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Beyond the first dose: Systematic review on external beam radiotherapy for locoregional breast cancer recurrence

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ABSTRACT

Background: The optimal management of locoregional breast cancer recurrence after prior radiotherapy remains challenging. Reirradiation (ReRT) may allow repeat breast-conserving surgery as an alternative to mastectomy; however, prospective evidence is scarce, and existing data are largely retrospective, with the strongest support for brachytherapy. Despite this, external beam reirradiation (EBreRT) is widely used because of its availability. This systematic review evaluated the feasibility, oncologic outcomes, toxicity, and patient-reported outcomes of external-beam ReRT for locoregional breast cancer recurrence.

Methods: Following the PRISMA guidelines (PROSPERO CRD420251003760), seven databases were searched until November 2025 to identify studies evaluating adjuvant external beam reirradiation for locoregional breast cancer recurrence. The outcomes of interest included disease control, survival, toxicity, and patient-reported outcomes, which were summarized descriptively.

Results: Twenty-four studies published between the mid-1980s and 2024, comprising 1252 patients, were included; most were retrospective, heterogeneous, single-institution cohorts with moderate quality. Reirradiation was predominantly delivered as partial-breast photon-based EBreRT using conventional fractionation.

Conclusions: Evidence on EBreRT for locoregional breast cancer recurrence remains insufficient to define optimal dose regimens, treatment intervals, or standardized patient selection criteria, as the available studies are predominantly retrospective and heterogeneous. Nevertheless, the available data suggest that EBreRT may be a feasible therapeutic option, provided that careful case-by-case patient selection is applied.

1. Introduction

Locoregional breast cancer recurrence after prior radiotherapy remains a major clinical challenge. In patients with ipsilateral breast tumor recurrence (IBTR) following primary breast-conserving surgery (BCS) and whole-breast irradiation, treatment decisions are complex and must balance oncologic safety with quality of life. Traditionally, salvage mastectomy has been considered the standard of care, particularly in high-risk cases, as repeat BCS alone is associated with high local recurrence rates [1–3] and mortality [4].

However, increasing evidence supports a second breast-conserving approach in selected patients. Importantly, this strategy is primarily patient-driven and should be considered only when a clear preference for breast preservation is expressed. In such cases, treatment is typically discussed in a multidisciplinary setting and involves repeat BCS followed by reirradiation of the tumor bed. Repeat BCS followed by reirradiation (ReRT) has been shown to improve local control compared

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Abbreviations

BCS – breast-conserving surgery
CTV – clinical target volume
CTCAE – Common Terminology Criteria for Adverse Events
CW – chest wall
DEGRO – German Society for Radiation Oncology
DMFS – distant metastasis–free survival
EBRT – external beam radiotherapy
EBreRT – external-beam re-irradiation
EQD_2 – equivalent dose in 2-Gy fractions
ER – estrogen receptor
ESTRO – European Society for Radiotherapy and Oncology
GEC-ESTRO – Groupe Européen de Curiethérapie–ESTRO
Gy – gray
HER2 – human epidermal growth factor receptor 2
HR – hormone receptor
IMRT – intensity-modulated radiotherapy
IORT – intraoperative radiotherapy
LC – local control
M0 – no distant metastasis
OS – overall survival
PBI – partial-breast irradiation
PR – progesterone receptor
PRDR – pulsed reduced dose rate
PROM(s) – patient-reported outcome measure(s)
PTV – planning target volume
ReRT – re-irradiation
RBE – relative biological effectiveness
RT – radiotherapy
VMAT – volumetric modulated arc therapy
WBI – whole-breast irradiation

with surgery alone and may achieve outcomes comparable to mastectomy in appropriately selected cases [5,6]. Importantly, this approach preserves the psychosocial and cosmetic benefits of breast conservation while maintaining oncologic safety and is therefore increasingly considered in patients with favorable disease characteristics [7–9]. In addition to in-breast recurrence, reirradiation is also applied in chest-wall recurrences after mastectomy and in selected patients with unresectable or symptomatic locoregional relapse for local control or palliation [5].

Optimizing salvage treatment strategies requires a clear understanding of recurrence patterns and their relationship to prior therapy. Evidence suggests that the location of local and regional failures is influenced by both surgical approach and radiotherapy volumes, with a proportion of recurrences occurring outside previously irradiated fields, highlighting the importance of accurate target delineation [10]. These findings underscore the importance of precise target delineation and provide a rationale for modern, individualized reirradiation strategies.

Several radiotherapy techniques are available for ReRT, including external beam radiotherapy (EBRT), brachytherapy, and intraoperative radiotherapy (IORT). Among these, brachytherapy has the most robust evidence for second conservative treatment but is limited by availability and technical requirements [11]. EBRT, in contrast, is widely accessible and increasingly used in clinical practice, including both photon- and proton-based techniques. Despite its widespread use, evidence for EBRT-based reirradiation remains heterogeneous and largely retrospective. While large analyses mainly based on brachytherapy from the GEC-ESTRO group have demonstrated encouraging oncologic and toxicity outcomes for reirradiation and contributed to patient selection, evidence specific to external-beam reirradiation remains limited.

[12,13]. In cases where reirradiation is confined to the tumor bed, treatment concepts are like partial breast irradiation (PBI), and existing contouring guidelines from primary breast cancer can be applied. However, important uncertainties remain regarding optimal dose and fractionation in the reirradiation setting, necessitating individualized decision-making to balance cumulative toxicity risks against oncologic benefit [14]. As a result, clinical practice varies considerably between institutions [15].

Given the frequent clinical use of EBRT for reirradiation, this systematic review synthesizes the available evidence on the feasibility, efficacy, safety, and toxicity for locoregionally recurrent breast cancer, with a primary focus on external-beam techniques across all fractionation regimens. In addition to clinical outcomes, we specifically evaluated patient-reported outcomes, including quality of life and cosmetic results, as key indicators of treatment success.

2. Materials and methods

This study was conducted as a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Appendix 1) and registered in the PROSPERO database (CRD420251003760) [16]. Due to substantial clinical and methodological heterogeneity across included studies, particularly regarding patient populations, treatment techniques, and outcome reporting, a quantitative meta-analysis was not considered appropriate. Therefore, results were synthesized descriptively using a structured narrative approach.

2.1. Data sources and search strategy

We combined terms for breast cancer, reirradiation therapy, and recurrence keywords to identify potentially relevant studies. An electronic search of seven databases, including PubMed via MEDLINE ALL (Ovid), EMBASE, Web of Science Core Collection, Scopus, PsychInfo, CINAHL, and Cochrane Central, was performed until November 18, 2025. An expert research librarian developed the search strategy. The search results were imported into EndNote and de-duplicated using the method described previously [17]. The details of the search strategy and keywords are presented in Supplementary Appendix 2 (keywords: breast cancer recurrence, locoregional recurrence, reirradiation). To complete our search, the references of the included studies and published reviews were manually screened. We also manually searched the clinical trial registry database clinicaltrials.gov to identify ongoing prospective studies (observational or interventional) on breast cancer recurrence.

We selected original published studies if they had [1] prospective, cross-sectional, or clinical trial design [2]; evaluated reirradiation at breast cancer recurrence (repeat surgery followed by adjuvant radiation therapy using EBRT; studies with other forms of radiation therapy such as for e.g. brachytherapy were excluded). Conference abstracts, ecological studies, case reports, case series, letters to the editor, conference proceedings, narrative reviews, systematic reviews, and studies conducted in animals and children were excluded. We did not include non-English articles.

2.2. Study selection and data extraction

All titles and abstracts were screened independently and in duplicate by five reviewers (YS, SHZ, ANB, RSA, and RSA) according to the predefined eligibility criteria. The full-text articles selected for inclusion were subsequently reviewed in duplicate. Data from the included studies were extracted using a standardized, pre-designed form, with both screening and extraction conducted in EndNote 20. The extracted data

included study characteristics, patient information at initial diagnosis and recurrence, treatment details for both treatment courses, and efficacy outcomes (overall survival, local control, distant metastasis–free survival, progression-free survival, local/locoregional failure, and recurrence-free survival). In addition, data on acute and late toxicity during both initial and recurrent radiation therapy and quality-of-life outcomes (when reported) were collected.

2.3. Risk of bias assessment

Risk of bias assessments were conducted in duplicate by independent reviewers (YS, SHZ, ANB, RSA, and RSA), and disagreements were resolved by consensus (JN). We evaluated the risk of bias in the observational studies using a modified version of the Newcastle-Ottawa Scale (NOS) [18]. Each study was assessed on a 2- or 3-point scale across domains of selection (representativeness of cohort, ascertainment of exposure, outcome of interest not present at the start of study) and outcome (assessment of outcome, clarity of definition, follow-up sufficiently long, and time to occurrence reported). The scores for each domain were summed to a total score of up to nine. The two publications from the prospective phase II trial by Arthur et al. were evaluated using criteria appropriate for interventional study designs, with the Risk Of Bias In Non-randomized Studies–of Interventions (ROBINS-I) tool applied to assess potential bias across seven domains: confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selection of the reported result, each rated as low, moderate, serious, or critical risk of bias.

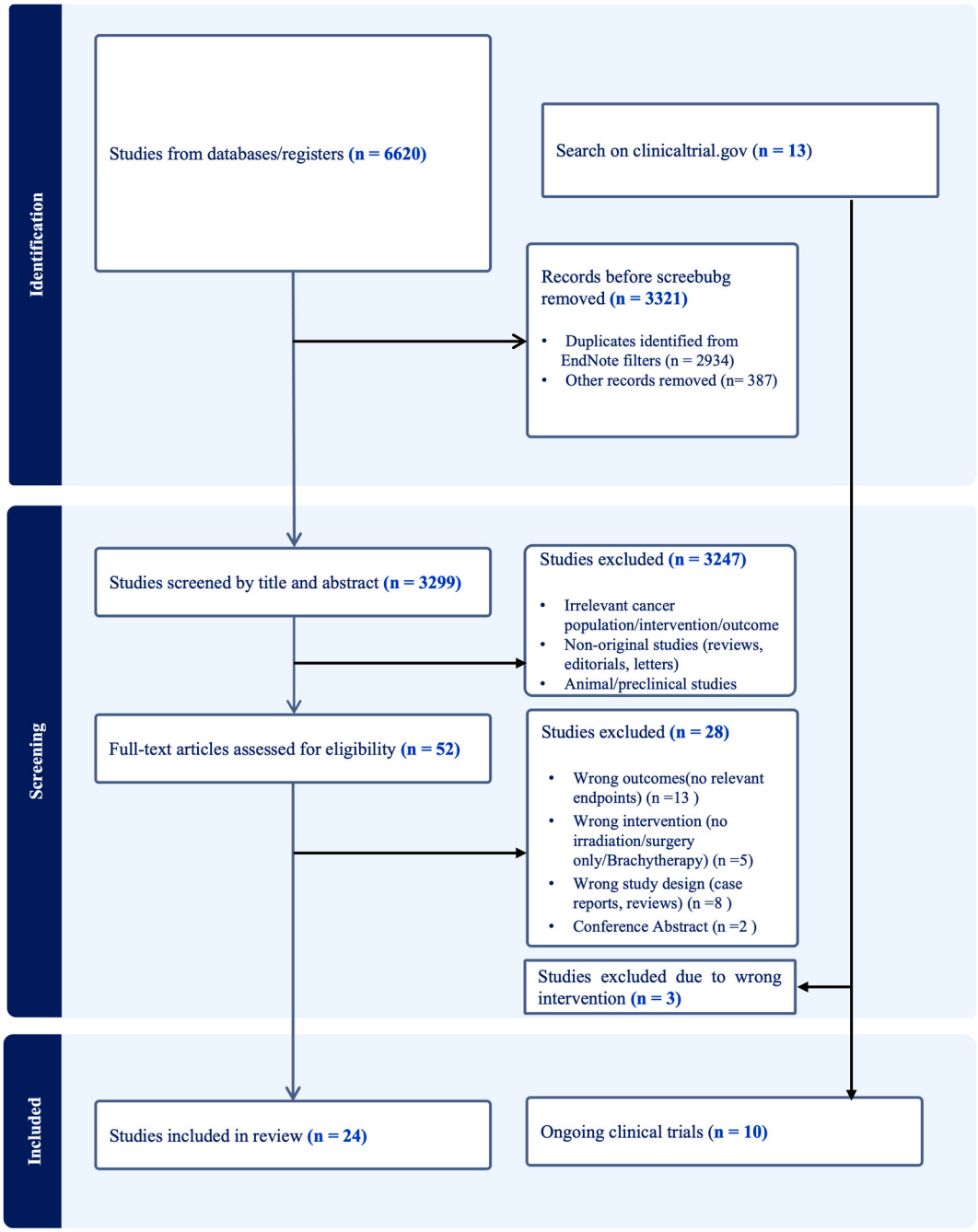


Fig. 1. PRISMA flowchart of study selection.

3. Data analysis

Due to the high heterogeneity in the designs, subjects included, outcomes, and metrics, we could not perform a meta-analysis of the results. Instead, we provided a descriptive analysis of patient and treatment characteristics, disease control and survival parameters, toxicities, and patient-reported outcomes when available. Graphical representations, including bubble plots and Sankey diagrams were used to visually synthesize the data. For toxicities, we summarized the total number of reported acute and late events in each study and summarized the proportions per grade, as well as per domain of toxicity (including skin/deep connective tissue-related events, pain, lymphedema, brachial plexopathy, fatigue, dysphagia or esophagitis, pneumonitis, rib fracture or osteonecrosis, pericarditis, or myocardial infarction related to treatment). When feasible, doses delivered at recurrence were converted to equivalent doses in 2-Gy fractions (EQD_2) using the linear–quadratic model with an α/β ratio of 3 based on reported fractionation schedules. If the full dose information was incomplete, the EQD_2 values were estimated from the available data.

4. Results

4.1. Eligible studies

Of the 3299 unique citations generated from the search strategy, 52 full-text articles were retrieved for full-text assessment. Of these, only 24 met our inclusion criteria and were included in the final analysis. Fig. 1 shows the PRISMA flowchart of the study selection.

Across the 24 included studies, a total of 1307 patients were included (after accounting for overlapping cohorts from the two Arthur et al. trial publications, the dataset comprised approximately 1252 unique patients), representing cohorts from the USA (n = 15), Germany (n = 4), Italy (n = 2), Israel (n = 1), Canada (n = 1), and France (n = 1) (Supplementary Table S1 and S2). Most studies were retrospective single-institution analyses, with only two publications of a prospective Phase II trial (NRG Oncology/Phase 2 Clinical Trial) [19,20]. The study periods ranged from the mid-1980s to 2024, reflecting more than three decades of evolving practice. Most cohorts included women with ipsilateral breast or chest wall recurrence following prior lumpectomy and adjuvant whole-breast irradiation (WBI), although several studies also enrolled patients after postmastectomy RT or with locoregional recurrences involving lymph nodes. Most studies used photon-based therapy, except for three that employed proton beam therapy [21–23]. Across studies, the median age at recurrence was approximately 62

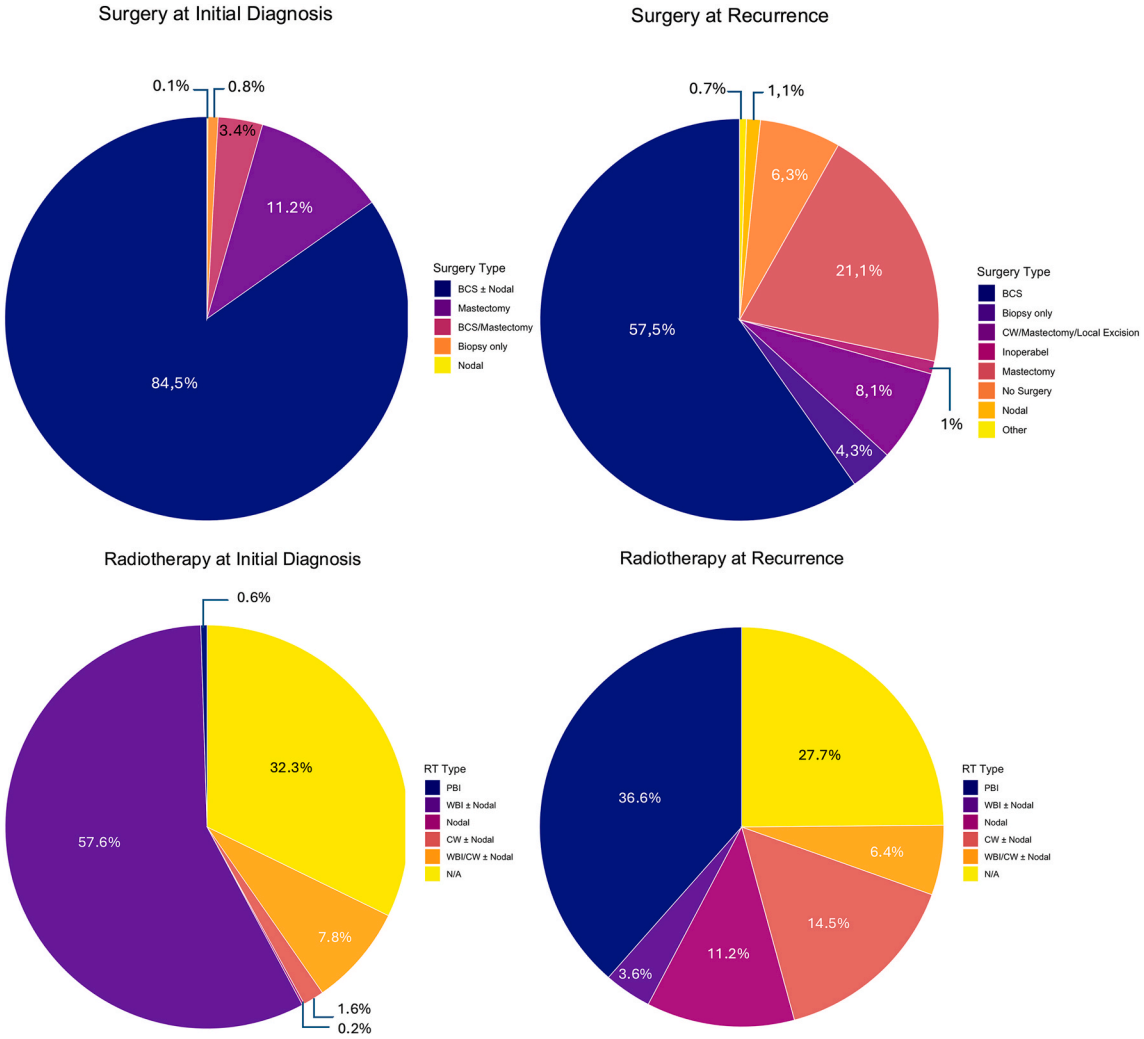


Fig. 2. The pie charts illustrate the distribution of surgery and radiation therapy approaches at initial diagnosis and at recurrence across the included studies. Abbreviations: BCS, breast conserving surgery; RT, radiation therapy; PBI, partial breast irradiation; WBI, whole-breast irradiation. Some categories represent study cohorts in which multiple treatment approaches were used across patients. "N/A" represents studies with no available information.

years (range, 30–99 years), whereas the median interval between the initial diagnosis and breast cancer recurrence was approximately 5.8 years. These intervals may not fully reflect current clinical practice, where longer intervals are often observed, and are likely influenced by the inclusion of older studies with shorter follow-up durations and earlier recurrence patterns. The median interval between the initial and second courses was approximately 7.4 years, with the longest reported median being 14 years. Although ReRT was usually delivered at the time of the first recurrence, patients in some studies experienced multiple local recurrences before receiving a second course of RT, which further prolonged the overall interval between courses compared to the time to first recurrence.

4.2. Initial diagnosis and first radiotherapy

At initial diagnosis, most patients had early stage, localized disease characterized by T1–T2 tumors, node-negative status in approximately two-thirds of cases, and absence of distant metastases (M0) (Table S1). At initial diagnosis, surgical management was dominated by breast-conserving surgery (BCS), performed in 84.5% of patients, while mastectomy was performed in 11.2% (Fig. 2). Across studies, the total radiation dose delivered during the initial course of therapy predominantly ranged between 45 and 66 Gy, typically administered in fractions of 1.8–2 Gy over 25–33 sessions (Table S2). At initial treatment, RT mostly consisted of WBI with or without regional nodal irradiation, which was reported in 57.6% of patients. A substantial proportion of studies (32.3%) did not provide detailed information on the initial volumes (Fig. 2). Regarding treatment modalities, earlier studies primarily used 2D or 3D-conformal radiotherapy (3D-CRT) with tangential photon fields, whereas later reports incorporated intensity-modulated (IMRT/VMAT) and proton-based techniques. Only three studies explicitly reported the definitions of clinical and planning target volumes [24–26].

4.3. Study characteristics at recurrence

Across studies, most recurrences were confined to the ipsilateral breast or chest wall, with regional nodal or distant involvement reported less frequently (Table S1 and S2). Other tumor characteristics are shown in Table S1. The median tumor size ranged from 0.8 to 4.5 cm, with most studies reporting T1–T2 recurrences, and most patients were node-negative with non-metastatic disease (M0) at the time of recurrence. Recurrences were largely hormone receptor–positive, with ER positivity in 65–80%, PR positivity in 50–65%, HER2 positivity in 5–20%, and triple-negative disease in 10–20%. Notably, these pathological characteristics are broadly consistent with those observed in primary tumors, which may limit the clinical relevance of the traditional distinction between true recurrence and new primary disease.

Endocrine therapy was administered in 40–70% of HR-positive patients. Systemic therapy was administered to 20–60% of patients, either as adjuvant therapy or in combination with ReRT. At locoregional recurrence, re-BCS remained the most common surgical strategy but decreased to 57.5%, whereas the proportion of patients who underwent mastectomy increased to 21.1% (Fig. 2). Notably, a substantial minority of patients were managed without standard curative surgery at recurrence, including no surgery (6.3%), biopsy-only procedures (4.3%), and chest wall or local excision (8.1%), while nodal-only surgery (1.1%) and inoperable disease (1.0%) were uncommon.

4.4. Reirradiation technique

At recurrence (Fig. 2), partial breast irradiation (PBI) was the most frequently applied treatment, accounting for 36.6% of cases. Chest wall with or without regional nodal irradiation was performed in 14.5% of patients, while combined whole-breast/chest wall with regional nodal irradiation accounted for 11.9% of patients. Nodal-only irradiation was applied in 6.4% of patients, whereas whole-breast irradiation with or without regional nodal RT was uncommon (3.6%). Information on volumes at recurrence was unavailable in 24.9% of the cases. Across studies, the median dose ranged from 40 to 55 Gy (range between 30 and 70 Gy). Most studies employed conventional fractionation with 1.8–2 Gy per fraction over 25–28 fractions of treatment. Hyperfractionated regimens, most commonly 45 Gy delivered in 1.5 Gy twice-daily fractions for 30 sessions, were reported in four studies [19,20,22,27], reflecting the schedule in RTOG 1014. A smaller subset of newer studies used hypofractionation regimes (ranging from 2.66 to 3 Gy/fraction), reflecting the growing interest in shorter regimens [28–31]. When studies were stratified into predefined eras representing clinically relevant changes in oncologic care (early, transition, contemporary), a significant decline in median EQD_2 over time was observed ($r = -0.4$, $p = 0.038$), decreasing from 48.6 Gy (≤2009) to 46.6 Gy (2010–2017) and 43.2 Gy (2018–2024). This trend is accompanied by increasing variability in more recent studies, indicating a shift away from uniform conventional dosing toward more heterogeneous and often lower-dose regimens. Fig. 3 illustrates the distribution of EQD_2 at recurrence across individual studies. Reirradiation following second breast-conserving surgery is marked separately (denoted by "+"), highlighting its distinct clinical context compared with studies including mixed or post-mastectomy cohorts. Across all studies, moderate-dose strategies predominate; however, substantial heterogeneity in dose selection, target volumes, and treatment approaches is evident. This variability likely reflects the inclusion of studies spanning more than three decades, during which radiotherapy techniques, imaging, and systemic therapies have evolved considerably. Consequently, cross-study comparisons and the derivation of generalizable dose recommendations remain limited. Photon-only was the most frequently reported modality (33.3%), followed by mixed-modality (20.8%). Electron- and proton-only techniques accounted for 12.5% and 16.7% of studies, respectively, while the treatment modality was not specified in 16.7% of cases.

Cumulative dose reporting was sparse in the studies. Where available, cumulative physical doses after initial and recurrent treatment were typically around 100–110 Gy, while cumulative EQD_2 ($\alpha/\beta = 3$) generally ranged from 78 to 120 Gy, with reported medians around ~100 Gy.

4.5. Disease control and overall survival

The oncologic outcomes after ReRT were heterogeneous, reflecting substantial variations in patient selection, treatment intent, disease burden, and duration of follow-up. The median follow-up duration was 22 months, with follow-up reported for over 14 years (Table S3). Local control (LC) after ReRT was generally favorable across studies, although the results varied depending on the treatment intent, disease burden, and follow-up duration. The reported 1-year rates ranged from 60% to 100%, and the 2-year rates from 50% to 90%. Long-term results have shown 5-year local control rates between 59% and 100%, with the most durable responses observed in patients treated with curative intent or microscopic residual disease (Table S3). In contrast, patients with gross or palliative disease demonstrated lower 2-year LC, typically 57–74%. Long-term LC was reported by Sellam in 2019, with 5-, 10-, and 14-year LC rates of 100%, 97.8%, and 95.8%, respectively, highlighting the feasibility of durable control after repeat irradiation [32]. Overall, these findings indicate that ReRT can achieve high rates of durable LC (≥80%) in carefully selected patients, particularly when performed with curative intent and conformal techniques.

Data on distant metastasis-free survival (DMFS) were inconsistently reported across studies. Among those providing information, the 2-year DMFS ranged from 59% to 93%, and the 3-year DMFS from 60% to 93%, with higher values observed in patients treated with curative intent than in palliative cohorts (Table S3). The 5-year DMFS was available in a few long-term studies and remained favorable, between 70% and 95% in

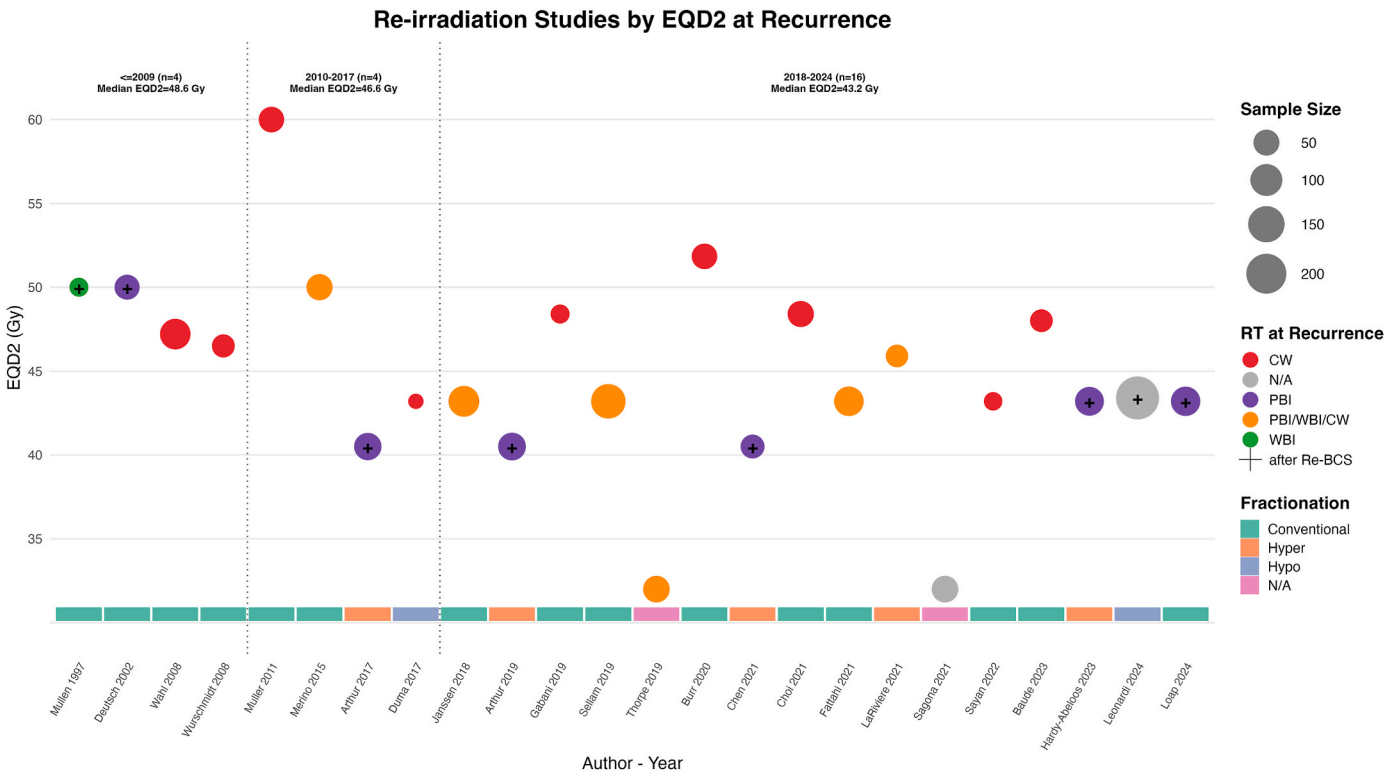


Fig. 3. Overview of included reirradiation studies according to the equivalent dose in 2-Gy fractions (EQD_2) at recurrence. Each study is represented by a bubble positioned according to its median EQD_2 at recurrence. Vertical dotted lines delineate predefined eras reflecting clinically relevant changes in oncologic care (≤2009, 2010–2017, 2018–2024). Bubble size reflects the study sample size, and color indicates the radiotherapy modality at recurrence (whole-breast (WBI), partial-breast (PBI), chest wall (CW), combined modalities within a study (PBI/WBI/CW) or N/A, not known). Fractionation category (conventional, hypofractionated (Hypo), or hyperfractionated (Hyper), or not reported (N/A)) is indicated by the color stripe adjacent to the study labels. EQD_2 values were calculated from the reported total dose at recurrence and fractionation using an α/β ratio of 3 Gy. When fractionation details were incomplete, EQD_2 was estimated using the most frequently reported fractionation schedule within the study. For fractionation category, the most frequently applied fractionation scheme within each study was used when multiple schemes were reported. Studies by Sagona (2021) and Thorpe (2019) did not report total dose or fractionation and are therefore positioned at the beginning of the x-axis. A plus symbol (+) identifies studies in which reirradiation was performed following second breast-conserving surgery (re-BCS). Studies without this annotation include patients treated after mastectomy or mixed cohorts comprising both post-mastectomy and post–breast-conserving scenarios. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

selected populations.

Overall survival (OS) outcomes were highly variable, reflecting the heterogeneity of patient selection, disease stage, and treatment intent. The reported 1-year OS ranges from 60% to 96%, with most contemporary studies demonstrating >70% survival at 1 year. Two-year OS rates typically ranged between 65% and 94%, whereas the 5-year OS varied from 59% to 100%. The most favorable outcomes were observed in patients treated with curative intent and localized disease, with a 5-year OS exceeding 90% in several studies. In contrast, studies including patients with metastatic or palliative disease reported substantially lower survival, with a 2-year OS between 17% and 50%. Long-term data from selected cohorts showed a 10-year OS of approximately 63–98% and a 15-year OS of 46%.

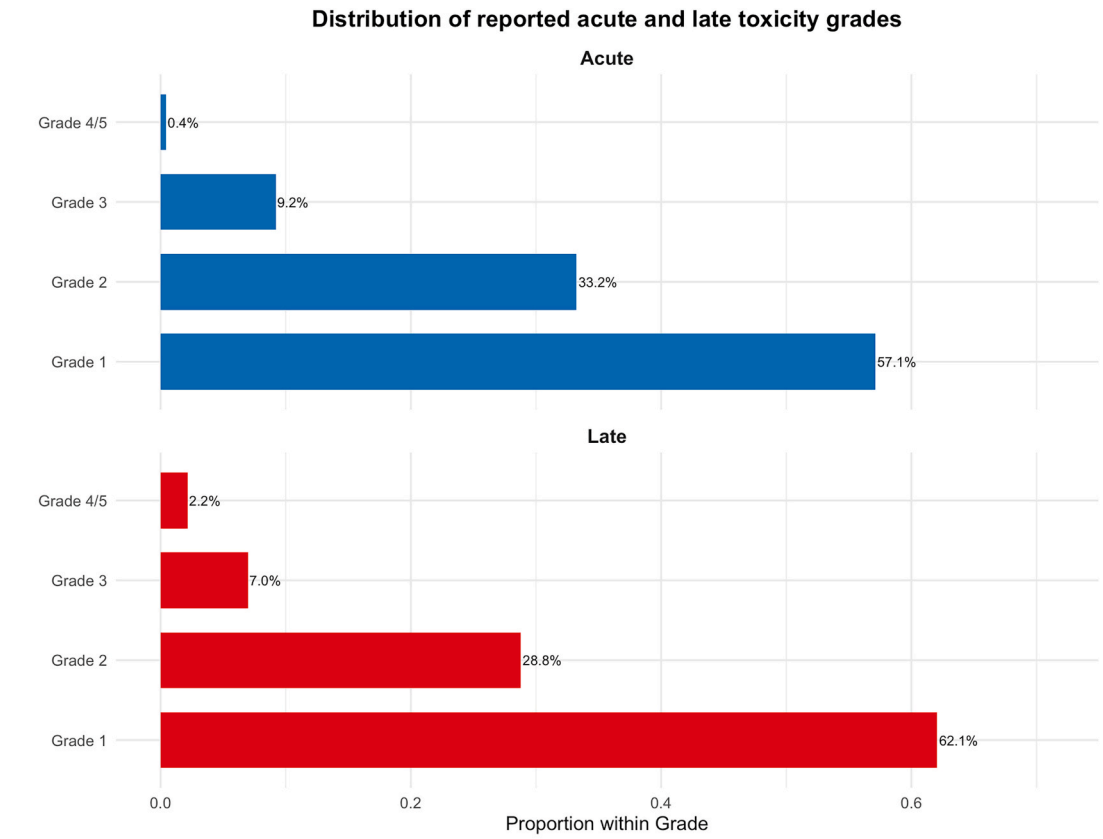
4.6. Acute and late toxicities

Across the included studies, a total of 1284 graded toxicity events were reported, with the distribution of toxicity grades differing between acute and late phases (Fig. 4A). Grade 1 toxicities (59.0% of all graded events) were the most frequently reported, accounting for 56.7% of all acute toxicities (n = 385) and 61.7% of all late toxicities (n = 373). Grade 2 toxicities comprised 33.0% of acute (n = 224) and 28.6% of late events (n = 173), corresponding to 30.9% of all toxicities (n = 397). Grade 3 events were less common, comprising 8.8% of all reports, accounting for 9.9% of acute (n = 67) and 7.6% of late toxicities (n = 46), with acute cases primarily involving severe dermatitis followed by fibrosis, lymphedema, breast pain and late cases most often related to fibrosis or telangiectasia. Severe Grade 4–5 toxicities were rare (1.3%), representing 0.4% of acute events (n = 3) and 2.2% of late events (n = 13), limited to severe dermatitis/fibrosis, one case of myocardial infarction, and nine cardiac-related deaths from an observational study [33,34]. These findings should be interpreted cautiously, as limited comorbidity data prevent assessment of causality. When categorized by type of toxicity (Fig. 4B), acute toxicities were most frequently dermatologic (dermatitis, desquamation, necrosis, ulceration, induration), pain syndromes (breast/chest wall pain), pulmonary events (pneumonitis), and fatigue. Late toxicities were dominated by fibrotic reactions, skin changes (telangiectasia, pigmentation changes, seroma formation), lymphatic complications (lymphedema), and skeletal sequelae (rib fracture, osteonecrosis). Neurological and cardiac toxicities, such as brachial plexopathy and pericarditis or myocardial injury, were infrequent.

When interpreting these findings collectively, it should be emphasized that the inclusion of studies employing heterogeneous reirradiation techniques, dose–fractionation schedules, and target volumes likely contributes to variability in reported toxicity rates, particularly for late effects, and limits cross-study comparability.

4.7. Patient-reported outcomes

Only a few studies explicitly assessed patient perspectives on cosmetic or quality-of-life outcomes. The NRG Oncology RTOG 1014



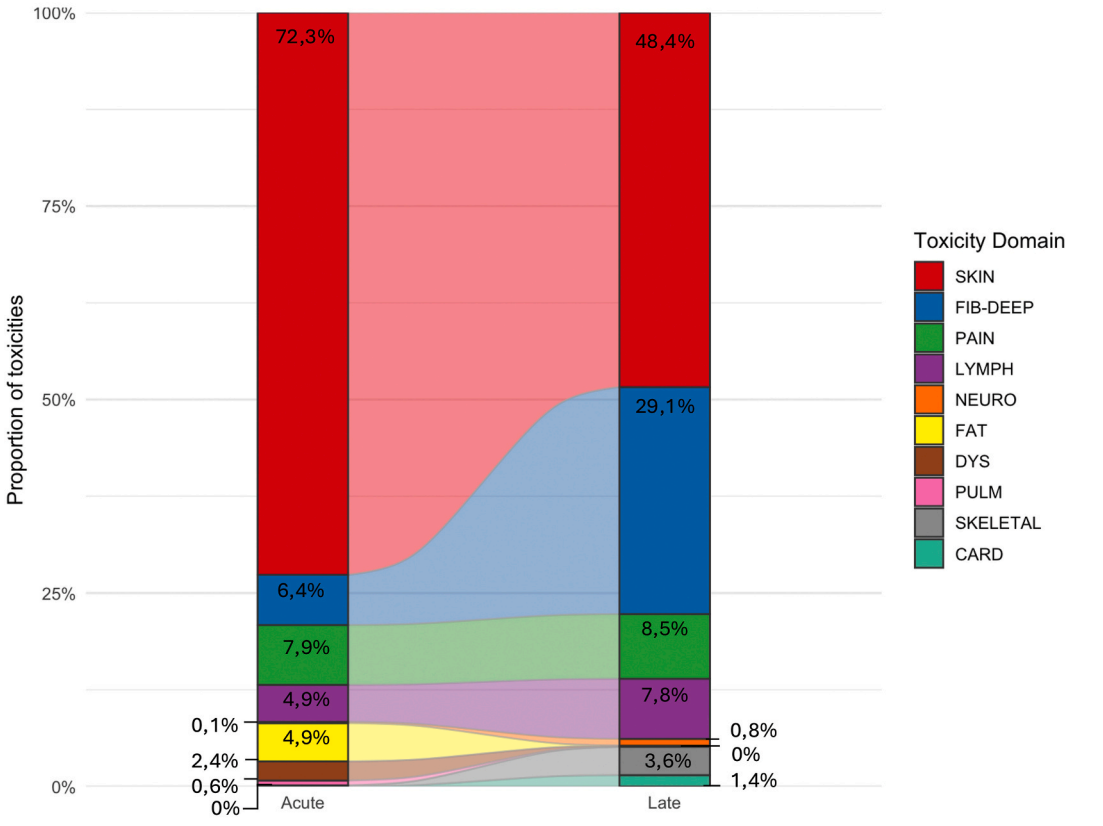


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Fig. 4. A) Distribution of reported acute and late toxicity grades across included studies (n = 1284 events) on radiotherapy at recurrence. Bar plots show the proportions of reported adverse events by severity grade (Grade 1–5 CTCAE) for acute (blue) and late (red) toxicities. B) Plot illustrating the distribution of acute and late toxicities by domain after breast reirradiation. Each vertical bar represents the proportion of all reported toxicity events across studies (acute vs late), and the height of each colored stratum corresponds to the relative contribution of a specific domain. Connecting flows visualize domain changes from the acute to the late toxicities. Domains: SKIN (radiodermatitis, moist desquamation, ulcerations, necrosis, hyperpigmentation, telangiectasia, seroma, cellulitis), FIB-DEEP (deep tissue fibrosis/induration/atrophy/restricted motion), PAIN (localized or regional pain), LYMPH (lymphedema), NEURO (neurological symptoms, plexopathy), FAT (fatigue), DYS (dysphagia), PULM (pneumonitis), SKELETAL (rib fracture, osteonecrosis), and CARD (cardiac events, pericarditis, myocardial infarction). Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

trial prospectively included cosmesis as a secondary endpoint, recognizing its importance for treatment evaluation, although results have not yet been fully reported [20]. In Sayan et al. [35], 91% of patients reported favorable cosmetic outcomes, with most rating results as excellent or good. Two other studies [36,37] included qualitative, physician-reported assessments of cosmesis and found mostly good to excellent results among patients achieving local control. Similarly, Leonardi et al. reported that cosmetic outcomes were rated as excellent or good in approximately 60% of cases by both physicians and patients [29]. Together, these findings highlight a major evidence gap and emphasize the need for future trials to systematically incorporate patient-reported outcome measures (PROMs) and standardized cosmetic assessments to better capture the patient-centered impact of breast.

4.8. Quality of the studies

The median NOS score across non-randomized studies was 5 out of 9 (range, 4–6), reflecting overall moderate methodological quality (Table S4). Most studies included representative patient cohorts, provided clear documentation of exposure, and reported outcomes using well-defined assessment methods. However, the majority lacked a non-exposed comparator group and did not adjust for potential confounding factors. In addition, less than half of the studies had short or insufficient follow-up durations (<2 years), limiting the reliability of long-term outcome evaluation. The prospective Phase II clinical trials were assessed separately using the ROBINS-I tool and demonstrated a low to moderate overall risk of bias.

4.9. Ongoing clinical trials

We identified ten actively recruiting trials at clinicaltrials.gov investigating strategies for breast tumour recurrence following prior (Table S5). Most studies focus on PBI using either external beam photon therapy or proton therapy, typically delivered in hypofractionated or ultra-hypofractionated schedules. Seven of the trials (NCT06954623, NCT05772390, NCT06129747, NCT06640881, NCT05592938, NCT06362616, NCT06867484) specifically evaluate PBI approaches, with total doses ranging from 26 Gy in 5 fractions to 40 Gy RBE (Relative Biological Effectiveness) in 15 fractions. Predominantly being Phase II prospective studies, these studies assess treatment-related toxicity (acute or late) and cosmetic outcomes as primary endpoints, with secondary objectives including distant metastasis-free survival and quality of life. Two preoperative PBI protocols (NCT06640881, NCT06362616) explore ReRT before repeat BCS, aiming to optimize tumor control and tissue response while minimizing fibrosis and cosmetic impairment. Additionally, a large multicenter proton therapy study (NCT05313191) investigates pencil-beam scanning proton for various previously treated malignancies, including breast cancer, comparing outcomes to photon therapy. Enrollment sizes vary substantially, from small feasibility trials (20–30 participants) to large multicenter initiatives. Collectively, these studies reflect growing international interest in refining conformal, image-guided, and particle-based techniques for locally recurrent breast cancer. However, the optimal dose and fractionation schedule for breast ReRT remain to be defined, and the results of these trials are expected to inform future treatment guidelines. At the same time, PBI itself is a relatively new modality that has gained increasing attention in recent years. The reported rates of recurrence following PBI remain variable, as no prospective study to date has provided conclusive long-term evidence.

5. Discussion

5.1. Summary of existing evidence

In this systematic review of 24 mostly retrospective studies, EBreRT for locoregional breast cancer recurrence was found to be a feasible treatment approach across several clinical indications, with acceptable toxicity when applied in carefully selected patients. The most robust evidence pertains to patients with in-breast tumor recurrence treated with re-BCS, where adjuvant partial-breast reirradiation has emerged as a breast conserving alternative to mastectomy. In this curative-intent, regimens around 45 Gy, as established by RTOG 1014 [24], consistently report excellent control (~95% at 5 years) and low rates of severe toxicity (<10%), findings reproduced in contemporary institutional studies. Hypofractionated schedules, such as 40 Gy in 15 fractions or 30 Gy in 5 fractions are increasingly being adopted in recent years as convenient alternatives to the traditional twice-daily 45 Gy regimen. Evidence from primary PBI trials (such as IMPORT LOW, Florence) and small retrospective studies suggests that these shorter courses offer acceptable toxicity and promising [38,39]. Beyond the re-BCS setting, EBreRT has also been applied to other locoregional indications, including chest-wall, regional nodal, unresectable or palliative recurrences, where the evidence is more heterogeneous and largely retrospective. Overall, despite these encouraging clinical results and growing use of ReRT in practice and guidelines, the supporting evidence remains limited, derived from small heterogenous, single-institutional cohorts. Consequently, while implementation of evidence is substantial, guideline recommendations rest on low-level evidence. Robust multicenter trials with standardized protocols, uniform dose constraints, long term follow-up, and inclusion of patient-reported outcomes are urgently needed to define best practice and ensure safe, evidence-based application of breast ReRT.

5.2. Heterogeneity of included studies

The included studies were highly heterogeneous across methodological and clinical domains. Treatment intent varied substantially, ranging from curative-intent cohorts with microscopic in-breast recurrences to patients treated for gross chest-wall disease or palliative indications. Treatment regimens and target volumes were inconsistently defined, ranging from partial-breast, whole-breast, and chest-wall to regional nodal irradiation. Follow-up duration (12 months to >14 years) and outcome definitions were also highly variable. This heterogeneity in patient selection, technical approaches, and reporting precluded quantitative synthesis and highlights the need for standardized trial designs and uniform reporting in breast research. Compared with other disease sites such as glioma or head and neck cancer, breast cancer reirradiation remains less systematically studied, underscoring the need for coordinated research efforts [40].

5.3. Lack of patient-reported outcomes

Patient-reported outcomes after ReRT were markedly underexplored. Only a few studies evaluated cosmetic outcomes or quality of life, with most patients reporting good to excellent cosmesis and acceptable functional outcomes. No study used standardized or validated PROM instruments underscoring a critical evidence gap. This lack of robust patient-centered data is particularly relevant, given that cosmesis, breast preservation, and post-treatment comfort are key determinants in the decision-making process for repeat breast-conserving therapy. Without standardized assessment tools, the long-term functional and psychosocial impact of reirradiation remains insufficiently characterized. Future studies should therefore incorporate validated PROMs to enable a comprehensive evaluation of patient-centered outcomes. In parallel, patient preferences should be systematically integrated into shared decision-making, as emphasized by recent international survey data demonstrating the central role of patient values, expectations, and information needs in treatment selection [41].

5.4. Repeat BCS with reirradiation as an alternative to mastectomy

Although single-arm prospective trials (e.g. NRG/RTOG 1014) support the feasibility and safety of external-beam partial-breast reirradiation, there are currently no completed randomized or other prospective controlled trials directly comparing repeat BCS with mastectomy or with repeat BCS alone. In this context, the highest level of available comparative evidence is derived from matched-pair and propensity score–adjusted analyses, which aim to mitigate selection bias inherent to retrospective datasets. Notably, several matched-cohort studies have demonstrated comparable oncologic outcomes between repeat BCS plus reirradiation and mastectomy in carefully selected patients, including similar local control and survival endpoints, while preserving the breast [4,12,42–44]. However, despite these methodological refinements, residual confounding cannot be fully excluded, and patient selection remains a critical determinant of outcomes. Therefore, while the accumulating matched-pair evidence supports the oncologic safety of repeat breast-conserving approaches in selected populations, true equivalence cannot be definitively established in the absence of randomized data. The conduct of such trials remains challenging due to ethical considerations, strong patient preferences, and the large sample sizes required. Ongoing prospective studies, including preoperative external beam PBI (REPEAT) and proton-based trials, are expected to provide higher-quality evidence, although their results are not yet available [45].

To date, the most robust evidence for second breast-conserving treatment of ipsilateral breast tumor recurrence derives from brachytherapy (the evaluation of brachytherapy-based approaches was not the focus of the present work). The large GEC-ESTRO multicenter study including 1327 patients reported grade $\geq$3 toxicity in 9.5%, predominantly cutaneous and subcutaneous fibrosis, with 5- and 10-year cumulative incidences of mastectomy for second in-breast recurrence or treatment-related complications of 3.1% and 6.7%, respectively, demonstrating durable local control with acceptable toxicity [12]. However, brachytherapy requires substantial expertise and dedicated infrastructure and is invasive and time-intensive, limiting its availability to specialized centers and selected patients. Other forms of radiation therapy such as IORT, delivering a single-dose boost to the tumor bed at the time of re-excision, has been shown from small retrospective studies, with 5-year LC around 89-92% and low rates of significant toxicity [46–48]. Elfgen et al. compared BCS and IORT in 26 patients vs those treated with mastectomy and reconstruction (87 patients) and found no significant difference in disease-free survival between groups [8]. While selected single-institution studies have reported acceptable and toxicity outcomes, the available evidence remains limited and non-comparative.

In parallel, a key limitation across studies is the lack of validated prognostic factors to guide patient selection for second breast-conserving treatment. Except for one study [29], none of the included investigations performed dedicated analyses to identify predictors of outcome after reirradiation, leaving clinical decision-making largely dependent on expert opinion and heterogeneous guideline recommendations.

The recently proposed TAM score by GEC-ESTRO represents a promising step toward structured patient selection, incorporating clinical and pathological factors to stratify outcomes after second breast-conserving treatment. While validated in cohorts treated with brachytherapy-based reirradiation and shown to be relevant in patients undergoing mastectomy [13], it has not been specifically evaluated for EBRT, where treatment volumes, dose distributions, and toxicity profiles differ substantially. As a result, no evidence-based selection tool currently exists for EBRT, and treatment decisions remain individualized.

This uncertainty in patient selection is further highlighted by emerging data suggesting that a small subset of low-risk patients may achieve favorable outcomes with repeat breast-conserving surgery alone, without reirradiation. In a recent retrospective study, Gaillard et al. reported favorable outcomes in patients with small, node-negative, hormone receptor–positive recurrences treated with surgery alone, with low recurrence rates and no breast cancer–related mortality [49]. However, given the retrospective design, limited follow-up, and strict selection criteria, this approach is not generalizable and requires prospective validation. External beam reirradiation therefore remains an important component of breast-conserving strategies for most patients, particularly those with higher-risk features.

Overall, there is still no consensus on the preferred modality (brachytherapy, IORT, EBRT) or on dose–fractionation. Each technique has advantages and limitations, and access varies across centers. National surveys such as the Dutch Walstra survey, the UK MARECA study, and recommendations from Italian (AIRO) and German (DEGRO) societies show substantial heterogeneity in how clinicians approach second recurrences [5,11,15,50]. This variability underscores the lack of strong comparative evidence and consensus.

5.5. External-beam reirradiation beyond repeat breast-conserving surgery

Patterns of care in the present review demonstrate that at recurrence is often extended beyond breast-limited treatment, with roughly one third of patients receiving chest-wall irradiation with or without regional nodal fields or nodal-only irradiation. Collectively, these findings indicate that a substantial proportion of ReRT is delivered in non–breast-conserving contexts, involving larger target volumes and more heterogeneous treatment strategies. These real-world treatment patterns align with DEGRO recommendations [5], which support individualized ReRT in previously irradiated patients at high risk of further locoregional recurrence or with unresectable disease, considering prior radiation interval, late toxicity, disease extent, and concurrent systemic therapy. Notably, these recommendations are largely based on retrospective evidence and expert consensus, reflecting the lack of prospective trials in non–breast-conserving ReRT settings.

5.6. Strengths and limitations

This systematic review provides a comprehensive synthesis of current evidence on EBreRT for locoregional breast cancer recurrence, summarizing more than three decades of clinical experience. Its strengths include the inclusion of diverse modalities and fractionation schedules, and integration of recent prospective and ongoing clinical trials to contextualize evolving practice. However, most included studies were retrospective, single-institution analyses with small sample sizes, and moderate methodological quality. Marked heterogeneity in patient selection, including studies comprising for e.g. patients treated after second breast-conserving surgery or mastectomy, together with variability in treatment techniques spanning three decades and differences

in toxicity grading, precluded meta-analysis and limited cross-study comparability. Reporting cumulative doses, organ-at-risk constraints, and patient-reported outcomes was mostly incomplete, and only one study performed multivariable analyses to identify prognostic factors. These limitations highlight the need for standardized, prospective trials to refine patient selection and optimize dose–response and toxicity models in breast.

5.7. Future directions and ongoing initiatives

Growing number of coordinated initiatives are emerging to strengthen the evidence base for EBreRT in locoregional breast cancer. In Germany, a coordinated initiative is currently underway to systematically analyze EBreRT outcomes for locoregional breast cancer recurrence, with the long-term vision of extending this effort to a European, multicenter level. Such an initiative would enable robust data collection across institutions and facilitate more reliable comparative analyses. A propensity-matched comparison with mastectomy outcomes from the large GEC-ESTRO database appears feasible and would substantially strengthen the evidence base, given the absence of prospective controlled trials. While a Phase III randomized trial comparing repeat breast-conserving surgery plus EBreRT versus mastectomy would represent the ideal design to determine oncologic equivalence, this seems challenging due to ethical considerations, low event rates, and the large sample sizes that would be required [41]. Beyond these activities, other international initiatives have recently been launched. The EORTC ReIrradiate Registry and the ReCog Consortium are developing large, prospective, registry-based infrastructures to systematically capture practice and outcomes across tumor sites, including breast cancer [51]. Coordinated registry-based analyses therefore represent the most pragmatic and ethically acceptable approach to improving the evidence base for EBreRT in this setting.

In parallel, emerging approaches such as artificial intelligence and radiomics may further enhance patient selection for reirradiation. By integrating clinical, imaging, and dosimetric data, these tools have the potential to improve risk stratification, predict treatment response and toxicity, and support more individualized decision-making. Although still investigational, such approaches may play an important role in refining indications for reirradiation in the future.

6. Conclusion

The current evidence base for EBReRT in locoregional breast cancer recurrence is insufficient to define optimal dose regimens, treatment intervals, or patient selection criteria. Available studies are predominantly retrospective and heterogeneous, precluding definitive conclusions on oncologic efficacy; however, no unexpected toxicity patterns were identified across techniques, fractionation schemes, or clinical settings. Importantly, the oncologic safety of EBReRT combined with repeat breast-conserving surgery as an alternative to mastectomy cannot be established from the existing literature. Until more robust prospective or comparative data are available, oncologic outcomes and selection criteria for this approach should be interpreted cautiously and, where necessary, extrapolated from larger propensity-based brachytherapy studies.

Data availability statement

All data underlying this study were derived from previously published articles and are presented within the manuscript and its supplementary materials. Further details of the extracted dataset are available from the corresponding author upon reasonable request.

Ethics approval

Ethical approval and informed consent were not required because the study is based exclusively on previously published data, in accordance with institutional and national guidelines.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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During the preparation of this work the author(s) used ChatGPT (GPT-5) to improve language and stylistic editing. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

Appendix A. Supplementary data

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