

Review Article



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The Italian Association of Radiotherapy and Oncology Recommendation for Breast Tumor Recurrence: Grades of Recommendation, Assessment, Development and Evaluation Criteria

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ABSTRACT

Salvage mastectomy is currently considered the standard of care for ipsilateral breast tumor recurrence (IBTR) after breast-conserving surgery (BCS) and postoperative radiotherapy (RT). Alternative treatment options for these patients, such as a second BCS followed by repeated RT, have been suggested.

The panel of the Italian Association of Radiotherapy and Clinical Oncology developed clinical recommendations for second BCS followed by re-irradiation over mastectomy alone for women with IBTR using the Grades of Recommendation, Assessment, Development, and Evaluation methodology and the evidence to decision framework. The following outcomes were identified by the panel: locoregional control, metastasis-free survival, overall survival, and cancer-specific survival; acute and late toxicity, specific late toxicity, second locoregional tumor, and death related to treatment.

An Embase and PubMed literature search was performed by two independent authors. Five retrospective observational studies were eligible for inclusion in the present analysis.

According to the reports in the literature and our analysis, the advantages of second quadrantectomy and re-irradiation (re-QUART) outweigh its side effects, with overall good rates of survival and adequate toxicity without increasing costs.

Given the very low level of evidence, the panel stated that a second BCS plus re-irradiation can be considered as an alternative to salvage mastectomy for selected patients with IBTR.

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Conflict of Interest

The authors declare that they have no competing interests.

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INTRODUCTION

Breast cancer (BC) is the most common malignancy in women [1]. Despite all the available local treatment options, the 10-year rate of ipsilateral breast tumor recurrence (IBTR) still ranges from 8 to 11% [2]. Several risk factors are associated with the development of IBTR, such as younger age, inherited susceptibility, characteristics of the primary tumor, omission of adjuvant radiotherapy (RT) after breast-conserving surgery (BCS), positive surgical margins, and other lifestyle factors, such as obesity and alcohol consumption [3-6].

The rate of a second local recurrence (2ndLR) after salvage mastectomy (sMT) ranges from 3 to 22% [2]. When repeated BCS without re-RT is performed, the 2ndLR rates are even higher (26% with a range of 4%–50%) [7]. The rates drop when RT follows BCS, but the high risk of severe delayed side effects after high-dose RT delivered to the entire breast led physicians to choose sMT as the standard approach over the last decades. Nevertheless, in selected cases, partial breast re-irradiation with interstitial brachytherapy (iBT) or external beam radiotherapy is successfully used [2,3,8-10].

For patients with IBTR, sMT is still considered the standard of care. The current recommendations in the main national and international guidelines are as follows:

- The National Comprehensive Cancer Network Breast Cancer Guidelines, version 1.2019 [11] recommends total mastectomy and axillary node staging for cases where axillary dissection has not been previously performed.
- The Italian Association of Medical Oncology [12] recommends mastectomy and axillary node staging when axillary dissection has not been previously performed. They suggest, for particular cases, a second BCS + whole breast- or partial breast-RT (women with a local recurrence < 2 cm, or more than 4 years from primary surgery) with a 10% risk of late toxicity.

None of these recommendations were developed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach [13]. In 2018, the panel for the Italian Association of Radiotherapy and Clinical Oncology (AIRO) guidelines developed a clinical recommendation for BC using the GRADE approach to address the dilemma associated with choosing to perform a second BCS plus RT or sMT for women presenting with a local relapse who were previously treated with lumpectomy plus RT.

METHODS

The AIRO guidelines on breast cancer panel

A multidisciplinary panel updates the AIRO guidelines for BC. The draft of the updated guidelines is sent to external reviewers before the final publication on the AIRO website [14]. External reviewers are nominated by the AIRO.

Development of clinical question

The clinical question was developed using the P.I.C.O. approach, which requires the definition of the population (P), intervention (I), comparison (C), and outcomes (O).

For the 2019 version of the AIRO Guidelines on Breast Cancer, the panel decided to address the following clinical question:

- In patients with IBTR previously treated with BCS and whole breast irradiation (WBI), are the outcomes of a second BCS plus re-irradiation equivalent to those of mastectomy alone?

Women with IBTR who were formerly treated with BCS plus RT represented the population of interest, as defined by the panel. In formulating the question, the panel considered SMT as the standard treatment because it is the preferred treatment recommended by AIRO and other BC guidelines for these patients [11,12]. Therefore, the intervention was the second BCS followed by re-irradiation.

Identification of outcomes

The panel identified the following beneficial outcomes: locoregional control (LC), metastasis-free survival, overall survival (OS), and cancer-specific survival (CSS). All these outcomes were deemed critical for decision-making.

The panel identified the following unsatisfactory outcomes: late and acute toxicity, late specific toxicity (fibrosis, telangiectasia, rib fracture), treatment-related death, and second regional tumor, which were all judged as critical.

Search strategies and data extraction

A PubMed and Embase literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method was performed in March 2019 by two independent authors (VB and MB) from January 1980 to March 2019 using the following keyword search terms: 1) "ipsilateral breast tumor recurrence," 2) "ipsilateral AND breast AND cancer AND recurrence," and 3) "re-irradiation OR re-irradiation." No meta-analysis was found, and only one systematic review was identified and selected. Three studies were selected from the first analysis of these papers. Since the literature search for this paper was discontinued in June 2018, the literature research was updated to July 2019 using the same keywords. The literature search returned 12 records (four from Medline and eight from Embase). The titles and abstracts were used to screen for the initial study decisions. The clinical studies published in English language journals were identified and screened for duplicates; when multiple articles with the same study population were found, the survival data from the article with the longest follow-up were included in the analysis. Disagreements and discrepancies were resolved through discussion. After exclusion of the duplicates, five records were screened, three full-text articles were assessed for eligibility, and two met the eligibility criteria and were included in the qualitative analysis (**Figure 1**).

Smanykó et al. [2] retrospectively analyzed 195 women with IBTR treated between 1999 and 2016 with conservative surgery and WBI and salvaged with a second BCS with perioperative high-dose iBT (39 patients) or SMT (156 patients). The second BCS group received a total dose of 22 Gy in 5 fractions of 4.4 Gy in the tumor bed for 3 consecutive days. The tumor bed with an additional margin of 2 cm represented the target volume. The second BCS was performed when the following conditions were met: isolated and unicentric tumor,

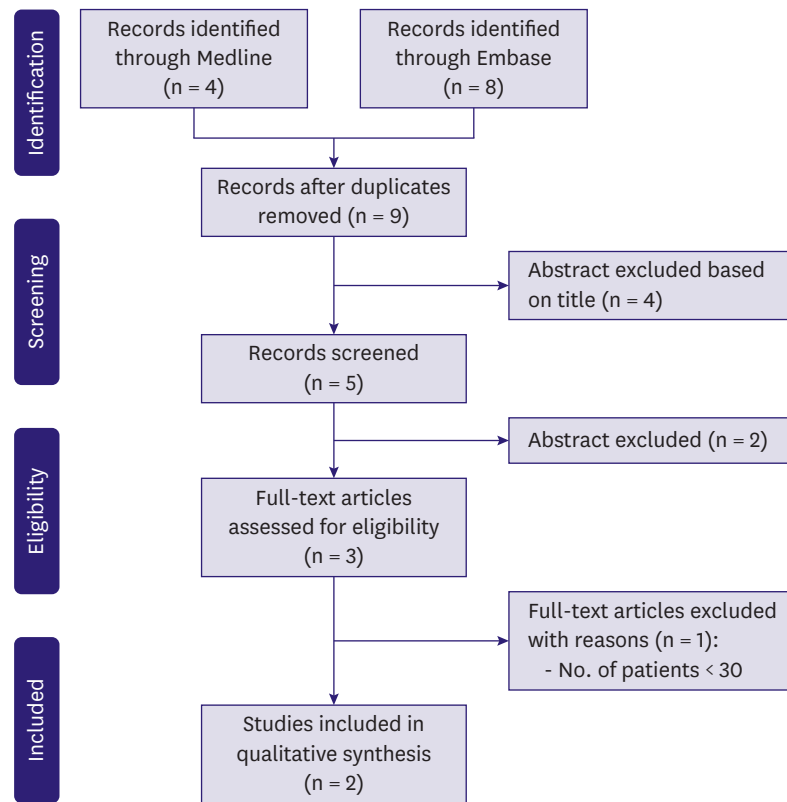


Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart.

parenchymal tumor recurrence without regional and distant metastasis, tumor size of < 3 cm based on clinical and mammographic examination, recurrence at least 2 cm from the skin surface, and a strong preference for repeated BCS. Patients with multifocal or multicentric local recurrences were excluded.

Houvenaeghel et al. [10] in their retrospective monocentric study compared the survival outcomes of sMT (232 pts) and second BCS + multi-catheter low-dose iBT (116 BCS, only 62 received iBT) for the treatment of IBTR occurring after primary BCS. A total of 348 women were treated between 1981 and 2009. The target volume was defined as the volume of the tumor bed plus 1–2 cm margins. Clips were inserted to facilitate the tumor bed visualization, and the total dose delivered was 45 or 46 Gy.

The GEC-ESTRO (Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology) Breast Cancer Working Group in their multicenter study [3] analyzed the clinical outcomes of 217 patients treated between 2000 and 2010 with accelerated partial breast irradiation iBT as the second conservative treatment for IBTR. Multi-catheter brachytherapy (BT) was delivered to the tumor bed using a low-dose rate (LDR), pulsed-dose rate (PDR), or high-dose rate (HDR). The median total dose delivered was 46 Gy (range: 30–55 Gy) using LDR, 50.4 Gy (range: 49–50 Gy) using and PDR BT, and 32 Gy (range: 22–36 Gy) in 5–10 fractions (twice daily) using HDR BT.

The NRG Oncology- Radiation Therapy Oncology Group (RTOG) Study 1014 [8] was a phase 2 trial investigating partial breast re-irradiation with three-dimensional conformal

radiotherapy (3D-CRT) after a second BCS for patients experiencing breast failure after WBI. Eligibility criteria included recurrence occurring >1 year after WBI, tumor size of <3 cm, unifocal, and resection with negative margins. The primary objective was to evaluate the rates of grade 3 treatment-related skin adverse events (AEs), fibrosis, and/or breast pain that occurred a year after re-treatment. Partial breast re-irradiation was targeted at the surgical cavity plus 1.5 cm; the total dose was 45 Gy administered as 1.5 Gy twice daily in 30 fractions. A total of 65 patients were recruited between 2010 and 2013, and the first 55 eligible patients who had undergone 1-year follow-ups were analyzed. All patients were clinically node-negative, and systemic therapy was administered to 51% of them.

Montagne et al. [9] analyzed the impact of the GEC-ESTRO-accelerated partial breast irradiation classification on the oncological outcomes in 159 patients undergoing accelerated partial breast re-irradiation for a second ipsilateral breast tumor after primary radio-surgical treatment. Accelerated partial breast re-irradiation was performed using either LD BT (prescribed dose ranged from 30 to 55 Gy) or HD BT (prescribed dose ranged from 28 to 34 Gy in 8-10 fractions, twice daily, delivered over 5 consecutive days).

Quality of evidence evaluation

Based on the GRADE approach, an evaluation of the certainty of evidence for each outcome was performed. The GRADE evaluation includes five main domains: study limitations, imprecision, indirectness, inconsistency, and publication bias. For the study design, the certainty level started at a pre-specified level (high certainty for randomized controlled trials). The detection of limitations in one or more domains can downgrade the certainty of evidence. The final judgment can be as follows: high, moderate, low, and very low. A summary of the certainty of evidence and quantitative synthesis of the effects for each outcome is reported in **Figure 2**.

Evidence to decision (EtD) framework

The EtD framework provides a transparent and structured approach to support the decision-making process [15]. It allows summarizing the evidence related to the priority of the problem, substantiality of desirable and undesirable effects, balance of effects, certainty of evidence, patient preference, use of resources, equity, acceptability, and feasibility.

Benefit/harm balance and clinical recommendation

The panel rated the interventions as one of the following based on their benefits and negative outcomes and comparison: favorable, uncertain/favorable, uncertain (both for intervention or comparison), uncertain/unfavorable, and unfavorable. The panel also rated the strength of the recommendation as one of the following: strong positive, conditional positive, conditional negative, and strong negative. The AGREE-reporting checklist was used to guide the recommendations [15].

RESULTS

Positive outcome

Table 1 reports a summary of the impact and certainty of the evidence assessment.

Re-QUART compared with mastectomy for locally recurrent BC after the primary QUART

No. of participants (studies) follow-up	Certainty assessment						Summary of findings		Impact
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		
							With mastectomy	With Re-QUART	
5-year overall survival, Smanyakó 2019 [2] (follow-up: median 59 months; assessed with: KM)									
95 (1 observational study)	Not serious	Not serious	Not serious	Serious ^a	None	⊕○○○ Very low	81% BCS + RT	66% Mx (<i>p</i> = 0.15)	
5-year overall survival, Houvenaeghel 2017 [10] (follow-up: median 73 months; assessed with: KM)									
294 (1 observational study)	Serious ^b	Not serious	Not serious	Not serious	None	⊕○○○ Very low	86% BCS + RT vs.	82.3% Mx	
10-year overall survival, Houvenaeghel 2017 [10] (follow-up: median 73 months; assessed with: KM)									
294 (1 observational study)	Serious ^b	Not serious	Not serious	Not serious	None	⊕○○○ Very low	86% BCS + RT vs.	64% Mx	
5-year disease free survival, Smanyakó 2019 [2] (follow-up: median 59 months; assessed with: KM)									
95 (1 observational study)	Not serious	Not serious	Not serious	Serious ^a	None	⊕○○○ Very low	69% BCS + RT vs.	65% Mx	
5-year cancer specific survival, Smanyakó 2019 [2] (follow-up: median 59 months; assessed with: KM)									
95 (1 observational study)	Not serious	Not serious	Not serious	Serious ^a	None	⊕○○○ Very low	85% BCS + RT vs.	78% Mx	
Re-QUART, late grade 1 toxicity									
470 (4 observational studies)	Not serious	Serious ^c	Not serious	Not serious	None	⊕○○○ Very low	4 studies analyzed (Hannoun-Levi 2013, Arthur 2017, Montagne 2019, Smanyakó 2019) with 176 events: pooled analysis: 44% (95% CI: 30–58%) I ² : 89%		
Re-QUART, late grade 2 toxicity									
470 (4 observational studies)	Not serious	Serious ^d	Not serious	Not serious	None	⊕○○○ Very low	4 studies analyzed (Hannoun-Levi 2013, Arthur 2017, Montagne 2019, Smanyakó 2019) with 107 events: pooled analysis: 20% (95% CI: 11–30%) I ² : 84%		
Re-QUART, late grade 3 toxicity									
470 (4 observational studies)	Not serious	Not serious ^e	Not serious	Not serious	None	⊕+○○ Low	4 studies analyzed (Hannoun-Levi 2013, Arthur 2017, Montagne 2019, Smanyakó 2019) with 22 events: pooled analysis: 4% (95% CI: 1–6%) I ² : 46%		
Re-QUART, late grade 4 toxicity									
470 (4 observational studies)	Not serious	Not serious ^f	Not serious	Not serious	None	⊕+○○ Low	4 studies analyzed (Hannoun-Levi 2013, Arthur 2017, Montagne 2019, Smanyakó 2019) with 2 events: pooled analysis: 0.5% (95% CI: 0–1%) I ² : 0%		
Re-QUART, telangiectasia									
431 (4 observational studies)	Not serious	Serious ^g	Not serious	Not serious	None	⊕○○○ Very low	3 studies analyzed (Hannoun-Levi 2013, Arthur 2017, Montagne 2019) with 37 events: pooled analysis: 8% (95% CI: 4–11%) I ² : 58%		

Explanations

^aSmall sample size; ^bPatients who received simple mastectomy had poor prognostic factors more frequently; ^cI²: 89%; ^dI²: 84%; ^eI²: 46%; ^fI²: 0%; ^gI²: 58%

Figure 2. Evidence profile table for the GRADE assessment: Re-QUART compared with mastectomy for locally recurrent breast cancer after the primary QUART. QUART = quadrantectomy plus radiotherapy; BC = breast cancer; BCS = breast-conserving surgery; RT = radiotherapy; CI = confidence interval; GRADE = Grades of Recommendation, Assessment, Development, and Evaluation.

Table 1. The final recommendation

Quality of evidence	Recommendation	Strength of recommendation
Very low	In patients with ipsilateral breast tumor recurrence previously treated with breast conserving surgery and radiotherapy, a second breast conserving surgery plus re-irradiation can be considered as an alternative to radical mastectomy +/- reconstruction.	Weak positive

OS

Two of the identified studies reported OS rates [2,10]. In their retrospective observational studies, Smanyakó et al. [2] reported a 5-year OS rate of 81% for the second BCS + RT group and 66% for the sMT group (*p* = 0.15). The certainty of evidence was judged “very low” due to the imprecision related to the small sample of patients analyzed (only 39 patients underwent a second BCS + RT) and the observational nature of the study.

Houvenaeghel et al. [10] analyzed both 5- and 10-year OS rates: the 5-year rates were 86% for 2ndBCT + BT and 82.3% for sMT; the 10-year rates were 86% and 64%, respectively. The certainty of evidence was judged as “very low” due to the selection bias related to the worst prognostic factors for all the women who underwent sMT and the observational nature of the study.

DFS

Only one study [2] included disease free survival (DFS) in the analysis, with 5-year rates of 69% and 65% for the second BCS+RT and sMT, respectively. The certainty of evidence was judged as “very low” due to the imprecision related to the small sample of patients analyzed (only 39 patients underwent a second BCS+RT) and the observational nature of the study.

CSS

Only Smanyakó et al. [2] reported on CSS, with 5-year rates of 85% for the second BCS+RT and 78% for sMT. The certainty of evidence was judged as “very low” due to the imprecision related to the small sample of patients analyzed (only 39 patients underwent 2nd BCS+RT) and the observational nature of the study.

Negative outcomes

Acute and late toxicity

No data on acute toxicity were reported in the identified studies [2,3,8,9]. Four studies were analyzed to evaluate treatment-related late toxicity.

- Montagne et al. [9] evaluated late toxicity in 159 patients with a median follow-up of 71 months using the Common Classification for Adverse Events 4.0. The late toxicity rates were 33% (47 patients), 26% (37 patients), 2.8% (4 patients), and 0.7% (1 patient) for grades 1, 2, 3, and 4, respectively.
- Arthur et al. [8] evaluated late toxicity in the first 55 eligible patients who completed treatment and underwent a year of follow-up using the Common Classification for Adverse Events 4.0. The treatment-related skin adverse events, fibrosis, and/or breast pain were graded as 1 in 64%, 2 in 7%, and 3 in < 2% (1 patient). No grade 4 or 5 was reported. The documented grade 3 adverse event represented fibrosis of the deep connective tissue.
- Hannoun-Levi et al. [3] performed a toxicity assessment in 217 patients using the Common Classification for Adverse Events 3.0. The late toxicities were graded as 1 in 50%, 2 in 39%, 3 in 10%, and 4 in 1% of the patients.
- Smanyakó et al. [2] analyzed late toxicity in 39 patients with a median follow-up duration of 59 months (1-189) using the RTOG/EORTC late radiation morbidity scoring scheme. Grade 2 and 3 late skin toxicities occurred in 11 (28%) and 3 patients (8%), respectively. Asymptomatic fat necrosis was detected in 7 women (18%) and required no surgical intervention.

Late specific toxicity (fibrosis, telangiectasia, ribs fracture)

- Montagne et al. [9] evaluated late toxicity in 159 patients with a median follow-up of 71 months using the Common Classification for Adverse Events 4.0. The observed complications consisted mainly of cutaneous (32.5%) and subcutaneous (30.1%) fibrosis, while telangiectasia (8.4%) and hyperpigmentation (17%) were less common. One patient presented with grade 4 ulcerations.
- Arthur et al. [8] evaluated late toxicity in the first 55 eligible patients who completed treatment and underwent a year of follow-up using the Common Classification for Adverse Events 4.0. The adverse events, including treatment-related skin events,

fibrosis, and/or breast pain, were graded 1 in 64%, 2 in 7%, and 3 in < 2% (1 patient) of the patients. No grade 4 or 5 was reported. The documented grade 3 adverse events represented fibrosis of the deep connective tissue.

- Hannoun-Levi et al. [3] performed toxicity assessments of 217 patients using the Common Classification for Adverse Events 3.0. The long-term side effects of breast tissues were cutaneous and subcutaneous fibrosis (67%), telangiectasia (16%), hyperpigmentation (9%), and ulceration (1%).
- Smanykó et al. [2] analyzed late toxicity in 39 patients with a median follow-up duration of 59 months (1-189) using the RTOG/EORTC late radiation morbidity scoring scheme. Asymptomatic fat necrosis was detected in 7 women (18%) and required no surgical intervention. Grade 2 and 3 fibrosis developed in 9 (23%) and 1 patient (2%), respectively.

No data on rib fractures were reported in the identified studies.

Death related to treatment and second regional tumor

No data on deaths related to the treatment and secondary regional tumors have been reported in the identified studies [2,3,8-10].

Pooled analysis of toxicity results

To evaluate the certainty of evidence for each late toxicity outcome (G1-G4) and telangiectasia using the GRADE approach, a pooled analysis of four studies was performed (**Figures 3 and 4**).

For grade 1 late toxicity, the pooled analysis included four studies with 176 events in 470 patients. The probability was 44% (95% confidence interval [CI], 30%–58%) and I^2 was 89% (**Figure 3A**).

For grade 2 late toxicity, the pooled analysis included four studies with 107 events in 470 patients. The probability was 20% (95% CI, 11%–30%) and I^2 was 84% (**Figure 3B**).

For grade 3 late toxicity, the pooled analysis included four studies with 22 events in 470 patients. The probability was 4% (95% CI, 1%–6%) and I^2 was 46% (**Figure 3C**).

For grade 4 late toxicity, the pooled analysis included four studies with two events in 470 patients. The probability was 0.5% (95% CI, 0%–1%) and I^2 was 0% (**Figure 3D**).

For telangiectasia, the pooled analysis included three studies with 37 events in 431 patients. The probability was 8% (95% CI, 4%–11%) and I^2 was 58% (**Figure 4**).

The certainty of evidence for the late toxicities of grades 1 and 2 and telangiectasia was judged as “very low” due to the high inconsistency (I^2 : 89%, 84%, 58%). The certainty of evidence for the late toxicities of grades 3 and 4 was judged “low” due to the low inconsistency (I^2 : 46% and 0%).

EtD framework

A full EtD table is presented in **Table 1**. In summary, the panel judged the problem addressed by the clinical question as a priority. The panel acknowledged no positive impact of BCS+RT or sMT on the survival (OS, CSS, LC) of patients with IBTR. However, since no differences in the outcomes were observed between the patients treated with sMT and BCS+RT, the

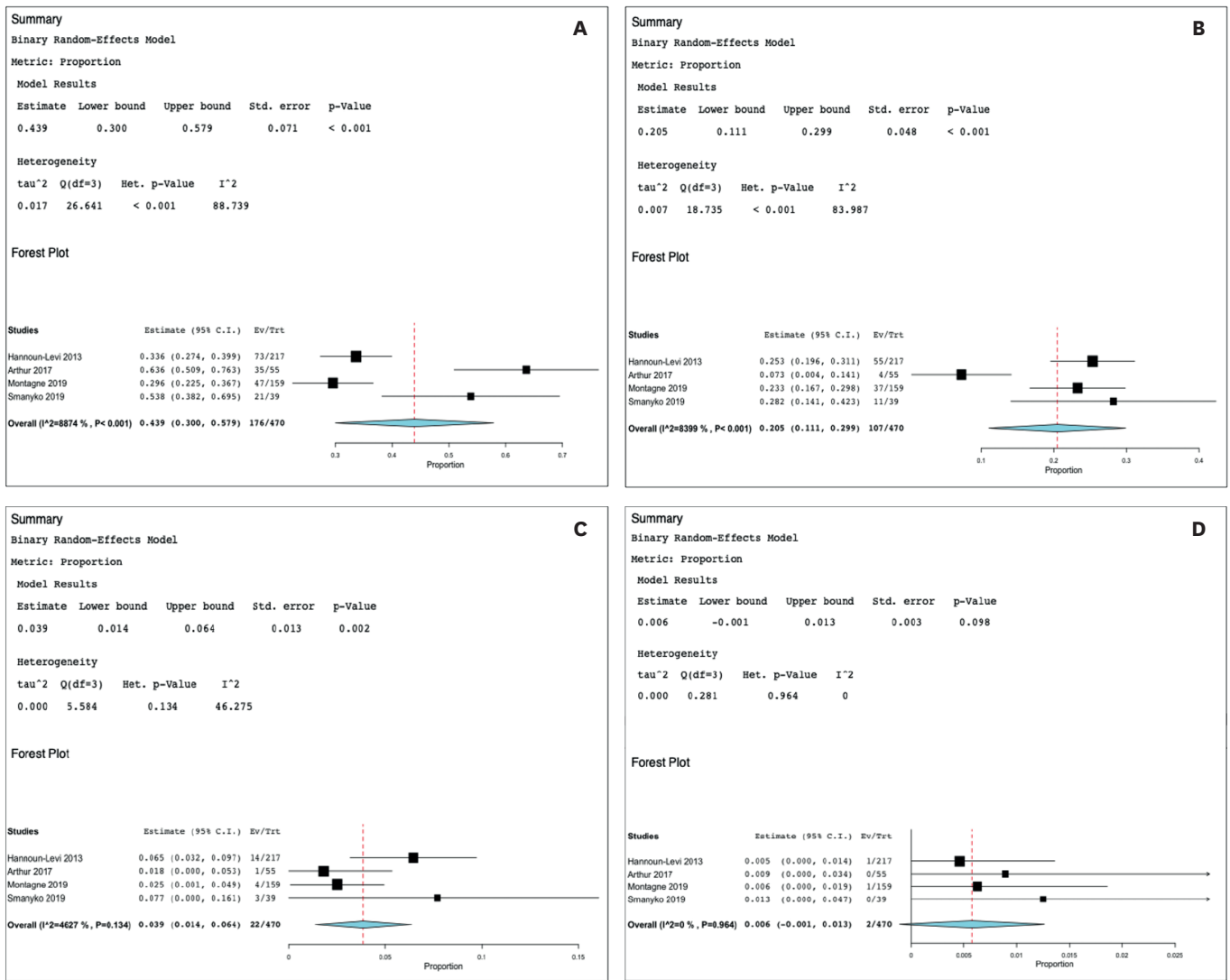


Figure 3. Pooled analysis results for late toxicity (A) GRADE 1; (B) GRADE 2; (C) GRADE 3; (D) GRADE 4. CI = confidence interval; GRADE = Grades of Recommendation, Assessment, Development, and Evaluation.

panel judged the substantiality of the anticipated desirable effects as “very low.” The panel considered the imprecision related to the small sample of patients analyzed (only 39 patients underwent 2nd BCS+RT), the selection bias related to the worst prognostic factors of all the women who underwent SMT, and the observational nature of the studies in this evaluation.

The panel judged the substantiality of undesirable effects as “low,” due to the low inconsistency (I^2 : 46% and 0%) in the pooled analysis results for the late toxicities of grades 3 and 4 (only two events out of 470).

Benefit/harm balance and final recommendation

The panel voted for the benefit/harm balance as uncertain–favorable (five votes out of five members). Five out of the five panel members voted the strength of the recommendation as weakly positive.

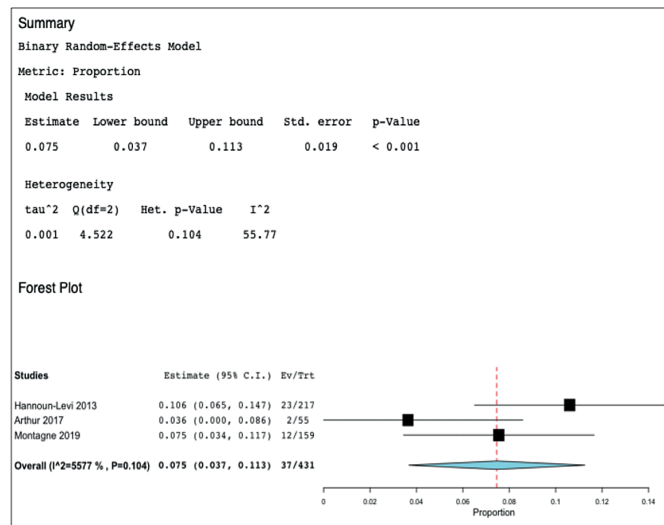


Figure 4. Pooled analysis results for Telangiectasia. CI = confidence interval.

Therefore, the final recommendation by the panel was as follows. In patients with IBTR previously treated with BCS and RT, a second BCS plus re-irradiation can be considered as an alternative to radical mastectomy with or without reconstruction. The final recommendation is provided in **Table 1**.

DISCUSSION

sMT continues to be the recommended approach by international guidelines for women with IBTR [11,12]. Some patients refuse radical surgery and request alternative treatment, and clinicians may be reluctant to propose sMT for cases of very small tumors in patients with large breasts.

The AIRO Clinical Practice Guidelines on Breast Cancer panel suggested a second BCS + RT as an alternative for women presenting with IBTR formerly treated for primary BC with BCS + RT. To date, no prospective randomized trials have compared these two treatment modalities in the setting of patients. Since all the studies analyzed were observational and retrospective, involved small samples, and had some bias due to the selection of more advanced cases for sMT, the overall quality of the evidence gathered in our analysis is very low.

Nevertheless, second quadrantectomy and re-irradiation (re-QUART) seems to be associated with good survival (OS, CSS, and LC); however, the durations of follow-up reported have not been more than 10 years. The 5-year OS ranged from 81% to 86% [2,10], the 10-year OS rate reported by Houvenaeghel was 86%, and the 5-year CSS was 86%, as reported by Smankyó et al. [2].

Regarding the severe radiation-induced toxicity, the results are acceptable (G3, 4%; G4, 0.5%) compared with the higher complexity and morbidity associated with sMT and the eventual breast reconstruction in patients already treated with RT not reported by any of the studies included in the analysis.

Reports in the literature data and the outcomes of our analysis show that the advantages of re-QUART exceed its side effects, with good OS and lesser toxicity without increasing costs.

Re-QUART may be a less invasive alternative to sMT, especially for small recurrent tumors in large breasts and women motivated to pursue this treatment.

Other considerations

The panel acknowledges that the majority of the studies used BT after the second BCS, which can limit the applicability of this strategy because not all radiation oncology centers in our country can administer BT. This may represent an indirectness for intervention; nevertheless, recent results from the RTOG 1014 trial [8] investigating the role of partial breast re-irradiation after a second BCS using the 3D-CRT technique showed safety, feasibility, and good rates of toxicity.

Moreover, the panel suggests the implementation of this therapeutic strategy for patients presenting with unifocal recurrence and luminal-like disease at least 5 years after the primary BC.

The management of these patients in accredited high-volume specialized breast centers is essential for the implementation of this new approach. The lack of patient-reported outcomes, especially cosmetic, is an important limitation of all the studies analyzed. Finally, all patients should be evaluated by a multidisciplinary team of experts and educated about the possible benefits and adverse events related to this treatment.

The results of all the observational studies analyzed suggest good local control rates and negligible grade 3–4 toxicity rates for re-QUART with respect to sMT plus eventual breast reconstruction and all treatment-related morbidity. Re-QUART can be considered an alternative treatment for patients with IBTR previously treated with BCS plus RT.

Patient selection, a multidisciplinary approach, and a comprehensive discussion with patients about the risks, benefits, and alternatives remain key elements in selecting treatment.

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