National Institute for Health and Care Excellence

Draft

Early and locally advanced breast cancer: diagnosis and management

[A] Evidence reviews for effectiveness of different hypofractionation radiotherapy regimens in people with early-stage or locally advanced invasive breast cancer

NICE guideline NG101

Evidence reviews underpinning recommendations 1.10.13 to 1.10.16 and research recommendations in the NICE guideline

March 2023

Draft for Consultation

These evidence reviews were developed by the Guideline Development Team

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Effectiveness of different hypofractionation radiotherapy regimens in people with early-stage or locally advanced invasive breast cancer

1.1 Review question

What is the effectiveness and cost-effectiveness of different hypofractionation radiotherapy regimens in patients with early-stage or locally advanced invasive breast cancer?

1.1.1 Introduction

The current update is being undertaken based on identification of the 5-year results of the FAST-Forward trial (Murray Brunt et al 2020) by the NICE surveillance team, which was judged to have the potential to alter the existing recommendations.

Over the years, recent publications established the effectiveness and safety of hypofractionated radiotherapy as standard of care for people with breast cancer. Following the COVID-19 pandemic, there have been substantial pressures on radiotherapy machine capacity in the NHS and a 5-fraction regimen has become more prevalent than the 15-fraction regimen that is currently recommended by NICE. As such, the new evidence for radiotherapy hypofractionation needs to be considered to determine which hypofractionation regimens are the most effective.

1.1.2 Summary of the protocol

Table 1: PICO for different radiotherapy hypofractionation regimens

Population	Inclusion: Adults (18 and over) with early stage or locally advanced breast cancer who have undergone any of the following alone or in combination: • breast-conserving surgery • mastectomy (which can include reconstruction) • axillary clearance • sentinel lymph node biopsy • axillary node sampling There are no exclusion criteria
Interventions	Radiotherapy hypofractionation with or without regional node radiotherapy: Using greater than 2Gy per fraction for a) whole breast radiotherapy

	b) chest wall radiotherapy c) partial breast radiotherapy
Comparator	Any other hypofractionation radiotherapy regimen
Outcomes	Longest follow up available: • Quality of life (using validated measures such as EORTC and BREAST-Q) • Breast cancer mortality • All-cause mortality • Local Recurrence • Distant recurrence (also referred to as distant relapse) • Normal tissue effects • Treatment-related adverse events • Cosmesis (including breast appearance, breast oedema, appearance of scar, breast size, shape, colour, nipple position, shape of areola in comparison with untreated breast)
Study type	RCTs

For the full protocol see appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods section in Appendix L.

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

1.1.3.1 Search methods

The searches for the effectiveness evidence were run on 05 December 2022. The following databases were searched: Medline ALL (Ovid); Embase (Ovid); Emcare (Ovid); Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Cochrane Database of Systematic Reviews (CDSR) (Wiley). Full search strategies for each database are provided in Appendix B.

The database searches were supplemented with additional search methods. A forwards citation searching was conducted on Web of Science (Clarivate). Full details are provided in Appendix B.

The searches for the cost effectiveness evidence were run on 09 December 2022. The following databases were searched: Medline ALL (Ovid); Embase (Ovid); Econlit (Ovid); (NHS Economic Evaluation Database) (CRD); (Health Technology Assessment) (CRD); INAHTA (International HTA database). Full search strategies for each database are provided in Appendix B.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 2325 references (see appendix B for the literature search strategy).

These 2325 references were screened at title and abstract level against the review protocol, with 2228 excluded at this level. 10% of references were screened separately by two reviewers. Discrepancies were resolved by discussion.

97 articles were ordered for full-text review. 6 of these studies met the criteria specified in the review protocol (appendix A) and were included in the review. The FAST trial (Brunt 2020) had 1 secondary publication that did not report data from the latest timepoint. Similarly, the FAST-Forward trial (Brunt 2020) had 2 secondary publications and the START trial (Haviland 2013) had 5 secondary publications that did not report data from the latest timepoints. The clinical evidence study selection is presented as a PRISMA diagram in Appendix C.

Due to the variation in hypofractionation regimens reported, the studies were further categorised and presented within the following comparisons:

- Dose comparisons: studies using a different dose over the same number of fractions and over the same time period.
    - FAST trial Brunt 2020: 28.5 Gy in 5 fractions (5 weeks) vs 30 Gy in 5 fractions (5 weeks)
- Dose and fraction comparisons: studies using a different dose and different number of fractions over the same time period.
    - Haviland START 2013: 39 Gy over 13 fractions (5 weeks) vs 41.6 Gy over 16 fractions (5 weeks)
- Dose, fraction and time period comparisons: studies using a different dose, number of fractions over a different time period.
    - Aboziada 2016: 42.4 Gy over 16 fractions (3 weeks) vs 25 Gy over 5 fractions (1 week)
    - FAST-Forward trial Brunt 2020: 40 Gy over 15 fractions (3 weeks) vs 26 Gy over 5 fractions (1 week) vs 27 Gy over 5 fractions (1 week)
    - Ivanov 2022: 40 Gy over 15 fractions (3 weeks) vs 26 Gy over 5 fractions (1 week)

- Shahid 2009: 40 Gy over 15 fractions (3 weeks) vs 35 Gy over 10 fractions (2 weeks) vs 27 Gy over 5 fractions (1 week)

For a summary of the 6 included studies see Table 2.

See section 1.1.14 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2 Summary of studies included in the effectiveness evidence – dose comparisons

Author/Country/Study design	Population	Intervention	Comparator	Follow-up	Outcomes
FAST trial Brunt 2020 **United Kingdom** **RCT**	• N=915 women aged 50-88 years women with invasive early breast cancer and who would have received breast-conserving surgery were randomised to receive different whole-breast radiation hypofractionation regimens. • Key exclusion criteria: women age <50 years, women who received a mastectomy, lymphatic radiotherapy, or tumour bed boost dose and neoadjuvant/adjuvant cytotoxic therapy. Study included results from 3 trial arms comparing 50Gy/25 fractions, 30Gy/5 fractions and 28.5Gy/5 fractions. Only data from the 30Gy/5 fractions and 28.5Gy/5 fractions arms were analysed in this evidence review as they matched the population specified in the review protocol of people who received greater than 2Gy per fraction.	30Gy/5 fractions over 5 weeks	28.5Gy/5 fractions over 5 weeks	5 years	**Primary outcomes:** • All-cause mortality • Breast cancer-related mortality • Local recurrence • Loco-regional relapse • Distant relapse • Normal tissue effects

Table 3 Summary of studies included in the effectiveness evidence – dose and fraction comparisons

Author / Country / Study design	Population	Intervention	Comparator	Follow-up	Outcome(s)
START trial Haviland 2013 **United Kingdom** **RCT**	• N=2236 women aged 24-87 years with early breast cancer were randomised to receive different whole-breast radiation hypofractionation regimens. • Key exclusion criteria: participants requiring axillary radiotherapy after >Level 1 axillary dissection or after >10 lymph nodes were removed.	41.6Gy/16 fractions over 5 weeks	39Gy/13 fractions over 5 weeks	10 years	**Primary outcomes:** • All-cause mortality • Breast cancer-related mortality • Local relapse • Local-regional relapse • Distant relapse • Normal tissue effects

Table 4 Summary of studies included in the effectiveness evidence – dose, fractions and time period comparisons

Author / Country / Study design	Population	Intervention	Comparator	Follow-up	Outcome(s)
Aboziada 2016 **Egypt** **RCT**	• N=100 women aged 30-66 years with confirmed breast invasive ductal carcinoma and were randomised to receive whole breast radiation hypofractionation regimens. • Key exclusion criteria: locally advanced inflammatory or non-inflammatory breast carcinoma, women who underwent previous radiotherapy or pregnant women.	39Gy/13 fractions; 5 fractions per week (2.6 weeks)	42.4Gy/16 fractions; 5 fractions per week (3.2 weeks)	2 years	**Primary outcomes:** • Adverse events
FAST-Forward trial Brunt 2020 **United Kingdom** **RCT**	• N=4096 women aged 25-90 years participants with invasive carcinoma of the breast and breast-conserving surgery, or mastectomy were randomised to receive different whole-breast radiation hypofractionation regimens. • Key exclusion criteria: concurrent chemotherapy, or nodal irradiation.	26Gy/5 fractions over 1 week 27Gy/5 fractions over 1 week	40Gy/15 fractions over 3 weeks	10 years (only 5-year results reported)	**Primary outcomes:** • All-cause mortality • Breast cancer-related mortality • Local relapse • Locoregional relapse • Distant relapse • Adverse events

Author / Country / Study design	Population	Intervention	Comparator	Follow-up	Outcome(s)
					• Cosmesis (breast appearance changed, breast smaller, breast harder/firmer, shoulder stiffness, skin appearance) • Normal tissue effects Quality of life (EORTC-QLQ-BR23)
Ivanov 2022 **Serbia** **RCT**	• N= 60 women aged 45-83 years with early breast cancer requiring radiotherapy and with previous preserving breast surgery were randomised to receive different whole-breast radiation hypofractionation regimens. • Key exclusion criteria: women <40 years, women with postmastectomy irradiation or planned sequential boost or an indication for nodal treatment.	26Gy/5 fractions over 1 week	40Gy/15 fractions over 3 weeks	18 months	**Primary outcomes:** • Normal tissue effects

Author / Country / Study design	Population	Intervention	Comparator	Follow-up	Outcome(s)
Shahid 2009 **Pakistan** **RCT**	• N= 300 women with breast cancer were randomised to receive different hypofractionation regimens after mastectomy. • Study did not report full details of eligibility criteria.	**Intervention 1:** 27Gy/5 fractions over 1 week **Intervention 2:** 35Gy/10 fractions over 2 weeks	40Gy/15 fractions over 3 weeks	12 months	**Primary outcomes:** • All-cause mortality • Disease free survival • Overall survival • Loco-regional relapse • Disease free survival • Metastatic disease • Adverse events

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Dose comparisons (studies using different doses but the same number of fractions over the same time period)

Table 5 Hypofractionation regimen: 28.5 Gy in 5 fractions over 5 weeks (whole breast) compared to 30 Gy in 5 fractions over 5 weeks (whole-breast)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 30Gy/5 fractions	Risk difference with 28.5Gy/5 fractions (95% CI)
Normal tissue effects in breasts (G1-G4) - None [MID +/- 0.8 to 1.25]	260 (1 study[3]) 10 years	⨁⨁⨁⨀ **MODERATE**[1] due to imprecision	**RR 1.09** (0.87 to 1.37)	**508 per 1000**	**46 more per 1000** (from 66 fewer to 188 more)
Normal tissue effects in breast (G1-G4) - Mild [MID +/- 0.8 to 1.25]	260 (1 study[3]) 10 years	⨁⨁⨀⨀ **LOW**[2] due to imprecision	**RR 0.98** (0.67 to 1.41)	**308 per 1000**	**6 fewer per 1000** (from 102 fewer to 126 more)
Normal tissue effects in breast (G1-G4) - Moderate [MID +/- 0.8 to 1.25]	260 (1 study[3]) 10 years	⨁⨁⨀⨀ **LOW**[2] due to imprecision	**RR 0.94** (0.51 to 1.75)	**138 per 1000**	**8 fewer per 1000** (from 68 fewer to 104 more)
Normal tissue effects in breast (G1-G4) - Marked [MID +/- 0.8 to 1.25]	260 (1 study[3]) 10 years	⨁⨁⨀⨀ **LOW**[2] due to imprecision	**RR 0.33** (0.07 to 1.62)	**46 per 1000**	**31 fewer per 1000** (from 43 fewer to 29 more)
All-cause mortality [MID +/- 0.8 to 1.25]	613 (1 study[3]) 10 years	⨁⨁⨀⨀ **LOW**[2] due to imprecision	**RR 1.01** (0.64 to 1.59)	**108 per 1000**	**1 more per 1000** (from 39 fewer to 64 more)
Breast cancer-related mortality [MID +/- 0.8 to 1.25]	613 (1 study[3]) 10 years	⨁⨁⨀⨀ **LOW**[2] due to imprecision	**RR 1.26** (0.51 to 3.16)	**33 per 1000**	**9 more per 1000** (from 16 fewer to 71 more)

Local relapse [MID +/- 0.8 to 1.25]	613 (1 study[3]) 10 years	⊕⊕⊖⊖ **LOW**[2] due to imprecision	**RR 1.01** (0.21 to 4.96)	**10 per 1000**	**0 more per 1000** (from 8 fewer to 39 more)
Loco-regional relapse [MID +/- 0.8 to 1.25]	613 (1 study[3]) 10 years	⊕⊕⊖⊖ **LOW**[2] due to imprecision	**RR 7.07** (0.37 to 136.27)	**10 per 1000**	**60 more per 1000** (from 6 fewer to 1000 more)
Distant relapse [MID +/- 0.8 to 1.25]	613 (1 study[3]) 10 years	⊕⊕⊖⊖ **LOW**[2] due to imprecision	**RR 1.01** (0.50 to 2.03)	**49 per 1000**	**0 more per 1000** (from 25 fewer to 51 more)
Adverse events [MID +/- 0.8 to 1.25]	613 (1 study[3]) 10 years	⊕⊕⊖⊖ **LOW**[2] due to imprecision	**RR 0.50** (0.13 to 2.00)	**10 per 1000**	**5 fewer per 1000** (from 9 fewer to 10 more)

CI: Confidence interval; **MID:** Minimally important difference **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
[2] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.
[3] FAST trial Brunt 2020

Dose and fraction comparisons (studies using different doses, different number of fractions over the same time period)

Table 6 Hypofractionation regimen: 39 Gy in 13 fractions over 5 weeks (whole breast) compared to 41.6 Gy in 16 fractions over 5 weeks (whole-breast)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 41.6Gy/16 fractions	Risk difference with 39Gy/13 fractions (95% CI)
All-cause mortality [MID +/- 0.8 to 1.25]	1487 (1 study[1]) 10 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 1.03** (0.83 to 1.29)	**171 per 1000**	**5 more per 1000** (from 29 fewer to 49 more)
Local relapse [MID +/- 0.8 to 1.25]	1487 (1 study[1]) 10 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 1.29** (0.85 to 1.96)	**49 per 1000**	**14 more per 1000** (from 7 fewer to 47 more)
Loco-regional relapse [MID +/- 0.8 to 1.25]	1487 (1 study[1]) 10 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 1.26** (0.85 to 1.87)	**56 per 1000**	**15 more per 1000** (from 8 fewer to 49 more)
Distant relapse [MID +/- 0.8 to 1.25]	1487 (1 study[1]) 10 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 1.12** (0.88 to 1.42)	**147 per 1000**	**18 more per 1000** (from 18 fewer to 62 more)
Normal tissue effects: breast shrinkage [MID +/- 0.8 to 1.25]	1244 (1 study[1]) 10 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 0.85** (0.7 to 1.03)	**268 per 1000**	**40 fewer per 1000** (from 80 fewer to 8 more)
Normal tissue effects: breast induration (tumour bed) [MID +/- 0.8 to 1.25]	1244 (1 study[1]) 10 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 0.75** (0.6 to 0.93)	**239 per 1000**	**60 fewer per 1000** (from 17 fewer to 96 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 41.6Gy/16 fractions	Risk difference with 39Gy/13 fractions (95% CI)
Normal tissue effects: telangiectasia [MID +/- 0.8 to 1.25]	1456 (1 study[1]) 10 years	⨁⨁⨁⨁ **HIGH**	**RR 0.42** (0.25 to 0.73)	**59 per 1000**	**34 fewer per 1000** (from 16 fewer to 44 fewer)
Normal tissue effects: breast oedema [MID +/- 0.8 to 1.25]	1244 (1 study[1]) 10 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 0.65** (0.45 to 0.94)	**107 per 1000**	**37 fewer per 1000** (from 6 fewer to 59 fewer)
Normal tissue effects: shoulder stiffness [MID +/- 0.8 to 1.25]	187 (1 study[1]) 10 years	⨁⨁⊖⊖ **LOW**[3] due to imprecision	**RR 0.83** (0.34 to 2)	**105 per 1000**	**18 fewer per 1000** (from 69 fewer to 105 more)
Normal tissue effects: arm oedema [MID +/- 0.8 to 1.25]	187 (1 study[1]) 10 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 0.39** (0.16 to 0.95)	**168 per 1000**	**103 fewer per 1000** (from 8 fewer to 141 fewer)
Normal tissue effects: other [MID +/- 0.8 to 1.25]	1457 (1 study[1]) 10 years	⨁⨁⊖⊖ **LOW**[3] due to imprecision	**RR 1.21** (0.68 to 2.18)	**27 per 1000**	**6 more per 1000** (from 9 fewer to 32 more)
Adverse events: symptomatic rib fracture [MID +/- 0.8 to 1.25]	1487 (1 study[1]) 10 years	⨁⨁⊖⊖ **LOW**[3] due to imprecision	**RR 3.05** (0.12 to 74.82)	**0 per 1000**	**-**
Adverse events: symptomatic lung fibrosis [MID +/- 0.8 to 1.25]	1487 (1 study[1]) 10 years	⨁⨁⊖⊖ **LOW**[3] due to imprecision	**RR 0.51** (0.05 to 5.6)	**3 per 1000**	**1 fewer per 1000** (from 3 fewer to 12 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 41.6Gy/16 fractions	Risk difference with 39Gy/13 fractions (95% CI)
Adverse events: ischaemic heart disease [MID +/- 0.8 to 1.25]	1487 (1 study[1]) 10 years	⨁⨁⨀⨀ **LOW**[3] due to imprecision	**RR 1.22** (0.37 to 3.98)	**7 per 1000**	**1 more per 1000** (from 4 fewer to 20 more)
Adverse events: brachial plexopathy [MID +/- 0.8 to 1.25]	1487 (1 study[1]) 10 years	⨁⨁⨀⨀ **LOW**[3] due to imprecision	**RR 0.34** (0.01 to 8.31)	**1 per 1000**	**1 fewer per 1000** (from 1 fewer to 10 more)

CI: Confidence interval; **MID:** Minimally important difference; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Haviland START 2013
[2] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
[3] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.

Dose, fraction and time period comparisons (studies using different doses, different number of fractions over different time periods)

Table 7 Hypofractionation regimen: 39 Gy in 13 fractions over 2.6 weeks (whole breast) compared to 42.4 Gy in 16 fractions over 3.3 weeks (whole breast)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 39Gy/13 fractions	Risk difference with 42.4Gy/16 fractions (95% CI)
Radiation dermatitis - Grade 1 [MID +/- 0.8 to 1.25]	100 (1 study[1]) 2 years	⨁⊖⊖⊖ **VERY LOW**[2,4] due to risk of bias, imprecision	**RR 0.59** (0.4 to 0.87)	**680 per 1000**	**279 fewer per 1000** (from 88 fewer to 408 fewer)
Radiation dermatitis - Grade 2 [MID +/- 0.8 to 1.25]	100 (1 study[1]) 2 years	⨁⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, imprecision	**RR 0.43** (0.12 to 1.56)	**140 per 1000**	**80 fewer per 1000** (from 123 fewer to 78 more)
Acute pneumonitis - Grade 1 [MID +/- 0.8 to 1.25]	100 (1 study[1]) 2 years	⨁⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, imprecision	**RR 0.17** (0.02 to 1.33)	**120 per 1000**	**100 fewer per 1000** (from 118 fewer to 40 more)
Acute pneumonitis - Grade 2 [MID +/- 0.8 to 1.25]	100 (1 study[1]) 2 years	⨁⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, imprecision	**RR 4** (0.46 to 34.54)	**20 per 1000**	**60 more per 1000** (from 11 fewer to 671 more)
Subcutaneous fibrosis - Grade 1 [MID +/- 0.8 to 1.25]	100 (1 study[1]) 2 years	⨁⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, imprecision	**RR 1.75** (0.55 to 5.61)	**80 per 1000**	**60 more per 1000** (from 36 fewer to 369 more)
Subcutaneous fibrosis - Grade 2 [MID +/- 0.8 to 1.25]	100 (1 study[1]) 2 years	⨁⊖⊖⊖ **VERY LOW**[2,4] due to risk of bias, imprecision	**RR 0.2** (0.05 to 0.87)	**200 per 1000**	**160 fewer per 1000** (from 26 fewer to 190 fewer)
Incidence of lymphoedema - Grade 1 [MID +/- 0.8 to 1.25]	100 (1 study[1]) 2 years	⨁⊖⊖⊖ **VERY LOW**[2,3]	**RR 1** (0.35 to 2.89)	**120 per 1000**	**0 fewer per 1000** (from 78 fewer to 227 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 39Gy/13 fractions	Risk difference with 42.4Gy/16 fractions (95% CI)
		due to risk of bias, imprecision			
Incidence of lymphoedema - Grade 2 [MID +/- 0.8 to 1.25]	100 (1 study[1]) 2 years	⨁⊖⊖⊖ **VERY LOW**[2,4] due to risk of bias, imprecision	**RR 0.38** (0.15 to 1)	**260 per 1000**	**161 fewer per 1000** (from 221 fewer to 0 more)

CI: Confidence interval; **MID:** Minimally important difference; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Aboziada 2016
[2] Study at high risk of bias. Quality of the outcome downgraded twice.
[3] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.
[4] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.

Table 8 Hypofractionation regimen: 40 Gy in 15 fractions over 3 weeks (whole breast) compared to 26 Gy in 5 fractions over 1 week (whole breast)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 26Gy/5 fractions	Risk difference with 40Gy/15 fractions (95% CI)
All-cause mortality [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	⨁⨁⨀⨀ **LOW**[5] due to imprecision	**RR 1.03** (0.78 to 1.36)	**66 per 1000**	**2 more per 1000** (from 14 fewer to 24 more)
Breast cancer related mortality [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	⨁⨁⨀⨀ **LOW**[5] due to imprecision	**RR 0.89** (0.61 to 1.31)	**39 per 1000**	**4 fewer per 1000** (from 15 fewer to 12 more)
Local relapse [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	⨁⨁⨁⨀ **MODERATE**[2] due to imprecision	**RR 1.48** (0.86 to 2.57)	**15 per 1000**	**7 more per 1000** (from 2 fewer to 24 more)
Loco-regional relapse [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	⨁⨁⨁⨀ **MODERATE**[2] due to imprecision	**RR 1.49** (0.94 to 2.37)	**21 per 1000**	**10 more per 1000** (from 1 fewer to 29 more)
Distant relapse [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	⨁⨁⨁⨀ **MODERATE**[2] due to imprecision	**RR 0.78** (0.56 to 1.09)	**56 per 1000**	**12 fewer per 1000** (from 24 fewer to 5 more)
Acute skin toxicity - 1 point [MID +/- 0.8 to 1.25] CTCAE	60 (1 study[3]) 18 months	⨁⨁⨀⨀ **LOW**[2,4] due to risk of bias, imprecision	**RR 1.39** (0.86 to 2.22)	**455 per 1000**	**177 more per 1000** (from 64 fewer to 555 more)
Acute skin toxicity - 2 points [MID +/- 0.8 to 1.25] CTCAE	60 (1 study[3]) 18 months	⨁⨀⨀⨀ **VERY LOW**[4,5] due to risk of bias, imprecision	**RR 6.11** (0.76 to 49.21)	**30 per 1000**	**155 more per 1000** (from 7 fewer to 1000 more)
Late skin toxicity [MID +/- 0.8 to 1.25] RESS-RTOG/EORTC	60 (1 study[3]) 18 months	⨁⨀⨀⨀ **VERY LOW**[4,5] due to risk of bias, imprecision	**RR 0.55** (0.22 to 1.34)	**333 per 1000**	**150 fewer per 1000** (from 260 fewer to 113 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 26Gy/5 fractions	Risk difference with 40Gy/15 fractions (95% CI)
Subcutaneous tissue toxicity - 1 point [MID +/- 0.8 to 1.25] RESS-EORTC	60 (1 study[3]) 18 months	⨁⊖⊖⊖ **VERY LOW**[4,5] due to risk of bias, imprecision	**RR 0.94** (0.39 to 2.25)	**259 per 1000**	**16 fewer per 1000** (from 158 fewer to 324 more)
Subcutaneous tissue toxicity - 2 points [MID +/- 0.8 to 1.25] RESS-EORTC	60 (1 study[3]) 18 months	⨁⊖⊖⊖ **VERY LOW**[4,5] due to risk of bias, imprecision	**RR 0.07** (0 to 1.3)	**185 per 1000**	**172 fewer per 1000** (from 185 fewer to 56 more)
Cosmetic results - 1 point [MID +/- 0.8 to 1.25]	60 (1 study[3]) 18 months	⨁⨁⊖⊖ **LOW**[2,4] due to risk of bias, imprecision	**RR 1.29** (0.83 to 1.99)	**519 per 1000**	**150 more per 1000** (from 88 fewer to 513 more)
Cosmetic results - 2 points [MID +/- 0.8 to 1.25]	60 (1 study[3]) 18 months	⨁⊖⊖⊖ **VERY LOW**[4,5] due to risk of bias, imprecision	**RR 0.69** (0.37 to 1.29)	**481 per 1000**	**149 fewer per 1000** (from 303 fewer to 140 more)
Adverse events (clinician assessed) [MID +/- 0.8 to 1.25]	12448 (1 study[1]) 5 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 0.87** (0.79 to 0.96)	**122 per 1000**	**16 fewer per 1000** (from 5 fewer to 26 fewer)
EORTC QLQ-BR23 - Arm or shoulder pain [MID +/- 0.8 to 1.25]	5136 (1 study[1]) 5 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 0.9** (0.8 to 1.02)	**175 per 1000**	**18 fewer per 1000** (from 35 fewer to 4 more)
EORTC QLQ-BR23 - Swollen arm or hand [MID +/- 0.8 to 1.25]	5128 (1 study[1]) 5 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 0.83** (0.64 to 1.08)	**48 per 1000**	**8 fewer per 1000** (from 17 fewer to 4 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 26Gy/5 fractions	Risk difference with 40Gy/15 fractions (95% CI)
EORTC QLQ-BR23 - Difficulty raising arm [MID +/- 0.8 to 1.25]	5129 (1 study[1]) 5 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 0.93** (0.76 to 1.14)	**72 per 1000**	**5 fewer per 1000** (from 17 fewer to 10 more)
EORTC QLQ-BR23 - Breast pain [MID +/- 0.8 to 1.25]	5135 (1 study[1]) 5 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 0.83** (0.73 to 0.95)	**161 per 1000**	**27 fewer per 1000** (from 8 fewer to 43 fewer)
EORTC QLQ-BR23 - Breast swollen [MID +/- 0.8 to 1.25]	5137 (1 study[1]) 5 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 0.65** (0.52 to 0.81)	**74 per 1000**	**26 fewer per 1000** (from 14 fewer to 35 fewer)
EORTC QLQ-BR23 - Breast oversensitive [MID +/- 0.8 to 1.25]	5115 (1 study[1]) 5 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 0.91** (0.78 to 1.06)	**123 per 1000**	**11 fewer per 1000** (from 27 fewer to 7 more)
EORTC QLQ-BR23 - Skin problems in breast [MID +/- 0.8 to 1.25]	5131 (1 study[1]) 5 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 0.97** (0.79 to 1.2)	**63 per 1000**	**2 fewer per 1000** (from 13 fewer to 13 more)
Normal tissue effects - Breast appearance changed [MID +/- 0.8 to 1.25]	5043 (1 study[1]) 5 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 1.04** (0.96 to 1.13)	**300 per 1000**	**12 more per 1000** (from 12 fewer to 39 more)
Normal tissue effects - Breast smaller [MID +/- 0.8 to 1.25]	4987 (1 study[1]) 5 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 1.18** (1.06 to 1.31)	**203 per 1000**	**36 more per 1000** (from 12 more to 63 more)
Normal tissue effects - Breast harder or firmer [MID +/- 0.8 to 1.25]	4980 (1 study[1]) 5 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 0.83** (0.74 to 0.92)	**247 per 1000**	**42 fewer per 1000** (from 20 fewer to 64 fewer)
Normal tissue effects - Skin appearance changed [MID +/- 0.8 to 1.25]	5081 (1 study[1]) 5 years	⨁⨁⨁⊖ **MODERATE**[2] due to imprecision	**RR 1.05** (0.91 to 1.21)	**131 per 1000**	**7 more per 1000** (from 12 fewer to 28 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 26Gy/5 fractions	Risk difference with 40Gy/15 fractions (95% CI)
CI: Confidence interval; **MID:** Minimally important difference; **RR:** Risk ratio;					
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.					
[1] FAST-Forward Brunt 2020 [2] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once. [3] Ivanov 2022 [4] Study at moderate risk of bias. Quality of the outcome downgraded once. [5] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.					

Table 9 Hypofractionation regimen: 40 Gy in 15 fractions over 3 weeks (whole breast) compared to 27 Gy in 5 fractions over 1 week (whole-breast)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 27Gy/5 fractions	Risk difference with 40Gy/15 fractions (95% CI)
All-cause mortality [MID +/- 0.8 to 1.25]	2928 (2 studies[1,2])	⨁⨁⨁⊖ **MODERATE**[3] due to imprecision	**RR 0.92** (0.72 to 1.18)	**83 per 1000**	**7 fewer per 1000** (from 23 fewer to 15 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 27Gy/5 fractions	Risk difference with 40Gy/15 fractions (95% CI)
Breast cancer related mortality [MID +/- 0.8 to 1.25]	2728 (1 study[1]) 5 years	⨁⨁⨁⨀ **MODERATE**[3] due to imprecision	**RR 1.05** (0.82 to 1.34)	**83 per 1000**	**4 more per 1000** (from 15 fewer to 28 more)
Locoregional relapse [MID +/- 0.8 to 1.25]	2928 (2 studies[1,2])	⨁⨁⨀⨀ **LOW**[4] due to imprecision	**RR 1.16** (0.79 to 1.7)	**31 per 1000**	**5 more per 1000** (from 7 fewer to 22 more)
Metastatic disease [MID +/- 0.8 to 1.25]	2928 (2 studies[1,2])	⨁⨁⨁⨀ **MODERATE**[3] due to imprecision	**RR 0.92** (0.7 to 1.21)	**65 per 1000**	**5 fewer per 1000** (from 19 fewer to 14 more)
Overall survival [MID +/- 0.8 to 1.25]	200 (1 study[2]) 6 months	⨁⨁⨁⨀ **MODERATE**[6] due to risk of bias	**RR 0.94** (0.84 to 1.06)	**870 per 1000**	**52 fewer per 1000** (from 139 fewer to 52 more)
Disease free survival [MID +/- 0.8 to 1.25]	200 (1 study[2]) 6 months	⨁⨁⨁⨀ **MODERATE**[6] due to risk of bias	**RR 1** (0.84 to 1.19)	**710 per 1000**	**0 fewer per 1000** (from 114 fewer to 135 more)
Adverse events - Any adverse event [MID +/- 0.8 to 1.25]	12424 (1 study[1]) 5 years	⨁⨁⨀⨀ **LOW**[4] due to imprecision	**RR 0.67** (0.61 to 0.73)	**159 per 1000**	**53 fewer per 1000** (from 43 fewer to 62 fewer)
Adverse events - Radiation pneumonitis [MID +/- 0.8 to 1.25]	200 (1 study[2]) 6 months	⨁⨀⨀⨀ **VERY LOW**[4,6] due to risk of bias, imprecision	**RR 1.25** (0.35 to 4.52)	**40 per 1000**	**10 more per 1000** (from 26 fewer to 141 more)
Adverse events - Sore throat & dysphagia [MID +/- 0.8 to 1.25]	200 (1 study[2]) 6 months	⨁⨀⨀⨀ **VERY LOW**[4,6] due to risk of bias, imprecision	**RR 0.83** (0.45 to 1.56)	**180 per 1000**	**31 fewer per 1000** (from 99 fewer to 101 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 27Gy/5 fractions	Risk difference with 40Gy/15 fractions (95% CI)
Incidence of lymphoedema (G1-G3) [MID +/- 0.8 to 1.25]	200 (1 study[2]) 6 months	⨁⨁⨀⨀ **LOW**[3,6] due to risk of bias, imprecision	**RR 1.17** (0.82 to 1.67)	**350 per 1000**	**59 more per 1000** (from 63 fewer to 234 more)
Adverse events - Skin reactions (G1-G4) [MID +/- 0.8 to 1.25]	200 (1 study[2]) 6 months	⨁⨁⨁⨀ **MODERATE**[6] due to risk of bias, imprecision	**RR 1** (0.98 to 1.02)	**1000 per 1000**	**0 fewer per 1000** (from 20 fewer to 20 more)
EORTC QLQ-BR23 - Arm or shoulder pain [MID +/- 0.8 to 1.25]	5138 (1 study[1]) 5 years	⨁⨁⨁⨀ **MODERATE**[3] due to imprecision	**RR 0.93** (0.82 to 1.05)	**170 per 1000**	**12 fewer per 1000** (from 31 fewer to 8 more)
EORTC QLQ-BR23 - Swollen arm or hand [MID +/- 0.8 to 1.25]	5136 (1 study[1]) 5 years	⨁⨁⨀⨀ **LOW**[4] due to imprecision	**RR 1.01** (0.77 to 1.32)	**40 per 1000**	**0 more per 1000** (from 9 fewer to 13 more)
EORTC QLQ-BR23 - Difficulty raising arm [MID +/- 0.8 to 1.25]	5132 (1 study[1]) 5 years	⨁⨁⨁⨀ **MODERATE**[3] due to imprecision	**RR 0.84** (0.69 to 1.02)	**80 per 1000**	**13 fewer per 1000** (from 25 fewer to 2 more)
EORTC QLQ-BR23 - Breast pain [MID +/- 0.8 to 1.25]	5139 (1 study[1]) 5 years	⨁⨁⨁⨀ **MODERATE**[3] due to imprecision	**RR 0.81** (0.71 to 0.92)	**165 per 1000**	**31 fewer per 1000** (from 13 fewer to 48 fewer)
EORTC QLQ-BR23 - Breast swollen [MID +/- 0.8 to 1.25]	5135 (1 study[1]) 5 years	⨁⨁⨀⨀ **LOW**[4] due to imprecision	**RR 0.53** (0.43 to 0.65)	**91 per 1000**	**43 fewer per 1000** (from 32 fewer to 52 fewer)
EORTC QLQ-BR23 - Breast oversensitive [MID +/- 0.8 to 1.25]	5124 (1 study[1]) 5 years	⨁⨁⨁⨀ **MODERATE**[3] due to imprecision	**RR 0.87** (0.75 to 1.01)	**129 per 1000**	**17 fewer per 1000** (from 32 fewer to 1 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 27Gy/5 fractions	Risk difference with 40Gy/15 fractions (95% CI)
EORTC QLQ-BR23 - Skin problems in breast [MID +/- 0.8 to 1.25]	5135 (1 study[1]) 5 years	⨁⨁⨁⨀ **MODERATE**[3] due to imprecision	**RR 0.76** (0.62 to 0.93)	**81 per 1000**	**19 fewer per 1000** (from 6 fewer to 31 fewer)
Normal tissue effects - Breast appearance changed [MID +/- 0.8 to 1.25]	5030 (1 study[1]) 5 years	⨁⨁⨁⨁ **HIGH**	**RR 0.86** (0.8 to 0.93)	**364 per 1000**	**51 fewer per 1000** (from 26 fewer to 73 fewer)
Normal tissue effects - Breast smaller [MID +/- 0.8 to 1.25]	4965 (1 study[1]) 5 years	⨁⨁⨁⨁ **HIGH**	**RR 0.99** (0.9 to 1.1)	**240 per 1000**	**2 fewer per 1000** (from 24 fewer to 24 more)
Normal tissue effects - Breast harder or firmer [MID +/- 0.8 to 1.25]	4958 (1 study[1]) 5 years	⨁⨁⨁⨀ **MODERATE**[3] due to imprecision	**RR 0.74** (0.67 to 0.82)	**275 per 1000**	**71 fewer per 1000** (from 49 fewer to 91 fewer)
Normal tissue effects - Skin appearance changed [MID +/- 0.8 to 1.25]	5076 (1 study[1]) 5 years	⨁⨁⨁⨀ **MODERATE**[3] due to imprecision	**RR 0.89** (0.78 to 1.02)	**152 per 1000**	**17 fewer per 1000** (from 34 fewer to 3 more)

CI: Confidence interval; **MID:** Minimally important difference; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] FAST-Forward Brunt 2020
[2] Shahid 2009
[3] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
[4] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.
[6] Study at moderate risk of bias. Quality of the outcome downgraded once.

Table 10 Hypofractionation regimen: 26 Gy in 5 fractions over 1 week (whole breast) compared to 27 Gy in 5 fractions over 1 week (whole breast)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 27Gy/5 fractions	Risk difference with 26Gy/5 fractions (95% CI)
All-cause mortality [MID +/- 0.8 to 1.25]	2735 (1 study[1]) 5 years	⨁⨁⨁◯ **MODERATE**[2] due to imprecision	**RR 0.86** (0.65 to 1.12)	**77 per 1000**	**11 fewer per 1000** (from 27 fewer to 9 more)
Breast cancer related mortality [MID +/- 0.8 to 1.25]	2735 (1 study[1]) 5 years	⨁⨁◯◯ **LOW**[3] due to imprecision	**RR 1** (0.78 to 1.28)	**83 per 1000**	**0 fewer per 1000** (from 18 fewer to 23 more)
Local relapse [MID +/- 0.8 to 1.25]	2735 (1 study[1]) 5 years	⨁⨁◯◯ **LOW**[3] due to imprecision	**RR 0.78** (0.44 to 1.37)	**77 per 1000**	**17 fewer per 1000** (from 43 fewer to 28 more)
Loco-regional relapse [MID +/- 0.8 to 1.25]	2735 (1 study[1]) 5 years	⨁⨁◯◯ **LOW**[3] due to imprecision	**RR 0.83** (0.51 to 1.35)	**26 per 1000**	**4 fewer per 1000** (from 13 fewer to 9 more)
Metastatic disease [MID +/- 0.8 to 1.25]	2735 (1 study[1]) 5 years	⨁⨁⨁◯ **MODERATE**[2] due to imprecision	**RR 1.10** (0.80 to 1.51)	**50 per 1000**	**5 more per 1000** (from 10 fewer to 26 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 27Gy/5 fractions	Risk difference with 26Gy/5 fractions (95% CI)
Normal tissue effects - Breast appearance changed [MID +/- 0.8 to 1.25]	5113 (1 study[1]) 5 years	⨁⨁⨁◯ **MODERATE**[2] due to imprecision	**RR 0.82** (0.76 to 0.89)	**364 per 1000**	**66 fewer per 1000** (from 40 fewer to 87 fewer)
Normal tissue effects - Breast smaller [MID +/- 0.8 to 1.25]	5062 (1 study[1]) 5 years	⨁⨁⨁◯ **MODERATE**[2] due to imprecision	**RR 0.84** (0.76 to 0.93)	**240 per 1000**	**38 fewer per 1000** (from 17 fewer to 58 fewer)
Normal tissue effects - Breast harder or firmer [MID +/- 0.8 to 1.25]	5046 (1 study[1]) 5 years	⨁⨁⨁⨁ **HIGH**	**RR 0.9** (0.82 to 0.99)	**275 per 1000**	**27 fewer per 1000** (from 3 fewer to 49 fewer)
Normal tissue effects - Skin appearance changed [MID +/- 0.8 to 1.25]	5147 (1 study[1]) 5 years	⨁⨁⨁◯ **MODERATE**[2] due to imprecision	**RR 0.86** (0.75 to 0.98)	**152 per 1000**	**21 fewer per 1000** (from 3 fewer to 38 fewer)
Adverse events - Any adverse event [MID +/- 0.8 to 1.25]	12630 (1 study[1]) 5 years	⨁⨁⨁◯ **MODERATE**[2] due to imprecision	**RR 0.77** (0.7 to 0.84)	**159 per 1000**	**37 fewer per 1000** (from 25 fewer to 48 fewer)
EORTC QLQ-BR23 - Arm or shoulder pain [MID +/- 0.8 to 1.25]	5200 (1 study[1]) 5 years	⨁⨁⨁⨁ **HIGH**	**RR 1.03** (0.92 to 1.16)	**170 per 1000**	**5 more per 1000** (from 14 fewer to 27 more)
EORTC QLQ-BR23 - Swollen arm or hand [MID +/- 0.8 to 1.25]	5192 (1 study[1]) 5 years	⨁⨁⨁◯ **MODERATE**[2] due to imprecision	**RR 1.21** (0.94 to 1.56)	**40 per 1000**	**8 more per 1000** (from 2 fewer to 22 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 27Gy/5 fractions	Risk difference with 26Gy/5 fractions (95% CI)
EORTC QLQ-BR23 - Difficulty raising arm [MID +/- 0.8 to 1.25]	5195 (1 study[1]) 5 years	⨁⨁⨁⨀ **MODERATE**[2] due to imprecision	**RR 0.9** (0.75 to 1.09)	**80 per 1000**	**8 fewer per 1000** (from 20 fewer to 7 more)
EORTC QLQ-BR23 - Breast pain [MID +/- 0.8 to 1.25]	5198 (1 study[1]) 5 years	⨁⨁⨁⨁ **HIGH**	**RR 0.98** (0.86 to 1.1)	**165 per 1000**	**3 fewer per 1000** (from 23 fewer to 16 more)
EORTC QLQ-BR23 - Breast swollen [MID +/- 0.8 to 1.25]	5196 (1 study[1]) 5 years	⨁⨁⨁⨀ **MODERATE**[2] due to imprecision	**RR 0.81** (0.68 to 0.98)	**91 per 1000**	**17 fewer per 1000** (from 2 fewer to 29 fewer)
EORTC QLQ-BR23 - Breast oversensitive [MID +/- 0.8 to 1.25]	5183 (1 study [1]) 5 years	⨁⨁⨁⨁ **HIGH**	**RR 0.96** (0.83 to 1.11)	**129 per 1000**	**5 fewer per 1000** (from 22 fewer to 14 more)
EORTC QLQ-BR23 - Skin problems in breast [MID +/- 0.8 to 1.25]	5188 (1 study[1]) 5 years	⨁⨁⨁⨀ **MODERATE**[2] due to imprecision	**RR 0.79** (0.65 to 0.96)	**81 per 1000**	**17 fewer per 1000** (from 3 fewer to 28 fewer)

CI: Confidence interval; **MID:** Minimally important difference; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 27Gy/5 fractions	Risk difference with 26Gy/5 fractions (95% CI)

[1] FAST-Forward Brunt 2020
[2] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
[3] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.

Table 11 Hypofractionation regimen: 35 Gy in 10 fractions over 2 weeks (whole breast) compared to 27 Gy in 5 fractions over 1 week (whole breast)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 27Gy/5 fractions	Risk difference with 35Gy/10 fractions (95% CI)
All-cause mortality [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	⨁⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, imprecision	**RR 1.06** (0.58 to 1.93)	**170 per 1000**	**10 more per 1000** (from 71 fewer to 158 more)
Locoregional relapse [MID +/- 0.8 to 1.25]	200 (1 study[4]) 6 months	⨁⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, imprecision	**RR 1.09** (0.51 to 2.36)	**110 per 1000**	**10 more per 1000** (from 54 fewer to 150 more)
Metastatic disease [MID +/- 0.8 to 1.25]	200 (1 study[4]) 6 months	⨁⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, imprecision	**RR 0.92** (0.57 to 1.49)	**260 per 1000**	**21 fewer per 1000** (from 112 fewer to 127 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 27Gy/5 fractions	Risk difference with 35Gy/10 fractions (95% CI)
Overall survival [MID +/- 0.8 to 1.25]	200 (1 study[4]) 6 months	⨁⨁⨁⨀ **MODERATE**[2] due to risk of bias	**RR 0.95** (0.85 to 1.07)	**870 per 1000**	**44 fewer per 1000** (from 130 fewer to 61 more)
Disease free survival [MID +/- 0.8 to 1.25]	200 (1 study[4]) 6 months	⨁⨁⨁⨀ **MODERATE**[2] due to risk of bias	**RR 1.01** (0.85 to 1.21)	**710 per 1000**	**7 more per 1000** (from 106 fewer to 149 more)
Adverse events - Incidence of lymphoedema (G1-G3) [MID +/- 0.8 to 1.25]	200 (1 study[4]) 6 months	⨁⨀⨀⨀ **VERY LOW**[2,3] due to risk of bias, imprecision	**RR 0.97** (0.66 to 1.42)	**350 per 1000**	**10 fewer per 1000** (from 119 fewer to 147 more)
Adverse events - Radiation pneumonitis [MID +/- 0.8 to 1.25]	200 (1 study[4]) 6 months	⨁⨀⨀⨀ **VERY LOW**[2,3] due to risk of bias, imprecision	**RR 1.25** (0.35 to 4.52)	**40 per 1000**	**10 more per 1000** (from 26 fewer to 141 more)
Adverse events - Sore throat & dysphagia [MID +/- 0.8 to 1.25]	200 (1 study[4]) 6 months	⨁⨀⨀⨀ **VERY LOW**[2,3] due to risk of bias, imprecision	**RR 1.11** (0.63 to 1.97)	**180 per 1000**	**20 more per 1000** (from 67 fewer to 175 more)
Adverse events - Skin reactions (G1-G4) [MID +/- 0.8 to 1.25]	200 (1 study[4]) 6 months	⨁⨁⨁⨀ **MODERATE**[2] due to risk of bias	**RR 1** (0.98 to 1.02)	**1000 per 1000**	**0 fewer per 1000** (from 20 fewer to 20 more)

CI: Confidence interval; **MID:** Minimally important difference; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 27Gy/5 fractions	Risk difference with 35Gy/10 fractions (95% CI)
estimate. **Very low quality:** We are very uncertain about the estimate.					

[1] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
[2] Study at moderate risk of bias. Quality of the outcome downgraded once.
[3] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.
[4] Shahid 2009

Table 12 Hypofractionation regimen: 40 Gy in 15 fractions over 3 weeks (whole breast) compared to 35 Gy in 10 fractions over 2 weeks (whole breast)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 35Gy/10 fractions	Risk difference with 40Gy/15 fractions (95% CI)
All-cause mortality [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	⨁⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, imprecision	**RR 1.11** (0.63 to 1.97)	**180 per 1000**	**20 more per 1000** (from 67 fewer to 175 more)
Locoregional relapse [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	⨁⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, imprecision	**RR 0.83** (0.38 to 1.84)	**120 per 1000**	**20 fewer per 1000** (from 74 fewer to 101 more)
Metastatic disease [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	⨁⊖⊖⊖ **VERY LOW**[2,3]	**RR 1.17** (0.73 to 1.87)	**240 per 1000**	**41 more per 1000** (from 65 fewer to 209 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 35Gy/10 fractions	Risk difference with 40Gy/15 fractions (95% CI)
		due to risk of bias, imprecision			
Overall survival [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	⨁⨁⨁⨀ **MODERATE**[2] due to risk of bias	**RR 0.99** (0.87 to 1.12)	**830 per 1000**	**8 fewer per 1000** (from 108 fewer to 100 more)
Disease free survival [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	⨁⨁⨁⨀ **MODERATE**[2] due to risk of bias	**RR 0.99** (0.83 to 1.17)	**720 per 1000**	**7 fewer per 1000** (from 122 fewer to 122 more)
Adverse events - Incidence of lymphoedema (G1-G3) [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	⨁⨁⨀⨀ **LOW**[2,5] due to risk of bias, imprecision	**RR 1.21** (0.84 to 1.73)	**340 per 1000**	**71 more per 1000** (from 54 fewer to 248 more)
Adverse events - Radiation pneumonitis [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	⨁⨀⨀⨀ **VERY LOW**[2,3] due to risk of bias, imprecision	**RR 1** (0.3 to 3.35)	**50 per 1000**	**0 fewer per 1000** (from 35 fewer to 117 more)
Adverse events - Sore throat & dysphagia [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	⨁⨀⨀⨀ **VERY LOW**[2,3] due to risk of bias, imprecision	**RR 0.75** (0.41 to 1.38)	**200 per 1000**	**50 fewer per 1000** (from 118 fewer to 76 more)
Adverse events - Skin reactions (G1-G4) [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	⨁⨁⨁⨀ **MODERATE**[2] due to risk of bias	**RR 1** (0.98 to 1.02)	**1000 per 1000**	**0 fewer per 1000** (from 20 fewer to 20 more)
Adverse events - Cardiac toxicity >10% LVEF reduction [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	⨁⨀⨀⨀ **VERY LOW**[2,3] due to risk of bias, imprecision	**RR 0.83** (0.26 to 2.64)	**60 per 1000**	**10 fewer per 1000** (from 44 fewer to 98 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 35Gy/10 fractions	Risk difference with 40Gy/15 fractions (95% CI)
CI: Confidence interval; **MID:** Minimally important difference; **RR:** Risk ratio;					
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.					
[1] Shahid 2009 [2] Study at moderate risk of bias. Quality of the outcome downgraded once. [3] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice. [5] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.					

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3 See appendix F for full GRADE tables .

1.1.7 Economic evidence

1.1.7.1 Included studies

A search was performed to identify published economic evaluations of relevance to this guideline update (see Appendix G). This search retrieved 162 studies. Based on title and abstract screening, 156 of the studies were excluded for this question. Following the full-text review, we excluded a further 5 studies. Thus, the review for this question includes 1 study from the existing literature.

1.1.7.2 Excluded studies

See Appendix J for excluded studies and reasons for exclusion.

1.1.8 Summary of included economic evidence

Table 2 provides summary details of the included study. See Appendix H for a full evidence table and assessment of applicability and limitations.

Table 13 Summary of included economic evidence

Study	Applicability	Limitations	Comparators[1]	Incremental			Uncertainty[1]
				Cost	Effects (QALYs)	ICER[1] (Cost/QALY)	
Glynn 2022 Setting: UK NHS and PSS perspective Subgroup 1: WB5F[1] Subgroup 2: WB5F Adults who have undergone breast-conserving surgery or mastectomy for early breast cancer (stage I,II,IIIa). Divided into two subgroups: 1 was eligible for partial breast (PB) therapy, 2 was not eligible for PB therapy.	Directly applicable	Some minor limitations	Subgroup 1: PB5F, WB15F, PB15F Subgroup 2: WB15F	Subgroup 1: Not reported Subgroup 2: WB15F has an additional cost of £2,162 (95%CI £1,282 to £3,169) compared with WB5F.	Subgroup 1: Not reported Subgroup 2: WB5F has additional QALYs of 0.05 (95%CI 0.01 to 0.12) compared with WB15F.	Subgroup 1: PB5F dominated PB15F, WB5F and WB15 (PB5F cost less and was more effective than all other options) Subgroup 2: WB5F was dominant over WB15F (i.e. WB5F cost less and was more effective than WB15F)	For subgroup 1, there was a 62% chance that PB5F either dominated all alternatives or had an ICER below £15,000/QALY. In a range of scenario analyses, PB5F dominated all options except when using the distant recurrence hazard ratio results reported in the trials. In this scenario, PB15F compared with PB5F was expected to be more expensive by £1,014 (95%CI -£263 to £1,922) and more effective

Study	Applicability	Limitations	Comparators[1]	Incremental			Uncertainty[1]
				Cost	Effects (QALYs)	ICER[1] (Cost/QALY)	
							by 0.07 additional QALYs (95%CI −0.05 to 0.24). For a threshold of £15,000/QALY, there was a 56% probability that PB5F was cost-effective compared to PB15F. For subgroup 2, there was a 100% chance that WB5F either dominated WB15F or had an ICER below £15,000. WB5F remained the dominant treatment option across a range of scenario analyses. When using

Study	Applicability	Limitations	Comparators[1]	Incremental			Uncertainty[1]
				Cost	Effects (QALYs)	ICER[1] (Cost/QALY)	
							the distant recurrence hazard ratio results reported in the trials, WB15F was expected to be more expensive at £472 (95%CI -£2,214 to £2,942) and more effective by 0.25 additional QALYs (95%CI -0.18 to 0.69). In this scenario, the expected ICER for WB15F was £1,899/QALY.

[1]WB5F: Whole breast 26 Gy delivered in 5 fractions; PB5F: Partial breast 26 Gy delivered in 5 fractions; WB15F: Whole breast 40 Gy delivered in 15 fractions; PB15F: Partial breast 40 Gy delivered in 15 fractions

1.1.9 Economic model

This question was not prioritised for original economic analysis.

1.1.10 Unit costs

Resource	Unit costs	Source
Preparation for Simple Radiotherapy with Imaging and Simple Calculation	£323.44	NHS Cost Collection FY2019/20
Deliver a Fraction of Treatment[1] on a Megavoltage Machine	£144.54	
[1]Unit cost corresponds to the delivery of a radiotherapy fraction, regardless of dose in Gy		

1.1.11 Evidence statements

- One cost-utility analysis from the UK (Glynn et al. 2022) found that in adults who have undergone breast-conserving surgery or mastectomy for early breast cancer (stage I,II,IIIa), partial breast 26 Gy in 5 fractions (PB5F) was likely to be an effective use of NHS resources as it was the most effective and least costly regimen compared with partial breast 40 Gy in 15 fractions (PB15F) and whole breast 40 Gy in 15 fractions (WB15F) and 26 Gy in 5 fractions (WB5F). For those who are ineligible for partial breast radiotherapy, whole breast 26 Gy in 5 fractions (WB5F) was a cost-effective option compared with 40 Gy in 15 fractions.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The committee agreed that the outcomes for clinical decision making were those related to mortality, adverse events (including normal tissue effects) and tumour recurrence. The committee also agreed that in their experience, people receiving radiotherapy treatment may consider adverse events and cosmetic outcomes important in their decision making and weigh these against the benefits of treatment. The committee thought that both short-term and long-term information related to these outcomes is important in informing clinical practice and decision-making. However, there was limited long-term data available from the evidence in this review.

1.1.12.2 The quality of the evidence

The majority of the evidence ranged from moderate to very low quality with the main reasons for downgrading being due to imprecision and risk of bias from some of the trials. In some of the evidence, imprecision was rated serious or very serious with the 95% confidence

intervals crossing one or two ends of the default minimally important difference (MIDs) thresholds. Some of the studies were downgraded for risk of bias due to lack of information on randomisation, allocation concealment and blinding. All studies were considered fully applicable to the review. There were a wide range of different hypofractionation regimens reported by different studies. This made it difficult for meta-analysis to be carried out, meaning that most of the evidence for the outcomes were based on the results from single studies.

The studies used a range of hypofractionation regimens, some of which the committee considered less relevant to current practice. Some of the hypofractionation regimens explored in the studies were higher than those that are used in current practice or had longer treatment periods than are used currently. The committee focused on the studies that were most in line with current practice (Brunt 2020, Ivanov 2022, Shahid 2009). These studies were conducted in Pakistan (Shahid 2009), Serbia (Ivanov 2022) and the United Kingdom (Brunt 2020). Participants in each of these studies received whole breast hypofractionated radiotherapy and two of these studies (Brunt 2020 and Shahid 2009) randomised participants to receive 26 Gy in 5 fractions over 1 week compared with 40 Gy in 15 fractions over 3 weeks. The committee considered these two studies to be the most important for decision making, as these are the hypofractionation regimens that are used in current practice in the UK.

The longest follow up in any of the studies that were most relevant to current practice was 5 years. While this is useful for decision making, the committee noted more long-term information about these outcomes is needed for informing clinical decisions. Longer term data will provide more information about the distant recurrence of tumours, disease free survival for people with breast cancer and the long-term adverse events associated with each treatment regimen. However, they were aware that longer-term data from the FAST-Forward trial (Brunt 2020) would soon be available, and this would provide more information for clinicians when considering the most effective treatment options.

Although the evidence considered a range of people who have breast cancer, there were some groups who were not included in the trials. This included people receiving concurrent chemotherapy, and those receiving regional lymph node irradiation. The committee were aware that a sub-study of the FAST-Forward trial (Brunt 2020) included participants who received regional lymph node irradiation and has not yet reported results. The committee also noted that there is variation in radiotherapy practice for people who are offered autologous compared to implant-based breast reconstruction. Although the FAST-Forward trial included some people with breast reconstruction, they were a limited population and no

further subgroup analyses were made. This made it difficult for the committee to be as confident in the effects of the different hypofractionation regimens for these groups of people, as currently there is limited evidence. As such, the committee made 2 research recommendations to further explore the effectiveness of the 26 Gy in 5 fractions regimen, one for people who receive concurrent chemotherapy, or breast reconstruction and another for people who are receiving nodal irradiation.

1.1.12.3 Benefits and harms

The entire body of evidence could not distinguish between the effectiveness of all the different hypofractionation regimens compared to each other for the outcomes of mortality, local recurrence, or distant recurrence (defined as the location of a subsequent cancer in relation to the first episode that led to treatment). This indicates that regimens that require fewer fractions over fewer weeks, may have a similar level of effectiveness, or are non-inferior, to those that require a higher number of fractions over a greater number of weeks. While some of the effect estimates favoured one treatment over another, most of the results had wide confidence intervals which crossed the line of no effect. Based on this, the committee could not differentiate between the effects of different hypofractionation regimens.

The committee discussed how shorter regimens with fewer fractions may have benefits for people who are having radiotherapy, especially those in the groups identified in the equalities and health inequalities assessment (EHIA). Many of the issues that people face when they are having radiotherapy are associated with the time and costs relating to travel to multiple appointments. The time needed to attend multiple appointments can be a particular issue for people who need to arrange appointments around work or carer responsibilities, or for those who live far from their nearest treatment centre. As such, the committee highlighted that a shorter treatment duration time may make treatment more accessible for many people. However, the committee acknowledged that there are some people for who potential adverse effects may make the shorter treatment duration less acceptable, such as those with the risk of increased fatigue with a shorter treatment regimen. In these instances, treatment with a longer regimen may be more appropriate.

In addition to the benefits for people who are having radiotherapy, the committee highlighted how using fewer fractions has benefits for the centres that are providing radiotherapy. A hypofractionation regimen with fewer fractions over a shorter period of time means that centres can treat people more quickly compared to when radiotherapy takes place over a longer period of time, thereby reducing waiting lists.

Although the evidence could not differentiate between radiotherapy with fewer fractions and radiotherapy with a greater number of fractions, there were some differences in the number of adverse events. Regimens with fewer fractions were generally associated with a higher number of adverse events, such as normal tissue effects, and lower quality of life scores were reported in relation to swollen breasts and harder or firmer breasts. However, the committee agreed that the adverse events did not indicate any potential serious harms and in their experience the effects reduced further over time. The committee also discussed how, in their experience, many people who are given radiotherapy will favour higher doses per fraction in a shorter duration, than lower doses over a longer duration because they consider that the benefits of reduced treatment time outweigh the risks of increased adverse events. For this reason, the committee made a recommendation in favour of offering a regimen over one week with fewer fractions (26 Gy in 5 fractions) for most people.

The committee noted that the studies that used the 26 Gy over 5 fractions regimen excluded people who had concurrent chemotherapy and there was little evidence on people with conditions that increase sensitivity to radiotherapy or people who had received implant-based reconstruction. As such, the committee made a recommendation to consider the 40 Gy over 15 fractions regimen in these groups of people as there was no evidence which evaluated the benefits and harms of the lower fraction regimen for these people. They also recommended that the 15-fraction regimen should be considered for other people who have factors that may make 15 fractions more acceptable. The committee stated that these factors could include people that experienced high levels of fatigue. The committee thought that decisions on treatments for these groups should be based on discussions of the potential benefits and harms between a patient and a clinician. Given the limited evidence on the effectiveness of the 26 Gy in 5 fractions over 1 week for people receiving concurrent radiotherapy or for people who received breast reconstruction, the committee developed a research recommendation for these groups (see Appendix K).

An additional group that was not considered in the evidence were people who were receiving regional lymph node radiotherapy. The committee noted the specific concerns for this group around adverse effects, such as lymphoedema and neuropathy. This group of people will be evaluated within the FAST-Forward nodal irradiation sub-study, and this will address these concerns. The committee thought it was important that this group continued to receive the 40 Gy in 15 fraction regimen until the results are available and so they made a recommendation to highlight this. The committee also highlighted that there was a lack of evidence on the effectiveness of a 26 Gy in 5 fractions regimen in people who had nodal irradiation. As such,

the committee developed a research recommendation to encourage more research in the area.

In addition to the number of fractions, the committee also discussed the dose per fraction. The committee noted that RCTs with long term follow up had already established the dose per fraction over a specified time period (for example, Brunt 2020 comparing doses over 5 weeks). They also noted that the FAST-Forward study did include a comparison between 26 Gy and 27 Gy per fraction, both over 5 fractions. The committee noted that the incidence of adverse events was lower in the 26 Gy group, with no clear difference in effectiveness. For example, there was a lower incidence of normal tissue effects, adverse events, swollen breasts and skin problems in the breast for people randomised to receive 26 Gy in 5 fractions compared to 27 Gy in 5 fractions. They agreed that this supported the use of this regimen in current practice.

1.1.12.4 Cost effectiveness and resource use

The committee reviewed evidence on the cost effectiveness of different hypofractionation radiotherapy regimens in patients with early-stage and locally advanced invasive breast cancer from the existing literature. The evidence from the literature came from one cost-utility analysis from the UK (Glynn et al. 2022). Though a minor limitation of the evidence was that results are reported with a £15,000 per health benefit (QALY) threshold, the committee's discussion of the evidence was based on an academic in confidence analysis with NICE's £20,000 per QALY threshold, that was generated by the authors of the analysis for our decision making.

The study presents evidence for two subgroups of people based on eligibility for partial breast radiotherapy. For those eligible for partial breast radiotherapy, the study compares whole breast radiotherapy with 15 fractions (WB15F), whole breast radiotherapy with 5 fractions (WB5F), partial breast radiotherapy with 15 fractions (PB15F), and partial breast radiotherapy with 5 fractions (PB5F). For those ineligible for partial breast radiotherapy, the study compares whole breast radiotherapy with 15 fractions (WB15F) and whole breast radiotherapy with 5 fractions (WB5F). The difference in event risks between the two hypofractionation regimens is based on evidence from the FAST Forward trial, and the difference in event risks between partial and whole breast radiotherapy is from the IMPORT LOW trial. In the base case analysis, a key assumption is that the transition pattern from alive and disease free to distant recurrence is common between each type of radiotherapy regimen; this was based on the clinical argument that radiotherapy is a local treatment and

so its causal impact on distant recurrence would only occur through reducing locoregional recurrence.

In the base case analysis, for those eligible for partial breast radiotherapy, PB5F has lower costs and higher QALYs than all of the other hypofractionation strategies, and has a 62% likelihood of being an effective use of NHS resources based on a £15,000 per QALY threshold; for those not eligible for partial breast radiotherapy, WB5F has lower overall costs and greater QALYs than WB15F, and has a 100% likelihood of being an effective use of resources.

These results remain robust to the majority of scenarios that are explored. However, one scenario that incorporates the direct treatment effect on distant recurrence estimated from the analysis of the trials generates notably different results to the base case. In this scenario, the hazard ratio (HR) of 5F relative to 15F is 1.27 (95%CI 0.90 to 1.79) and so while not statistically significant, the result favours 15F instead of 5F. In this scenario, PB15F has a cost per health benefit of £15,050 per QALY compared with PB5F, and these have a similar likelihood of being cost-effective for those people who are eligible for partial breast radiotherapy. For those ineligible for partial breast radiotherapy, the cost per health benefit for WB15F compared with WB5F is £3,937 per QALY, and therefore WB5F is not an effective use of resources. Under this scenario, the WB15F regimen is still more expensive than WB5F by £472, but leads to greater health benefits because of its assumed relatively lower impact on distant recurrence.

The committee felt that, in principle, the assumption where radiotherapy would have a direct impact on distant recurrence was plausible. However, they felt that this outcome happened further in the future than with locoregional recurrence, and that at least 10 to 15 years of data after treatment would be required in order to capture this accurately. As such, given the lack of data beyond the 5-year follow up trial duration, the clinical assumption made in the base case, that the impact of radiotherapy on distant recurrence occurs only indirectly through its impact on loco-regional recurrence, is more robust. The committee therefore preferred to refer to the results of the base case analysis when drafting recommendations. As such, they considered the evidence sufficient to offer radiotherapy in 5 fractions for people with early-stage locally advanced breast cancer.

While an acute skin toxicity sub-study of FAST forward (Brunt et al. 2016) noted no concerns that 5F lead to more severe acute skin reactions compared with 15F, the committee noted that in their experience, the higher dose of radiotherapy delivered per fraction can result in worse adverse events and is therefore less acceptable to some patients. However, the authors of the economic analysis were not able to capture the subsequent impact on quality of life due to a lack of quality of life data from the trials or the literature. The committee were

unclear on how the absence of this impact would affect the cost effectiveness results for the typical patient. In their experience, acute skin reactions would be unacceptable for certain people with comorbidities, as they would be less likely to tolerate them and they would experience larger impacts to their quality of life.

Though 5F is likely to be an effective use of NHS resources and indeed to have additional societal benefits, the committee felt it was still important to acknowledge the relevance of 15F for cases in which the toxicity of 26 Gy over 5F may not be appropriate for some patients. Because of this, the committee noted that the economic evidence is weaker for certain groups and believed it was important to make space in the recommendations to consider 15F for those people.

The committee acknowledged additional benefits of delivering radiotherapy in 5 fractions that were not captured in the economic analysis. The committee discussed how with 5F, fewer appointments for radiotherapy would be preferable for people in that it would reduce their personal costs of travelling to appointments as well as mitigate the stress of getting time off work. This benefit is particularly valuable for people in precarious employment, and for people living further away from radiotherapy treatment centres. In this respect, offering radiotherapy in 5 fractions to people would address some health inequalities.

Prior to the COVID-19 pandemic, the standard of care for radiotherapy was to offer 40 Gy in 15F. However, when the FAST Forward trial was published and 26 Gy over 5F was found to be noninferior, COVID accelerated the adoption of this practice because of the capacity constraints experienced by the health system at the time, as well as because of concerns of vulnerable patients about being exposed to the virus in the hospital setting. As a result of this, it is now standard practice in some centres to offer the 5F regimen and there is variation in practice across the country. For those centres already offering 5F, the committee noted that it would be difficult to revert to 15F for all patients, given the additional resources that would be required both in terms of available staff and the need for equipment. Given all of this, the committee thought that offering 5F would encourage centres to adopt this new regimen, and would have a net positive resource impact as well as a positive effect on health service provision.

1.1.12.5 Other factors the committee took into account

The committee highlighted how the publication of the results from the FAST-Forward trial (Brunt 2020) informed the consensus statements from the Royal College of Radiologists, resulting in many centres already adopting the 26 Gy over 5 fractions regimen. They discussed how the COVID-19 pandemic accelerated these changes more quickly than would

typically happen in normal practice, as centres were faced with reduced capacity and shorter treatment times were an advantage. The committee felt that the evidence supported these changes for many people who are given radiotherapy for breast cancer.

The committee noted that while a shorter regimen would potentially lessen the burden some groups have in accessing treatment (for example, people on lower incomes will have less visits to hospital requiring reduced travel and costs) this did not address the underlying difficulty that for some people any travel or added costs is prohibitive in accessing treatment.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.10.13 – 1.10.16.

1.1.14 References – included studies

1.1.14.1 Effectiveness

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1.1.14.2 Economic

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1 Appendices

Appendix A – Review protocol

Review protocol for radiotherapy hypofractionation regimens

ID	Field	Content
1.	Review title	Effectiveness of different hypofractionation radiotherapy regimens in people with early-stage or locally advanced invasive breast cancer
2.	Review question	2.1 What is the effectiveness and cost-effectiveness of different hypofractionation radiotherapy regimens in patients with early-stage or locally advanced invasive breast cancer?
3.	Objective	To assess the effectiveness of different hypofractionation radiotherapy regimens in patients with early-stage or locally advanced invasive breast cancer.
4.	Searches	The following databases will be searched for the clinical review: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • MEDLINE Epub Ahead-of-Print • Medline in Process • Emcare • Web of Science (for forward citation search)

ID	Field	Content
		For the economics review the following databases will be searched: • Embase • MEDLINE • Medline in Process • Medline EPub Ahead of Print • Econlit • HTA (legacy records) • NHS EED (legacy records) • INAHTA Searches will be restricted by: • Date limitations: 2008 onwards • English language • Human studies • Abstracts, conference presentations and theses • Study design RCT will be applied Other searches: • Citation searching forward citation search using Brunt (2020) paper The full search strategies will be published in the final review.

ID	Field	Content
5.	Condition or domain being studied	Early-stage and locally advanced invasive breast cancer
6.	Population	Inclusion: Adults (18 and over) with early or locally advanced breast cancer who have undergone any of the following alone or in combination: breast-conserving surgery mastectomy (which can include reconstruction) axillary clearance sentinel lymph node biopsy axillary node sampling There are no exclusion criteria
7.	Intervention	Radiotherapy hypofractionation with or without regional node radiotherapy: Using greater than 2Gy per fraction for

ID	Field	Content
		a) whole breast radiotherapy b) chest wall radiotherapy c) partial breast radiotherapy
8.	Comparator	Any other hypofractionation radiotherapy schedule
9.	Types of study to be included	RCTs
10.	Other exclusion criteria	Abstracts, conference presentations and theses Non-human studies Non-English language studies
11.	Context	This is an update of existing NICE guidance (NG101) on radiotherapy dose fractionation for women with early and locally advanced breast cancer undergoing external beam radiotherapy after surgical excision of breast cancer. The current update is being undertaken based on identification of the 5-year results of the FAST-Forward trial (Murray Brunt et al 2020) by the NICE surveillance team, which was judged to have the potential to alter the existing recommendations. Reference: Murray Brunt A, Haviland JS, Wheatley DA, et al. (2020) Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a

ID	Field	Content
		multicentre, non-inferiority, randomised, phase 3 trial. Lancet. 2020 May 23;395(10237):1613-1626. doi: 10.1016/S0140-6736(20)30932-6. Epub 2020 Apr 28. PMID: 32580883; PMCID: PMC7262592.
12.	Primary outcomes (critical outcomes)	Outcomes will be reported at the latest time point reported by the study Quality of life (using validated measures such as EORTC and BREAST-Q) Breast cancer mortality All-cause mortality Local Recurrence Distant recurrence (also referred as distant relapse) Normal tissue effects Treatment-related adverse events Cosmesis (including breast appearance, breast oedema, appearance of scar, breast size, shape, colour, nipple position, shape of areola in comparison with untreated breast)
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. This review will make use of the priority screening functionality within the EPPI-reviewer software.

ID	Field	Content
		The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the Cochrane Risk of Bias v.2.0 checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Where possible, meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions. Where data can be disambiguated it will be separated into the subgroups identified in section 17 (below). Continuous outcomes will be analysed as mean differences, unless multiple scales are used to measure the same factor. In these cases, standardised mean differences will be used instead. Pooled relative risks will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Absolute risks will be presented where possible. Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be deemed to be inappropriate if one or both of the following conditions is met: Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the

ID	Field	Content
		reviewer in advance of data analysis. The presence of significant statistical heterogeneity in the meta-analysis, defined as I2≥50%. In any meta-analyses where some (but not all) of the data comes from studies at high risk of bias, a sensitivity analysis will be conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses will be reported. Similarly, in any meta-analyses where some (but not all) of the data comes from indirect studies, a sensitivity analysis will be conducted, excluding those studies from the analysis. GRADE will be used to assess the quality of the outcomes. All outcomes in this review will come from RCTs and will be rated as high quality initially and downgraded from this point. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically (visually) assess the potential for publication bias.
17.	Analysis of sub-groups	Type of radiotherapy (whole breast, chest wall, partial breast, with or without regional node radiotherapy) People who are also given external beam breast boost radiotherapy vs those who are not given breast boost People who have undergone breast reconstruction surgery (including implants or using autologous methods such as deep inferior epigastric perforator (DIEP) or lateral intercostal artery perforator (LICAP) flap

ID	Field	Content		
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service delivery ☐ Other		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	10 October 2022		
22.	Anticipated completion date	23 February 2023		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**

ID	Field	Content		
		Preliminary searches		
		Piloting of the study selection process		
		Formal screening of search results against eligibility criteria		
		Data extraction		
		Risk of bias (quality) assessment		

ID	Field	Content		
		Data analysis		
24.	Named contact	**5a. Named contact** Centre for Guidelines, NICE. **5b Named contact e-mail** TBC **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and Guideline Development Team.		
25.	Review team members	From the Guideline Development Team: • Marie Harrisingh, Technical adviser • Clare Dadswell, Senior technical analyst • Yolanda Martinez, Technical analyst • Omnia Bilal, Technical analyst • Lindsay Claxton, Health economist adviser • Jeremy Dietz, Health economist analyst • Daniel Tuvey, Information specialist		
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team which receives funding from NICE.		

ID	Field	Content
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Early and locally advanced breast cancer: diagnosis and management – Radiotherapy.
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Breast cancer; radiotherapy dose fractionation; external beam radiotherapy
33.	Details of existing review of same topic by same authors	Not applicable

ID	Field	Content
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35.	Additional information	None
36.	Details of final publication	www.nice.org.uk

1

Appendix B – Literature search strategies

What is the effectiveness and cost-effectiveness of different hypofractionation radiotherapy regimens in patients with early-stage and locally advanced invasive breast cancer?

Background and development

Search design and peer review

A NICE information specialist conducted the literature searches for the evidence review. The searches were run between 1 December 2022 and 09 December 2022. This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The search strategy was based on the terms used for the NG101 NICE guideline. Modifications were made to these original search strategies for the specifications in the review protocol.

Text analysis for additional keywords/subject headings was carried on a set of includes from the 2009 guideline. PubMedReminer and Medline Ranker were used for the text analysis.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude conferences and clinical trials in Embase, Emcare and Cochran Library were applied in adherence to standard NICE practice and the review protocol.

The search was limited from April 2008 to December 2022 as defined in the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin K, Scherer R & Lefebvre C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Search filters and classifiers

Clinical searches

- RCT filters:
    - McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.
      Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

    - McMaster Therapy – Embase "best balance of sensitivity and specificity" version.
      Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association, 94(1), 41-47.

Cost effectiveness searches

The following search filters (precise version) were applied to the search strategies in MEDLINE and Embase to identify cost-utility studies:

Hubbard, W, Walsh N, Hudson T, Heath A, Dietz J, and Rogers G. (2022) Development and validation of paired Medline and Embase search filters for cost-utility studies. Manuscript submitted for publication.

Key decisions

The search strategy was developed to find evidence for the specified population and intervention in the review protocol.

A forward citation was carried out on the following key paper identified in the NICE surveillance report (July 2022):

Murray Brunt A, Haviland JS, Wheatley DA, et al. (2020) Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet*;395(10237):1613-1626.

Clinical/public health searches

Main search – Databases

Database	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	05/12/22	Wiley	Issue 11 of 12, November 2022	992
Cochrane Database of Systematic Reviews (CDSR)	05/12/22	Wiley	Issue 11 of 12, November 2022	7
Embase	05/12/22	Ovid	Embase 1996 to 2022 December 02	1,686
Emcare	05/12/22	Oivd	Ovid Emcare 1995 to 2022 Week 46	692
MEDLINE ALL	05/12/22	Ovid	Ovid MEDLINE(R) ALL 1946 to December 02, 2022	1,240

Main search – Additional methods

Additional method	Date searched	No. of results downloaded
Forwards citation searching	06/12/22	258

Search strategy history

Database name: Medline ALL

1exp Breast Neoplasms/334059
2Carcinoma, Ductal, Breast/16823
3Carcinoma, Lobular/6031
4Carcinoma, Medullary/3367
5Carcinoma, Intraductal, Noninfiltrating/10497
6or/1-5337899
7exp Breast/51979
8breast*.ti,ab,kw.533089
97 or 8542931
10(breast adj milk).ti,ab,kw.15033
11(breast adj tender*).ti,ab,kw.575
1210 or 1115606
139 not 12527325
14exp Neoplasms/3766015
1513 and 14347403
16 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignanc*)).ti,ab,kw.394139
17 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignanc*)).ti,ab,kw.35715
18Paget's Disease, Mammary/801
19(paget* and (breast* or mammary or nipple*)).ti,ab,kw.1419
20or/15-19450057
216 or 20491369
22exp Radiotherapy Dosage/67170
23exp Radiation Dosage/87920
24(hypofraction* or hf-rt or hrft).ti,ab,kw.4821
25fraction*.ti,ab,kw.636645
26 ((irradiation or radiation or radiotherap*) adj4 (schedule* or regime* or technique* or approach* or programme* or program* or dos* or deliver* or administrat*)).ti,ab,kw.111036
27(Gy or ((over or greater*) adj3 gray)).ti,ab,kw.71306
28or/22-27841213
29(Fast adj5 (forward* or trial*)).ti,ab,kw.1366
3021 and 2822788
3129 or 3024127
32randomized controlled trial.pt.582037
33randomi?ed.mp.1034007
34placebo.mp.241323
35or/32-341097768
3631 and 352059
37limit 36 to english language1929
38animals/ not humans/5037093
3937 not 381914
40limit 39 to ed=20080422-202212021097
41limit 39 to dt=20080422-202212021224
4240 or 411240

Database name: Embase

1exp breast cancer/485450
2exp breast carcinoma/71652
3exp medullary carcinoma/10068
4ductal breast carcinoma in situ/1243
5exp breast tumor/543941
6lobular carcinoma/3074
7or/1-6552718
8exp breast/86400
9breast*.ti,ab,kw.651732
108 or 9666246
11(breast adj milk).ti,ab,kw.15870
12(breast adj tender*).ti,ab,kw.593
1311 or 1216458
1410 not 13649788
15exp neoplasm/4418318
1614 and 15500812
17 (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 or malignanc*)).ti,ab,kw.507101
18 (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 or malignanc*)).ti,ab,kw.28242
19exp Paget nipple disease/6927
20(paget* and (breast* or mammary or nipple*)).ti,ab,kw.1379
21or/16-20560698
227 or 21660769
23exp radiotherapy dosage/8133
24exp radiation dose fractionation/21676
25exp radiation dose/141127
26radiation dose response/702
27(hypofraction* or hf-rt or hrft).ti,ab,kw.9942
28fraction*.ti,ab,kw.655511
29 ((irradiation or radiation or radiotherap*) adj4 (schedule* or regime* or technique* or approach* or programme* or program* or dos* or deliver* or administrat*)).ti,ab,kw.140165
30(Gy or ((over or greater*) adj3 gray)).ti,ab,kw.110675
31or/23-30877589
32(Fast adj5 (forward* or trial*)).ti,ab,kw.1895
3322 and 3135126
3432 or 3336940
35random:.tw.1727985
36placebo:.mp.428133
37double-blind:.tw.190506
38or/35-371933466
3934 and 384170
40limit 39 to english language4039
41nonhuman/ not human/3819910
4240 not 413963
43limit 42 to dc=20080422-202212023445
44 (conference abstract* or conference review or conference paper or conference proceeding or preprint).db,pt,su.5129067
4543 not 441686

Database name: Emcare

1exp breast cancer/87257
2exp breast carcinoma/10683
3exp medullary carcinoma/1191
4ductal breast carcinoma in situ/18
5exp breast tumor/91249
6lobular carcinoma/301
7or/1-692224
8exp breast/19221
9breast*.ti,ab,kw.157942
108 or 9159888
11(breast adj milk).ti,ab,kw.5967
12(breast adj tender*).ti,ab,kw.206
1311 or 126170
1410 not 13153718
15exp neoplasm/583674
1614 and 1577943
17(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 or malignanc*)).ti,ab,kw.106299
18(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 or malignanc*)).ti,ab,kw.3295
19exp Paget nipple disease/1094
20(paget* and (breast* or mammary or nipple*)).ti,ab,kw.229
21or/16-20115343
227 or 21134746
23exp radiotherapy dosage/456
24exp radiation dose fractionation/5017
25exp radiation dose/29646
26radiation dose response/45
27(hypofraction* or hf-rt or hrft).ti,ab,kw.2248
28fraction*.ti,ab,kw.108358
29((irradiation or radiation or radiotherap*) adj4 (schedule* or regime* or technique* or approach* or programme* or program* or dos* or deliver* or administrat*)).ti,ab,kw.34902
30(Gy or ((over or greater*) adj3 gray)).ti,ab,kw.21727
31or/23-30159060
32(Fast adj5 (forward* or trial*)).ti,ab,kw.507
3322 and 317039
3432 or 337532
35random:.tw.558352
36placebo:.mp.118380
37double-blind:.tw.57788
38or/35-37612411
3934 and 38963
40limit 39 to english language932
41nonhuman/ not human/360235
4240 not 41920
43limit 42 to dc=20080422-20221202698
44conference*.pt,su,so.175905
4543 not 44692

Database name: Cochrane Database of Systematic Reviews

#1 MeSH descriptor: [Breast Neoplasms] explode all trees 14892
#2 MeSH descriptor: [Carcinoma, Ductal, Breast] this term only 378
#3 MeSH descriptor: [Carcinoma, Lobular] this term only 176
#4 MeSH descriptor: [Carcinoma, Medullary] this term only 16
#5 MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] this term only 209
#6 {OR #1-#5} 14924
#7 MeSH descriptor: [Breast] explode all trees 852
#8 breast*:ti,ab 55501
#9 #7 or #8 55588
#10 (breast NEXT milk):ti,ab 2478
#11 (breast NEXT tender*):ti,ab 246
#12 #10 or #11 2724
#13 #9 not #12 52864
#14 MeSH descriptor: [Neoplasms] explode all trees 90536
#15 #13 and #14 15159
#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 or malignanc*)):ti,ab 39952
#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 or malignanc*)):ti,ab 272
#18 MeSH descriptor: [Paget's Disease, Mammary] explode all trees 3
#19 (paget* and (breast* or mammary or nipple*)):ti,ab 18
#20 {OR #15-#19} 40725
#21 #6 or #20 41492
#22 MeSH descriptor: [Radiotherapy Dosage] explode all trees 2650
#23 MeSH descriptor: [Radiation Dosage] explode all trees 1513
#24 (hypofraction* or hf-rt or hrft):ti,ab 1184
#25 (fraction*):ti,ab 37828
#26 ((irradiation or radiation or radiotherap*) near/4 (schedule* or regime* or technique* or approach* or programme* or program* or dos* or deliver* or administrat*)):ti,ab 8921
#27 (Gy or ((over or greater*) near/3 gray)):ti,ab 9656
#28 #22 or #23 or #24 or #25 or #26 or #27 48829
#29 (Fast near/5 (forward* or trial*)):ti,ab 610
#30 #21 AND #28 2529
#31 #29 or #30 3110
#32 "conference":pt or (clinicaltrials or trialsearch):so 656457
#33 #31 not #32 with Publication Year from 2008 to 2022, in Trials 992
#34 #31 not #32 with Cochrane Library publication date Between Apr 2008 and Dec 2022, in Cochrane Reviews 7

Database name: Cochrane CENTRAL

#1 MeSH descriptor: [Breast Neoplasms] explode all trees 14892
#2 MeSH descriptor: [Carcinoma, Ductal, Breast] this term only 378
#3 MeSH descriptor: [Carcinoma, Lobular] this term only 176
#4 MeSH descriptor: [Carcinoma, Medullary] this term only 16
#5 MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] this term only 209
#6 {OR #1-#5} 14924
#7 MeSH descriptor: [Breast] explode all trees 852

#8 breast*:ti,ab 55501
#9 #7 or #8 55588
#10 (breast NEXT milk):ti,ab 2478
#11 (breast NEXT tender*):ti,ab 246
#12 #10 or #11 2724
#13 #9 not #12 52864
#14 MeSH descriptor: [Neoplasms] explode all trees 90536
#15 #13 and #14 15159
#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 or malignanc*)):ti,ab 39952
#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 or malignanc*)):ti,ab 272
#18 MeSH descriptor: [Paget's Disease, Mammary] explode all trees 3
#19 (paget* and (breast* or mammary or nipple*)):ti,ab 18
#20 {OR #15-#19} 40725
#21 #6 or #20 41492
#22 MeSH descriptor: [Radiotherapy Dosage] explode all trees 2650
#23 MeSH descriptor: [Radiation Dosage] explode all trees 1513
#24 (hypofraction* or hf-rt or hrft):ti,ab 1184
#25 (fraction*):ti,ab 37828
#26 ((irradiation or radiation or radiotherap*) near/4 (schedule* or regime* or technique* or approach* or programme* or program* or dos* or deliver* or administrat*)):ti,ab 8921
#27 (Gy or ((over or greater*) near/3 gray)):ti,ab 9656
#28 #22 or #23 or #24 or #25 or #26 or #27 48829
#29 (Fast near/5 (forward* or trial*)):ti,ab 610
#30 #21 AND #28 2529
#31 #29 or #30 3110
#32 "conference":pt or (clinicaltrials or trialsearch):so 656457
#33 #31 not #32 with Publication Year from 2008 to 2022, in Trials 992

Additional search methods

Source name: Web of Science

Forward citation search using:

Murray Brunt A, Haviland JS, Wheatley DA, et al. (2020) Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet*; 395(10237):1613-1626

Cost-effectiveness searches

Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
EconLit	09/12/22	OVID	Ovid Emcare 1995 to 2022 Week 48	31
NHS EED (NHS Economic Evaluation Database)	09/12/22	CRD	Legacy database	12
Embase	09/12/22	Ovid	Embase 1996 to 2022 December 09	66
HTA (Health Technology Assessment)	09/12/22	CRD	Legacy database	6
INAHTA (International HTA database)	09/12/22	INAHTA	N/A	35
MEDLINE ALL	09/12/22	Ovid	Ovid MEDLINE(R) ALL 1946 to December 09, 2022	70

Search strategy history

Database name: Medline ALL

1exp Breast Neoplasms/334165
2Carcinoma, Ductal, Breast/16832
3Carcinoma, Lobular/6033
4Carcinoma, Medullary/3368
5Carcinoma, Intraductal, Noninfiltrating/10508
6or/1-5338008
7exp Breast/51998
8breast*.ti,ab,kw.533465
97 or 8543310
10(breast adj milk).ti,ab,kw.15036
11(breast adj tender*).ti,ab,kw.575
1210 or 1115609
139 not 12527701
14exp Neoplasms/3766933
1513 and 14347500

16 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignanc*)).ti,ab,kw.394398
17 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignanc*)).ti,ab,kw.35724
18Paget's Disease, Mammary/801
19(paget* and (breast* or mammary or nipple*)).ti,ab,kw.1420
20or/15-19450328
216 or 20491648
22exp Radiotherapy Dosage/67157
23exp Radiation Dosage/87927
24(hypofraction* or hf-rt or hrft).ti,ab,kw.4834
25fraction*.ti,ab,kw.636968
26 ((irradiation or radiation or radiotherap*) adj4 (schedule* or regime* or technique* or approach* or programme* or program* or dos* or deliver* or administrat*)).ti,ab,kw.111105
27(Gy or ((over or greater*) adj3 gray)).ti,ab,kw.71357
28or/22-27841602
29(Fast adj5 (forward* or trial*)).ti,ab,kw.1363
3021 and 2822790
3129 or 3024126
32Cost-Benefit Analysis/91233
33(cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw.16466
34((incremental* adj2 cost*) or ICER).tw.16913
35(cost adj2 utilit*).tw.6544
36 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw.2152
37((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw.22459
38(cost and (effect* or utilit*)).ti.37172
39or/32-38111393
4031 and 39102
41limit 40 to english language91
42animals/ not humans/5037924
4341 not 4291
44limit 43 to ed=20080422-2022120960
45limit 43 to dt=20080422-2022120970
4644 or 4570

Database name: Embase

1exp breast cancer/485840
2exp breast carcinoma/71732
3exp medullary carcinoma/10085
4ductal breast carcinoma in situ/1278
5exp breast tumor/544430
6lobular carcinoma/3082
7or/1-6553219
8exp breast/86392
9breast*.ti,ab,kw.652072
108 or 9666585
11(breast adj milk).ti,ab,kw.15887
12(breast adj tender*).ti,ab,kw.594
1311 or 1216476

1410 not 13650109
15exp neoplasm/4421260
1614 and 15501007
17 (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 or malignanc*)).ti,ab,kw.507312
18 (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 or malignanc*)).ti,ab,kw.28247
19exp Paget nipple disease/6925
20(paget* and (breast* or mammary or nipple*)).ti,ab,kw.1379
21or/16-20560952
227 or 21661362
23exp radiotherapy dosage/8170
24exp radiation dose fractionation/21706
25exp radiation dose/141345
26radiation dose response/708
27(hypofraction* or hf-rt or hrft).ti,ab,kw.9950
28fraction*.ti,ab,kw.655774
29 ((irradiation or radiation or radiotherap*) adj4 (schedule* or regime* or technique* or approach* or programme* or program* or dos* or deliver* or administrat*)).ti,ab,kw.140248
30(Gy or ((over or greater*) adj3 gray)).ti,ab,kw.110717
31or/23-30878070
32(Fast adj5 (forward* or trial*)).ti,ab,kw.1896
3322 and 3135157
3432 or 3336972
35cost utility analysis/11535
36(cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw.27736
37((incremental* adj2 cost*) or ICER).tw.28410
38(cost adj2 utilit*).tw.10005
39 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw.2872
40((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw.33646
41(cost and (effect* or utilit*)).ti.50257
42or/35-4180912
4334 and 42129
44limit 43 to english language126
45nonhuman/ not human/3821276
4644 not 45126
47limit 46 to dc=20080422-20221209116
48 (conference abstract* or conference review or conference paper or conference proceeding or preprint).db,pt,su.5133450
4947 not 4866

Database name: Econlit

1 (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 or malignanc*)).ti,ab.381

2 (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 or malignanc*)).ti,ab.1
3(paget* and (breast* or mammary or nipple*)).ti,ab.0
41 or 2 or 3382
5(hypofraction* or hf-rt or hrft).ti,ab.0
6fraction*.ti,ab.10695
7 ((irradiation or radiation or radiotherap*) adj4 (schedule* or regime* or technique* or approach* or programme* or program* or dos* or deliver* or administrat*)).ti,ab.32
8(Gy or ((over or greater*) adj3 gray)).ti,ab.9
95 or 6 or 7 or 810735
104 and 96
11(Fast adj5 (forward* or trial*)).ti,ab.31
1210 or 1137
13limit 12 to english37
14limit 13 to yr="2008 -Current" 31

Database name: HTA

1MeSH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES1798
2MeSH DESCRIPTOR Carcinoma, Ductal, Breast26
3MeSH DESCRIPTOR Carcinoma, Lobular7
4MeSH DESCRIPTOR Carcinoma, Medullary7
5MeSH DESCRIPTOR Carcinoma, Intraductal, Noninfiltrating13
6#1 OR #2 OR #3 OR #4 OR #51806
7MeSH DESCRIPTOR Breast EXPLODE ALL TREES97
8((breast*))3002
9#7 OR #83002
10(((breast adj milk)))66
11(((breast adj tender*)))14
12#10 OR #1180
13#9 NOT #122922
14MeSH DESCRIPTOR Neoplasms EXPLODE ALL TREES12016
15#13 AND #142071
16 (((breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignanc*))))2414
17 (((mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignanc*))))7
18MeSH DESCRIPTOR Paget's Disease, Mammary EXPLODE ALL TREES1
19(((paget* and (breast* or mammary or nipple*))))4
20#15 OR #16 OR #17 OR #18 OR #192455
21#6 OR #202463
22MeSH DESCRIPTOR Radiotherapy Dosage EXPLODE ALL TREES112
23MeSH DESCRIPTOR Radiation Dosage EXPLODE ALL TREES105
24((hypofraction* or hf-rt or hrft))12
25(fraction*)877
26 (((irradiation or radiation or radiotherap*) adj4 (schedule* or regime* or technique* or approach* or programme* or program* or dos* or deliver* or administrat*)))432
27(Gy)177

28(((over or greater*) adj3 gray))1
29#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #281332
30#21 AND #2991
31(((Fast adj5 (forward* or trial*))))6
32#30 OR #3197
33* FROM 2008 TO 202252790
34#32 AND #3350
35* IN NHSEED17613
36#34 AND #356
37* IN HTA17351
38#34 AND #3712

Database name: NHS EED

1MeSH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES1798
2MeSH DESCRIPTOR Carcinoma, Ductal, Breast26
3MeSH DESCRIPTOR Carcinoma, Lobular7
4MeSH DESCRIPTOR Carcinoma, Medullary7
5MeSH DESCRIPTOR Carcinoma, Intraductal, Noninfiltrating13
6#1 OR #2 OR #3 OR #4 OR #51806
7MeSH DESCRIPTOR Breast EXPLODE ALL TREES97
8((breast*))3002
9#7 OR #83002
10(((breast adj milk)))66
11(((breast adj tender*)))14
12#10 OR #1180
13#9 NOT #122922
14MeSH DESCRIPTOR Neoplasms EXPLODE ALL TREES12016
15#13 AND #142071
16 (((breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignanc*))))2414
17 (((mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignanc*))))7
18MeSH DESCRIPTOR Paget's Disease, Mammary EXPLODE ALL TREES1
19(((paget* and (breast* or mammary or nipple*))))4
20#15 OR #16 OR #17 OR #18 OR #192455
21#6 OR #202463
22MeSH DESCRIPTOR Radiotherapy Dosage EXPLODE ALL TREES112
23MeSH DESCRIPTOR Radiation Dosage EXPLODE ALL TREES105
24((hypofraction* or hf-rt or hrft))12
25(fraction*)877
26 (((irradiation or radiation or radiotherap*) adj4 (schedule* or regime* or technique* or approach* or programme* or program* or dos* or deliver* or administrat*)))432
27(Gy)177
28(((over or greater*) adj3 gray))1
29#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #281332
30#21 AND #2991
31(((Fast adj5 (forward* or trial*))))6
32#30 OR #3197
33* FROM 2008 TO 202252790

34#32 AND #3350
35* IN NHSEED17613
36#34 AND #356

Database name: INAHTA

((((breast* AND (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignanc*))) OR ((mammar* AND (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignanc*))) OR ((paget* AND (breast* or mammary or nipple*)))) OR ("Paget's Disease Mammary"[mh]) OR ("Carcinoma Intraductal Noninfiltrating"[mh]) OR ("Carcinoma Medullary"[mh]) OR ("Carcinoma Lobular"[mh]) OR ("Breast Neoplasms"[mhe])) AND ((((over or greater*) AND gray)) OR (Gy*) OR (((irradiation or radiation or radiotherap*) AND (schedule* or regime* or technique* or approach* or programme* or program* or dos* or deliver* or administrat*))) OR (fraction*) OR ((hypofraction* or hf-rt or hrft)) OR ((Radiation Dosage)[mh]) OR ((Radiotherapy Dosage)[mh]))

Appendix C – Effectiveness evidence study selection

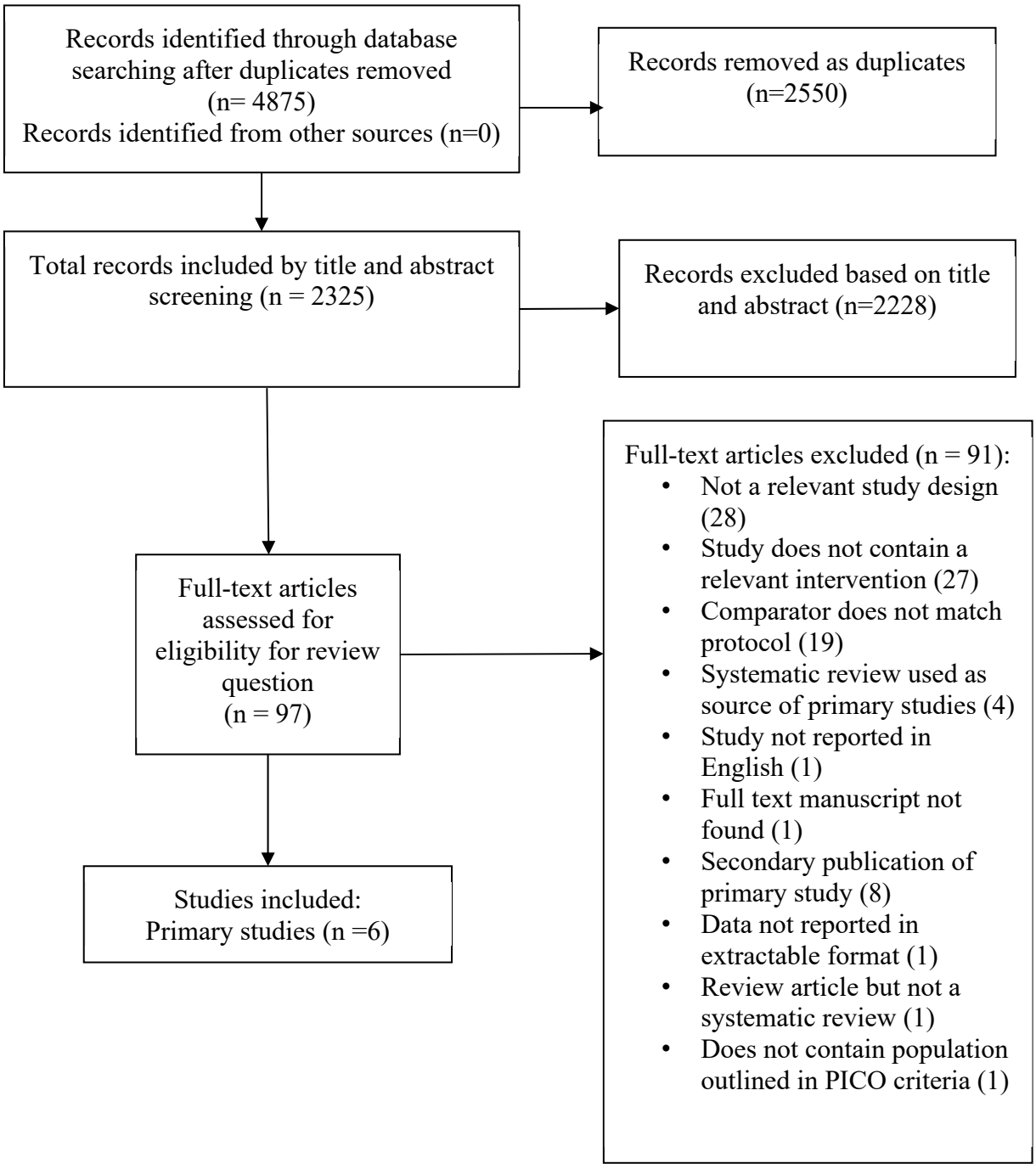


Figure 1: Study selection flow for Effectiveness of different hypofractionation radiotherapy regimens in people with early-stage and locally advanced invasive breast cancer

Appendix D – Effectiveness evidence

Aboziada 2016

Bibliographic Reference	Aboziada, M.A.; Shehata, S.; Acute and late adverse effects of breast cancer radiation: Two hypo-fractionation protocols; Journal of Solid Tumors; 2017; vol. 7 (no. 2); 1-6

Study details

Secondary publication of another included study- see primary study for details	Not applicable
Other publications associated with this study included in review	Not applicable
Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Egypt
Study setting	In hospital
Study dates	Between December 2009 and February 2012
Sources of funding	Not reported
Inclusion criteria	Confirmed histology of breast invasive ductal carcinoma Age =>18 years old ECOG performance 0-2 Negative histological margins Operable clinical stage I-IIIA breast cancer
Exclusion criteria	Lobular carcinoma in situ alone

	Locally advanced inflammatory or non-inflammatory carcinoma of breast Non-epithelial malignancies Previous radiotherapy Pregnancy
Intervention(s)	Accelerated hypofractionation 39Gy/13 fractions/5 fractions per week.
Comparator	Accelerated hypofractionation 42.4Gy/16 fractions/5 fractions per week.
Outcome measures	Acute radiation dermatitis Acute pneumonitis Subcutaneous fibrosis Cardiac toxicities Lymphoedema
Number of participants	100 female participants
Duration of follow-up	2 years
Loss to follow-up	Not reported
Methods of analysis	Data was represented as numbers, percentages or means and standard deviations; a t-test was used to compare between means. Chi-square test was used for comparison between groups. Local control and disease-free survival were calculated according to the Kaplan-Meier method.
Additional comments	All participants were female. The study reported on the adverse effects of accelerated breast cancer radiation. People with breast-conserving surgery and younger than 50 years received a boost dose of 14Gy/7 fractions to the tumour bed. Radiation techniques: All patients were simulated with 3D planning. Clinical target volumes included whole breasts in patients with BCS or chest wall post-mastectomy. The ipsilateral supraclavicular lymph node was treated in cases of positive axillary lymph nodes. Medial and lateral tangential fields were used to treat breast and/or chest wall. An anterior supraclavicular field is used with 6 MV photon beams. The treatment plan was acceptable if ≤ 10% of the heart volume and ≤ 25% of the ipsilateral lung volume received 25 Gy. Re-evaluation is done during radiotherapy and one week after by clinical assessment every week for skin complications then re-assessment every 6 months for two years. The RTOG/European Organisation for Research and Treatment of Cancer Radiation Morbidity Scoring Scheme scored skin, subcutaneous, and pulmonary side effects. Echocardiography of left-sided patients was repeated two months after radiation. A fall of more than 10% in ejection fraction was considered as a

	significant reduction in the LVEF whether the patient was symptomatic or not. Lymphoedema was monitored by measuring the arm circumference at 10 cm above and below the olecranon process of the ulna. Measurements were taken at the end of radiation 6 months, one year and two years. Suspected injury to the brachial plexus was evaluated by MRI.

Study arms

39Gy/13 fractions/2.6 weeks (N = 50)
Treatment was administered at 5 fractions per week

42.4Gy/16 fractions/3.2 weeks (N = 50)
Treatment was administered at 5 fractions per week

Characteristics

Arm-level characteristics

Characteristic	39Gy/13 fractions/2.6 weeks (N = 50)	42.4Gy/16 fractions/3.2 weeks (N = 50)
median age Median (IQR)	49 (30 to 66)	45 (30 to 65)
stage I No of events	n = 3 ; % = 6	n = 3 ; % = 6
Stage II No of events	n = 21 ; % = 42	n = 17 ; % = 34
Stage III No of events	n = 26 ; % = 52	n = 30 ; % = 60
Hormonal therapy No of events	n = 33 ; % = 66	n = 37 ; % = 74
Chemotherapy No of events	n = 47 ; % = 94	n = 49 ; % = 98

Risk of Bias Assessment (Cochrane Risk of Bias tool 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Randomisation, allocation concealment and blinding details were not reported, as such the effects of assignment to intervention, effects of randomisation are not accounted for.)*
Overall bias and Directness	Overall Directness	Directly applicable

FAST Brunt, 2020

Bibliographic Reference	Brunt, A.M.; Haviland, J.S.; Sydenham, M.; Agrawal, R.K.; Algurafi, H.; Alhasso, A.; Barrett-Lee, P.; Bliss, P.; Bloomfield, D.; Bowen, J.; Donovan, E.; Goodman, A.; Harnett, A.; Hogg, M.; Kumar, S.; Passant, H.; Quigley, M.; Sherwin, L.; Stewart, A.; Syndikus, I.; Tremlett, J.; Tsang, Y.; Venables, K.; Wheatley, D.; Bliss, J.M.; Yarnold, J.R.; Ten-year results of fast: A randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer; Journal of Clinical Oncology; 2020; vol. 38 (no. 28); 3261-3272

Study details

Secondary publication of another included study- see primary study for details	The primary publication of Fast trials
Other publications associated with this study included in review	Yarnold 2011
Trial registration number and/or trial name	ISRCTN62488883
Study type	Randomised controlled trial (RCT)
Study location	United Kingdom
Study setting	In hospital
Study dates	Between October 2004 and March 2007
Sources of funding	The Institute of Cancer Research UK
Inclusion criteria	Age => 50 years Pathologic tumour size <3 cm
Exclusion criteria	Participants requiring mastectomy Cytotoxic therapy Participants with planned sequential boost or postmastectomy irradiation or an indication for nodal treatment
Intervention(s)	30Gy over 5 fractions over 5 weeks

Comparator	28.5Gy over 5 fractions over 5 weeks
Outcome measures	Local relapse Normal tissue effects Mortality Breast cancer-related mortality Loco-regional relapse Distant relapse
Number of participants	915 participants were randomised
Duration of follow-up	10 years
Loss to follow-up	3 participants in the intervention group 3 participants in the comparator group
Methods of analysis	Scores for change in photographic breast appearance at 2 and 5 years were modelled using generalised estimating equations (GEE). Mild and marked categories were combined because marked change was rare. Pairwise comparisons of mild/marked change between regimens were described by odds ratios (ORs, with 95% CI) obtained from the GEE models and the Wald test. Cross-sectional analyses of physician-assessed breast NTE at 5 and 10 years compared frequencies of moderate/ marked effects versus none/mild between pairs of regimens using risk ratios and risk differences (with 95% CI), and Fisher's exact test. Longitudinal analyses of moderate/marked physician-assessed NTE (versus none/mild) used GEE models including all annual assessments, comparing regimens across the whole follow-up period using OR (with 95% CI) and the Wald test; a term representing years of follow-up was included, enabling time trends to be modelled. Survival analysis methods analysed time to first moderate/marked physician-assessed NTE, including Kaplan-Meier plots and estimates of cumulative incidence rates. Hazard ratios (HRs, with 95% CI) were obtained from Cox proportional hazards regression, and regimens were compared using the log-rank test. Inconsistencies between the GEE and Cox models for some end points appeared to be due to more patients in the 28.5-Gy group having only 1 event, which has a greater influence on the time-to-event analysis (where only 1 event is needed) compared with the longitudinal models including all events over follow-up. Kaplan-Meier estimates (with 95% CI) of 5- and 10-year cumulative incidence of ipsilateral disease in the breast were calculated, and HR (with 95% CI) compared regimens obtained from Cox proportional hazards regression, with patients censored at date of distant metastases, new primary cancer (contralateral breast or non-breast), death, or date of last follow-up. Estimates of the a/b ratio for late NTE were obtained by fitting GEE models to all follow-up assessments (photographic and physician), including terms for total dose and total dose multiplied by fraction size. The a/b ratio was calculated as estimate for total dose/estimate for total dose 3 fraction size, with 95% CI estimated from the model (lower confidence limits were

	truncated at zero when the calculated limit was negative). Isoeffect doses in 2.0-Gy equivalents were calculated for the experimental regimens, and the 5-fraction regimen estimated to be isoeffective with 50 Gy/25 fractions was derived. All analyses were performed on an intention-to-treat basis, from a database snapshot taken on July 17, 2018; Stata version 15 (StataCorp, College Station, TX) was used.
Additional comments	This was the pilot Fast study that compared 5 fraction regimens and informed the FAST-Forward trial protocol. All participants were women. Baseline characteristics were balanced. Radiation techniques: Patients lay supine on an inclined plane in a position that remained unchanged during imaging/simulation and treatment, verified by orthogonal laser beams. Clinical target volume included soft tissues of the whole breast down to deep fascia but not including underlying muscle, ribcage, overlying skin, or excision scar. Planning target volume included the entire breast with 1-cm margins to palpable breast tissue. Medial and lateral borders did not normally extend beyond the anterior midline or the midaxilla. Margins were reduced in selected patients if the tumour bed did not encroach, to exclude or reduce the volume of heart and/or lung within the high-dose volume. The deep margin extended down to the deep fascia. Transverse cross-sections of the patient were taken through the centre of the planning target volume; a minimum of 5 slices was recommended, spaced appropriately. Sixteen out of 18 centres used full-dose compensation with computerised tomography; others used optical outlining devices capturing the central external contour supplemented by 2 additional outlines collected 1 cm inside the superior field border and 1 cm superior to the inframammary fold. The maximum thickness of lung included in the tangential field was 2 cm; cardiac shielding used multi-leaf collimator (MLC) or other technique. The dose distribution across the target volume was modified to ensure homogeneity within ICRU50/62 guidelines. Doses were prescribed to the reference point at/near the centre of the target volume. Maximum and minimum doses were # 10% of doses on the central plane after full dose compensation; where full dose compensation was not possible, maximum doses in the superior plane and plane through the inframammary fold were recorded. Three main dose compensation methods were used to improve dose homogeneity: (1) physical breast compensators, (2) simple forward-planned intensity-modulated radiation therapy (IMRT) MLC segment fields/field-in-field technique, and (3) inverse-planned IMRT MLC segment fields.

Study arms

28.5Gy/5 fractions (5.7Gy) (N = 305)

30Gy/5 fractions (6Gy) (N = 308)

Characteristics

Arm-level characteristics

Characteristic	28.5Gy/5 fractions (5.7Gy) (N = 305)	30Gy/5 fractions (6Gy) (N = 308)
Mean age (SD) Mean (SD)	62.7 (6.8)	62.9 (7.5)
Grade 1 No of events	n = 102 ; % = 33.4	n = 113 ; % = 36.7
Grade 2 No of events	n = 168 ; % = 55.1	n = 159 ; % = 51.6
Grade 3 No of events	n = 34 ; % = 11.1	n = 35 ; % = 11.4
Not known No of events	n = 1 ; % = 0.3	n = 1 ; % = 0.3
None No of events	n = 30 ; % = 9.8	n = 37 ; % = 12
Tamoxifen No of events	n = 224 ; % = 73.4	n = 243 ; % = 78.9
Aromatase inhibitor No of events	n = 45 ; % = 14.8	n = 26 ; % = 8.4

Risk of Bias Assessment (Cochrane Risk of Bias tool 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(The trial reported details of randomisation and why intervention allocation was not blinded.)*
Overall bias and Directness	Overall Directness	Directly applicable

FAST-Forward Brunt, 2020

Bibliographic Reference	Murray Brunt, A.; Haviland, J.S.; Wheatley, D.A.; Sydenham, M.A.; Alhasso, A.; Bloomfield, D.J.; Chan, C.; Churn, M.; Cleator, S.; Coles,

C.E.; Harnett, A.; Kirby, A.M.; Kirwan, C.C.; Morris, C.; Nabi, Z.; Sawyer, E.; Somaiah, N.; Stones, L.; Syndikus, I.; Bliss, J.M.; Yarnold, J.R.; Armstrong, A.; Bliss, J.; Bloomfield, D.; Bowen, J.; Brunt, M.; Chantler, H.; Coles, C.; Donovan, E.; Goodman, A.; Griffin, S.; Haviland, J.; Hopwood, P.; Kirby, A.; Kirk, J.; MacLennan, M.; Sculphur, M.; Sinclair, J.; Sydenham, M.; Tremlett, J.; Venables, K.; Wheatley, D.; Yarnold, J.; Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial; The Lancet; 2020; vol. 395 (no. 10237); 1613-1626

Study details

Secondary publication of another included study- see primary study for details	Primary study
Other publications associated with this study included in review	Brunt 2021 Brunt 2016
Trial registration number and/or trial name	NCT00107497 - FAST Forward
Study type	Randomised controlled trial (RCT)
Study location	United Kingdom
Study setting	In hospital
Study dates	Between November 24th, 2011, and June 19th 2014
Sources of funding	Cancer Research UK
Inclusion criteria	Age =>18 years old Invasive carcinoma of the breast (T1-3, pN0-1, M0) Breast conserving surgery or mastectomy (reconstruction allowed) Complete microscopic excision of primary tumour
Exclusion criteria	Participants receiving concurrent chemotherapy Participants requiring nodal radiotherapy
Intervention(s)	1. 26 Gy over 5 fractions over 1 week

	2. 27 Gy over 5 fractions over 1 week
Comparator	40 Gy over 15 fractions over 3 weeks
Outcome measures	Local relapse Quality of life Adverse events Normal tissue effects Mortality Breast cancer-related mortality Loco-regional relapse Distant realpse
Number of participants	4096 participants
Duration of follow-up	10 years. The study currently reports 5-year results only. 10-year follow-up data is yet to be published.
Loss to follow-up	7 participants lost to follow-up
Methods of analysis	Scores for change in photographic breast appearance at 2 and 5 years were modelled using generalized estimating equations (GEE). Mild and marked categories were combined, because marked change was rare. Pairwise comparisons of mild/marked change between regimens were described by odds ratios (ORs, with 95% CI) obtained from the GEE models and the Wald test. Cross-sectional analyses of physician-assessed breast NTE at 5 and 10 years compared frequencies of moderate/ marked effects versus none/mild between pairs of regimens using risk ratios and risk differences (with 95% CI), and Fisher's exact test. Longitudinal analyses of moderate/marked physician-assessed NTE (v none/mild) used GEE models including all annual assessments, comparing regimens across the whole follow-up period using OR (with 95% CI) and the Wald test; a term representing years of follow-up was included, enabling time trends to be modelled. Survival analysis methods analysed time to first moderate/marked physician-assessed NTE, including Kaplan-Meier plots and estimates of cumulative incidence rates. Hazard ratios (HRs, with 95% CI) were obtained from Cox proportional hazards regression, and regimens were compared using the log-rank test. Inconsistencies between the GEE and Cox models for some end points appeared to be due to more patients in the 28.5- Gy group having only 1 event, which has a greater influence on the time-to-event analysis (where only 1 event is needed) compared with the longitudinal models including all events over follow-up. Kaplan-Meier estimates (with 95% CI) of 5- and 10-year cumulative incidence of ipsilateral disease in the breast were calculated, and HR (with 95% CI) compared regimens obtained from Cox proportional hazards regression, with patients censored at date of distant metastases, new primary cancer

	(contralateral breast or non-breast), death, or date of last follow-up. Estimates of the a/b ratio for late NTE were obtained by fitting GEE models to all follow-up assessments (photographic and physician), including terms for total dose and total dose multiplied by fraction size. The a/b ratio was calculated as estimate for total dose/estimate for total dose 3 fraction size, with 95% CI estimated from the model (lower confidence limits were truncated at zero when the calculated limit was negative). Isoeffect doses in 2.0-Gy equivalents were calculated for the experimental regimens, and the 5-fraction regimen estimated to be isoeffective with 50 Gy/25 fractions was derived. All analyses were performed on an intention-to-treat basis, from a database snapshot taken on July 17, 2018; Stata version 15 (StataCorp, College Station, TX) was used.
Additional comments	Baseline characteristics were balanced. The study included 12 males in the randomised population. Radiation techniques: The whole breast clinical target volume, including the soft tissues from 5 mm below the skin surface to the deep fascia, was either established from field-based tangential fields or the volume was contoured prospectively. Postmastectomy chest wall clinical target volume encompassed post-surgical skin flaps and underlying soft tissues to the deep fascia; both excluded underlying muscle and rib cage. Surgeons were strongly encouraged to mark the tumour cavity walls with titanium clips or gold seeds at the time of breast conservation surgery in order to aid placement of tangential fields and delineation of tumour bed. A typical margin of 10 mm was added around the breast or chest wall clinical target volume accounting for set-up error, breast swelling, and breathing to create a planning target volume (PTV). For all patients, a full 3D CT set of outlines covering the whole breast and organs at risk was collected with a slice separation up to 5 mm, and organs at risk were outlined prospectively. A tangential opposing pair beam arrangement encompassed the whole breast or chest wall PTV, minimising the ipsilateral lung and heart exposure. The treatment plan was optimised with 3D dose compensation to achieve the following PTV dose distribution: more than 95% of PTV received 95% of the prescribed dose, less than 5% of PTV received 105% or more, less than 2% of PTV received 107% or more, and a global maximum of less than 110%. Dose constraints for the control group were as follows: volume of ipsilateral lung receiving 12 Gy less than 15%, and volume of heart receiving 2 Gy less than 30% and that receiving 10 Gy less than 5%. Dose constraints for the five-fraction regimens were as follows: volume of ipsilateral lung receiving 8 Gy less than 15%, and volume of heart receiving 1·5 Gy less than 30% and that receiving 7 Gy less than 5%. X-ray beam energies for treatment were 6 MV or 10 MV, but a mixture of energies—e.g., 6 MV and 10–15 MV—was allowed for larger patients, assessed on a case-by-case basis. Tumour bed boost was delivered via electrons or photons. Verification was done using electronic portal imaging using MV or kV x-rays. Control group treatment verification was required for at least three fractions in the first week with correction for any systematic error and then once weekly with a tolerance of 5 mm. The five-fraction regimens required verification imaging for each fraction with

	recommendations to correct all measured displacements. A comprehensive quality assurance programme involved every radiotherapy centre before trial activation and continued throughout trial accrual; this was coordinated by the UK Radiotherapy Trials Quality Assurance team based at Mount Vernon Hospital, Northwood, UK. [OB1]27Gy/5 fractions not 15 fractions; change

Study arms

40Gy/15 fractions/3 weeks (N = 1361)

27Gy/5 fractions/1 week (N = 1367)

26Gy/5 fractions/1 week (N = 1368)

Characteristics

Arm-level characteristics

Characteristic	40Gy/15 fractions/3 weeks (N = 1361)	27Gy/5 fractions/1 week (N = 1367)	26Gy/5 fractions/1 week (N = 1368)
Age Median (IQR)	50 (53 to 66)	61 (53 to 67)	61 (52 to 66)
Female No of events	n = 1355 ; % = 99.6	n = 1365 ; % = 99.9	n = 1362 ; % = 99.6
Male No of events	n = 6 ; % = 0.4	n = 2 ; % = 0.1	n = 4 ; % = 0.3
Unknown No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 2 ; % = 0.1
Breast conservation therapy No of events	n = 1270 ; % = 9.3	n = 1278 ; % = 93.5	n = 1284 ; % = 93.9
Mastectomy No of events	n = 91 ; % = 6.7	n = 89 ; % = 6.5	n = 84 ; % = 6.1
Chemotherapy No of events	n = 333 ; % = 24.5	n = 324 ; % = 23.7	n = 370 ; % = 27.1
Endocrine therapy No of events	n = 1169 ; % = 96.1	n = 1186 ; % = 95.9	n = 1157 ; % = 96.7
Grade 1	n = 315 ; % = 23.1	n = 315 ; % = 23	n = 300 ; % = 21.9

Characteristic	40Gy/15 fractions/3 weeks (N = 1361)	27Gy/5 fractions/1 week (N = 1367)	26Gy/5 fractions/1 week (N = 1368)
No of events			
Grade 2 No of events	n = 660 ; % = 48.5	n = 663 ; % = 48.5	n = 690 ; % = 50.4
Grade 3 No of events	n = 386 ; % = 28.4	n = 389 ; % = 28.5	n = 378 ; % = 27.6

Risk of Bias Assessment (Cochrane Risk of Bias tool 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(Randomisation and masking details were reported. Participants and assessors were aware of the intervention, but this knowledge could not impact assessment of the outcomes.)*
Overall bias and Directness	Overall Directness	Directly applicable

START Haviland, 2013

Bibliographic Reference	Haviland, J.S.; Owen, J.R.; Dewar, J.A.; Agrawal, R.K.; Barrett, J.; Barrett-Lee, P.J.; Dobbs, H.J.; Hopwood, P.; Lawton, P.A.; Magee, B.J.; Mills, J.; Simmons, S.; Sydenham, M.A.; Venables, K.; Bliss, J.M.; Yarnold, J.R.; The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials; The Lancet Oncology; 2013; vol. 14 (no. 11); 1086-1094

Study details

Secondary publication of another included study- see primary study for details	START A - 2008 START B- 2008 Hopwood - 2010 Haviland - 2016 Haviland - 2018
Other publications associated with this study	START A - 2008 START B- 2008 Hopwood - 2010

included in review	Haviland - 2016 Haviland - 2018
Trial registration number and/or trial name	START trial - ISCRCTN59368779
Study type	Randomised controlled trial (RCT)
Study location	United Kingdom
Study setting	In hospital
Study dates	From 1999 to 2002
Sources of funding	Cancer Research UK UK Medical Research Council UK Department of Health
Inclusion criteria	Age =>18 years old Invasive carcinoma of the breast (T1-3, pN0-1, M0) Participants who did not have an immediate reconstruction Women with operable invasive breast cancer, requiring radiotherapy after primary surgery (with clear tumour margins =>1mm)
Exclusion criteria	Participants with planned sequential boost or postmastectomy irradiation or an indication for nodal treatment
Intervention(s)	1. 41.6Gy/13 fractions/5 weeks
Comparator	1. 39Gy/13 fractions/5 weeks 2. 50Gy/25 fractions/5 weeks (data not reported as it does not meet review protocol criteria)
Outcome measures	Local relapse Normal tissue effects Quality of life Adverse events Mortality Breast cancer-related mortality Loco-regional relapse Distant relapse

Number of participants	2236 participants
Duration of follow-up	10 years
Loss to follow-up	None
Methods of analysis	START-A had a target sample size of 2000 patients to provide 80% power to detect a difference of 5% in the local-regional relapse rate between the control and each test schedule (two-sided α=0·05). START-B had a target of 1840 patients to provide 95% power to exclude an increase of 5% in the local regional relapse rate in the 40 Gy regimen compared with control (one-sided α=0·025). A survival analysis was used in the methods to compare endpoint occurrences between fractionation schedules. Length of follow-up was calculated as time from randomisation until time of first event or last follow-up assessment, whichever occurred first. Patients were still evaluable for local-regional relapse after distant relapse. For the physician assessments of normal tissue effects, an event was defi ned as the first occurrence of a moderate or marked symptom (graded as “quite a bit” or “very much”). Kaplan-Meier estimates of 10-year rates (with 95% CIs) were calculated and the Wald test was used to compare regimens. Cox proportional hazards regression models were used to obtain crude hazard ratios (HRs) and 95% CIs. Both one-sided and two-sided 95% CIs were calculated for the absolute difference in local-regional relapse rates because the upper limit is of greater clinical interest, in view of concern about a possible excess risk caused by hypofractionated regimens. Kaplan-Meier survival curves were plotted and cumulative hazard rates according to fractionation regimen, censoring at the median length of follow-up. Direct estimates of the α/β value for breast cancer and the dose-limiting normal tissues were obtained from Cox proportional hazards regression models containing terms for total dose, and total dose multiplied by dose per fraction as well as known prognostic factors (appendix). The α/β value is derived from an empirical model that describes sensitivity of a normal or malignant tissue to fraction size; α/β values less than 10 Gy indicate relative sensitivity to fraction size. A meta-analyses of START-A, START-B, and the START pilot trial was conducted by fitting the Cox proportional hazards regression models to all individual patient data from the three trials. The analyses were stratified by trial to enable baseline hazards to vary according to trial but assuming equal treatment effects. The analyses included all enrolled patients on an intention-to-treat basis. Analyses were done with SPSS (version 19) and Stata (version 9).
Additional comments	This 10-year publication combines results from all START trials. Only START A results meet the review protocol criteria for this evidence review. As such, only data from the relevant arms of START A were reported. Data from the 50 Gy/25 fractions arm was not reported as it does not meet the criteria in the review protocol and is not in line with current practice in the UK. All participants were female and baseline characteristics were balanced. Sequential boosts were allowed at 10Gy/5 fractions (pre-specified)

	Radiation techniques: Patients lay in a supine treatment position. The planning target volume was defi ned as the whole breast with a 1 cm margin to palpable breast tissue; where regional radiotherapy was indicated, the planning target volume was supraclavicular nodes with or without axillary chain with a 1 cm margin. The decision to give regional radiotherapy was made before randomisation and was only used in 14% of patients. In two patients prescribed radiotherapy to the breast and supraclavicular fossa and randomised to the 41·6 Gy regimen, the total dose administered to the supraclavicular fossa was reduced to 39 Gy because of the sensitivity of brachial plexus to fraction size. Most patients were treated with 6 MV x-rays, although treatment with higher energies or cobalt γ-rays was allowed after discussion with the START Trial radiotherapy quality assurance team. Planning protocols were specified at the time of notification of participation into the study and had to conform to the minimum quality criteria described in the START Trial A protocol. Planning protocols varied slightly between centres, but within each centre they were identical in each fractionation group. Doses were prescribed to international reference points. Departments were required to have a protocol specifying whether patients who had breast-conserving surgery would receive a boost to the tumour bed, and to use an electron fi eld of appropriate energy to deliver 10 Gy in five daily fractions to the 100% isodose after initial radiotherapy. All centres submitted details of the standard radiotherapy technique, after which a visit by the quality assurance team checked dosimetric measurements in a 2D and 3D breast phantom, including the junction region between supraclavicular fossa and tangential breast or chest wall fields. The mean difference between prescribed and measured dose in a phantom was 2·1%. Additionally, a third of the radiotherapy treatment plans were collected and analysed by the quality assurance team to ensure compliance with the protocol in terms of prescription point, dose homogeneity, and lung depth. A random sample of patients had in-vivo thermoluminescent dosimeter measurements taken. The protocol allowed for a dose variation (in the planning target volume) between 95% and 105% of that at the reference point on the central axis. Lung depth data was obtained by the radiotherapy quality assurance programme, and analysis indicated that most patients had less than 2 cm of lung within the treatment volume. These results confirmed a good compliance with the technical aspects of the trial protocol

Study arms

41.6Gy/13 fractions/5 weeks (N = 750)

39Gy/13 fractions/5 weeks (N = 737)

Characteristics

Arm-level characteristics

Characteristic	41.6Gy/13 fractions/5 weeks (N = 750)	39Gy/13 fractions/5 weeks (N = 737)
Mean age (SD)	57 (10.7)	57.1 (10.5)

Characteristic	41.6Gy/13 fractions/5 weeks (N = 750)	39Gy/13 fractions/5 weeks (N = 737)
Mean (SD)		
Breast conserving surgery No of events	n = 641 ; % = 85.5	n = 628 ; % = 85.2
Mastectomy No of events	n = 109 ; % = 14.5	n = 109 ; % = 14.8
Grade 1 No of events	n = 150 ; % = 20	n = 149 ; % = 20.2
Grade 2 No of events	n = 379 ; % = 50.5	n = 368 ; % = 49.9
Grade 3 No of events	n = 207 ; % = 27.6	n = 210 ; % = 28.5
Tamoxifen/no chemotherapy No of events	n = 218 ; % = 55.7	n = 376 ; % = 51
Chemotherapy/no tamoxifen No of events	n = 77 ; % = 10.3	n = 82 ; % = 11.1
Tamoxifen + chemotherapy No of events	n = 187 ; % = 25	n = 188 ; % = 25.5
Other endocrine therapy No of events	n = 13 ; % = 1.7	n = 17 ; % = 2.3
None No of events	n = 53 ; % = 7.1	n = 67 ; % = 9.1
Not known No of events	n = 2 ; % = 0.2	n = 7 ; % = 0.9

Risk of Bias Assessment (Cochrane Risk of Bias tool 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(The study was randomised but treatment allocation was not blinded from participants or assessors. However, to mitigate*

Section	Question	Answer
		for any potential bias a separate observer (who was blinded to treatment allocation) was designated to measure outcomes.)
Overall bias and Directness	Overall Directness	Directly applicable

Ivanov, 2022

Bibliographic Reference	Ivanov, O.; Milovancev, A.; Petrovic, B.; Prvulovic Bunovic, N.; Licina, J.; Bojovic, M.; Koprivica, I.; Rakin, M.; Marjanovic, M.; Ivanov, D.; Lalic, N.; Ultra-Hypofractionated vs. Moderate Fractionated Whole Breast Three-Dimensional Conformal Radiotherapy during the COVID-19 Pandemic; Medicina (Kaunas, Lithuania); 2022; vol. 58 (no. 6)

Study details

Secondary publication of another included study- see primary study for details	Not applicable
Other publications associated with this study included in review	Not applicable
Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Serbia
Study setting	In hospital
Study dates	Between March 2020 and July 2020
Sources of funding	Not reported
Inclusion criteria	Invasive carcinoma of the breast (T1-3, pN0-1, M0) Requiring radiotherapy with previously preserving surgery

	Complete macroscopic resection of invasive carcinoma
Exclusion criteria	Age under 40 years Participants with planned sequential boost or postmastectomy irradiation or an indication for nodal treatment
Intervention(s)	Participants were randomised to 26Gy in 5 fractions over 1 week
Comparator	Participants were randomised to 40Gy in 15 fractions over 3 weeks
Outcome measures	Normal tissue effects Includes: acute skin toxicity, subcutaneous tissue toxicity and cosmetic results
Number of participants	60 participants
Duration of follow-up	18 months
Loss to follow-up	Not reported
Methods of analysis	Descriptive statistics are presented as percentages, mean ± SD or median and interquartile range (IQR). Independent-Samples t-test was used to compare age and other continuous variables between two groups. Chi-squared and Fisher-Freeman-Halton tests were used to identify differences for categorical variables between two groups where appropriate. Mann-Whitney U test was used to compare doses to the lung, heart, and left anterior descending artery between two groups. Shapiro Wilk test was used to test normality of distribution. p-value less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS 23.0 for Windows (IBM Co., Armonk, NY, USA) and Jamovi V2.2.2 computer statistical software. Retrieved from https://www.jamovi.org (accessed on 1 April 2022), Sydney, Australia.
Additional comments	All participants were female. Radiation techniques: The treatment protocol was the same for the 5-fractions and 15-fractions group. Active breathing control was used for patients with left-sided breast cancer. Patients were scanned in supination with a breast immobilization device (Wing-board, Civco, Kalona, IA, USA). A spiral CT simulation was performed from the mandible angle to the 5 cm below the visible breast tissue with 2mm slice thickness. All the scanned images were uploaded to the treatment planning system (TPS) Eclipse and Aria, Varian Medical Systems INC, Palo Alto CA USA, or Monaco TPS ver.5.11.02, Elekta, Stockholm, Sweden. Target and organs at risk delineation were according to the ICRU 50 and 62 recommendations. Clinical target volume (CTV) included whole breast tissue and margin of 10 mm was added accounting for set-up error to create a planning target volume (PTV). Delineation of lungs, heart, LAD, skin and bone marrow was performed as organs at risk (OAR) constrains were V8 < 15% (ideal) and V8 < 17% (acceptable) for the ipsilateral lung, V1,5 Gy < 30%, and V7 < 5% for the heart. Mean heart dose had to be less than 3 Gy. The organ at risk (OAR) constraints are based on FAST Forward trial (1 week regime) and START trials (3-week

	regime). Median doses (D mean) to the OAR and particular volumes were measured in both groups. For the ipsilateral lung, MLD, total volume expressed in cm3 , V20 and V8 volumes were measured. Median dose, total heart volume and V8 were recorded for left-sided breast cancer patients' subgroup of 5-fractions group and whole 15-fractions group. Median and maximal doses for the LAD were measured. Verification imaging was obtained for each fraction in 5-fractions group, using MV or kV X-rays. In 15-fractions group verification imaging was obtained according to the radiation oncologist preference, minimally for the first three fractions following once-weekly imaging.

Study arms

26Gy/5 fractions/1 week (N = 27)

40Gy/15 fractions/3 weeks (N = 33)

Characteristics

Arm-level characteristics

Characteristic	26Gy/5 fractions/1 week (N = 27)	40Gy/15 fractions/3 weeks (N = 33)
Mean age (SD) Mean (SD)	62.8 (8.6)	63.6 (9.8)
Stage 1 No of events	n = 11 ; % = 40.7	n = 13 ; % = 39.4
Stage 2 No of events	n = 16 ; % = 59.3	n = 20 ; % = 60.6

Risk of Bias Assessment (Cochrane Risk of Bias tool 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(The study did not report details on randomisation, masking and allocation concealment as such it may have been difficult to fully assess the effect of assignment to the intervention)*
Overall bias and Directness	Overall Directness	Directly applicable

Shahid, 2009

Bibliographic Reference	Shahid, A.; Athar, M.A.; Asghar, S.; Zubairi, T.; Murad, S.; Yunas, N.; Post mastectomy adjuvant radiotherapy in breast cancer: A comparision of three hypofractionated protocols; Journal of the Pakistan Medical Association; 2009; vol. 59 (no. 5); 282-287

Study details

Secondary publication of another included study- see primary study for details	Not applicable
Other publications associated with this study included in review	Not applicable
Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Pakistan
Study setting	In hospital
Study dates	Between 1998 and 2004
Sources of funding	Not reported
Inclusion criteria	Female participants between 20-60 years Participants with T2-T4 primary lesions and N1, N2, N3 Nx, N0 nodal status Post mastectomy status with or without axillary dissection
Exclusion criteria	Not reported
Intervention(s)	1. 25Gy in 10 fractions/2 weeks 2. 27Gy in 5 fractions/1 week
Comparator	1. 40Gy in 15 fractions/3 weeks
Outcome measures	Local relapse Disease free survival Adverse events

	Including but not limited to the incidence of lymphoedema, skin toxicity, cardiac toxicity. Normal tissue effects
Number of participants	300 participants
Duration of follow-up	6 months
Loss to follow-up	Not reported
Methods of analysis	Pearson Chi-square test was used to determine the statistical significance between the three arms. A p-value of <0.05 was regarded as statistically significant. The data was analysed using SPSS version 14.
Additional comments	All participants were female. Study does not report details of randomisation or follow-up period. Radiation techniques: Patients were planned on 2D planning system and treated on Co 60. Two tangential portals for the chest wall were planned on simulator with lung slice not exceeding 2.5 cm. Direct anterior filed to the supraclavicular and axillary areas was planned with 0.5 cm gap junction from tangential fields. Superior divergence of tangential portals was eliminated by 5° couch rotation. Inferior border divergence of anterior nodal field was removed by moving the gantry a few degrees following a 90° couch rotation. Head of humerus was shielded. A posterior axillary boost was added to compensate the midline dose twice a week treated at 80 cm SSD. The lung and heart slice included in the tangential portals and brachial plexus in the nodal fields received the full prescribed dose.

Study arms

27Gy/5 fractions/1 week (N = 100)

35Gy/10 fractions/2 weeks (N = 100)

40Gy/15 fractions/ 3 weeks (N = 100)

Characteristics

Arm-level characteristics

Characteristic	27Gy/5 fractions/1 week (N = 100)	35Gy/10 fractions/2 weeks (N = 100)	40Gy/15 fractions/ 3 weeks (N = 100)
21–30 years No of events	n = 12 ; % = 12	n = 10 ; % = 10	n = 10 ; % = 10

Characteristic	27Gy/5 fractions/1 week (N = 100)	35Gy/10 fractions/2 weeks (N = 100)	40Gy/15 fractions/ 3 weeks (N = 100)
31-40 years No of events	n = 28 ; % = 28	n = 25 ; % = 25	n = 26 ; % = 26
41-50 years No of events	n = 30 ; % = 30	n = 33 ; % = 33	n = 32 ; % = 32
51–60 years No of events	n = 30 ; % = 30	n = 32 ; % = 32	n = 32 ; % = 32
Chemotherapy No of events	n = 41 ; % = 41	n = 39 ; % = 39	n = 38 ; % = 38

Risk of Bias Assessment (Cochrane Risk of Bias tool 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Details on randomisation and allocation concealment were not reported. Some baseline characteristics were reported in graphs so were difficult to extract in order to determine inter-group variation.)*
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E – Forest plots

Dose comparisons

Hypofractionation regimen 28.5Gy over 5 fractions (5 weeks) vs 30Gy over 5 fractions (5 weeks)

Figure 2: All-cause mortality

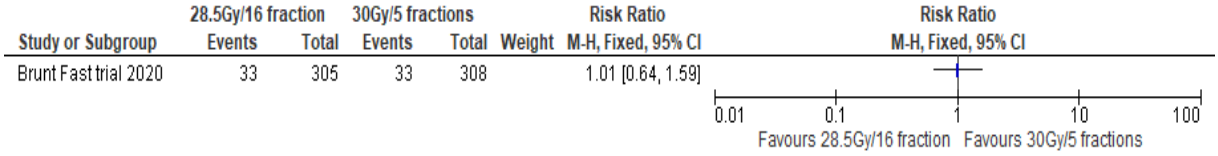


Figure 3: Breast-cancer related mortality

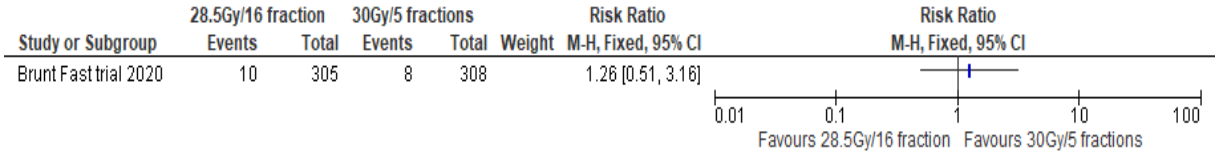


Figure 4: Local relapse

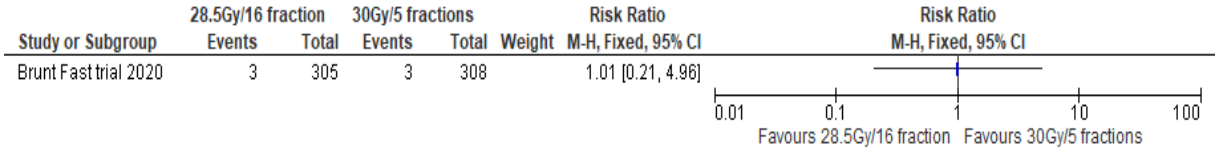


Figure 5: Loco-regional relapse

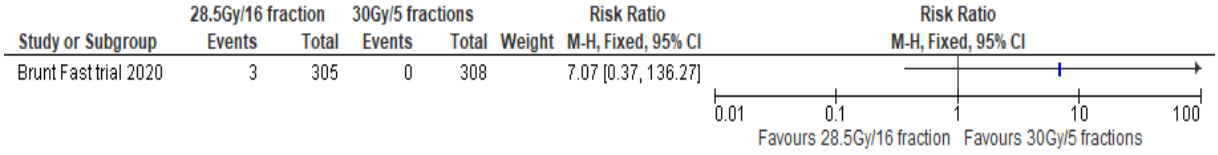


Figure 6: Distant relapse

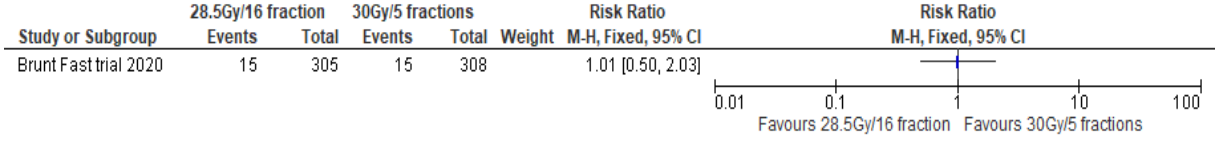


Figure 7: Adverse events

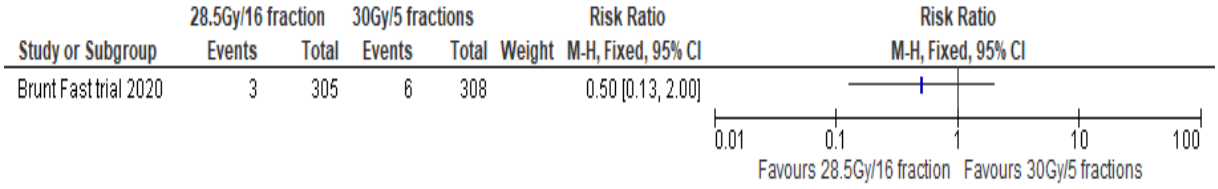
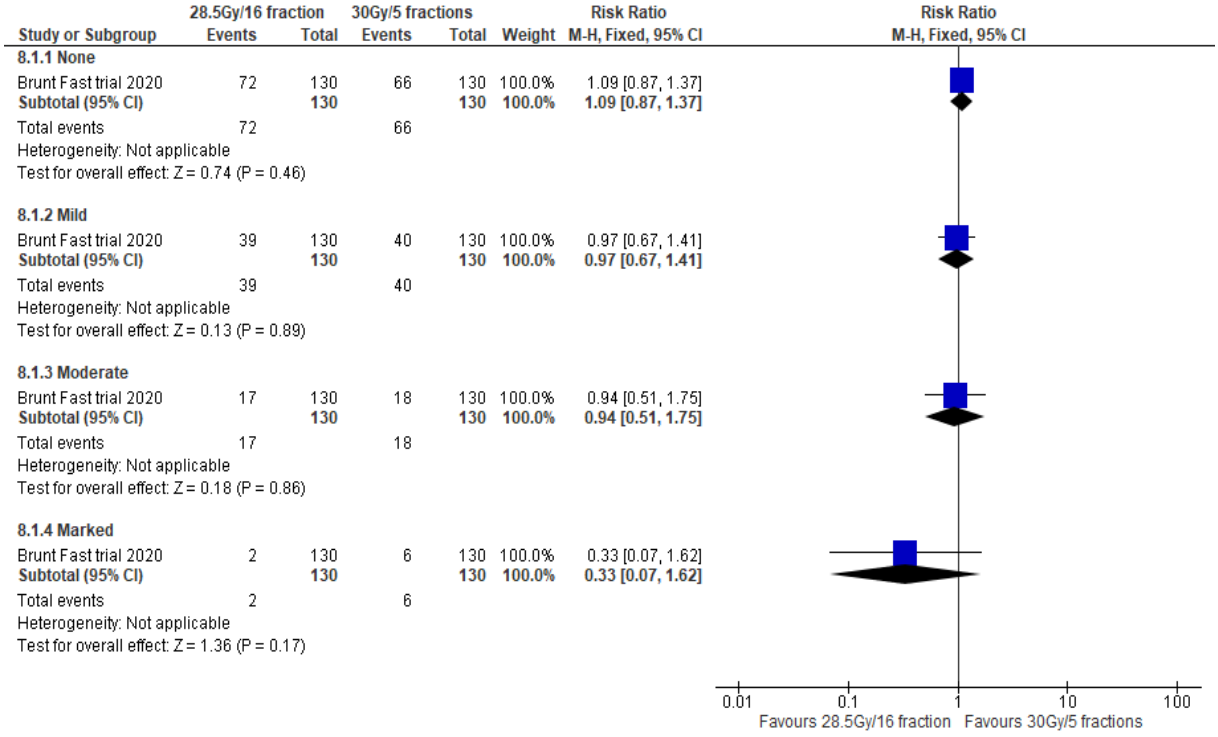


Figure 8: Normal tissue effects (G1-G4)



Dose and fraction comparisons

Hypofractionation regimen: 39Gy over 13 fractions (5 weeks) vs 41.6Gy over 16 fractions (5 weeks)

Figure 9: All-cause mortality

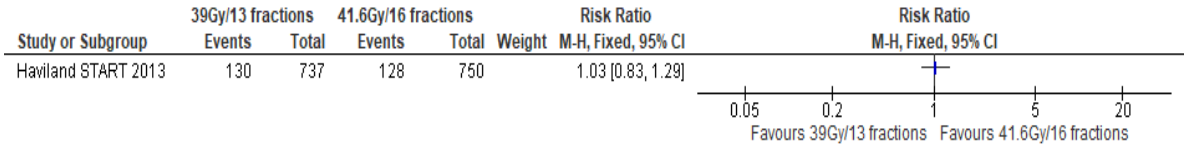


Figure 10: Local relapse

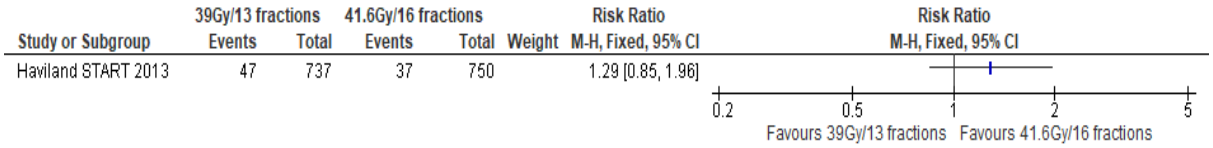


Figure 11: Loco-regional relapse

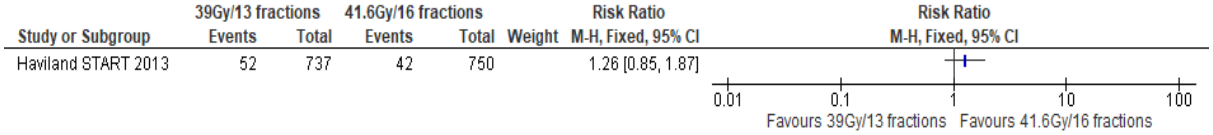


Figure 12: Distant relapse

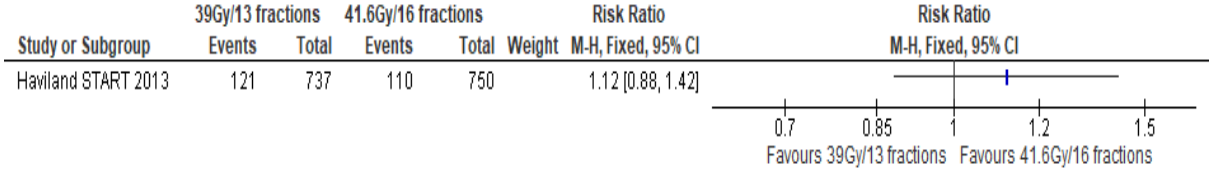


Figure 13: Normal tissue effects

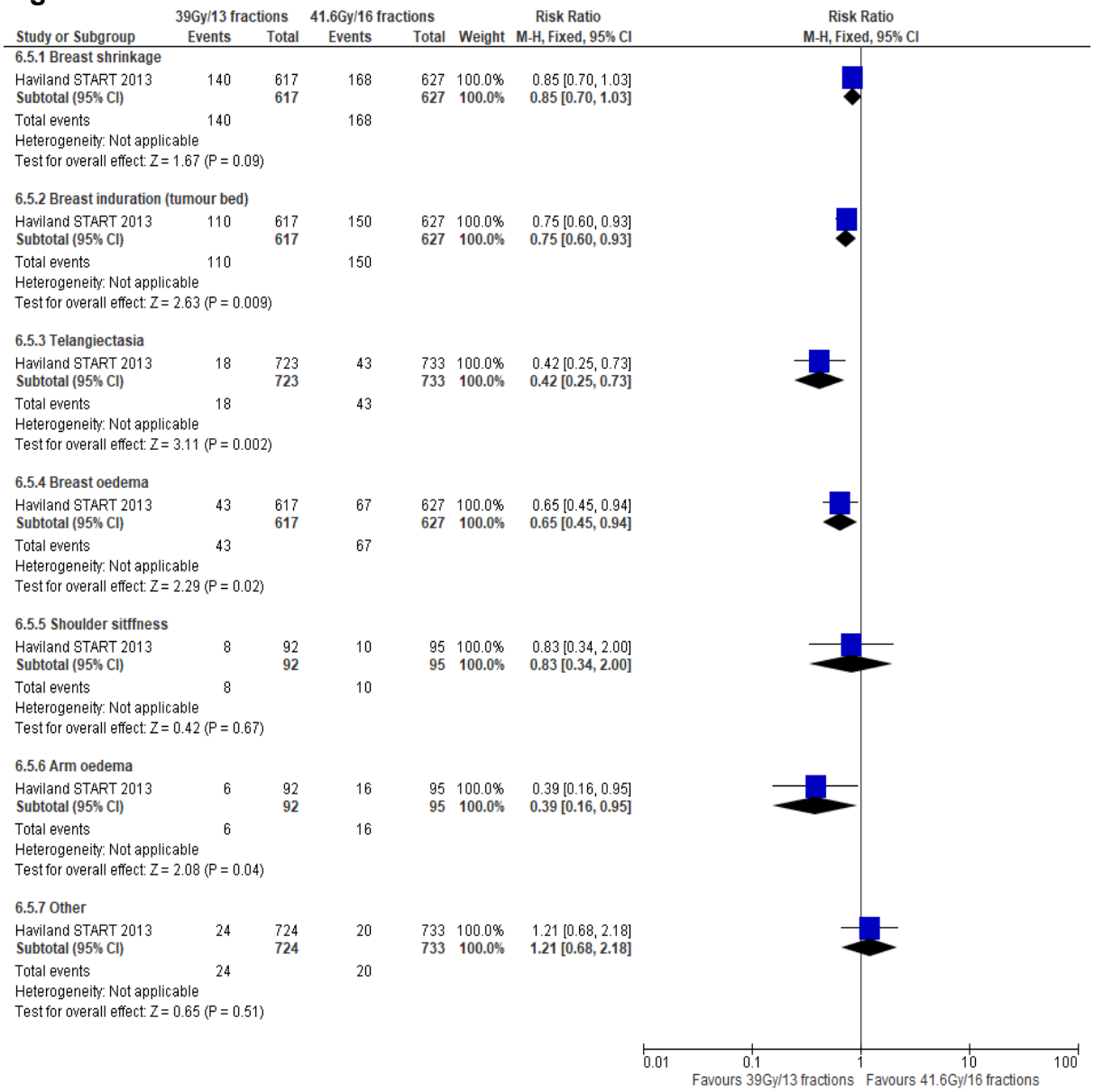
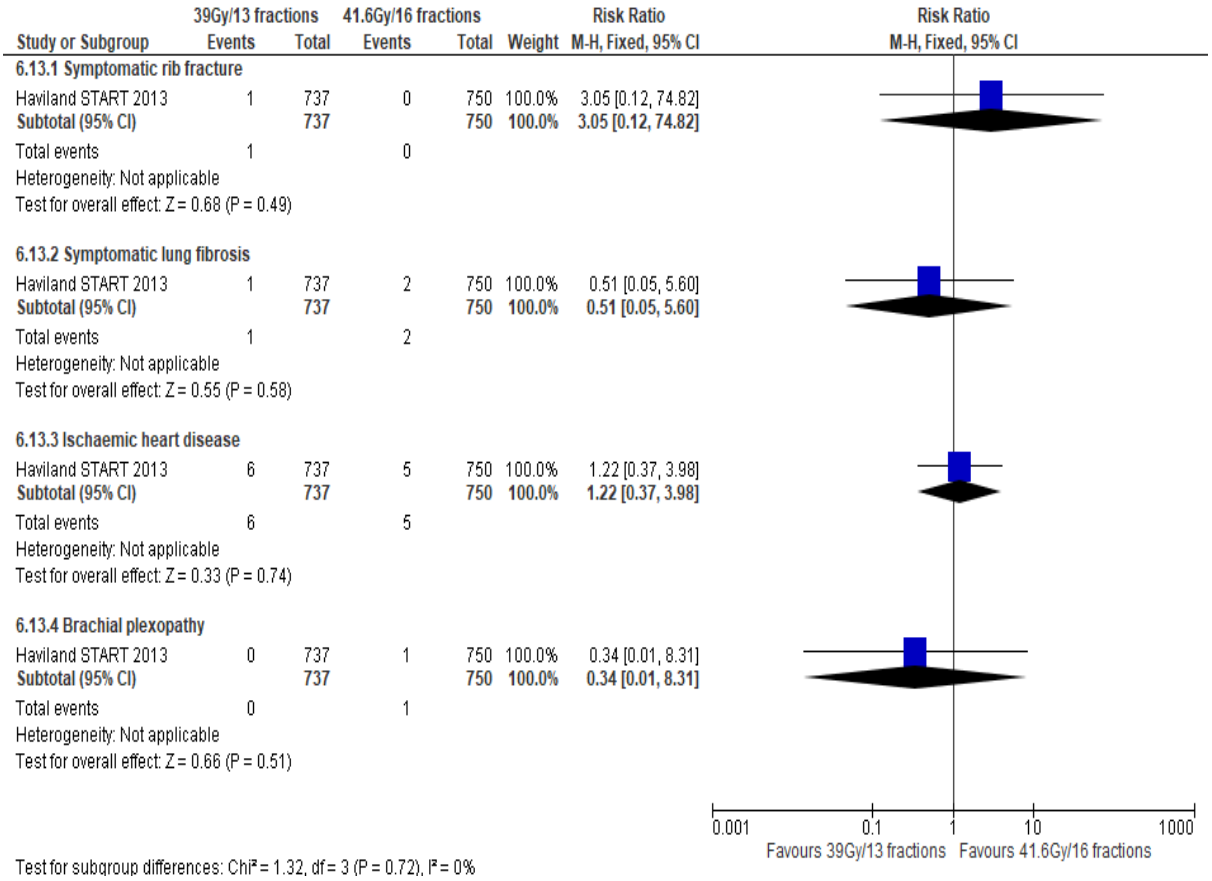


Figure 14: Adverse events



Dose, fraction and time period comparisons

Hypofractionation regimen: 42.4Gy over 16 fractions (3.2 weeks) vs 39Gy over 13 fractions (2.6 weeks)

Figure 15: Radiation dermatitis

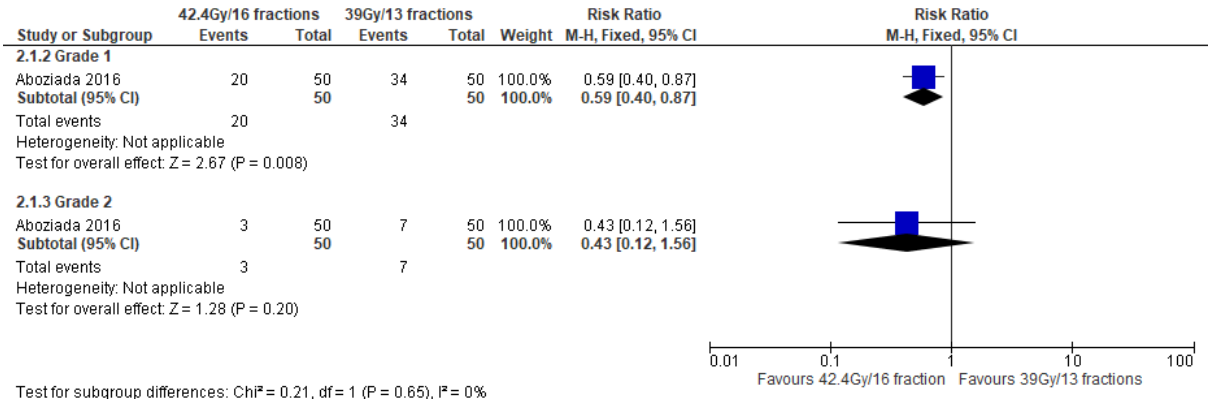


Figure 16: Acute pneumonitis

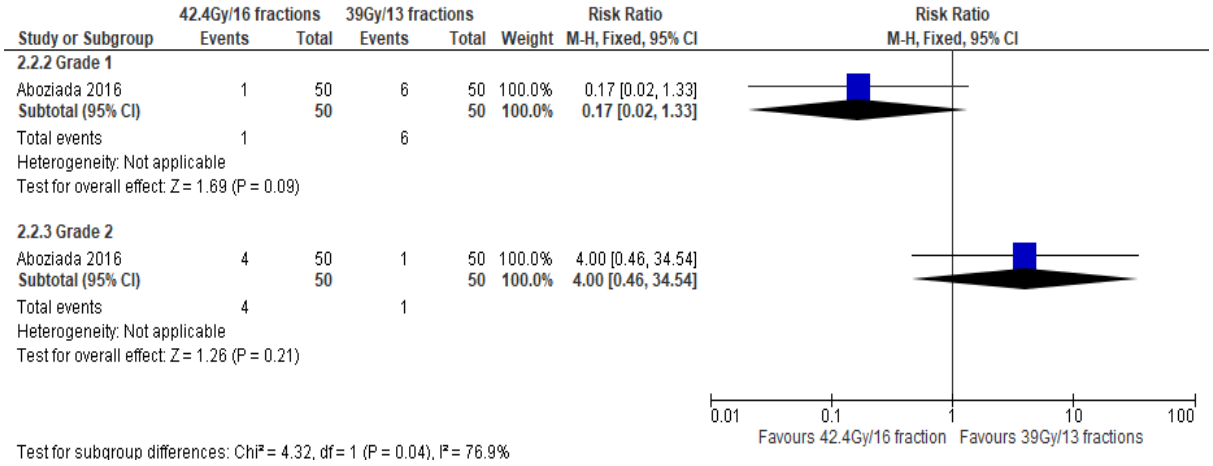


Figure 17: Subcutaneous fibrosis

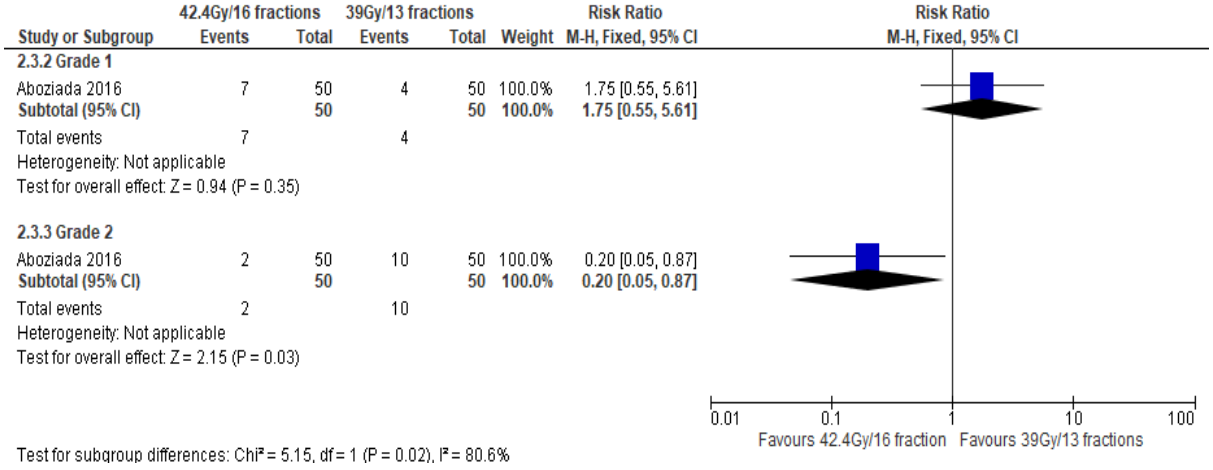
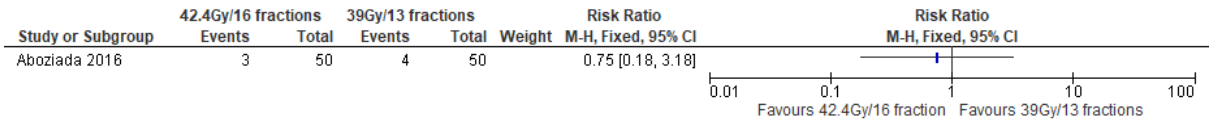
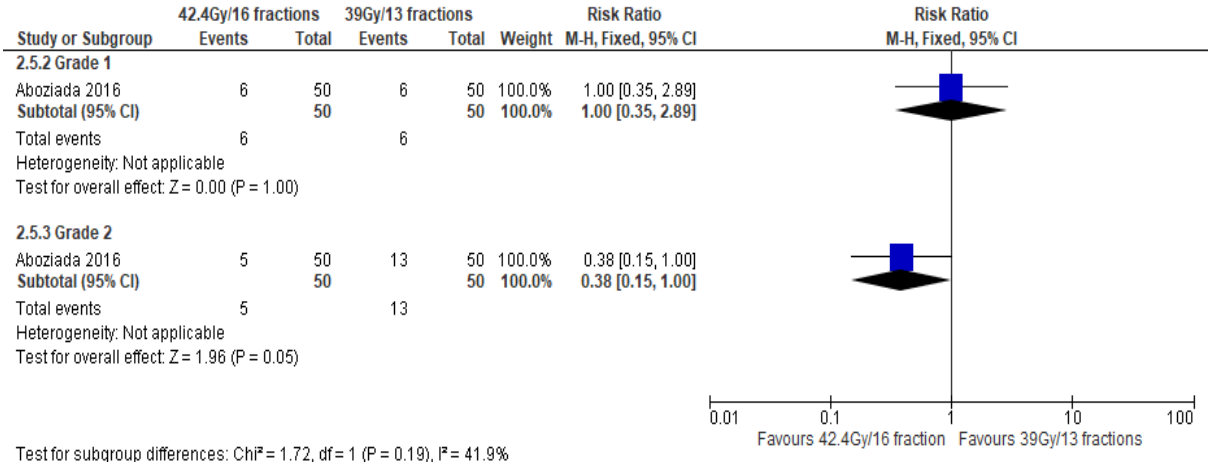


Figure 18: Cardiac toxicity



Cardiac toxicity: LVEF reduction >10%

Figure 19: Incidence of lymphoedema



Hypofractionation regimen: 40Gy over 15 fractions (3 weeks) vs 26Gy over 5 fractions (1 week)

Figure 20: All-cause mortality

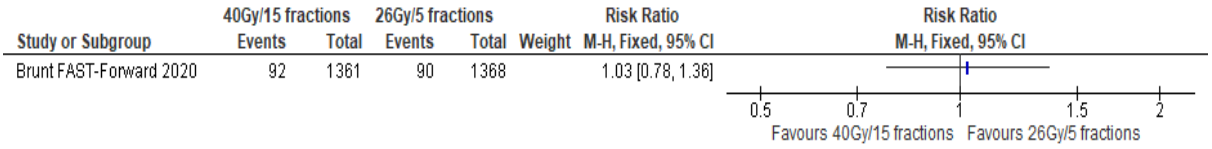


Figure 21: Breast cancer related mortality

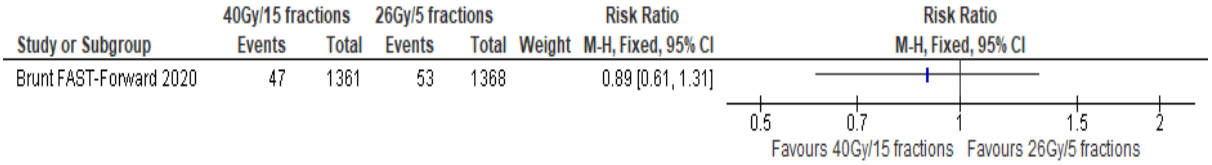


Figure 22: Local relapse

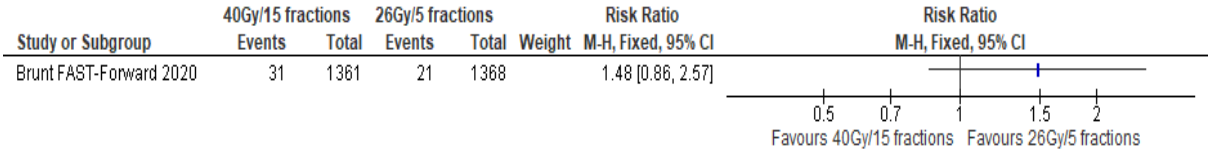


Figure 23: Loco-regional relapse

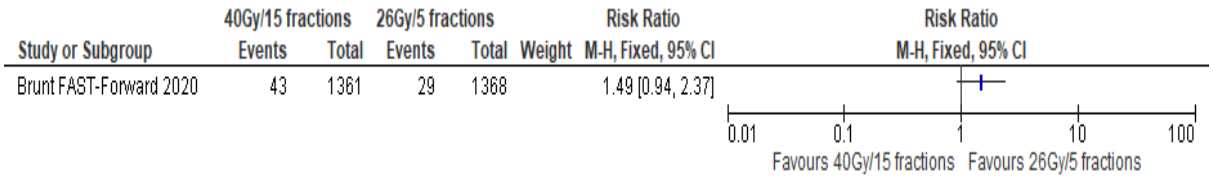


Figure 24: Distant relapse

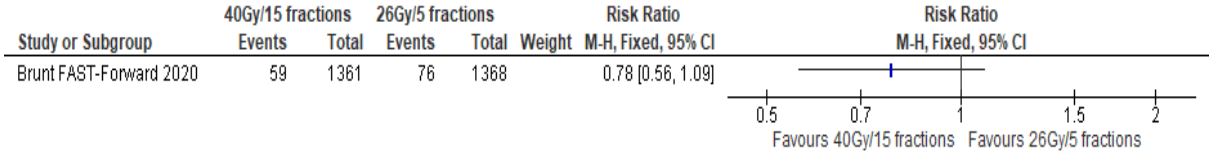


Figure 25: Acute skin toxicity

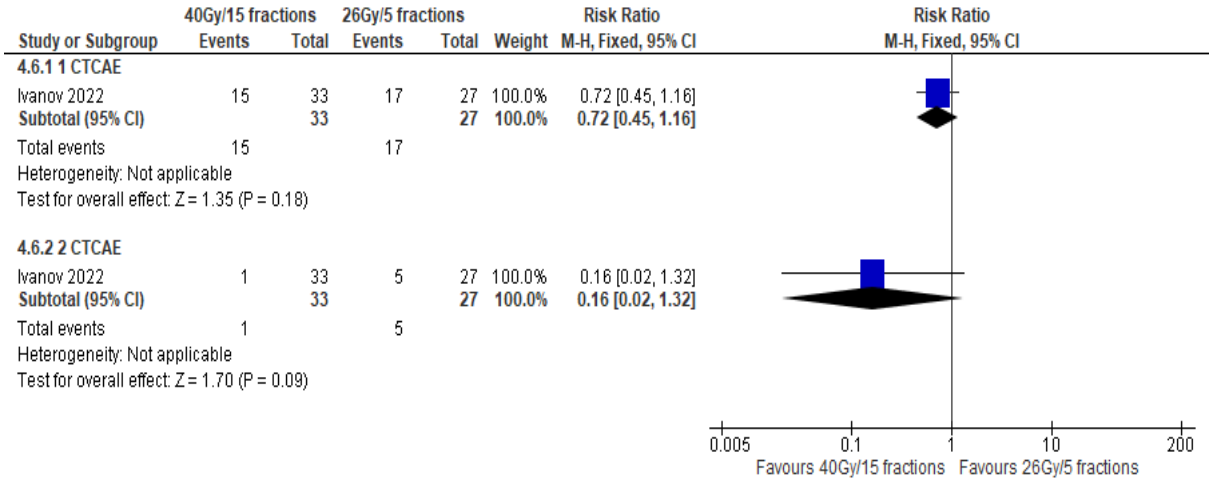


Figure 26: Late skin toxicity (RESS-RTOG/EORTC)

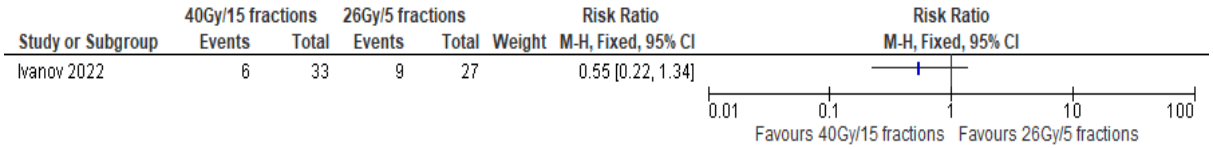


Figure 27: Subcutaneous tissue toxicity (RESS-EORTC)

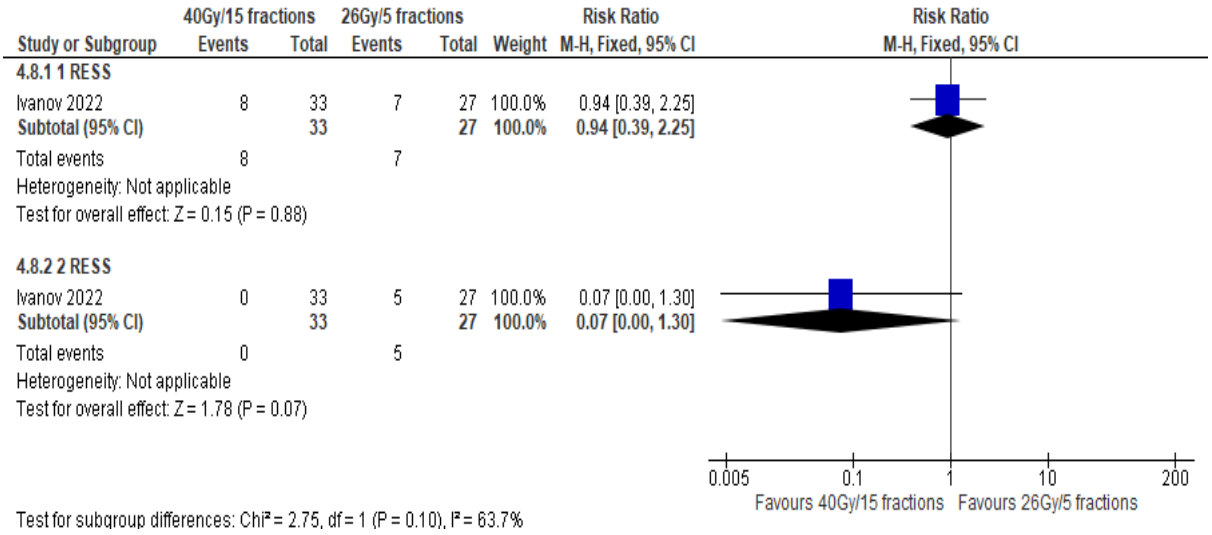


Figure 28: Cosmetic results

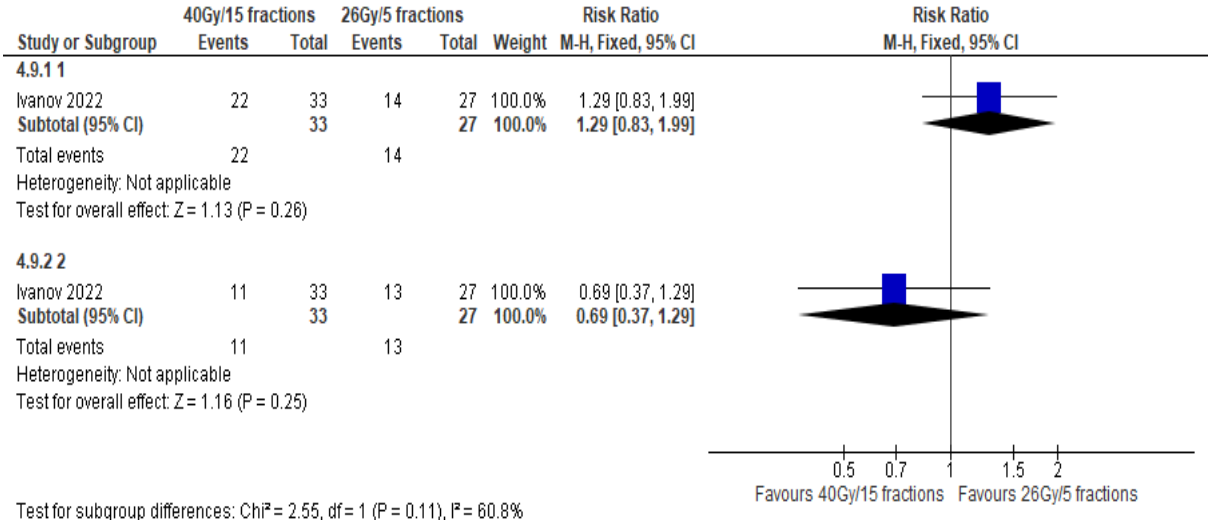


Figure 29: Adverse events (clinician assessed)

Figure 30: Quality of life (EORTC QLQ-BR23)

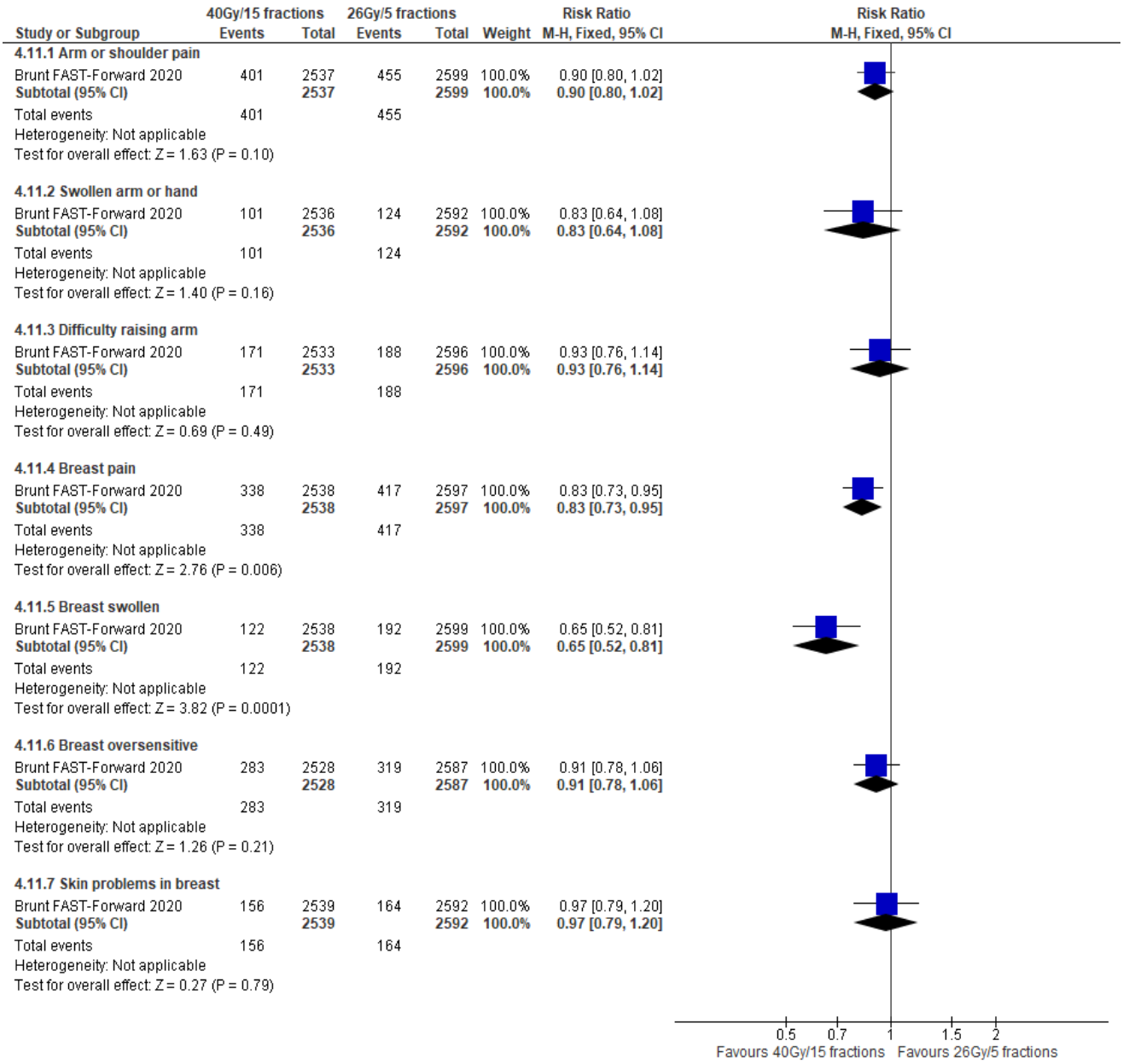
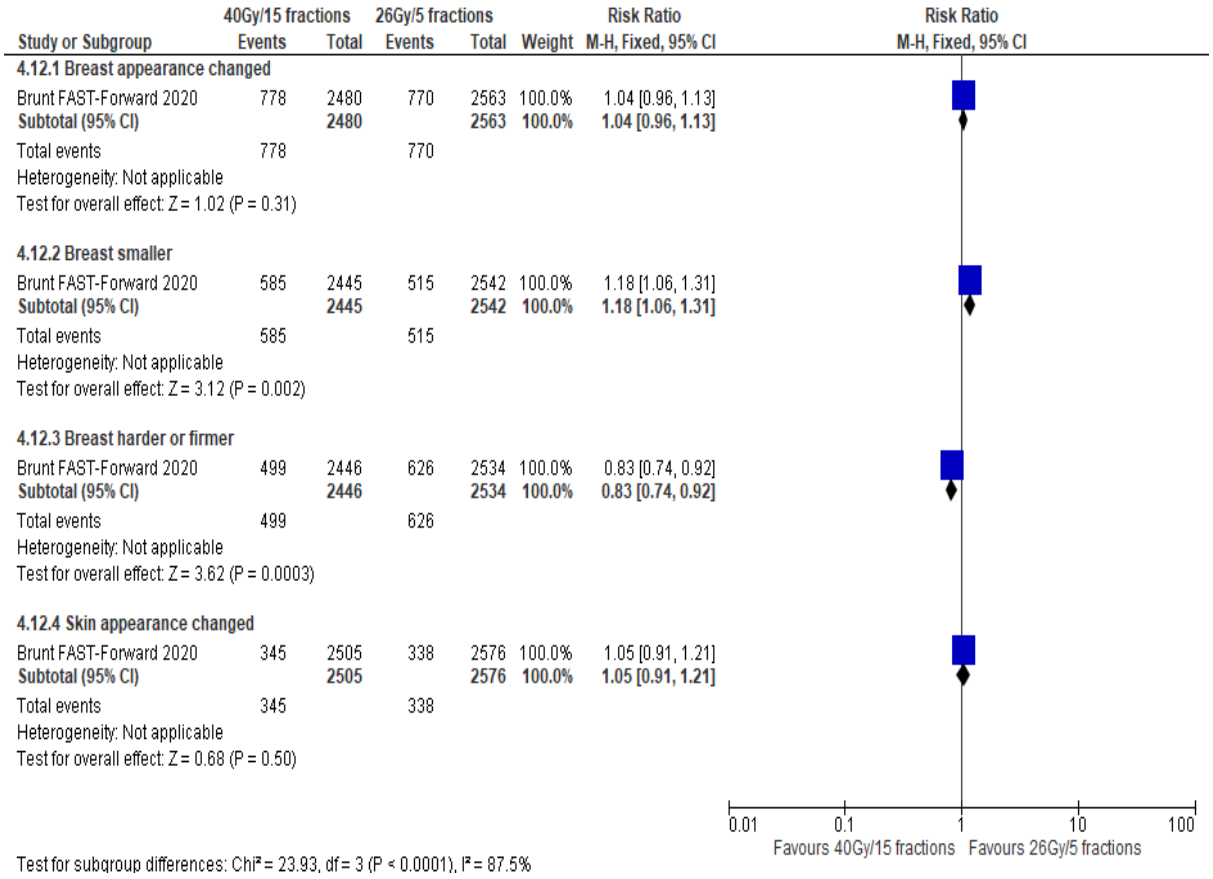


Figure 31: Normal tissue effects



Hypofractionation regimen: 40Gy/15 fractions (3 weeks) vs 27Gy/5 fractions (1 week)

Figure 32: All-cause mortality

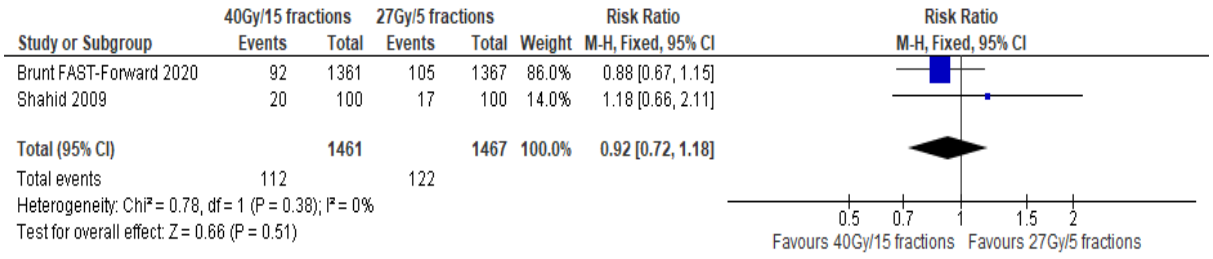


Figure 33: Breast cancer-related mortality

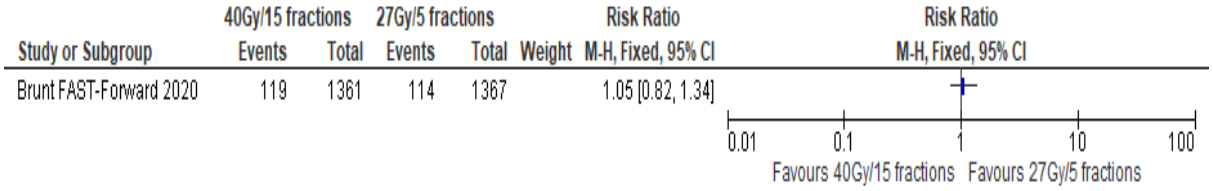


Figure 34: Local relapse

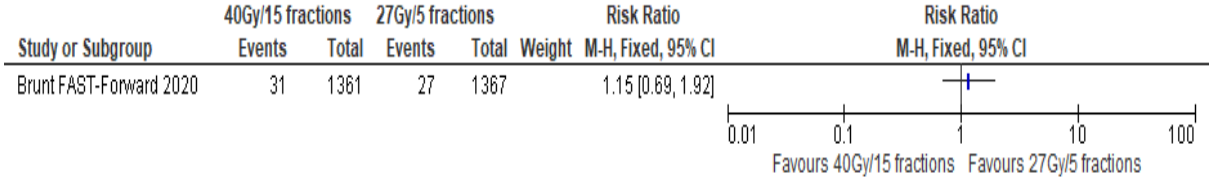


Figure 35: Locoregional relapse

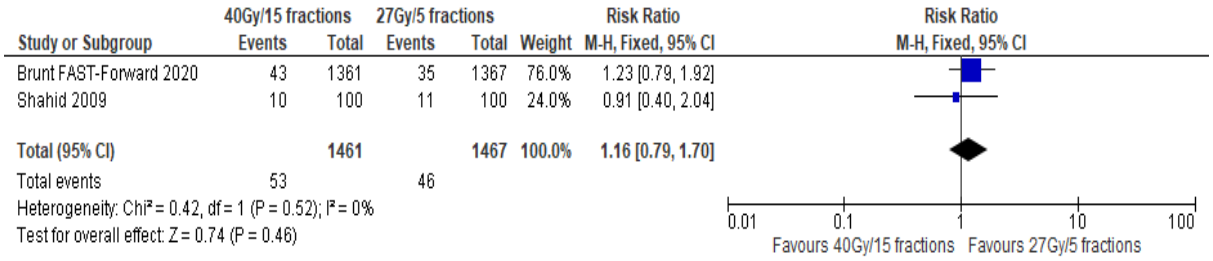


Figure 36: Metastatic disease

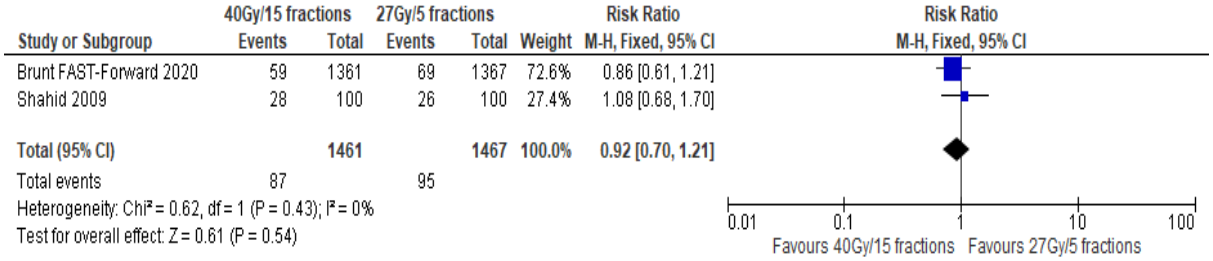


Figure 37: Overall survival

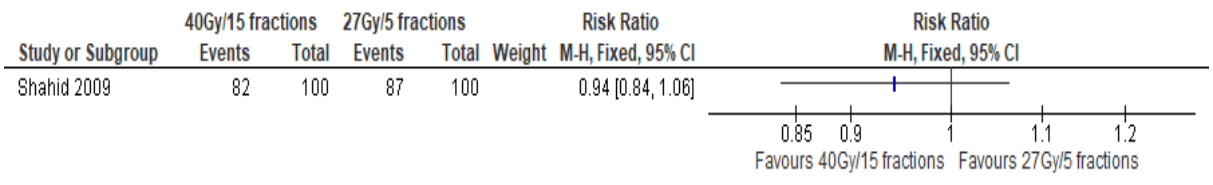


Figure 38: Disease free survival

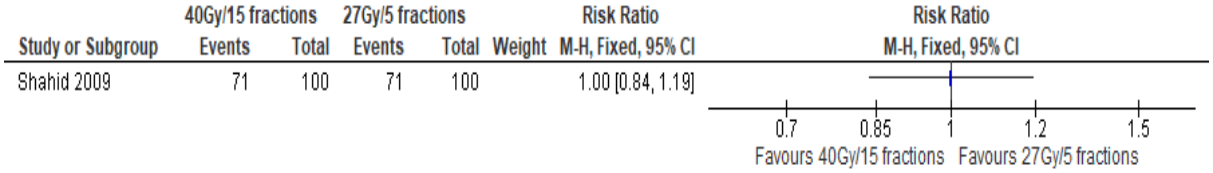


Figure 39: Incidence of lymphoedema (G1-G3)

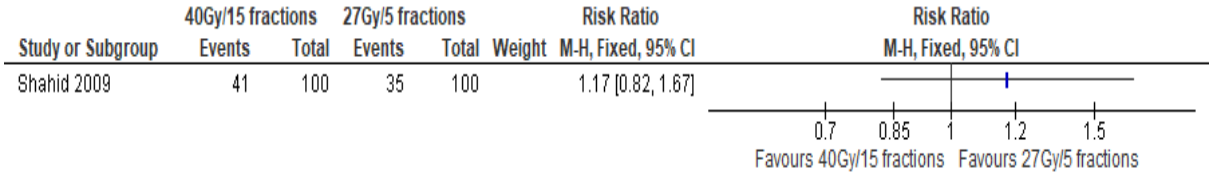


Figure 40: Adverse events

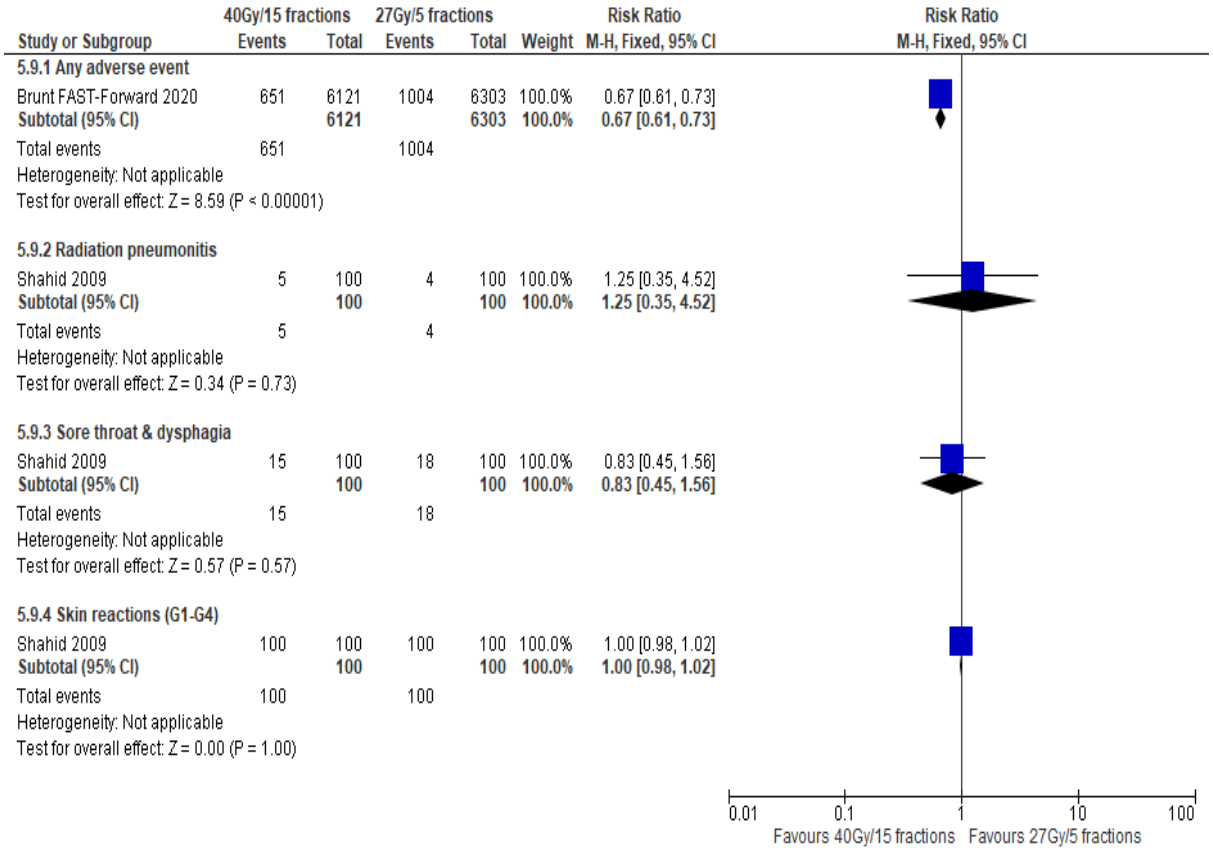


Figure 41: Quality of life (EORTC QLQ-BR23)

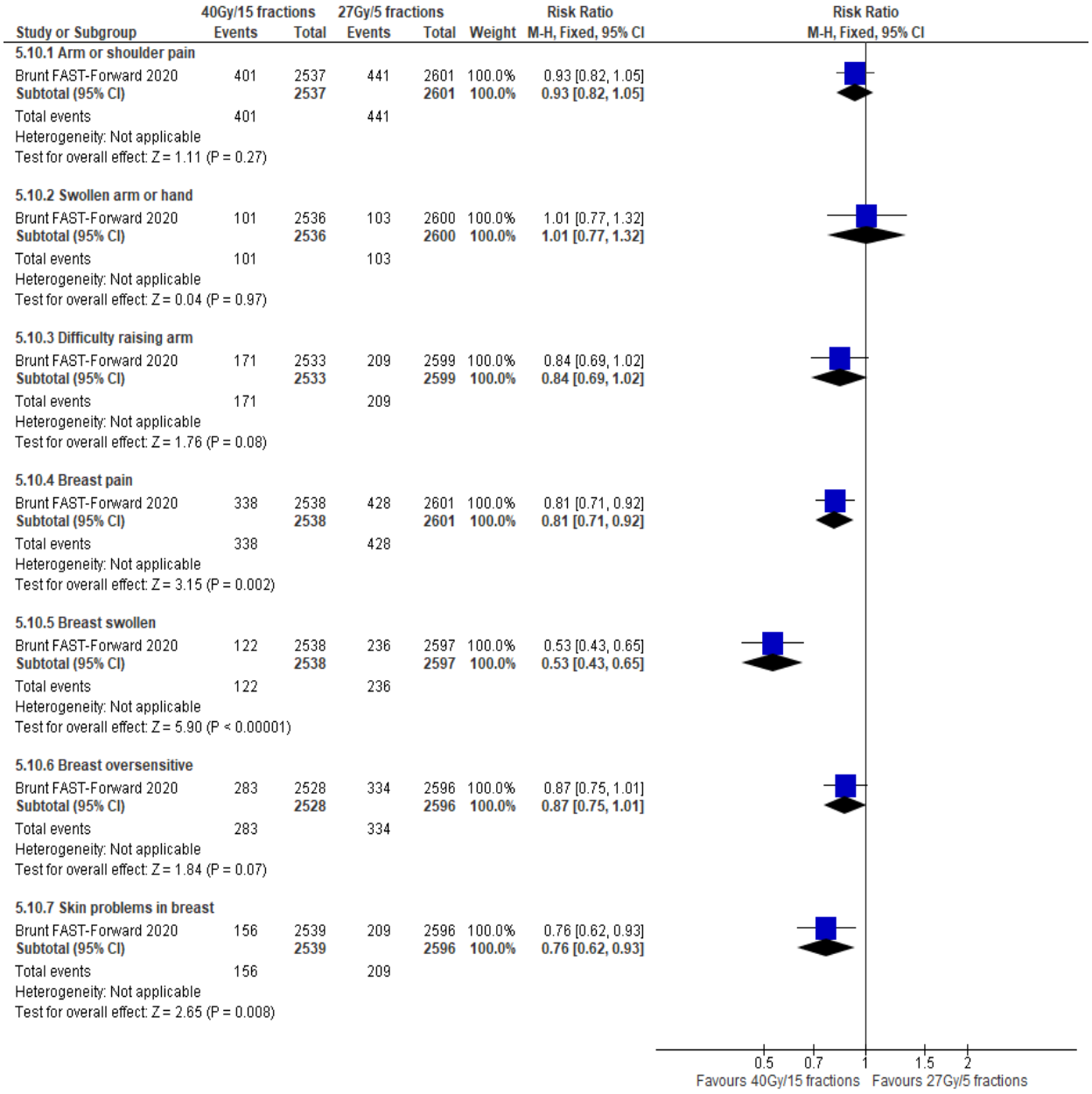
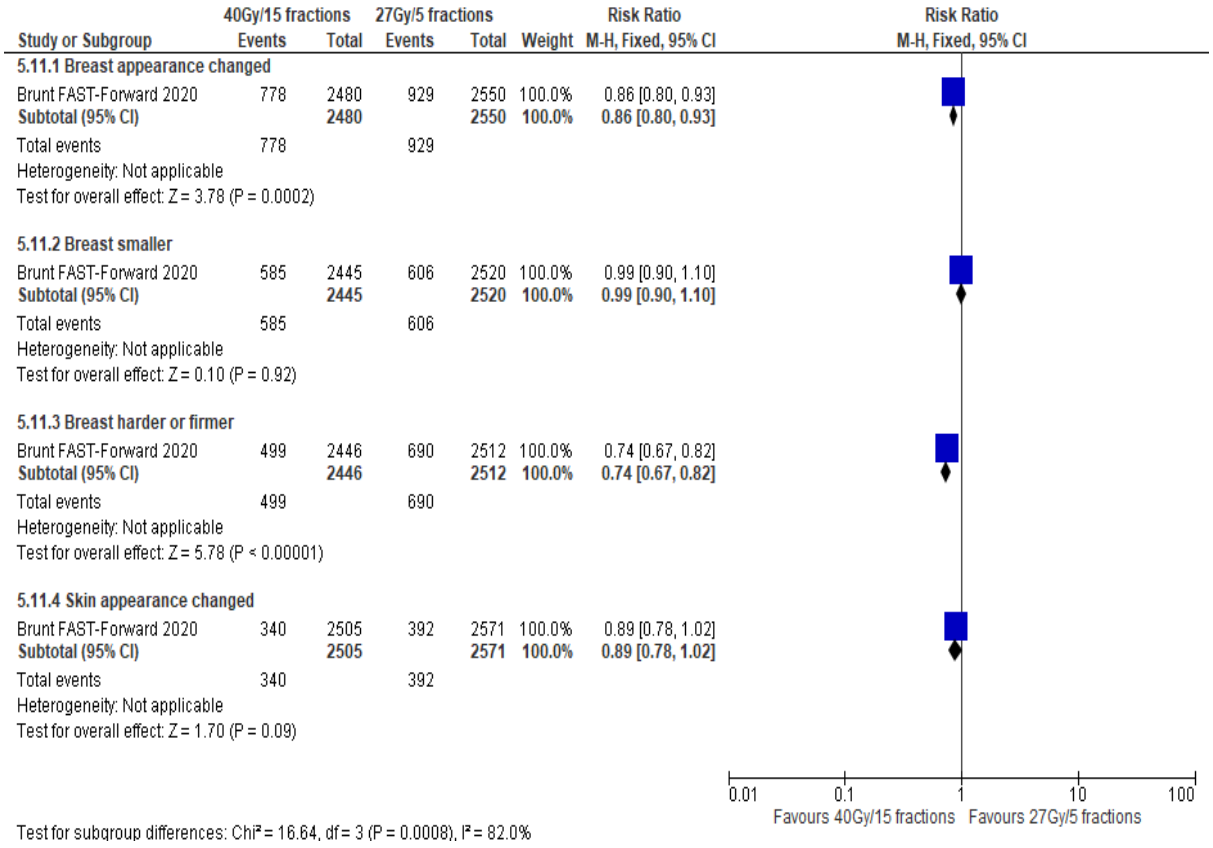


Figure 42: Normal tissue effects



Hypofractionation regimen: 26Gy over 5 fractions (1 week) vs 27Gy/5 fractions (1 week)

Figure 43: All-cause mortality

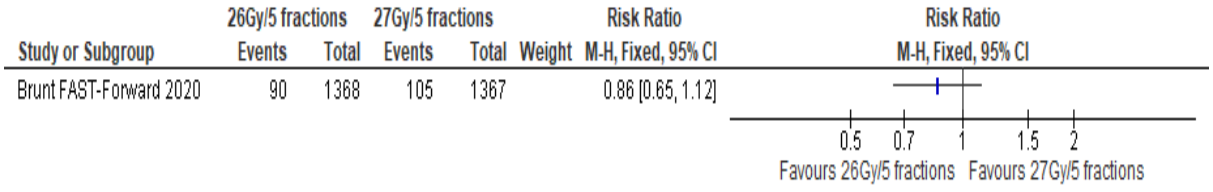


Figure 44: Breast cancer-related mortality

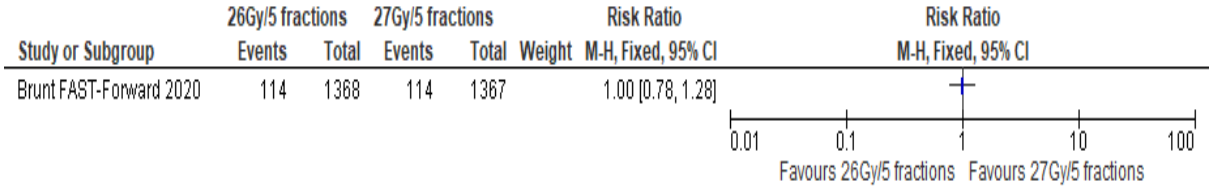


Figure 45: Local relapse

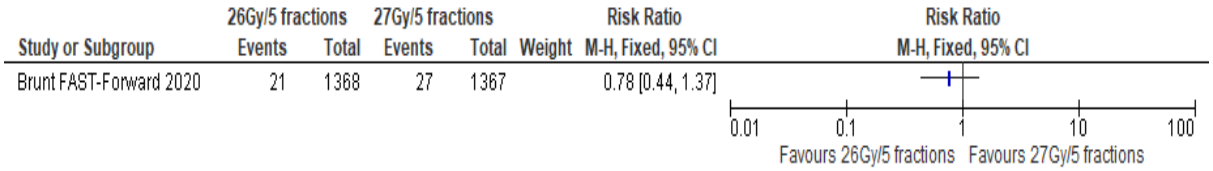


Figure 46: Loco-regional relapse

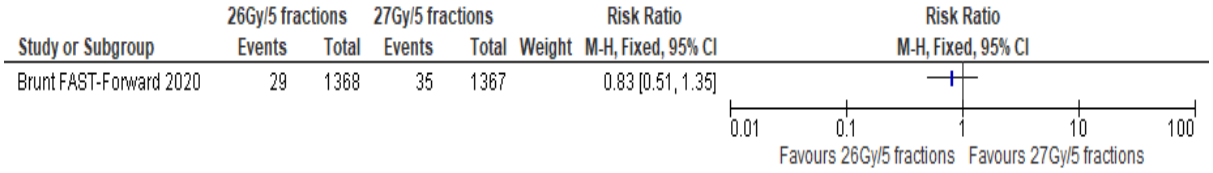


Figure 47: Metastatic disease

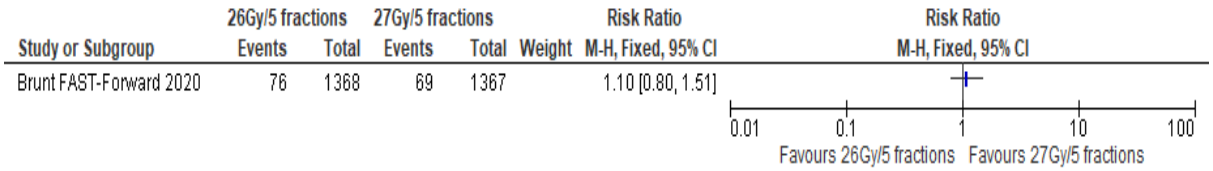


Figure 48: Normal tissue effects

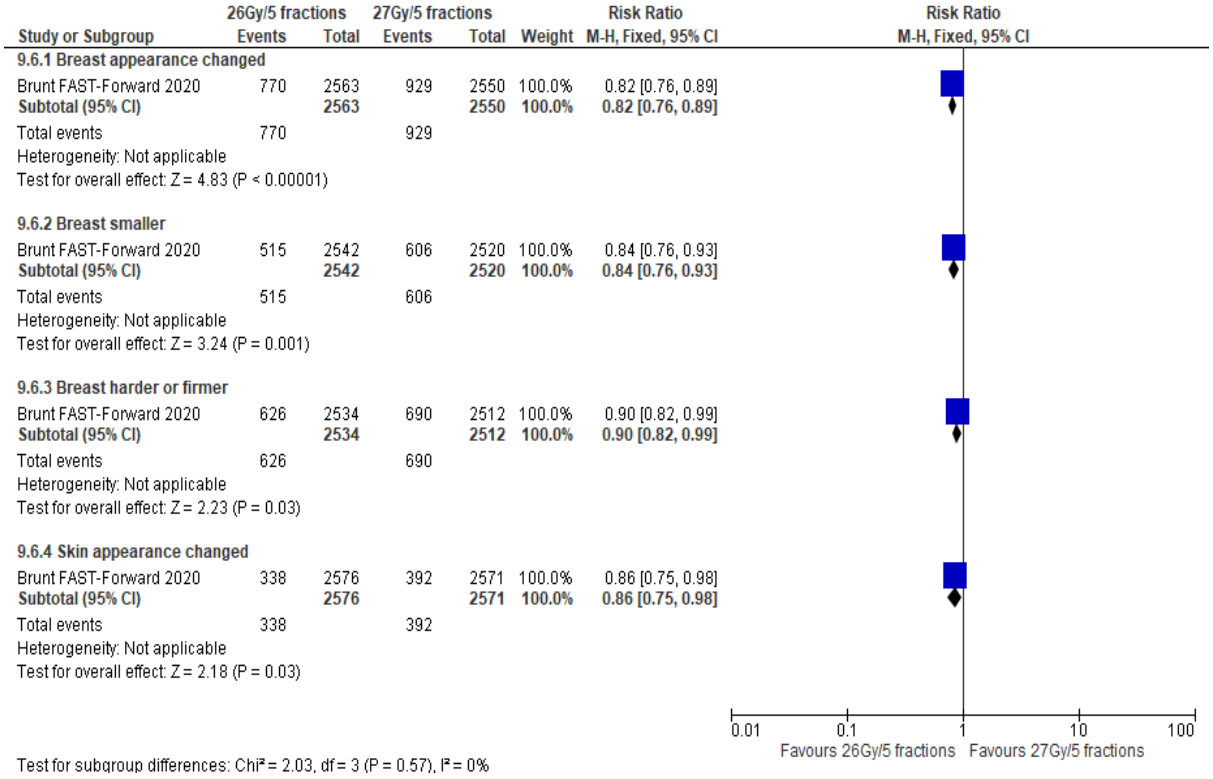


Figure 49: Adverse events

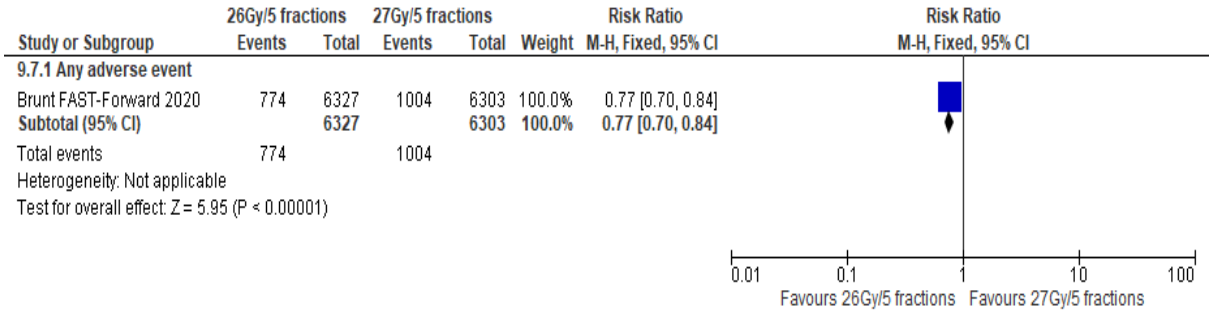
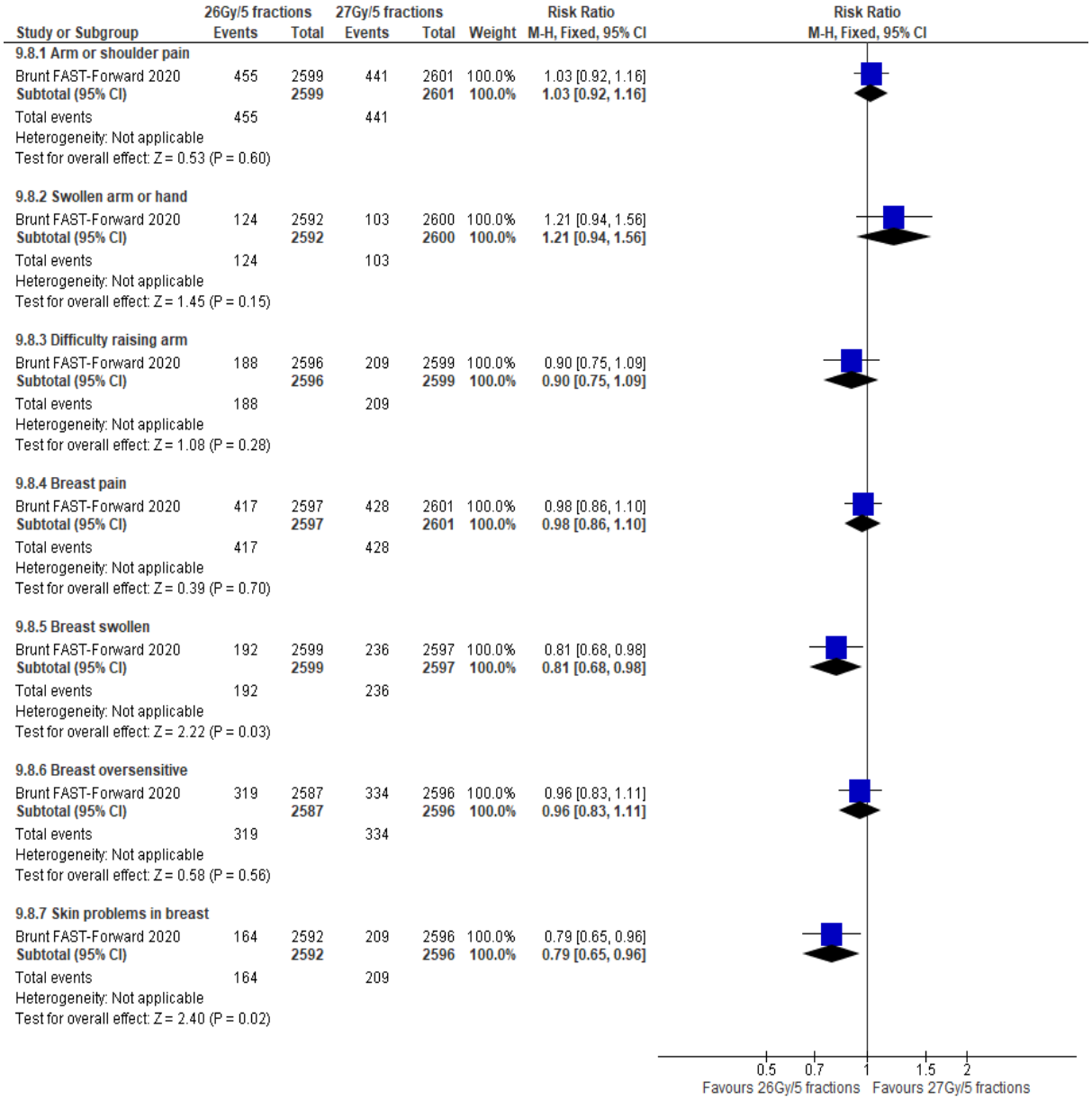


Figure 50: Quality of life (EORTC QLQ-BR23)



Hypofractionation regimen: 40Gy over 15 fractions (3 weeks) vs 35Gy over 10 fractions (2 weeks)

Figure 51: All-cause mortality

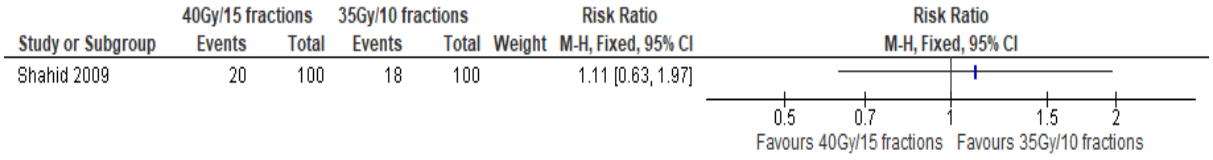


Figure 52: Loco-regional relapse

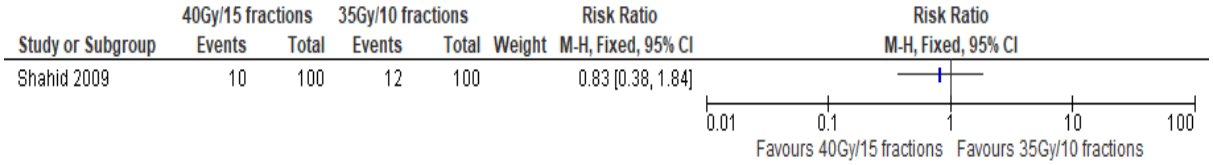


Figure 53: Metastatic disease

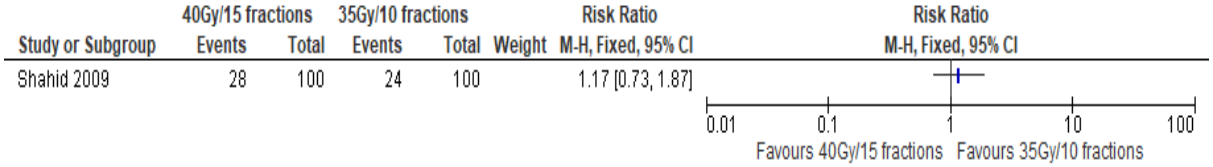


Figure 54: Overall survival

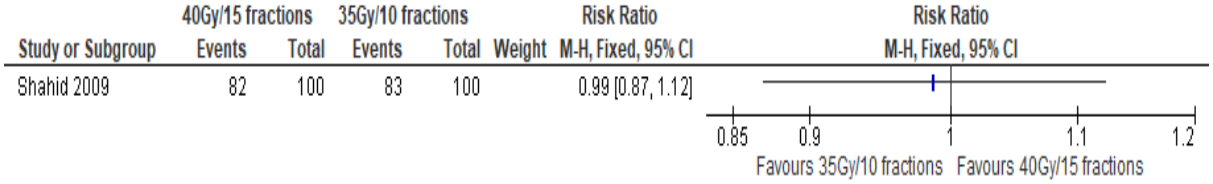


Figure 55: Disease free survival

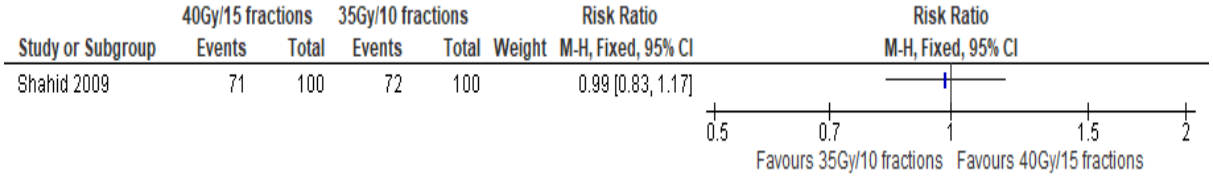
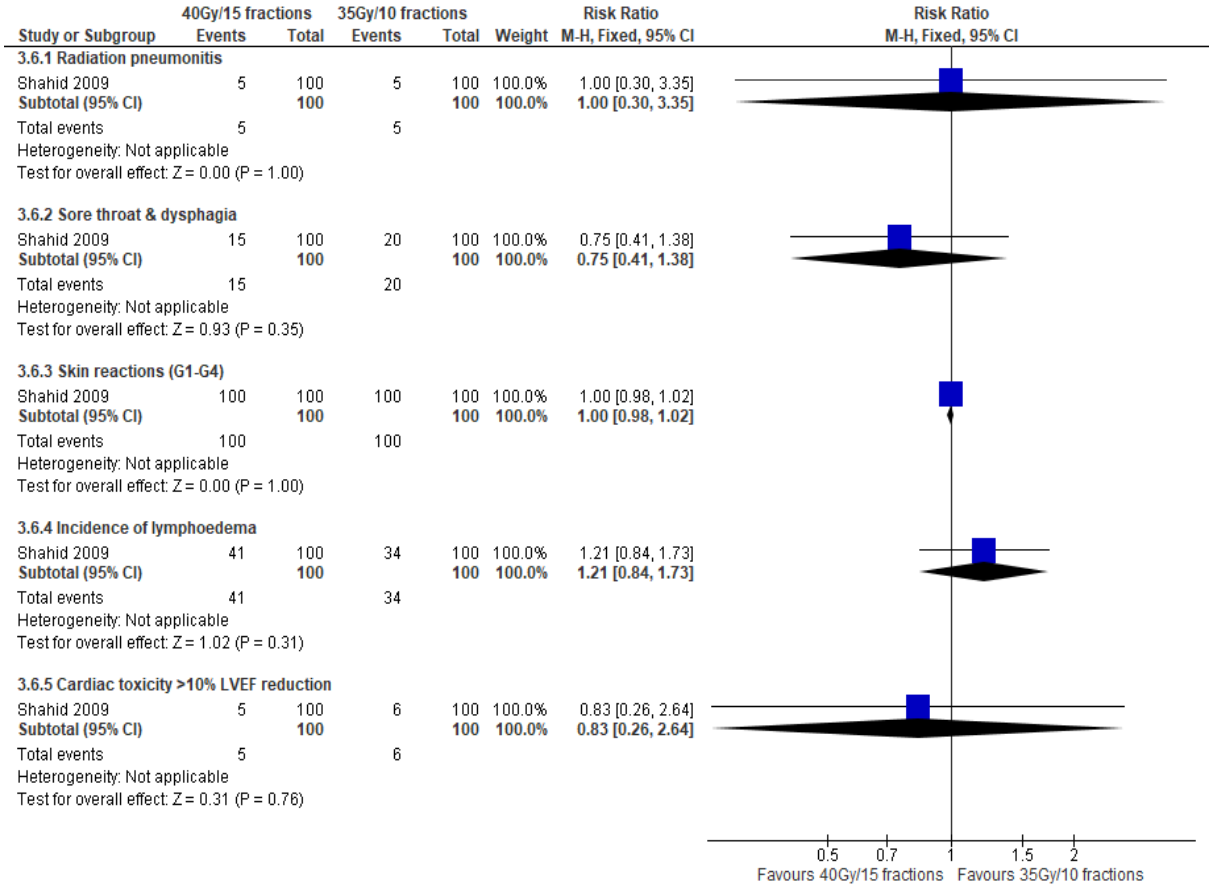


Figure 56: Adverse events



Hypofractionation regimen: 35Gy over 10 fractions (2 weeks) vs 27Gy over 5 fractions (1 week)

Figure 57: All-cause mortality

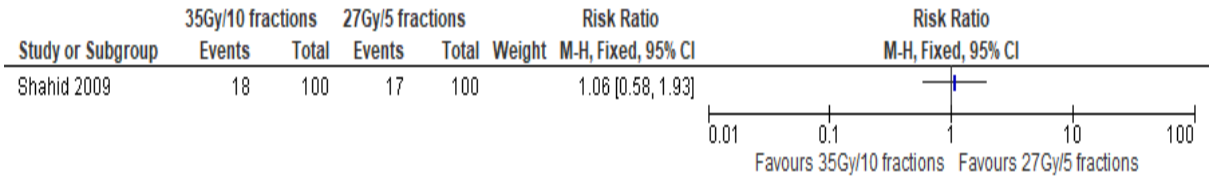


Figure 58: Loco-regional relapse

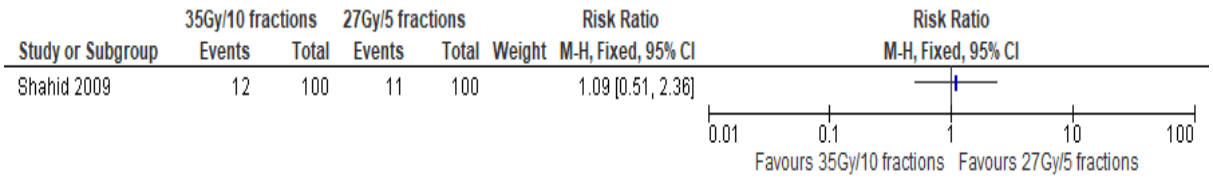


Figure 59: Metastatic disease

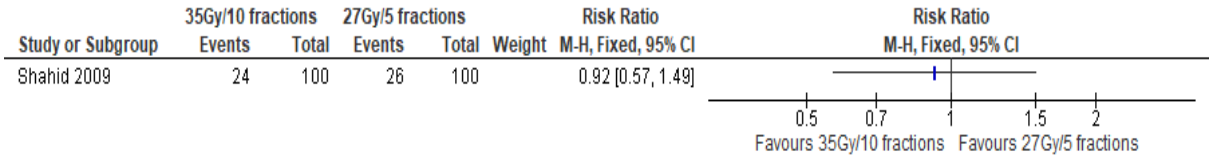


Figure 60: Overall survival

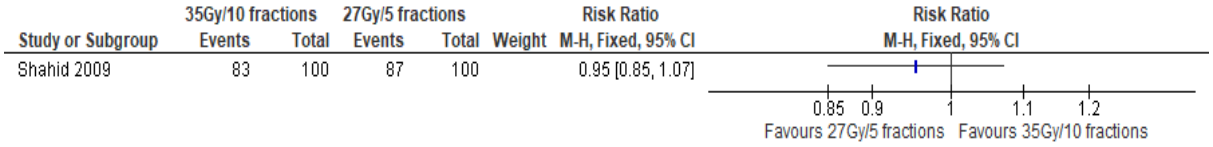


Figure 61: Disease free survival

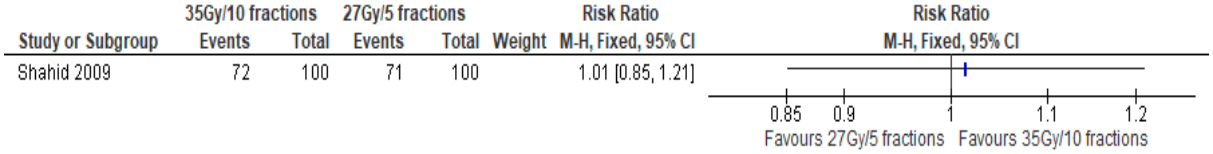
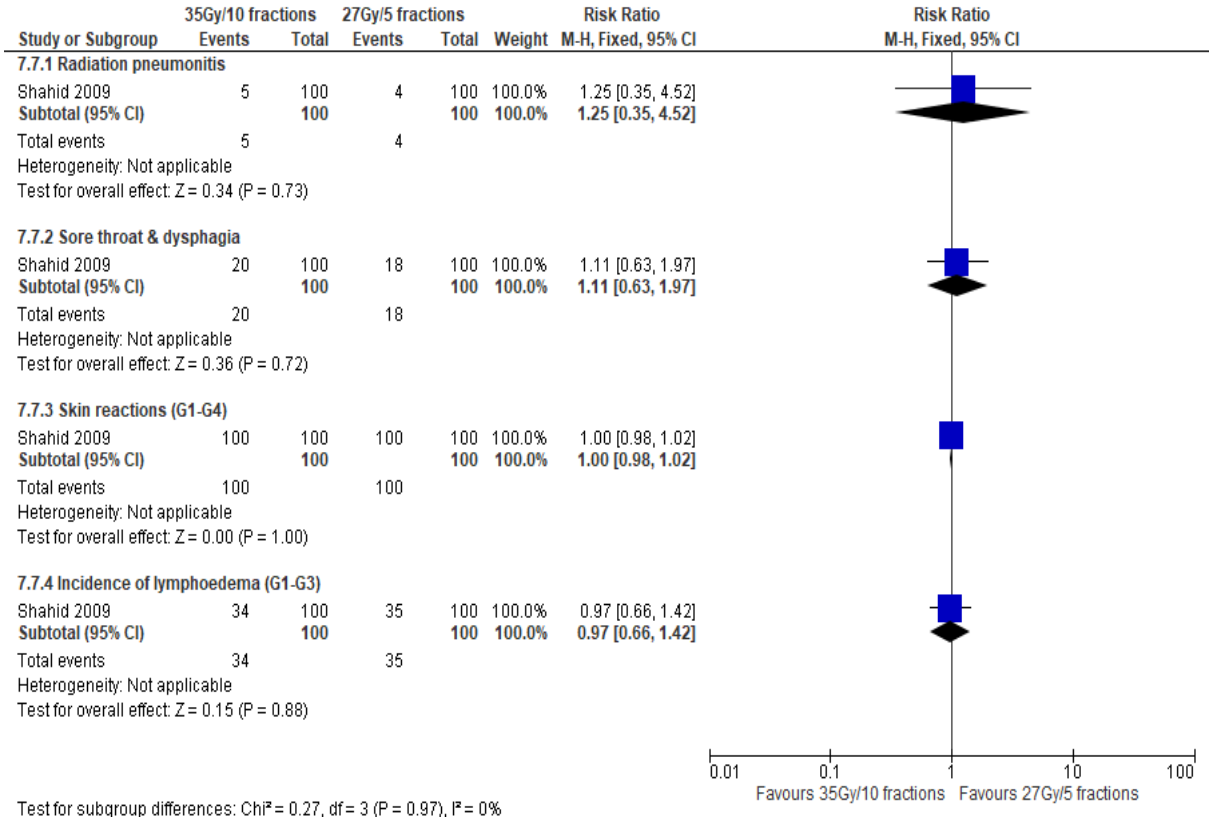


Figure 62: Adverse events



Appendix F – GRADE tables

Dose comparisons (studies using different doses but the same number of fractions over the same time period)

Table 14 Hypofractionation regimen: 28.5 Gy in 5 fractions (whole breast) compared to 30 Gy in 5 fractions over 5 weeks (whole-breast)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	28.5Gy/5 fractions	30Gy/5 fractions	Relative (95% CI)	Absolute		
Normal tissue effects in breasts (G1-G4) - None [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	72/130 (55.4%)	66/130 (50.8%)	RR 1.09 (0.87 to 1.37)	46 more per 1000 (from 66 fewer to 188 more)	⊕⊕⊕O MODERATE	CRITICAL
Normal tissue effects in breast (G1-G4) - Mild [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	39/130 (30%)	40/130 (30.8%)	RR 0.98 (0.67 to 1.41)	6 fewer per 1000 (from 102 fewer to 126 more)	⊕⊕OO LOW	CRITICAL
Normal tissue effects in breast (G1-G4) - Moderate [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	17/130 (13.1%)	18/130 (13.8%)	RR 0.94 (0.51 to 1.75)	8 fewer per 1000 (from 68 fewer to 104 more)	⊕⊕OO LOW	CRITICAL
Normal tissue effects in breast (G1-G4) - Marked [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/130 (1.5%)	6/130 (4.6%)	RR 0.33 (0.07 to 1.62)	31 fewer per 1000 (from 43 fewer to 29 more)	⊕⊕OO LOW	CRITICAL
All-cause mortality [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	33/308 (10.7%)	33/305 (10.8%)	RR 1.01 (0.64 to 1.59)	1 more per 1000 (from 39 fewer to 64 more)	⊕⊕OO LOW	CRITICAL
Breast cancer-related mortality [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/308 (2.6%)	10/305 (3.3%)	RR 1.26 (0.51 to 3.16)	9 more per 1000 (from 16 fewer to 71 more)	⊕⊕OO LOW	CRITICAL
Local relapse [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/308 (0.97%)	3/305 (0.98%)	RR 1.01 (0.21 to 4.96)	0 more per 1000 (from 8 fewer to 39 more)	⊕⊕OO LOW	CRITICAL
Loco-regional relapse [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/308 (0%)	3/305 (0.98%)	RR 7.07 (0.37 to 136.27)	60 more per 1000 (from 6 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
Distant relapse [MID +/- 0.8 to 1.25] (follow-up 10 years)												

1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	15/308 (4.9%)	15/305 (4.9%)	RR 1.01 (0.50 to 2.03)	0 more per 1000 (from 25 fewer to 51 more)	⊕⊕OO LOW	CRITICAL
Adverse events [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	6/308 (1.9%)	3/305 (0.98%)	RR 0.50 (0.13 to 2.00)	5 fewer per 1000 (from 9 fewer to 10 more)	⊕⊕OO LOW	CRITICAL

[1] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
[2] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.
[3] FAST trial Brunt 2020

Dose, fractions comparisons (studies used different doses, different number of fractions over the same time period)

Table 15 Hypofractionation regimen: 39 Gy in 13 fractions over 5 weeks (whole breast) compared to 41.6 Gy in 16 fractions over 5 weeks (whole-breast)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	30Gy/13 fractions	41.6Gy/16 fractions	Relative (95% CI)	Absolute		
All-cause mortality [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	130/737 (17.6%)	128/750 (17.1%)	RR 1.03 (0.83 to 1.29)	5 more per 1000 (from 29 fewer to 49 more)	⊕⊕⊕O MODERATE	CRITICAL
Local relapse [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	47/737 (6.4%)	37/750 (4.9%)	RR 1.29 (0.85 to 1.96)	14 more per 1000 (from 7 fewer to 47 more)	⊕⊕⊕O MODERATE	CRITICAL
Loco-regional relapse [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	52/737 (7.1%)	42/750 (5.6%)	RR 1.26 (0.85 to 1.87)	15 more per 1000 (from 8 fewer to 49 more)	⊕⊕⊕O MODERATE	CRITICAL
Distant relapse [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	121/737 (16.4%)	110/750 (14.7%)	RR 1.12 (0.88 to 1.42)	18 more per 1000 (from 18 fewer to 62 more)	⊕⊕⊕O MODERATE	CRITICAL
Normal tissue effects: breast shrinkage [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	140/617 (22.7%)	168/627 (26.8%)	RR 0.85 (0.7 to 1.03)	40 fewer per 1000 (from 80 fewer to 8 more)	⊕⊕⊕O MODERATE	CRITICAL
Normal tissue effects: breast induration (tumour bed) [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	110/617 (17.8%)	150/627 (23.9%)	RR 0.75 (0.6 to 0.93)	60 fewer per 1000 (from 17 fewer to 96 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Normal tissue effects: telangiectasia [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	18/723 (2.5%)	43/733 (5.9%)	RR 0.42 (0.25 to 0.73)	34 fewer per 1000 (from 16 fewer to 44 fewer)	⊕⊕OO LOW	CRITICAL
Normal tissue effects: breast oedema [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	43/617 (7%)	67/627 (10.7%)	RR 0.65 (0.45 to 0.94)	37 fewer per 1000 (from 6 fewer to 59 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Normal tissue effects: shoulder stiffness [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	8/92 (8.7%)	10/95 (10.5%)	RR 0.83 (0.34 to 2)	18 fewer per 1000 (from 69 fewer to 105 more)	⊕⊕OO LOW	CRITICAL

Normal tissue effects: arm oedema [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	6/92 (6.5%)	16/95 (16.8%)	RR 0.39 (0.16 to 0.95)	103 fewer per 1000 (from 8 fewer to 141 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Normal tissue effects: other [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	24/724 (3.3%)	20/733 (2.7%)	RR 1.21 (0.68 to 2.18)	6 more per 1000 (from 9 fewer to 32 more)	⊕⊕OO LOW	CRITICAL
Adverse events: symptomatic rib fracture [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1/737 (0.14%)	0/750 (0%)	RR 3.05 (0.12 to 74.82)	-	⊕⊕OO LOW	CRITICAL
Adverse events: symptomatic lung fibrosis [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1/737 (0.14%)	2/750 (0.27%)	RR 0.51 (0.05 to 5.6)	1 fewer per 1000 (from 3 fewer to 12 more)	⊕⊕OO LOW	CRITICAL
Adverse events: ischaemic heart disease [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	6/737 (0.81%)	5/750 (0.67%)	RR 1.22 (0.37 to 3.98)	1 more per 1000 (from 4 fewer to 20 more)	⊕⊕OO LOW	CRITICAL
Adverse events: brachial plexopathy [MID +/- 0.8 to 1.25] (follow-up 10 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/737 (0%)	1/750 (0.13%)	RR 0.34 (0.01 to 8.31)	1 fewer per 1000 (from 1 fewer to 10 more)	⊕⊕OO LOW	CRITICAL

[1] Haviland START 2013
[2] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
[3] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.

Dose, fraction and time period comparisons (studies using different doses, different number of fractions over different time periods)

Table 16 Hypofractionation regimen: 39 Gy in 13 fractions over 2.6 weeks (whole breast) compared to 42.4 Gy in 16 fractions over 3.3 weeks (whole-breast)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**42.4Gy/16 fractions**	**39Gy/13 fractions**	**Relative (95% CI)**	**Absolute**		
Radiation dermatitis - Grade 1 [MID +/- 0.8 to 1.25] (follow-up 2 years)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	20/50 (40%)	34/50 (68%)	RR 0.59 (0.4 to 0.87)	279 fewer per 1000 (from 88 fewer to 408 fewer)	⊕OOO VERY LOW	CRITICAL

Radiation dermatitis - Grade 2 [MID +/- 0.8 to 1.25] (follow-up 2 years)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/50 (6%)	7/50 (14%)	RR 0.43 (0.12 to 1.56)	80 fewer per 1000 (from 123 fewer to 78 more)	⊕OOO VERY LOW	CRITICAL
Acute pneumonitis - Grade 1 [MID +/- 0.8 to 1.25] (follow-up 2 years)												
1[1]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/50 (2%)	6/50 (12%)	RR 0.17 (0.02 to 1.33)	100 fewer per 1000 (from 118 fewer to 40 more)	⊕OOO VERY LOW	CRITICAL
Acute pneumonitis - Grade 2 [MID +/- 0.8 to 1.25] (follow-up 2 years)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/50 (8%)	1/50 (2%)	RR 4 (0.46 to 34.54)	60 more per 1000 (from 11 fewer to 671 more)	⊕OOO VERY LOW	CRITICAL
Subcutaneous fibrosis - Grade 1 [MID +/- 0.8 to 1.25] (follow-up 2 years)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/50 (14%)	4/50 (8%)	RR 1.75 (0.55 to 5.61)	60 more per 1000 (from 36 fewer to 369 more)	⊕OOO VERY LOW	CRITICAL
Subcutaneous fibrosis - Grade 2 [MID +/- 0.8 to 1.25] (follow-up 2 years)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	2/50 (4%)	10/50 (20%)	RR 0.2 (0.05 to 0.87)	160 fewer per 1000 (from 26 fewer to 190 fewer)	⊕OOO VERY LOW	CRITICAL
Incidence of lymphoedema - Grade 1 [MID +/- 0.8 to 1.25] (follow-up 2 years)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/50 (12%)	6/50 (12%)	RR 1 (0.35 to 2.89)	0 fewer per 1000 (from 78 fewer to 227 more)	⊕OOO VERY LOW	CRITICAL
Incidence of lymphoedema - Grade 2 [MID +/- 0.8 to 1.25] (follow-up 2 years)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	5/50 (10%)	13/50 (26%)	RR 0.38 (0.15 to 1)	161 fewer per 1000 (from 221 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL

[1] Aboziada 2016
[2] Study at high risk of bias. Quality of the outcome downgraded twice.
[3] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.
[4] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.

Table 17 Hypofractionation regimen: 40 Gy in 15 fractions over 3 weeks (whole breast) compared to 26 Gy in 5 fractions over 1 week (whole-breast)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**40Gy/15 fractions**	**26Gy/5 fractions**	**Relative (95% CI)**	**Absolute**		
All-cause mortality [MID +/- 0.8 to 1.25] (follow-up 5 years)												

1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	92/1361 (6.8%)	90/1368 (6.6%)	RR 1.03 (0.78 to 1.36)	2 more per 1000 (from 14 fewer to 24 more)	⊕⊕OO LOW	CRITICAL
Breast cancer related mortality [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	47/1361 (3.5%)	53/1368 (3.9%)	RR 0.89 (0.61 to 1.31)	4 fewer per 1000 (from 15 fewer to 12 more)	⊕⊕OO LOW	CRITICAL
Local relapse [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	31/1361 (2.3%)	21/1368 (1.5%)	RR 1.48 (0.86 to 2.57)	7 more per 1000 (from 2 fewer to 24 more)	⊕⊕⊕O MODERATE	CRITICAL
Loco-regional relapse [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	43/1361 (3.2%)	29/1368 (2.1%)	RR 1.49 (0.94 to 2.37)	10 more per 1000 (from 1 fewer to 29 more)	⊕⊕⊕O MODERATE	CRITICAL
Distant relapse [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	59/1361 (4.3%)	76/1368 (5.6%)	RR 0.78 (0.56 to 1.09)	12 fewer per 1000 (from 24 fewer to 5 more)	⊕⊕⊕O MODERATE	CRITICAL
Acute skin toxicity - 1 point [MID +/- 0.8 to 1.25] (follow-up 18 months; assessed with: CTCAE)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	17/27 (63%)	15/33 (45.5%)	RR 1.39 (0.86 to 2.22)	177 more per 1000 (from 64 fewer to 555 more)	⊕⊕⊕O MODERATE	CRITICAL
Acute skin toxicity - 2 points [MID +/- 0.8 to 1.25] (follow-up 18 months; assessed with: CTCAE)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	5/27 (18.5%)	1/33 (3%)	RR 6.11 (0.76 to 49.21)	155 more per 1000 (from 7 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Late skin toxicity [MID +/- 0.8 to 1.25] (follow-up 18 months; assessed with: RESS-RTOG/EORTC)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	6/33 (18.2%)	9/27 (33.3%)	RR 0.55 (0.22 to 1.34)	150 fewer per 1000 (from 260 fewer to 113 more)	⊕OOO VERY LOW	CRITICAL
Subcutaneous tissue toxicity - 1 point [MID +/- 0.8 to 1.25] (follow-up 18 months; assessed with: RESS-EORTC)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	8/33 (24.2%)	7/27 (25.9%)	RR 0.94 (0.39 to 2.25)	16 fewer per 1000 (from 158 fewer to 324 more)	⊕OOO VERY LOW	CRITICAL
Subcutaneous tissue toxicity - 2 points [MID +/- 0.8 to 1.25] (follow-up 18 months; assessed with: RESS-EORTC)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/33 (0%)	5/27 (18.5%)	RR 0.07 (0 to 1.3)	172 fewer per 1000 (from 185 fewer to 56 more)	⊕OOO VERY LOW	CRITICAL
Cosmetic results - 1 point [MID +/- 0.8 to 1.25] (follow-up 18 months)												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	22/33 (66.7%)	14/27 (51.9%)	RR 1.29 (0.83 to 1.99)	150 more per 1000 (from 88 fewer to 513 more)	⊕⊕OO LOW	CRITICAL
Cosmetic results - 2 points [MID +/- 0.8 to 1.25] (follow-up 18 months)												

1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	11/33 (33.3%)	13/27 (48.1%)	RR 0.69 (0.37 to 1.29)	149 fewer per 1000 (from 303 fewer to 140 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (clinician assessed) [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	651/6121 (10.6%)	774/6327 (12.2%)	RR 0.87 (0.79 to 0.96)	16 fewer per 1000 (from 5 fewer to 26 fewer)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Arm or shoulder pain [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	401/2537 (15.8%)	455/2599 (17.5%)	RR 0.9 (0.8 to 1.02)	18 fewer per 1000 (from 35 fewer to 4 more)	⊕⊕⊕⊕ HIGH	CRITICAL
EORTC QLQ-BR23 - Swollen arm or hand [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	101/2536 (4%)	124/2592 (4.8%)	RR 0.83 (0.64 to 1.08)	8 fewer per 1000 (from 17 fewer to 4 more)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Difficulty raising arm [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	171/2533 (6.8%)	188/2596 (7.2%)	RR 0.93 (0.76 to 1.14)	5 fewer per 1000 (from 17 fewer to 10 more)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Breast pain [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	338/2538 (13.3%)	417/2597 (16.1%)	RR 0.83 (0.73 to 0.95)	27 fewer per 1000 (from 8 fewer to 43 fewer)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Breast swollen [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	122/2538 (4.8%)	192/2599 (7.4%)	RR 0.65 (0.52 to 0.81)	26 fewer per 1000 (from 14 fewer to 35 fewer)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Breast oversensitive [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	283/2528 (11.2%)	319/2587 (12.3%)	RR 0.91 (0.78 to 1.06)	11 fewer per 1000 (from 27 fewer to 7 more)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Skin problems in breast [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	156/2539 (6.1%)	164/2592 (6.3%)	RR 0.97 (0.79 to 1.2)	2 fewer per 1000 (from 13 fewer to 13 more)	⊕⊕⊕O MODERATE	CRITICAL
Normal tissue effects - Breast appearance changed [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	778/2480 (31.4%)	770/2563 (30%)	RR 1.04 (0.96 to 1.13)	12 more per 1000 (from 12 fewer to 39 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Normal tissue effects - Breast smaller [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	585/2445 (23.9%)	515/2542 (20.3%)	RR 1.18 (1.06 to 1.31)	36 more per 1000 (from 12 more to 63 more)	⊕⊕⊕O MODERATE	CRITICAL

Normal tissue effects - Breast harder or firmer [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	499/2446 (20.4%)	626/2534 (24.7%)	RR 0.83 (0.74 to 0.92)	42 fewer per 1000 (from 20 fewer to 64 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Normal tissue effects - Skin appearance changed [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	345/2505 (13.8%)	338/2576 (13.1%)	RR 1.05 (0.91 to 1.21)	7 more per 1000 (from 12 fewer to 28 more)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] FAST-Forward Brunt 2020
[2] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
[3] Ivanov 2022
[4] Study at moderate risk of bias. Quality of the outcome downgraded once.
[5] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.

Table 18 Hypofractionation regimen: 40 Gy in 15 fractions over 3 weeks (whole breast) compared to 27 Gy in 5 fractions over 1 week (whole breast)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**40Gy/15 fractions**	**27Gy/5 fractions**	**Relative (95% CI)**	**Absolute**		
All-cause mortality [MID +/- 0.8 to 1.25]												
2[1,2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	112/1461 (7.7%)	122/1467 (8.3%)	RR 0.92 (0.72 to 1.18)	7 fewer per 1000 (from 23 fewer to 15 more)	⊕⊕⊕O MODERATE	CRITICAL
Breast cancer related mortality [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	119/1361 (8.7%)	114/1367 (8.3%)	RR 1.05 (0.82 to 1.34)	4 more per 1000 (from 15 fewer to 28 more)	⊕⊕⊕O MODERATE	CRITICAL
Locoregional relapse [MID +/- 0.8 to 1.25]												
2[1,2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	53/1461 (3.6%)	46/1467 (3.1%)	RR 1.16 (0.79 to 1.7)	5 more per 1000 (from 7 fewer to 22 more)	⊕⊕OO LOW	CRITICAL
Metastatic disease [MID +/- 0.8 to 1.25]												
2[1,2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	87/1461 (6%)	95/1467 (6.5%)	RR 0.92 (0.7 to 1.21)	5 fewer per 1000 (from 19 fewer to 14 more)	⊕⊕⊕O MODERATE	CRITICAL
Overall survival [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[2]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	82/100 (82%)	87/100 (87%)	RR 0.94 (0.84 to 1.06)	52 fewer per 1000 (from 139 fewer to 52 more)	⊕⊕⊕O MODERATE	CRITICAL
Disease free survival [MID +/- 0.8 to 1.25] (follow-up 6 months)												

1[2]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71/100 (71%)	71/100 (71%)	RR 1 (0.84 to 1.19)	0 fewer per 1000 (from 114 fewer to 135 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events - Any adverse event [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	651/6121 (10.6%)	1004/6303 (15.9%)	RR 0.67 (0.61 to 0.73)	53 fewer per 1000 (from 43 fewer to 62 fewer)	⊕⊕OO LOW	CRITICAL
Adverse events - Radiation pneumonitis [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[2]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/100 (5%)	4/100 (4%)	RR 1.25 (0.35 to 4.52)	10 more per 1000 (from 26 fewer to 141 more)	⊕OOO VERY LOW	CRITICAL
Adverse events - Sore throat & dysphagia [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[2]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[4]	none	15/100 (15%)	18/100 (18%)	RR 0.83 (0.45 to 1.56)	31 fewer per 1000 (from 99 fewer to 101 more)	⊕OOO VERY LOW	CRITICAL
Incidence of lymphoedema (G1-G3) [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[2]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[3]	none	41/100 (41%)	35/100 (35%)	RR 1.17 (0.82 to 1.67)	59 more per 1000 (from 63 fewer to 234 more)	⊕⊕OO LOW	CRITICAL
Adverse events - Skin reactions (G1-G4) [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[2]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	100/100 (100%)	100/100 (100%)	RR 1 (0.98 to 1.02)	0 fewer per 1000 (from 20 fewer to 20 more)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Arm or shoulder pain [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	401/2537 (15.8%)	441/2601 (17%)	RR 0.93 (0.82 to 1.05)	12 fewer per 1000 (from 31 fewer to 8 more)	⊕⊕⊕⊕ HIGH	CRITICAL
EORTC QLQ-BR23 - Swollen arm or hand [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	101/2536 (4%)	103/2600 (4%)	RR 1.01 (0.77 to 1.32)	0 more per 1000 (from 9 fewer to 13 more)	⊕⊕OO LOW	CRITICAL
EORTC QLQ-BR23 - Difficulty raising arm [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	171/2533 (6.8%)	209/2599 (8%)	RR 0.84 (0.69 to 1.02)	13 fewer per 1000 (from 25 fewer to 2 more)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Breast pain [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	338/2538 (13.3%)	428/2601 (16.5%)	RR 0.81 (0.71 to 0.92)	31 fewer per 1000 (from 13 fewer to 48 fewer)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Breast swollen [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	122/2538 (4.8%)	236/2597 (9.1%)	RR 0.53 (0.43 to 0.65)	43 fewer per 1000 (from 32 fewer to 52 fewer)	⊕⊕OO LOW	CRITICAL

EORTC QLQ-BR23 - Breast oversensitive [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	283/2528 (11.2%)	334/2596 (12.9%)	RR 0.87 (0.75 to 1.01)	17 fewer per 1000 (from 32 fewer to 1 more)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Skin problems in breast [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	156/2539 (6.1%)	209/2596 (8.1%)	RR 0.76 (0.62 to 0.93)	19 fewer per 1000 (from 6 fewer to 31 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Normal tissue effects - Breast appearance changed [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	778/2480 (31.4%)	929/2550 (36.4%)	RR 0.86 (0.8 to 0.93)	51 fewer per 1000 (from 26 fewer to 73 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Normal tissue effects - Breast smaller [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	585/2445 (23.9%)	606/2520 (24%)	RR 0.99 (0.9 to 1.1)	2 fewer per 1000 (from 24 fewer to 24 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Normal tissue effects - Breast harder or firmer [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	499/2446 (20.4%)	690/2512 (27.5%)	RR 0.74 (0.67 to 0.82)	71 fewer per 1000 (from 49 fewer to 91 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Normal tissue effects - Skin appearance changed [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	340/2505 (13.6%)	392/2571 (15.2%)	RR 0.89 (0.78 to 1.02)	17 fewer per 1000 (from 34 fewer to 3 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] FAST-Forward Brunt 2020
[2] Shahid 2009
[3] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
[4] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.
[6] Study at moderate risk of bias. Quality of the outcome downgraded once.

Table 19 Hypofractionation regimen: 26 Gy in 5 fractions over 1 week (whole breast) compared to 27 Gy in 5 fractions over 1 week (whole breast)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**26Gy/5 fractions**	**27Gy/5 fractions**	**Relative (95% CI)**	**Absolute**		
All-cause mortality [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	90/1368 (6.6%)	105/1367 (7.7%)	RR 0.86 (0.65 to 1.12)	11 fewer per 1000 (from 27 fewer to 9 more)	⊕⊕⊕O MODERATE	CRITICAL

Breast cancer related mortality [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	114/1368 (8.3%)	114/1367 (8.3%)	RR 1 (0.78 to 1.28)	0 fewer per 1000 (from 18 fewer to 23 more)	⊕⊕OO LOW	CRITICAL
Local relapse [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	90/1368 (6.6%)	105/1367 (7.7%)	RR 0.78 (0.44 to 1.37)	17 fewer per 1000 (from 43 fewer to 28 more)	⊕⊕OO LOW	CRITICAL
Loco-regional relapse [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	29/1368 (2.1%)	35/1367 (2.6%)	RR 0.83 (0.51 to 1.35)	4 fewer per 1000 (from 13 fewer to 9 more)	⊕⊕OO LOW	CRITICAL
Metastatic disease [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	76/1368 (5.6%)	69/1367 (5%)	RR 1.10 (0.80 to 1.51)	5 more per 1000 (from 10 fewer to 26 more)	⊕⊕⊕O MODERATE	CRITICAL
Normal tissue effects - Breast appearance changed [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	770/2563 (30%)	929/2550 (36.4%)	RR 0.82 (0.76 to 0.89)	66 fewer per 1000 (from 40 fewer to 87 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Normal tissue effects - Breast smaller [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	515/2542 (20.3%)	606/2520 (24%)	RR 0.84 (0.76 to 0.93)	38 fewer per 1000 (from 17 fewer to 58 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Normal tissue effects - Breast harder or firmer [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	626/2534 (24.7%)	690/2512 (27.5%)	RR 0.9 (0.82 to 0.99)	27 fewer per 1000 (from 3 fewer to 49 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Normal tissue effects - Skin appearance changed [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	338/2576 (13.1%)	392/2571 (15.2%)	RR 0.86 (0.75 to 0.98)	21 fewer per 1000 (from 3 fewer to 38 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events - Any adverse event [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	774/6327 (12.2%)	1004/6303 (15.9%)	RR 0.77 (0.7 to 0.84)	37 fewer per 1000 (from 25 fewer to 48 fewer)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Arm or shoulder pain [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	455/2599 (17.5%)	441/2601 (17%)	RR 1.03 (0.92 to 1.16)	5 more per 1000 (from 14 fewer to 27 more)	⊕⊕⊕⊕ HIGH	CRITICAL
EORTC QLQ-BR23 - Swollen arm or hand [MID +/- 0.8 to 1.25] (follow-up 5 years)												

1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	124/2592 (4.8%)	103/2600 (4%)	RR 1.21 (0.94 to 1.56)	8 more per 1000 (from 2 fewer to 22 more)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Difficulty raising arm [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	188/2596 (7.2%)	209/2599 (8%)	RR 0.9 (0.75 to 1.09)	8 fewer per 1000 (from 20 fewer to 7 more)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Breast pain [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	417/2597 (16.1%)	428/2601 (16.5%)	RR 0.98 (0.86 to 1.1)	3 fewer per 1000 (from 23 fewer to 16 more)	⊕⊕⊕⊕ HIGH	CRITICAL
EORTC QLQ-BR23 - Breast swollen [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	192/2599 (7.4%)	236/2597 (9.1%)	RR 0.81 (0.68 to 0.98)	17 fewer per 1000 (from 2 fewer to 29 fewer)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Breast oversensitive [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	319/2587 (12.3%)	334/2596 (12.9%)	RR 0.96 (0.83 to 1.11)	5 fewer per 1000 (from 22 fewer to 14 more)	⊕⊕⊕⊕ HIGH	CRITICAL
EORTC QLQ-BR23 - Skin problems in breast [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	164/2592 (6.3%)	209/2596 (8.1%)	RR 0.79 (0.65 to 0.96)	17 fewer per 1000 (from 3 fewer to 28 fewer)	⊕⊕⊕O MODERATE	CRITICAL

[1] FAST-Forward Brunt 2020
[2] 95% confidence interval crosses one end of defined MID. Quality of the outcome downgraded once
[3] 95% confidence interval crosses both ends of defined MID. Quality of the outcome downgraded twice.

Table 20 Hypofractionation regimen: 35 Gy in 10 fractions over 2 weeks (whole breast) compared to 27 Gy in 5 fractions over 1 week (whole breast)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**35Gy/10 fractions**	**27Gy/5 fractions**	**Relative (95% CI)**	**Absolute**		
All-cause mortality [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	18/100 (18%)	17/100 (17%)	RR 1.06 (0.58 to 1.93)	10 more per 1000 (from 71 fewer to 158 more)	⊕OOO VERY LOW	CRITICAL
Locoregional relapse [MID +/- 0.8 to 1.25] (follow-up 6 months)												

1[4]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	12/100 (12%)	11/100 (11%)	RR 1.09 (0.51 to 2.36)	10 more per 1000 (from 54 fewer to 150 more)	⊕OOO VERY LOW	CRITICAL
Metastatic disease [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[4]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	24/100 (24%)	26/100 (26%)	RR 0.92 (0.57 to 1.49)	21 fewer per 1000 (from 112 fewer to 127 more)	⊕OOO VERY LOW	CRITICAL
Overall survival [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[4]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	83/100 (83%)	87/100 (87%)	RR 0.95 (0.85 to 1.07)	44 fewer per 1000 (from 130 fewer to 61 more)	⊕⊕⊕O MODERATE	CRITICAL
Disease free survival [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[4]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	72/100 (72%)	71/100 (71%)	RR 1.01 (0.85 to 1.21)	7 more per 1000 (from 106 fewer to 149 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events - Incidence of lymphoedema (G1-G3) [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[4]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	34/100 (34%)	35/100 (35%)	RR 0.97 (0.66 to 1.42)	10 fewer per 1000 (from 119 fewer to 147 more)	⊕OOO VERY LOW	CRITICAL
Adverse events - Radiation pneumonitis [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[4]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/100 (5%)	4/100 (4%)	RR 1.25 (0.35 to 4.52)	10 more per 1000 (from 26 fewer to 141 more)	⊕OOO VERY LOW	CRITICAL
Adverse events - Sore throat & dysphagia [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[4]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	20/100 (20%)	18/100 (18%)	RR 1.11 (0.63 to 1.97)	20 more per 1000 (from 67 fewer to 175 more)	⊕OOO VERY LOW	CRITICAL
Adverse events - Skin reactions (G1-G4) [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[4]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	100/100 (100%)	100/100 (100%)	RR 1 (0.98 to 1.02)	0 fewer per 1000 (from 20 fewer to 20 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
[2] Study at moderate risk of bias. Quality of the outcome downgraded once.
[3] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.
[4] Shahid 2009

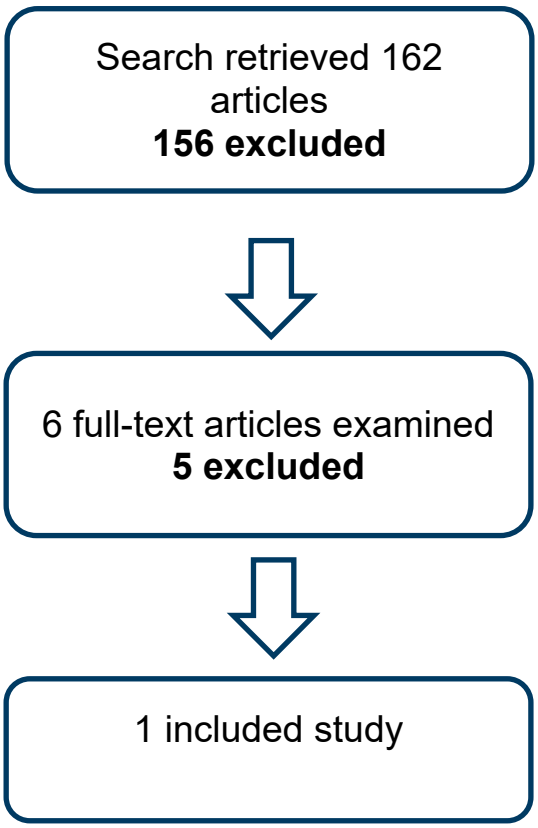
Table 21 Hypofractionation regimen: 40 Gy in 15 fractions over 3 weeks (whole breast) compared to 35 Gy in 10 fractions over 2 weeks (whole breast)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**40Gy/15 fractions**	**35Gy/10 fractions**	**Relative (95% CI)**	**Absolute**		

All-cause mortality [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	20/100 (20%)	18/100 (18%)	RR 1.11 (0.63 to 1.97)	20 more per 1000 (from 67 fewer to 175 more)	⊕OOO VERY LOW	CRITICAL
Locoregional relapse [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/100 (10%)	12/100 (12%)	RR 0.83 (0.38 to 1.84)	20 fewer per 1000 (from 74 fewer to 101 more)	⊕OOO VERY LOW	CRITICAL
Metastatic disease [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	28/100 (28%)	24/100 (24%)	RR 1.17 (0.73 to 1.87)	41 more per 1000 (from 65 fewer to 209 more)	⊕OOO VERY LOW	CRITICAL
Overall survival [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	82/100 (82%)	83/100 (83%)	RR 0.99 (0.87 to 1.12)	8 fewer per 1000 (from 108 fewer to 100 more)	⊕⊕⊕O MODERATE	CRITICAL
Disease free survival [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71/100 (71%)	72/100 (72%)	RR 0.99 (0.83 to 1.17)	7 fewer per 1000 (from 122 fewer to 122 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events - Incidence of lymphoedema (G1-G3) [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	41/100 (41%)	34/100 (34%)	RR 1.21 (0.84 to 1.73)	71 more per 1000 (from 54 fewer to 248 more)	⊕⊕OO LOW	CRITICAL
Adverse events - Radiation pneumonitis [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/100 (5%)	5/100 (5%)	RR 1 (0.3 to 3.35)	0 fewer per 1000 (from 35 fewer to 117 more)	⊕OOO VERY LOW	CRITICAL
Adverse events - Sore throat & dysphagia [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	15/100 (15%)	20/100 (20%)	RR 0.75 (0.41 to 1.38)	50 fewer per 1000 (from 118 fewer to 76 more)	⊕OOO VERY LOW	CRITICAL
Adverse events - Skin reactions (G1-G4) [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	100/100 (100%)	100/100 (100%)	RR 1 (0.98 to 1.02)	0 fewer per 1000 (from 20 fewer to 20 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events - Cardiac toxicity >10% LVEF reduction [MID +/- 0.8 to 1.25] (follow-up 6 months)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/100 (5%)	6/100 (6%)	RR 0.83 (0.26 to 2.64)	10 fewer per 1000 (from 44 fewer to 98 more)	⊕OOO VERY LOW	CRITICAL

[1] Shahid 2009
[2] Study at moderate risk of bias. Quality of the outcome downgraded once.
[3] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.
[5] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

Table 22: Economic evidence table

Study	Glynn D, Bliss J, Brunt AM, Coles CE, Wheatley D, Haviland JS, Kirby AM, Longo F, Faria R, Yarnold JR, Griffin S. Cost-effectiveness of 5 fraction and partial breast radiotherapy for early breast cancer in the UK: model-based multi-trial analysis. Breast Cancer Res Treat. 2023 Jan;197(2):405-416. doi: 10.1007/s10549-022-06802-1. Epub 2022 Nov 17. PMID: 36396774; PMCID: PMC9672618.			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis **Study design:** decision analytic model: decision tree and Markov model **Approach to analysis:** Model health states included disease-free, locoregional relapse, distant relapse and dead. Movement between health states based on the FAST Forward and the IMPORT LOW trials. Costs and QALYs were assigned to health states, and total costs and QALYs were calculated for each arm. These results were then used to perform an incremental analysis using a cost-effectiveness threshold of £15,000 per QALY, estimated by Claxton (2015). **Perspective:** UK NHS and Personal Social Services (PSS) **Time horizon:** Fifty years **Discounting:** 3.5% per annum for both costs	**Population:** Adults who have undergone breast-conserving surgery or mastectomy for early breast cancer (stage I,II,IIIa). Divided into two subgroups: 1 was eligible for PB therapy, 2 was not eligible for PB therapy. **Intervention Subgroup 1:** WB5F, PB5F **Comparator subgroup 1:** WB15F, PB15F **Intervention Subgroup 2:** WB5F **Comparator Subgroup 2:** WB15F	**Cost difference:** Subgroup 1: Not reported (NR). Subgroup 2: £2,162 (95% CI £1,282 to £3,169) **Currency and cost year:** British Pound Sterling 2019 **Costs included:** Costs of delivering radiotherapy and costs of managing acute side effects, including. general practitioner costs, nursing costs, and hospitalisations. Unit costs were applied to resource use to construct per patient costs. Following the first year of locoregional relapse, costs of supportive care were considered as one GP visit and one mammogram per year.	**QALY difference:** Subgroup 1: NR Subgroup 2: 0.05 (95% CI 0.01 to 0.12).	**Incremental analysis:** ICERs were compared to a cost-effectiveness threshold of £15,000/QALY For subgroup 1, all treatment options were dominated by PB5F. For subgroup 2, WB5F dominated WB15F. **Analysis of uncertainty:** Uncertainties in inputs due to sample size were indicated in distributions, the joint impact of which were further explored through a PSA. One-way sensitivity analyses were run to explore sensitivity of results to inputs and assumptions, for instance, distant recurrence assumption, mortality rate, costs and disutility of distant relapse, and rate of adverse skin reactions. For subgroup 1, there was a 62% chance that PB5F either dominated all alternatives or

Study	Glynn D, Bliss J, Brunt AM, Coles CE, Wheatley D, Haviland JS, Kirby AM, Longo F, Faria R, Yarnold JR, Griffin S. Cost-effectiveness of 5 fraction and partial breast radiotherapy for early breast cancer in the UK: model-based multi-trial analysis. Breast Cancer Res Treat. 2023 Jan;197(2):405-416. doi: 10.1007/s10549-022-06802-1. Epub 2022 Nov 17. PMID: 36396774; PMCID: PMC9672618.			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
and health effects				had an ICER below £15,000/QALY. PB5F dominated all options except when using the distant recurrence hazard ratio results reported in the trials. In this scenario, PB15F compared with PB5F was expected to be more expensive by £1,014 (95% confidence interval £-263 to £1,922) and more effective by 0.07 additional QALYs (95% confidence interval − 0.05 to 0.24) for a threshold of £15,000/QALY. However, there remained a higher probability that PB5F was cost-effective compared to PB15F (56%). For subgroup 2, there was a 100% chance that WB5F either dominated WB15F or had an ICER below £15,000. When using the distant recurrence hazard ratio results reported in the trials, WB15F was expected to be more expensive at £472 (95% confidence interval £-2214 to £2,942) and more effective by 0.25 additional QALYs (95% interval -0.18 to 0.69). In this scenario, the expected ICER for

Study	Glynn D, Bliss J, Brunt AM, Coles CE, Wheatley D, Haviland JS, Kirby AM, Longo F, Faria R, Yarnold JR, Griffin S. Cost-effectiveness of 5 fraction and partial breast radiotherapy for early breast cancer in the UK: model-based multi-trial analysis. Breast Cancer Res Treat. 2023 Jan;197(2):405-416. doi: 10.1007/s10549-022-06802-1. Epub 2022 Nov 17. PMID: 36396774; PMCID: PMC9672618.			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
				WB15F was £1,899/QALY

Data sources

Interventions and comparators: WB5F: Whole breast 26 Gy delivered in 5 fractions; PB5F: Partial breast 26 Gy delivered in 5 fractions; WB15F: Whole breast 40 Gy delivered in 15 fractions; PB15F: Partial breast 40 Gy delivered in 15 fractions
Outcomes: Time to locoregional relapse, distant relapse, radiotherapy-related adverse events, and all-cause mortality. These were estimated using observations from two UK trials: FAST-Forward (FF) to inform the impact of 15F versus 5Fs hypofractionation regimens, and IMPORT LOW (IL) to inform the impact of WB versus PB. Risk of all-cause mortality was assumed to be the same as age-matched general population if no distant relapse had occurred. For those who had, risk was based on French study of metastatic breast cancer.
Quality of life: HRQoL was estimated for the alive and disease-free state using data from both FF and IL. Measured using the EQ-5D-5L questionnaire in FF and EQ-5D-3L in IL. 5L was mapped to 3L for consistency. A GLM was used to model disutility based on the first wave of data after treatment in each study (3 months for FF and 6 months for IL) Quality of life post locoregional relapse was assumed the same for all treatments. Decrement in HRQoL with distant relapse was taken from a previous radiotherapy model. Decline with age was based on a 2010 health survey for England study. The HRQoL impact of acute adverse events was omitted due to a lack of data.
Costs: The FF questionnaire was used to estimate costs as it was considered more complete than the IL cost questionnaire. Costs for the alive and disease-free state were estimated from FF**.** Costs for the remaining health states were sourced from the wider literature as there were insufficient observations to estimate them from FF. Supportive care and treatment costs for distant relapse were sourced from a UK study of 77 women. Cost of delivery of radiotherapy was sourced from National Cost Collection data 2018/19. Expert opinion was used to inform the proportions receiving cardiac breath hold. (Main difference between PB and WB assumed to result from reduced use of cardiac breath hold with PB). Costs were assigned to the management of acute adverse events.

Comments

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Overall applicability

Directly applicable

Overall quality

Some minor limitations including analysis being based on a £15,000/QALY threshold which differs from NICE's reference case; analysis not taking into account QoL impact of acute adverse skin reactions; and uncertainty of distance recurrence treatment effect in sensitivity analysis due to limited follow up in trials (5 years).

Table 23: Applicability checklist

Study	1.1 Is the study population appropriate for the review question?	1.2 Are the interventions appropriate for the review question?	1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	1.4 Is the perspective for costs appropriate for the review question?	1.5 Is the perspective for outcomes appropriate for the review question?	1.6 Are all future costs and outcomes discounted appropriately?	1.7 Are QALYs derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome?	1.8 Overall judgement
Glynn et al. (2022)	Yes	Yes	Yes (UK based study)	Yes (NHS and PSS perspective)	Yes	3.5% is used	Yes – EQ-5D-5L utility values used and were mapped onto 3L	Directly applicable

Table 24: Limitations checklist

Study	2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	2.3 Are all important and relevant outcomes included?	2.4 Are the estimates of baseline outcomes from the best available source?	2.5 Are the estimates of relative intervention effects from the best available source?	2.6 Are all important and relevant costs included?	2.7 Are the estimates of resource use from the best available source?	2.8 Are the unit costs of resources from the best available source?	2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	2.11 Has no potential financial conflict of interest been declared?	2.12 Overall assessment
Glynn et al. (2022)	Yes	Yes, but extrapolation is based on 5 year follow up period in trials which may not be long enough to understand extent of treatment effects.	Yes	Yes.	Yes, although distance recurrence ratio used in sensitivity analysis is uncertain given follow-up period in trials is limited to 5 years. In addition, there was no available data on QoL for adverse skin reactions and therefore this is not accounted for in the model.	Yes	Yes	Yes – UK study	Yes. Opportunity cost of a QALY assumed to be £15,000, not consistent with NICE Reference Case	Yes	Yes	Some minor limitations

Appendix I – Health economic model

Economic modelling was not conducted for this review question.

Appendix J – Excluded studies

Study	Reason for exclusion
Arsenault, J., Parpia, S., Goldberg, M. et al. (2020) Acute Toxicity and Quality of Life of Hypofractionated Radiation Therapy for Breast Cancer. International Journal of Radiation Oncology Biology Physics 107(5): 943-948	- Not a relevant study design *Non-randomised, cohort study*
Brunt, A.M., Wheatley, D., Yarnold, J. et al. (2016) Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial. Radiotherapy and Oncology 120(1): 114-118	- Secondary publication of primary study
Brunt, AM Haviland, JS Kirby, AM Somaiah, N Wheatley, DA Bliss, JM Yarnold, JR (2021) Five-fraction Radiotherapy for Breast Cancer: FAST-Forward to Implementation. CLINICAL ONCOLOGY 33(7): 430 - 439	- Secondary publication of primary study
Belkacemi, Y., Bourgier, C., Kramar, A. et al. (2013) Share: A french multicenter phase iii trial comparing accelerated partial irradiation versus standard or hypofractionated whole breast irradiation in breast cancer patients at low risk of local recurrence. Clinical Advances in Hematology and Oncology 11(2): 76-83	- Systematic review used as source of primary studies
Berrang, T.S., Olivotto, I., Kim, D.-H. et al. (2011) Three-year outcomes of a Canadian multicenter study of accelerated partial breast irradiation using conformal radiation therapy. International Journal of Radiation Oncology Biology Physics 81(5): 1220-1227	- Not a relevant study design *Non-randomised, cohort study*
Boutrus, R.R., El Sherif, S., Abdelazim, Y. et al. (2021) Once Daily Versus Twice Daily External Beam Accelerated Partial Breast Irradiation: A Randomized Prospective Study. International Journal of Radiation Oncology Biology Physics 109(5): 1296-1300	- Study does not contain a relevant intervention
Chadha, Manjeet, Vongtama, Dan, Friedmann, Patricia et al. (2012) Comparative acute toxicity from whole breast irradiation using 3-week accelerated schedule with concomitant boost and the 6.5-week conventional schedule with sequential boost for early-stage breast cancer. Clinical breast cancer 12(1): 57-62	- Study does not contain a relevant intervention
Chen, S., Sun, G., Wang, S. et al. (2021) Delay in Initiating Postmastectomy Radiotherapy is Associated with Inferior Clinical Oncologic Outcomes for High-Risk Breast Cancer.	- Not a relevant study design *Non-randomised, cohort study*

Study	Reason for exclusion
International journal of radiation oncology, biology, physics 111(3): 36-s37	
Chen, X., Yang, T.-X., Xia, Y.-X. et al. (2022) Optimal radiotherapy after breast-conserving surgery for early breast cancer: A network meta-analysis of 23,418 patients. Cancer/Radiotherapie 26(8): 1054-1063	- Not a relevant study design *Network meta-analysis of randomised and non-randomised trials*
Chua, B.H., Link, E.K., Kunkler, I.H. et al. (2022) Radiation doses and fractionation schedules in non-low-risk ductal carcinoma in situ in the breast (BIG 3-07/TROG 07.01): a randomised, factorial, multicentre, open-label, phase 3 study. The Lancet 400(10350): 431-440	- Study does not contain a relevant intervention
Coles, C. E., Griffin, C. L., Kirby, A. M., Titley, J., Agrawal, R. K., Alhasso, A., … Thompson, A. (2017). Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *The Lancet*, *390*(10099), 1048–1060. doi:10.1016/s0140-6736(17)31145-5	- Comparator does not match protocol
Combs, S.E. (2017) Hypofractionated radiotherapy of breast carcinoma. Best Practice Onkologie 12(5): 194-200	- Study not reported in English
Cooper, B.T., Formenti-Ujlaki, G.F., Li, X. et al. (2016) Prospective randomized trial of prone accelerated intensity modulated breast radiation therapy with a daily versus weekly boost to the tumor bed. International Journal of Radiation Oncology Biology Physics 95(2): 571-578	- Study does not contain a relevant intervention
De Rose, F, Fogliata, A, Franceschini, D et al. (2016) Phase II trial of hypofractionated VMAT-based treatment for early-stage breast cancer: 2-year toxicity and clinical results. Radiation oncology (London, England) 11(1nopagination)	- Not a relevant study design *Non-randomised, prospective cohort study*
El Raouf, E.S.A., Sarhan, A.M., Dorgham, Y.T. et al. (2022) Accelerated Partial Breast Radiotherapy in Comparison with Conventional Whole Breast Radiotherapy in Early Breast Cancer. Latin American Journal of Pharmacy 41(specialissue): 102-108	- Full text manuscript not found
Eldeeb, H.; Awad, I.; Elhanafy, O. (2012) Hypofractionation in post-mastectomy breast cancer patients: Seven-year follow-up. Medical Oncology 29(4): 2570-2576	- Not a relevant study design *Non-randomised, observational study*

Study	Reason for exclusion
Eldredge-Hindy, H Pan, JM Rai, SN Reshko, LB Dragun, A Riley, EC McMasters, KM Ajkay, N (2021) A Phase II Trial of Once Weekly Hypofractionated Breast Irradiation for Early-Stage Breast Cancer. ANNALS OF SURGICAL ONCOLOGY 28(11): 5880 - 5892	- Not a relevant study design *Non-randomised, observational study*
Fastner, G, Reitsamer, R, Gaisberger, C et al. (2022) Hypofractionated Whole Breast Irradiation and Boost-IOERT in Early-Stage Breast Cancer (HIOB): first Clinical Results of a Prospective Multicenter Trial (NCT01343459). Cancers 14(6)	- Not a relevant study design *Non-randomised, prospective cohort study*
Fekete, G., Ujhidy, D., Egyud, Z. et al. (2015) Partial breast radiotherapy with simple teletherapy techniques. Medical Dosimetry 40(4): 290-295	- Comparator does not match protocol
Fernando, I.N., Bowden, S.J., Herring, K. et al. (2020) Synchronous versus sequential chemo-radiotherapy in patients with early-stage breast cancer (SECRAB): A randomised, phase III, trial. Radiotherapy and Oncology 142: 52-61	- Data not reported in an extractable format
Finkel, M.A., Cooper, B.T., Li, X. et al. (2016) Quality of life in women undergoing breast irradiation in a randomized, controlled clinical trial evaluating different tumor bed boost fractionations. International Journal of Radiation Oncology Biology Physics 95(2): 579-589	- Study does not contain a relevant intervention
Franceschini, D Fogliata, A Spoto, R Dominici, L Lo Faro, L Franzese, C Comito, T Lobefalo, F Reggiori, G Cozzi, L Sagona, A Gentile, D Scorsetti, M (2021) Long term results of a phase II trial of hypofractionated adjuvant radiotherapy for early-stage breast cancer with volumetric modulated arc therapy and simultaneous integrated boost. RADIOTHERAPY AND ONCOLOGY 164: 50 - 56	- Not a relevant study design *Non-randomised, prospective cohort study*
Franceschini, D., Loi, M., Chiola, I. et al. (2021) Preliminary Results of a Randomized Study on Postmenopausal Women with Early-Stage Breast Cancer: Adjuvant Hypofractionated Whole Breast Irradiation Versus Accelerated Partial Breast Irradiation (HYPAB Trial). Clinical Breast Cancer 21(3): 231-238	- Study does not contain a relevant intervention
Hashemi, F.A., Barzegartahamtan, M., Mohammadpour, R.A. et al. (2016) Comparison of conventional and hypofractionated radiotherapy in breast cancer patients in terms of 5-year survival, locoregional recurrence, late skin complications and cosmetic results. Asian Pacific Journal of Cancer Prevention 17(11): 4819-4823	- Comparator does not match protocol

Study	Reason for exclusion
Hepel, Jaroslaw T, Yashar, Catheryn, Leonard, Kara L et al. (2018) Five fraction accelerated partial breast irradiation using noninvasive image-guided breast brachytherapy: Feasibility and acute toxicity. Brachytherapy 17(5): 825-830	- Study does not contain a relevant intervention
Haviland, J.S., Bentzen, S.M., Bliss, J.M. et al. (2016) Prolongation of overall treatment time as a cause of treatment failure in early breast cancer: An analysis of the UK START (Standardisation of Breast Radiotherapy) trials of radiotherapy fractionation. Radiotherapy and Oncology 121(3): 420-423	- Secondary publication of primary study
Haviland, Joanne S, Mannino, Mariella, Griffin, Clare et al. (2018) Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: Results from the UK START (Standardisation of Breast Radiotherapy) trials. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 126(1): 155-162	- Secondary publication of primary study
Hopwood, P., Haviland, J.S., Sumo, G. et al. (2010) Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. The Lancet Oncology 11(3): 231-240	- Secondary publication of primary study
Hosseini, S., Shahabadi, M., Salek, R. et al. (2019) Accelerated hypofractionated whole breast radiotherapy for early breast cancer; arandomized phase iii clinical trial. Acta Medica Iranica 57(11): 645-652	- Comparator does not match protocol
Hou, H.-L., Song, Y.-C., Li, R.-Y. et al. (2015) Similar outcomes of standard radiotherapy and hypofractionated radiotherapy following breast-conserving surgery. Medical Science Monitor 21: 2251-2256	- Comparator does not match protocol
Issoufaly, I., Petit, C., Guihard, S. et al. (2022) Favorable safety profile of moderate hypofractionated over normofractionated radiotherapy in breast cancer patients: a multicentric prospective real-life data farming analysis. Radiation Oncology 17(1): 80	- Not a relevant study design *Non-randomised, prospective real-world evidence*
Jacobs, DHM Charaghvandi, RK Horeweg, N Maduro, JH Speijer, G Roeloffzen, EMA Mast, M Bantema-Joppe, E Petoukhova, AL van den Bongard, DHJG Koper, P Crijns, APG Marijnen, CAM Verkooijen, HM (2021) Health-related quality	- Study does not contain a relevant intervention

Study	Reason for exclusion
of life of early-stage breast cancer patients after different radiotherapy regimens. BREAST CANCER RESEARCH AND TREATMENT 189(2): 387 - 398	
Jain, N Sharma, R Sachdeva, K Kaur, A Sudan, M (2022) Conventional Versus Different Hypofractionated Radiotherapy Dosage Schedules in Postmastectomy Advanced Breast Cancer. JOURNAL OF MEDICAL PHYSICS 47(2): 141 - 144	- Not a relevant study design *Non-randomised, retrospective cohort study*
James, Melissa L, Lehman, Margot, Hider, Phil N et al. (2010) Fraction size in radiation treatment for breast conservation in early breast cancer. The Cochrane database of systematic reviews: cd003860	- Review article but not a systematic review
Jiang, HY Meng, LL Zhang, HJ Dai, XK Zhang, Q Ju, ZJ Yu, W Ma, L (2021) Hypofractionated radiotherapy in ten fractions for postmastectomy patients: a phase II study compared with another hypofractionation schedule with sixteen fractions. BMC CANCER 21(1)	- Not a relevant study design *Non-randomised, prospective cohort study*
Khan, A.J., Poppe, M.M., Goyal, S. et al. (2017) Hypofractionated postmastectomy radiation therapy is safe and effective: First Results from a prospective phase II trial. Journal of Clinical Oncology 35(18): 2037-2043	- Not a relevant study design *Non-randomised, prospective cohort study*
Kim, D.-Y., Park, E., Heo, C.Y. et al. (2021) Hypofractionated versus conventional fractionated radiotherapy for breast cancer in patients with reconstructed breast: Toxicity analysis. Breast 55: 37-44	- Not a relevant study design *Non-randomised, observational study*
King, M.T., Link, E.K., Whelan, T.J. et al. (2020) Quality of life after breast-conserving therapy and adjuvant radiotherapy for non-low-risk ductal carcinoma in situ (BIG 3-07/TROG 07.01): 2-year results of a randomised, controlled, phase 3 trial. The Lancet Oncology 21(5): 685-698	- Comparator does not match protocol
Kirova, Y.M., Campana, F., Savignoni, A. et al. (2009) Breast-Conserving Treatment in the Elderly: Long-Term Results of Adjuvant Hypofractionated and Normofractionated Radiotherapy. International Journal of Radiation Oncology Biology Physics 75(1): 76-81	- Not a relevant study design *Non-randomised, cohort study*
Ko, D.-H.I., Norriss, A., Harrington, C.R. et al. (2015) Hypofractionated radiation treatment following mastectomy in early breast cancer: The Christchurch experience. Journal of Medical Imaging and Radiation Oncology 59(2): 243-247	- Not a relevant study design *Non-randomised, retrospective cohort study*

Study	Reason for exclusion
Koukourakis, IM Panteliadou, M Giakzidis, AG Nanos, C Abatzoglou, I Giatromanolaki, A Koukourakis, MI (2021) Long-Term Results of Postoperative Hypofractionated Accelerated Breast and Lymph Node Radiotherapy (HypoAR) with Hypofractionated Boost. CURRENT ONCOLOGY 28(5): 3474 - 3487	- Not a relevant study design *Non-randomised, cohort study*
Krug, D., Koder, C., Hafner, M.F. et al. (2020) Acute toxicity of normofractionated intensity modulated radiotherapy with simultaneous integrated boost compared to three-dimensional conformal radiotherapy with sequential boost in the adjuvant treatment of breast cancer. Radiation Oncology 15(1): 235	- Study does not contain a relevant intervention
Livi, L., Meattini, I., Marrazzo, L. et al. (2015) Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. European Journal of Cancer 51(4): 451-463	- Study does not contain a relevant intervention
Lukens, J.N., Mick, R., Huang, A.C. et al. (2021) Final Results of a Phase I "RadVax" Trial of Hypofractionated Radiation Combined with Pembrolizumab in Patients With Metastatic Solid Tumors. International journal of radiation oncology, biology, physics 111(3): 67-s68	- Not a relevant study design *Non-randomised, cohort study*
Maiti, S., Meyur, S., Mandal, B.C. et al. (2021) Comparison of conventional and hypofractionated radiation after mastectomy in locally advanced breast cancer: A prospective randomised study on dosimetric evaluation and treatment outcome. Journal of Radiotherapy in Practice 20(1): 30-38	- Comparator does not match protocol
Meattini, I., Marrazzo, L., Saieva, C. et al. (2020) Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: Long-term results of the randomized phase III APBI-IMRT-florence trial. Journal of Clinical Oncology 38(35): 4175-4183	- Study does not contain a relevant intervention
Meattini, I., Saieva, C., Marrazzo, L. et al. (2015) Accelerated partial breast irradiation using intensity-modulated radiotherapy technique compared to whole breast irradiation for patients aged 70 years or older: subgroup analysis from a randomized phase 3 trial. Breast Cancer Research and Treatment 153(3): 539-547	- Study does not contain a relevant intervention
Meattini, I., Saieva, C., Miccinesi, G. et al. (2017) Accelerated partial breast irradiation using intensity modulated radiotherapy versus whole breast	- Study does not contain a relevant intervention

Study	Reason for exclusion
irradiation: Health-related quality of life final analysis from the Florence phase 3 trial. European Journal of Cancer 76: 17-26	
Monten, C, Lievens, Y, Olteanu, LAM et al. (2017) Highly Accelerated Irradiation in 5 Fractions (HAI-5): feasibility in Elderly Women with Early or Locally Advanced Breast Cancer. International journal of radiation oncology biology physics. (No pagination), 2017 dateofpublicationnovember03	- Not a relevant study design *Non-randomised, prospective cohort study*
Morales, MG Martinez-Monge, R Martinez-Regueira, F Rodriguez-Spiteri, N Olartecoechea, B Ramos, L Ayestaran, A Insausti, LP Elizalde, A Abengozar, M Rubio, I Esgueva, A Sobrido, C Cambeiro, M (2022) Four-fraction ultra-accelerated minimal breast irradiation in early breast cancer: The initial feasibility results of an institutional experience. BRACHYTHERAPY 21(4): 475 - 486	- Not a relevant study design *Non-randomised, feasibility study*
Mukesh, M.B., Barnett, G.C., Wilkinson, J.S. et al. (2013) Randomized controlled trial of intensity-modulated radiotherapy for early breast cancer: 5-year results confirm superior overall cosmesis. Journal of Clinical Oncology 31(36): 4488-4495	- Study does not contain a relevant intervention
Mulliez, T., Veldeman, L., Van Greveling, A. et al. (2013) Hypofractionated whole breast irradiation for patients with large breasts: A randomized trial comparing prone and supine positions. Radiotherapy and Oncology 108(2): 203-208	- Study does not contain a relevant intervention
Najas, GF Stuart, SR Marta, GN Teixeira, LAB Gico, VD Serante, AR Mauro, GP Lima, MC Carvalho, HD (2021) Hypofractionated radiotherapy in breast cancer: a 10-year single institution experience. REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 26(6): 920 - 927	- Not a relevant study design *Non-randomised, retrospective cohort study*
Nichols, E, Kesmodel, SB, Bellavance, E et al. (2017) Preoperative Accelerated Partial Breast Irradiation for Early-Stage Breast Cancer: preliminary Results of a Prospective, Phase 2 Trial. International journal of radiation oncology biology physics 97(4): 747-753	- Study does not contain a relevant intervention
Ott, OJ, Strnad, V, Stillkrieg, W et al. (2017) Accelerated partial breast irradiation with external beam radiotherapy: first results of the German phase 2 trial. Strahlentherapie und Onkologie 193(1): 55-61	- Study does not contain a relevant intervention
Pfaffendorf, C., Vonthein, R., Krockenberger-Ziegler, K. et al. (2022) Hypofractionation with simultaneous integrated boost after breast-	- Study does not contain a relevant intervention

Study	Reason for exclusion
conserving surgery: Long term results of two phase-II trials. Breast 64: 136-142	
Poppe, M.M., Yehia, Z.A., Baker, C. et al. (2020) 5-Year Update of a Multi-Institution, Prospective Phase 2 Hypofractionated Postmastectomy Radiation Therapy Trial. International Journal of Radiation Oncology Biology Physics 107(4): 694-700	- Not a relevant study design *Non-randomised, prospective cohort study*
Poppe, MM, Yehia, ZA, Baker, C et al. (2020) 5-year Update of a Multi Institution Prospective Phase II Hypofractionated Post-Mastectomy Radiation Therapy Trial. International journal of radiation oncology, biology, physics	- Not a relevant study design *Non-randomised, prospective cohort study*
Prionas, N.D.; Stephens, S.J.; Blitzblau, R.C. (2022) Early-stage Breast Cancer: Tailored External Beam Fractionation Approaches for Treatment of the Whole or Partial Breast. Seminars in Radiation Oncology 32(3): 245-253	- Systematic review used as source of primary studies
Rahimi, A, Thomas, K, Spangler, A et al. (2017) Preliminary Results of a Phase 1 Dose-Escalation Trial for Early-Stage Breast Cancer Using 5-Fraction Stereotactic Body Radiation Therapy for Partial-Breast Irradiation. International journal of radiation oncology biology physics 98(1): 196-205.e2	- Not a relevant study design *Non-randomised, prospective cohort study*
Rastogi, Kartick, Jain, Sandeep, Bhatnagar, Aseem Rai et al. (2018) A Comparative Study of Hypofractionated and Conventional Radiotherapy in Postmastectomy Breast Cancer Patients. Asia-Pacific journal of oncology nursing 5(1): 107-113	- Comparator does not match protocol
Reshko, LB Pan, JM Rai, SN Ajkay, N Dragun, A Roberts, TL Riley, EC Quillo, AR Scoggins, CR McMasters, KM Eldredge-Hindy, H (2022) Final Analysis of a Phase 2 Trial of Once Weekly Hypofractionated Whole Breast Irradiation for Early-Stage Breast Cancer. INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS 112(1): 56 - 65	- Not a relevant study design *Non-randomised, analysis of cohort study*
Robijns, J., Lodewijckx, J., Puts, S. et al. (2022) Photobiomodulation therapy for the prevention of acute radiation dermatitis in breast cancer patients undergoing hypofractioned whole-breast irradiation (LABRA trial). Lasers in Surgery and Medicine 54(3): 374-383	- Study does not contain a relevant intervention
Sayed, M.M., El-Sayed, M.I., Attia, A.M. et al. (2015) Concurrent boost with adjuvant breast hypofractionated radiotherapy and toxicity	- Not a relevant study design *Non-randomised, cohort study*

Study	Reason for exclusion
assessment. Middle East Journal of Cancer 6(1): 21-27	
Schafer, R., Strnad, V., Polgar, C. et al. (2018) Quality-of-life results for accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation in early breast cancer after breast-conserving surgery (GEC-ESTRO): 5-year results of a randomised, phase 3 trial. The Lancet Oncology 19(6): 834-844	- Study does not contain a relevant intervention
Schmeel, L.C., Koch, D., Schmeel, F.C. et al. (2020) Acute radiation-induced skin toxicity in hypofractionated vs. conventional whole-breast irradiation: An objective, randomized multicenter assessment using spectrophotometry. Radiotherapy and Oncology 146: 172-179	- Comparator does not match protocol
Shaitelman, S.F., Lei, X., Thompson, A. et al. (2018) Three-year outcomes with hypofractionated versus conventionally fractionated whole-breast irradiation: Results of a randomized, noninferiority clinical trial. Journal of Clinical Oncology 36(35): 3495-3503	- Comparator does not match protocol
Shaitelman, S.F., Schlembach, P.J., Arzu, I. et al. (2015) Acute and Short-term Toxic Effects of Conventionally Fractionated vs Hypofractionated Whole-Breast Irradiation: A Randomized Clinical Trial. JAMA oncology 1(7): 931-941	- Comparator does not match protocol
Spooner, D., Stocken, D.D., Jordan, S. et al. (2012) A Randomised Controlled Trial to Evaluate both the Role and the Optimal Fractionation of Radiotherapy in the Conservative Management of Early Breast Cancer. Clinical Oncology 24(10): 697-706	- Study does not contain a relevant intervention
START Trialists', Group, Bentzen, S M, Agrawal, R K et al. (2008) The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet (London, England) 371(9618): 1098-107	- Secondary publication of primary study
START Trialists', Group, Bentzen, S M, Agrawal, R K et al. (2008) The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. The Lancet. Oncology 9(4): 331-41	- Secondary publication of primary study
Trovo, Marco, Furlan, Carlo, Polesel, Jerry et al. (2018) Radical radiation therapy for oligometastatic breast cancer: Results of a prospective phase II trial. Radiotherapy and oncology : journal of the	- Does not contain a population of people with early0locally advanced cancer *Population has advanced breast cancer.*

Study	Reason for exclusion
European Society for Therapeutic Radiology and Oncology 126(1): 177-180	
Van Hulle, H., Desaunois, E., Vakaet, V. et al. (2021) Two-year toxicity of simultaneous integrated boost in hypofractionated prone breast cancer irradiation: Comparison with sequential boost in a randomized trial. Radiotherapy and Oncology 158: 62-66	- Study does not contain a relevant intervention
Van Hulle, H., Vakaet, V., Monten, C. et al. (2021) Acute toxicity and health-related quality of life after accelerated whole breast irradiation in 5 fractions with simultaneous integrated boost. Breast 55: 105-111	- Study does not contain a relevant intervention
Vassilis, K., Ioannis, G., Anna, Z. et al. (2017) A unique hypofractionated radiotherapy schedule with 51.3 Gy in 18 fractions three times per week for early breast cancer: outcomes including local control, acute and late skin toxicity. Breast Cancer 24(2): 263-270	- Not a relevant study design *Non-randomised, retrospective cohort study*
Verbanck, S., Van Parijs, H., Schuermans, D. et al. (2022) Lung Restriction in Patients with Breast Cancer After Hypofractionated and Conventional Radiation Therapy: A 10-Year Follow-up. International Journal of Radiation Oncology Biology Physics 113(3): 561-569	- Comparator does not match protocol
Versmessen, H., Vinh-Hung, V., Van Parijs, H. et al. (2012) Health-related quality of life in survivors of stage I-II breast cancer: randomized trial of post-operative conventional radiotherapy and hypofractionated tomotherapy. BMC Cancer 12: 495	- Comparator does not match protocol
Vicini, F.A., Cecchini, R.S., White, J.R. et al. (2019) Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. The Lancet 394(10215): 2155-2164	- Study does not contain a relevant intervention
Vrieling, C., Van Werkhoven, E., Maingon, P. et al. (2017) Prognostic factors for local control in breast cancer after long-term follow-up in the EORTC boost vs no boost trial: A randomized clinical trial. JAMA Oncology 3(1): 42-48	- Comparator does not match protocol
Wang, S.-L., Fang, H., Song, Y.-W. et al. (2019) Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial. The Lancet Oncology 20(3): 352-360	- Comparator does not match protocol

Study	Reason for exclusion
Weng, J.K., Lei, X., Schlembach, P. et al. (2021) Five-Year Longitudinal Analysis of Patient-Reported Outcomes and Cosmesis in a Randomized Trial of Conventionally Fractionated Versus Hypofractionated Whole-Breast Irradiation. International Journal of Radiation Oncology Biology Physics 111(2): 360-370	- Comparator does not match protocol
Whelan, T.J., Pignol, J.-P., Levine, M.N. et al. (2010) Long-term results of hypofractionated radiation therapy for breast cancer. New England Journal of Medicine 362(6): 513-520	- Comparator does not match protocol
Yarnold, J.R. (2011) First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). Radiotherapy and Oncology 100(1): 93-100	- Secondary publication of primary study

Economic Studies

Study	Reason for exclusion
Lanni T, Keisch M, Shah C, Wobb, J, Kestin L, Vicini F. A cost comparison analysis of adjuvant radiation therapy techniques after breast-conserving surgery. The Breast Journal 2013 Feb;19(2):162-167.	- Inappropriate intervention (traditional, conventionally fractionated radiotherapy)
Shah C, Lanni, TB, Saini H, Nanavati A, Wilkinson J.B, Badiyan S, Vicini F. Cost-efficacy of acceleration partial-breast irradiation compared with whole-breast irradiation. Breast cancer research and treatment. 2013 Jan; 138:127–135.	- Setting inappropriate (U.S.)
Monten C; Lievens Y. Adjuvant breast radiotherapy: How to trade-off cost and effectiveness? Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2018 Jan; 126(1):132-138.	- Systematic review included studies not meeting inclusion criteria in the protocol
Shah C, Ward MC, Tendulkar RD; Cherian S; Vicini F; Singer ME. Cost and Cost-Effectiveness of Image Guided Partial Breast Irradiation in Comparison to Hypofractionated Whole Breast Irradiation. International journal of radiation oncology, biology, physics. 2019 Feb; 103(2):397-402.	- Setting inappropriate (U.S.)
McGuffin M, Merino T, Keller B, Pignol J-P. Who Should Bear the Cost of Convenience? A Cost-effectiveness Analysis Comparing	- Inappropriate interventions (conventionally fractionated therapy and partial breast seed implants)

Study	Reason for exclusion
External Beam and Brachytherapy Radiotherapy Techniques for Early-Stage Breast Cancer. Clinical Oncology. 2017 March; 29(3), E57-E63.	

Appendix K – Research recommendations – full details

K.1.1 Research recommendation

What is the effectiveness of radiotherapy given in 26 Gy in 5 fractions over 1 week compared to 40 Gy in 15 fractions over 3 weeks in people with early or locally advanced invasive breast cancer who are offered concurrent chemotherapy or breast reconstruction?

K.1.2 Why this is important

There is some evidence that radiotherapy given as 26 Gy in 5 fractions over 1 week may have similar effects to radiotherapy given as 40 Gy in 15 fractions over 3 weeks. However, there is limited research that compares the effectiveness of these 2 regimens for people who are having concurrent chemotherapy, or those having breast reconstruction procedures. This has led to a variation in current practice when these groups of people are offered radiotherapy. As such, research is needed to determine the effectiveness of the different hypofractionation regimens in these groups of people.

K.1.3 Rationale for research recommendation

Importance to 'patients' or the population	If the 5 fractions regimen is found to be as effective and safe as the 15 fractions regimen, then people having concurrent chemotherapy or breast reconstruction can be more widely offered the shorter radiotherapy regimen. This will reduce the number of radiotherapy sessions that people need to have, while still providing effective treatment.
Relevance to NICE guidance	It is currently unclear whether the 5 fractions in 1 week regimen is as effective as the 15 fractions in 3 weeks regimen for people having concurrent chemotherapy or those having breast reconstruction. If new evidence shows that the 5 fractions regimen is effective for these people, then future guideline updates may be able to make stronger recommendations in favour of the 5 fractions regimen.
Relevance to the NHS	Use of the 5 fractions regimen means that radiotherapy centres can treat people more quickly and reduce waiting times. Evidence that 5 fractions are effective for these groups of people will also reduce variation in practice across the NHS.
National priorities	Medium
Current evidence base	There is currently no evidence for these groups.
Equality considerations	None known

K.1.4 Modified PICO table

Population	Adults (18 years or older) with early or locally advanced invasive breast cancer and who are having concurrent chemotherapy or breast reconstruction
Intervention	26 Gy in 5 fractions over 1 week
Comparator	40 Gy in 15 fractions over 3 weeks
Outcomes	Quality of life (using validated measures such as EORTC and BREAST-Q) Breast cancer mortality All-cause mortality Local Recurrence Distant recurrence (also referred as distant relapse) Normal tissue effects Treatment-related adverse events Cosmesis (including breast appearance, breast oedema, appearance of scar, breast size, shape, colour, nipple position, shape of areola in comparison with untreated breast)
Study design	RCT
Timeframe	Longest time-frame available
Additional information	Not applicable

K.1.5 Research recommendation

What is the effectiveness of radiotherapy given in 26 Gy in 5 fractions over 1 week compared to 40 Gy in 15 fractions over 3 weeks in people with early or locally advanced invasive breast cancer who are also offered nodal irradiation?

K.1.6 Why this is important

There is currently limited evidence reporting on the effectiveness of the 26 Gy in 5 fractions over 1 week regimen in people with early or locally advanced breast cancer who are also receiving nodal irradiation. This may lead to variation in practice across treatment centres. As such, more research is needed in the area to determine the effectiveness of the 26 Gy in 5 fractions over 1 week in these groups of people.

K.1.7 Rationale for research recommendation

Importance to 'patients' or the population	If the 5 fractions regimen is found to be as effective and safe as the 15 fractions regimen, then people having nodal irradiation can be more widely offered the shorter radiotherapy regimen. This will reduce the number of

	radiotherapy sessions that people need to have, while still providing effective treatment.
Relevance to NICE guidance	It is currently unclear whether the 5 fractions in 1 week regimen is as effective as the 15 fractions in 3 weeks regimen for people having nodal irradiation. If new evidence shows that the 5 fractions regimen is effective for these people, then future guideline updates may be able to make stronger recommendations in favour of the 5 fractions regimen.
Relevance to the NHS	Use of the 5 fractions regimen means that radiotherapy centres can treat people more quickly and reduce waiting times. Evidence that 5 fractions are effective for these groups of people will also reduce variation in practice across the NHS.
National priorities	Medium
Current evidence base	There is currently no evidence for these groups.
Equality considerations	None known

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K.1.8 Modified PICO table

Population	Adults (18 years or older) with early or locally advanced invasive breast cancer, who are receiving nodal irradiation for the management of their condition
Intervention	26 Gy in 5 fractions over 1 week
Comparator	40 Gy in 15 fractions over 3 weeks
Outcomes	Quality of life (using validated measures such as EORTC and BREAST-Q) Breast cancer mortality All-cause mortality Local Recurrence Distant recurrence (also referred as distant relapse) Normal tissue effects Treatment-related adverse events Cosmesis (including breast appearance, breast oedema, appearance of scar, breast size, shape, colour, nipple position, shape of areola in comparison with untreated breast)
Study design	RCT
Timeframe	Longest time-frame available
Additional information	Not applicable

Appendix L – Methods

Appraising the quality of evidence

Intervention studies (relative effect estimates)

RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Evidence on each outcome for each individual study was classified into one of the following groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Data synthesis for intervention studies

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome.

Pairwise meta-analysis

Pairwise meta-analyses were performed in Cochrane Review Manager V5.3, with the exception of incidence rate ratio analyses which were carried out in R version 4.1.0. using the package ‘metafor’. A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the risk in the comparator arm of the meta-analysis (calculated as the total number events in the comparator arms of studies in the meta-analysis divided by the total number of participants in the comparator arms of studies in the meta-analysis).
For all syntheses, fixed- and random-effects models were fitted, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the

assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if there was significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

Minimally important differences (MIDs) and clinical decision thresholds

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline that might aid the committee in identifying clinical decision thresholds for the purpose of GRADE.

Clinical decision thresholds were used to assess imprecision using GRADE and aid interpretation of the size of effects for different outcomes. The Guideline Committee did not want to pre-specify any thresholds and no specific thresholds were found on the COMET database. As such, for relative risks and hazard ratios, a default clinical decision threshold for dichotomous outcomes of 0.8 to 1.25 was used.

GRADE for intervention studies analysed using pairwise analysis

GRADE was used to assess the quality of evidence for the outcomes specified in the review protocol. Data from randomised controlled trials were initially rated as high quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in table 1. These criteria were used to apply preliminary ratings, but were overridden in cases where, in the view of the analyst or committee the uncertainty identified was unlikely to have a meaningful impact on decision making.

Table 1:Rationale for downgrading quality of evidence for intervention studies

(a) GRADE criteria	(b) Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Extremely serious: If greater than 33.3% of the weight in a meta-analysis came from studies at critical risk of bias, the outcome was downgraded three levels
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded.

(a) GRADE criteria	(b) Reasons for downgrading quality
	Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e., the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.
Publication bias	Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias. When a funnel plot showed convincing evidence of publication bias, or the review team became aware of other evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias

(a) GRADE criteria	(b) Reasons for downgrading quality
	was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.

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