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Moderately hypofractionated post-operative radiation therapy for breast cancer: Systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Introduction: We provide a critical assessment regarding current evidence for the use of moderately hypofractionated irradiation for patients with breast cancer. The aim of the study was to summarize the available evidence regarding outcomes after moderately hypofractionated compared with conventional radiation doses in the post-operative treatment of patients with breast cancer.

Material and methods: The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and LILACS databases were searched until March 25, 2021. All randomized phase 3 clinical trials that compared moderately hypofractionated with conventional radiation doses in the post-operative treatment of patients with breast cancer were selected. This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.

Results: Eight clinical trials satisfied the eligibility criteria and were the focus of the analysis. A total of 12,139 breast cancer patients was randomly assigned for moderately hypofractionated compared with conventional irradiation. Meta-analysis of the trials regarding local recurrence, loco-regional recurrence, disease-free survival, and overall survival outcomes did not demonstrate any significant difference between moderately hypofractionated irradiation and conventional radiation doses groups. The rate of severe side effects was low in both groups; acute and late side effects and cosmesis were similar or even tended to be lower after moderately hypofractionated than after conventional irradiation.

Conclusions: Moderately hypofractionated is at least as effective and safe as conventional radiation irradiation regimens and should be considered as a treatment option for most, if not all, breast cancer patients.

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1. Introduction

Post-operative radiation therapy (RT) is a key oncologic treatment for patients with breast cancer receiving either mastectomy or breast-

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Table 1
Features of the included trials.

Study	Trial Register	Start/ End, year	Country	Sample zize	Inclusion criteria	Histology, n (%)		Type of surgery, n (%)		Radiation therapy techniques	Interventions		Chemo therapy, n (%)	Boost, n (%)	Regional nodal irradiation, n (%)	Outcomes	Follow-up	Funding sources
						Invasive tumour	Ductal carcinoma in situ	Breast-conserving surgery	Mastectomy		Control arm	Experimental arm						
START Pilot Trial (5,15)	ISRCTN 59368779 /NCT 00005588	1986-1998	UK	1410	T1-3;N01; M0 maximum of one positive node	1410 (100)	0 (0.0)	1410 (100)	0 (0.0)	Conventional (2D)	50 Gy in 25 fractions, 5 weeks (n = 470)	39 Gy (n = 474) or 42.9 Gy (n = 466) in 13 fractions, 5 weeks	196 (13.9)	1051 (74.5)	290 (20.5)	Primary: Cosmesis (late change in breast appearance) Secondary: Local recurrence	Median of 9.7 years	Institute of Cancer Research (UK), Medical Research Council (UK)
START Trial A (17,18)	ISRC TN59368779/ NCT00005588	1998–2002	UK	2236	T1-3; N0-1; M0 with clear tumour margins ≥1 mm	2236 (100)	0 (0.0)	1900 (85.0)	336 (15.0)	Conventional (2D) and conformal (3D)	50 Gy in 25 fractions, 5 weeks (n = 749)	39 Gy (n = 737) or 41.6 Gy (n = 750) in 13 fractions	793 (35.4)	1152 (60.6)	318 (14.2)	Primary: Local-regional tumour relapse Secondary: Overall survival; systemic recurrence; late radiation therapy-related toxicity; cosmesis; quality of life	Median of 9.3 years	Institute of Cancer Research (UK), Medical Research Council (UK)
START Trial B (16,18)	ISRCTN 59368779/ NCT00005588	1999–2001	UK	2215	T1- 3; N0-1; M0 with clear tumour margins ≥1 mm	2215 (100)	0 (0.0)	2038 (92.0)	177 (8.0)	Conventional (2D) and conformal (3D)	50 Gy in 25 fractions (n = 1105)	40.5 Gy in 15 fractions (n = 1110)	491 (22,2)	868 (42.6)	161 (7.3)	Primary: Local-regional tumour relapse Secondary: Overall survival; systemic recurrence; late radiation therapy-related toxicity; cosmesis; quality of life	Median of 9.9 years	Institute of Cancer Research (UK), Medical Research Council (UK)
OCOG (4,14)	NCT00156052	1993–1996	Canada	1234	T1-2; N0; M0	1234 (100)	0 (0.0)	1234 (100)	0 (0.0)	Conventional (2D) and conformal (3D)	50 Gy in 25 fractions (n = 612)	42.56 Gy in 16 fractions (n = 622)	136 (11.0)	0 (0.0)	0 (0.0)	Primary: Local recurrence Secundary: Overall survival; acute and late radiation therapy-related toxicity	Median of 12.0 years	Canadian Breast Cancer Re-search Alliance and the Canadian Cancer Society
Beijing Trial (19)	NCT00793962	2008–2016	China	820	T3-T4; N2-3; M0 had at least four positive axillary	820 (100)	0 (0.0)	0 (0)	820 (100)	Conventional (2D)	50 Gy in 25 fractions (n = 414)	43.5 Gy in 15 fractions (n = 406)	820 (100)	0 (0.0)	820 (100)	Primary: 5-year locoregional recurrence Secundary: Overall survival;	Median 58.5 months	National Key Projects of Research and

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Table 1 (*continued*)

Study	Trial Register	Start/ End, year	Country	Sample zize	Inclusion criteria	Histology, n (%)		Type of surgery, n (%)		Radiation therapy techniques	Interventions		Chemo therapy, n (%)	Boost, n (%)	Regional nodal irradiation, n (%)	Outcomes	Follow-up	Funding sources
						Invasive tumour	Ductal carcinoma in situ	Breast-conserving surgery	Mastectomy		Control arm	Experimental arm						
					lymph nodes or primary tumour stage T3–4 disease											acute and late radiation therapy-related toxicity; nodal recurrence		Development of China; the Chinese Academy of Medical Science Innovation Fund for Medical Sciences; Beijing Marathon of Hope, Cancer Foundation of China
Chinese Trial (22)	NCT01413269	2010–2015	China	734	T1-2N0-3; M0	734 (100)	0 (0.0)	734 (100)	0 (0.0)	Conformal (3D) and Intensity modulated radiation therapy (IMRT)	50 Gy in 25 fractions (n = 366)	43.5 Gy in 15 fractions (n = 368)	477 (64.9)	732 (99.7)	28 (3.9)	Primary: 5-year locoregional recurrence Secundary: Overall survival; acute and late radiation therapy-related toxicity; Local recurrence; disease-free survival, nodal recurrence; cosmesis	Median of 73.5 months	Chinese Academy of Medical Science Innovation Fund for Medical Sciences; National Key Projects of Research and Development of China; and Beijing Marathon of Hope, Cancer Foundation of China
DBCG HYPO Trial (21)	NCT00909818	2009–2014	Denmark	1882	pTis-T2, N0–N1 (mic); M0	1854 (86.7)	246 (13.2)	1854 (100)	0 (0.0)	Conformal (3D)	50 Gy in 25 fractions (n = 937)	40 Gy in 15 fractions (n = 917)	578 (30)	429 (23.1)	0 (0.0)	Primary: Breast induration Secundary: overall survival; Locorregional recurrence; acute radiation therapy-related toxicity; cosmesis	Median of 7.26 years	Danish Cancer Society, the Center for Inter ventional Research in Radiation Oncology, and the Danish Comprehensive Cancer

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Table 1 (*continued*)

Study	Trial Register	Start/ End, year	Country	Sample size	Inclusion criteria	Histology, n (%)		Type of surgery, n (%)		Radiation therapy techniques	Interventions		Chemo therapy, n (%)	Boost, n (%)	Regional nodal irradiation, n (%)	Outcomes	Follow-up	Funding sources
						Invasive tumour	Ductal carcinoma in situ	Breast-conserving surgery	Mastectomy		Control arm	Experimental arm						
BIG 3–07/ TROG 07.01 (20)	NCT00470236	2007–2014	Multicentric trial	1608	pTis; N0M0	0 (0.0)	1208 (100)	1208 (100)	0 (0.0)	Conventional (2D) and conformal (3D)	50 Gy in 25 fractions plus boost 16Gy in 8 fractions (n = 415)	42.5 Gy in 16 fractions plus boost 16Gy in 8 fractions (n = 388)	0 (0.0)	803 (49.9)	0 (0.0)	Primary: Local recurrence Secondary: Time to local recurrence; overall survival; time to disease recurrence; cosmesis; toxicity; quality of life	Median of 6.6 years	Center Radio therapy Group National Health and Medical Research Council, Susan G Komen for the Cure, Breast Cancer Now, OncoSuisse, Dutch Cancer Society
Total n (%)	–	–	–	12139 (100)	–	10685 (88.9)	1454 (11.9)	10809 (89.1)	1333 (10.9)	–	–	–	3491 (28.7)	5035 (41.4)	1617 (13.3)	–	–	–

conserving surgery [1,2]. Conventional radiation doses range from 50 to 50.4 Gy, typically delivered in 25–28 fractions over a period of 5–6 weeks as a standard schedule. This historical regimen was incorporated into clinical practice based on the hypothesis that a total dose over 50 Gy, delivered in 1.8–2.0 Gy per fraction, obtains tumour control whilst limiting normal-tissue toxicity. This comes from the traditional radiobiology about the doses needed to treat subclinical disease combined with the historical assumption that breast cancer is less sensitive to changes in the dose per fraction than dose-limiting healthy normal tissues [3].

The moderately hypofractionated irradiation approach as post-operative RT was developed many years ago, assuming that increasing the dose per fraction (up to 3 Gy) and reducing the overall length of treatment course would lead to an equivalent safety and effectiveness as compared to the prolonged conventionally fractionated schedules [4,5]. Moderately hypofractionated irradiation reduces the total number of RT fractions, offering a more comfortable treatment plan for patients, and improves health care providers' treatment schedules. Hypofractionation might also optimise the waiting list of RT facilities, warranting an improved health-care equity of access and resulting in a significant decrease in terms of direct and indirect costs [6–8].

Although several randomized trials have determined the efficacy of moderately hypofractionated irradiation regarding clinical outcomes, we synthesized all current available evidences to provide a comprehensive, robust recommendation on the use of moderately hypofractionated irradiation [3]. Therefore, this systematic review and meta-analysis was performed to investigate the effectiveness and safety of moderately hypofractionated compared with conventional irradiation in the post-operative treatment of patients with breast cancer.

2. Methods

2.1. Design

The protocol was submitted in the PROSPERO database (CRD42021237630, available from https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=237630). The systematic review and meta-analysis were designed and conducted in accordance with to the Cochrane Handbook for Systematic Reviews of Interventions [9]. This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [10].

2.2. Eligibility criteria

2.2.1. Study design

We considered randomized phase 3 clinical trials (RCTs) with parallel design. Observational studies, reviews, and commentaries were not eligible. If RCTs employing a cluster design were captured, we would consider them for inclusion and adjusted during the data analysis using an intracluster correlation coefficient. We did not expect to find crossover trials, considering the progressive course of the disease. However, if captured, they would be included and only the first phase of intervention would be considered.

2.2.2. Population

Patients with non-metastatic breast cancer that received post-operative RT.

2.2.3. Intervention

The use of moderately hypofractionated irradiation, which includes: fraction sizes up to 3 Gy, a reduced total dose given in 13–16 fractions, dose range 2.65 Gy–3.3 Gy over a course of 3 weeks.

2.2.4. Comparator/control

Conventional radiation doses involving doses ranging from 45 to

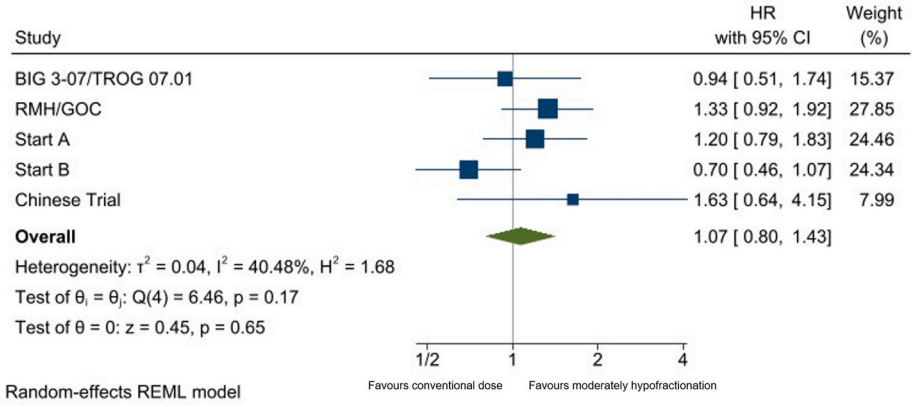

Fig. 1. Local recurrence.

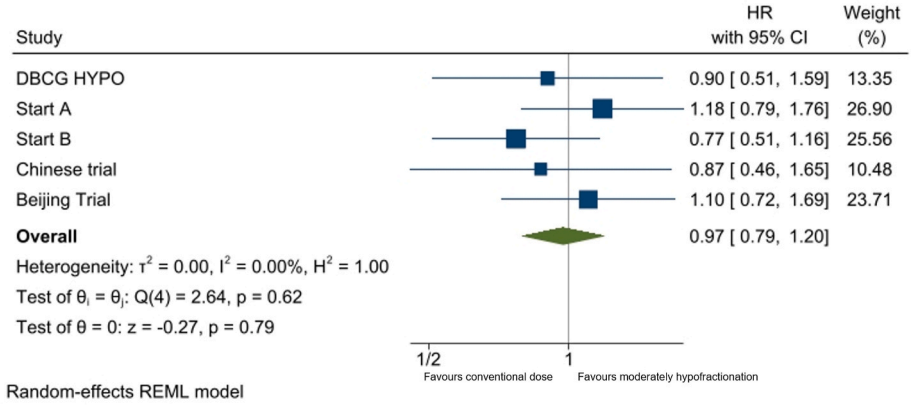

Fig. 2. Loco-reginal recurrence.

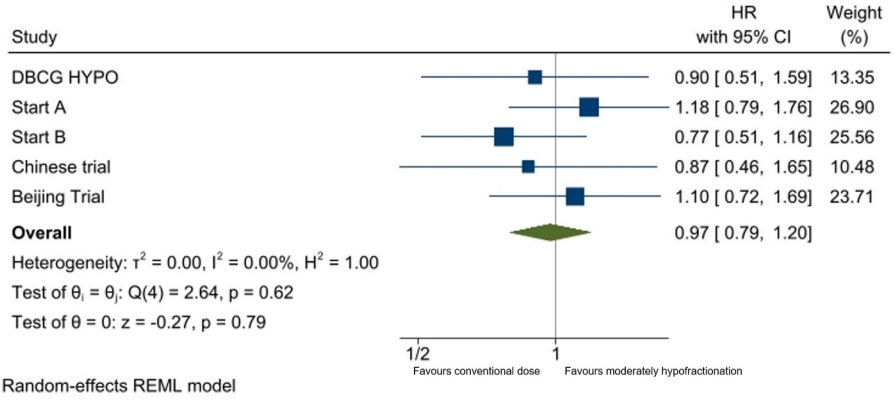

Fig. 3. Disease free survival.

50.4 Gy, fraction sizes up to 1.8 Gy–2.0 Gy, given in 25–28 fractions over a course of 5–6 weeks. Additional boost dose to the tumour bed was permitted in the intervention and comparator groups.

2.5. Outcomes

The primary outcome was local recurrence of breast/chest wall cancer. Secondary outcomes included loco-regional recurrence, disease-free survival, overall survival, acute and late radiation therapy-related side effects and cosmesis.

We considered all time-points reported by the RCTs, but we pooled in meta-analyses only those that were similar. We defined acute toxicity assessment as up to three months, subacute toxicity as three to nine months and late toxicity as more than nine months after treatment completion.

2.6. Database search

The following electronic databases were searched until March 25, 2021: CENTRAL (Cochrane Library Central Register of Controlled Trials, via Wiley), EMBASE (via Elsevier), Latin American & Caribbean Health Sciences Literature (LILACS, via Biblioteca Virtual em Saúde, BVS), Medical Literature Analysis and Retrieval System Online (MEDLINE, via PubMed). No restriction related to the status, language, or date of

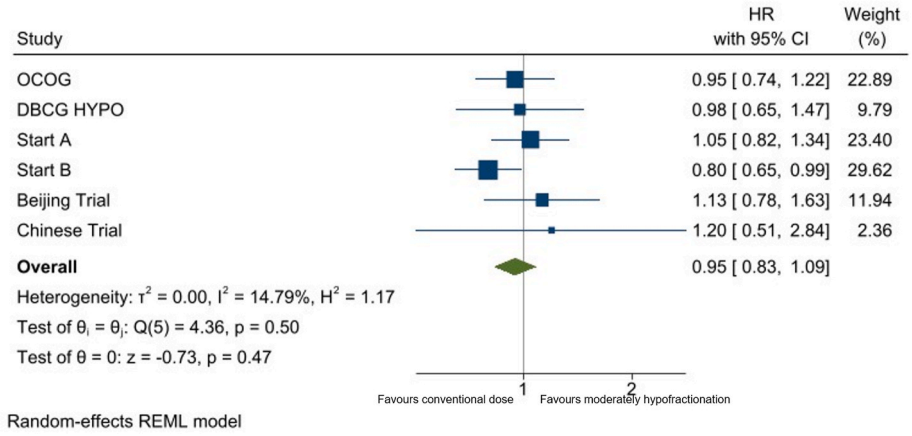

Fig. 4. Overall survival.

publication were imposed. Additional searches were performed in ClinicalTrials.gov and the Inter International Clinical Trials Register Platform (ICTRP, maintained by the World Health Organization, WHO). Grey literature was searched in the OpenGrey database (https://opengrey.eu) and a manual search was performed in the reference lists of the relevant studies. The search strategies developed and used for each electronic database are presented in the Supplement 1.

2.7. Study selection and data collection

The process for selecting studies was conducted in two stages using the Rayyan platform [11]. In the first step, two reviewers (GNM, RLP) independently screened all titles and abstracts retrieved by the searches. Studies deemed potentially eligible were identified and progressed to the second step, where the same independent reviewers assessed the full text to confirm eligibility. Disagreements were resolved by consulting a third reviewer (RR). Studies excluded during the second step were listed in the 'excluded studies table' along with the reasons for exclusion.

Two reviewers independently extracted data from the included studies. Key domains included general information (study authors, year, setting, conflicts of interest, funding source), methodological aspects (design, eligibility criteria, follow-up), participant details (age, sex, breast cancer stage, comorbidities), intervention/control criteria (doses, scheme and duration), and outcomes data (primary outcome, time-points/follow-up).

2.8. Assessing the risk of bias of included studies

We adopted the Cochrane Risk of Bias (RoB) table to assess the risk of bias of included RCTs [9]. This tool encompasses six domains: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants/personnel, (4) blinding of outcomes assessors, (5) incomplete outcome data, (6) selective reporting of outcomes and (7) other potential sources of bias. Study-level assessment was applied for domains 1,2,6,7 and outcome-level assessment for domains 3,4 and 5. Two independent reviewers assessed the risk of bias of each trial and a third investigator was consulted in case of disagreements. We detailed the reasons for each judgment assumed.

2.9. Unit of analysis, measures of treatment effect and data synthesis

We considered the individual participant as the main unit of analysis. For the treatment effects estimate, we calculated hazard ratio (HR) for time-to-event variables, risk ratio (RR) for dichotomous variables and mean differences (MD) for continuous variables.

2.10. Meta-analysis

When possible (depending on the availability of data and diversity across studies), we pooled the results from studies into random-effects models. The data extraction for time-to-event outcomes was performed following the Cochrane handbook [9]. We assessed the presence of inconsistency (statistical heterogeneity) by visual inspection of forest plots and Chi [2] tests ($p > 0.10$ was considered indicative of statistical heterogeneity). We used I^2 tests to measure the extension of this inconsistency ($I^2 > 50\%$ was considered indicative of significant inconsistency) [12]. We planned to explore reasons for heterogeneity by conducting subgroup and sensitivity analyses. Analysis was conducted using the software STATA 17. A 95% confidence interval (CI) was assumed for all analyses.

The hazard ratio was used to summarize time-to-event data in view of the last follow-up available. The comparing interventions in meta-analysis was calculated considering that the hazard ratio is constant across the follow-up time, albeit hazards themselves might differ continuously (proportional hazards assumption methodology) [9].

2.11. Sensitivity analysis

We planned to conduct a sensitivity analysis considering only high quality RCT (low risk of bias for all domains of RoB table). We planned to investigate publication bias exploring funnel plots, if 10 or more studies were included in the same meta-analysis.

2.12. Assessing the certainty of the evidence

We adopted the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluations) to assess the quality (certainty) of the overall body of evidence [13]. The GRADE comprises five domains to downgrade the certainty of the evidence from RCTs (methodological limitations, inconsistency, imprecision, indirectness and publication bias). We created a summary of findings table using the GRADEpro GDT software (Copyright © 2020, McMaster University and Evidence Prime Inc.) and the reasons to downgrade the certainty of the evidence were justified.

3. Results

3.1. Search results and characteristics of included studies

The selection process was detailed in a PRISMA flow diagram (Supplement 2). A total of 1031 references were retrieved. After assessment of the titles and abstracts and full-text stage, 1015 references were excluded, and 16 full-text manuscripts were eligible. Of these,

eight clinical trials reported in 16 references satisfied the eligibility criteria and formed the scope of the analysis [4,5,14–22].

The characteristics of the included trials (n = 12,139) are detailed in Table 1. Briefly, a total of 12,139 breast cancer patients were randomly assigned for moderately hypofractionated irradiation versus conventional radiation doses. Most of the patients underwent breast-conserving surgery (N = 10,809, 89.1%); 3491 (28.7%) of patients received chemotherapy; boost and reginal nodal irradiation were performed in 5035 (41.4%) and 1617 (13.3%) patients respectively.

3.2. Results based on outcome

3.2.1. Local recurrence

Six trials evaluated local breast/chest wall cancer recurrence [15–18,20,22], and five studies were included in the quantitative synthesis because one trial [4] did not report sufficient data to be included in the analysis (the authors did not report the HR or the p-value of Cox's analysis). Local recurrence rates did not differ significantly in the patients treated with moderately hypofractionated irradiation compared to those that received conventional radiation doses (pooled HR = 1.07, 95%CI: 0.80 to 1.43, p = 0.65) with respect to local recurrence (Fig. 1).

3.2.2. Loco-regional recurrence

Five trials were included in the loco-regional control analysis [18,19,21,22]. Loco-regional control rates were not significantly different among patients treated with moderately hypofractionated irradiation compared to patients who underwent conventional radiation doses (HR 0.97, 95% CI 0.79 to 1.20; p = 0.79). (Fig. 2).

3.2.3. Disease-free survival

Three trials analyzed disease-free survival outcome [14,19,22]. For the pooled-in disease-free survival analysis, there was no significant difference in the HR between moderately hypofractionated irradiation versus conventional radiation doses (HR = 0.96, 95%CI: 0.76 to 1.16, p = 0.67) (Fig. 3).

3.2.4. Overall survival

Six studies reported overall survival [15,18,19,21,22], and no difference between the moderately hypofractionated irradiation and conventional radiation doses groups was observed. The pooled HR was 0.95 (95% IC; 0.83 to 1.09; p = 0.47) (Fig. 4).

3.2.5. Side effects and cosmesis

Due to substantial diversity of assessment methods with diverse endpoints, a meta-analysis was not performed concerning side effects and cosmesis.

Overall, the rate of severe side effects was low and comparable in both treatment groups within the trials. Acute and late side effects are similar or tended to be lower after hypofractionation than after conventional fractionation. Likewise, cosmesis was slightly better in the moderately hypofractionated irradiation group in one trial [15], while in the other studies, there was no difference between cosmetic outcomes [14,21]. Additional details can be found in the Supplement 3 and the Supplement 4.

3.3. Risk of bias of included studies and GRADE

The methodological quality of the included trials is demonstrated in the Supplement 5 and the Supplement 6.

Overall, all the eight trials were classified as high risk of bias considering the lack of blinding of patients and/or outcome evaluators. The GRADE Working Group grades of evidence was described in the Supplement 7.

6. Discussion

In our systematic review and meta-analysis, we found no differences in local recurrence, local-regional recurrence, disease-free survival, or overall survival rates between patients receiving moderately hypofractionated irradiation or conventional radiation doses for post-operative RT.

Our study was the first meta-analysis to include patients with ductal carcinoma in situ and more locally advanced breast cancer patients that received mastectomy and/or those requiring regional nodal irradiation. Although a specific subgroup analysis for these patients was not performed, there is a strong sign that moderately hypofractionated irradiation can be used for this subset of patients. Analysis of the available data presented in the individual clinical trials was assessed and found moderately hypofractionated irradiation to be as effective and safe when compared to conventional radiation doses for all clinical outcomes. Although ductal carcinoma in situ and locally advanced breast cancer patients were lower represented, these findings are in agreement with radiobiological considerations that indicate that there is no reason why these patients should have inferior outcomes with moderately hypofractionated irradiation [3]. Some recent guidelines suggest the use of moderately hypofractionated irradiation for patients with breast cancer regardless of the patient's age, the use of systemic regimens, and disease stage, although there is hesitancy regarding regional lymph node and chest wall irradiation [23,24]. It is important to recognized that these guidelines were published before the Beijing Trial [19] wherein all patients received regional lymph node and chest wall irradiation which may result less reluctance to accept moderate hypofractionation for this subgroup of patients.

Few experts maintain the view that the use of moderately hypofractionated irradiation for regional nodal irradiation must be evaluated very carefully until current evidence demonstrates that long-term side effects are minimal, especially regarding to lung function and heart [25,26]. Two studies identified in our review, the START trials and the Beijing trial, demonstrated extremely low rates of lung fibrosis and heart disorder [18,19,27] and patients rarely develop pulmonary or cardiac side effects that demand medical care [19,26–28]. However, some reported concerns on the late effects of moderately hypofractionated irradiation subgroups including young patients, patients with advanced disease, and those who receive adjuvant systemic treatments [29]. However, adjuvant chemotherapy was broadly used in the MD Anderson [30] and Chinese trials [19], with acceptable side effects and no differences between fracxtionation schedules. Moreover, in a real-life practice, the use of moderately hypofractionated irradiation in young patients was associated with excellent clinical outcomes [31]. This is in agreement with the European Society for Radiotherapy and Oncology (ESTRO) Advisory Committee in Radiation Oncology Practice (ACROP) consensus recommendations that advise moderately hypofractionated irradiation for all patients [32].

Side effects and cosmesis were evaluated by different methods in the included trials and were not combined in a meta-analysis. However, acute and late side effects were comparable or tended to be lower after moderately hypofractionated irradiation than after conventional radiation doses. Comparable results were also observed regarding cosmesis [14,21]. RT-related side effects are perhaps more associated with the RT technique type rather than to the dose regimen. Moreover, with increasing fraction sizes, the need for using appropriated techniques to obtain homogenous dose distributions increases as well, since dose inhomogeneity might exert a more expressed negative impact in case of hypofractionation [3]. This perception is recognized in some countries, such as the UK and the Netherlands, where a moderate hypofractionation schedule represented since several years the standard-of-care for nearly all patients with breast-cancer regardless of target volumes. This includes regional nodal irradiation and treatment after mastectomy, with or without breast reconstruction [33,34]. Recent data from European Institute of Oncology demonstrated that the use of moderately

hypofractionated irradiation to implant-based immediate breast reconstruction did not appear to increase the risk of reconstruction failure [35]. This concept is in line with the 2021 St Gallen consensus conference, where the majority of breast cancer experts (63.64%) recommend that moderately hypofractionated irradiation schedules can be used without restriction after immediate reconstruction even though none of the available clinical trials specifically included these patients [36].

A Cochrane meta-analysis that compared treatment results in breast cancer patients treated with moderately hypofractionated irradiation or conventional radiation doses included only early breast cancer treated with breast-conserving therapy (search was updated on 2015). We found similar results: the use of hypofractionated RT was associated with the same local recurrence and overall survival rates compared to conventional radiation doses and a reduction in acute and long-term side effects was observed [37]. Although other meta-analyses of moderate hypofractionation were previously published, we did include the recent trials to be more up to date and helpful for clinicians.

A limitation of this meta-analysis is represented by the differences in the moderately hypofractionated irradiation schedules used across included studies. Despite the assumed differences in biological effective dose (BED) between the moderately hypofractionated irradiation schedules, the results are very similar independently of the moderately hypofractionated irradiation regimen used. Another limitation is that all eight trials were classified as having a high risk of bias, primarily due to the lack of blinding of patients and/or outcome evaluators. Nevertheless, masking is not possible in this kind of intervention, and it is improbable that survival outcomes such as local control, loco-regional control, disease-free and overall survival might be influenced by the lack of blinding. We also recognize that the results of one trial on ductal carcinoma in situ were available only in abstract form, which limits the amount of the data that are currently available [20]. However, the median follow-up of the 1608 patients was already 6.6 years, which is shown in other studies to be very representative for the outcomes after longer follow-up. We planned to perform subgroup analyses as described on our protocol available in the PROSPERO registration base (CRD42021237630). However, the subgroup analyses on type of surgery, pathological stage, regional lymph nodes irradiation, and type of systemic therapy could not be performed due to insufficient availability of data.

The investigation of safety and effectiveness of moderately hypofractionated, as compared to conventional radiation irradiation, for patients with breast cancer is still ongoing in several other clinical settings (NCT02700386, NCT02690636, NCT03127995, and NCT02958774). The results of these trials will add more evidence to clarify the effectiveness of moderately hypofractionated as compared to conventional radiation irradiation. Towards extending the philosophy of hypofractionation, the first results for the tumour- and side-effect endpoints from the FAST-Forward trial are now available. In this multicentre, phase 3, randomized, non-inferiority trial, an ultra-hypofractionated treatment schedule of 26 Gy or 27 Gy in five fractions delivered in 1 week was tested in pT1-3, pN0-1, M0 breast cancer patients, aged at least 18 years, after mastectomy or breast conservation surgery. After nearly 6 years of median follow up, this UK-based study demonstrated that the ultra-hypofractionation schedule was non-inferior to the standard of 40 Gy in 15 fractions over 3 weeks regarding the actuarial 5-year incidence of ipsilateral breast tumour relapse. Additionally, the ultra-hypofractionated schedule of 26 Gy was as safe in terms of normal tissue effects as the moderately hypofractionated regimen. It must be recognized that the clinical outcomes of this trial could support in the adoption of this schedule as a treatment option for most of early breast cancer patients, replacing the moderately hypofractionated [38].

In conclusion, no differences in local recurrence, loco-regional recurrence, disease-free survival, and overall survival rates were observed between moderately hypofractionated irradiation and conventional radiation doses groups. The rate of severe side effects was low in both groups; acute and late side effects and cosmesis are comparable or tend to be lower after moderately hypofractionated irradiation than after conventional radiation doses.

Author contributions

GNM and PP conceived the project; GNM, RR, RLP, ALCM, IM and OKP performed the literature search; all authors contributed to the literature analysis and synthesis of data; GNM, RR, RLP, ALCM created the figures and tables; GNM, RR, RLP wrote the review; and all authors were involved in further editing and finalising the manuscript.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.01.018.

References

[1] Early Breast Cancer Trialists' Collaborative G, Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378(9804):1707–16.
[2] Ebctcg, McGale P, Taylor C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014;383(9935):2127–35.
[3] Marta GN, Coles C, Kaidar-Person O, et al. The use of moderately hypofractionated post-operative radiation therapy for breast cancer in clinical practice: a critical review. Crit Rev Oncol Hematol 2020;156:103090.
[4] Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst 2002;94(15):1143–50.
[5] Yarnold J, Ashton A, Bliss J, et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. Radiother Oncol 2005;75(1):9–17.
[6] Lievens Y, van den Bogaert W, Kesteloot K. Activity-based costing: a practical model for cost calculation in radiotherapy. Int J Radiat Oncol Biol Phys 2003;57(2):522–35.
[7] Fang M, Marta GN. Hypofractionated and hyper-hypofractionated radiation therapy in postoperative breast cancer treatment. Rev Assoc Med Bras 1992;66(9):1301–6. 2020.
[8] Marta GN, Ramiah D, Kaidar-Person O, et al. The financial impact on reimbursement of moderately hypofractionated postoperative radiation therapy for breast cancer: an international consortium report. Clin Oncol 2021;33(5):322–30.
[9] Higgins JPT, Thomas J, Chandler J, et al., editors. Cochrane handbook for systematic reviews of interventions; 2016 (updated July 2019), version 6.0. www.training.cochrane.org/handbook. [Accessed 29 January 2021].
[10] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
[11] Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5(1):210.
[12] Higgins JPT GSe. Cochrane handbook for systematic reviews of interventions:. 2008. The Cochrane Collaboration; 2011 [updated September 2011], version 5.0.2.
[13] Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. Chest 2006;129(1):174–81.
[14] Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362(6):513–20.
[15] Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol 2006;7(6):467–71.
[16] Group ST, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 2008;371(9618):1098–107.
[17] Group ST, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol 2008;9(4):331–41.

[18] Haviland JS, Owen JR, Dewar JA, et al. 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. Lancet Oncol 2013;14(11):1086–94.
[19] Wang SL, Fang H, Song YW, et al. Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial. Lancet Oncol 2019;20(3):352–60.
[20] Chua BH, Link E, Kunkler I, et al. A randomized phase III study of radiation doses and fractionation schedules in non-low risk ductal carcinoma in situ (DCIS) of the breast. BIG 3-07/TROG 07.01), https://cancerres.aacrjournals.org/content/81/4_Supplement/GS2-04.article-info. [Accessed 29 January 2021].
[21] Offersen BV, Alsner J, Nielsen HM, et al. Hypofractionated versus standard fractionated radiotherapy in patients with early breast cancer or ductal carcinoma in situ in a randomized phase III trial: the DBCG HYPO trial. J Clin Oncol 2020;38(31):3615–25.
[22] Wang SL, Fang H, Hu C, et al. Hypofractionated versus conventional fractionated radiotherapy after breast-conserving surgery in the modern treatment Era: a multicenter, randomized controlled trial from China. J Clin Oncol 2020;38(31):3604–14.
[23] Smith BD, Bellon JR, Blitzblau R, et al. Radiation therapy for the whole breast: executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Pract Radiat Oncol 2018;8(3):145–52.
[24] Sbrt BSoR, Freitas NMA, Rosa AA, et al. Recommendations for hypofractionated whole-breast irradiation. Rev Assoc Med Bras 2018;64(9):770–7. 1992.
[25] Vinh-Hung V, Nguyen NP, Verschraegen C. Hypofractionated nodal irradiation for breast cancer: a case for caution. JAMA Oncol 2019;5(1):13–4.
[26] Verbanck S, Hanon S, Schuermans D, et al. Mild lung restriction in breast cancer patients after hypofractionated and conventional radiation therapy: a 3-year follow-up. Int J Radiat Oncol Biol Phys 2016;95(3):937–45.
[27] Liss AL, Marsh RB, Kapadia NS, et al. Decreased lung perfusion after breast/chest wall irradiation: quantitative results from a prospective clinical trial. Int J Radiat Oncol Biol Phys 2017;97(2):296–302.
[28] Chan EK, Woods R, McBride ML, et al. Adjuvant hypofractionated versus conventional whole breast radiation therapy for early-stage breast cancer: long-term hospital-related morbidity from cardiac causes. Int J Radiat Oncol Biol Phys 2014;88(4):786–92.
[29] Recht A. Hypofractionated whole-breast irradiation: case closed? J Clin Oncol 2020;38(31):3584–6.
[30] Shaitelman SF, Lei X, Thompson A, et al. Three-year outcomes with hypofractionated versus conventionally fractionated whole-breast irradiation: results of a randomized, noninferiority clinical trial. J Clin Oncol 2018;36(35):3495–503. https://doi.org/10.1200/JCO.18.00317.
[31] Meattini I, Poortmans P, Kirova Y, et al. Hypofractionated whole breast irradiation after conservative surgery for patients aged less than 60 years: a multi-centre comparative study. Acta Oncol 2020;59(2):188–95.
[32] Meattini I, Becherini C, Boersma L, et al. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. Lancet Oncol 2022;23(1):e21–31.
[33] Lansu JT, Essers M, Voogd AC, et al. The influence of simultaneous integrated boost, hypofractionation and oncoplastic surgery on cosmetic outcome and PROMs after breast conserving therapy. Eur J Surg Oncol 2015;41(10):1411–6.
[34] Bloomfield DJ. Core group facilitated by the royal college of R. Development of postoperative radiotherapy for breast cancer: UK consensus statements - a model of patient, clinical and commissioner engagement? Clin Oncol 2017;29(10):639–41.
[35] Rojas DP, Leonardi MC, Frassoni S, et al. Implant risk failure in patients undergoing postmastectomy 3-week hypofractionated radiotherapy after immediate reconstruction. Radiother Oncol 2021;163:105–13.
[36] Thomssen C, Balic M, Harbeck N, Gnant M. St. Gallen/Vienna 2021: a brief summary of the consensus discussion on customizing therapies for women with early breast cancer. Breast Care 2021;16(2):135–43.
[37] Hickey BE, James ML, Lehman M, et al. Fraction size in radiation therapy for breast conservation in early breast cancer. Cochrane Database Syst Rev 2016;7.CD003860.
[38] Murray Brunt A, Haviland JS, Wheatley DA, et al. 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 2020;395(10237):1613–26.