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Scientific Article

Interventions for Radiation-Induced Fibrosis in Patients With Breast Cancer: Systematic Review and Meta-analyses

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Abstract

Purpose: Radiation therapy can affect normal tissues in patients with breast cancer, causing adverse effects such as fibrosis. Although there are several interventions for radiation-induced fibrosis, the efficacy of these procedures is still unclear. The purpose of this review is to evaluate the efficacy of interventions for radiation-induced fibrosis in patients with breast cancer.

Methods and Materials: This is a systematic review of randomized clinical trials. Studies that compared any intervention for fibrosis to another intervention, placebo, or no intervention were included. Outcomes assessed were fibrosis, adverse events, quality of life, treatment adherence, pain, and functionality.

Results: A total of 2501 publications were found, and 7 studies were selected because they met the inclusion criteria. The interventions for fibrosis were pentoxifylline and vitamin E, grape seed extract, kinesiotherapy, and endermotherapy. The results showed great heterogeneity in the treatment protocols for radiation-induced fibrosis in patients with breast cancer and in their evaluation metrics. The meta-analyses showed no benefit in using pentoxifylline and vitamin E compared with placebo or no intervention (standardized mean difference: −0.30; 95% confidence interval, −0.79 to 0.20; $P = .24$ [very low evidence]) compared with placebo and vitamin E (standardized mean difference: −0.09; 95% confidence interval, −0.66 to 0.49; $P = .77$ [moderate evidence]), respectively, assessed by the Late Effects Normal Tissue Task Force−Subjective, Objective, Management, and Analytic (LENT-SOMA) scoring scale.

Conclusions: The effectiveness of these interventions for the treatment of radiation-induced fibrosis in patients with breast cancer could not be determined. Although isolated studies show significant results favorable to the experimental groups, caution should be exercised in these findings because of the small number, small sample size, and high risk of bias presented by some of the included studies, which makes the recommendation for clinical practice still weak.

Introduction

Radiation-induced fibrosis is becoming a common and disabling condition characterized by an abnormal and excessive formation of fibrous connective tissue that leads

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to structural and functional changes. Fibrosis usually begins within 4 to 12 months after the end of radiation therapy, with progression for years, and it can affect the skin, underlying fascia and muscles, organs, and bones. The perpetuation of radiation-induced fibrosis can promote decreased joint range of motion, pain, lymphatic and vascular dysfunction, as well as breast hardening, and lead to breast retraction and fixation.[1-4] Currently, there are several options available for the treatment of radiation-induced fibrosis. One should be cautious with the use of drugs because these in vitro or in animals may show promising results, but when in humans, the doses are extrapolated and have high toxicity.[5]

Treatments described in the literature include kinesiotherapy, manual massage, endermotherapy,[1,6-8] pentoxifylline,[9] pentoxifylline e vitamin E,[10-16] hyperbaric oxygen therapy,[17] proteinase inhibitors,[18] grape seed extract,[19] pirfenidone,[20] mesenchymal stem cells,[21] imatinib,[3] superoxide dismutase,[22-25] pravastatin,[4] and antioxidants.[26]

The responses found in the studies are not uniform. Therefore, because there are divergent studies, observed in isolation, it is not possible to state that the intervention in question is really effective and safe for use in clinical practice. Thus, the objective of the present systematic review was to evaluate the efficacy of interventions proposed for the treatment of radiation-induced fibrosis in patients with breast cancer.

Methods and Materials

A systematic review of randomized clinical trials was performed following the Cochrane Handbook of Systematic Reviews of Interventions methodology[27] and is registered in the International Prospective Register of Systematic Reviews (CRD42019139573). Participants older than 18 years, with diagnosis of breast cancer at any stage of the disease, treated with radiation therapy (exclusively or in combination), and that reported some intervention for radiation-induced fibrosis were eligible for inclusion. As for the type of intervention, any type of treatment could be performed with the intention to improve or resolve the radiation-induced fibrosis, and the control group could perform any other intervention, as well as placebo treatment or no intervention. The endpoints were incidence of fibrosis, intervention-related adverse events, quality of life, adherence, pain, and functionality of the affected region.

Searches were performed in the following databases: Cochrane Central Library of Controlled Trials, MEDLINE, Embase, LILACS, BIREME, SciELO, Scopus, Web of Science, Pedro, Sigma Nursing Repository, ClinicalTrials.gov, OpenGrey, WorldCat, and University of São Paulo's Integrated Search Portal. There were no language restrictions. The instrument used was the Revised Cochrane risk-of-bias tool for randomized trials, RoB 2.[28] Data that could be pooled were analyzed in a meta-analysis using RevMan version 5.3 software.[29] Studies with heterogeneous data were described in a narrative summary. For continuous outcomes, mean differences between treatment groups at the end of follow-up were pooled across studies that measured outcomes by the same scale. Random model effect with inverse variance was used for the meta-analyses, and evaluation of heterogeneity by Higgins' inconsistency test (I^2) was proposed.

Results

Study selection

A total of 2501 publications were found, resulting in 2110 publications for analysis of the inclusion and exclusion criteria after duplicates were removed. We excluded 2094 after title and abstract analysis and 7 after reading the full text. Nine publications (7 studies) were included: Bourgeois et al,[7] Brooker et al[19] and their protocol NCT00041223,[30] Delanian et al,[12] Gothard et al,[14] Jacobson et al[16] and their protocol NCT00583700,[31] Magnusson et al[15] and Oliveira et al.[8] The main characteristics of the 7 included studies are presented in Table 1.

Bias risk assessment

After judging the risk of bias, we observed methodological limitations with high risk of bias in 18% of the domains. The highest probability of risk of bias was found in the measurement of outcomes. The judgments for each domain for each study can be seen in Figure 1. The narrative synthesis of the data is described below and presented in Tables 2 and 3, and the meta-analyses are presented in Figure 2.

Similar studies that could be pooled to assess the fibrosis outcome were Delanian et al,[12] Magnusson et al, and Jacobson et al. Data from these studies were pooled into 2 meta-analyses (Fig 2). In these studies, the experimental group received treatment with pentoxifylline associated with vitamin E and were assessed by the Late Effects Normal Tissue Task Force–Subjective, Objective, Management, and Analytic (LENT-SOMA) scoring scale[32] at 6 months in the study by Delanian et al, at 12 months in the study by Magnusson et al, and at 18 months in the study by Jacobson et al.

One of the meta-analyses (Fig 2A) compared treatment with pentoxifylline and vitamin E versus placebo or no intervention. In the study by Delanian et al,[12] data from the pentoxifylline and vitamin E group and the double placebo group were used. The other meta-analysis (Fig 2B) compared treatment with pentoxifylline and vitamin E versus placebo and vitamin E. In the study by

Table 1 Characteristics of the 7 included studies

	Delanian et al (2003)[12]	Gothard et al (2004)[14]	Brooker et al (2006)[19]	Bourgeois et al (2008)[7]	Magnusson et al (2009)[15]	Oliveira et al (2009)[8]	Jacobson et al (2013)[16]
Number of reports	1	1	2	1	1	1	2
Country of origin	France	United Kingdom	United Kingdom	France	Sweden	Brazil	United States
Number of groups	4	2	2	2	2	2	2
Allocation	1:1:1:1	1:1	2:1	1:1	1:1	1:1	1:1
All patients, n	24	68	66	20	83	69	53
Total E, n	6/6/6	35	44	10	42	35	26
Total C, n	6	33	22	10	41	34	27
Total losses, n (%)	2 (8.3)	5 (7.3)	5 (7.6)	0 (0)	23 (27.7)	9 (13)	6 (11.3)
Losses E, n	1	NI	4	0	12	6	3
Losses C, n	1	NI	1	0	11	3	3
Female sex, %	24	67	66	20	83	66	NI
Male sex, %	0	1	0	0	0	0	NI
Middle age, y	Middle of 57 (±8)	Between 37 and 87 (63)	Middle of 65	Between 43 and 55	Between 46 and 65 (56.5)	Middle of 50 (±10)	Middle of 57
Oncologic treatment previous to study	RXT w/w to QT and SUR	SUR (66), AE and RXT	SUR and RXT	SUR and RXT	SUR w/w AE, assoc. or not QT and RXT	SUR w/w AE, assoc. or not QT	SUR, SL, AE, and QT
Did start the study during or after RXT?	After; middle of 7 y (±4) of RXT	After; middle of 2-41 y of RXT; middle 15.5	After; middle of 11 y of RXT	After; between 6 and 16 mo of RXT	After 1-3 mo of RXT	During (at first day RXT)	After; next
Experimental group(s)	Group A: PTX 800 mg and vit. E 1000 mg oral; Group B: PTX 800 mg and placebo oral; Group C: placebo and vit. E 1000 mg oral	PTX 800 mg and vit. E 1000 mg oral	Grape seed extract 300 mg oral	Endermotherapy LPG technique	PTX 1200 mg and vit. E 300 mg oral	Kinesiotherapy	PTX 1200 mg and vit. E 1200 UI oral
Control group	Group D: just placebo oral	Placebo oral	Placebo oral	Medical supervision	Placebo + vit. E 300 mg oral	Without kinesiotherapy	Standard treatment
Duration	6 mo	6 mo	6 mo	1 mo	12 mo	1.5 mo	6 mo
Follow-up	NI	3-6 mo	3 and 6 mo	1 mo	NI	The end of RXT to 6 mo after RXT	Middle of 51 mo

Abbreviations: AE = axillary emptying; assoc. = associated; C = control; E = experimental; NI = not informed; PTX = pentoxifylline; QT = chemotherapy; RXT = radiation therapy; SL = sentinel lymph node; SUR = surgery; w/w = with or without; vit. = vitamin.

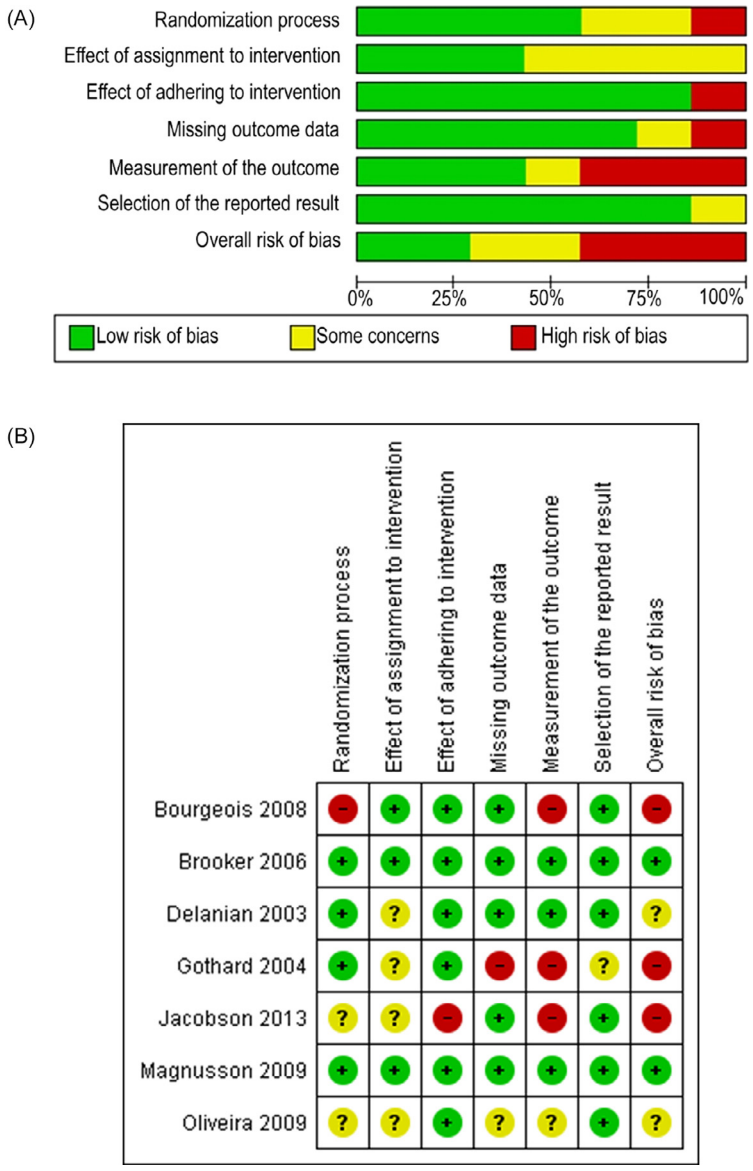

Fig. 1 Graph and summary of the risk of bias judgment for each domain. **(A)** Graph of judgment of risk of bias for each domain in percentages. **(B)** Summary of the risk of bias judgment for each included study. *Abbreviations*: + = low risk of bias; ? = some concerns; - = high risk of bias.

Delanian et al,[12] data from the pentoxifylline and vitamin E group and the placebo and vitamin E group were used. Although similar for data synthesis, the 3 studies had some differences. Although the participants received the same drugs (pentoxifylline and oral vitamin E), they were applied at different doses.

The placebo group of Delanian et al[12] was compared with the no intervention group of Jacobson et al, but they had some differences in relation to the LENT-SOMA scale, in relation to the timing of data collection, and in relation to the time interval from the end of radiation therapy to the start of treatment. Delanian et al used the LENT-SOMA Skin/Subcutaneous Tissue scale and collected data 6 months after treatment, and the mean interval between radiation therapy and intervention was 7 (±4) years.

The group in the study by Delanian et al[12] that received vitamin E and placebo was compared with the group in the study by Magnusson et al that received the same treatment. These 2 studies showed differences in relation to the LENT-SOMA scale, in relation to the time of data collection, and in relation to the time interval from the end of radiation therapy to the start of treatment. In the study by Magnusson et al, the LENT-SOMA

Table 2 Summary of results for fibrosis (and other related), quality of life, and functionality outcomes

Comparison of interventions	Included study and sample size	Treatment or prevention	Outcome	Data collection	Metric	Result/effect size
Kinesiotherapy versus without kinesiotherapy	Oliveira et al (2009),[8] N = 69	Prevention	Scar adhesion	6 mo after RXT;	Palpation of the scar and adjacent area (present/absent);	Group without kinesiotherapy had 48.8% of patients with adherence, and the group with kinesiotherapy had 24% of patients with adherence (P = .04) (favoring kinesiotherapy group).
		Functionality (range of motion of the shoulder)		6 mo after RXT	Goniometry	Kinesiotherapy group had increased flexion (3.2 degrees), abduction (7 degrees), and external rotation (3.2 degrees), while the group without kinesiotherapy had decreased flexion (1.9 degrees) and abduction (0.2 degrees) and increased external rotation (0.6 degrees). There was no difference for external rotation (P = .71) for flexion (P = .02) and abduction (P = .006) (favoring kinesiotherapy group).
		Functional shoulder capacity		6 mo after RXT	Functional scale (0 = no difficulty, 1 = mild, 2 = moderate, 3 = maximum, and 4 = inability to perform)(0-24)	Kinesiotherapy group started the study with 5.5 (± 5.7) and ended the 6 months with a score of 4.0 (± 5.6), and the group without kinesiotherapy started with 3.6 (± 4.4) and ended with 5.0 (± 5.3) (P = .43).
Endermotherapy LPG technique versus medical supervision	Bourgeois et al (2008),[7] N = 20	Treatment	Skin tightening;	1 and 2 mo;	EVA (0-10)	In the endermotherapy group, 85.72% of the patients reduced the induration in 2 mo, and in the follow-up group, the number of patients with induration increased by 50%.
PTX and vit. E versus PTX and placebo versus placebo and vit. E vs double placebo	Delanian et al (2003),[12] N = 24	Treatment	Fibrosis surface (cm^2)	6 mo	Clinical evaluation	PTX and vit. E group decreased by 60% while double placebo group reduced by 43% (P = .038). Two-way ANOVA for the 4 groups without significance.
			Fibrosis volume (cm^3)	3 and 6 mo	Ultrasound	PTX and vit. E group reduced 73% while double placebo group reduced 51% (P = .054). Two-way ANOVA for the 4 groups without significance.
			Slope of the surface and volume of fibrosis (%)	per mo	Clinical evaluation	PTX and vit. E group (P = .018) as a placebo group (P = .025). The PTX and vit. E group had a faster inclination compared with the others (P = .036).
			Fibrosis	6 mo	LENT-SOMA Skin/Subcutaneous Tissue scale	There was no significant difference between the 4 groups at 6 mo. The final results were 7.0 (1.7) for the PTX and vit. E group, 7.6 (2.9) for the PTX and placebo group, 6.0 (2.2) for the placebo and vit. E group, and 7.4 (2.2) for the double placebo group (data gross presented).
PTX and vit. E versus placebo	Jacobson et al (2013),[16] N = 53	Prevention	Fibrosis	18 mo	RTOG/EORTC	Both groups showed similar results. Only the PTX and vit. E group had 1 patient with grade 6 (P = .60).
				18 mo	TCM (0-60 mm)	PTX and vit. E group had an average of 0.88 (1.96) and the placebo group 2.10 (2.16) (P = .047; favoring the PTX and vit. E group).
				18 mo	LENT-SOMA Breast scale	PTX and vit. E group had a final average of 1.00 (1.19) and the placebo group had a final average of 1.59 (1.53) (P = .1599).

(*continued on next page*)

Table 2 (*Continued*)

Comparison of interventions	Included study and sample size	Treatment or prevention	Outcome	Data collection	Metric	Result/effect size
PTX and vit. E versus PTX and placebo	Gothard et al (2004),[14] N = 68	Treatment	Skin hardening;	12 mo	Scale 0-3 (palpation)	PTX and vit. E group improved 19% and PTX and placebo improved 24%.
			Skin appearance	No information	Photography	No additional information (images not shown).
			Quality of life	6 mo from the end of treatment	Self-application of EORTC questionnaires (QLQ-C30 and BR23)	There was no significant change in either group (data not shown).
PTX and vit. E versus placebo and vit. E	Magnusson et al (2009),[15] N = 83	Treatment	Fibrosis	12 mo	LENT-SOMA Breast scale	No significant difference was found between the groups in the total score of the scale or in the subscale of objective fibrosis.
Grape seed extract versus placebo	Brooker et al (2006),[19] N = 66	Treatment	Touchable hardening area	12 mo	Measuring tape and electronic planimetry	29.5% in the grape seed extract group reduced ≥50% of the area and 27.3% of the patients in the placebo group reduced ≥50% ($P = 1.00$).
			Breast appearance	12 mo	Photography	One patient of the placebo group showed improvement and 2 of the grape seed extract group worsened.
			Self-assessment of hardening	12 mo	Self-applied questionnaire (score 0-3 degrees)	Improvement of more than 2 degrees was noted in 2.3% of patients in the grape seed extract group and in 4.5% of patients in the placebo group.Improvement of at least 1 degree was noted in 50% of the patients in the grape seed extract group and in 45.5% of the patients in the placebo group.
			Touchable hardening	12 mo	Clinical palpation (score 0-3 degrees)	One patient improved 2 degrees (grape seed extract group), 1 patient completely regressed (placebo group), and 29.5% of patients in the grape seed extract group and 27.3% of patients in the placebo group had an improvement of 1 degree.

Abbreviations: EORTC = European Organization for Research and Treatment of Cancer; FACT-H&N = Functional Assessment of Cancer Therapy—Head & Neck; LENT-SOMA = Late Effects Normal Tissue Task Force—Subjective, Objective, Management, and Analytic; PTX = pentoxifylline; RTOG = Radiation Therapy Oncology Group; TCM = tissue compliance meter; vit. = vitamin.

Table 3 Summary of results for pain and adverse event outcomes

Comparison of interventions	Included study and sample size	Treatment or prevention	Outcome	Data collection	Metric	Result/effect size
PTX and vit. E versus placebo	Jacobson et al (2013),[16] N = 53	Prevention	Adverse events	During the study	Clinical evaluation	Several patients with nausea without vomiting. Effect disappeared after 1 wk of treatment. Treatment interruption: 1 patient in the PTX and vit. E group (rash).
			Pain	18 mo	VAS	92.3% of patients in the PTX and vit. E group had no pain, while in the placebo group 81.48% of patients had no pain (P = .4203).
Grape seed extract versus placebo	Brooker et al (2006),[19] N = 66	Treatment	Breast pain, hardness, and tenderness	12 mo	Self-applied questionnaire (0 = none, 1 = mild, 2 = moderate, and 3 = marked)	11.4% of the patients in the grape seed extract group and 9.1% of the patients in the placebo group reduced between 1 and 2 degrees. 27.3% of the patients in the grape seed extract group and 31.8% of the patients in the placebo group reduced between 0 and 1 degree, and 50% of the patients in the grape seed extract group and 54.5% of the patients in the group placebo showed no improvement or worsening.
Endermotherapy LPG technique versus medical supervision	Bourgeois et al (2008),[7] N = 20	Treatment	Dry skin	2 mo	Clinical	No patient had dryness in 2 mo.
			Erythema	2 mo	Clinical	In the massage group, 2 patients remained with erythema, while none remained with erythema in the supervision group.
			Itching	2 mo	VAS	One patient remained in the massage group and 3 in the supervision group.
			Pain	2 mo	VAS	Massage group reduced pain patients from 4 to 1 since the first assessment. Supervision group presented 1 at the beginning, rose to 2 (1 mo) and finished with 1 (2 mo).
PTX and vit. E versus placebo and vit. E	Magnusson et al (2009),[15] N = 83	Treatment	Adverse events	During the study	Clinical	Nausea, bruising, neuropathic pain, thyrotoxicosis, bleeding from the conjunctiva, vomiting, gastritis, diarrhea, gastrointestinal disorder, depression, dizziness, tiredness, insomnia, investigations, weight loss, headache, and increased sweating. Dose reduction: 2 patients in the PTX and vit. E group and 1 patient in the placebo and vit. E group. Treatment interruption: 3 patients in the PTX and vit. E group and 1 patient in the placebo and vit. E group. (There were serious events, but none related to the study.)
			Subjective pain and pain management	12 mo	LENT-SOMA	The placebo and vit. E group showed a significant reduction (P = .0022) while the PTX and vit. E group did not obtain significance (P = .35). Pain management showed an increase in medication use in the PTX and vit. E group (P = .0248).
			Pain and discomfort	12 mo	VAS (0-100 mm)	There was significantly decreased pain (skin stiffness) in the PTX and vit. E group (P = .0001) but not in the placebo and vit. E group (P = .77).
PTX and vit. E versus PTX and placebo versus placebo and vit. E versus double placebo	Delanian et al (2003),[12] N = 24	Treatment	Adverse events	During the study	Clinical	A total of 10 of 22 patients experienced adverse events. PTX and vit. E group: hot flashes (1), asthenia (1), vertigo and headache (1). PTX and placebo group: nausea and epigastric pain (2), hot flashes (1), asthenia (3). Placebo and vit. E group: no adverse events. Double placebo group: nausea and epigastric pain (3), hot flashes (1).

Abbreviations: LENT-SOMA = Late Effects Normal Tissue Task Force—Subjective, Objective, Management, and Analytic; PTX = Pentoxifylline; VAS = visual analog scale; Vit. E = Vitamin E.

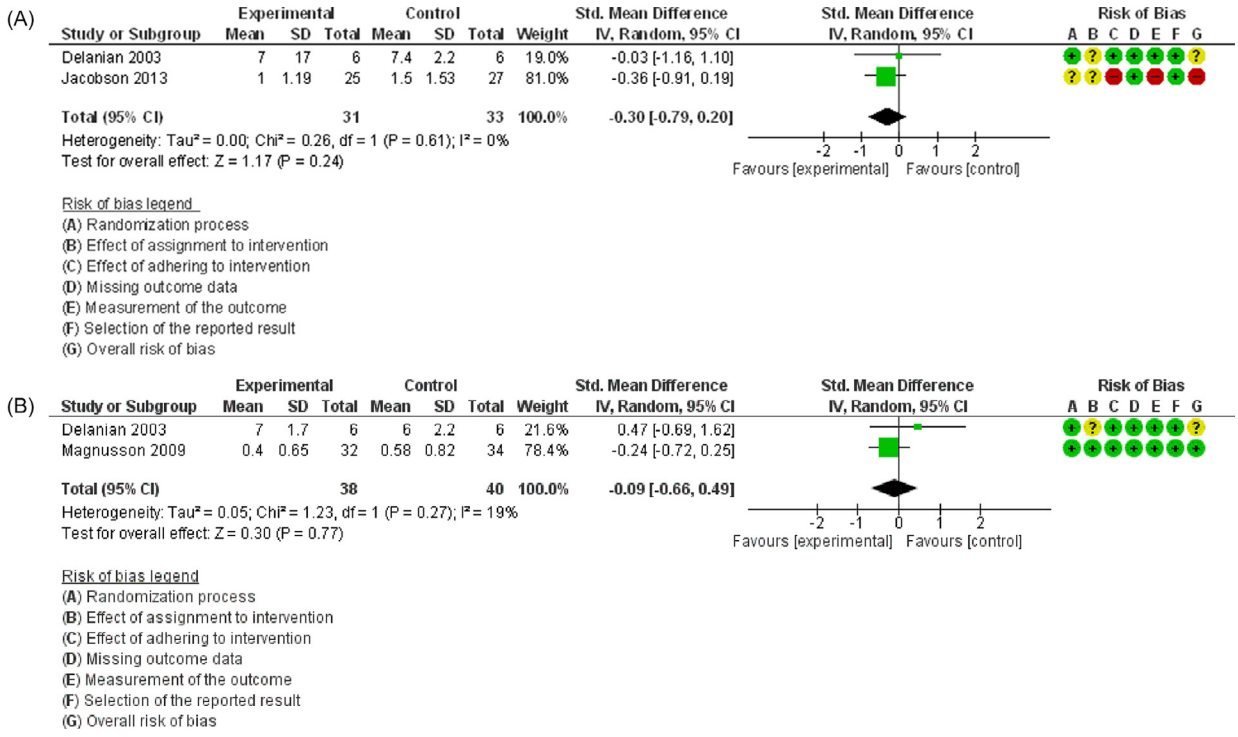

Fig. 2 Forest plots of the meta-analyses. **(A)** Forest plot of comparison: pentoxifylline and vitamin E versus placebo or no intervention. Outcome: fibrosis measured by the LENT-SOMA scoring scale. **(B)** Forest plot of comparison: pentoxifylline and vitamin E versus placebo and vitamin E. Outcome: fibrosis measured by the LENT-SOMA scale. *Abbreviations*: + = low risk of bias; ? = some concerns; - = high risk of bias; CI = confidence interval; IV = inverse variance; LENT-SOMA = Late Effects Normal Tissue Task Force–Subjective, Objective, Management, and Analytic; SD = standard deviation; Std. = standardized.

Breast scale was used, data collection occurred for 12 months, and the intervention started 1 to 3 months after the end of radiation therapy.

Narrative data synthesis

The other 4 included studies[7,8,14,19] could not be grouped because they had differences in protocols, metrics, or outcomes assessed and had their results described under each outcome of interest in this review.

Delanian et al,[12] Gothard et al,[14] Magnusson et al, and Jacobson et al used in the experimental group the oral administration of the association of the drugs pentoxifylline and vitamin E. Delanian et al and Gothard et al used the same dosage for both drugs (pentoxifylline 800 mg/d and vitamin E 1000 mg/d), but could not have their data pooled owing to different metrics in the evaluation of the outcomes. Brooker et al orally administered grape seed extract (300 mg) and 2 other studies used physical resources such as endermotherapy[7] and kinesiotherapy.[8] Regarding the outcomes of interest in this review, none of the studies evaluated all the outcomes. Only the fibrosis outcome was evaluated by the 7 studies. Some studies evaluated this outcome directly and others indirectly.

Adherence to the intervention and number of participants lost were reported in all studies. In the study by Gothard et al,[14] there were 5 losses (adherence 93%) and analysis was performed per protocol. Bourgeois et al obtained 100% adherence and performed analysis by intention to treat. In the study by Brooker et al, there were 5 losses (4 in the experimental group and 1 in the control group) at the 12-month reevaluation and the analysis was performed by intention-to-treat. Magnusson et al lost 23 participants (27.7%). Of these, 4 dropped out of the study because of adverse effects (3 from the experimental group and 1 from the control) and 7 were withdrawn during the study (4 from the experimental group and 3 from the control) because of tumor progression during treatment. Eight participants (4 from each group) dropped out of the study owing to less than 75% research compliance and 4 participants dropped out (1 from the experimental group and 3 from the control). Magnusson et al performed an intention-to-treat analysis as well as a protocol analysis. In the study by Delanian et al,[12] there were 2 losses (1 in group A and 1 in group B) and analysis by protocol was performed. In the study by Jacobson et al, there were 6 losses. One patient in the experimental group did not adhere to treatment and stopped treatment before the 7-month follow-up (1/26). All controls completed the

Table 4 GRADE judgment of the quality of evidence for the fibrosis outcome

Judgment of the quality of evidence of the fibrosis outcome analyzed in Delanian et al (2003)[12] and Magnusson et al (2009)[15]						
Pentoxifylline with vitamin E compared with placebo and vitamin E for women treated for breast cancer with radiation-induced fibrosis						
Patients: women treated for breast cancer Context: treatment for radiation-induced fibrosis Intervention: pentoxifylline with vitamin E Comparison: placebo and vitamin E						
	Anticipated absolute effects* (95% CI)					
Outcome	**Risk with placebo and vitamin E**	**Risk with pentoxifylline and vitamin E**	**Relative effect (95% CI)**	**Number of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
Fibrosis assessed with LENT-SOMA scoring scale. Follow-up: 6-12 mo	The mean fibrosis score was 3.29.	SMD: 0.09; SD lower (0.66 lower to 0.49 higher)		78 (2 RTCs)	⨁⨁⨁◯ MODERATE[a]	Pentoxifylline with vitamin E probably results in very little or no difference in fibrosis. The study by Delanian et al[12] presented methodologic limitations and imprecision of the results. In addition, both studies did not show significant differences between groups.
Judgment of the quality of evidence of the fibrosis outcome analyzed in Delanian et al (2003)[12] and Jacobson et al (2013)[16]						
Pentoxifylline with vitamin E compared with placebo or standard follow-up for women treated for breast cancer with radiation-induced fibrosis						
Patients: women treated for breast cancer Context: treatment for radiation-induced fibrosis Intervention: pentoxifylline with vitamin E Comparison: placebo or standard follow-up						
	Anticipated absolute effects* (95% CI)					
Outcome	**Risk with placebo and vitamin E**	**Risk with pentoxifylline and vitamin E**	**Relative effect (95% CI)**	**Number of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
Fibrosis assessed with LENT-SOMA scoring scale. Follow-up: 6-18 mo	The mean fibrosis score was 4.45.	SMD: 0.3; SD lower (0.79 lower to 0.2 higher)		64 (2 RTCs)	⨁◯◯◯ VERY LOW[1,2,a,b]	Pentoxifylline with vitamin E probably results in very little or no difference in fibrosis. The study by Delanian et al[12] and Jacobson et al[16] presented methodologic limitations, and the study by Delanian et al presented imprecision of the results. In addition, the studies did not show significant differences between groups.

Abbreviations: CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; LENT-SOMA = Late Effects Normal Tissue Task Force–Subjective, Objective, Management, and Analytic; RCT = randomized clinical trials; SD = standard deviation; SMD = standardized mean difference.

* The risk in the intervention group (and its 95% CI) is based on the risk assumed by the comparator group and the relative effect of the intervention (and its 95% CI).

The GRADE Working Group grades of evidence are the following:

- High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

7-month follow-up. Three patients in the experimental group and 3 in the control group did not return for the 18-month follow-up. Twenty-three patients in the experimental group and 24 in the control group had their evaluation after 18 months of treatment. This study performed analysis by protocol. In the study by Oliveira et al, there were 9 losses. Three patients in the experimental group were discharged between the first and second evaluation, either owing to infection and complications of chemotherapy (n = 2) or by withdrawal from treatment (n = 1). These patients' data were not considered in the analysis. Another 6 patients did not receive the third evaluation, either because they died (2 in the experimental group and 1 in the control group) or because they changed address (1 in the experimental group and 2 in the control group). However, the data from these patients were considered in the analysis.

Tables 2 and 3 show the narrative synthesis of the data of the other outcomes analyzed with their respective results and related studies. The studies that obtained favorable results for the experimental group are listed at the beginning of the tables.

Regarding the fibrosis outcome, 4 studies showed significant results favorable to the experimental groups: Oliveira et al, Bourgeois et al, Delanian et al,[12] and Jacobson et al. Although these studies evaluated the same outcome (fibrosis), they did not have the same intervention (except 2),[12,16] which made it impossible to analyze the data together to obtain reliable evidence, and they also had few participants (between 20 and 78). Only the study by

Gothard et al[14] analyzed the quality of life outcome, finding no significant differences between the groups. For functionality, only the study by Oliveira et al analyzed this outcome and showed results significantly favorable with improvement in shoulder joint range of motion in the experimental group (kinesiotherapy). For the pain outcome, the 2 studies that showed significantly favorable results for the experimental group were Bourgeois et al and Magnusson et al.

Four studies reported adverse events: Delanian et al,[12] Jacobson et al, Magnusson et al, and Bourgeois et al. The first 3 studies[12,15,16] had significant adverse events that led to discontinuation of some participants. The daily dose of 1200 mg pentoxifylline was the highest dose used in the studies in this review. The studies by Jacobson et al and Magnusson et al used the 1200 mg/d dose of pentoxifylline and were the ones that reported the most important adverse events. With the exception of the Magnusson et al study, which had a longer duration (12 months), all other studies that used pentoxifylline and vitamin E had a duration of 6 months.

Oliveira et al was the only study that obtained significantly favorable results for the experimental group (kinesiotherapy) in 2 outcomes (functionality and fibrosis).

An overall judgment of the quality of evidence (Table 4) was performed using the GRADEpro GDT (Grading of Recommendations Assessment, Development and Evaluation) software. The quality of evidence was considered very low on the fibrosis outcome when the pentoxifylline with vitamin E group was compared with the placebo group or standard follow-up, as both studies[12,15] had methodologic limitations. The study by Delanian et al[12] also showed imprecision of the results (Table 4).

The analysis of the studies by Delanian et al[12] and Jacobson et al, shown in Figure 2A, included 64 participants and there was no significant difference ($P = .24$) in favor of the experimental group (standardized mean difference: −0.30; 95% CI, −0.79-0.20).

The quality of evidence was judged as moderate for the fibrosis outcome when the pentoxifylline and vitamin E group was compared with the placebo and vitamin E group, because the Delanian et al study[12] had methodologic limitations and imprecision of results (Table 4). The analysis of the Delanian et al[12] and Magnusson et al studies, shown in Figure 2B, included 78 participants and also showed no significant difference ($P = .77$) in favor of the experimental group (standardized mean difference: −0.09; 95% CI, −0.66-0.49).

Discussion

From the studies included in this systematic review, it is not yet possible to conclude on the efficacy of treatment protocols for radioinduced fibrosis in patients with breast cancer. Although the database search may have been quite comprehensive (2501 references obtained), the number of randomized clinical trials on the topic is still scarce (n = 7). The studies are very heterogeneous methodologically, which makes it difficult to group them into further meta-analyses. It was not possible to perform subgroup analysis.

The investigations of Oliveira et al and Bourgeois et al were the nonpharmacologic studies that showed favorable results to the experimental group in the fibrosis outcome and were shown to be safe by the absence of adverse effects. The effects reported in the study by Bourgeois et al (erythema and itching) do not seem to be related to the treatment itself but to the post−radiation therapy effects.

Although the results of Oliveira et al and Bourgeois et al were significant, there is uncertainty about the potential effect of these interventions, considering that the samples of the included studies were too small for us to ensure a good external validity of these protocols.

In addition, we found 18% of the domains evaluated in the included studies with high risk of bias. This result should be taken into consideration when interpreting the results presented. Even with results favorable to the experimental group, the reliability of obtaining these is poor. Therefore, the evidence presented by the studies included in this review lacked rigorous control for the randomization process, for the masking of patients and researchers or evaluators, and for the measurement of results, which creates uncertainty about the efficacy or otherwise of the findings of these primary studies and meta-analyses.

The causes of the high risk of bias observed in this review stem mainly from the lack of standardization and reliability of assessment methods for fibrosis, as many proved to be inadequate, nonstandardized, and subjective. Another factor that increased the risk of bias was the small sample size. Delanian et al[12] reported that larger randomized studies are needed to confirm the antifibrotic action of the association pentoxifylline and vitamin E.

The difficulty of standardization and the use of inadequate metrics or reporting of results increase the risk of study bias. Helping to minimize methodological limitations, some studies used quantitative methods to assess fibrosis. In the study by Bourgeois et al, a 3-dimensional profilometric analysis of skin contours obtained by a silicone skin replica was used, and in the study by Jacobson et al, a mechanical tissue compliance meter was used to measure fibrosis.

Another issue observed was in relation to patient follow-up. Two of the 7 studies did not report whether they performed follow-up,[12,16] one study performed for 1 month,[7] and 2 others performed for 3 to 6 months.[14,19] Because radiation-induced fibrosis is a chronic condition that can appear late and evolve for many months or years, it is essential that follow-up be done for a long period, especially in preventive interventions that begin

simultaneously or soon after radiation therapy. The question of the interval between radiation therapy and the initiation of treatment for fibrosis should be analyzed with caution. The presence of a wide interval between patients in the same group may lead to heterogeneity and the need for subgroup analysis.

The performance of immediate reconstruction presents benefits (aesthetic, psychological and economic) for the patient, but one must take into consideration the adverse effects of radiation therapy in breast reconstruction. Reconstruction before radiation therapy has been a factor that may lead to a higher incidence of fibrosis or contracture of the breast in the long term, as well as impairing the oncologic safety of the patient. A consensus has been formed to perform reconstruction after radiation therapy is completed.[33,34]

Although there are still studies with controversial results, an association between immediate reconstruction with silicone implant and adjuvant radiation therapy has been established, with cosmetic impairment, in addition to loco-regional complications and systemic symptoms, such as breast implant disease.[35] Immediate reconstruction with implant has relative contraindication when it is known that adjuvant radiation therapy will be required. To minimize the complications of radiation therapy and obtain cosmetic improvement, it is necessary to opt for a 2-stage reconstruction using an expander. Regarding immediate autologous reconstruction, they also have controversial results, but are shown to be less severe than immediate reconstructions with silicone implants.[36]

Dewael et al[33] evaluated late complications in patients who underwent immediate autologous reconstruction compared with patients who underwent late autologous reconstruction (after radiation therapy). The results showed an incidence of fibrosis or contracture in 60% of the women who underwent immediate autologous reconstruction and in 2.5% of the women who underwent late autologous reconstruction.[33]

A systematic review[37] was conducted of 292 studies that evaluated acute and late complication rates, and found that both did not differ between postmastectomy irradiated patients who underwent immediate or delayed autologous breast reconstruction. The authors of this study conclude that due to the benefits, immediate breast reconstruction may be feasible for patients eligible for adjuvant radiation therapy, but further studies are needed due to limitations found (absence of data on the occurrence of fibrosis). Of the 44 studies included in the meta-analysis, only 9 of them quantified fibrosis or contracture. These 9 studies evaluated fibrosis in women with immediate reconstruction, and all (except one) reported incidence of fibrosis. No meta-analysis of this variable was performed due to lack of data likely caused by difficulty in standardization.[37]

Delayed autologous reconstruction is a possibility to minimize the adverse effects of radiation therapy, presenting better cosmetic results, lower complication rates and greater patient satisfaction, but not all are candidates for late autologous reconstruction or because they do not want the technique, opting for silicone implant.[36]

The results of the present systematic review point to the need for new multicenter randomized clinical trials to obtain larger samples and with better methodological designs. In addition, it is suggested that the time gap between the end of radiation therapy and the beginning of the intervention should be as short as possible to achieve better treatment results. New studies with the drugs pentoxifylline and vitamin E, with similar protocols and dosage to the existing studies described in this review, are suggested, so that a future update of this review can elaborate an evidence of the effects of this intervention. We encourage researchers to develop protocols with the use of kinesiotherapy and endermotherapy for the treatment of radiation-induced fibrosis since these therapies showed significantly favorable outcomes and no adverse events.

Conclusion

It is not possible to conclude on the effectiveness of any intervention studied to treat radiation-induced fibrosis in breast cancer patients. The studies included a diversity of treatments and metrics for outcomes. The results of this review should be viewed with caution due to the small number and sample size of studies, and the high risk of bias presented by some of the included studies. Some isolated randomized controlled trials indicate effectiveness in reducing radiation-induced fibrosis with endermotherapy, kinesiotherapy as assessed by the LENT-SOMA scale, as well as the combination of pentoxifylline with vitamin E when assessing fibrosis by the Tissue Compliance Meter. Kinesiotherapy also indicated a benefit in shoulder function. Grape seed extract was also analyzed but did not show effectiveness. More studies analyzed the effect of pentoxifylline associated with vitamin E, and although some indicated effect with proposed statistical analysis, when the relative risk was analyzed, the results did not hold, even when meta-analysis was possible. All studies with pentoxifylline and vitamin E had clinically relevant adverse events, unlike the other interventions investigated.

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