indirectness	No serious imprecision	None	175/1424 (12.3%)	451/1472 (30.6%)	Rate ratio 0.38 (0.32 to 0.45)	190 fewer per 1000 (from 169 fewer to	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute		
										208 fewer)		
First locoregional recurrence during years 0-9 *[women with clinically node-positive disease]*												
3[4]	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	None	116/740 (15.7%)	291/741 (39.3%)	Rate ratio 0.35 (0.28 to 0.42)	255 fewer per 1000 (from 228 fewer to 283 fewer)	MODERATE	CRITICAL
20-year all-cause mortality *[women with clinically node-negative disease]*												
3[1]	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1043/1424 (73.2%)	1055/1472 (71.7%)	Rate ratio 1.06 (0.97 to 1.16)	43 more per 1000 (from 22 fewer to 115 more)	MODERATE	CRITICAL
20-year all-cause mortality *[women with clinically node-positive disease]*												
3[4]	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	None	582/740 (78.6%)	606/741 (81.8%)	Rate ratio 0.91 (0.81 to 1.02)	74 fewer per 1000 (from 155 fewer to 16 more)	MODERATE	CRITICAL
20-year breast cancer mortality *[women with clinically node-negative disease]*												
3[1]	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	710/1424 (49.9%)	788/1472 (53.5%)	Rate ratio 0.98 (0.9 to 1.07)	11 fewer per 1000 (from 54 fewer to	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute		
										37 more)		
20-year breast cancer mortality *[women with clinically node-positive disease]*												
3[4]	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	None	416/740 (56.2%)	474/741 (64%)	Rate ratio 0.86 (0.75 to 0.98)	90 fewer per 1000 (from 13 fewer to 160 fewer)	MODERATE	IMPORTANT
Treatment related morbidity: women with arm oedema on final measurement at 2 to 5 years follow-up												
1[6]	Randomised trials	Very serious[7]	No serious inconsistency	No serious indirectness	No serious imprecision	None	84/568 (14.8%)	225/889 (25.3%)	RR 0.58 (0.47 to 0.73)	106 fewer per 1000 (from 68 fewer to 134 fewer)	LOW	CRITICAL
Treatment related mortality: cardiac deaths at 5 years *[all participants]*												
1[8]	Randomised trials	Very serious[9]	No serious inconsistency	No serious indirectness	No serious imprecision	None	Number of events not reported	Number of events not reported	RR 1.52 (1.01 to 2.29)	-	VERY LOW	IMPORTANT
Treatment related mortality: cardiac deaths at 5 years *[left breast]*												
1[8]	Randomised trials	Very serious[9]	No serious inconsistency	No serious indirectness	No serious imprecision	None	Number of events not reported	Number of events not reported	RR 1.92 (1.09 to 3.38)	-	LOW	IMPORTANT
Treatment related mortality: cardiac deaths at 5 years *[right breast]*												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute		
1[8]	Randomised trials	Very serious[9]	No serious inconsistency	No serious indirectness	Very serious[10]	None	Number of events not reported	Number of events not reported	RR 1.19 (0.66 to 2.15)	-	VERY LOW	IMPORTANT

CI, confidence interval; RR, risk ratio
[1] EBCTCG 2014 meta-analysis with 3 RCTs: Fisher 1990 & Deutsch 2008 (NSABP-04); Houghton 1994 (Kings/ Cambridge); & Stewart 2001 (Scottish D)
[2] Downgraded by 1 level due to unclear randomization and allocation concealment in the 3 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[3] Downgraded by 1 level due to serious inconsistency (I2=85%). It was not downgraded by 2 because all studies showed a similar direction of effect. Heterogeneity could not be explored as subgroup data was not available. Random effect could not be performed in Revman as this option is not available.
[4] EBCTCG 2014 meta-analysis with 3 RCTs: Houghton 1984 (Kings/ Cambridge); Lythgoe 1982 (Manchester RBS1) & Stewart 2001 (Scottish D)
[5] Downgraded by 1 level due to unclear randomization and allocation concealment in the 3 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[6] Fisher 1990 & Deutsch 2008 (NSABP B-04)
[7] Downgraded by 2 levels due to unclear randomization, allocation concealment, and blinding of participants, personnel and outcome assessors
[8] Houghton 1994 (Kings/ Cambridge)
[9] Downgraded by 2 level due to unclear randomization and allocation concealment. Outcome poorly reported, as number of events in not available per group. Blinding was also unclear butit is not likely to impact objective outcomes
[10] Downgraded by 2 level as the 95% CI crosses the line of null effect, and both minimally important differences (0.8 and 1.25) based on GRADE default values

Table 15: GRADE evidence profile: Comparison 2.2. Radiotherapy to the chest wall + nodes versus no radiotherapy following mastectomy with axillary surgery in women with invasive breast cancer and node-negative disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute		
First locoregional recurrence during years 0-9 *[Mastectomy + axillary dissection]*												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute		
8[1]	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	None	9/346 (2.6%)	5/352 (1.4%)	Rate ratio 1.85 (0.64 to 5.37)	12 more per 1000 (from 5 fewer to 62 more)	LOW	CRITICAL
First locoregional recurrence during years 0-9 *[Mastectomy + axillary sampling]*												
5[4]	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	Serious[3]	None	14/425 (3.3%)	72/445 (16.2%)	Rate ratio 0.25 (0.16 to 0.39)	121 fewer per 1000 (from 99 fewer to 136 fewer)	LOW	CRITICAL
20-year all-cause mortality *[Mastectomy + axillary dissection]*												
9[7]	Randomised trials	Serious[7]	No serious inconsistency	No serious indirectness	No serious imprecision	None	242/347 (69.7%)	238/353 (67.4%)	Rate ratio 1.23 (1.02 to 1.49)	155 more per 1000 (from 13 more to 330 more)	MODERATE	CRITICAL
20-year all-cause mortality *[Mastectomy + axillary sampling]*												
5[4]	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	No serious imprecision	None	298/425 (70.1%)	297/445 (66.7%)	Rate ratio 1 (0.84 to 1.18)	0 fewer per 1000 (from 107 fewer to 120 more)	MODERATE	CRITICAL
20-year breast cancer mortality *[Mastectomy + axillary dissection]*												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute		
9[7]	Randomised trials	Serious [6]	No serious inconsistency	No serious indirectness	Serious[3]	None	111/347 (32%)	106/353 (30%)	Rate ratio 1.18 (0.89 to 1.55)	54 more per 1000 (from 33 fewer to 165 more)	LOW	IMPORTANT
20-year breast cancer mortality *[Mastectomy + axillary sampling]*												
5[4]	Randomised trials	Serious [5]	No serious inconsistency	No serious indirectness	No serious imprecision	None	154/425 (36.2%)	171/445 (38.4%)	Rate ratio 0.97 (0.77 to 1.22)	12 fewer per 1000 (from 88 fewer to 85 more)	MODERATE	IMPORTANT

CI, confidence interval
[1] EBCTCG 2014 MA with 8 RCTs: Anderson 1999 & Kyndi 2009 (DBCG 82b); Host 1986 (Oslo X-ray); Killander 2007 (Sweden); McArdle 2010 (Glasgow); Olson 1997 (ECOG EST3181); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Papaionnou 1985 (Metaxas Athens) and Saphiro 1998 (DFCI Boston)
[2] Downgraded by 1 level due to unclear randomization and allocation concealment in the 8 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[3] Downgraded by 1 level as <300 events (OIS for dichotomous outcomes = 300)
[4] EBCTCG 2014 MA with 5 RCTs: Andersson 1999 & Kyndi 2009 (DBCG 82b); Gyenes 1988 (Stockholm A); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Stewart 1994 (Edinbourgh I) and Turnbull (DBCI Boston)
[5] Downgraded by 1 level due to unclear randomization and allocation concealment in the 5 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[6] EBCTCG 2014 MA with 9 RCTs: Anderson 1999 & Kyndi 2009 (DBCG 82b); Host 1986 (Oslo X-ray); Katz 2000 (MD Ander); Killander 2007 (Sweden); McArdle 2010 (Glasgow); Olson 1997 (ECOG EST3181); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Papaionnou 1985 (Metaxas Athens) and Saphiro 1998 (DFCI Boston)
[7]Downgraded by 1 level due to unclear randomization and allocation concealment in the 9 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes

Table 16: GRADE evidence profile: Comparison 2.3. Radiotherapy to the chest wall + nodes versus no radiotherapy following mastectomy with axillary surgery in women with invasive breast cancer and node positive disease

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute		
First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes *[Mastectomy + axillary dissection]*												
11[1]	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	None	19/625 (3%)	112/669 (16.7%)	Rate ratio 0.24 (0.17 to 0.34)	127 fewer per 1000 (from 110 fewer to 139 fewer)	LOW	CRITICAL
First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes *[Mastectomy + axillary sampling]*												
5[4]	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	Serious[3]	None	30/722 (4.2%)	162/690 (23.5%)	Rate ratio 0.21 (0.16 to 0.28)	185 fewer per 1000 (from 169 fewer to 197 fewer)	LOW	CRITICAL
First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes *[subgroup analysis: tumour grade - low grade]*												
1[6]	Randomised trials	Serious[7]	Cannot be assessed[8]	No serious indirectness	Serious[9]	None	4/64 (6.3%)	7/48 (14.6%)	Rate ratio 0.32 (0.09 to 1.2)	99 fewer per 1000 (from 133 fewer to 29 more)	LOW	CRITICAL
First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes *[subgroup analysis: tumour grade - intermediate grade]*												
1[6]	Randomised trials	Serious[7]	Cannot be assessed[8]	No serious indirectness	Serious[3]	None	4/81 (4.9%)	21/95 (22.1%)	Rate ratio 0.26	164 fewer per	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute	Quality	Importance
									(0.11 to 0.59)	1000 (from 91 fewer to 197 fewer)		
First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes *[subgroup analysis: tumour grade - high grade]*												
1[6]	Randomised trials	Serious[7]	Cannot be assessed[8]	No serious indirectness	Serious[3]	None	1/50 (2%)	9/57 (15.8%)	Rate ratio 0.27 (0.07 to 0.99)	115 fewer per 1000 (from 2 fewer to 147 fewer)	LOW	
First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes *[subgroup analysis: tumour size - 0-19 mm.]*												
1[6]	Randomised trials	Serious[7]	Cannot be assessed[8]	No serious indirectness	Serious[3]	None	4/138 (2.9%)	26/148 (17.6%)	Rate ratio 0.23 (0.11 to 0.47)	135 fewer per 1000 (from 93 fewer to 156 fewer)	LOW	CRITICAL
First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes *[subgroup analysis: tumour size - 20 to 49 mm.]*												
1[6]	Randomised trials	Serious[7]	Cannot be assessed[8]	No serious indirectness	Serious[3]	None	5/148 (3.4%)	37/187 (19.8%)	Rate ratio 0.24 (0.13 to 0.46)	150 fewer per 1000 (from 107 fewer to 172 fewer)	LOW	
First locoregional recurrence during years 0-9 in women with 1-3 pathologically positive nodes *[subgroup analysis: tumour size - 50+ mm.]*												
1[6]	Randomised trials	Serious[7]	Cannot be assessed[8]	No serious indirectness	Serious[3]	None	2/32 (6.3%)	5/28 (17.9%)	Rate ratio	136 fewer	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute	Quality	Importance
									0.24 (0.14 to 0.42)	per 1000 (from 104 fewer to 154 fewer)		
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[Mastectomy + axillary dissection]*												
13[10]	Randomised trials	Serious[11]	No serious inconsistency	No serious indirectness	Serious[3]	None	78/869 (9%)	172/849 (20.3%)	Rate ratio 0.39 (0.3 to 0.5)	124 fewer per 1000 (from 101 fewer to 142 fewer)	LOW	CRITICAL
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[Mastectomy + axillary sampling]*												
4[12]	Randomised trials	Serious[13]	Serious[14]	No serious indirectness	Serious[3]	None	22/339 (6.5%)	120/355 (33.8%)	Rate ratio 0.19 (0.14 to 0.27)	274 fewer per 1000 (from 247 fewer to 291 fewer)	VERY LOW	CRITICAL
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[subgroup analysis: tumour grade - low grade]*												
1[6]	Randomised trials	Serious[7]	Cannot be assessed[8]	No serious indirectness	Serious[9]	None	3/36 (8.3%)	8/37 (21.6%)	Rate ratio 0.35 (0.09 to 1.4)	141 fewer per 1000 (from 197 fewer to 86 more)	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute		
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[subgroup analysis: tumour grade - intermediate grade]*												
1[6]	Randomised trials	Serious[7]	Cannot be assessed[8]	No serious indirectness	Serious[3]	None	4/104 (3.8%)	34/103 (33%)	Rate ratio 0.14 (0.07 to 0.27)	284 fewer per 1000 (from 241 fewer to 307 fewer)	LOW	CRITICAL
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[subgroup analysis: tumour grade - high grade]*												
1[6]	Randomised trials	Serious[7]	Cannot be assessed[8]	No serious indirectness	Serious[3]	None	7/83 (8.4%)	24/80 (30%)	Rate ratio 0.33 (0.16 to 0.7)	201 fewer per 1000 (from 90 fewer to 252 fewer)	LOW	CRITICAL
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[subgroup analysis: tumour size - 0-19 mm.]*												
1[6]	Randomised trials	Serious[7]	Cannot be assessed[8]	No serious indirectness	Serious[3]	None	6/93 (6.5%)	22/101 (21.8%)	Rate ratio 0.29 (0.13 to 0.62)	155 fewer per 1000 (from 83 fewer to 190 fewer)	LOW	CRITICAL
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[subgroup analysis: tumour size - 20-49 mm.]*												
1[6]	Randomised trials	Serious[7]	Cannot be assessed[8]	No serious indirectness	Serious[3]	None	19/227 (8.4%)	55/199 (27.6%)	Rate ratio 0.26 (0.16 to 0.42)	205 fewer per 1000 (from 160 fewer to	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute		
										232 fewer)		
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[subgroup analysis: tumour size - 50+ mm.]*												
1[6]	Randomised trials	Serious[7]	Cannot be assessed[8]	No serious indirectness	Serious[3]	None	7/118 (5.9%)	31/131 (23.7%)	Rate ratio 0.29 (0.14 to 0.6)	168 fewer per 1000 (from 95 fewer to 204 fewer)	LOW	CRITICAL
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[subgroup analysis: number of positive nodes - 4-9 positive nodes]*												
1[6]	Randomised trials	Serious[7]	Cannot be assessed[8]	No serious indirectness	Serious[3]	None	20/267 (7.5%)	60/246 (24.4%)	Rate ratio 0.28 (0.18 to 0.44)	176 fewer per 1000 (from 137 fewer to 200 fewer)	LOW	CRITICAL
First locoregional recurrence during years 0-9 in women with 4+ pathologically positive nodes *[subgroup analysis: number of positive nodes - 10+ positive nodes]*												
1[6]	Randomised trials	Serious[7]	Cannot be assessed[8]	No serious indirectness	Serious[3]	None	15/201 (7.5%)	52/205 (25.4%)	Rate ratio 0.30 (0.18 to 0.5)	178 fewer per 1000 (from 127 fewer to 208 fewer)	LOW	CRITICAL
20-year all-cause mortality in women with 1-3 pathologically positive nodes *[Mastectomy + axillary dissection]*												
12[15]	Randomised trials	Serious[16]	No serious inconsistency	No serious indirectness	No serious imprecision	None	352/632 (55.7%)	407/682 (59.7%)	Rate ratio 0.89	66 fewer per 1000 (from	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radiotherapy to the chest wall + nodes**	**No radiotherapy**	**Relative (95% CI)**	**Absolute**		
									(0.77 to 1.04)	137 fewer to 24 more)		
20-year all-cause mortality in women with 1-3 pathologically positive nodes *[Mastectomy + axillary sampling]*												
6[17]	Randomised trials	Serious[18]	No serious inconsistency	No serious indirectness	No serious imprecision	None	413/726 (56.9%)	447/694 (64.4%)	Rate ratio 0.82 (0.71 to 0.94)	116 fewer per 1000 (from 39 fewer to 187 fewer)	MODERATE	CRITICAL
20-year all-cause mortality in women with 4+ pathologically positive nodes *[Mastectomy + axillary dissection]*												
14[19]	Randomised trials	Serious[20]	Serious[21]	No serious indirectness	No serious imprecision	None	631/893 (70.7%)	655/879 (74.5%)	Rate ratio 0.89 (0.78 to 1)	82 fewer per 1000 (from 164 fewer to 0 more)	LOW	CRITICAL
20-year all-cause mortality in women with 4+ pathologically positive nodes *[Mastectomy + axillary sampling]*												
5[22]	Randomised trials	Serious[23]	Serious[24]	No serious indirectness	No serious imprecision	None	264/342 (77.2%)	314/361 (87%)	Rate ratio 0.78 (0.65 to 0.93)	191 fewer per 1000 (from 61 fewer to 304 fewer)	LOW	CRITICAL
20-year breast cancer mortality in women with 1-3 pathologically positive nodes – *[Mastectomy + axillary dissection]*												
12[15]	Randomised trials	Serious[16]	Serious inconsistency[25]	No serious indirectness	No serious imprecision	None	248/632 (39.2%)	325/682 (47.7%)	Rate ratio 0.8 (0.67 to 0.95)	55 fewer per 1000 (from 13 fewer to	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute	Quality	Importance
										98 fewer)		
20-year breast cancer mortality in women with 1-3 pathologically positive nodes – *[Mastectomy + axillary sampling]*												
6[17]	Randomised trials	Serious[28]	No serious inconsistency	No serious indirectness	No serious imprecision	None	329/726 (45.3%)	394/694 (56.8%)	Rate ratio 0.76 (0.65 to 0.88)	68 fewer per 1000 (from 32 fewer to 107 fewer)	MODERATE	IMPORTANT
20-year breast cancer mortality in women with 4+ pathologically positive nodes *[Mastectomy + axillary dissection]*												
14[26]	Randomised trials	Serious[27]	Serious[28]	No serious indirectness	No serious imprecision	None	567/893 (63.5%)	605/879 (68.8%)	Rate ratio 0.88 (0.77 to 0.99)	83 fewer per 1000 (from 7 fewer to 158 fewer)	LOW	IMPORTANT
20-year breast cancer mortality in women with 4+ pathologically positive nodes *[Mastectomy + axillary sampling]*												
5[29]	Randomised trials	Serious[30]	Serious[31]	No serious indirectness	No serious imprecision	None	239/342 (69.9%)	293/361 (81.2%)	Rate ratio 0.77 (0.64 to 0.94)	187 fewer per 1000 (from 49 fewer to 292 fewer)	LOW	IMPORTANT
Treatment-related morbidity in women with node positive disease - ischaemic heart disease morbidity at 10 years												
1[32]	Randomised trials	Serious[33]	No serious inconsistency	No serious indirectness	Serious[34]	None	0/1525 Number of events not reported	0/1521 Number of events not reported	HR 0.86 (0.57 to 1.3)	-	LOW	CRITICAL
Treatment-related morbidity in women with node-positive disease - acute myocardial infarction morbidity at 10 years												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute		
1[32]	Randomised trials	Serious[33]	No serious inconsistency	No serious indirectness	Serious[34]	None	N=1525 Number of events not reported	N=1521 Number of events not reported	HR 1.1 (0.62 to 1.95)	-	LOW	CRITICAL
Treatment-related morbidity in women with node-positive disease - arm oedema requiring intervention, at 15 years												
1[35]	Randomised trials	Serious[33]	No serious inconsistency	No serious indirectness	Serious[9]	None	6/164 (3.7%)	1/154 (0.65%)	RR 5.63 (0.69 to 46.27)	30 more per 1000 (from 2 fewer to 294 more)	LOW	CRITICAL
Treatment-related morbidity in women with node-positive disease - pneumonitis, at 15 years												
1[35]	Randomised trials	Serious[33]	No serious inconsistency	No serious indirectness	Serious[9]	None	1/164 (0.61%)	0/154 (0%)	RR 2.82 (0.12 to 68.66)	-	LOW	CRITICAL
Treatment-related morbidity in women with node-positive disease - cardiac events (congestive heart failure or myocardial infarction), at 6 years *[low RT vs no RT]*												
1[36]	Randomised trials	Serious[33]	No serious inconsistency	No serious indirectness	Serious[9]	None	1/45 (2.2%)	13/154 (8.4%)	RR 0.26 (0.04 to 1.96)	62 fewer per 1000 (from 81 fewer to 81 more)	LOW	CRITICAL
Treatment-related morbidity in women with node-positive disease - cardiac events (congestive heart failure or myocardial infarction), at 6 years *[moderate RT vs no RT]*												
1[34]	Randomised trials	Serious[33]	No serious inconsistency	No serious indirectness	Serious[9]	None	4/48 (8.3%)	13/154 (8.4%)	RR 0.99 (0.34 to 2.89)	1 fewer per 1000 (from 56 fewer to	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute		
										160 more)		
Treatment-related morbidity in women with node-positive disease - cardiac events (congestive heart failure or myocardial infarction), at 6 years *[high RT vs no RT]*												
1[36]	Randomised trials	Serious[33]	No serious inconsistency	No serious indirectness	Serious[9]	None	4/29 (13.8%)	13/154 (8.4%)	RR 1.63 (0.57 to 4.66)	53 more per 1000 (from 36 fewer to 309 more)	LOW	CRITICAL
Treatment-related morbidity in women with node-positive disease - congestive heart failure, at 15 years												
1[35]	Randomised trials	Serious[33]	No serious inconsistency	No serious indirectness	Serious[9]	None	1/164 (0.61%)	0/154 (0%)	RR 2.82 (0.12 to 68.66)	-	LOW	CRITICAL
Treatment-related morbidity in women with node-positive disease - myocardial infarction, at 20 years												
1[37]	Randomised trials	Serious[33]	No serious inconsistency	No serious indirectness	Serious[3]	None	17/323 (5.3%)	21/321 (6.5%)	RR 0.8 (0.43 to 1.5)	13 fewer per 1000 (from 37 fewer to 33 more)	LOW	CRITICAL
Treatment-related mortality in women with node-positive disease- death from ischaemic heart disease at 10 years												
1[32]	Randomised trials	Serious[33]	No serious inconsistency	No serious indirectness	Serious[34]	None	N=1525 Number of events not reported	N=1521 Number of events not reported	HR 0.84 (0.38 to 1.86)	-	LOW	IMPORTANT
Treatment-related mortality in women with node-positive disease - death from acute myocardial infarction at 10 years												
1[32]	Randomised trials	Serious[33]	No serious inconsistency	No serious indirectness	Serious[34]	None	N=1525	N=1521		-	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	No radiotherapy	Relative (95% CI)	Absolute		
							Number of events not reported	Number of events not reported	HR 0.5 (0.17 to 1.47)			
Treatment-related mortality in women with node-positive disease - death from cardiovascular disease, at 20 years												
1[37]	Randomised trials	Serious[33]	No serious inconsistency	No serious indirectness	Serious[9]	None	19/223 (8.5%)	17/321 (5.3%)	RR 1.61 (0.86 to 3.03)	32 more per 1000 (from 7 fewer to 108 more)	LOW	IMPORTANT
Treatment-related mortality in women with node-positive disease - death from ischemic heart disease, at 20 years												
1[37]	Randomised trials	Serious[33]	No serious inconsistency	No serious indirectness	Serious[9]	None	12/223 (5.4%)	10/321 (3.1%)	RR 1.73 (0.76 to 3.93)	23 more per 1000 (from 7 fewer to 91 more)	LOW	IMPORTANT
Treatment-related mortality in women with node-positive disease - death from myocardial infarction, at 20 years												
1[37]	Randomised trials	Serious[33]	No serious inconsistency	No serious indirectness	Serious[9]	None	7/223 (3.1%)	10/321 (3.1%)	RR 1.01 (0.39 to 2.61)	0 more per 1000 (from 19 fewer to 50 more)	LOW	IMPORTANT

CI, confidence interval; HR, hazard ratio; RR, risk ratio; RT, radiotherapy
[1] EBCTCG 2014 MA with 11 RCTs: Anderson 1999 & Kyndi 2009 (DBCG 82b); Host 1986 (Oslo X-ray); Killander 2007 (Sweden); McArdle 2010 (Glasgow); Olson 1997 (ECOG EST3181); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Papaionnou 1985 (Metaxas Athens), Ragaz 1997 (BCCA Vancouver); Saarto 1997 (Helsinki); Saphiro 1998 (DFCI Boston) and Velez-Garcia (SECSG 1)
[2] Downgraded by 1 level due to unclear randomization and allocation concealment in the 11 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[3] Downgraded by 1 level as <300 event (OIS for dichotomous outcomes = 300)

[4] EBCTCG 2014 MA with 5 RCTs: Andersson 1999 & Kyndi 2009 (DBCG 82b); De Oliveira 1984 (Coimbra); Gyenes 1988 (Stockholm A); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Schoomor 2002 (GB03 Germany)
[5] Downgraded by 1 level due to unclear randomization and allocation concealment in the 5 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[6] EBCTCG 2014 MA: unknown number of trials, pooled result only
[7] Only pooled data was available, however it was downgraded by 1 due to serious risk of bias as it can be assumed that this subgroup analysis includes the same trials as the previous comparison
[8] Cannot be assessed as only pooled data was available
[9] Downgraded by 1 level as <300 events (OIS for dichotomous outcomes = 300)
[10] EBCTCG 2014 MA with 13 RCTs: Anderson 1999 & Kyndi 2009 (DBCG 82b); Faber 1979 (Dusseldorf U); Host 1986 (Oslo X-ray); Killander 2007 (Sweden); McArdle 2010 (Glasgow); Muss 1991 (Piedmont OA); Olson 1997 (ECOG EST3181); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Papaionnou 1985 (Metaxas Athens), Ragaz 1997 (BCCA Vancouver); Saarto 1997 (Helsinki); Saphiro 1998 (DFCI Boston) and Velez-Garcia (SECSG 1)
[11] Downgraded by 1 level due to unclear randomization and allocation concealment in the 13 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[12] EBCTCG 2014 MA with 4 RCTs: Andersson 1999 & Kyndi 2009 (DBCG 82b); De Oliveira 1984 (Coimbra); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Schoomor 2002 (GB03 Germany)
[13] Downgraded by 1 level due to unclear randomization and allocation concealment in the 4 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[14] Downgraded by 1 level due to serious inconsistency (I2=64%). Heterogeneity could not be explored as data for subgroup analysis was not available. Random model could not be conduted in Revman.
[15] EBCTCG 2014 MA with 12 RCTs: Anderson 1999 & Kyndi 2009 (DBCG 82b); Katz 2000 (MD Ander); Killander 2007 (Sweden); McArdle 2010 (Glasgow); Olson 1997 (ECOG EST3181); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Papaionnou 1985 (Metaxas Athens), Ragaz 1997 (BCCA Vancouver); Saarto 1997 (Helsinki); Saphiro 1998 (DFCI Boston) and Velez-Garcia (SECSG 1)
[16] Downgraded by 1 level due to unclear randomization and allocation concealment in the 12 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[17] EBCTCG 2014 MA with 6 RCTs: Andersson 1999 & Kyndi 2009 (DBCG 82b); De Oliveira 1984 (Coimbra); Gyenes 1988 (Stockholm A); Katz 2000 (MD Ander); Overgaard 1999 & Kyndi 2009 (DBCG 82c) and Schoomor 2002 (GB03 Germany)
[18] Downgraded by 1 level due to unclear randomization and allocation concealment in the 6 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[19] EBCTCG 2014 MA with 14 RCTs: Anderson 1999 & Kyndi 2009 (DBCG 82b); Faber 1979 (Dusseldorf U); Host 1986 (Oslo X-ray); Katz 2000 (MD Ander); Killander 2007 (Sweden); McArdle 2010 (Glasgow); Muss 1991 (Piedmont OA); Olson 1997 (ECOG EST3181); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Papaionnou 1985 (Metaxas Athens), Ragaz 1997 (BCCA Vancouver); Saarto 1997 (Helsinki); Saphiro 1998 (DFCI Boston) and Velez-Garcia (SECSG 1)
[20] Downgraded by 1 level due to unclear randomization and allocation concealment in the 14 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[21] Downgraded by 1 level due to moderate inconsistency (I2=46%). Heterogeneity could not be explored further as data for subgroup analysis was not available. A random model could not be performed in Revman
[22] EBCTCG 2014 MA with 5 RCTs: Andersson 1999 & Kyndi 2009 (DBCG 82b); De Oliveira 1984 (Coimbra); Katz 2000 (MD Ander); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Schoomor 2002 (GB03 Germany)
[23] Downgraded by 1 level due to unclear randomization and allocation concealment in the 5 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[24] Downgraded by 1 level due to moderate inconsistency (I2=58%). Heterogeneity could not be explored further as data for subgroup analysis was not available. A random model could not be performed in Revman

[25] Downgraded by 1 level due to moderate inconsistency (I2=27%). Heterogeneity could not be explored further as data for subgroup analysis was not available. A random model could not be performed in Revman
[26] EBCTCG 2014 MA with 14 RCTs: Anderson 1999 & Kyndi 2009 (DBCG 82b); Host 1986 (Oslo X-ray); Katz 2000 (MD Ander); Killander 2007 (Sweden); McArdle 2010 (Glasgow); Olson 1997 (ECOG EST3181); Overgaard 1999 & Kyndi 2009 (DBCG 82c); Papaionnou 1985 (Metaxas Athens), Ragaz 1997 (BCCA Vancouver); Saarto 1997 (Helsinki); Saphiro 1998 (DFCI Boston) and Velez-Garcia (SECSG 1)
[27] Downgraded by 1 level due to unclear randomization and allocation concealment in the 14 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[28] Downgraded by 1 level due to moderate inconsistency (I2=54%). Heterogeneity could not be explored further as data for subgroup analysis was not available. A random model could not be performed in Revman
[29] EBCTCG 2014 MA with 5 trials: Anderson 1999 & Kyndi 2009 (DBCG 82b); De Oliverira 1984 (Coimbra); Katz 2000 (MD Ander); Overgaard 1999 & Kyndi 1999 (DBCG 82c) and Schomoor (GBSG 03 Germany)
[30] Downgraded by 1 level due to unclear randomization and allocation concealment in the 5 trials. Blinding was also unclear but it was not downgraded further as it is not likely to impact objective outcomes
[31] Downgraded by 1 level due to moderate to high inconsistency (I2=59%). The 2 largest trials showed inconsistent results. Heterogeneity could not be explored further as data for subgroup analysis was not available. A random model could not be performed in Revman
[32] Hojiris 1999 (DBCG 82b&c)
[33] Downgraded by 1 level due to unclear randomization and allocation concealment. Blinding was unclear, but it was not downgraded further as it is unlikely to affect the outcomes.
[34] Downgraded 1 level as 95% confidence interval crosses null effect and minimally important difference (0.8) based on GRADE default value
[35] Ragaz 1997 (BCCA Vancouver)
[36] Shapiro 1998 (DFCI Boston)
[37] Gyenes 1998 (Stockholm A)

Comparison 3. Radiotherapy to the chest wall plus nodes versus radiotherapy to the chest wall alone

Table 17: GRADE evidence profile: Comparison 3. Radiotherapy to the chest wall plus nodes versus radiotherapy to the chest wall alone

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radiotherapy to the chest wall + nodes**	**Radiotherapy to the chest wall alone**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival at 10 years												
1[1]	Randomised trials	No serious risk of bias[2]	No serious inconsistency	No serious indirectness	Serious[3]	None	139/476 (29.2%)	150/479 (31.3%)	HR 0.91 (0.72 to 1.15)	24 fewer per 1000 (from 76 fewer to	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy to the chest wall + nodes	Radiotherapy to the chest wall alone	Relative (95% CI)	Absolute	Quality	Importance
										38 more)		

CI, confidence interval; HR, hazard ratio
[1] *Poortmans 2014*
[2] *Unclear whether blinding was performed, but the evidence was not downgraded as blinding is unlikely to affect objective outcomes*
[3] *Downgraded by 1 level as <300 events (OIS for dichotomous outcomes = 300)*

GRADE tables for 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?

Table 18: Clinical evidence profile: Comparison 1. Immediate reconstruction versus delayed reconstruction

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute	Quality	Importance
Patient satisfaction - aesthetic - Mixed PMRT; mixed reconstruction type (6 month follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	105/153 (68.6%)	62/110 (56.4%)	RR 1.22 (1 to 1.48)	124 more per 1000 (from 0 more to 271 more)	VERY LOW	CRITICAL
Patient satisfaction - aesthetic - PMRT+; mixed reconstruction type (3.9 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[4]	None	23/37 (62.2%)	20/40 (50%)	RR 1.24 (0.83 to 1.85)	120 more per 1000 (from 85 fewer to 425 more)	VERY LOW	CRITICAL
Patient satisfaction - aesthetic - PMRT+; implant (2.3 to 5.4 year follow-up)												
2	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	6/13 (46.2%)	0/2 (0%)	RR 1.87 (0.32 to 11.11)	-	VERY LOW	CRITICAL
Patient satisfaction - aesthetic - PMRT+; autologous (2.3 to 5.4 year follow-up)												
2	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Serious[4]	None	32/48 (66.7%)	33/56 (58.9%)	RR 1.13 (0.84 to 1.52)	77 more per 1000 (from 94 fewer to 306 more)	VERY LOW	CRITICAL
Patient satisfaction -aesthetic - Mixed PMRT; mixed reconstruction type (Better indicated by higher values) (6 month follow-up)												
1	Observational studies	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[7]	None	30	30	-	SMD 0.45 higher	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute		
										(0.07 lower to 0.96 higher)		
Patient satisfaction -aesthetic - Mixed PMRT; autologous (Better indicated by higher values) (6 month follow-up)												
1	Observational studies	Very serious [6]	No serious inconsistency	No serious indirectness	Very serious[7]	None	30	20	-	SMD 0 higher (0.57 lower to 0.57 higher)	VERY LOW	CRITICAL
Patient satisfaction -aesthetic - PMRT+; mixed reconstruction type (Better indicated by higher values) (follow-up not reported)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Serious[8]	None	13	8	-	SMD 1.52 higher (0.5 to 2.53 higher)	VERY LOW	CRITICAL
Patient satisfaction - general - PMRT+; implant (2.3 to 5.4 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/6 (33.3%)	0/1 (0%)	RR 1.43 (0.11 to 19.2)	-	VERY LOW	CRITICAL
Patient satisfaction - general - PMRT+; autologous (2.3 to 5.4 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	18/24 (75%)	20/27 (74.1%)	RR 1.01 (0.73 to 1.4)	7 more per 1000 (from 200 fewer to 296 more)	VERY LOW	CRITICAL
Patient satisfaction - general - Mixed PMRT; mixed reconstruction type (Better indicated by higher values) (6 month follow-up)												
1	Observational studies	Very serious [6]	No serious inconsistency	No serious indirectness	Very serious[7]	None	30	30	-	SMD 0.09 higher (0.41	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute		
										lower to 0.6 higher)		
Patient satisfaction - general - Mixed PMRT; autologous (Better indicated by higher values) (6 to 12 month follow-up)												
2	Observational studies	Very serious [9]	No serious inconsistency	Serious[10]	Very serious[7]	None	60	96	-	SMD 0.4 lower (0.93 lower to 0.13 higher)	VERY LOW	CRITICAL
Patient satisfaction - general - PMRT+; mixed reconstruction type (Better indicated by higher values) (follow-up not reported)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[7]	None	13	8	-	SMD 0.08 higher (0.8 lower to 0.96 higher)	VERY LOW	CRITICAL
Delay in adjuvant therapy - Chemotherapy initiated >= 8 weeks after definitive surgery												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[4]	None	53/596 (8.9%)	3/100 (3%)	RR 2.96 (0.94 to 9.3)	59 more per 1000 (from 2 fewer to 249 more)	VERY LOW	CRITICAL
Delay in adjuvant therapy - Chemotherapy not administered												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[4]	None	97/596 (16.3%)	10/100 (10%)	RR 1.63 (0.88 to 3.01)	63 more per 1000 (from 12 fewer to 201 more)	VERY LOW	CRITICAL
Complication rates - any - Mixed PMRT; mixed reconstruction type (3.2 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute		
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	22/66 (33.3%)	9/24 (37.5%)	RR 0.89 (0.48 to 1.65)	41 fewer per 1000 (from 195 fewer to 244 more)	VERY LOW	CRITICAL
Complication rates - any - PMRT+; mixed reconstruction type (3.9 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[4]	None	23/37 (62.2%)	20/40 (50%)	RR 1.24 (0.83 to 1.85)	120 more per 1000 (from 85 fewer to 425 more)	VERY LOW	CRITICAL
Complication rates - any - PMRT+; autologous; early complications (within 3 months of reconstruction)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	3/36 (8.3%)	9/43 (20.9%)	RR 0.4 (0.12 to 1.36)	126 fewer per 1000 (from 184 fewer to 75 more)	VERY LOW	CRITICAL
Complication rates - any - PMRT+; autologous; late complications (3.9 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	7/36 (19.4%)	5/43 (11.6%)	RR 1.67 (0.58 to 4.82)	78 more per 1000 (from 49 fewer to 444 more)	VERY LOW	CRITICAL
Complication rates - any - PMRT+; implant; early complications (within 3 months of reconstruction)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/13 (15.4%)	0/1 (0%)	RR 0.71 (0.05 to 10.11)	-	VERY LOW	CRITICAL
Complication rates - any - PMRT+; implant; late complications (3.9 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute		
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	8/13 (61.5%)	0/1 (0%)	RR 2.43 (0.21 to 27.78)	-	VERY LOW	CRITICAL
Complication rates - any surgical - Mixed PMRT; mixed reconstruction type (11 to 12 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/28 (7.1%)	4/23 (17.4%)	RR 0.41 (0.08 to 2.05)	103 fewer per 1000 (from 160 fewer to 183 more)	VERY LOW	CRITICAL
Complication rates - any surgical - Mixed PMRT; autologous (follow-up not reported)												
1	Observational studies	Very serious[11]	No serious inconsistency	No serious indirectness	Serious[2]	None	171/2854 (6%)	82/810 (10.1%)	RR 0.59 (0.46 to 0.76)	42 fewer per 1000 (from 24 fewer to 55 fewer)	VERY LOW	CRITICAL
Complication rates - any surgical - Mixed PMRT; implant (follow-up not reported)												
1	Observational studies	Very serious[11]	No serious inconsistency	No serious indirectness	No serious imprecision	None	553/13513 (4.1%)	135/2047 (6.6%)	RR 0.62 (0.52 to 0.74)	25 fewer per 1000 (from 17 fewer to 32 fewer)	VERY LOW	CRITICAL
Complication rates - any donor site (17 to 18 month follow-up)												
2	Observational studies	Serious[12]	No serious inconsistency	Serious[13]	Very serious[4]	None	115/1414 (8.1%)	67/1023 (6.5%)	RR 1.24 (0.92 to 1.65)	16 more per 1000 (from 5 fewer to 43 more)	VERY LOW	CRITICAL
Complication rates - any mastectomy site - Mixed PMRT; autologous (18 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	Serious[13]	Very serious[4]	None	109/1375 (7.9%)	60/987 (6.1%)	RR 1.3 (0.96 to 1.77)	18 more per 1000 (from 2	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute		
										fewer to 47 more)		
Complication rates - any mastectomy site - Mixed PMRT; implant (18 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	Serious[13]	Serious[2]	None	111/1207 (9.2%)	8/280 (2.9%)	RR 3.22 (1.59 to 6.52)	63 more per 1000 (from 17 more to 158 more)	VERY LOW	CRITICAL
Complication rates - any implant related (18 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	Serious[13]	Very serious[14]	None	10/1207 (0.83%)	6/280 (2.1%)	RR 0.39 (0.14 to 1.05)	13 fewer per 1000 (from 18 fewer to 1 more)	VERY LOW	CRITICAL
Complication rates - any flap related (18 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	Serious[13]	Serious[2]	None	61/1375 (4.4%)	86/987 (8.7%)	RR 0.51 (0.37 to 0.7)	43 fewer per 1000 (from 26 fewer to 55 fewer)	VERY LOW	CRITICAL
Complication rates - flap/prosthesis failure - Mixed PMRT; mixed reconstruction type (1 to 17 month follow-up)												
2	Observational studies	Serious[3]	No serious inconsistency	Serious[15]	Serious[2]	None	28/997 (2.8%)	1/486 (0.21%)	RR 10.90 (2.12 to 55.97)	20 more per 1000 (from 2 more to 113 more)	VERY LOW	CRITICAL
Complication rates - flap/prosthesis failure - Mixed PMRT; autologous (follow-up not reported)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Serious[2]	None	82/2854 (2.9%)	11/810 (1.4%)	RR 2.12 (1.13 to 3.95)	15 more per 1000 (from 2 more to 40 more)	VERY LOW	CRITICAL
Complication rates - flap/prosthesis failure - Mixed PMRT; implant (follow-up not reported)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute	Quality	Importance
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	100/13513 (0.74%)	10/2047 (0.49%)	RR 1.51 (0.79 to 2.9)	2 more per 1000 (from 1 fewer to 9 more)	VERY LOW	CRITICAL
Complication rates - any radiological (follow-up not reported)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Serious[2]	None	3/4 (75%)	1/17 (5.9%)	RR 12.75 (1.75 to 92.7)	691 more per 1000 (from 44 more to 1000 more)	VERY LOW	CRITICAL
Complication rates – lymphoedema (11 to 12 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[14]	None	4/28 (14.3%)	9/23 (39.1%)	RR 0.37 (0.13 to 1.03)	247 fewer per 1000 (from 340 fewer to 12 more)	VERY LOW	CRITICAL
Complication rates - heart attack (1 to 18 month follow-up)												
3	Observational studies	Serious[3]	No serious inconsistency	Serious[13]	Very serious[5]	None	6/2550 (0.24%)	4/1178 (0.34%)	RR 0.72 (0.22 to 2.41)	1 fewer per 1000 (from 3 fewer to 5 more)	VERY LOW	CRITICAL
Complication rates - capsular contracture (cosmetic) - Mixed PMRT; mixed reconstruction type (6 month to 4 year follow-up)												
2	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	36/206 (17.5%)	11/203 (5.4%)	RR 1.23 (0.06 to 23.51)	12 more per 1000 (from 51 fewer to 1000 more)	VERY LOW	CRITICAL
Complication rates - capsular contracture (cosmetic) - Mixed PMRT; implant (12 to 36 month follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute		
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	10/197 (5.1%)	0/30 (0%)	RR 3.29 (0.2 to 54.7)	-	VERY LOW	CRITICAL
Complication rates - capsular contracture (cosmetic) - PMRT+; mixed reconstruction type (3.9 year follow-up)												
2	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Serious[2]	None	12/70 (17.1%)	1/65 (1.5%)	RR 6.54 (1.21 to 35.36)	85 more per 1000 (from 3 more to 529 more)	VERY LOW	CRITICAL
Complication rates - capsular contracture (cosmetic) - PMRT-; implant (1 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	4/143 (2.8%)	2/61 (3.3%)	RR 0.85 (0.16 to 4.54)	5 fewer per 1000 (from 28 fewer to 116 more)	VERY LOW	CRITICAL
Complication rates - implant malposition (cosmetic) - Mixed PMRT; mixed reconstruction type (6 month to 4 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	3/167 (1.8%)	1/167 (0.6%)	RR 3 (0.32 to 28.55)	12 more per 1000 (from 4 fewer to 165 more)	VERY LOW	CRITICAL
Complication rates - implant malposition (cosmetic) - PMRT+; mixed reconstruction type (3.9 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/57 (3.5%)	1/57 (1.8%)	RR 2 (0.19 to 21.44)	18 more per 1000 (from 14 fewer to 359 more)	VERY LOW	CRITICAL
Complication rates - implant malposition (cosmetic) - PMRT-; implant (1 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	22/143 (15.4%)	12/61 (19.7%)	RR 0.78 (0.41 to 1.48)	43 fewer per 1000 (from	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute	Quality	Importance
										116 fewer to 94 more)		
Complication rates - implant rupture/extrusion (implant loss) - Mixed PMRT; mixed reconstruction type (6 month to 4 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/167 (1.2%)	0/167 (0%)	RR 5 (0.24 to 103.36)	-	VERY LOW	CRITICAL
Complication rates - implant rupture/extrusion (implant loss) - PMRT+; mixed reconstruction type (3.9 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/57 (3.5%)	1/57 (1.8%)	RR 2 (0.19 to 21.44)	18 more per 1000 (from 14 fewer to 359 more)	VERY LOW	CRITICAL
Complication rates - implant rupture/extrusion (implant loss) - PMRT-; implant (1 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	1/143 (0.7%)	0/61 (0%)	RR 1.29 (0.05 to 31.27)	-	VERY LOW	CRITICAL
Complication rates - implant deflation (implant loss) (6 month to 4 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	4/167 (2.4%)	5/167 (3%)	RR 0.8 (0.22 to 2.93)	6 fewer per 1000 (from 23 fewer to 58 more)	VERY LOW	CRITICAL
Complication rates - implant removed due to dissatisfaction/pain; PMRT+; mixed reconstruction type (implant loss) (3.9 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	1/57 (1.8%)	0/57 (0%)	RR 3 (0.12 to 72.13)	-	VERY LOW	CRITICAL
Complication rates - flap loss (flap loss) - Mixed PMRT; mixed reconstruction type; total flap loss (6 month to 4 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	4/167 (2.4%)	5/167 (3%)	RR 0.8 (0.22 to 2.93)	6 fewer per 1000 (from 23 fewer to 58 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute		
Complication rates - flap loss (flap loss) - Mixed PMRT; mixed reconstruction type; partial flap loss (6 month to 4 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	3/167 (1.8%)	4/167 (2.4%)	RR 0.75 (0.17 to 3.3)	6 fewer per 1000 (from 20 fewer to 55 more)	VERY LOW	CRITICAL
Complication rates - flap loss (flap loss) - PMRT+; mixed reconstruction type (3.9 year follow-up)												
2	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/70 (2.9%)	2/65 (3.1%)	RR 0.82 (0.05 to 12.54)	6 fewer per 1000 (from 29 fewer to 355 more)	VERY LOW	CRITICAL
Complication rates - flap loss (flap loss) - PMRT+; autologous (follow-up not reported)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	1/38 (2.6%)	0/20 (0%)	RR 1.62 (0.07 to 37.94)	-	VERY LOW	CRITICAL
Complication rates - major fat necrosis (flap loss) - Mixed PMRT; mixed reconstruction type (6 month to 4 year follow-up)												
3	Observational studies	Serious[3]	No serious inconsistency	Serious[13]	Serious[2]	None	85/1759 (4.8%)	69/895 (7.7%)	RR 0.72 (0.53 to 0.98)	22 fewer per 1000 (from 2 fewer to 36 fewer)	VERY LOW	CRITICAL
Complication rates - major fat necrosis (flap loss) - Mixed PMRT; autologous (4.25 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/13 (15.4%)	1/11 (9.1%)	RR 1.69 (0.18 to 16.25)	63 more per 1000 (from 75 fewer to 1000 more)	VERY LOW	CRITICAL
Complication rates - major fat necrosis (flap loss) - PMRT+; mixed reconstruction type (3.9 year follow-up)												
2	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/70 (2.9%)	5/65 (7.7%)	RR 0.46 (0.05 to 3.99)	42 fewer per 1000 (from 73	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute		
										fewer to 230 more)		
Complication rates - major fat necrosis (flap loss) - PMRT+; autologous (follow-up not reported)												
1	Observational studies	Very serious [6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	8/25 (32%)	2/15 (13.3%)	RR 2.4 (0.59 to 9.84)	187 more per 1000 (from 55 fewer to 1000 more)	VERY LOW	CRITICAL
Complication rates - major fat necrosis (flap loss) - PMRT-; autologous (follow-up not reported)												
1	Observational studies	Very serious [6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	23/149 (15.4%)	1/28 (3.6%)	RR 4.32 (0.61 to 30.71)	119 more per 1000 (from 14 fewer to 1000 more)	VERY LOW	CRITICAL
Complication rates - valve obstruction; PMRT-; implant (flap loss) (1 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	1/143 (0.7%)	2/61 (3.3%)	RR 0.21 (0.02 to 2.31)	26 fewer per 1000 (from 32 fewer to 43 more)	VERY LOW	CRITICAL
Complication rates - valve displacement; PMRT-; implant (flap loss) (1 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/143 (1.4%)	3/61 (4.9%)	RR 0.28 (0.05 to 1.66)	35 fewer per 1000 (from 47 fewer to 32 more)	VERY LOW	CRITICAL
Complication rates - hematoma (bleeding) - Mixed PMRT; mixed reconstruction type (6 month to 4 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	6/167 (3.6%)	1/167 (0.6%)	RR 6 (0.73 to 49.3)	30 more per 1000 (from 2	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute		
										fewer to 289 more)		
Complication rates - hematoma (bleeding) - PMRT+; mixed reconstruction type (follow-up not reported)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	0/13 (0%)	1/8 (12.5%)	RR 0.21 (0.01 to 4.71)	99 fewer per 1000 (from 124 fewer to 464 more)	VERY LOW	CRITICAL
Complication rates - hematoma (bleeding) - PMRT+; mixed reconstruction type; donor site hematoma (3.9 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/57 (3.5%)	0/57 (0%)	RR 5 (0.25 to 101.89)	-	VERY LOW	CRITICAL
Complication rates - hematoma (bleeding) - PMRT+; mixed reconstruction type; recipient site hematoma (3.9 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/57 (3.5%)	3/57 (5.3%)	RR 0.67 (0.12 to 3.84)	17 fewer per 1000 (from 46 fewer to 149 more)	VERY LOW	CRITICAL
Complication rates - hematoma (bleeding) - PMRT+; autologous (follow-up not reported)												
1	Observational studies	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[16]	None	0/25 (0%)	0/15 (0%)	-	-	VERY LOW	CRITICAL
Complication rates - hematoma (bleeding) - PMRT-; autologous (follow-up not reported)												
1	Observational studies	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	3/149 (2%)	0/28 (0%)	RR 1.35 (0.07 to 25.51)	-	VERY LOW	CRITICAL
Complication rates - bleeding requiring transfusion/surgery; mixed PMRT; mixed reconstruction type (bleeding) (18 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	Serious[13]	Very serious[5]	None	26/1553 (1.7%)	13/692 (1.9%)	RR 0.89 (0.46 to 1.72)	2 fewer per 1000 (from 10	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute		
										fewer to 14 more)		
Complication rates - bleeding; PMRT-; implant (bleeding) (1 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	9/143 (6.3%)	5/61 (8.2%)	RR 0.77 (0.27 to 2.2)	19 fewer per 1000 (from 60 fewer to 98 more)	VERY LOW	CRITICAL
Complication rates - hernia/fascial defect (flap donor site) - Mixed PMRT; mixed reconstruction type (18 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	Serious[13]	Very serious[5]	None	70/1553 (4.5%)	27/692 (3.9%)	RR 1.16 (0.75 to 1.78)	6 more per 1000 (from 10 fewer to 30 more)	VERY LOW	CRITICAL
Complication rates - hernia/fascial defect (flap donor site) - PMRT+; mixed reconstruction type (3.9 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	1/57 (1.8%)	0/57 (0%)	RR 3 (0.12 to 72.13)	-	VERY LOW	CRITICAL
Complication rates - infection (wound) - Flap donor site; PMRT+; mixed reconstruction type (3.9 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	0/57 (0%)	2/57 (3.5%)	RR 0.2 (0.01 to 4.08)	28 fewer per 1000 (from 35 fewer to 108 more)	VERY LOW	CRITICAL
Complication rates - infection (wound) - Recipient site; PMRT+; mixed reconstruction type (3.9 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/57 (3.5%)	2/57 (3.5%)	RR 1 (0.15 to 6.86)	0 fewer per 1000 (from 30 fewer to 206 more)	VERY LOW	CRITICAL
Complication rates - infection (wound) - Site not reported; mixed PMRT; mixed reconstruction (1 month to 4 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute		
4	Observational studies	Serious[3]	No serious inconsistency	Serious[13]	No serious imprecision	None	416/2717 (15.3%)	204/1345 (15.2%)	RR 0.93 (0.8 to 1.07)	11 fewer per 1000 (from 30 fewer to 11 more)	VERY LOW	CRITICAL
Complication rates - infection (wound) - Site not reported; PMRT+; autologous (follow-up not reported)												
1	Observational studies	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[16]	None	0/25 (0%)	0/15 (0%)	-	-	VERY LOW	CRITICAL
Complication rates - infection (wound) - Site not reported; PMRT-; autologous (follow-up not reported)												
1	Observational studies	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	1/149 (0.7%)	0/28 (0%)	RR 0.58 (0.02 to 13.89)	-	VERY LOW	CRITICAL
Complication rates - infection (wound) - Site not reported; PMRT-; implant (1 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/143 (1.4%)	0/61 (0%)	RR 2.15 (0.1 to 44.19)	-	VERY LOW	CRITICAL
Complication rates - wound dehiscence (wound) - Mixed PMRT; mixed reconstruction type (1 to 17 month follow-up)												
2	Observational studies	Serious[3]	No serious inconsistency	Serious[15]	Very serious[5]	None	19/997 (1.9%)	9/486 (1.9%)	RR 0.66 (0.07 to 6.42)	6 fewer per 1000 (from 17 fewer to 100 more)	VERY LOW	CRITICAL
Complication rates - wound dehiscence (wound) - PMRT+; mixed reconstruction type (3.9 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/57 (3.5%)	3/57 (5.3%)	RR 0.67 (0.12 to 3.84)	17 fewer per 1000 (from 46 fewer to 149 more)	VERY LOW	CRITICAL
Complication rates - wound dehiscence (wound) - PMRT-; implant (1 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute		
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	7/143 (4.9%)	1/61 (1.6%)	RR 2.99 (0.38 to 23.75)	33 more per 1000 (from 10 fewer to 373 more)	VERY LOW	CRITICAL
Complication rates - delayed wound healing (wound) (6 month to 4 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	3/167 (1.8%)	6/167 (3.6%)	RR 0.5 (0.13 to 1.97)	18 fewer per 1000 (from 31 fewer to 35 more)	VERY LOW	CRITICAL
Complication rates - skin flap necrosis (mastectomy skin flaps) - Mixed PMRT; mixed reconstruction type (2 month to 4 year follow-up)												
4	Observational studies	Serious[3]	Serious[17]	Serious[13]	Very serious[5]	None	119/1951 (6.1%)	54/942 (5.7%)	RR 2.82 (0.59 to 13.4)	104 more per 1000 (from 24 fewer to 711 more)	VERY LOW	CRITICAL
Complication rates - skin flap necrosis (mastectomy skin flaps) - PMRT+; autologous (follow-up not reported)												
1	Observational studies	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	3/25 (12%)	1/15 (6.7%)	RR 1.8 (0.21 to 15.78)	53 more per 1000 (from 53 fewer to 985 more)	VERY LOW	CRITICAL
Complication rates - skin flap necrosis (mastectomy skin flaps) - PMRT-; autologous (follow-up not reported)												
1	Observational studies	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	24/149 (16.1%)	0/28 (0%)	RR 9.47 (0.59 to 151.42)	-	VERY LOW	CRITICAL
Complication rates - skin loss; PMRT+; mixed reconstruction type (mastectomy skin flaps) (3.9 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	0/57 (0%)	3/57 (5.3%)	RR 0.14 (0.01 to 2.7)	45 fewer per 1000 (from 52	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 89 more)		
Complication rates - additional surgery - Reason not reported; mixed PMRT; mixed reconstruction type (1 to 18 month follow-up)												
3	Observational studies	Serious[3]	Serious[18]	Serious[13]	Very serious[19]	None	292/2550 (11.5%)	122/1178 (10.4%)	RR 1.15 (0.56 to 2.38)	16 more per 1000 (from 46 fewer to 143 more)	VERY LOW	CRITICAL
Complication rates - additional surgery - Reason not reported; mixed PMRT; autologous (follow-up not reported)												
1	Observational studies	Very serious[11]	No serious inconsistency	No serious indirectness	No serious imprecision	None	298/2854 (10.4%)	106/810 (13.1%)	RR 0.8 (0.65 to 0.98)	26 fewer per 1000 (from 3 fewer to 46 fewer)	VERY LOW	CRITICAL
Complication rates - additional surgery - Reason not reported; mixed PMRT; implant (12 to 36 month follow-up)												
2	Observational studies	Very serious[11]	Very serious[20]	No serious indirectness	Very serious[19]	None	1020/13710 (7.4%)	177/2077 (8.5%)	RR 0.45 (0.1 to 1.98)	47 fewer per 1000 (from 77 fewer to 84 more)	VERY LOW	CRITICAL
Complication rates - additional surgery - Reason not reported; PMRT+; mixed reconstruction type (2.6 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	14/33 (42.4%)	2/9 (22.2%)	RR 1.91 (0.53 to 6.9)	202 more per 1000 (from 104 fewer to 1000 more)	VERY LOW	CRITICAL
Complication rates - additional surgery - Reason not reported; PMRT+; autologous (follow-up not reported)												
1	Observational studies	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	3/25 (12%)	0/15 (0%)	RR 4.31 (0.24 to 78.05)	-	VERY LOW	CRITICAL
Complication rates - additional surgery - Reason not reported; PMRT-; mixed reconstruction type (2.6 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute		
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	16/98 (16.3%)	0/12 (0%)	RR 4.33 (0.28 to 68.02)	-	VERY LOW	CRITICAL
Complication rates - additional surgery - Reason not reported; PMRT-; autologous (follow-up not reported)												
1	Observational studies	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	24/128 (18.8%)	2/16 (12.5%)	RR 1.5 (0.39 to 5.76)	62 more per 1000 (from 76 fewer to 595 more)	VERY LOW	CRITICAL
Complication rates - additional surgery - Wound opening; mixed PMRT; mixed reconstruction type (18 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	Serious[13]	Very serious[5]	None	79/1553 (5.1%)	42/692 (6.1%)	RR 0.84 (0.58 to 1.21)	10 fewer per 1000 (from 25 fewer to 13 more)	VERY LOW	CRITICAL
Complication rates - additional surgery - Flap removal; mixed PMRT; mixed reconstruction type (18 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	Serious[13]	Serious[2]	None	48/1553 (3.1%)	34/692 (4.9%)	RR 0.63 (0.41 to 0.97)	18 fewer per 1000 (from 1 fewer to 29 fewer)	VERY LOW	CRITICAL
Complication rates - additional surgery - Flap reposition; mixed PMRT; autologous (4.25 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	0/13 (0%)	1/11 (9.1%)	RR 0.29 (0.01 to 6.38)	65 fewer per 1000 (from 90 fewer to 489 more)	VERY LOW	CRITICAL
Complication rates - additional surgery - Symmetrisation; mixed PMRT; mixed reconstruction type (3 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	18/153 (11.8%)	186/433 (43%)	RR 0.27 (0.18 to 0.43)	314 fewer per 1000 (from 245	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute		
										fewer to 352 fewer)		
Complication rates - additional surgery - Symmetrisation: mixed PMRT; autologous (4.25 year follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	2/13 (15.4%)	2/11 (18.2%)	RR 0.85 (0.14 to 5.06)	27 fewer per 1000 (from 156 fewer to 738 more)	VERY LOW	CRITICAL
Complication rates - additional surgery - Symmetrisation; PMRT-; implant (1 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	12/143 (8.4%)	8/61 (13.1%)	RR 0.64 (0.28 to 1.49)	47 fewer per 1000 (from 94 fewer to 64 more)	VERY LOW	CRITICAL
Complication rates - pneumothorax; PMRT-; implant (1 year follow-up)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[5]	None	0/143 (0%)	1/61 (1.6%)	RR 0.14 (0.01 to 3.47)	14 fewer per 1000 (from 16 fewer to 40 more)	VERY LOW	CRITICAL
Cosmetic result; mixed PMRT; mixed reconstruction type - Excellent (as measured by the Christie scale) (6 month follow-up)												
1	Observational studies	Very serious[6]	No serious inconsistency	No serious indirectness	Serious[2]	None	21/30 (70%)	11/30 (36.7%)	RR 1.91 (1.13 to 3.23)	334 more per 1000 (from 48 more to 818 more)	VERY LOW	IMPORTANT
Cosmetic result; mixed PMRT; mixed reconstruction type - Good (as measured by the Christie scale) (6 month follow-up)												
1	Observational studies	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	6/30 (20%)	12/30 (40%)	RR 0.5 (0.22 to 1.16)	200 fewer per 1000	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute		
										(from 312 fewer to 64 more)		
Cosmetic result; mixed PMRT; mixed reconstruction type - Fair (as measured by the Christie scale) (6 month follow-up)												
1	Observational studies	Very serious [6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	3/30 (10%)	4/30 (13.3%)	RR 0.75 (0.18 to 3.07)	33 fewer per 1000 (from 109 fewer to 276 more)	VERY LOW	IMPORTANT
Cosmetic result; mixed PMRT; mixed reconstruction type - Poor (as measured by the Christie scale) (6 month follow-up)												
1	Observational studies	Very serious [6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	0/30 (0%)	3/30 (10%)	RR 0.14 (0.01 to 2.65)	86 fewer per 1000 (from 99 fewer to 165 more)	VERY LOW	IMPORTANT
Health-related quality of life - general - Mixed PMRT; mixed reconstruction type (Better indicated by higher values) (6 to 11 month follow-up)												
2	Observational studies	Very serious [6]	Very serious[21]	No serious indirectness	Serious[8]	None	58	53	-	SMD 1.43 higher (0.17 to 2.69 higher)	VERY LOW	IMPORTANT
Health-related quality of life - general - Mixed PMRT; autologous (Better indicated by higher values) (6 month follow-up)												
1	Observational studies	Very serious [6]	No serious inconsistency	No serious indirectness	Serious[8]	None	30	20	-	SMD 2.17 higher (1.45 to 2.88 higher)	VERY LOW	IMPORTANT
Health-related quality of life - social; mixed PMRT; mixed reconstruction type (Better indicated by higher values) (11 to 12 month follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute		
2	Observational studies	Serious[3]	No serious inconsistency	Serious[10]	Very serious[7]	None	58	99	-	SMD 0.28 higher (0.05 lower to 0.62 higher)	VERY LOW	IMPORTANT
Health-related quality of life - social (change from pre- to post-reconstruction FACT-B social wellbeing scale); mixed PMRT; mixed reconstruction type (Better indicated by higher values) (2 year follow-up)												
1	Observational studies	Very serious[6]	No serious inconsistency	No serious indirectness	Very serious[7]	None	115	54	-	MD 0.65 lower (2.04 lower to 0.74 higher)	VERY LOW	IMPORTANT
Health-related quality of life - physical - General (measured by EORTC QLQ-30); mixed PMRT; mixed reconstruction type (Better indicated by higher values) (11 to 12 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Serious[8]	None	28	23	-	SMD 0.89 higher (0.31 to 1.47 higher)	VERY LOW	IMPORTANT
Health-related quality of life - physical - Chest (measured by BREAST-Q): mixed PMRT; autologous (Better indicated by higher values) (12 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	Serious[10]	Serious[8]	None	30	76	-	SMD 0.04 lower (0.46 lower to 0.39 higher)	VERY LOW	IMPORTANT
Health-related quality of life - physical - Abdomen (measured by BREAST-Q): mixed PMRT; autologous (Better indicated by higher values) (12 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	Serious[10]	Serious[8]	None	30	76	-	SMD 0.05 higher (0.37 lower to	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute	Quality	Importance
										0.47 higher)		
Health-related quality of life - sexual (measured by BREAST-Q); mixed PMRT; autologous (Better indicated by higher values) (12 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Serious[8]	None	30	76	-	MD 5.4 higher (5.13 lower to 15.93 higher)	VERY LOW	IMPORTANT
Health-related quality of life - role functioning (measured by EORTC QLQ-30); mixed PMRT; mixed reconstruction type (Better indicated by higher values) (11 to 12 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[7]	None	28	23	-	MD 1.35 lower (10.07 lower to 7.37 higher)	VERY LOW	IMPORTANT
Health-related quality of life - emotional functioning (measured by EORTC QLQ-30); mixed PMRT; mixed reconstruction type (Better indicated by higher values) (11 to 12 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[7]	None	28	23	-	MD 9.22 higher (0.27 lower to 18.71 higher)	VERY LOW	IMPORTANT
Health-related quality of life - cognitive functioning (measured by EORTC QLQ-30); mixed PMRT; mixed reconstruction type (Better indicated by higher values) (11 to 12 month follow-up)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[7]	None	28	23	-	MD 0.26 higher (10.05 lower to 10.57 higher)	VERY LOW	IMPORTANT
Health-related quality of life - functional (change from pre- to post-reconstruction FACT-B functional wellbeing scale); mixed PMRT; mixed reconstruction type (Better indicated by higher values) (2 year follow-up)												
1	Observational studies	Very serious[6]	No serious inconsistency	No serious indirectness	Serious[8]	None	116	55	-	MD 2.06 higher (0.51 to	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate	Delayed	Relative (95% CI)	Absolute	Quality	Importance
										3.61 higher)		

CI: Confidence interval; EORTC QLQ-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-B; Functional assessment of cancer therapy – Breast cancer; HR: Hazards ratio; MD, mean difference; PMRT: postmastectomy radiotherapy; RR: Risk ratio; SMD, standardised mean difference

[1] *Unclear if groups were comparable at baseline*
[2] *<300 events*
[3] *Groups not comparable at baseline*
[4] *<300 events; 95% confidence interval crosses both boundary for no effect (1) and minimally important difference (1.25) based on GRADE default values*
[5] *<300 events; 95% confidence interval crosses boundary for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values*
[6] *Insufficient information about method of selection and groups not comparable at baseline*
[7] *sample size <400; 95% confidence interval crosses both boundary of no effect (0) and minimally important difference (0.5 times SD) based on GRADE default values*
[8] *sample size <400*
[9] *Insufficient information about method of selection for Zahra 2014 and groups not comparable at baseline*
[10] *25% of Zhong 2016 had in situ breast cancer*
[11] *Groups not comparable at baseline and follow-up limited*
[12] *Groups not comparable at baseline for Jeevan 2014 which has 99% of weight in analysis*
[13] *29% of Jeevan 2014 had in situ breast cancer*
[14] *<300 events; 95% confidence interval crosses both no effect (1) and minimally important difference (0.80) based on GRADE default values*
[15] *Unclear what proportion of patients had delayed-immediate reconstruction*
[16] *No events*
[17] *I2 64% - significant unexplained heterogeneity; no further subgroups of interest identified by guideline committee*
[18] *I2 79% - significant unexplained heterogeneity; no further subgroups of interest identified by guideline committee*
[19] *95% confidence interval crosses both boundary for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values*
[20] *I2 95% - significant unexplained heterogeneity; no further subgroups of interest identified by guideline committee*
[21] *I2 88% - significant unexplained heterogeneity; no further subgroups of interest identified by guideline committee*

Appendix G – Economic evidence study selection

Economic evidence study selection for 9.1 What are the indications for postmastectomy radiotherapy for people with early and locally advanced breast cancer?

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

Economic evidence study selection for 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?

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

Appendix H – Economic evidence tables

Economic evidence tables for 9.1 What are the indications for postmastectomy radiotherapy for people with early and locally advanced breast cancer?

No economic evidence was identified for this review question.

Economic evidence tables for 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?

No economic evidence was identified for this review question.

Appendix I – Health economic evidence profiles

Health economic evidence profiles for 9.1 What are the indications for postmastectomy radiotherapy for people with early and locally advanced breast cancer?

No economic evidence was identified for this review question.

Health economic evidence profiles for 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?

No economic evidence was identified for this review question.

Appendix J – Health economic analysis

Health economic analysis for 9.1 What are the indications for postmastectomy radiotherapy for people with early and locally advanced breast cancer?

No health economic analysis was conducted for this review question.

Health economic analysis for 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?

No health economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for 9.1 What are the indications for postmastectomy radiotherapy for people with early and locally advanced breast cancer?

Clinical studies

Excluded studies -9.1 What are the indications for post mastectomy radiotherapy for people with early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Bellon, J. R., Katz, A., Taghian, A., Radiation Therapy for Breast Cancer, Hematology/Oncology Clinics of North America, 20, 239-257, 2006	Included in old guideline. Narrative review. The included trials are included in EBCTCG 2014.
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	SR. No additional relevant trials identified.
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	Duplicate (see Killander 2014).
Clarke, M., Collins, R., Darby, S., Davies, C., Elphinstone, P., Evans, V., Godwin, J., Gray, R., Hicks, C., James, S., MacKinnon, E., McGale, P., McHugh, T., Peto, R., Taylor, C., Wang, Y., Early Breast Cancer Trialists' Collaborative, Group, Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials, Lancet, 366, 2087-106, 2005	Included in old guideline. Excluded from the update as the updated meta-analysis has been included (see EBCTCG 2014).
Danish Breast Cancer Cooperative, Group, Nielsen, H. M., Overgaard, M., Grau, C., Jensen, A. R., Overgaard, J., Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies, Journal of clinical oncology, 24, 2268-75, 2006	Included in old guideline. Excluded from this update as it is a follow-up study of 2 trials already included in EBCTCG 2014 MA.

Excluded studies -9.1 What are the indications for post mastectomy radiotherapy for people with early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Fisher, B., Jeong, J. H., Anderson, S., Bryant, J., Fisher, E. R., Wolmark, N., Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation, New England Journal of Medicine, 347, 567-575, 2002	Included in old guideline. This trial was excluded from the update, as it was already included in Clarke 2005 MA.
Gebski, V., Lagleva, M., Keech, A., Simes, J., Langlands, A. O., Survival effects of postmastectomy adjuvant radiation therapy using biologically equivalent doses: A clinical perspective, Journal of the National Cancer Institute, 98, 26-38, 2006	Included in old guideline. Excluded in the update, as the SR included in the MA had already been included in previous MA (Clarke 2005). Additional comparisons (radiation volume) are not relevant to the review protocol.
Goodwin,Annabel, Parker,Sharon, Ghersi,Davina, Wilcken,Nicholas, Post-operative radiotherapy for ductal carcinoma in situ of the breast, Cochrane Database of Systematic Reviews, -, 2013	Not relevant intervention. Cochrane SR. Includes any trial comparing breast conserving surgery(lumpectomy, quadrantectomy, segmental mastectomy) with or without RT.
Gustavsson, A., Bendahl, P. O., Cwikiel, M., Eskilsson, J., Thapper, K. L., Pahlm, O., No serious late cardiac effects after adjuvant radiotherapy following mastectomy in premenopausal women with early breast cancer, International Journal of Radiation Oncology Biology Physics, 43, 745-754, 1999	Included in old guideline. Excluded from the update as it does not include relevant outcomes.
Haffty, B. G., Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: Meta-analysis of individual patient data for 8135 women in 22 randomised trials, Breast Diseases, 25, 343-344, 2015	Duplicate (ECBTCG 2014).
Headon, H., Kasem, A., Almukbel, R., Mokbel, K., Improvement of survival with postmastectomy radiotherapy in patients with 1-3 positive axillary lymph nodes: A systematic review and meta-analysis of the current literature, Molecular and Clinical Oncology, 5, 429-436, 2016	This meta-analysis includes 2 RCTs that had already been included in EBCTCG 2014.
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, International Journal of Radiation Oncology Biology Physics, 86, 860-866, 2013	No relevant comparison. All women received chest wall RT and medial supraclavicular nodes, and then were randomised to receive RT to internal mammary nodes or not.
Hickey, Brigid E, James, Melissa L, Lehman, Margot, Hider, Phil N, Jeffery, Mark, Francis, Daniel P, See, Adrienne M, Fraction size in radiation therapy	Cochrane review. Not relevant comparison.

Excluded studies -9.1 What are the indications for post mastectomy radiotherapy for people with early and locally advanced breast cancer?	
Study	**Reason for exclusion**
for breast conservation in early breast cancer, Cochrane Database of Systematic Reviews, 2016	
Holmberg, L., Garmo, H., Granstrand, B., Ringberg, A., Arnesson, L. G., Sandelin, K., Karlsson, P., Anderson, H., Emdin, S., Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma in situ of the breast, Journal of Clinical Oncology, 26, 1247-1252, 2008	Population not relevant (breast conserving surgery).
Killander, F., Anderson, H., Ryden, S., Moller, T., Hafstrom, L. O., Malmstrom, P., Efficient reduction of locoregional recurrences but no effect on mortality twenty years after postmastectomy radiation in premenopausal women with stage II breast cancer - a randomized trial from the South Sweden Breast Cancer Group, Breast, 18, 309-15, 2009	This trial is already included in EBCTCG 2014 MA
Kunkler, I., Local treatment, European Journal of Cancer, 48, S46, 2012	Conference abstract.
Kunkler, I. H., Canney, P., Dunlop, J., Anderson, N., Aird, E., Denvir, M., Velikova, G., Russell, N., Van Tienhoven, G., Bartlett, J. M., MRC supremo (Selected use of postoperative radiotherapy after mastectomy) (Big 2-04/EORTC 22051)- A Phase III multicentre international randomised trial assessing the role of adjuvant chest wall irradiation in 'intermediate risk' operable breast cancer following mastectomy and axillary surgery, Annals of Oncology, 20, ii28, 2009	Conference abstract (SUPREMO trial). No results reported.
Kyndi,M., Sorensen,F.B., Knudsen,H., Overgaard,M., Nielsen,H.M., Overgaard,J., Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: The Danish Breast Cancer Cooperative Group, Journal of Clinical Oncology, 26, 1419-1426, 2008	Included in old guideline. Excluded from the update, at this trial is already included in EBCTCG 2014.
Lakhanpal, R., Jensen, K., Shadbolt, B., Sullivan, L., Omission of whole breast irradiation for postmenopausal women with early breast cancer, Cochrane Database of Systematic Reviews, 2017 (1) (no pagination), 2017	Protocol for a Cochrane systematic review.
Li, Y., Moran, M. S., Huo, Q., Yang, Q., Haffty, B. G., Post-mastectomy radiotherapy for breast cancer patients with t1-t2 and 1-3 positive lymph nodes: a meta-analysis, 8, e81765, 2013	Meta-analysis of non-randomised studies.

Excluded studies -9.1 What are the indications for post mastectomy radiotherapy for people with early and locally advanced breast cancer?	
Study	**Reason for exclusion**
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	Same meta-analysis as Budach 2015.
Nielsen, H. M., Overgaard, M., Grau, C., Jensen, A. R., Overgaard, J., Locoregional recurrence after mastectomy in high-risk breast cancer-risk and prognosis. An analysis of patients from the DBCG 82 b&c randomization trials, Radiotherapy and Oncology, 79, 147-155, 2006	Included in the old guideline. Excluded from the update as the trials are already included in EBCTCG 2014.
O'Rorke, M. A., Murray, L. J., Brand, J. S., Bhoo-Pathy, N., The value of adjuvant radiotherapy on survival and recurrence in triple-negative breast cancer: A systematic review and meta-analysis of 5507 patients, Cancer treatment reviews, 47, 12-21, 2016	Only relevant study already included in EBCTCG 2014.
Poortmans, P., Kouloulias, V., van Tienhoven, G., Collette, L., Struikmans, H., Venselaar, J. L., Van den Bogaert, W., Davis, J. B., Lambin, P., Eortc Radiation Oncology, Breast Cancer, Groups, Quality assurance in the EORTC randomized trial 22922/10925 investigating the role of irradiation of the internal mammary and medial supraclavicular lymph node chain works, Strahlentherapie und Onkologie, 182, 576-82, 2006	Not RCT.
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. Full published study has been included (see Poortmans 2015).
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. Full published study has been included (see Poortmans 2015).
Recht, A., Edge, S. B., Solin, L. J., Robinson, D. S., Estabrook, A., Fine, R. E., Fleming, G. F., Formenti, S., Hudis, C., Kirshner, J. J., Krause, D. A., Kuske, R. R., Langer, A. S., Sledge, G. W., Jr., Whelan, T. J., Pfister, D. G., Post-mastectomy radiotherapy: Clinical practice guidelines of the American Society of Clinical Oncology, Journal of Clinical Oncology, 19, 1539-1569, 2001	Included in the old guideline. Excluded from the update as all relevant trials are already included in EBCTCG 2014.

Excluded studies -9.1 What are the indications for post mastectomy radiotherapy for people with early and locally advanced breast cancer?	
Study	**Reason for exclusion**
Rowell, N. P., Radiotherapy to the chest wall following mastectomy for node-negative breast cancer: A systematic review, Radiotherapy and Oncology, 91, 23-32, 2009	All relevant trials are already included in EBCTCG 2014.
Smith, B. D., Haffty, B. G., Hurria, A., Galusha, D. H., Gross, C. P., Post-mastectomy radiation and survival in older women with breast cancer, Journal of Clinical Oncology, 24, 4901-4907, 2006	Included in the old guideline. Excluded in the guideline updated because it's a retrospective cohort study.
Thomas, J. S., Hanby, A. M., Russell, N., van Tienhoven, G., Riddle, K., Anderson, N., Cameron, D. A., Bartlett, J. M. S., Piper, T., Cunningham, C., Canney, P., Kunkler, I. H., On Behalf Of The Supremo Trial Management, Group, The BIG 2.04 MRC/EORTC SUPREMO Trial: pathology quality assurance of a large phase 3 randomised international clinical trial of postmastectomy radiotherapy in intermediate-risk breast cancer, Breast Cancer Research and Treatment, 1-7, 2017	Conference abstract (SUPREMO trial). No results reported.
Thomas, J., Hanby, A., Van Tienhoven, G., Russell, N., Riddle, K., Cameron, D., Bartlett, J., Piper, T., Cunningham, C., Canney, P., Kunkler, I., The SUPREMO Trial-Pathology quality assurance of a large phase 3 randomised international clinical trial, European Journal of Cancer, 57, S48, 2016	Conference abstract (SUPREMO trial). No results reported.
Truong, P. T., Olivotto, I. A., Whelan, T. J., Levine, M., Clinical practice guidelines for the care and treatment of breast cancer: 16. Locoregional postmastectomy radiotherapy, CMAJ Canadian Medical Association JournalCmaj, 170, 1263-1273, 2004	Included in the old guideline. Excluded as all the trials in the MA had already been included in other MA.
Van De Steene, J., Soete, G., Storme, G., Adjuvant radiotherapy for breast cancer significantly improves overall survival: The missing link, Radiotherapy and Oncology, 55, 263-272, 2000	Included in the old guideline. Excluded from the update as it includes the same trials as EBCTCG 2014.
Velikova, G., Williams, L., Willis, S., Cairns, J., Riddle, K., Hermiston, S., Russell, N., Kunkler, I., Quality of life results of BIG 02-04 MRC EORTC SUPREMO trial of chest wall radiotherapy in patients with intermediate risk stage II breast cancer after mastectomy, European Journal of Surgical Oncology, 42 (11), S246, 2016	Conference abstract (SUPREMO trial).
Whelan, T. J., Julian, J., Wright, J., Jadad, A. R., Levine, M. L., Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis, Journal of Clinical Oncology, 18, 1220-1229, 2000	Included in the old guideline. Excluded from the update as all relevant trials are included in EBCTCG 2014.

EBCTCG, Early Breast Cancer Trialists' Collaborative Group; MA, meta-analysis; RCT, randomised controlled trial; RT, radiotherapy; SR, systematic review; SUPREMO, Selective Use of Postoperative Radiotherapy aftEr MastectOmy

Economic studies

No health economic evidence was identified for this review question.

Excluded studies for 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?

Clinical studies

Excluded studies - 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?	
Study	**Reason for Exclusion**
Agarwal, J., Agarwal, S., Pappas, L., Neumayer, L., A population-based study of breast cancer-specific survival following mastectomy and immediate or early-delayed breast reconstruction, Breast Journal, 18, 226-232, 2012	Comparison outside scope: reconstruction vs no reconstruction
Anavekar, N. S., Rozen, W. M., Le Roux, C. M., Ashton, M. W., Achieving autologous breast reconstruction for breast cancer patients in the setting of postmastectomy radiotherapy, Journal of Cancer Survivorship, 5, 1-7, 2011	Contains comparisons outside scope
Atisha, D., Alderman, A. K., Janiga, T., Singal, B., Wilkins, E. G., The efficacy of the surgical delay procedure in pedicle TRAM breast reconstruction, Annals of plastic surgery, 63, 383-388, 2009	Comparison outside scope: TRAM surgical delay procedure
Aurilio, G., Bagnardi, V., Graffeo, R., Nole, F., Petit, J. Y., Locatelli, M., Martella, S., Iera, M., Rey, P., Curigliano, G., Rotmensz, N., Munzone, E., Goldhirsch, A., Does immediate breast reconstruction after mastectomy and neoadjuvant chemotherapy influence the outcome of patients with non-endocrine responsive breast cancer?, Anticancer research, 34, 6677-6683, 2014	Comparison outside scope: IBR vs. no IBR
Aurilio, G., Bagnardi, V., Nole, F., Pruneri, G., Graffeo, R., Petit, J. Y., Cullura, D., Martella, S., Locatelli, M., Iera, M., Rey, P., Curigliano, G., Rotmensz, N., Munzone, E., Goldhirsch, A., Outcome of Immediate Breast Reconstruction in Patients with Nonendocrine-Responsive Breast Cancer: A Monoinstitutional Case-Control Study, Clinical breast cancer, 15, e237-e241, 2015	Comparison outside scope: IBR vs no reconstruction
Barry, M., Kell, M. R., Radiotherapy and breast reconstruction: A meta-analysis, Breast cancer research and treatment, 127, 15-22, 2011	Contains comparisons outside scope
Berbers, J., Van Baardwijk, A., Houben, R., Heuts, E., Smidt, M., Keymeulen, K., Bessems, M., Tuinder, S., Boersma, L. J., 'Reconstruction: Before or after postmastectomy radiotherapy?' A systematic review of the literature, European journal of cancer, 50, 2752-2762, 2014	Contains non-comparative studies
Bezuhly, M., Temple, C., Sigurdson, L. J., Davis, R. B., Flowerdew, G., Cook Jr, E. F., Immediate postmastectomy reconstruction is associated with improved breast cancer-specific survival: Evidence and new challenges from the surveillance, epidemiology, and end results database, Cancer, 115, 4648-4654, 2009	Comparison outside scope: IBR vs no reconstruction
Bodin, F., Dissaux, C., Lutz, J. C., Hendriks, S., Fiquet, C., Bruant-Rodier, C., The DIEP flap breast reconstruction: Starting from scratch in a university hospital, Annales de chirurgie plastique et esthetique, 60, 171-8, 2015	No comparison between immediate and delayed
Chang, E. I., Liu, T. S., Festekjian, J. H., Da Lio, A. L., Crisera, C. A., Effects of radiation therapy for breast cancer based on type of free flap reconstruction, Plastic and Reconstructive Surgery, 131, 1e-8e, 2013	No comparison of IBR vs DBR

Excluded studies - 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?	
Study	**Reason for Exclusion**
Claen, J., Nitzsche, S., Wallwiener, D., Kristen, P., Souchon, R., Bamberg, M., Brucker, S., Fibrotic changes after postmastectomy radiotherapy and reconstructive surgery in breast cancer: A retrospective analysis in 109 patients, Strahlentherapie und Onkologie, 186, 630-636, 2010	No comparison between immediate and delayed
Clemens, M. W., Kronowitz, S. J., Current perspectives on radiation therapy in autologous and prosthetic breast reconstruction, Gland Surgery, 4, 222-31, 2015	No comparison of IBR vs DBR
Collier, P., Williams, J., Edhayan, G., Kanneganti, K., Edhayan, E., The effect of timing of postmastectomy radiation on implant-based breast reconstruction: A retrospective comparison of complication outcomes, American Journal of Surgery, 207, 408-411, 2014	Comparison outside scope: timing of switch from tissue expander to permanent implant
Cordeiro, P. G., Breast reconstruction after surgery for breast cancer, New England Journal of Medicine, 359, 1590-601, 2008	Case study/narrative review
D'Souza,Nigel, Darmanin,Geraldine, Fedorowicz,Zbys, Immediate versus delayed reconstruction following surgery for breast cancer, Cochrane Database of Systematic Reviews, -, 2011	Contains comparisons outside scope
Duraes, E. F. R., Durand, P., Duraes, L. C., Orra, S., Moreira-Gonzalez, A., Sousa, J. B. D., Djohan, R. S., Zins, J., Bernard, S., Schwarz, G. S., Comparison of preoperative quality of life in breast reconstruction, breast aesthetic and non-breast plastic surgery patients: A cross-sectional study, Journal of Plastic, Reconstructive and Aesthetic Surgery, 69, 1478-1485, 2016	Comparison outside scope: 'delayed' group had not had reconstruction
El-Sabawi, B., Sosin, M., Carey, J. N., Nahabedian, M. Y., Patel, K. M., Breast reconstruction and adjuvant therapy: A systematic review of surgical outcomes, Journal of surgical oncology, 112, 458-64, 2015	Insufficient information about included studies
Giacalone, P. L., Rathat, G., Daures, J. P., Benos, P., Azria, D., Rouleau, C., New concept for immediate breast reconstruction for invasive cancers: Feasibility, oncological safety and esthetic outcome of post-neoadjuvant therapy immediate breast reconstruction versus delayed breast reconstruction: A prospective pilot study, Breast cancer research and treatment, 122, 439-451, 2010	Intervention outside scope: those who had immediate reconstruction had neoadjuvant chemotherapy and radiotherapy
Gieni, M., Avram, R., Dickson, L., Farrokhyar, F., Lovrics, P., Faidi, S., Sne, N., Local breast cancer recurrence after mastectomy and immediate breast reconstruction for invasive cancer: A meta-analysis, Breast, 21, 230-236, 2012	Comparisons outside scope
Henry, L. R., Morris, L. L., Downs, R., Schwarz, R. E., The impact of immediate breast reconstruction after mastectomy on time to first adjuvant treatment in women with breast cancer in a community setting, American Journal of Surgery., 21, 2016	Comparison outside scope: IBR vs no reconstruction
Kronowitz, S. J., Current status of autologous tissue-based breast reconstruction in patients receiving postmastectomy radiation therapy, Plastic and Reconstructive Surgery, 130, 282-292, 2012	Contains comparisons outside scope
Kronowitz, S. J., Current status of implant-based breast reconstruction in patients receiving postmastectomy radiation therapy, Plastic and Reconstructive Surgery, 130, 513e-524e, 2012	Contains comparisons outside scope

Excluded studies - 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?	
Study	**Reason for Exclusion**
Kronowitz, S. J., Robb, G. L., Radiation therapy and breast reconstruction: A critical review of the literature, Plastic and Reconstructive Surgery, 124, 395-408, 2009	Insufficient information about included studies
Lee, K. T., Mun, G. H., Prosthetic breast reconstruction in previously irradiated breasts: A meta-analysis, Journal of surgical oncology, 112, 468-475, 2015	Contains comparisons outside scope
Lee, K. T., Mun, G. H., Lim, S. Y., Pyon, J. K., Oh, K. S., Bang, S. I., The impact of immediate breast reconstruction on postmastectomy lymphedema in patients undergoing modified radical mastectomy, Breast, 22, 53-57, 2013	Comparison outside scope: IBR vs no reconstruction
Liljegren, A., Unukovych, D., Gagliardi, G., Bjohle, J., Wickman, M., Johansson, H., Sandelin, K., No difference in dose distribution in organs at risk in postmastectomy radiotherapy with or without breast implant reconstruction, Radiation Oncology, 9, 14, 2014	Comparison outside scope: IBR vs no reconstruction
Lisa, A., Klinger, F., Caviggioli, F., Maione, L., Murolo, M., Klinger, M. E., Comparison of Delayed and Immediate Tissue Expander Breast Reconstruction in the Setting of Postmastectomy Radiation Therapy, Annals of plastic surgery, 75, 246, 2015	Commentary
Losk, K., Vaz-Luis, I., Camuso, K., Batista, R., Lloyd, M., Tukenmez, M., Golshan, M., Lin, N. U., Bunnell, C. A., Factors associated with delays in chemotherapy initiation among Patients with breast cancer at a comprehensive cancer center, JNCCN Journal of the National Comprehensive Cancer Network, 14, 1519-1526, 2016	No comparison between immediate and delayed reconstruction
Magarakis, M., Venkat, R., Dellon, A. L., Shridharani, S. M., Bellamy, J., Vaca, E. E., Jeter, S. C., Zoras, O., Manahan, M. A., Rosson, G. D., Pilot study of breast sensation after breast reconstruction: evaluating the effects of radiation therapy and perforator flap neurotization on sensory recovery, Microsurgery, 33, 421-31, 2013	Outcome outside scope
Marta, G. N., Hanna, S. A., Martella, E., Silva, J. L., Radiotherapy and breast reconstruction after surgical treatment of breast cancer, Revista da Associacao Medica Brasileira (1992), 57, 132-133, 2011	Opinion piece
Masoomi, H., Paydar, K. Z., Wirth, G. A., Aly, A., Kobayashi, M. R., Evans, G. R., Predictive risk factors of venous thromboembolism in autologous breast reconstruction surgery, Annals of plastic surgery, 72, 30-33, 2014	Insufficient presentation of results
McCarthy, C. M., Mehrara, B. J., Riedel, E., Davidge, K., Hinson, A., Disa, J. J., Cordeiro, P. G., Pusic, A. L., Predicting complications following expander/implant breast reconstruction: An outcomes analysis based on preoperative clinical risk, Plastic and Reconstructive Surgery, 121, 1886-1892, 2008	Intervention/control outside scope: temporary tissue expanders
Menezes, M. M., Bello, M. A., Millen, E., Lucas, F. A. S., Carvalho, F. N., Andrade, M. F. C., Pereira, A. C. P. R., Koifman, R. J., Bergmann, A., Breast reconstruction and risk of lymphedema after mastectomy: A prospective cohort study with 10 years of follow-up, Journal of Plastic, Reconstructive and Aesthetic Surgery, 69, 1218-1226, 2016	No comparison between IBR and DBR
Metcalfe, K. A., Semple, J., Quan, M. L., Vadaparampil, S. T., Holloway, C., Brown, M., Bower, B., Sun, P., Narod, S. A., Changes in psychosocial functioning 1 year after mastectomy alone, delayed breast reconstruction, or immediate breast reconstruction, Annals of surgical oncology, 19, 233-41, 2012	Insufficient presentations of results

Excluded studies - 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?	
Study	**Reason for Exclusion**
Momoh, A. O., Ahmed, R., Kelley, B. P., Aliu, O., Kidwell, K. M., Kozlow, J. H., Chung, K. C., A systematic review of complications of implant-based breast reconstruction with prereconstruction and postreconstruction radiotherapy, Annals of surgical oncology, 21, 118-24, 2014	Contains comparisons outside scope
Nahabedian, M. Y., Momen, B., The impact of breast reconstruction on the oncologic efficacy of radiation therapy: a retrospective analysis, Annals of plastic surgery, 60, 244-250, 2008	No comparison of IBR vs DBR
Pestana, I. A., Campbell, D. C., Bharti, G., Thompson, J. T., Factors affecting complications in radiated breast reconstruction, Annals of plastic surgery, 70, 542-545, 2013	No comparison of IBR vs DBR
Ribuffo, D., Vaia, N., Petrianni, G. M., Comparison of Delayed and Immediate Tissue Expander Breast Reconstruction in the Setting of Postmastectomy Radiation Therapy, Annals of plastic surgery, 76, 743-4, 2016	Commentary
Robb, G. L., Breast reconstruction after therapy for early breast cancer, Clinical Advances in Hematology and Oncology, 6, 341-344, 2008	Interview
Rozen, W. M., Ashton, M. W., Taylor, G. I., Defining the role for autologous breast reconstruction after mastectomy: Social and oncologic implications, Clinical breast cancer, 8, 132-142, 2008	Insufficient information about included studies
Sandberg, L. J., Clemens, M. W., Symmans, W. F., Valero, V., Caudle, A. S., Smith, B., Kuerer, H. M., Hsu, L., Kronowitz, S. J., Molecular Profiling Using Breast Cancer Subtype to Plan for Breast Reconstruction, Plastic & Reconstructive Surgery, 139, 586e-596e, 2017	Insufficient presentation of results
Schaverien, M. V., Macmillan, R. D., McCulley, S. J., Is immediate autologous breast reconstruction with postoperative radiotherapy good practice?: A systematic review of the literature, Journal of Plastic, Reconstructive and Aesthetic Surgery, 66, 1637-1651, 2013	Contains comparisons outside scope
Seth, A. K., Silver, H. R., Hirsch, E. M., Kim, J. Y., Fine, N. A., Comparison of Delayed and Immediate Tissue Expander Breast Reconstruction in the Setting of Postmastectomy Radiation Therapy, Annals of plastic surgery, 75, 503-507, 2015	Intervention/control outside scope: temporary tissue expanders
Shah, C., Kundu, N., Arthur, D., Vicini, F., Radiation therapy following postmastectomy reconstruction: a systematic review, Annals of surgical oncology, 20, 1313-22, 2013	Contains comparisons outside scope
Teo, I., Reece, G. P., Christie, I. C., Guindani, M., Markey, M. K., Heinberg, L. J., Crosby, M. A., Fingeret, M. C., Body image and quality of life of breast cancer patients: influence of timing and stage of breast reconstruction, Psycho-oncology, 1106-1112, 2016	Insufficient presentation of results
Thiruchelvam, P. T. R., McNeill, F., Jallali, N., Harris, P., Hogben, K., Post-mastectomy breast reconstruction, BMJ (Online), 347 (7929) (no pagination), 2013	Insufficient information about included studies
van Wingerden, J. J., A simple guide during early expansion following immediate breast reconstruction, Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS, 62, 617, 2009	Clinical advice

Excluded studies - 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?	
Study	**Reason for Exclusion**
Wilkins, Eg, Hamill, Jb, Kim, Hm, Kim, Jy, Greco, Rj, Qi, J, Pusic, Al, Complications in Postmastectomy Breast Reconstruction: one-year Outcomes of the Mastectomy Reconstruction Outcomes Consortium (MROC) Study, Annals of surgery, (no pagination), 2017	Insufficient presentation of results
Winters, Z. E., Benson, J. R., Pusic, A. L., A systematic review of the clinical evidence to guide treatment recommendations in breast reconstruction based on patient-reported outcome measures and health-related quality of life, Annals of surgery, 252, 929-942, 2010	Contains comparisons outside scope
Xavier Harmeling, J., Kouwenberg, C. A. E., Bijlard, E., Burger, K. N. J., Jager, A., Mureau, M. A. M., The effect of immediate breast reconstruction on the timing of adjuvant chemotherapy: a systematic review, Breast Cancer Research and Treatment, 153, 241-251, 2015	No comparison between IBR vs DBR
Yang, X., Zhu, C., Gu, Y., The prognosis of breast cancer patients after mastectomy and immediate breast reconstruction: a meta-analysis, PLoS ONE [Electronic Resource], 10, e0125655, 2015	No comparison between IBR vs DBR
Ziswiler-Gietz, J., Makrodimou, M., Harder, Y., Banic, A., Erni, D., Outcome analysis of breast reconstruction with free transverse rectus abdominis musculocutaneous (TRAM) flaps, Swiss Medical Weekly, 138, 114-120, 2008	No comparison between IBR and DBR

DBR, delayed breast reconstruction; IBR, immediate breast reconstruction; TRAM; transverse rectus abdominus myocutaneous

Economic studies

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

Appendix L – Research recommendations

Research recommendations for 9.1 What are the indications for postmastectomy radiotherapy for people with early and locally advanced breast cancer?

No research recommendations were made for this review question.

Research recommendations for 9.2 Should the potential need for radiotherapy preclude immediate breast reconstruction?

What are the long-term outcomes for breast reconstruction in women having radiotherapy to the chest wall?

Why this is important

Postmastectomy breast reconstruction improves women's quality of life after mastectomy and is offered to women undergoing mastectomy. Reconstruction can be performed at the time of mastectomy (immediate breast reconstruction) or planned as a later procedure (delayed reconstruction). Some women need treatment with postmastectomy chest wall radiotherapy to reduce the risk of disease recurrence. However, it is known that radiotherapy can alter outcomes after breast reconstruction, including impairing cosmetic outcomes and increasing rates of re-operation and complications.

Research is therefore needed to understand whether immediate breast reconstruction or delayed breast reconstruction is optimal in women who may need postmastectomy radiotherapy, particularly regarding longer-term outcomes and different types of reconstruction.

Table 19: Research recommendation rationale

Research question	What are the long-term outcomes for breast reconstruction in women having chest wall radiotherapy?
Importance to 'patients' or the population	Improve patient satisfaction and psychological wellbeing Improved cosmetic results Reduce complications Reduce further surgery Minimise delays to adjuvant therapies
Relevance to NICE guidance	To enable clearer and more specific guidance
Relevance to the NHS	Improve satisfaction with treatment outcomes
National priorities	Reduce inequalities Achieving world class cancer outcomes: A strategy for England 2015-2020 Improving outcomes strategy for cancer (2011) Cancer reform strategy (2007) National cancer survivorship initiative (2010)
Current evidence base	Current evidence was graded as very low quality with high rates of imprecision

Research question	What are the long-term outcomes for breast reconstruction in women having chest wall radiotherapy?
Equality	Clear recommendations will reduce inequality by ensuring people all have access to all appropriate options

NHS, National Health Service; NICE, National Institute for Health and Care Excellence

Table 20: Research recommendation modified PICO table

Criterion	Explanation
Population	Adults (18 or over) with invasive breast cancer (M0) who undergo total breast reconstruction following mastectomy and receive radiotherapy
Intervention	Immediate (same time as mastectomy) total breast reconstruction
Comparator (without the risk factor)	• Delayed (after mastectomy – additional procedure) total breast reconstruction
Outcome	• Patient satisfaction • Delay in adjuvant therapy • Complication rates (unplanned additional surgery rates, number of operations) • Cosmetic result (such as Breast Q) • HRQoL • Implant loss rates • Cost effectiveness
Study design	Longitudinal observational cohort (as randomisation has previously been unsuccessful)
Timeframe	5-10 years
Additional information	Need to prospectively analysed by: Implant vs autologous Systemic treatments Comorbidities including: obesity/BMI diabetes smoking

HRQoL, health-related quality of life; M0, no distant metastases