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Review

Meta-analysis of long-term efficacy and safety of hypofractionated radiotherapy in the treatment of early breast cancer

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ABSTRACT

Purpose: To evaluate the efficacy and safety of hypofractionated radiotherapy in women with early stage breast cancer after breast conservative surgery.
Methods: We performed a search for randomized controlled trials (RCTs) that compare conventional fractioning and hypofractioned radiotherapy. The studied outcomes were local and loco-regional recurrence, disease-free survival, mortality, cardiac ischemia, rib fracture and pulmonary fibrosis up to 5 years and 5 years after treatment. Shrinkage of the breast, breast tightening, telangiectasia, breast edema, shoulder stiffness and arm edema were evaluated within 10 years. Cosmesis and acute skin radiation toxicity were evaluated.
Results: Ten publications of six RCTs were included. No statistical difference in local and loco-regional recurrence, disease-free survival, mortality, cardiac ischemia, ribs fracture and pulmonary fibrosis, shrinkage of the breast, breast tightening, shoulder stiffness, arm edema and cosmesis was found. However, there was a significant difference in favor of hypofractionated for breast edema (RR 0.68, 95% CI 0.53 to 0.88, p = 0.003, 4675 patients), telangiectasia (RR 0.41, 95% CI 0.19 a 0.87, p = 0.02, 5167 patients), and acute skin radiation toxicity (RR 0.34, 95% CI 0.19 to 0.61, p = 0.0003, 347 patients).
Conclusion: There is no difference between conventional fractionation and hypofractionated in terms of efficacy when we evaluate local recurrence, loco-regional recurrence, distance recurrence, disease-free survival and mortality. There is also no difference concerning safety when we assess the occurrence of fibrosis, ischemia and ribs fractures. Hypofractionated showed better results in relation to breast edema, telangiectasia, and acute skin radiation toxicity.

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1. Introduction

At first, patients with early stage breast cancer were treated with radical mastectomy. However, randomized controlled trials (RCTs) have shown that conservative treatment has an equivalent overall survival rate [1–4]. Conservative treatment is the complete surgical remove of the tumor, with negative surgical margins, followed by whole breast radiation therapy (WBRT) in order to eradicate any remaining disease [5].

Most women receive conventional WBRT in which the total dose administered is 45–50 Gy, applied fractionally (1.8–2 Gy daily for 5 days a week for 5 weeks), it can also be associated with a boost of 10–16 Gy, usually for 1–2 weeks. As an alternative to the conventional WBRT there is the hypofractioned schedule that allows a shorter treatment duration by administering a higher dose per fraction in a reduced number of fractions [2]. Also, this shorter fractionation schedule may result in cost savings of 20%–30% [6,7]. The efficacy, safety and cosmetic results of a hypofractionated scheme have been shown to be equivalent to a conventionally provided WBRT. However, these studies do not present a full range of possible and important outcomes to be analyzed [8]or mix conservative and non-conservative surgeries and study designs [9].

In this sense, we aimed to make a broader comparison of the outcomes of conventional fractionation in relation to hypofractionated radiotherapy, in women with early breast cancer that underwent conservative breast surgery, adding important outcomes to the patients and using only RCTs.

2. Materials and methods

We performed the systematic review and meta-analysis according to the recommendations from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol was registered in PROSPERO (CRD42015026477) [10].

2.1. Search strategy and selection criteria

We performed a computerized search of Excerpta Medica dataBASE (EMBASE), The United States National Library of Medicine and National Institutes of Health (PUBMED Medline), Latin American and Caribbean Health Sciences Literature (Lilacs) and Cochrane Library from inception to August 2018, which was not limited by date or language. The search comprised the following terms: “Breast Neoplasms”, “Breast Cancer”, “Radiotherapy”, “Radiotherapy Dosage”, “Dose Fractionation”, associated with the terms “systematic review”, “meta-analysis” and “randomized controlled trials”. Details of the search strategy utilized is in supplementary material S1.

We included randomized, controlled studies that compared WBRT using the conventional fractionation with hypofractionated radiotherapy. The women had to have performed breast-conserving surgery and also had their primary breast cancer histologically confirmed. We excluded studies that did not perform the selected comparison, that were narrative revisions, letters, editorials, scientific abstracts and animals’ studies.

2.2. Data extraction and bias analysis

After removing duplicate articles, two reviewers (TRM and MCMF) independently analyzed abstracts and titles; sequentially they reviewed, also independently the full-text articles of the selected eligible studies. The reviewers established consensus to address possible disagreements concerning the selection of articles.

Bias assessment was evaluated by using the Cochrane Collaboration tool and the certainty of evidence according to GRADE [11,12].

2.3. Outcomes

The outcomes were evaluated in two periods, within 5 years of treatment and after a minimum 5-year of treatment. We evaluated the following outcomes: local recurrence, loco regional recurrence, distant recurrence, mortality, cardiac ischemia, symptomatic rib fracture, symptomatic pulmonary fibrosis, breast reduction, breast tightening, telangiectasia, breast edema, shoulder stiffness, arm edema, cosmesis (fair/poor) and acute skin radiation toxicity. We also evaluated disease-free survival, defined as time from breast cancer diagnosis to any of the following events, local, regional, or distant relapse, breast cancer death, contralateral breast cancer or death due to cancer.

2.4. Statistical analysis

To measure the effect for survival outcomes we used hazard. We calculated the log rank statistic (O-E) and its variance for time-to-event outcomes using an Excel spreadsheet developed by Matthew Sydes (Cancer Division) in collaboration with the Meta-analysis Group of the MRC Clinical Trials Unit, London [13]. For survival outcomes, fixed-effects Peto odds ratios (ORs) were presented with 95% confidence intervals (CIs).

Dichotomous data, such as toxicity and cosmetic outcome, were expressed as risk ratios (RR) with 95% CIs. To combine results across studies we applied a random-effects meta-analytic model using the inverse variance in all calculations. Analyses were carried out by using Review Manager statistical software (Review Manager version 5.3) from the Cochrane Collaboration. Heterogeneity across studies was assessed using Q test (χ^2 test) with significance level of $p < 0.05$, and I^2 test. According to Cochrane handbook, I^2 of 50% or more indicates a considerable level of heterogeneity [11].

For studies with more than two intervention groups, we included each pair comparison separately and in agreement to the Cochrane Collaboration recommendation the number of events and of participants were evenly distributed between the comparisons,

once the control group was common [14].

We performed two sensitivity analyses. The first one considered only hypofractionated schemes (42.5 Gy, 41.6 Gy and 40 Gy) that seems to have equivalent efficacy to conventional fractionation as mentioned by American Society For Radiation Oncology (ASTRO) [15]. The second sensitivity analysis considered only the studies that used the boost in some part of the population.

3. Results

We retrieved 12.770 articles and after the extraction of the duplicates, 6.880 articles were left. After title and abstract analysis, 189 studies were fully evaluated. On total, nine publications were included in the meta-analysis pertaining six primary studies. Fig. 1 shows the flow chart of the literature search.

The characteristics of the included studies are described in Table 1. The risk of bias according to Cochrane Collaboration of included studies are presented in Fig. 2 and supplementary material S2.

3.1. Characteristics of the population and the radio-therapeutic parameters

In the six studies included in the meta-analysis with a total of 8075 women, included most of them with T1-2 (98.7%), N0, M0 breast cancers and over 50 years of age underwent conventional or hypofractionated radiotherapy. Except for the Taher et al. (2004) [16] study few participants had previous chemotherapy (0–35%). Most patients underwent conservative surgery, and few patients had high-grade tumors (see supplementary material S3).

Concerning the radiation therapy parameters, 45.6% of all patients received a boost dose; most centers used 2D planning and central axis dose homogeneity ranged between −10% and +10% (see supplementary material S4).

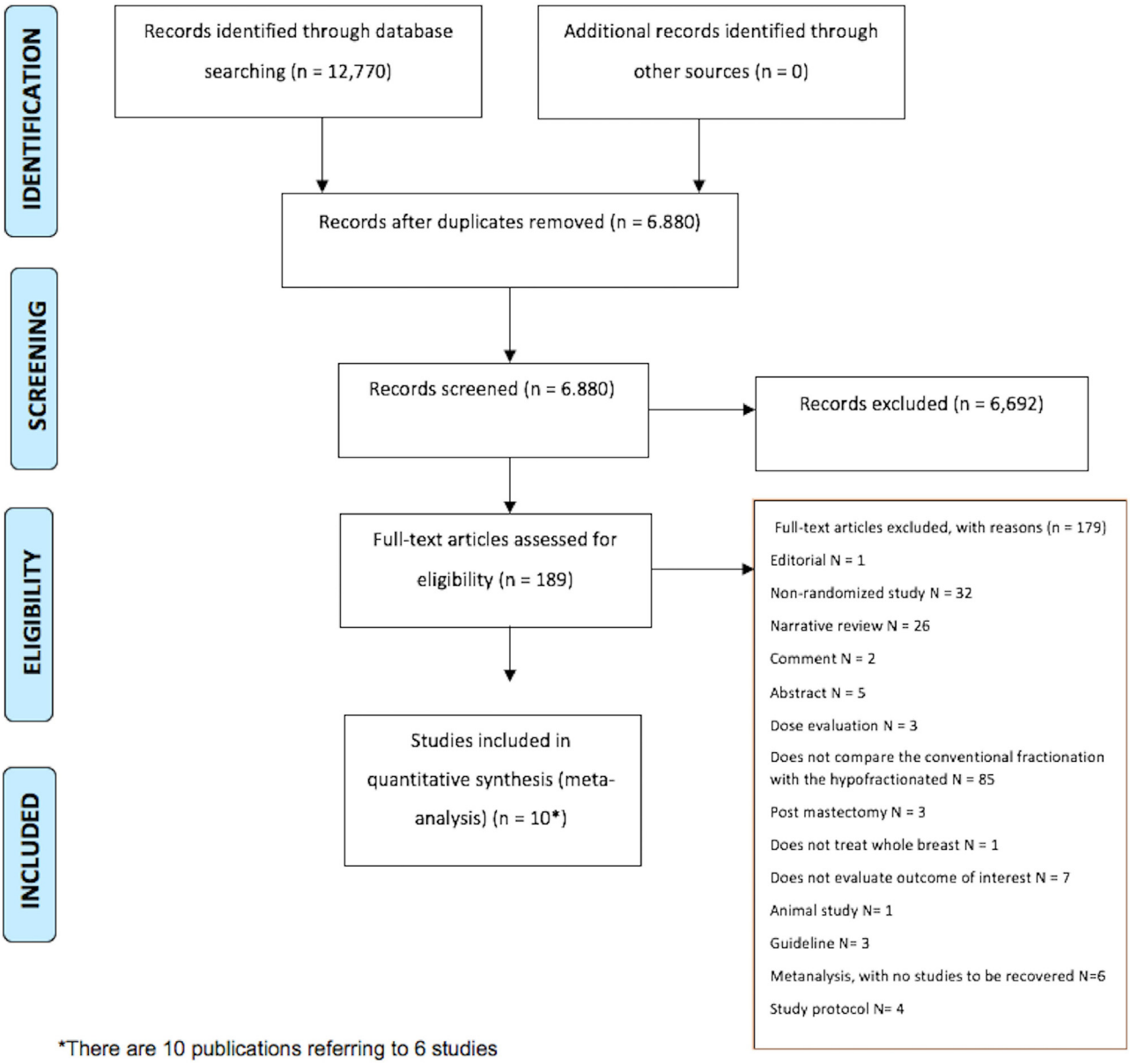

Fig. 1. Flowchart of systematic review studies recovery.

Table 1
Characteristics of included studies.

Study	Start A [1] [2]	Start B [2] [3]	RMH/GOC[4] [5]	Canadian [6] [7]	FAST 2011 [8]	Taher 2004 [9]
Population	Women with invasive operable primary breast cancer (T1-3, N0-1, M0)	Women with invasive operable primary breast cancer (T1-3, N0-1, M0)	Women with invasive operable primary breast cancer (T1-3, N0-1, M0)	Women with invasive operable primary breast cancer (T1-3, N0-1, M0)	Women > 50 years with invasive carcinoma, (T1-2, N0, M0)	Women > 60 years, T1-2, N0-M0, tumor larger than 1 cm
Number of patients (n)	2236	2215	1410	1234	950	30
Experimental group intervention	41.6 Gy/13 fractions/5 weeks (3.2 Gy/fraction) or 39 Gy/13 fractions/5 weeks (3 Gy/fraction)	40 Gy/15 fractions/3 weeks (2.67 Gy/fraction)	42.9 Gy/13 fractions/5 weeks (3.3 Gy/fraction) or 39 Gy/13 fractions/5 weeks (3 Gy/fraction)	42.5 Gy/16 fractions/4.4 weeks (2.66 Gy/fraction)	28.5 Gy/5 fractions/1 week (5.7 Gy/fraction) or 30 Gy/5 fractions/1 week (6 Gy/fraction)	42.5 Gy/16 fractions/4.4 weeks (2.66 Gy/fraction)
Control group intervention	50 Gy/25 fractions/5 weeks (2 Gy/fraction)	50 Gy/25 fractions/5 weeks (2 Gy/fraction)	50 Gy/25 fractions/5 weeks (2 Gy/fraction)	50 Gy/25 fractions/5 weeks (2 Gy/fraction)	50 Gy/25 fractions/5 weeks (2 Gy/fraction)	50 Gy/25 fractions/5 weeks (2 Gy/fraction)
Maximum *follow-up*	12.4 years	12.4 years	18.4 years	12 years	37.3 months *	27 months
Outcomes	Locoregional recurrence, effect on normal tissue, patient reported outcomes, disease-free survival, overall survival, secondary cancer due to primary, cases of ischemia, symptomatic rib fractures, and symptomatic pulmonary fibrosis.	Locoregional recurrence, effect on normal tissue, patient reported outcomes, disease-free survival, overall survival, secondary cancer due to primary, cases of ischemia, symptomatic rib fractures, and symptomatic pulmonary fibrosis.	Change in breast appearance. Ipsilateral recurrence, distant recurrence.	Local recurrence. Distant recurrence, outcomes reported by patients, late radiation toxicity, death	Breast appearance, changes in breast induced by radiation, local tumor control	Acute skin reaction due to radiation, late breast cosmetic results

START-standardization of breast radiotherapy. WMOBCG- West Midlands OncoloGy Breast Cancer Group. RMH/GOC- Royal Marsden Hospital/Gloucester OncoloGy Center. *Median Follow-up.

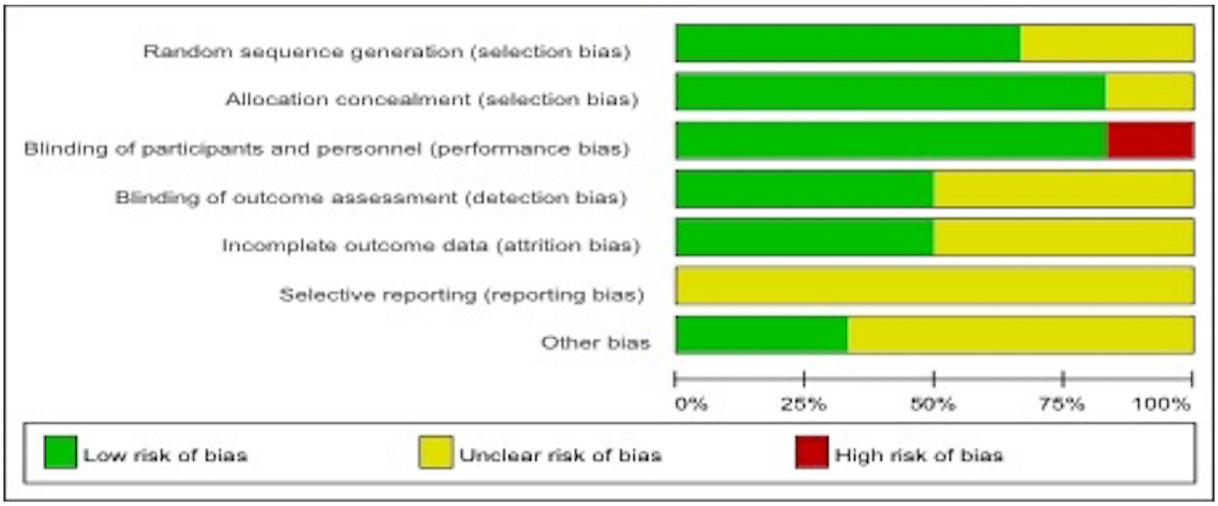

Fig. 2. Risk of bias according to Cochrane Collaboration.

3.2. Meta-analytic results

For the primary outcomes, there were no significant difference between conventional and hypofractionated radiotherapy in relation to local recurrence within 5 years and after 5 years (RR 0.96, 95% CI 0.71 to 1.29, $p = 0.79$, $I^2 = 0\%$, 6043 patients, and RR 0.97, 95% CI 0.78 to 1.20, $p = 0.78$, $I^2 = 23\%$, 5861 patients, respectively), and disease free-survival within 5 years and after 5 years (RR 0.89, 95% CI 0.77 to 1.03, $p = 0.19$, $I^2 = 35\%$, 5685 patients, and RR 0.90, 95% CI 0.78 to 1.03, $p = 0.11$, $I^2 = 44\%$, 4451 patients, respectively) (Table 2) (forest-plot in supplementary material S5–S6; S13–S14, respectively).

There was significant difference in telangiectasia (RR 0.41, 95% CI 0.19 a 0.87, $p = 0.02$, $I^2 = 93\%$, 5167 patients), breast edema (RR 0.68, 95% CI 0.53 to 0.88, $p = 0.003$, $I^2 = 49\%$, 4675 patients) and acute skin toxicity due to irradiation (RR 0.34, 95% CI 0.19 to 0.61, $p = 0.0003$, $I^2 = 61\%$, 357 patients) in favor to hypofractionated therapy (Table 2) (forest-plot in supplementary material S25–S26; S31, respectively). However, no significant difference was found between conventional and hypofractionated radiotherapy in relation to all others outcomes evaluated (Table 2) (forest-plot in supplementary material S7–S12; S15–S24; S27–S30, respectively).

3.3. Sensitivity analysis

The first sensitivity analysis, considering only the hypofractionated schemes of 40 Gy, 41.6 Gy and 42.5 Gy as proposed by ASTRO 2011, presented a significant difference for distant recurrence

Table 2
Meta-analytic results.

Outcome	In 5 Years						After 5-years					
	Number of studies	Number of pacients	HR (95% CI)	P	I^2	Certainty of the evidence	Number of studies	Number of pacients	HR (95% CI)	P	I^2	Certainty of the evidence
Local recurrence	START A, START B and Whelan 02	6043	0.96 [0.71, 1.29]	0.79	0%	Moderate	Haviland 13 and Owen 06	5861	0.97 [0.78, 1.20]	0.78	23%	Moderate
Loco-regional recurrence	START A, START B	4451	0.98 [0.71, 1.35]	0.90	0%	Moderate	Haviland 13	4451	0.92 [0.70, 1.20]	0,51	0%	Moderate
Distant recurrence	START A, START B	4451	0.88 [0.72, 1.06]	0.19	73%	Low	Haviland 13	4451	0.93 [0.79, 1.10]	0.42	73%	Low
Mortality	START A, START B and Whelan 02	5684	0.90 [0.76, 1.06]	0.20	0%	Moderate	Haviland 13 and Whelan 10	5.684	0.92 [0.81, 1.05]	0.22	0%	Moderate
Disease-free survival	START A, START B and Whelan 02	5685	0.89 [0.77, 1.03]	0.12	35%	Moderate	Haviland 13	4451	0.90 [0.78, 1.03]	0.11	44%	Moderate
Outcome	Number of studies	Number of pacients	RR (95% CI)	P	I^2	Certainty of the evidence	Number of studies	Number of pacients	RR (95% CI)	P	I^2	Certainty of the evidence
Cardiac ischemia (all women)	START A, START B	4451	0.73 [0.34, 1.57]	0.42	0%	Moderate	Haviland 13	4451	0.61 [0.33, 1.15]	0.13	0%	Moderate
Cardiac ischemia (women treated in the left breast)	START A, START B	4451	0.84 [0.21, 3.37]	0.80	13%	Low	Haviland 13	4451	0.72 [0.28, 1.86]	0.49	0%	Moderate
Ribs fracture	START A, START B	4451	1.02 [0.25, 4.20]	0.98	0%	Low	Haviland 13	4451	1.08 [0.26, 4.53]	0.91	0%	Low
Pulmonary fibrosis	START A, START B	4451	2.42 [0.50, 11.71]	0.27	0%	Low	Haviland 13	4451	3.16 [0.89, 11.21]	0,07	0%	Low
Breast shrinkage							Haviland 13 and Yarnold 05	4675	0.92 [0.85, 1.01]	0.09	3%	Moderate
Breast induration							Haviland 13 and Yarnold 05	4675	0.93 [0.74, 1.16]	0.53	70%	Low
Telangiectasia							Haviland 13 and Yarnold 05	**5167**	**0.41 [0.19, 0.87]**	**0.02**	**93%**	Low
Breast edema							Haviland 13 and Yarnold 05	4675	**0.68 [0.53, 0.88]**	**0.003**	**49%**	**Moderate**
Shoulder stiffness							Haviland 13 and Yarnold 05	1264	1.09 [0.64, 1.85]	0.76	46%	Low
Arm edema							Haviland 13 and Yarnold 05	1264	0.91 [0.57, 1.45]	0.69	25%	Low
Cosmesis (fair/poor)	Taher 04 and Whelan 10	1250	0.89 [0.72, 1.09]	0.26	0%	Moderate	Yarnold 05 and Whelan 10	2026	0.94 [0.80, 1.10]	0.43	60%	Moderate
Acute toxicity to skin due to radiation	**FAST 11 and Taher 04**	**357**	**0.34 [0.19, 0.61]**	**0.0003**	61%	Moderate						

within 5 years of treatment (HR 0.78, [95% CI 0.63 to 0.96, $I^2 = 42\%$, $p = 0.02$, 3714 patients), disease-free survival within 5 years and after 5 years of treatment (HR 0.84, 95% CI 0.72 to 0.99, $I^2 = 11\%$, $p = 0.03$, 4948 patients, and HR 0.85, 95% CI 0.73 to 0.99, $I^2 = 23\%$, $p = 0.03$, 3714 patients, respectively), in favor to hypofraction therapy when compared to the conventional therapy (Table 3) (supplementary material S36, S40–S41). There is an increased risk of pulmonary fibrosis after 5 years of treatment (RR 4.17, 95% CI 1.05 to 16.56, $I^2 = 0\%$, $p = 0.04$, 3714 patients) with hypofractioned therapy compared to conventional radiotherapy (supplementary material S48). All others outcomes showed no significant difference among the groups (supplementary material S32, S55).

In a second scenario, in which the studies compared hypofractionated radiotherapy and conventional radiotherapy in patients that received a boost dose, hypofractionated radiotherapy was favored for distant recurrence within 5 years (HR 0.78, [95% CI 0.63 to 0.96, $I^2 = 42\%$ $p = 0.02$, 3714 patients) and for disease-free survival within and after 5 years of treatment (HR 0.80, 95% CI 0.67 to 0.95, $I^2 = 0\%$, $p = 0.01$, 3714 patients, and HR 0.85, 95% CI 0.73 to 0.99, $I^2 = 23\%$, $p = 0.03$, 3714 patients, respectively) (supplementary material S60, S64–S65). However, pulmonary fibrosis after 5 years, showed an increase risk for hypofractionated radiotherapy in comparison to conventional treatment (RR 4.17, 95% CI 1.05 to 16.56; $I^2 = 0\%$, $p = 0.04$; 3715 patients) (Table 4) (supplementary material S72). All others outcomes showed no significant difference among the groups (supplementary material S56–S78).

4. Discussion

Our meta-analysis showed no statistical difference between the studied outcomes except for breast edema, telangiectasia, and acute skin radiation toxicity in favor for hypofractionated therapy. These results are in accordance with previously published meta-analyzes [8,9,17–19].

There are other meta-analyzes about the same theme. The most recent one from the Cochrane Collaboration (2016) [8], which is an updated publication of James ML et al. (2010) [20], does not present all the outcomes evaluated in this meta-analysis. We added loco-regional recurrence, distant recurrence and cardiac ischemia in all women, given their prognostic importance and shoulder stiffness and arm edema because of their importance to patients' quality of life. In this meta-analysis, two trials, START A and START B, had few patients that underwent mastectomy, 513 mastectomized out of 5816 patients (8.75%). Both were considered eligible in their meta-analysis. We also considered them eligible and included them in our work [8].

The second one by Zhou et al. (2015) [9] included both randomized and non-randomized studies in women with early breast cancer that underwent different types of conservative surgeries and mastectomy.

Regarding the two sensitivity analyzes we performed, the first showed a significantly higher number of cases of pulmonary fibrosis after 5 years in the hypofractionated group, when the two

Table 3
Meta-analytic result for sensitivity analysis-considered only hypofractionation schemes (42.5 Gy, 41.6 Gy and 40 Gy).

Outcome	In 5 Years					After 5 years				
	Number of studies	Number of pacients	HR (95% CI)	P	I^2	Number of studies	Number of pacients	HR (95% CI)	P	I^2
Local recurrence	START A, START B and Whelan 02	4948	0.91 [0.66, 1.25]	0.56	0%	Haviland 13	3714	0.79 [0.58, 1.08]	0.13	0%
Loco-regional recurrence	START A, START B	3714	0.90 [0.63, 1.29]	0.58	0%	Haviland 13	3714	0.83 [0.62, 1.12]	0.22	0%
Distant recurrence	**START A, START B**	**3714**	**0.78 [0.63, 0.96]**	**0.02**	**42%**	Haviland 13	3714	0.87 [0.73, 1.04]	0.13	0.76
Mortality	START A, START B and Whelan 02	4948	0.89 [0.75, 1.06]	0.19	31%	Haviland 13 and Whelan 10	4947	0.90 [0.79, 1.03]	0.13	8%
Disease-free survival	**START A, START B and Whelan 02**	**4948**	**0.84 [0.72, 0.99]**	**0.03**	**11%**	Haviland 13	3714	0.85 [0.73, 0.99]	0.03	23%
Outcome	In 5 Years					After 5 years				
	Number of studies	Number of pacients	RR (95% CI)	P	I^2	Number of studies	Number of pacients	RR (95% CI)	P	I^2
Cardiac ischemia (all women)	START A, START B	3714	0.60 [0.26, 1.36]	0.22	0%	Haviland 13	3714	0.57 [0.29, 1.11]	0.10	05
Cardiac ischemia (women treated in the left breast)	START A, START B	3714	0.65 [0.17, 2.50]	0.53	0%	Haviland 13	3714	0.59 [0.19, 1.81]	0.35	0%
Ribs fracture	START A, START B	3714	1.32 [0.29, 5.99]	0.72	0%					
Pulmonary fibrosis	START A, START B	3714	3.59 [0.59, 22.00]	0.17	0%	**Haviland 13**	**3714**	**4.17 [1.05, 16.56]**	**0.04**	**0%**
Breast shrinkage						Haviland 13	3252	0.92 [0.80, 1.07]	0.27	33%
Breast induration						Haviland 13	3252	0.94 [0.76, 1.15]	0.54	49%
Telangiectasia						Haviland 13	3638	0.81 [0.52, 1.27]	0.37	56%
Breast edema						Haviland 13	3252	0.70 [0.47, 1.03]	0.07	65%
Shoulder stiffness						Haviland 13	366	0.83 [0.42, 1.64]	0.59	0%
Arm edema						Haviland 13	366	0.82 [0.25, 2.63]	0.75	63%
Cosmesis (fair/poor)	Taher 04 and Whelan 10	1250	0.89 [0.72, 1.09]	0.26	0%					

fractions, 3 Gy/fraction and 3.3 Gy/fraction, which according to ASTRO does not to have equivalent efficacy in relation to the conventional fractioning, were not analyzed. The confidence interval of this outcome is very wide (1.05–16.56), and the measure of GRADE's certainty of evidence is low [21].

In the second analysis, when we considered only the patients that performed boost and the fractioning recommended by ASTRO (3.2 Gy/fraction and 2.67 Gy/fraction), we observe that in the short term (up to 5 years) the result was significantly favorable for hypofractioning in relation to distance relapse and disease-free survival.

After five years, there was also a higher incidence of cases of pulmonary fibrosis for the hypofractionated group as observed in the first scenario of the sensitivity analysis. However, we cannot be definitive in relation to the influence of the boost for pulmonary fibrosis, since the dose reinforcement was performed in different schemes and not in the entire population, and additionally a small part of the patients made use of chemotherapy [16,21–24].

Some outcomes presented high heterogeneity ($I^2 \geq 50\%$). They were distant recurrence within 5 years and distant recurrence after 5 years, breast induration, telangiectasia, cosmesis (fair/poor) up to 10 years and acute skin toxicity. However, for all these outcomes, the subgroup analysis by therapeutic dose was able to explain this heterogeneity.

In the sensitivity analysis contemplating the three fractionated doses, high heterogeneity was found in distant recurrence after 5 years, telangiectasia, breast edema and arm edema, and in the sensitivity analysis considering the boost dose, there was high heterogeneity in mortality within 5 years, telangiectasia, breast edema and arm edema. The heterogeneity for all mentioned outcomes were justified by the subgroup analysis presented.

A randomized study of 61 patients with early stage breast cancer evaluated the effect of using hypofractionated and conventional fractionation in the lung function of these patients. The results showed that there is no clinically meaningful or statistically significant difference in the incidence rates of radiation induced pulmonary toxicity between patients treated with conventional and hypofractionated radiotherapy [25]. Nevertheless, late lung fibrosis requires longer follow -up compared to the follow-up applied in this study [25]. Another randomized study evaluated lung function in 108 patients with early stage breast cancer, who underwent conservative surgery or mastectomy followed by hypofractionated or conventional fractionation radiation therapy with a 3-year follow-up. This study showed that both conventional and hypofractionated radiotherapy induce restrictive lung patterns over a 3-year period, regardless of the initial respiratory status or history of smoking [26].

Currently, there are techniques like collimator multi-leaf and intensity-modulated radiation therapy, which aim to both improve dose coverage in the treatment target and decrease the dose in

Table 4
Meta-analytic result for sensitivity analysis-considered only the studies that used the boost in some part of the population.

Outcome	In 5 Years					After 5 years				
	Number of studies	Number of pacients	HR (95% CI)	P	I^2	Number of studies	Number of pacients	HR (95% CI)	P	I^2
Local recurrence	START A, START B	3714	0.88 [0.61, 1.27]	0.49	16%	Haviland 13	3714	0.79 [0.58, 1.08]	0.13	0%
Loco-regional recurrence	START A, START B	3714	0.90 [0.63, 1.29]	0.58	0%	Haviland 13	3714	0.83 [0.62, 1.12]	0.22	0%
Distant recurrence	**START A, START B**	**3714**	**0.78 [0.63, 0.96]**	**0.02**	**42%**	Haviland 13	3714	0.87 [0.73, 1.04]	0.13	0.76
Mortality	START A, START B	3713	0.87 [0.71, 1.05]	0.14	60%	Haviland 13	4947	0.86 [0.74, 1.01]	0.07	19%
Disease-free survival	**START A, START B**	**3714**	**0.80 [0.67, 0.95]**	**0.01**	**0%**	**Haviland 13**	**3714**	**0.85 [0.73, 0.99]**	**0.03**	**23%**
Outcome	In 5 Years					After 5 years				
	Number of studies	Number of pacients	RR (95% CI)	P	I^2	Number of studies	Number of pacients	RR (95% CI)	P	I^2
Cardiac ischemia (all women)	START A, START B	3714	0.60 [0.26, 1.36]	0.22	0%	Haviland 13	3714	0.57 [0.29, 1.11]	0.10	05
Cardiac ischemia (women treated in the left breast)	START A, START B	3714	0.65 [0.17, 2.50]	0.53	0%	Haviland 13	3714	0.59 [0.19, 1.81]	0.35	0%
Ribs fracture	START A, START B	3714	1.32 [0.29, 5.99]	0.72	0%					
Pulmonary fibrosis	START A, START B	3714	3.59 [0.59, 22.00]	0.17	0%	**Haviland 13**	**3714**	**4.17 [1.05, 16.56]**	**0.04**	**0%**
Breast shrinkage						Haviland 13	3252	0.92 [0.80, 1.07]	0.27	33%
Breast induration						Haviland 13	3252	0.94 [0.76, 1.15]	0.54	49%
Telangiectasia						Haviland 13	3638	0.81 [0.52, 1.27]	0.37	56%
Breast edema						Haviland 13	3252	0.70 [0.47, 1.03]	0.07	65%
Shoulder stiffness						Haviland 13	366	0.83 [0.42, 1.64]	0.59	0%
Arm edema						Haviland 13	366	0.82 [0.25, 2.63]	0.75	63%

adjacent tissues [27,28]. The 3-D planning using intensity-modulated radiotherapy through the multi-leaf showed to be a potential tool for dose control in the cardiac region for women submitted to left breast radiotherapy [29]. Other techniques such as ventral decubitus and respiratory-gated radiation therapy also aim to decrease the dose in adjacent tissues. The updated ASTRO guideline, published in 2018, makes some recommendations for the techniques for WBRT treatment planning [30]. It recommends a three-dimensional conformational treatment with a “field-in-field” technique as the initial treatment approach, so that the dose does not exceed 105% in the volume of breast tissue. In addition, it is advisable to use treatment techniques that minimize the dose in the contralateral breast, lung and other normal tissues. Deep inspiration, prone positioning, and/or use of heart block are recommended in order to minimize the dose in the heart tissue. Those patients with a large breast size, prone positioning can be used to minimize the dose in normal tissues [30]. It is suggested that the delineation of target structures and organs at risk as recommended by breast cancer contouring atlas by RTOG or ESTRO [31,32].

Most of the study centers included in this meta-analysis utilized 2-D technique for radiotherapy planning without the use of the aforementioned techniques to reduce the radiation dose received by the adjacent tissue. Associating these techniques with hypofractionated radiotherapy would probably increase dose homogeneity, which in turn, may increase the efficacy and safety of the treatment. It also may increase the indication of hypofractionated to other patients, such as mastectomized patients or those who underwent chemotherapy. Still, the National Institute for Health and Care Excellence (NICE), England's Health Technology Assessment agency, recommends the use of hypofractionated as a standard practice in patients with postmenopausal invasive early stage breast cancer that underwent conservative surgery or mastectomy [33]. The recommended hypofractionated scheme is 40 Gy with 3 weeks of treatment, since it is the most commonly scheme used in many treatment centers in England. Actually, this scheme has proven its effectiveness in the START B study, however, NICE states that further studies are necessary that to show which hypofractionated scheme is most effective [34]. The NCCN recommends WBRT preferably with the hypofractionated technique, at doses of 40 Gy in 15 fractions or 42.5 Gy in 16 fractions [35].

This meta-analysis comparing the use of conventional fractionation and hypofractionated showed that there is no difference between the treatments in terms of efficacy. In addition, there is no difference in relation to safety. On the other hand, hypofractionated therapy had less negative outcomes, such as breast edema, telangiectasia, and acute skin radiation toxicity. Indeed, when the doses recommended by ASTRO (2011) are applied, hypofractionated therapy showed better results for distant recurrence within 5 years and disease-free survival within and after 5 years of treatment, however with increased risk for pulmonary fibrosis after 5 years.

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Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.08.001.

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