Randomised controlled trials on radiation dose fractionation in breast cancer: systematic review and meta-analysis with emphasis on side effects and cosmesis

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ABSTRACT

OBJECTIVE

To provide a comprehensive assessment of various fractionation schemes in radiation therapy for breast cancer, with a focus on side effects, cosmesis, quality of life, risks of recurrence, and survival outcomes.

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

Ovid MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (from inception to 23 October 2023).

STUDY SELECTION

Included studies were randomised controlled trials focusing on conventional fractionation (CF; daily fractions of 1.8-2 Gy, reaching a total dose of 50-50.4 Gy over 5-6 weeks), moderate hypofractionation (MHF; fraction sizes of 2.65-3.3 Gy for 13-16 fractions over 3-5 weeks), and/or ultra-hypofractionation (UHF; schedule of only 5 fractions).

DATA EXTRACTION

Two independent investigators screened studies and extracted data. Risk of bias and quality of evidence were assessed using the Cochrane Collaboration's tool and the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach, respectively.

DATA SYNTHESIS

Pooled risk ratios (RRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using a random effects model. Heterogeneity was analysed using Cochran's Q test and I^2 statistic. Network meta-analysis was used to integrate all available evidence.

MAIN OUTCOME MEASURES

The pre-specified primary outcome was grade ≥2 acute radiation dermatitis and late radiation therapy related side effects; secondary outcomes included cosmesis, quality of life, recurrence, and survival metrics.

RESULTS

From 1754 studies, 59 articles representing 35 trials (20 237 patients) were assessed; 21.6% of outcomes showed low risk of bias, whereas 78.4% had some concerns or high risk, particularly in outcome measurement (47.4%). The RR for grade ≥2 acute radiation dermatitis for MHF compared with CF was 0.54 (95% CI 0.49 to 0.61; P<0.001) and 0.68 (0.49 to 0.93; P=0.02) following breast conserving therapy and mastectomy, respectively. Hyperpigmentation and grade ≥2 breast shrinkage were less frequent after MHF than after CF, with RRs of 0.77 (0.62 to 0.95; P=0.02) and 0.92 (0.85 to 0.99; P=0.03), respectively, in the combined breast conserving therapy and mastectomy population. However, in the breast conserving therapy only trials, these differences in hyperpigmentation (RR 0.79, 0.60 to 1.03; P=0.08) and breast shrinkage (0.94, 0.83 to 1.07; P=0.35) were not statistically significant. The RR for grade ≥2 acute radiation dermatitis for UHF compared with MHF was 0.85 (0.47 to 1.55; P=0.60) for breast conserving therapy and mastectomy patients combined. MHF was associated with improved cosmesis and quality of life compared with CF, whereas data on UHF were less conclusive. Survival and recurrence outcomes were similar between UHF, MHF, and CF.

CONCLUSIONS

MHF shows improved safety profile, cosmesis, and quality of life compared with CF while maintaining equivalent oncological outcomes. Fewer randomised controlled trials have compared UHF with other fractionation schedules, but its safety and oncological effectiveness seem to be similar with short term follow-up. Given the advantages of reduced treatment time, enhanced convenience for patients, and potential cost effectiveness, MHF and UHF should be considered as preferred options over CF in appropriate

WHAT IS ALREADY KNOWN ON THIS TOPIC

Postoperative radiation therapy for breast cancer has been greatly influenced by clinical trials comparing conventional fractionation (CF) schemes with moderate hypofractionation (MHF) and more recently ultra-hypofractionation (UHF)

No comprehensive assessment has been made of the overall benefit, frequency and severity of potential side effects, aesthetic consequences, and implications for quality of life across fractionation schemes

WHAT THIS STUDY ADDS

A reduced risk of grade ≥2 acute radiation dermatitis was seen with MHF and UHF compared with CF following both post-mastectomy and breast conserving therapy

MHF shows an improved safety profile, cosmesis, and quality of life compared with CF while maintaining equivalent oncological outcomes

Fewer trials have compared UHF with other fractionation schedules, but its safety profile and oncological effectiveness seem to be comparable on the basis of early experience

clinical settings, with further research needed to solidify these findings.

SYSTEMATIC REVIEW REGISTRATION
PROSPERO CRD42023460249.

Introduction

Breast cancer is the most prevalent malignancy in women, contributing significantly to the global cancer burden.[1] Postoperative radiation therapy represents an essential part of the multi-modality treatment for breast cancer, especially after breast conserving therapy, with a primary goal of reducing locoregional recurrence and improving disease-free and overall survival rates.[2-4]

Conventional fractionation radiation therapy, typically consisting of a total dose of about 50 Gray (Gy) delivered over five to six weeks in 1.8-2 Gy daily fractions, has been the historical standard of care for treatment of patients with breast cancer in most of the world since the 1970s. In more recent years, hypofractionated radiation therapy has emerged as an increasingly used alternative, primarily owing to studies conducted by researchers in the UK and Canada.[5-11] This approach delivers a dose greater than 2 Gy per fraction to give a reduced total dose over a shorter overall treatment time than conventional fractionation.[12]

Hypofractionation regimens can be subdivided into moderate hypofractionation and ultra-hypofractionation, with the second generally defined as using fractions larger than 3.3 Gy.[11 12] Multiple randomised controlled trials conducted since the 1980s have shown that moderate hypofractionation is not inferior to conventional fractionation with regards to key oncological metrics such as overall survival and disease-free survival, with advantages in convenience, cost efficiency, and safety profile.[7 9-11 13-16] More recent trials have compared ultra-hypofractionation with moderate hypofractionation or conventional fractionation.[17-20]

Despite clinical evidence supporting these hypofractionated approaches, their integration into practice varies considerably across different healthcare settings, primarily owing to concerns about potential side effects and the relative novelty of ultra-hypofractionation, for which the follow-up data are shorter. Financial considerations may also play a role; for example, conventional fractionation may be preferred by practitioners in healthcare systems where reimbursement is calculated on a per fraction basis, whereas moderate hypofractionation or ultra-hypofractionation might be more popular where treatment reimbursement is capitated.[21 22]

Given the imperative to optimise patients' outcomes and convenience while minimising adverse effects, elucidating the impact of radiation therapy fractionation regimens on patients' daily lives is crucial, as this can significantly influence their treatment preferences. This systematic review and meta-analysis of randomised controlled trials goes beyond traditional comparisons of survival outcomes to provide a multidimensional perspective on the implications of choice of radiation therapy fractionation. By specifically emphasising side effects, cosmetic outcomes, and quality of life, areas essential for informed clinical decision making yet often under-represented in research, the study aims to offer insights that can guide both clinicians and patients towards treatments that not only extend life but also enhance its quality.

Methods

The analysis was conducted and findings were reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline.[23] The protocol was registered in the PROSPERO database (CRD42023460249). Two investigators (SFL and SKFK) independently did the literature search and assessed study eligibility following the strategies stated below. Any disagreement between the reviewers was resolved through discussion and consensus or through arbitration by a third investigator (HCYW).

Search strategy

We did a systematic search in Ovid MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify eligible articles on the efficacy and safety of postoperative radiation therapy for breast cancer. The initial search on 7 February 2023 was updated on 23 October 2023. Search terms included "breast cancer", "radiation therapy", and "hypofractionation". The detailed search strategies for each database are summarised in online appendix 1. We screened reference lists of relevant studies and reviews and consulted experts to uncover additional studies. We applied no geographical or language filters, but we included for analysis only studies conducted in humans and reported in the English language.

Inclusion and exclusion criteria

We categorised regimens as using conventional fractionation if the intact breast or chest wall/reconstructed breast was treated using daily fractions of 1.8-2 Gy, typically delivering a total dose of 50-50.4 Gy in 25-28 fractions over five to six weeks. We categorised trials as using moderate hypofractionation if they used fraction sizes of 2.65-3.3 Gy, giving 13-16 fractions over three to five weeks (supplementary table S1). Lastly, we categorised regimens as using ultra-hypofractionation when only five fractions were used. Some trials allowed the treating physicians to give an additional boost dose to the tumour bed for patients in the control and experimental arms, at their discretion, or incorporated randomisation to receive a boost or not.

Inclusion criteria were that the study was a randomised controlled trial; postoperative external beam radiation therapy was directed at the whole breast or chest wall, with or without regional nodal irradiation; and the study compared any combination of conventional fractionation, moderate

hypofractionation, and ultra-hypofractionation. We excluded studies if they used intraoperative or partial breast radiation therapy or proton therapy, failed to provide quantifiable data or adequate statistical parameters for analysis, or exclusively reported on patients aged under 18 years.

Data extraction

Data extraction in Microsoft Excel (version 2310) was carried out by SFL and checked independently by the second investigator (SKFK). Detailed information on radiation therapy technique in the intervention and control arms, such as radiation doses, scheme, and duration of treatment, was collected. Outcome data were extracted, including primary and secondary outcome measures and follow-up time points.

Quality and risk of bias assessment and certainty of evidence

Risk of bias and quality and certainty of evidence were independently assessed at the outcome levels by SFL and a second investigator (SKFK, HCYW, or AWC) using the Cochrane Collaboration's risk of bias tool 2.0 for randomised trials.[24] They typically classified a study as having a high risk of bias in the presence of one or more of the following characteristics: selection from multiple outcome measurements without multiple data analyses; no indication of a pre-specified data analysis plan; or substantial missing data for the primary outcome potentially affecting the results. For the assessment of the overall quality (certainty) of the evidence included in the meta-analysis, we adopted the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach, taking into consideration all relevant GRADE domains: methodological limitations, inconsistency, imprecision, indirectness, and publication bias.[25] In the case of network meta-analysis, we evaluated the confidence in the findings by using the web based application of the Confidence in Network Meta-Analysis (CINeMA) framework. This framework assesses six domains: within study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence.[26] Any disagreements were resolved through consensus or discussion with a third investigator (SC).

Systematic review and statistical analyses

Primary outcomes of interest were grade ≥2 acute radiation dermatitis and late radiation therapy related side effects. Secondary outcomes were cosmesis, quality of life, local recurrence (in the breast for patients treated with breast conserving therapy or in the chest wall for those undergoing mastectomy), locoregional recurrence, disease-free survival, and overall survival. We assessed Common Terminology Criteria for Adverse Events or Radiation Therapy Oncology Group grade ≥2 side effects (or at least moderate if grading was not reported) because of their clinical relevance, which typically require medical management and may affect the treatment course and quality of life. We categorised assessment of acute side effects as up to three months after the completion of radiation therapy and late side effects as occurring later than that. Some but not all trials also reported dosimetric analysis, alterations in pulmonary and cardiac function tests, occurrence of secondary primary cancers, economic implications related to health, and workload; we did not analyse these outcomes here.

For meta-analysis, we used a random effects model to calculate the summary estimate of each risk ratio and hazard ratio, along with 95% confidence intervals (CIs).[27] We quantified heterogeneity between effect estimates among studies by two statistical tests:

Table 1 | Overview of clinical trials comparing fractionation regimens in breast cancer radiation therapy

Fractionations	No of trials	Total No of patients	Dose fractionations in experimental arm	Dose fractionations in control arm	Median follow-up (months)
Breast conserving surgery trials					
Moderate hypofractionation versus conventional fractionation	14	8076	40 Gy in 15 fractions over 3 weeks; 39 Gy in 13 fractions over 5 weeks; 42.9 Gy in 13 fractions over 5 weeks; 42.5–43.2 Gy in 16 fractions over 3 weeks; 43.5 Gy in 15 fractions over 3 weeks	50 Gy in 25 fractions over 5 weeks	16-202.8
Ultra-hypofractionation versus moderate hypofractionation	2	260	28.5 Gy in 5 fractions over 1 week; 26 Gy in 5 fractions over 1 week	40 Gy in 15 fractions over 3 weeks	18
Ultra-hypofractionation versus conventional fractionation	1	915	30 Gy in 5 fractions over 5 weeks; 28.5 Gy in 5 fractions over 5 weeks	50 Gy in 25 fractions over 5 weeks	118.8
Mastectomy trials					
Moderate hypofractionation versus conventional fractionation	11	1659	39 Gy in 13 fractions over 3 weeks; 40 Gy in 15 fractions over 3 weeks; 42.5 Gy in 15 fractions over 3 weeks; 43.5 Gy in 15 fractions over 3 weeks; 42.6–42.7 Gy in 16 fractions over 3 weeks	50 Gy in 25 fractions over 5 weeks	34-58.5
Ultra-hypofractionation versus moderate hypofractionation	1	300	27 Gy in 5 fractions over 1 week	40 Gy in 15 fractions over 3 weeks	Not reported
Trials including both breast conserving surgery and mastectomy patients					
Moderate hypofractionation versus conventional fractionation	4	4660	39 Gy in 13 fractions over 5 weeks; 41.6 Gy in 13 fractions over 5 weeks; 40 Gy in 15 fractions over 3 weeks; 42 Gy in 15 fractions over 3 weeks	50 Gy in 25 fractions over 5 weeks	111.6-124.8
Ultra-hypofractionation versus moderate hypofractionation	2	4367	27 Gy in 5 fractions over 1 week; 26 Gy in 5 fractions over 1 week	40 Gy in 15 fractions over 3 weeks	71.5

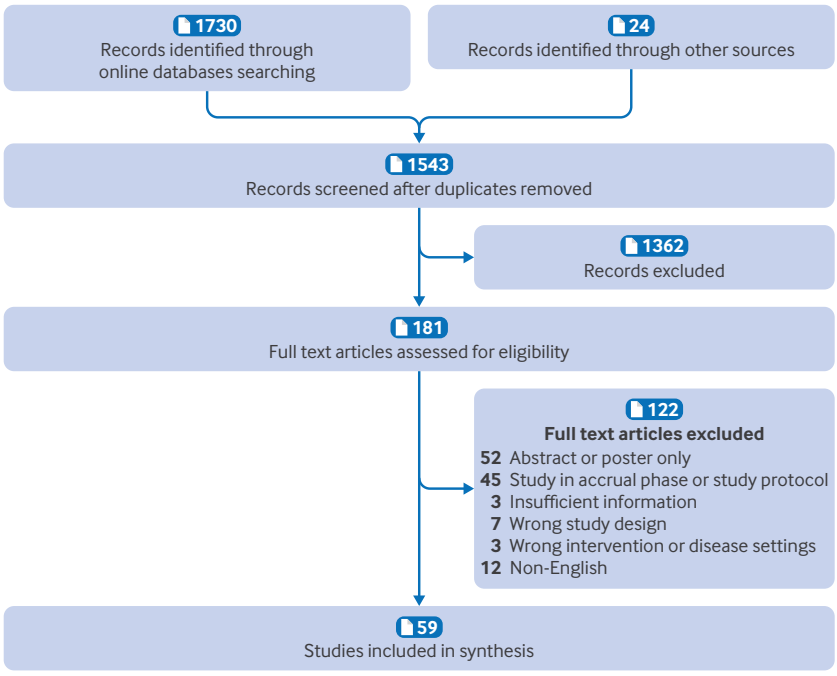

Fig 1 | PRISMA diagram of study selection

the Cochran's Q statistical test for between study variability and the I^2 statistic for the proportion of total variation across studies due to statistical heterogeneity instead of chance.[28] We did a sensitivity analysis to assess whether excluding studies with a high risk of bias influenced the estimated effect or heterogeneity of the outcome.

We also did network meta-analysis to combine all available data and to verify the findings from the main meta-analysis. The analysis used a frequentist random effects model for risk ratios and hazard ratios. We used the P score, which is analogous to the surface under the cumulative ranking curve and estimates the extent of certainty that one treatment is superior to another treatment, to rank the radiation therapy dose fractionation regimens.[29]

All P values were two tailed, and we considered P values of <0.05 to be statistically significant. The meta-analyses and graphs were generated using Review Manager (RevMan), version 5.4, and we used R Statistical Software (v4.3.2) and netmeta package to do the network meta-analysis.

Patient and public involvement

No patients were involved in setting the research question, outcome measures, study design, or data interpretation. Although members of the public were not directly involved in this study because of funding limitations, the focus of this work is aligned with the research priorities of patients with breast cancer, which include rigorous evaluations of dose fractionation regimens to optimise treatment outcome and quality of life. Plain language messages about the results will be shared with lay audience (for example, via social media feeds).

Results

Search results and characteristics of included studies

The initial literature search identified 1754 articles. After the exclusion of 211 duplicates, 1543 articles were screened for relevance on the basis of titles and abstracts, resulting in 59 studies that met the inclusion criteria. These studies encompassed 35 trials conducted from 1986 to 2023, with a cumulative patient count of 20 237. Patient enrolment per trial ranged from 30 to 4096. Our analysis incorporated data from 29 trials comparing moderate hypofractionation with conventional fractionation (14 395 patients), five trials comparing ultra-hypofractionation with moderate hypofractionation (4927 patients), and one trial comparing ultra-hypofractionation with conventional fractionation (915 patients) (table 1, fig 1, and table S2).[5-11 15-20 30-75]

Risk of bias and GRADE assessment

Overall, 21.6% of outcomes were rated as having a low risk of bias, and 78.4% were rated as having some concerns or a high risk of bias (fig 2). Specifically, the domain with the poorest reporting was the measurement of outcomes, with 47.4% categorised as having some concerns (see table 2 for a concise summary of results with certainty of evidence). The detailed risk of bias and GRADE assessments for the included studies are shown in tables S3 and S4, respectively. After the evaluation of level of evidence using CINeMA, most pairwise comparison results were deemed to have moderate or high confidence (table S5).

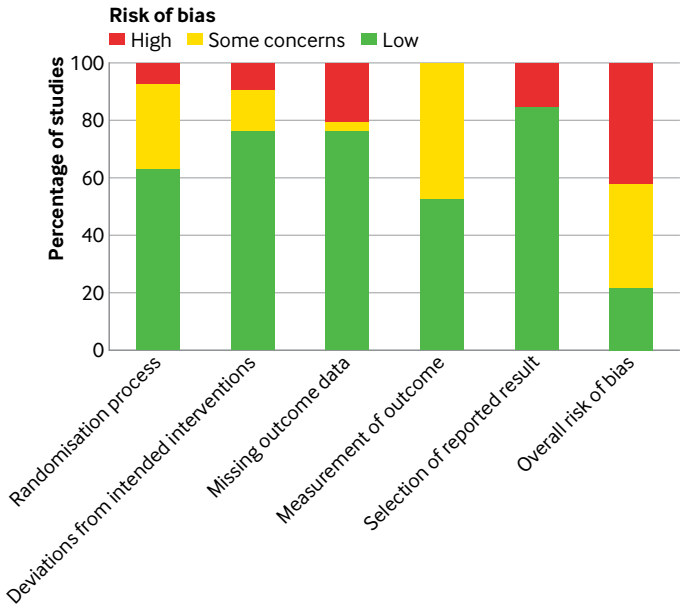

Fig 2 | Risk of bias by outcome (percentage)

Outcomes

Side effects outcomes: acute skin side effect

The risk ratio for grade ≥2 acute radiation dermatitis for moderate hypofractionation compared with

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conventional fractionation was 0.59 (95% CI 0.51 to 0.69; P<0.001; fig 3) in the 20 trials comparing them for all patients, 0.54 (0.49 to 0.61; P<0.001; fig 4) for the eight trials giving results for only patients treated with breast conserving therapy, and 0.68 (0.49 to 0.93; P=0.02; fig 5) for the 10 trials giving results for only those treated with mastectomy. Combining the six trials comparing ultra-hypofractionation with moderate hypofractionation, the risk ratio for grade ≥2 acute radiation dermatitis was 0.85 (95% CI 0.47 to 1.55; P=0.60; fig 6). We found significant heterogeneity between studies (χ^2=30.2, df=5; P<0.001; I^2=83%). In the two trials that specifically compared ultra-hypofractionation with moderate hypofractionation in patients treated with breast conserving therapy, the risk ratio was 1.72 (95% CI 0.24 to 12.40; P=0.59; fig 7). Of note, grade ≥2 acute dermatitis was particularly low in the two ultra-hypofractionation regimens (28.5 Gy or 30 Gy given in five fractions delivered once weekly over five weeks) of the FAST trial compared

Table 2 | Summary of findings for primary and secondary outcomes

Outcomes	Effect estimate (95% CI)	No of trials*	Certainty of evidence (GRADE)
Moderate hypofractionation *v* conventional fractionation			
Grade ≥2 acute radiation dermatitis	RR 0.59 (0.51 to 0.69)†	20	High
Grade ≥2 telangiectasia	RR 0.84 (0.66 to 1.06)	10	High
Any hyperpigmentation	RR 0.77 (0.62 to 0.95)†	4	Moderate‡
Grade ≥2 breast or chest wall induration/fibrosis	RR 0.92 (0.80 to 1.06)	15	Moderate‡
Grade ≥2 breast shrinkage	RR 0.92 (0.85 to 0.99)†	7	Moderate‡
Grade ≥2 breast oedema	RR 0.82 (0.62 to 1.09)	8	Low§
Grade ≥2 breast pain	RR 0.94 (0.43 to 2.06)	3	Moderate‡
Grade ≥2 lymphoedema	RR 1.00 (0.78 to 1.29)	13	Moderate‡
Grade ≥2 pneumonitis/symptomatic lung fibrosis	RR 1.57 (0.81 to 3.02)	16	Moderate¶
Ischaemic heart disease	RR 0.95 (0.56 to 1.58)	8	Moderate¶
Moderate/marked shoulder stiffness/dysfunction	RR 1.14 (0.69 to 1.89)	7	Low**
Symptomatic rib fracture	RR 2.82 (0.87 to 9.14)	8	Low**
Cosmetic outcomes	-	16	High
Quality of life	-	7	High
Local recurrence	HR 0.97 (0.80 to 1.18)	7	High
Locoregional recurrence	HR 0.98 (0.81 to 1.19)	6	High
Disease-free survival	HR 0.92 (0.84 to 1.02)	9	High
Overall survival	HR 0.96 (0.86 to 1.07)	8	High
Ultra-hypofractionation *v* moderate hypofractionation			
Grade ≥2 acute radiation dermatitis	RR 0.85 (0.47 to 1.55)	6	Low§
Grade ≥2 telangiectasia	RR 1.42 (0.88 to 2.30)	2	Moderate‡
Grade ≥2 breast or chest wall induration/fibrosis	RR 1.86 (1.19 to 2.92)†	3	Moderate‡
Grade ≥2 breast shrinkage	RR 1.38 (1.07 to 1.76)†	2	Moderate‡
Grade ≥2 breast oedema	RR 2.44 (1.32 to 4.52)†	2	Moderate‡
Grade ≥2 lymphoedema	RR 0.84 (0.61 to 1.16)	3	Moderate‡
Grade ≥2 pneumonitis/symptomatic lung fibrosis	RR 1.33 (0.63 to 2.80)	2	Low**
Ischaemic heart disease	RR 0.87 (0.49 to 1.56)	2	Low**
Moderate/marked shoulder stiffness/dysfunction	RR 0.89 (0.64 to 1.23)	2	Moderate‡
Symptomatic rib fracture	RR 2.07 (1.04 to 4.12)†	3	Low**
Cosmetic outcomes	-	3	Moderate‡
Quality of life	-	1	High
Local recurrence	HR 0.77 (0.52 to 1.13)	2	Moderate‡
Locoregional recurrence	HR 0.73 (0.53 to 1.01)	2	Moderate‡
Disease-free survival	HR 0.94 (0.78 to 1.12)	2	Moderate‡
Overall survival	HR 1.04 (0.85 to 1.27)	2	Moderate‡
Ultra-hypofractionation *v* conventional fractionation			
Grade ≥2 acute radiation dermatitis	RR 0.27 (0.19 to 0.40)†	2	High
Grade ≥2 telangiectasia	RR 1.86 (0.11 to 30.23)	2	Moderate¶
Grade ≥2 breast or chest wall induration/fibrosis	RR 1.97 (0.58 to 6.71)	2	Moderate¶
Grade ≥2 breast shrinkage	RR 1.83 (1.09 to 3.07)†	2	High
Grade ≥2 breast oedema	RR 3.05 (0.13 to 74.09)	2	Moderate¶
Grade ≥2 pneumonitis/symptomatic lung fibrosis	RR 0.82 (0.25 to 2.70)	2	Moderate¶
Ischaemic heart disease	RR 0.82 (0.25 to 2.70)	2	Moderate¶
Symptomatic rib fracture	RR 0.87 (0.31 to 2.45)	2	Moderate¶
Cosmesis	-	2	High
Ipsilateral breast disease	HR 1.35 (0.47 to 3.94)	2	High

CI=confidence interval; GRADE=Grading of Recommendations, Assessment, Development, and Evaluations; HR=hazard ratio; RR=risk ratio.
*Treatment arms using different dose fractionations in START-Pilot, START-A, START-B, and FAST trial were analysed separately in meta-analyses and shown separately in forest plots.
†Statistically significant.
‡Downgraded by one level for risk of bias of included studies.
§Downgraded by two levels for risk of bias and inconsistency of included studies.
¶Downgraded by one level for imprecision of included studies.
**Downgraded by two levels for risk of bias and imprecision of included studies.

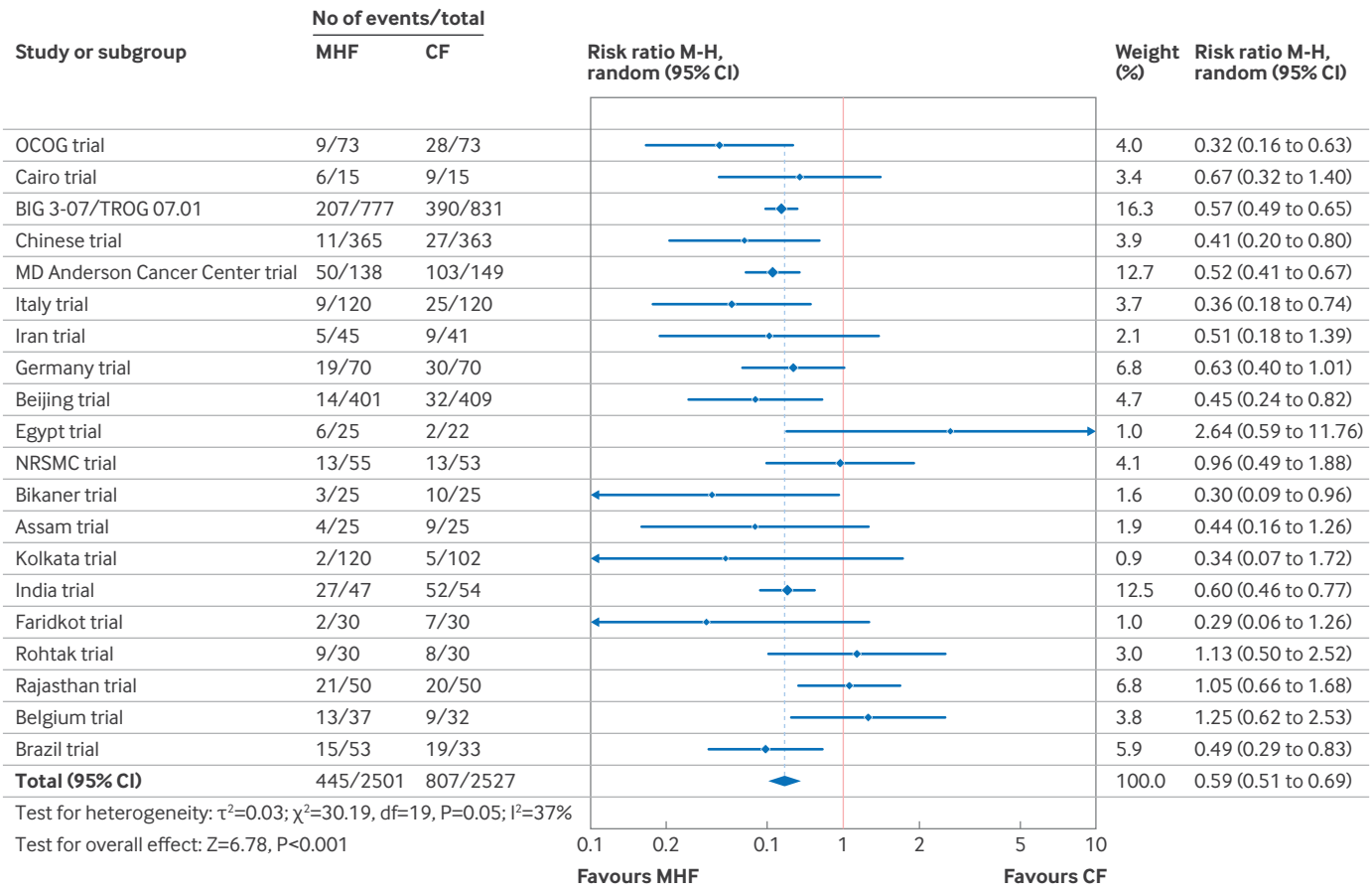

Fig 3 | Forest plot showing risk ratios for grade ≥2 acute radiation dermatitis for moderate versus conventional fractionation in all trials. Cairo trial used RTOG toxicity criteria for acute radiation dermatitis. Beijing trial reported incidence of acute radiation dermatitis across grade 1–2 and 3; however, only grade 3 data have been included in this forest plot for analysis. Kolkata trial reported incidence of only grade ≥3 acute radiation dermatitis. CF=conventional fractionation; CI=confidence interval; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

with conventional fractionation, with a risk ratio of 0.27 (95% CI 0.19 to 0.40; P<0.001 (figure S1).[18] In sensitivity analyses assessing the influence of studies at high risk of bias on the cumulative findings, the risk ratio for acute radiation dermatitis comparing moderate hypofractionation with conventional fractionation remained significant at 0.58 (95% CI 0.49 to 0.68; P<0.001; n=11), with no substantial heterogeneity observed (χ^2=13.67, df=10; P=0.19; I^2=27%) (figure S2).

Criteria for assessment and timing are detailed in table S6. We did subgroup analyses delineating individual fractionation regimens on the basis of the number of fractions (figure S3). Across the compared regimens, the 15 fraction and 16 fraction schedules showed similar decreased risk ratios (0.56, 95% CI 0.46 to 0.68; P<0.001; n=10 and 0.60, 0.47 to 0.76; P<0.001; n=10, respectively) for acute radiation dermatitis, compared with the 50 Gy in 25 fractions approach.

Side effects outcomes: late skin and soft tissue side effects

In trials comparing moderate hypofractionation with conventional fractionation, the risk ratio was 0.84 (95% CI 0.66 to 1.06; P=0.14; n=10; fig 8) for grade ≥2 telangiectasia, 0.77 (0.62 to 0.95; P=0.02; n=4; fig 9) for any hyperpigmentation, 0.92 (0.80 to 1.06; P=0.24; n=15; fig 10) for grade ≥2 breast or chest wall induration or fibrosis, 0.92 (0.85 to 0.99; P=0.03; n=7; fig 11) for grade ≥2 breast shrinkage, and 0.82 (0.62 to 1.09; P=0.18; n=8; fig 12) for grade ≥2 breast oedema. However, in the subset of trials that reported results exclusively for patients treated with breast conserving therapy, the outcomes for telangiectasia (fig 13), hyperpigmentation (fig 14), breast induration or fibrosis (fig 15), breast shrinkage (fig 16), breast oedema (fig 17), and breast pain (fig 18) were not found to be statistically significant.

Comparing ultra-hypofractionation with moderate hypofractionation, data mainly from the FAST-Forward trial indicated increased risks associated with ultra-hypofractionation in terms of induration or fibrosis (risk ratio 1.86, 95% CI 1.19 to 2.92; P=0.007; n=3; figure S4B), breast shrinkage (1.38, 1.07 to 1.76; P=0.01; n=2; figure S4C), and breast oedema (2.44, 1.32 to 4.52; P=0.005; n=2; figure S4D). The FAST trial also suggested higher risks of breast shrinkage for ultra-hypofractionation compared with conventional fractionation (risk ratio 1.83, 95% CI 1.09 to 3.07;

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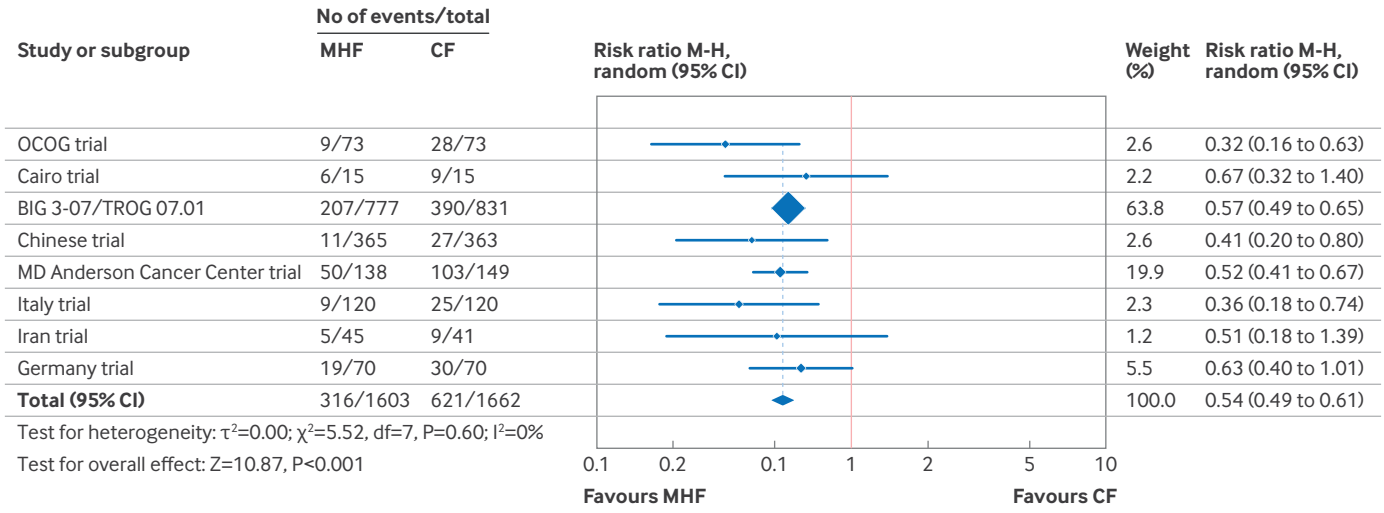

Fig 4 | Forest plot showing risk ratios for grade ≥2 acute radiation dermatitis for moderate versus conventional fractionation in breast conserving treatment trials. Cairo trial used RTOG toxicity criteria for acute radiation dermatitis. CF=conventional fractionation; CI=confidence interval; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

P=0.02; n=2; figure S5C). Subgroup analyses based on the number of fractions are shown in figures S6 to S8.

Side effects outcomes: late non-skin side effects

Comparing moderate hypofractionation and conventional fractionation, the risk ratio for grade ≥2 arm lymphoedema in the combined breast conserving therapy and mastectomy population was 1.00 (95% CI 0.78 to 1.29; P=0.98; n=13; fig 19). The risk ratio for grade ≥2 pneumonitis or symptomatic lung fibrosis was 1.57 (95% CI 0.81 to 3.02; P=0.18; n=16; fig 20). The risk ratio for ischaemic heart disease for all patients combined (regardless of surgery) was 0.95 (95% CI 0.56 to 1.58; P=0.83; n=8; fig 21). The risk ratio for shoulder stiffness or dysfunction was 1.14 (95% CI 0.69 to 1.89; P=0.62; n=7; fig 22), and the risk ratio for symptomatic rib fracture was 2.82 (0.87 to 9.14; P=0.08; n=8; fig 23). In a study assessing late side effects in the heart and lungs among patients with left breast carcinoma irradiated after mastectomy, pulmonary function tests and echocardiography did not show increased cardiopulmonary side effects of moderate hypofractionation (13 fractions) compared with conventional fractionation over an 18 month follow-up.[63] Figure S9 shows the forest plots for late non-skin side effects among the breast conserving

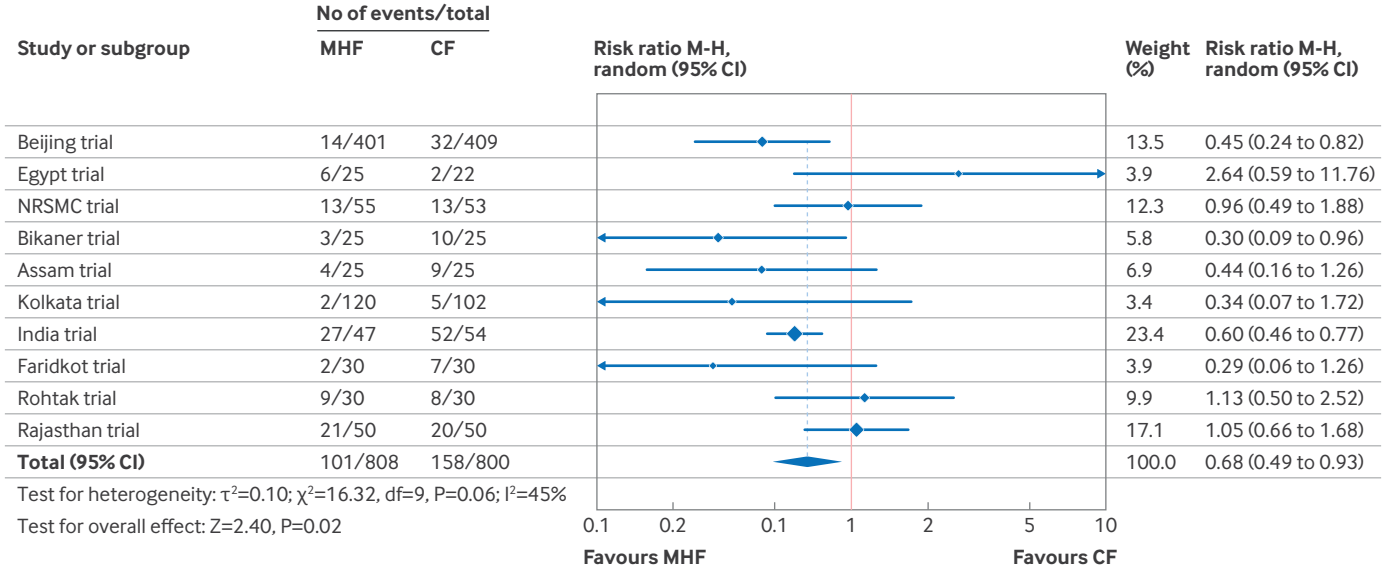

Fig 5 | Forest plot showing risk ratios for grade ≥2 acute radiation dermatitis for moderate versus conventional fractionation in mastectomy trials. Beijing trial reported incidence of acute radiation dermatitis across grade 1–2 and 3; however, only grade 3 data have been included in this forest plot for analysis. Kolkata trial reported incidence of only grade ≥3 acute radiation dermatitis. CF=conventional fractionation; CI=confidence interval; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

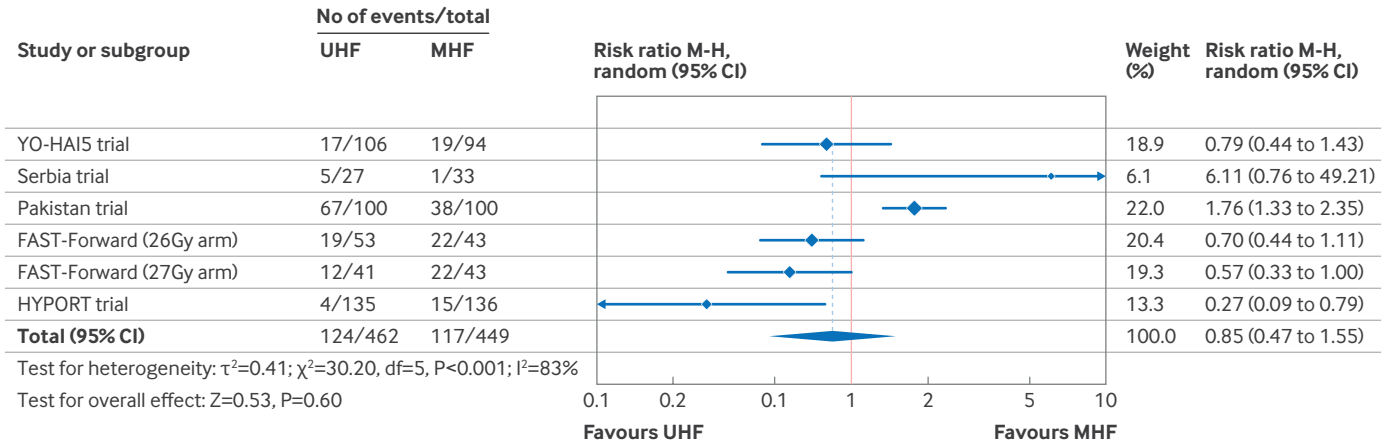

Fig 6 | Forest plot showing risk ratios for grade ≥2 acute radiation dermatitis for ultra-hypofractionation versus moderate hypofractionation in all trials. CI=confidence interval; M-H=Mantel-Haenszel; MHF=moderate hypofractionation; UHF= ultra-hypofractionation

therapy only and mastectomy only trials comparing moderate hypofractionation and conventional fractionation regimens.

For ultra-hypofractionation versus moderate hypofractionation, the risk ratio for symptomatic rib fractures was found to be statistically significant at 2.07 (95% CI 1.04 to 4.12; P=0.04; n=3; figure S10E), whereas for ultra-hypofractionation versus conventional fractionation, the comparisons did not yield statistically significant results (figure S11).

Severe late side effects were rare and comparable between moderate hypofractionation and conventional fractionation groups across studies. In the subgroup analysis focusing on individual fractionation regimens based on the number of fractions, we detected no significant variations in these late non-skin side effects across the studied regimens (figures S12-S14). Table S7 offers a detailed overview of late side effects when we compared different dose fractionation regimens, categorised by the time elapsed since breast/chest wall radiation therapy.

Cosmetic outcomes

The DBCG HYPO trial indicated a modest improvement in cosmetic outcomes with a moderate hypofractionation regimen.[39] The START-PILOT trial reported fewer cases of fair or poor cosmetic results at five and 10 years in patients receiving 39 Gy in 13 fractions compared with those treated with 50 Gy in 25 fractions.[11] Furthermore, the Germany trial found that cosmetic assessments were significantly better in patients undergoing moderate hypofractionation compared with conventional fractionation.[50] In the FAST-Forward trial, we observed no significant cosmetic differences when comparing an ultra-hypofractionation regimen at 26 Gy in five fractions with moderate hypofractionation at 40 Gy in 15 fractions. Nevertheless, a higher dose of ultra-hypofractionation at 27 Gy in five fractions was associated with a significant risk of changes in breast appearance at both two and five years, relative to moderate hypofractionation.[17] The FAST trial, comparing ultra-hypofractionation with conventional fractionation, showed that the incidence of mild or marked changes in photographic breast appearance at two or five years was significantly higher for 30 Gy than for 50 Gy. However, no significant difference was detected between 28.5 Gy and 50 Gy.[18] Details on the timing and methods of these assessments are available in table S8.

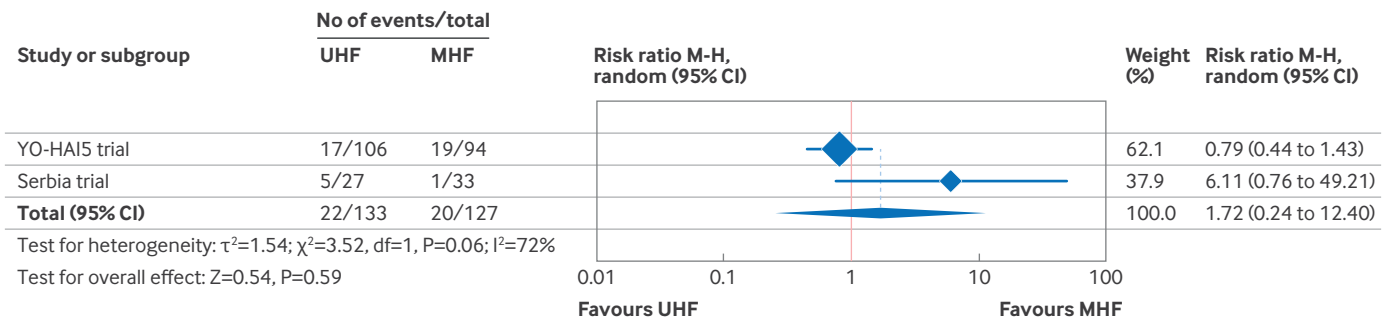

Fig 7 | Forest plot showing risk ratios for grade ≥2 acute radiation dermatitis for ultra-hypofractionation versus moderate hypofractionation in breast conserving surgery trials. CI=confidence interval; M-H=Mantel-Haenszel; MHF=moderate hypofractionation; UHF= ultra-hypofractionation

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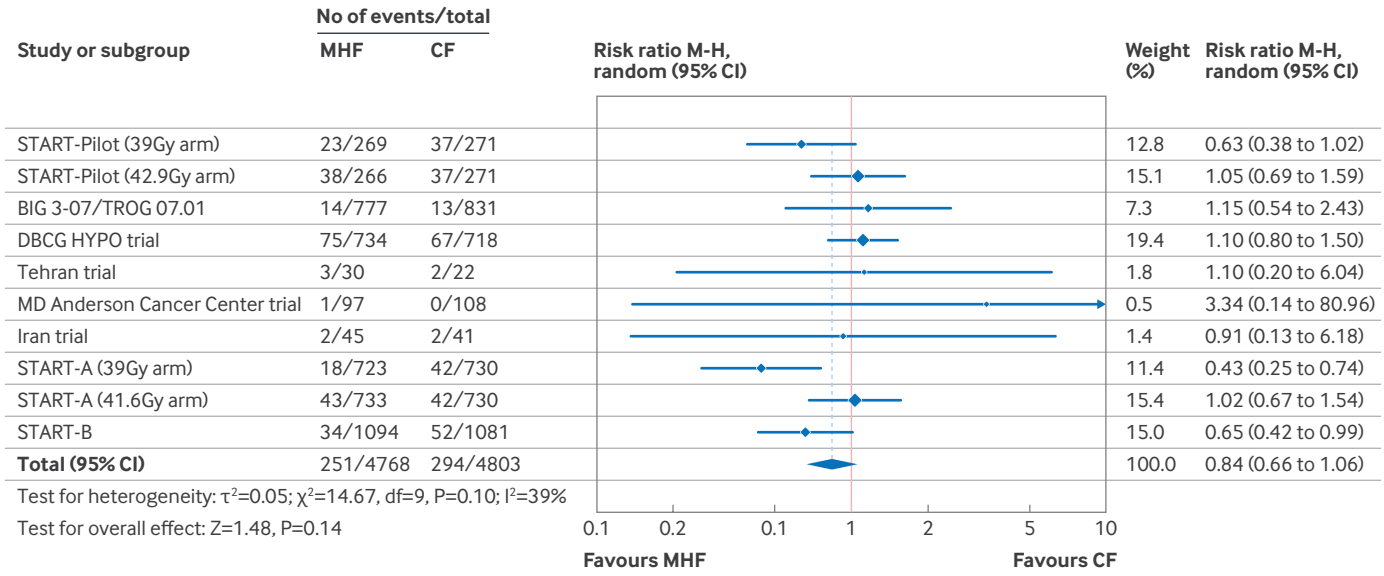

Fig 8 | Forest plot showing risk ratios for late skin and soft tissue side effects for moderate versus conventional fractionation trials: grade ≥2 telangiectasia in all trials. Iran trial, Tehran trial, and DBCG HYPO trial reported incidence of any grade of telangiectasia. CI=confidence interval; CF=conventional fractionation; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

Quality of life

The MD Anderson Cancer Center and BIG 3–07/TROG 07.01 trials showed that moderate hypofractionation improves physical well being at six months and enhances body image at the end of treatment, respectively, in comparison with conventional fractionation.[36 41 44] Additionally, the OCOG trial showed an improved quality of life relating to breast side effects, attractiveness, fatigue, and convenience at six weeks following moderate hypofractionation compared with conventional fractionation.[31] In the Belgium trial, moderate hypofractionation was associated with superior quality of life relative to conventional fractionation, highlighting the potential role of treatment delivery methods; specifically, the use of tomotherapy in moderate hypofractionation facilitated better dose homogeneity.[69 73] Conversely, the DBCG HYPO trial observed equivalent levels of satisfaction with breast appearance over a five year period across both moderate hypofractionation and conventional fractionation cohorts, and the START trials similarly noted minimal quality of life discrepancies between moderate hypofractionation and conventional fractionation.[39 65] Lastly, the YO-HAI5 trial, comparing ultra-hypofractionation and moderate hypofractionation, indicated that patients in the ultra-hypofractionation group showed less decline in the physical and social functioning aspects of quality of life two to four weeks after radiation therapy.[19]

Oncological outcomes

We found no statistically significant differences in the respective hazard ratios between moderate hypofractionation and conventional fractionation for local/locoregional recurrence, disease-free survival, and overall survival. Notably, we detected no significant heterogeneity for these estimates of survival (all P>0.05) (figure S15). In the subgroup analyses focusing on the number of fractions (comparing 13 fraction and 15 fraction regimens with 50 Gy in 25

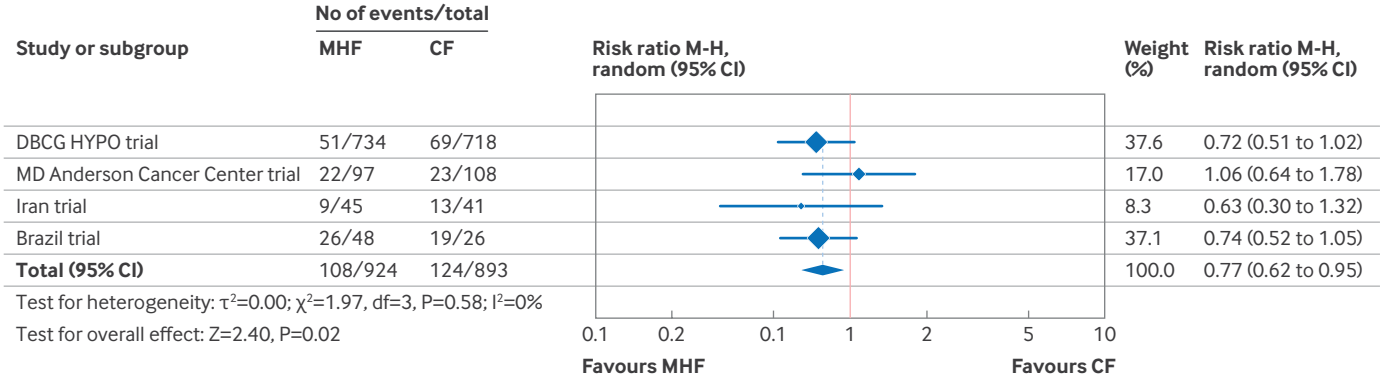

Fig 9 | Forest plot showing risk ratios for late skin and soft tissue side effects for moderate versus conventional fractionation trials: any hyperpigmentation in all trials. CI=confidence interval; CF=conventional fractionation; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

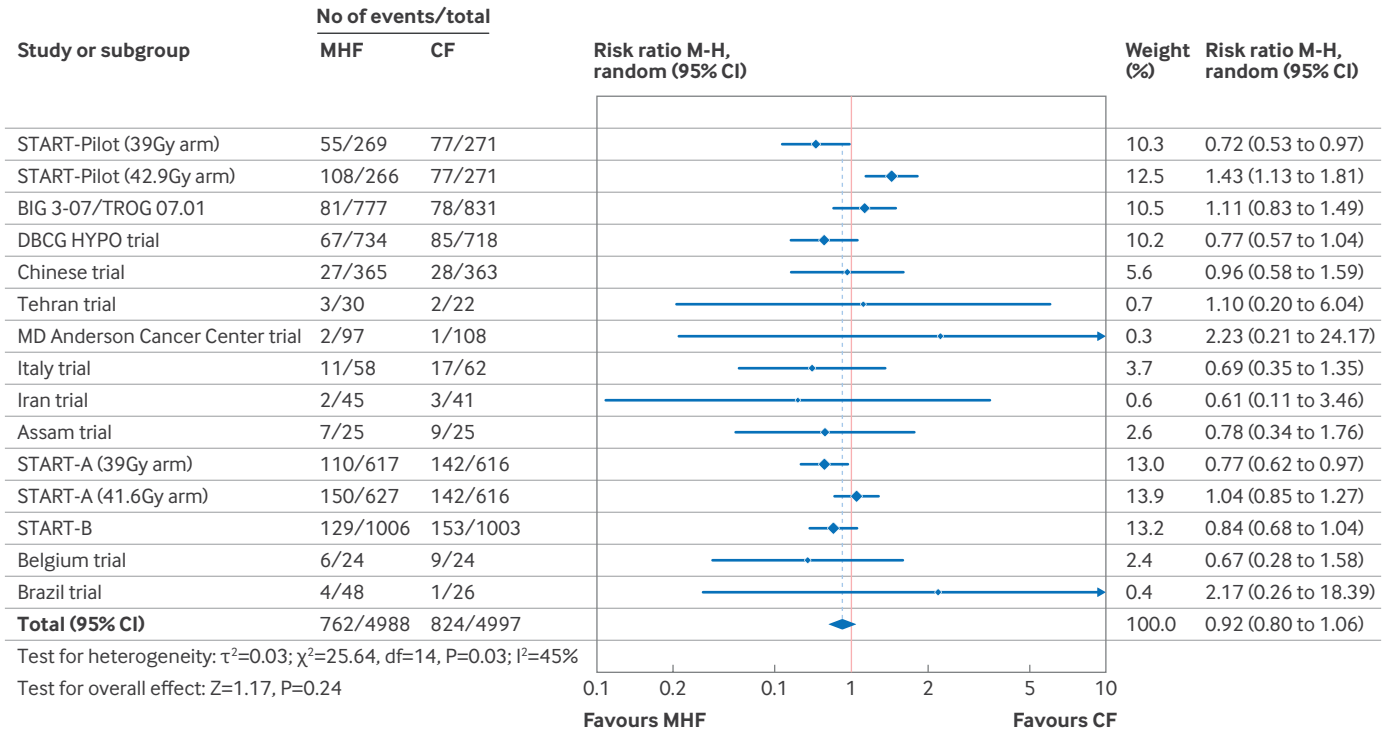

Fig 10 | Forest plot showing risk ratios for late skin and soft tissue side effects for moderate versus conventional fractionation trials: grade ≥2 breast or chest wall induration or fibrosis in all trials. Iran trial reported the incidence of grade ≥2 breast induration or fibrosis. Tehran trial, DBCG HYPO trial, Chinese trial, Italy trial, and Belgium trial reported incidence of any grade of breast induration or fibrosis. CI=confidence interval; CF=conventional fractionation; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

fractions), most survival outcomes did not show significant differences (figures S16-S18). However, the 15 fraction regimens showed a reduced hazard ratio for disease-free survival of 0.86 (95% CI 0.76 to 0.98; P=0.03; n=6; figure S17C) compared with 50 Gy in 25 fractions. Several randomised controlled trials did not provide enough information to be included in this meta-analysis, but generally the survival outcomes between the regimens show no statistically significant difference.[9 32 40 44 47 54 59 62 68 69 71]

The FAST-Forward trial compared two different doses of ultra-hypofractionation with moderate hypofractionation.[17] Neither 27 Gy in five fractions nor 26 Gy in five fractions resulted in significant differences compared with moderate hypofractionation in several crucial outcomes with a median follow-up of 71.5 months (figure S19).[17] Finally, in the FAST trial

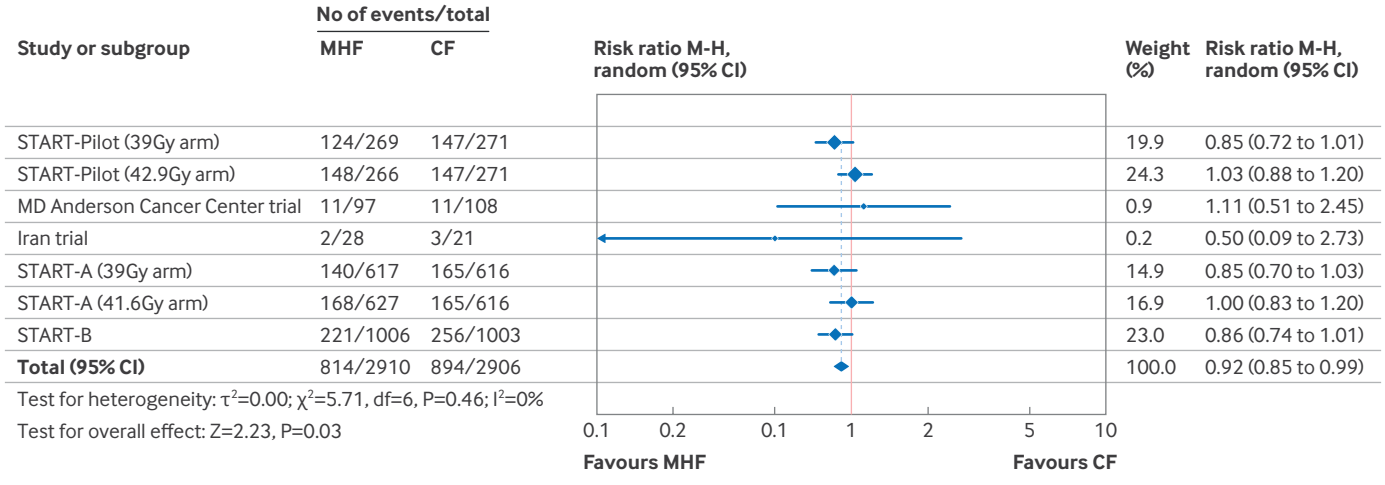

Fig 11 | Forest plot showing risk ratios for late skin and soft tissue side effects for moderate versus conventional fractionation trials: grade ≥2 breast shrinkage in all trials. Iran trial reported incidence of any grade of breast shrinkage. CI=confidence interval; CF=conventional fractionation; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

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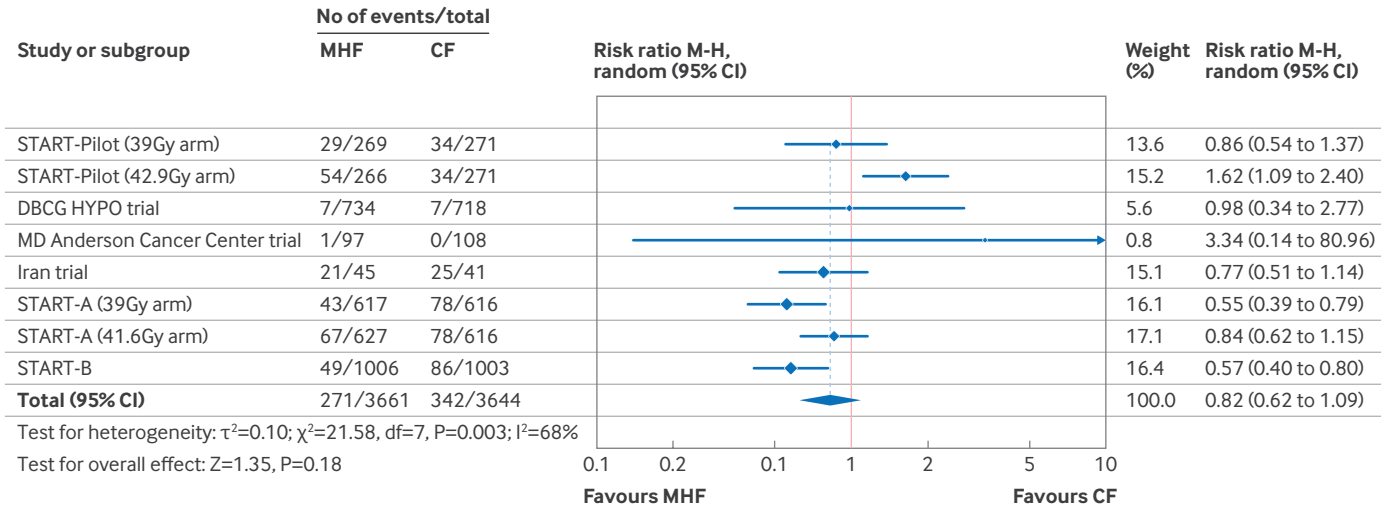

Fig 12 | Forest plot showing risk ratios for late skin and soft tissue side effects for moderate versus conventional fractionation trials: grade ≥2 breast oedema in all trials. Iran trial and DBCG HYPO trial reported incidence of any grade of breast oedema. CI=confidence interval; CF=conventional fractionation; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

comparing ultra-hypofractionation with conventional fractionation, the hazard ratio for ipsilateral breast recurrence combining both ultra-hypofractionation arms was 1.35 (95% CI 0.47 to 3.94; P=0.58) (figure S20).[18]

Effects of other factors on side effects

Results related to the effects of tumour bed boost, breast size, and smoking status are provided in the data supplement (appendix 2).

Network meta-analysis

For our network meta-analysis, we included data from 28 trials comparing moderate hypofractionation and conventional fractionation, encompassing 14 344 patients. Additionally, five trials compared ultra-hypofractionation and moderate hypofractionation, involving 4927 patients, and one trial compared ultra-hypofractionation and conventional fractionation, with 915 patients (table S9). On the basis of the network meta-analysis approach, we found that moderate hypofractionation significantly reduced the incidence of grade ≥2 acute radiation dermatitis compared with conventional fractionation, with a risk ratio of 0.56 (95% CI 0.46 to 0.68; P<0.001; figure S21A). Ultra-hypofractionation showed an even more favourable reduction in grade ≥2 acute radiation dermatitis compared with conventional fractionation (risk ratio 0.41, 95% CI 0.29 to 0.58; P<0.001; figure S21A) and a non-significant trend towards a lower

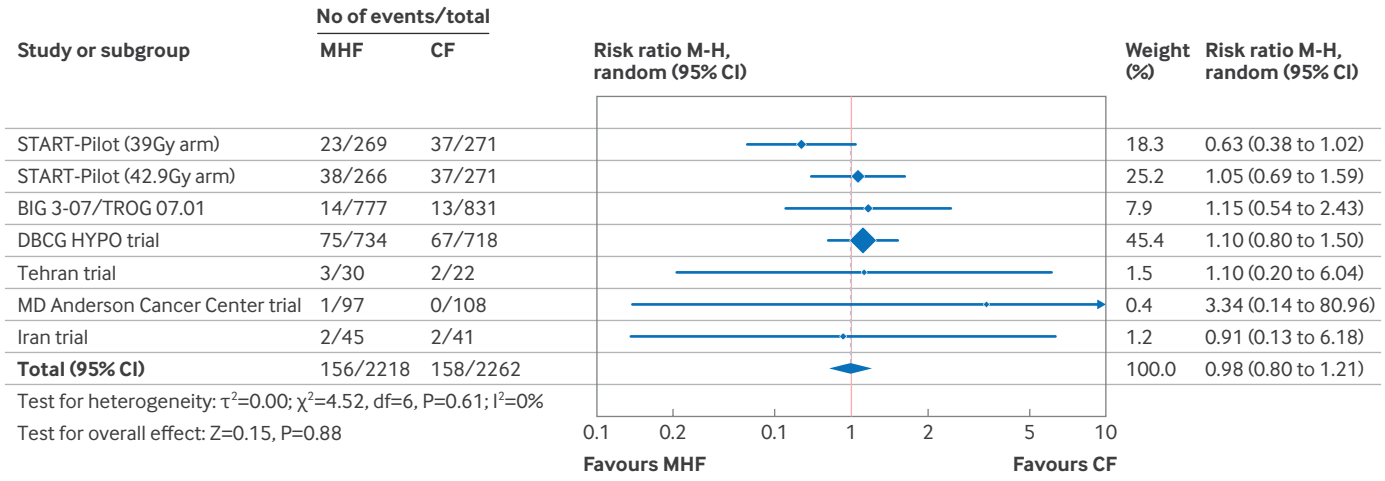

Fig 13 | Forest plot showing risk ratios for late skin and soft tissue side effects for moderate versus conventional fractionation trials: grade ≥2 telangiectasia in and breast conserving treatment trials. Iran trial, Tehran trial, and DBCG HYPO trial reported incidence of any grade of telangiectasia. CF=conventional fractionation; CI=confidence interval; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

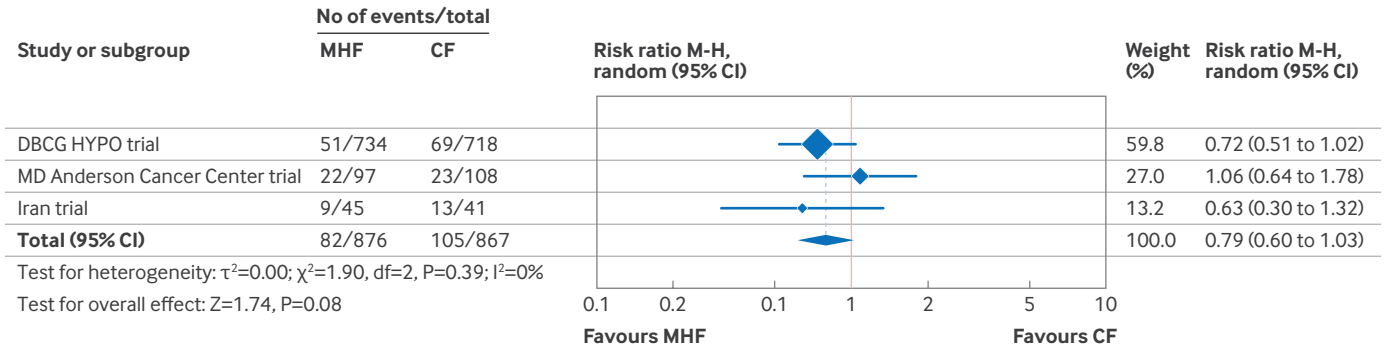

Fig 14| Forest plot showing risk ratios for late skin and soft tissue side effects for moderate versus conventional fractionation trials: any hyperpigmentation in breast conserving treatment trials. CF=conventional fractionation; CI=confidence interval; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

incidence than moderate hypofractionation (0.74, 0.53 to 1.02; P=0.07; figure S21B). According to P score rankings, ultra-hypofractionation (98.4%) was the most favourable option, followed by moderate hypofractionation (51.6%) and conventional fractionation (0%), despite significant heterogeneity being observed (I^2=65.1%, 95% CI 47.6% to 76.8%; Q test=74.50; P<0.001).

Additionally, moderate hypofractionation was associated with a reduced risk of breast shrinkage compared with conventional fractionation (risk ratio 0.92, 95% CI 0.86 to 0.99; P=0.04; figure S22E). Conversely, ultra-hypofractionation was linked to an increased risk of breast or chest wall induration and fibrosis (risk ratio 1.66, 95% CI 1.12 to 2.48; P=0.01 against conventional fractionation (figure S22C); 1.80, 1.23 to 2.64; P=0.002 against moderate hypofractionation (figure S22D)) and breast shrinkage (risk ratio 1.36, 1.08 to 1.71; P=0.009 against conventional fractionation (figure S22E); 1.47, 1.18 to 1.84; P=0.007 against moderate hypofractionation (figure S22F)) in comparison with both moderate hypofractionation and conventional fractionation. Heterogeneity across these outcomes was not significant. The P score rankings for breast or chest wall induration and fibrosis were highest for moderate hypofractionation at 94.0%, followed by conventional fractionation at 55.7% and ultra-hypofractionation at 0.4%. For grade ≥2 breast shrinkage, the rankings were moderate hypofractionation at 99.1%, conventional fractionation at 50.7%, and ultra-hypofractionation at 0.3%. Ultra-hypofractionation also increased the risk of grade ≥2 breast oedema compared with moderate hypofractionation (risk ratio 2.49, 95% CI 1.21 to 5.10; P=0.01; Figure S22H), with evidence of heterogeneity (I^2=58.4%, 95% CI 16.3% to 79.4%; Q test=21.66; P=0.01). The P score rankings for grade ≥2 breast oedema were most favourable for moderate hypofractionation at 96.0%, followed by conventional fractionation at 52.1% and ultra-hypofractionation

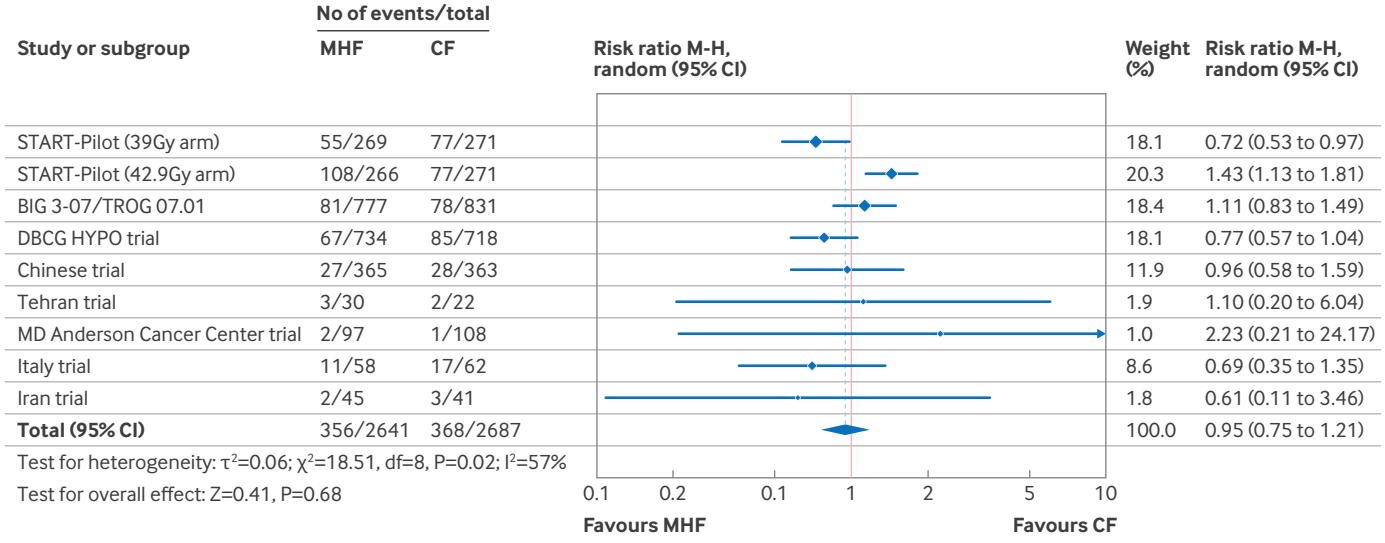

Fig 15 | Forest plot showing risk ratios for late skin and soft tissue side effects for moderate versus conventional fractionation trials: grade ≥2 breast or chest wall induration or fibrosis in breast conserving treatment trials. Tehran trial, DBCG HYPO trial, Chinese trial, and Italy trial reported incidence of any grade of breast induration or fibrosis. CF=conventional fractionation; CI=confidence interval; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

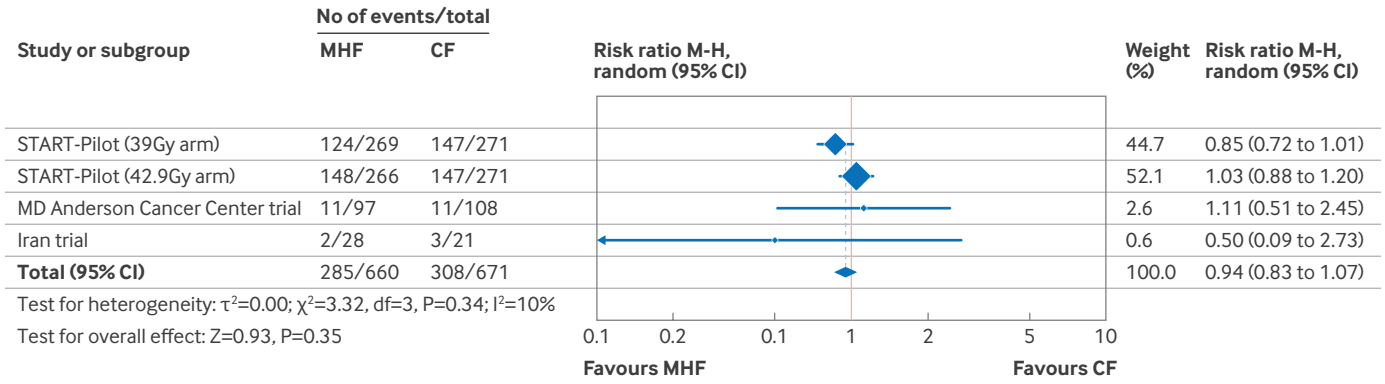

Fig 16 | Forest plot showing risk ratios for late skin and soft tissue side effects for moderate versus conventional fractionation trials: grade ≥2 breast shrinkage in breast conserving treatment trials. Iran trial reported incidence of any grade of breast shrinkage. CF=conventional fractionation; CI=confidence interval; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

at 2.0%. Late non-skin side effects and survival outcomes showed no significant differences across the fractionation regimens. Details of the network meta-analysis are in appendix 3. The forest plots, network plots, and league tables, which visualise the pairwise comparisons, can be found in figures S21-S35 and tables S10-S33, respectively.

Discussion

Previous systematic reviews and meta-analyses of trials of breast radiation therapy fractionation primarily focused on disease recurrences and survival metrics.[76-79] Our study adds a patient centred perspective crucial for informed decision making by examining not only oncological outcomes but also acute and late side effects, cosmetic outcomes, and quality of life associated with moderate hypofractionation and ultra-hypofractionation, compared with conventional fractionation. In our analysis, moderate hypofractionation showed either comparable or reduced acute and late side effects compared with conventional fractionation, and notably, improved cosmetic outcomes were reported in some cases. This suggests that moderate hypofractionation may provide superior quality of life for patients. Ultra-hypofractionation, although less extensively studied, has shown promising results, particularly with its substantial reduction in duration of treatment, which may further improve patients' convenience and quality of life. These findings have been corroborated by the network meta-analysis, and to our knowledge this is the first study assessing those outcomes by using this approach; the consistency of the results with those of the main analyses lends robust support to our conclusions. Our review also identified several factors influencing treatment outcomes, such as the application of a tumour bed boost, breast size, and smoking status. These factors highlight the need for tailored treatment approaches to optimise outcomes.[80 81]

Comparison with guidelines and other studies

Current guidelines recommend moderate hypofractionation as the standard of care for a broad range of patients with breast cancer, irrespective of the patient's age, systemic therapy, and disease

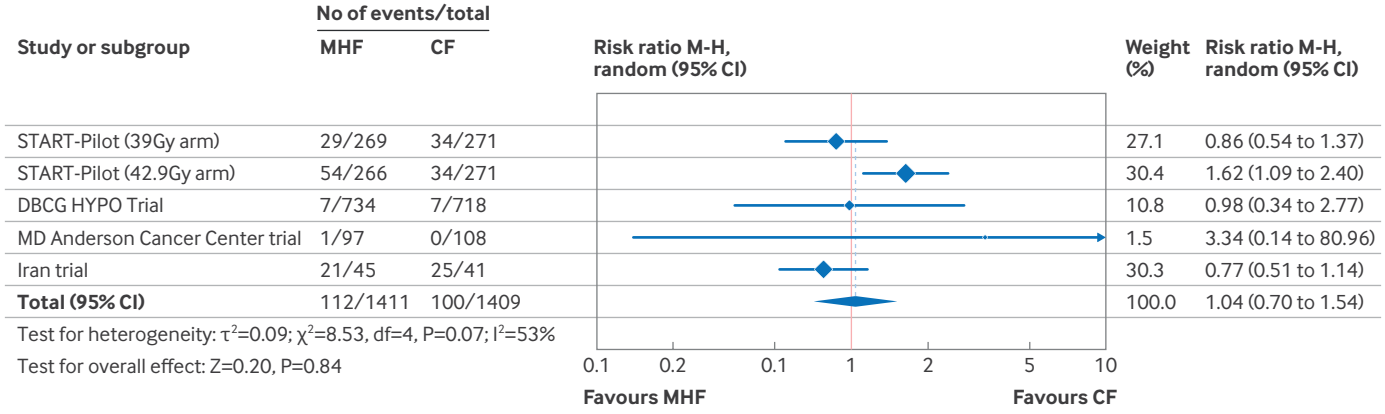

Fig 17 | Forest plot showing risk ratios for late skin and soft tissue side effects for moderate versus conventional fractionation trials: grade ≥2 breast oedema in breast conserving treatment trials. Iran trial and DBCG HYPO trial reported incidence of any grade of breast oedema. CF=conventional fractionation; CI=confidence interval; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

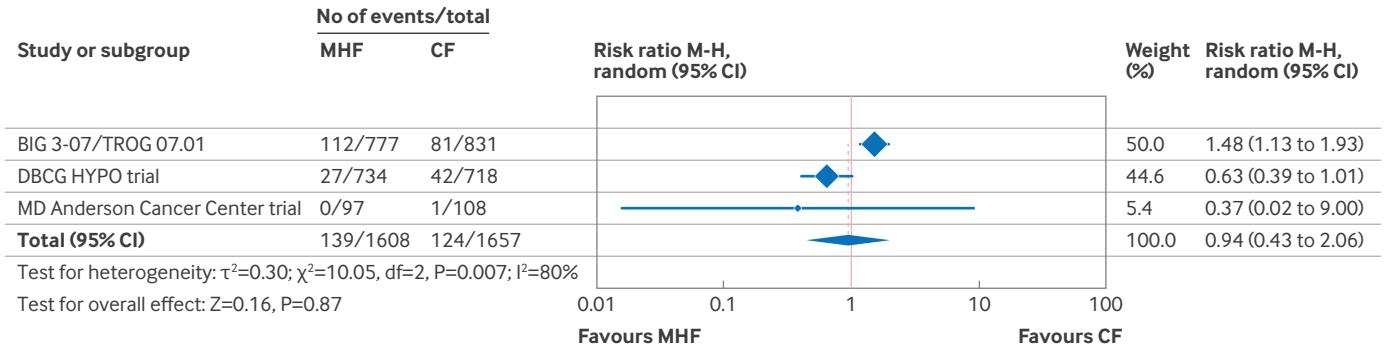

Fig 18| Forest plot showing risk ratios for late skin and soft tissue side effects for moderate versus conventional fractionation trials: grade ≥2 breast pain in breast conserving treatment trials. CF=conventional fractionation; CI=confidence interval; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

stage.[3 82] However, the need for robust evidence that confirms minimal differences between moderate hypofractionation and conventional fractionation in long term side effects, notably concerning lung and cardiac health,[83] has slowed the adoption of hypofractionation in the US.[84] The role of moderate hypofractionation in regional lymph node and chest wall irradiation remains controversial,[83] but the safety of moderate hypofractionation for these indications is increasingly supported by evidence from randomised controlled trials, including those from the START and Chinese trials.[7 15 85 86] Results from real world data and multiple randomised studies show that moderate hypofractionation also produces equivalent results to conventional fractionation for young patients and those treated with many different systemic therapies.[15 16 44 62 87 88]

The use of ultra-hypofractionation as per the FAST-Forward trial garners differing levels of endorsement across major guidelines, reflecting ongoing debates. The European Society for Radiotherapy and Oncology (ESTRO) and the Italian Association for Radiotherapy and Clinical Oncology endorse 26 Gy in five fractions for both whole breast and chest wall irradiation without reconstruction as standard of care.[82 89] For chest wall irradiation after breast reconstruction, ESTRO advises its use only within clinical trials.[82] Similarly, in the UK, the National Institute for Health

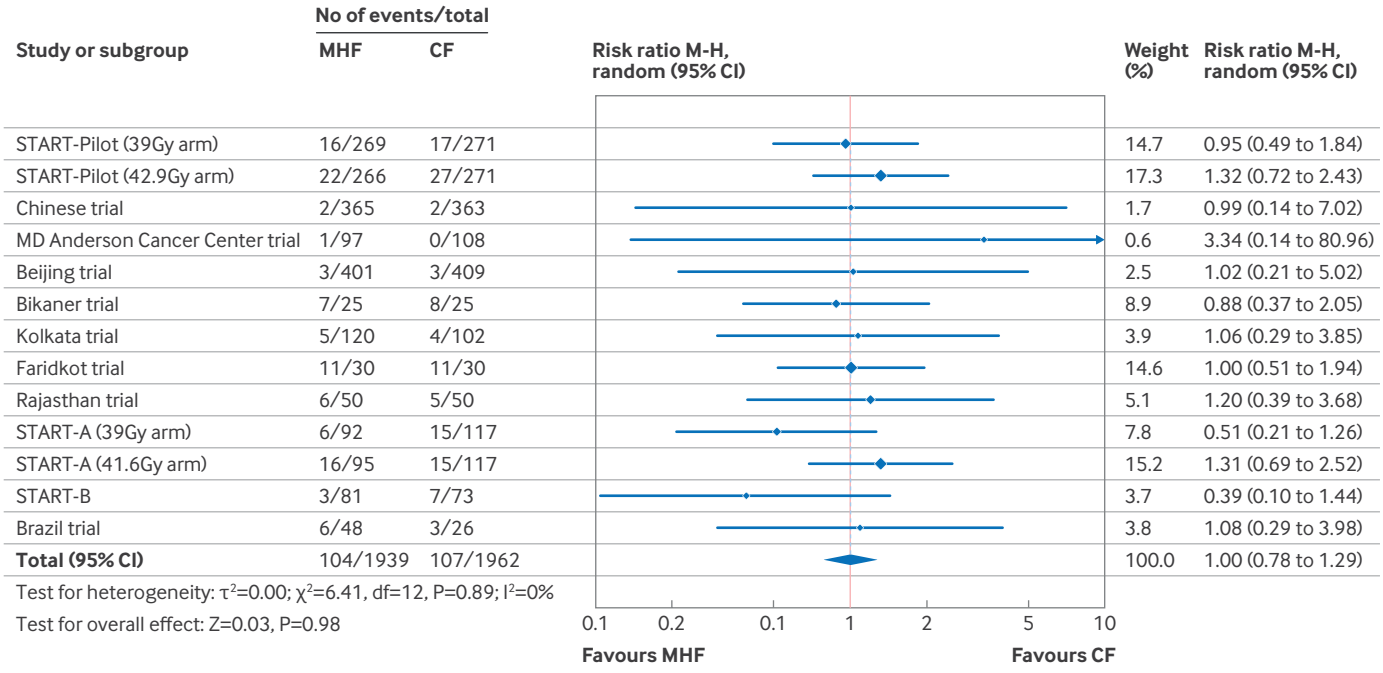

Fig 19 | Forest plot showing risk ratios for late non-skin side effects for moderate versus conventional fractionation: grade ≥2 lymphoedema. Beijing trial reported incidence of lymphoedema across grades 1-2 and grade 3; however, only grade 3 data have been included in this forest plot for analysis. Chinese trial reported only incidence of grade 2 lymphoedema. Kolkata trial reported incidence of only grade ≥3 lymphoedema. CF=conventional fractionation; CI=confidence interval; IHD=ischaemic heart disease; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

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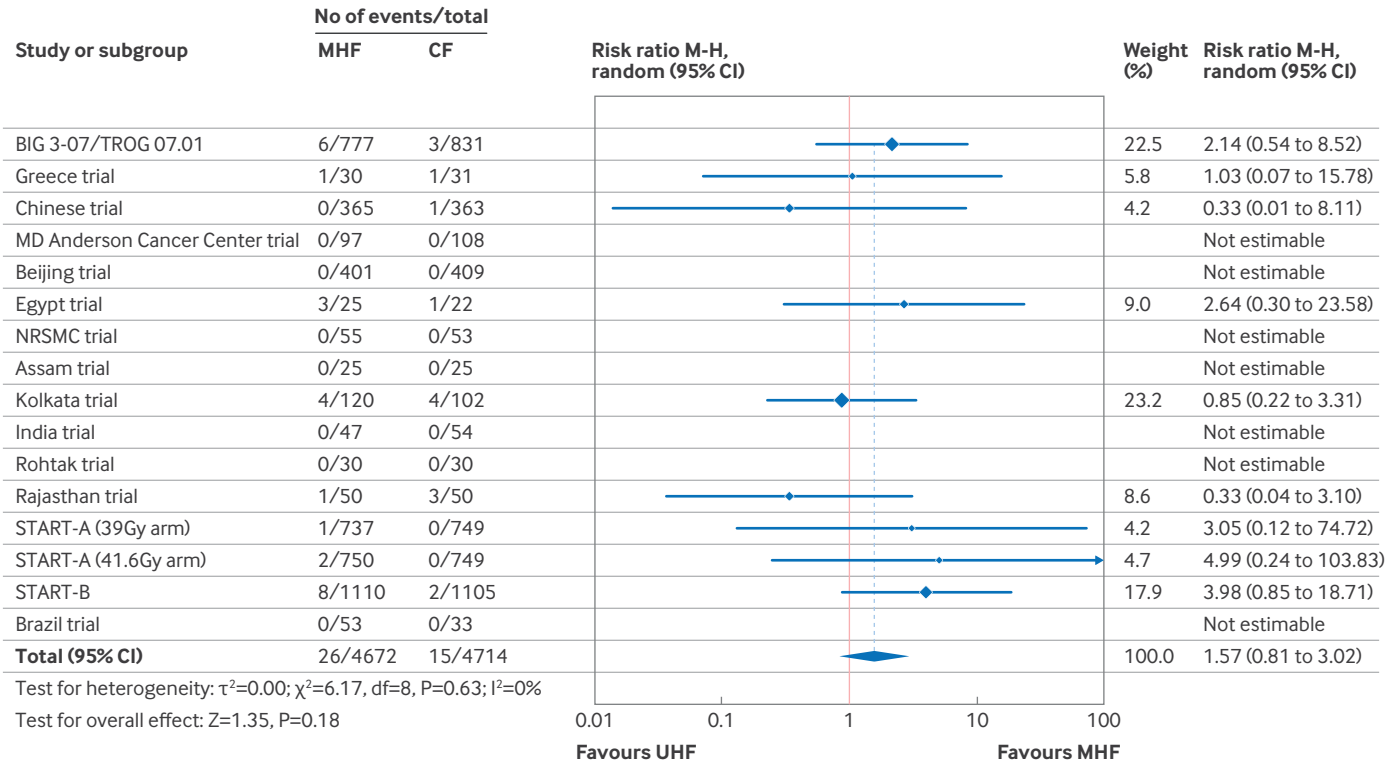

Fig 20 | Forest plot showing risk ratios for late non-skin side effects for moderate versus conventional fractionation: grade ≥2 pneumonitis or symptomatic lung fibrosis. Beijing trial reported incidence of lung fibrosis across grades 1-2 and grade 3; however, only grade 3 data have been included in this forest plot for analysis. Chinese trial reported only incidence of grade 2 lung fibrosis. Kolkata trial reported incidence of only grade ≥3 lung side effects. CF=conventional fractionation; CI=confidence interval; IHD=ischaemic heart disease; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

and Care Excellence (NICE) recommends 26 Gy in five fractions over one week for patients with invasive breast cancer undergoing partial breast, whole breast, or chest wall radiation therapy, excluding those requiring regional lymph node irradiation, following breast conserving therapy or mastectomy.[90] For implant based reconstruction, NICE recommends moderate hypofractionation using 40 Gy in 15 fractions.[90] By contrast, the National Comprehensive Cancer Network guideline recommends that the FAST-Forward regimen of 26 Gy in five fractions should be offered as an alternative to the FAST regimen (28.5 Gy in five weekly fractions) for selected early stage disease, noting that the efficacy and safety results of the former are not yet available beyond five years.[91] The German Society of Radiation Oncology (DEGRO)

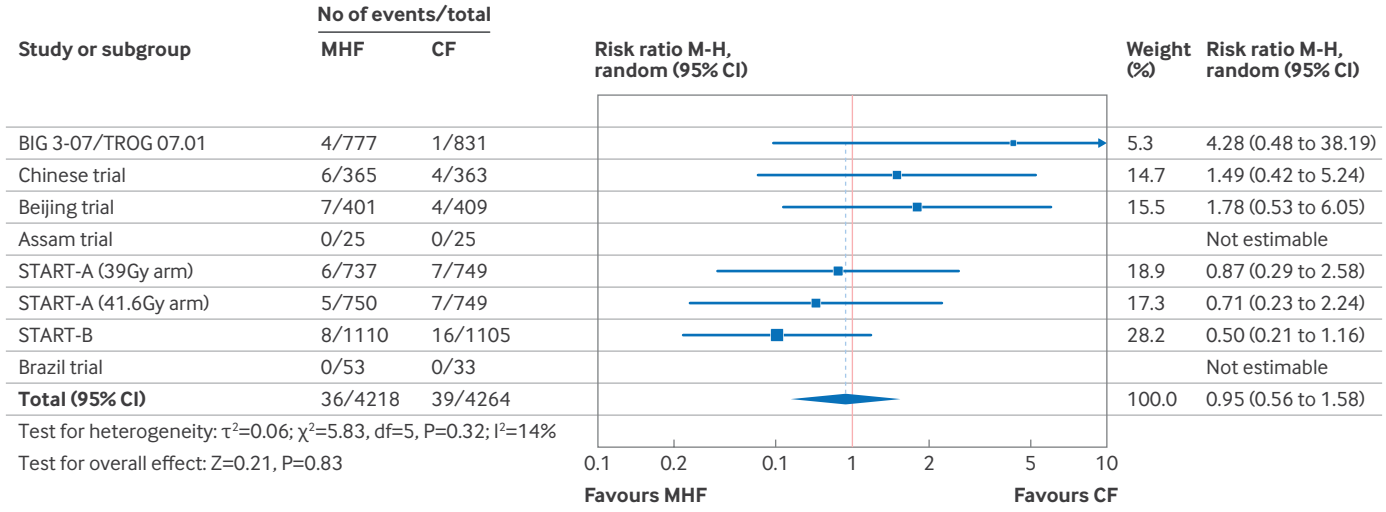

Fig 21 | Forest plot showing risk ratios for late non-skin side effects for moderate versus conventional fractionation: ischaemic heart disease. CF=conventional fractionation; CI=confidence interval; IHD=ischaemic heart disease; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

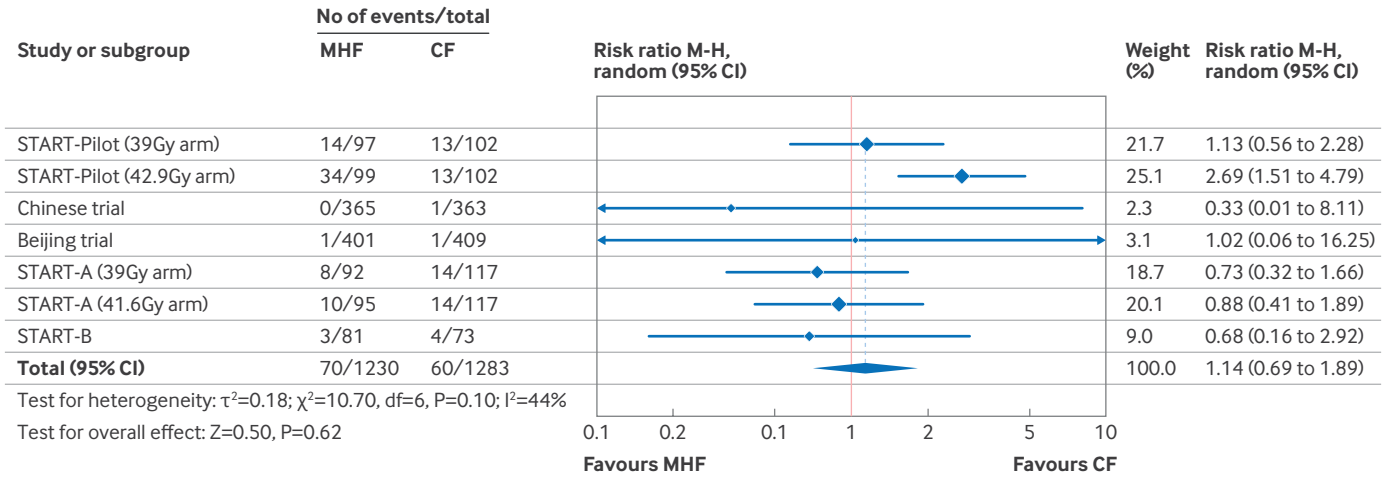

Fig 22 | Forest plot showing risk ratios for late non-skin side effects for moderate versus conventional fractionation: grade ≥2 shoulder stiffness or dysfunction. Beijing trial reported incidences of shoulder dysfunction across grades 1-2 and grade 3; however, only grade 3 data have been included in this forest plot for analysis. Chinese trial reported only incidence of grade 2 shoulder stiffness. CF=conventional fractionation; CI=confidence interval; IHD=ischaemic heart disease; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

recommends cautious use of postoperative whole breast radiation therapy in five fractions (FAST and FAST-Forward regimens), especially in patients with good long term prognosis.[92] DEGRO also advises against ultra-hypofractionation in post-mastectomy patients or those needing regional nodal irradiation and urges caution in younger patients.[92] These guidelines collectively indicate a growing acceptance of ultra-hypofractionation, particularly for early stage breast or chest wall radiation therapy. However, the body of evidence, particularly long term data, for ultra-hypofractionation is less comprehensive compared with that for moderate hypofractionation regimens, and hence uncertainty remains about its long term control and side effects.

Similarly to a previous meta-analysis,[79] our study found that moderate hypofractionation yields similar rates of local and locoregional recurrence and disease-free and overall survival to conventional fractionation. We observed a slightly improved disease-free survival for the 15 fraction moderate hypofractionation regimens compared with 50 Gy in 25 fractions. However, this subtle difference necessitates cautious interpretation, acknowledging the potential for statistical variance. Specifically, the observed variance may be related to an increased risk of type I errors stemming from multiple hypothesis testing.

Strengths and limitations of study

Our study has several limitations, including the risk of bias due to the lack of blinding of patients and/or outcome evaluators. However, masking is not possible in this kind of intervention, and survival outcomes such as local and locoregional control and disease-free and

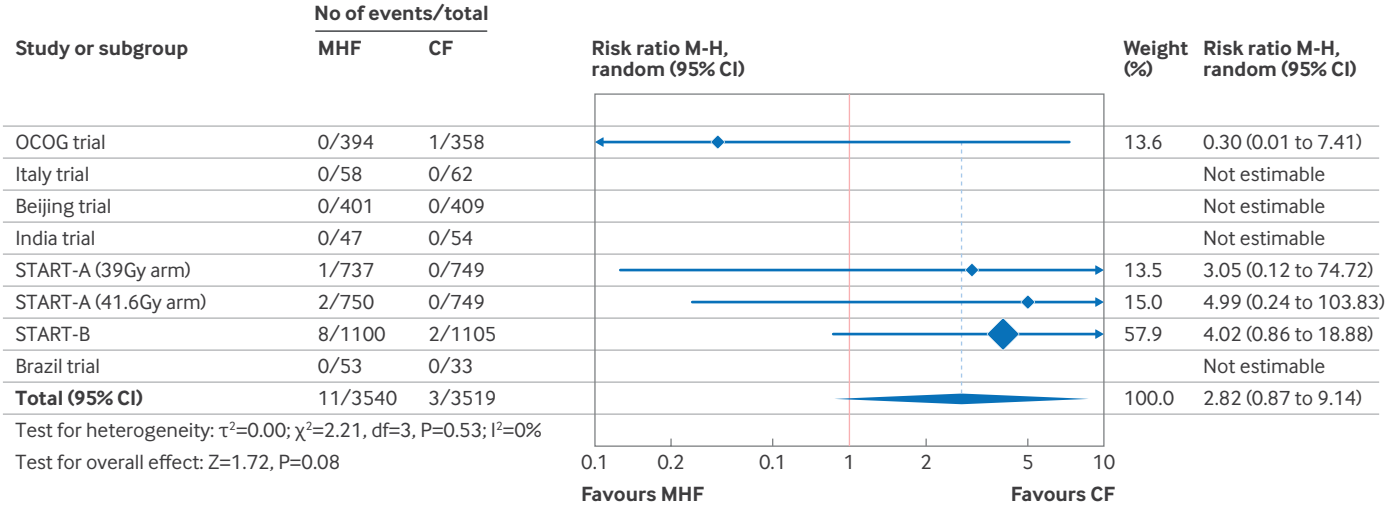

Fig 23 | Forest plot showing risk ratios for late non-skin side effects for moderate versus conventional fractionation: symptomatic rib fracture. CF=conventional fractionation; CI=confidence interval; IHD=ischaemic heart disease; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

overall survival are unlikely to have been influenced by the lack of blinding. To ensure a comprehensive assessment, we used a rigorous approach to evaluate the risk of bias and quality of evidence. Sensitivity analysis confirmed robustness even when high risk studies were excluded, reinforcing the strength of evidence despite limitations. Another limitation is that not all outcomes were reported for all trials, especially for side effects and cosmesis, hindering the drawing of definitive conclusions. Our findings nevertheless indicate a generally low heterogeneity between the included studies, enhancing the robustness of our conclusions.

Conclusions and policy implications

In summary, our study corroborates the efficacy of moderate hypofractionation in radiation therapy for breast cancer, highlighting additional benefits including reduced side effects, increased convenience, and potential cost effectiveness. These findings justify the wider adoption of moderate hypofractionation as the preferred approach, given its balance of therapeutic efficacy and improved safety. This approach not only enhances convenience for patients but also improves resource use in healthcare facilities by reducing administrative costs and boosting the operational efficiency of treatment centres through the reallocation of machine time to treat additional patients. Although conventional fractionation remains a treatment option in some parts of the world, our study should facilitate the choice between moderate hypofractionation and conventional fractionation, encouraging a personalised approach that considers patients' preferences and specific clinical circumstances. To date, results for ultra-hypofractionation support its use as a new strategy, particularly for breast and chest wall only radiation therapy, owing to its potential to further improve patients' convenience and quality of life. However, a definitive unrestricted adoption of ultra-hypofractionation awaits longer follow-up data. Future research should strengthen the evidence base for selecting fractionation regimens and ensure that clinical decisions align with economic sustainability and patient centred care.

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Data sharing: Data analysed were based on published data. Template data forms, the data extracted from included studies, and data used for analyses are available from the corresponding author on reasonable request. The study protocol is published on PROSPERO (ID: CRD42023460249)

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have

been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The results of this work will be disseminated to the public via press releases, presentations at conferences oriented towards clinicians who serve patients with breast cancer, and plain language summaries posted on websites and social media. These findings will also inform a future clinical trial that includes robust patient involvement in evaluation of the acceptability and tolerability of the intervention.

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Web appendix: Supplementary appendices, tables, and figures