Radiation Oncology

REVIEW

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Advances in breast cancer treatment: a systematic review of preoperative stereotactic body radiotherapy (SBRT) for breast cancer

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Abstract

Breast conserving treatment typically involves surgical excision of tumor and adjuvant radiotherapy targeting the breast area or tumor bed. Accurately defining the tumor bed is challenging and lead to irradiation of greater volume of healthy tissues. Preoperative stereotactic body radiotherapy (SBRT) which target tumor may solves that issues. We conducted a systematic literature review to evaluates the early toxicity and cosmetic outcomes of this promising treatment approach. Secondary we reviewed pathological complete response (pCR) rates, late toxicity, patient selection criteria and radiotherapy protocols. We retrieved literature from PubMed, Scopus, Web of Science, Cochrane, ScienceDirect, and ClinicalTrials.gov. The study adhered to the PRISMA 2020 guidelines. Ten prospective clinical trials (7 phase II, 3 phase I), encompassing 188 patients (aged 18–75 years, cT1-T3 cN0-N3 cM0, primarily with ER/PgR-positive, HER2-negative status,), were analyzed. Median follow-up was 15 months (range 3–30). Treatment involved single-fraction SBRT (15-21Gy) in five studies and fractionated (19.5–31.5Gy in 3 fractions) in the rest. Time interval from SBRT to surgery was 9.5 weeks (range 1–28). Acute and late G2 toxicity occurred in 0–17% and 0–19% of patients, respectively, G3 toxicity was rarely observed. The cosmetic outcome was excellent in 85–100%, fair in 0–10% and poor in only 1 patient. pCR varied, showing higher rates (up to 42%) with longer intervals between SBRT and surgery and when combined with neoadjuvant systemic therapy (up to 90%). Preoperative SBRT significantly reduce overall treatment time, enabling to minimalize volumes. Early results indicate excellent cosmetic effects and low toxicity.

Keywords Breast cancer, Breast neoplasm, Breast tumor, Stereotactic ablative body radiotherapy, Stereotactic body radiation therapy, SBRT, SABR, Preoperative, Neoadjuvant, Tumor bed

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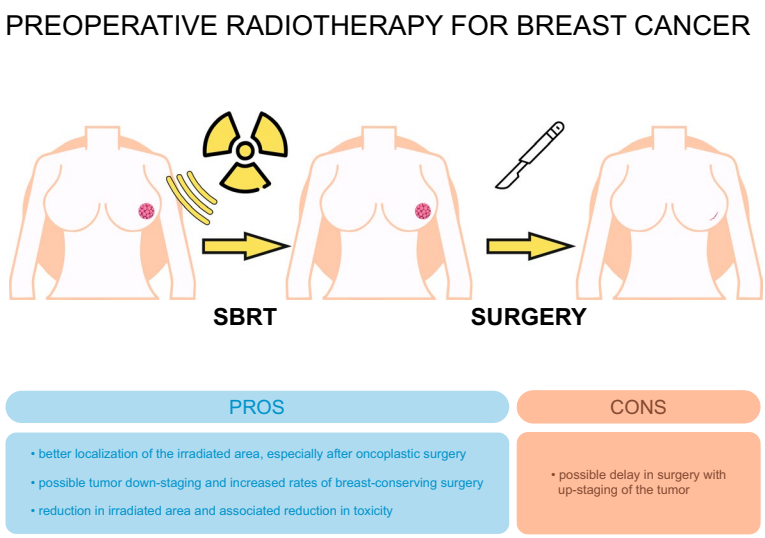
Graphical abstract



Background

The standard of care for breast cancer treatment is postoperative radiotherapy following breast-conserving surgery. However, accurately defining the tumor bed in this context is challenging and often leads to the irradiation of a greater volume of healthy tissues. Preoperative stereotactic body radiotherapy (SBRT) offers a promising alternative by enabling precise targeting of the tumor itself, as opposed to postoperative approaches that focus on the tumor bed. The precision of preoperative SBRT allows for a decreased target volume, reducing early treatment toxicity and enhancing pathologic complete response rates (pCR). Current data from cohort phase I and II trials provide valuable insights into early toxicity. Additionally, the paradigms of treatment sequences are evolving, with neoadjuvant treatments, such as systemic therapy, gaining prominence in the management of breast cancer. Therefore, determining the optimal timing for radiotherapy and understanding its impact on pCR and toxicity are key areas for future research. Given these advancements, SBRT may also become a standard neoadjuvant treatment option.

Introduction

In 2020, approximately 2.3 million cases of breast cancer were diagnosed in women worldwide and approximately 685,000 deaths were recorded. In Central and Eastern Europe, about 160 000 new cases were recorded. Out of 185 in 157 countries, breast cancer was the most frequently diagnosed cancer. It is estimated that by 2040 the number of diagnosed breast cancers will increase by more than 40%, i.e. by approximately 3 million cases per year [1]. A systematic review by Dafni et al. shows that Poland, together with Bulgaria, Slovakia and Romania, has been showing an increasing tendency in the incidence of breast cancer since 2010 compared to other countries in Central and Eastern Europe [2]. Prognosis and targeted treatment are tailored to the breast cancer biological subtype [3–5]. The treatment of early-stage breast cancer is based on an individual approach that depends on the molecular characteristics of the tumor, the stage, general condition and patient preferences, as recommended in the ESMO (European Society for Medical Oncology) and NCCN (National Comprehensive Cancer Network) guidelines [6, 7]. The classic treatment management for early breast cancer includes systemic therapy (if indicated), breast-conserving surgery, and then radiotherapy to the entire breast ± regional lymph nodes ± boost to the tumor bed, or partial breast irradiation (PBI) in selected low risk cases. Despite its effectiveness, this treatment concept can be associated with a certain degree of toxicity in individual cases, which could have a negative impact on quality of life in the perspective of long-term survival, which is why new solutions are being sought [8, 9]. Changing the classical sequence of up-front surgery in the treatment of breast cancer has been already applied in the setting of systemic therapy. Neoadjuvant chemotherapy is used in case of locally advanced disease to obtain higher rates of pCR which results in higher rates of breast preservation and nowadays is the mainstay of the treatment for many patients [10, 11]. A similar concept of neoadjuvant radiotherapy

was introduced over the last 10 years, however it has not yet gained widespread acceptance. This approach could have several advantages: better tumor volume identification, possible tumor downstaging with improved rates of breast preservation rates, improved cosmesis, shortening of treatment time, reduction of complication rates in patients requiring breast reconstruction. A growing number of reports indicate that preoperative radiotherapy for early-stage breast cancer significantly improves disease-free survival (DFS), and more importantly, results in a lower risk of side effects and better cosmetic outcomes [12]. One of the most promising modalities of radiotherapy is stereotactic ablative radiotherapy (SABR), which involves the delivery of a very high dose of radiation to the tumor volume with high precision using one or several fractions administered usually in 1 to 10 days [13]. SABR is a method used preoperatively that could potentially also eliminate or be an alternative to the subsequent surgical intervention, in well selected patients. It is an important goal in terms of patients' quality of life, but also makes it possible to reduce the health care costs and the time required for hospitalization and convalescence after treatment [14].

Based on these data, we conducted a systematic literature review to evaluate the outcomes of this promising treatment approach. We assessed toxicity, cosmetic outcomes, pathological complete response (pCR) rates, patient selection criteria, and radiotherapy protocols.

Materials and methods

Search strategy

We conducted a systematic review according to the Population, Intervention, Control, Outcome, Study Design (PICOS) method which is shown in Table 1. We followed the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

We searched five databases, namely PubMed, Scopus, Web of Science, Cochrane, ScienceDirect and ClinicalTrials.gov registry. An additional evaluation was conducted via citation searching from selected articles. Two blinded authors independently performed searches using the keywords: (breast cancer or breast neoplasm or breast tumor) and (stereotactic ablative body radiotherapy or stereotactic body radiation therapy or SBRT or SABR) and (neoadjuvant or preoperative or induction). In case of discrepancies, the third author verified the search. We identified potential studies and exported them to a reference management program (Mendeley Desktop) for inclusion based on title and abstract, and then the full article. The research involved an analysis of all studies published up to December 22, 2023.

Selection criteria

The inclusion criteria were as follows: (1) retrospective and prospective clinical trials with published results and (2) studies published in the English language.

Exclusion criteria were: (1) radiotherapy performed in postoperative setting only, (2) preoperative irradiation of the entire breast (3) non unifocal breast tumour (3) presence of distance metastases, (4) lack of access to the full text of the manuscript, (5) studies without results and unclear results (6) case reports, (7) review papers, (8) study protocols.

Data extraction

The extracted data consisted of the author, type of study, sample size, main endpoints, inclusion criteria, radiotherapy technique, contouring schema for gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV), dose and fractionation regimen, concomitant systemic treatment, doses to organs at risk (OARs), time from SBRT to surgery, rates of pCR, early and late toxicity, cosmesis analysis.

Results

During the initial database search found a total of 151 papers (49- Web of Science, 35—PubMed, 21- ScienceDirect, 16- Scopus, 14—Cochrane, 16- Clinicaltrials.gov). Before screening we have deleted 43 duplicates. In the next step, we excluded titles and abstracts that did not meet the inclusion and exclusion criteria (98 articles). We identified further 5 papers by searching for citations from the included articles. The full

Table 1 Study design according to the Population, Intervention, Control, Outcome, Study Design (PICOS) method

Population	Patients treated with preoperative stereotactic body radiotherapy (SBRT) for breast cancer
Intervention	SBRT to the primary tumor (fraction dose ≥ 5 Gy)
Control	Not applicable (the data will be pooled from single arm trials)
Outcome	Primary: early toxicity, cosmesis Secondary: rates of pathologic complete response (pCR), late toxicity
Study design	Any retrospective or prospective original studies describing clinical outcomes of patients treated with preoperative SBRT for primary breast cancer

text of the qualified articles was analyzed and a selection was made, after which 5 papers were excluded. Finally, 10 primary studies were included in the systematic review process (two studies on same cohort). Figure 1 shows the PRISMA 2020 flowchart with screening results. The list and characteristics of the included studies and their outcomes is shown on the Table 2. All 10 included studies have a prospective design. Two studies were a phase I dose escalation studies, one phase I feasibility study. Seven reports were phase II studies. All of the included studies were single arm and non-randomized [15–24]. The number of included patients was 188 and ranged from 6 to 36 among studies. Median follow up time was 15 (3–30) months.

Qualification criteria

The main qualification criterion for study inclusion was tumor diameter determined by magnetic resonance imaging (MRI) in all but one study by Tiberi et al. where computed tomography (CT) only was used [15–24]. Four studies included patients with a tumor size of ≤ 20 mm [15–17, 19]. Vasmel et al. also used this criterion for patients ≥ 50 years but for patients ≥ 70 years tumors up to 30 mm were also included [21, 22]. In the ROCK trial patients with tumors up to 25 mm were treated [18]. Older patients who were at least 50 years old were eligible for preoperative radiotherapy [15–19, 21, 22]. Bondieu et al. qualified patients aged 18 years and older. Their cohort also included patients with cT2-3 tumors and node positive (cN1) disease. A special feature of this study is that all patients of their cohort were not suitable for breast conserving surgery (BCS) [20]. Nine studies included low risk luminal A-like subtypes with ER or ER/PgR positive HER-2 negative and unifocal tumors [15–22, 24]. The inclusion criteria of the study of Horton et al. were absence of lymphovascular invasion (LVSI), ductal carcinoma in situ (DCIS) ≤ 2cm and low to intermediate grade tumors (G1-2) [19]. In contrast, Chen et al. included only triple negative breast cancer (TNBC) patients [23]. In this trial, inclusion criteria were patients aged 18–75 years with tumors ≥ 20 mm, mostly cT2 but also cT3, and cN0-N2 according to TNM [23]. In the Neocheck trial patients with cT2-3 cN0 and cT1b-3 cN1-3, with a tumor size of at least 15 mm were qualified [24]. Moreover, further inclusion criteria were a high-risk score in the MammaPrint genomic expression profiling test, high grade (G3) or a Ki67 of ≥ 15% [24]. In the SIGNAL trial an additional criterion for inclusion was a distance of ≥ 2 cm from the tumor to the skin and chest wall [15].

Target volumes definition and radiotherapy modalities

Gross tumor volume (GTV) was based on the planning CT with co-registered MRI [15, 17–24]. Tiberi et al. used only a planning CT only for GTV contouring [16]. The CTV was formed by adding an isotropic margin to the GTV which differed between the studies: 5 mm [15, 20], 10 mm [16], 15 mm [18–21, 22]. Liveringhouse et al. and De Caluwe et al. didn't report the details regarding the magnitude of the CTV margins [17, 24], while Chen et al. didn't include any information if any margins were added to the GTV [23]. The chest wall and pectoralis major muscle were excluded from the CTV in all studies, where CTV information was available. In the analysis of Meattini et al. and Bondiau et al. PTV were generated by adding 2–3 mm margin to the CTV [18, 20]. In their

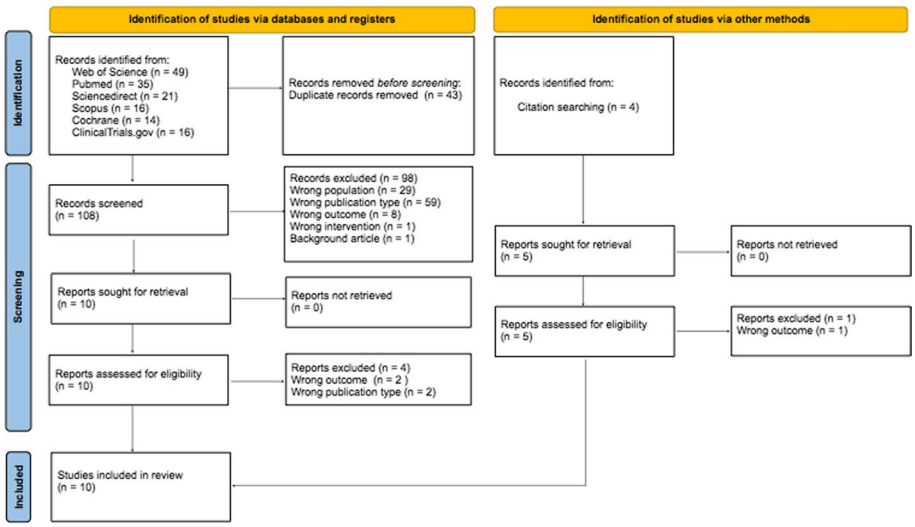


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram for the literature selection process

Table 2 Characteristic of selected studies for systematic review

	Guidolin et. al. [15]	Tiberi et. al. [16]	Liveringhouse et. al. [17]	Meattini et. al. [18]	Horton et. al. [19]	Bondiau et. al. [20]	Vasmel JE et. al. [21], [22]	Guanglei Chen et. al. [23]	De Caluwe et. al. [24]
Type of study	Phase II SIGNAL trial, prospective, single arm, non randomized	Phase II, prospective, single arm, nonrandomized	Phase II, prospective, single arm, nonrandomized	Phase II ROCK trial, prospective, single arm, non randomized	Phase I, dose escalation, prospective, single arm, nonrandomized	Phase I, dose escalation, prospective, single arm, non randomized	Phase II, prospective, single arm, non randomized	Phase II, prospective, single arm, non randomized	Phase I Neo-Checkray Trial, prospective, single arm, non randomized
Number of participants	27	10	20	22	32	25	36	10	6
Main endpoints	Feasibility, toxicity, cosmesis	Radiologic and pathologic response, toxicity	Radiologic and pathologic response	Pathologic response, toxicity, cosmesis	Radiologic response, toxicity, cosmesis	Toxicity, cosmetics, pathologic response, establishing maximum tolerable dose in combination with neoadjuvant therapy	Pathologic and radiologic response, toxicity, cosmesis	Pathologic complete resposne, objective resposne rate, residual cancer burden 0-I, safety	Feasibility of delivering SBRT, toxicity, cosmesis
Inclusion criteria TNM	Postmenopausal, unifocal, ≤ 20 mm, unifocal, ER positive, cN0 In initial ultrasound distance ≥ 2 cm between the lesion and the skin and the lesion and the chest wall	≥ 65 years, ≤ 20 mm, unifocal, ER positive, HER 2 negative, cN0, Grade1-2	≥ 50 years, Unifocal, ≤ 20 mm, ER positive, HER 2 negative, cN0	≥ 50 years, ER/PR positive, HER 2 negative unifocal, ≤ 25 mm, cN0	≥ 55 years, ER/PR positive, HER 2 negative, ≤ 20 mm, low/intermediate grade, no LVSI, DCIS ≤ 2cm, cN0	≥ 18 years, cT1-T3, cN0-N1, unifocal, not suitable for BCT	≥ 50 years, unifocal, ≤ 20 mm, ER positive, HER2 negative, cN0 or ≥ 70 years, unifocal, ≤ 30 mm, ER positive, HER2 negative, cN0	18–75 years, TNBC, cT2-T3N0-N2	≥ 18 years, Luminal B, Ki67 ≥ 15% or G3, MammaPrint high risk, cT2-3N0 or cT1b-3N1-3, size ≥ 1.5 cm
Contouring	GTV + 5 mm = CTV CTV + 5 mm = PTV	GTV + 10 mm = CTV CTV + 10 mm = PTV	GTV + 15 mm = CTV CTV + 3 mm = PTV	GTV + 15 mm = CTV CTV + 3 mm = PTV	GTV + 15 mm = CTV CTV + 3 mm = PTV	GTV + 5 mm = CTV CTV + 2 mm = PTV	GTV + 20 mm = CTV CTV + 3 mm = PTV	GTV, margins NR	GTV + margin NR

Table 2 (continued)

	Guidolin et. al. [15]	Tiberi et. al. [16]	Liveringhouse et. al. [17]	Meattini et. al. [18]	Horton et. al. [19]	Bondiau et. al. [20]	Vasmel JE et. al. [21], [22]	Guanglei Chen et. al. [23]	De Caluwe et. al. [24]
Concurrent systemic therapy	–	–	–	–	–	3 cycles of docetaxel (100 mg/m [2]), SBRT on 3 consecutive days during the second cycle but not in the chemotherapy days, 3 FEC cycles (fluorouracil 500 mg/m2, epirubicine 100 mg/m [2], and cyclophosphamide 500 mg/m [2]). Cycles q3w	Six patients (17%) -neoadjuvant endocrine started after NA-PBI	8 cycles of adebrelimab (20 mg/kg every 3 weeks). SBRT at the second cycle every other day, 6 cycles of nab-paclitaksel (125 mg/m [2] on 1st and 8th day) and carboplatin (area uder curve 6 mg/ml per min on 1st day) every 3 weeks since 3rd cycle	12 cycles of paclitaxel 80 mg/m [2] weekly then 4 cycles q2w dose dense doxorubicin-cyclophosphamide (60 mg/m [2] and 600 mg/m [2] respectively); then 5 administrations of durvalumab 1500 mg Every 5 weeks for five administrations q4w and 4 administrations oleclumab 3000 mg q2w for followed by q4w for 3 administrations SBRT given in week 4–5, followed by the week 5 systemic treatment
MRI coregistered to planning CT	+	–	+	+	+	+	+	+	+
System and Technique	LINAC/VMAT	LINAC/IMRT	LINAC/VMAT	Cybernife	LINAC/IMRT	Cyberknife	LINAC/VMAT	LINAC/IMRT	LINAC/VMAT
Dose fractionation schemas	21 Gy- 1 fraction	20 Gy-1 fraction	28.5 Gy- 3 fractions, 9.5 Gy daily	21 Gy- 1 fraction	15 Gy (n = 8), 18 Gy (n = 8), 21 Gy (n = 16) in 1 fraction	19.5 Gy (n = 3), 22.5 Gy (n = 3), 25.5 Gy, (n = 6), 28.5 Gy (n = 7), 31.5 Gy (n = 6)- 3 fractions q2d	20 Gy for GTV, 15 Gy for CTV-SIB—1 fraction	24 Gy- 3 fractions q2d	24 Gy- 3 fractions n consecutive days
Positioning	Surgical clip, cone-beam CT prone	Surgical clip, cone-beam CT supine	Surgical clip, cone-beam CT supine	Supine	Surgical clip, cone-beam CT prone	Supine	Surgical clip, cone-beam CT supine	NR	NR
Time from SBRT to surgery	1 week	11–13 weeks	6–8 weeks	2 weeks	10 days	19–23 weeks	6 months (n = 15), 8 months (n = 21)	21–23 weeks	16–20 weeks

Table 2 (continued)

	Guidolin et. al. [15]	Tiberi et. al. [16]	Liveringhouse et. al. [17]	Meattini et. al. [18]	Horton et. al. [19]	Bondiau et. al. [20]	Vasmel JE et. al. [21], [22]	Guanglei Chen et. al. [23]	De Caluwe et. al. [24]
pCR	NR	pCR—0 (0%), pPR- 80% (n = 8)	0 (0%)	2 (9%)	NR	9 (36%)	15 (42%), 5 (33%) after 6 months, 10 (48%) after 8 months, 12 (33%) near pCR	9 (90%)	2 (33.3%), 2 (33.3%) near pCR
Scales used to evaluate toxicity	CTCAE v. 4.03	CTCAE	CTCAE v. 4.0	RTOG/EORTC	CTCAE	NR	CTCAE v. 4.03	CTCAE v. 5.0	CTCAE v. 5.0
Acute and late toxicity related to SBRT	Acute—3 weeks postop.- 0 ≥ G2, Late—6 month postop.-1 (3.7%) G2 wound infection, 1 year postop.—No ≥ G2	Acute- 0 ≥ G2, Late- NR	Acute- 4 to 5 weeks after SBRT- G2-toxicity – breast pain – 1 (5%) and erythema – 1 (5%), no G3, Late: patients without postoperative WBRT (n = 16), G2 -3 (19%)-skin induration, breast pain, atrophy), G3—1wound complication. patients after WBRT: skin induration G2- 2 (50%), seroma G2 -1 (25%), atrophy G2 -1 (25%), G3 toxicity in 2: abscess -1 (25%), breast pain -1 (25%)	Acute (7–30 days after SBRT)—breast oedema-G2—1 (4.55%), Acute (30 days after SBRT) – breast induration G2 -1 (4,5%) Late (6–12 months after SBRT) G2 -1 (4,5%)	Acute G2: Wound infection – 1 (3%), breast pain 2 (6%), dermatitis 3 (10%) Late: fibrosis G2 -3 (10%), G3 -1 (3%), breast atrophy G2 -2 (6%), G3 – 1 (3%), breast pain G2 -2 (6%), dermatitis G2 1 (3%), infection G2 1 (3%), seroma G2 1 (3%), hyperpigmentation G2 1 (3%)	Acute—G2 skin erythema- 1 in 22.5 Gy cohort and 1 in 25.5 Gy cohort, G3 dermatologic erythema- 1 on 7 (14%) in 28,5 Gy cohort, Late- 0%	Before BCS r 6–8 months after SBRT: G2–chest pain- 1 (3%), breast pain-1 (3%), breast edema- 1 (3%) Late (12 months from SBRT) G2 – breast pain 2 (6%), chest pain -1 (3%), wound infection 5 (15%) Late G3—1 (3%) transient wound infection Late (18 months after BCS): n = 0	Related to sbrt Acute- 0 (0%) Late- 0 (0%)	Acute < G2- 1 (16.7%) breast pain Late- 0 (0%)

Table 2 (continued)

	Guidolin et. al. [15]	Tiberi et. al. [16]	Liveringhouse et. al. [17]	Meattini et. al. [18]	Horton et. al. [19]	Bondiau et. al. [20]	Vasmel JE et. al. [21], [22]	Guanglei Chen et. al. [23]	De Caluwe et. al. [24]
Cosmesis	Modified Harvard–Harris Cosmetic Scale-Physician-rated (good or excellent)-100% (baseline), 93% (3 weeks), 96% (6 months), 92% (1 year postoperatively) Patients rated –(good or excellent)-96% (baseline), 93% (3 weeks), 92% (6 months), 96% (1 year postoperatively) No significance difference from the baseline,	EORTC scale—NR	Overall physician- reported—„good"- 17 (85%), „fair"- 2 (10%), „poor"- 1 (5%)		NSABP B-39/RTOG 0413 cosmesis evaluation scale After 6 and 12 months: 28 (100%) -good/excellent	NR	94% of the patients very satisfied, satisfied, or not unsatisfied	NR	Excellent in 4 (66.6%) and good in 2 (33.3%)
Median Follow-up time	12 months	3 months	14 months	18 months	23 months	30 months	21 months	13 months	25.5 months
Adjuvant EBRT	none	none	In 4 patients (20%) with ypN +	In 2 patients	In 3 patients (6%)	All but 2 who refused	none	NR	NR

e2d—Every 2 days, q2w – Every 2 weeks, BCT- Breast conserving treatment, GTV- Gross tumor volume, CTV- Clinical target volume, PTV- Planning target volume, CTCAE—Common terminology criteria for adverse events, NR- Not reported, EORTC—European organisation for research and treatment of cancer, RTOG—Radiation therapy oncology group, pCR- Pathological complete response, LINAC—Linear accelerator, IMRT—Intensity modulated radiation therapy, VMAT—Volumetric arc therapy

studies SBRT was performed on a Cyberknife system [18, 20]. PTV for conventional linear accelerators (LINACs) based SBRT was generated by adding 3 mm [19, 21, 22] or 5 mm [15] to the CTVs. Tiberi et al. used larger CTV-PTV margin which was 10 mm [16]. All studies used an intensity modulated radiation therapy (IMRT) or volumetric arc therapy (VMAT) techniques which were performed on Cyberknife [18, 20] or LINACs. [15–17, 19, 21–24].

Fractionation schemes

Two included phase I trials were dose escalation protocols [19, 20]. Horton et al. used a single fraction regimen and escalated the dose in three cohorts of patients. Fifteen Gy in 8 patients, 18 Gy in 8 patients and 21 Gy in 16 patients were prescribed [19]. Bondiau et al. used 3 fractions, in every other day regime, and escalated the dose in 5 cohorts consisting of 3 patients each. 19.5 Gy, 22.5 Gy, 25.5 Gy, 28.5 Gy and 31.5 Gy were used [20]. Guidolin et al. and Tiberi et al. prescribed 20 Gy in single fraction [15, 16]. In the ROCK trial 21 Gy in one fraction was administered [18]. Vasmel et al. used two dose levels with a simultaneous integrated boost technique (SIB) consisting of 20 Gy to the GTV and 15 Gy to the CTV [21, 22]. Liveringhouse et al. used a fractionated regimen and administered 28.5 Gy in 3 daily fractions [17]. When et al. used 24 Gy in 3 fractions administered every other day [23]. In the NeoCheck trial also 24 Gy in 3 fractions were used but patients were irradiated every day [24].

Dose constraints to organs at risk (OARs)

Dose constrains for individual OARs varied between publications. Table 3 summarizes them along with the dose fractionation schemes that were used. In the studies by Guanglei Chen et Al. and De Caluwe et al. [23, 24] guidelines for dose constrains were not included.

Timing of surgery after SBRT

The time interval from SBRT to surgery was different in all of the included studies. The median time from SBRT to surgery was 9.5 weeks and it ranged from 1 to 28 weeks [15–24]. In 3 studies the timing between SBRT and surgery was very short, with only 1–2 weeks [15, 18, 19]. Two analyses used longer intervals of 6–13 weeks [16, 17]. However, over half of the included studies waited 16–28 weeks until surgery [20–24].

Concurrent systemic therapy

In three trials SBRT were tested with concomitant systemic therapy [20, 23, 24]. As already mentioned in the inclusion criteria all of this studies included patients with higher risk or more advanced disease compared to other trials. In the study of Bondiau et al. neoadjuvant chemotherapy included 3 cycles of docetaxel and 3 cycles FEC (5-fluorouracil, epirubicin, cyclophosphamide) with SBRT given during the second chemotherapy cycle but not on the same day as chemotherapy [20]. The systemic therapy regimen in the Chen trial consisted of 8 cycles of selective PD-L1 inhibitor – adebrelimab and 6 cycles of nab-paclitaxel and carboplatin, where SBRT was performed during the second cycle of immunotherapy [23]. The regimen used in the De Caluwe trial consisted of 19 weeks used paclitaxel, cyclophosphamide-doxorubicin, anti-PD-L1 antibody durvalumab and anti-CD73 antibody oleclumab with SBRT given in week 4–5. In the Vasmel trial 6 (17%) patients initiated neoadjuvant endocrine treatment after SBRT according to national guidelines [21].

Acute and late toxicity profile related to SBRT

One of the important objectives of preoperative early breast cancer SBRT trials was to assess cosmetic effects and mostly acute toxicity due to the usually short follow- up time. In the study by Vasmel et al. late G2 toxicity, asseses 12 months from SBRT involved breast pain (n = 2), chest pain (n = 1) and wound infection (n = 5) and one G3 wound infection [21]. Bondiau et al. reported no late treatment-related toxicities after 30 months. [20] Similarly no late toxicities were reported in Chen and De Caluve papers [23, 24]. In the study by Horton et al. late breast fibrosis was reported in 71% (mostly G1 in 56%) and atrophy in 20% of patients but no dose correlation analysis was performed. Early toxicity was mild including breast pain, dermatitis and breast edema [19]. In the study by Tiberi et al. six patients (60%) had G1 dermatitis in the irradiated area. No other significant post-radiotherapy complications were reported [16]. In the Liveringhouse trial, 3 patients who did not receive post-operative whole-breast RT (n = 16) experienced G2 toxicity (19%-skin induration, breast pain, atrophy) and one case of G3 toxicity of wound complication which required a re-excision lumpectomy. In 4 patients who received additional postoperative whole-breast RT, the following G2 toxicity was detected: skin induration in 2 patients (50%), seroma in one (25%), atrophy in one patient (25%), G3 toxicity in 2 patients: abscess (n = 1), and breast pain (n = 1). In 7 included studies with late toxicity reports G3 were reported in 2 patients who did not receive postoperative whole breast radiotherapy(WBRT). Details of early and late toxicity are shown in Table 2.

Cosmetic effect assessment

The cosmetic outcome after preoperative SBRT was reported in 6 selected studies. In the trial of Guidolin et al. cosmetic assessment was performed by patients and physicians using the Harvard-Harris cosmetic scale [15].

Table 3 Dose constraints to organs at risk (OARs) used in included studies

	Guidolin et al. [15]	Tiberi et al. [16]	Liveringhouse et al. [17]	Meattini ett, al. [18]	Horton et.al. [19]	Bondiau et al. [20]	Vasmel JE et al. [21, 22]
Dose fractionation schedule	21 Gy /1 fraction	20 Gy / 1 fraction	28,5 Gy / 3 fractions daily	21 Gy / 1 fraction	15 Gy (n = 8), 18 Gy (n = 8), 21 Gy (n = 16.) / 1 fraction	19,5 Gy (n = 3), 22,5 Gy (n = 3), 25,5 Gy, 9 (n = 6), 28,5 Gy (n = 7), 31,5 Gy (n = 6)- 3 fractions every other day	20 Gy for GTV, 15 Gy for CTV- SIB / 1 fraction
OAR							
Breast Uninvolved ipsilateral Contralateral	V10,5 Gy ≤ 50% V20 Gy ≤ 47% Dmax < 21 Gy Dmax < 1Gy	Dmax ≤ 3 Gy	V15Gy ≤ 25%; V25 Gy ≤ 10% V10 Gy < 7%, V5 Gy < 10%	V10.5Gy < 60% V22Gy < 35% < 1Gy	< 50% of the breast volume should receive 50% or more of the prescribed dose < 35% of the breast volume should receive prescription doese < 15% of the prescribed dose at any point	NR	Ratio PTV_{CTV} to ipsilateral breast volume < 25% Dmean < 5Gy
Lung Total Ipsilateral Contralateral	V11 Gy ≤ 35% V7,5 Gy ≤ 15% V1,7 Gy ≤ 15%	D10% ≤ 6 Gy D25% ≤ 2 Gy	V9 Gy < 5% V9 Gy < 3%	V7Gy < 1000 cm3 < 1Gy	V7Gy < 1000 cm3	V5 Gy < 5 cm3	V7.8Gy ≤ 5% Dmean < 3.6 Gy
Heart	Dmax < 22 Gy (Point dose) V3 Gy < 5 cm3 V16 Gy ≤ 15%	Right breast D5% ≤ 1 Gy Left breast D5% ≤ 3 Gy	Dmean ≤ 2 Gy V3Gy ≤ 10 cm3	V3Gy < 5 cm3	Dmax < 5 Gy V3 Gy < 5 cm3	NR	V2.8Gy ≤ 10% V4.7Gy ≤ 5%
Thyroid	Dmax < 1,1 Gy (Point dose)	D100% ≤ 0,6 Gy Dmax < 3 Gy	Dmax1,2 Gy (4% prescription)	-	Dmax < 3Gy (15% prescription)	-	-
Skin	V18,3 Gy < 5 cm3	D10cm3 ≤ 20 Gy Dmax ≤ 21 Gy	D10cm3 ≤ 15 Gy	V10Gy < 10 cm3 V20Gy < 1 cm3	evaluated on a case by case	V15 Gy < 10 cm3	D1cc < 16 Gy
Chest wall	V10 Gy < 10 cm3 V16 Gy < 2 cm3	D1cm3 ≤ 21 Gy Dmax ≤ 22 Gy	V28.5 Gy ≤ 30 cm3	V10Gy < 10 cm3	-	V15 Gy < 10 cm3	D16.3Gy < 20cc

DYY cm3 < XX Gy is the maximal dose to YY cm3 in the volume of the OAR that receives the highest doses. DMax is the near-point maximum dose, VXX Gy is the percentage volume of the organ receiving a dose of XX Gy or higher

There was no significant change in cosmetic compared to the baseline at 3 weeks and 6 months from surgery [15]. Meattini et al. used the BCCT.core software for cosmetic effect analysis and reported that 21 of 22 (95,4%) patient had "good" to "excellent" results, 1 patient (4.6%) reported a "fair" result after preoperative SBRT [18]. Horton et al. used the NSABP B-39/RTOG 0413 cosmetic evaluation scale. After 12 months 28 (100%) patients reported "good" or "excellent" cosmetic effects after SABR [19]. In the trial of Vasmel et al. 94% of the patients were very satisfied, satisfied, or not unsatisfied after preoperative stereotactic radiotherapy [21].

In Liveringhouse et al. cosmesis was rated "good" in 17 (85%), "fair" in 2 (10%), and "poor" in 1 (5%) patient, but in patients receiving additional postoperative RT (n = 4), cosmesis was "good" in 3 and "poor" in 1 patient [17]. Of all patients (n = 6) reported in the De Caluve trial 4 had "excellent" and 2 had a "good" cosmetic outcome, but out of 4 patients who received BCS, 3 were assessed as "excellent" and 1as "good". [24] Bondiau et al. reported that overall 94% of patients were very satisfied and satisfied with the cosmetic outcome [20].

Pathological response

In 8 studies pCR was analyzed [16–18, 20–24] In two [15, 19] no pathological response was assessed. In four of the single fraction SBRT studies pCR were ranged between 0%, 9%,and 42% [16, 18, 20, 21]. The studies by Vasmel et al. showed highest pCR rates among those included: 15 (42%) in total, 5 of 15 (33%) after first 6 months, 10 of 21 (48%) after 8 months and 12 (33%) near pCR (< 10% residual tumor cells), in 7 patients (19%) partial response (10%-50% residual tumor cells) and in 2 (6%) stable disease (> 50% residual tumor cells with features of response to treatment) have been reported. There were no patients without evidence of response. Neoadjuvant endocrine therapy was administered in 6 patients of whom pCR was reached in 2 patients, near pCR in 3 patients and a partial response(PR) in one patient [21, 22]. In this study the time interval from SBRT to surgery was also the longest, 6 months in 15 patients and 8 months in 21 patients [21]. Bondiau et al. reported 36% pCR in the whole cohort. It was very heterogenic, with 67% at a dose level of 25,5 Gy, 43% at 28,5 Gy, 33% at 31,5 Gy with no pCR cases in the 19,5 Gy and 22,5 Gy dose levels groups [20]. Residual cancer burden (RCB) according to Symmans et al. was measured in the De Caluve trial were 2 of 6 patients (33.3%) had a complete pathological response (RCB 0), two (33.3%) had a near pCR (RCB1) one (16.7%) a moderate residual disease (RCB 2) and one (16.7%) an extensive residual disease (RCB 3) [24]. The same measure was used in the Chen et al. trial showing pCR (RCB 0) in 9 patients (90%) and near pCR (RCB 1) in one patient (10%) [23]. Liveringhouse et al., reported no case of pCR and the median RCB was 30% with 2 patients with a 80% residual cancer burden whereas all other patients had ≤ 50% residual cellularity after stereotactic fractionated radiotherapy, 3- fraction scheme, and after median of 49 days from SBRT to breast conserving surgery (BCT) [21].

Discussion

The use of radiotherapy as a main neoadjuvant treatment or in combination with chemotherapy in a preoperative setting represents a newly intensively researched approach in early-stage breast cancer treatment [12, 25, 26]. The results of studies using moderate hypofractionation, as a preoperative treatment, showed good cosmetic effect and local control (LC), which encouraged researchers to look for shorter and more intensive treatment regimens [27, 28].

To the best of our knowledge, the above systematic review represents the most up-to-date compilation of studies evaluating the feasibility of preoperative PBI with the use of SBRT limited to 5 fractional doses [14, 29–31]. For the above review 10 studies were included (in 7 studies SBRT was used as the only neoadjuvant treatment modality, in 3 of them SBRT was used with concomitant systemic therapy [20, 23, 24]. In two studies published recently, SBRT was performed preoperatively with immune-chemotherapy [23, 24]. The main advantages and disadvantages of preoperative radiotherapy in breast cancer were summarized in Table 4.

SBRT is a method of external beam radiotherapy that allows highly precise delivery of a high dose of radiation to a limited target area with a large dose drop around the target. The biological efficacy of SBRT is not only based on the mechanism of DNA damage at the molecular level, but also on additional effects at the tissue and cellular level (damaging the vasculature and cell membranes),

Table 4 Advantages and disadvantages of preoperative PBI. [32]

Advantages of preoperative radiotherapy	Disadvantages of preoperative radiotherapy
Better localization of the irradiated area, better visibility of the primary tumor—possibility to insert tracers near the tumor during biopsy of the lesion, which minimizes the risk of geographic error; Possible tumor down-staging and increased rates of breast-conserving surgery; Preoperative radiotherapy reduces the problem of the possible technical treatment planning challenges after oncoplastic surgery Reduction in irradiated area and associated reduction in toxicity. With preoperative radiation therapy, we irradiate the tumor volume with a margin. Surgery is performed after radiation therapy, so the area of the breast receiving the highest dose of radiation is removed, which can lead to limited fibrosis and good cosmetic outcomes; Better oxygenation of tumor tissues which determines a better therapeutic effect of radiotherapy than in tissues undergoing surgical intervention; In favorable cases of breast cancer, postoperative WBRT may be omitted if preoperative PBI has been applied. Generation of an abscopal effect, which is not the case with postoperative radiotherapy; o Reduction in number of radiotherapy sessions	Possible delay in performing surgery due the duration or complications after radiation therapy-this problem does not apply to stereotactic radiation therapy performed in the shortest possible time, Upstaging of the tumor, positive margins after surgery, changing the receptor profile to a less favorable one which requires more aggressive treatment regimens like: irradiating the whole breast, nodal areas or chemotherapy

as well as on the abscopal effect of enhancing the anti-tumor immune response due to the action of high doses of radiotherapy on the cancerous tumor, which produces a therapeutic effect beyond the irradiated field [33–35].

Preoperative radiotherapy has become the standard treatment for rectal cancer and sarcoma. In the case of breast cancer, it is currently the subject of clinical trials. Beyond the improved target visualization and reduced risk of tumor cell dissemination during surgery, preoperative radiotherapy offers multiple radiobiological advantages. This include better oxygenation of non-operating tissues and immune-priming as outlined by Brackstone et al. [36] Additionally preoperative radiotherapy may significantly enhance immune responses against tumors. It can transform tumor into personalized in situ vaccine, teaching the immune system to recognize and combat cancer, what cannot be observed after irradiation of tumor bed [37, 38]. This may be important in eradicating subclinical diseases and distant micrometastases, potentially leading to long-lasting immune memory against future tumors [37–39]. In this context, it's noteworthy that two studies in this review specifically explored the combination of SBRT and immunotherapy [23, 23].

Target volume definition

Stereotactic radiotherapy employed in radical breast cancer treatment can be utilized postoperatively as a boost after WBRT or PBI [40, 41]. Due to its targeted approach, it requires meticulous target definition during treatment planning and consistent positioning accuracy to minimize geographic error risk. In post-operative setting, surgical clips are required to accurately identify the tumor bed. For the increasingly popular oncoplastic procedures, the location of the tumor bed poses a major challenge for the radiation oncologists and need collaborative target determination with surgeon.

Despite guidelines for contouring the tumor bed in PBI, challenges in delineation remain. The main issues include: [42, 43].

- Extent and location: often, the contoured area is disproportionately large compared to the original tumor or located differently than indicated by pre-surgery examination and imaging studies [44].
- Scattered clips (in 43 -73% of patients undergoing surgery, clips on postoperative CT imaging were visualized outside the original quadrant of the tumor) [45, 46].

Preoperative tumor delineation on CT scans leads to less inter-observer variability compared to postoperative delineation of tumor bed [47]. The target volume, the tumor, can be demarcated by implanting fiducial markers around it during the biopsy. The potential for fusion of imaging studies, such as magnetic resonance imaging (MRI) with planning computed tomography (CT) scans, is instrumental in accurately determining the tumor's exact extent. Compared to CT scans MRI better visualize irregularities and spikes in the tumor [48]. Vasmel et al. published consensus on contouring primary breast tumors on MRI in the setting of neoadjuvant PBI in trials [49]. In all but one study MRI was co-registered with CT scans for planning radiotherapy [16]. The GTV in Tiberi et al. study was defined as the primary tumor based on physical exam, CT scans, and breast ultrasonography [16].

The technical aspects of neoadjuvant PBI have been elegantly highlighted by Zerella et al. in recently published narrative review [50].

Preoperative PBI implementation techniques

The implementation of radiotherapy can be performed in prone or supine position using various immobilization systems. Diagnostic contrast-enhanced MRI is typically performed in prone position, which makes it easier to perform image fusion when realizing radiotherapy in an analogous position. When treating patients in the supine position, the solution may be to perform deformable fusion with diagnostic MRI images or to perform another MRI scan in the supine position like in the ongoing CRYSTAL study [51]. Widespread clinical introduction of the MR-LINAC (a linear accelerator (LINAC) with integrated MR scanner can be particularly helpful in the delivery of radiotherapy for breast cancer [52].

Comparison between PBI and WBRT

Comparison of postoperative WBRT and PBI show no differences in overall survival (OS) with favorable toxicity profile for the PBI technique in well selected low risk early breast cancer patients [53, 54]. In extended follow-up periods (up to 15 years), PBI may result in a marginally higher rate of local recurrence(LR) compared to WBRT [55]. However, advancements in systemic treatments, the integration of adjuvant therapies, and enhancements in local treatments have reduced local recurrence rates in breast cancer by half [56]. Consequently, there are emerging considerations for omitting postoperative radiotherapy in certain cases [7]. Within this context, PBI could emerge as an optimal balance. It is noteworthy that none of the analyzed studies reported tumor progression which is opposite to postoperative PBI where mature data are available.

Toxicity profile

By limiting the irradiated volume, dose to OARs can be significantly reduced, which is particularly important for the heart, the left anterior descending coronary artery (LAD), lung or contralateral breast, as it reduces the risk of secondary malignances and the incidence of cardiac and lung complications [57, 58]. The volume of the irradiated area for preoperative PBI is smaller than postoperatively which may translate into reduced toxicity in the long term follow-up.

The early toxicity profile of preoperative SBRT in breast cancer seems to be favorable. Among studies selected for the review, in terms of G3 acute toxicity events, only one erythema (14%) from 28.5 Gy cohort in Bondiau study was reported [20]. The late G3 toxicity was reported in one patient (2.8%) in Vasmel et al. trial and in one (6.3%) in Liveringhouse trial [17, 21].

PBI performed postoperatively is associated with better cosmetic outcome and fewer late radiation toxicities than WBRT. However, no direct comparative studies exist on the toxicity of stereotactic PBI when applied either preoperatively or postoperatively. Notably, the levels of both early and late toxicities are reportedly low [59, 60].

Comprehensive data on the late toxicity of preoperative SBRT used as PBI is still limited, necessitating a longer period of observation.In the above analysis, the longest follow up-25.5 months was reported by De Caluwe et al. During this time no late effect was reported [24].

It is also important to mention that addition of SBRT to immunochemotherapy does not increase the percentage of grade 3 or higher adverse effects (AEs) observed after immunochemotherapy [23, 24].

The optimal SBRT dose guidelines in preoperative setting

There is no established fractionation scheme for preoperative SBRT. In the above study, 1 and 3 fractional regimens were analyzed. The highest total dose of 21 Gy was given in one fraction in the SIGNAL study. In the 3 fractional regimens, the highest total dose was 31.5 Gy. In the currently ongoing dose escalation study the highest prescribed dose is 38 Gy/1fr [61].

The optimal time gap from radiotherapy to surgery

Notable in the above systematic review is the lack of a standardized radiotherapy dose and time interval between the end of radiotherapy and the performance of surgery. In the studies reviewed, the time varies from 1 week to 8 months. In ongoing ABLATIVE-2 study, the time between radiation therapy and surgery it is 12 months [62]. This is the longest time interval used in the analyzed completed and ongoing studies of preoperative radiotherapy in breast cancer [9].

The pCR rate following preoperative SBRT seems to be positively correlated with the duration between radiotherapy and surgery in a cohort of early-stage breast cancer patients possessing favorable prognostic factors. Vasmel JE et al. [21, 22] reported 33% pCR after 6 months, and 48% pCR after 8 months from radiotherapy to BCS among early stage breast cancer patients with favorable risk factors. The above observation prompts us to look for a group of patients in whom surgery can be abandoned as in rectal cancer [63].

Bondiau et al. [20] analyzed cases of patients ineligible for BCS who received preoperative radiotherapy in combination with chemotherapy achieving a pCR of 36% after 21–24 weeks. Guanglei Chen et al. [23] in a group of patients with TNBC breast cancer using radiotherapy in combination with chemo-immunotherapy (ICI: adebrelimab) achieved higher pCR rates: 90% after 21–23 weeks. In analogous group of patients (TNBC breast cancer patient who are candidates to neoadjuvant chemotherapy and received immunochemotherapy without preoperative radiotherapy) KEYNOTE522 study pCR: 58–64,8% were achieved [64]. It is speculated that preoperative SBRT exerts synergy with immunochemotherapy.

Similarly, high percentage of pCR were achieved in the PEARL study pCR at 74% in TNBC after SBRT: 24Gy/3fr and: with anti-PD(L)1—pembrolizumab in addition to neoadjuvant chemotherapy (NAC) [65].

Pathologic CR was achieved in less than 10% of cases in studies where the time gap from the end of radiotherapy to surgery was less than 13 weeks [16–19].

Markers of response to preoperative SBRT

In addition to determining the optimal time gap from radiotherapy to surgery translating into the highest pCR rates, research is underway to identify markers indicative of response to preoperative treatment. Bosma et al. analyzed gene expression patterns among 77 patients who received preoperative radiotherapy (10×4 Gy in 10 days or 5×6 Gy in 5 days) and a lumpectomy 6 weeks thereafter and observed no or very limited response in 22 patients. Clinically significant differences in gene expression between patients with and without response to radiotherapy were not identified. However, the authors found, by comparing samples before and after radiotherapy, that genes involved in p53 signaling, TNFA1 signaling, apoptosis, epithelial mesenchymal transition, and inflammatory response were upregulated, and genes involved in mitotic spindle, G2M checkpoint, and E2F targets were downregulated [66]. High Ki-67 before NAC was a predictor for pCR in breast cancer patients. Ongoing trials may explore whether this approach will be effective in preoperative radio-chemotherapy [67]. In ABLATIVE trial Vasmel

Table 5 Ongoing trials on preoperative PBI with SBRT

	ClinicalTrials.gov ID/ Study status	Inclusion criteria	Study plan	Primary/secondary endpoints
Feasibility Study of Stereotactic Body Radiotherapy for Early Breast Cancer (ARTEMIS) [73]	NCT02065960/ Unknown status	Age ≥ 70 years; invasive carcinoma, G I/II, ER and PR positive, HER2 negative Stage I (T1 N0 M0) on clinical and radiological assessment with MRI of the breasts and axillary ultrasound; Candidate for BCS;	SBRT: 40 Gy in 5 fractions delivered every other day,followed by BCS	Primary: Feasibility Secondary: Acute and late Radiation Toxicity, pCR, Ipsilateral Breast Tumour Recurrence, DFS
Preoperative Single-Fraction Radiotherapy in Early Stage Breast Cancer [74]	NCT02482376/ Active, not-recruiting	Age ≥ 60 years or 50–59 with a low Oncotype score (0–17); Clinical T1N0M0 invasive carcinoma or DCIS < or equal to 2cm; ER positive; HER2 negative; Candidate for BCS;	SBRT: 21Gy followed by breast conserving surgery	Primary: Physician reported cosmesis outcomes Secondary: Ki-67 as a measure of tumor response;Patient reported cosmesis outcomes; LC; Assess the impact of RT on: gene expression, circulating cell free DNA
CMP-001 and Pre-operative Stereotactic Body Radiation Therapy (SBRT) in Early Stage Triple Negative Breast Cancer (TNBC) [75]	NCT04807192/ recruiting	Age ≥ 18 years; TNBC, cT1-2, at least 5 mm, cN0-1 cM0); ECOG: 0–1; planned BCS or mastectomy; No planned neoadjuvant chemotherapy/ endocrine therapy or other anticancer therapy; Presence of measurable disease in the breast; Primary tumor accessible to injections and biopsy. The lesion to be injected should be confined in a single irradiation volume that does not result in more than 30% of the whole breast; The injected tumor should be located at least 5 mm from the skin or pectoral muscle	Arm 1: SBRT: 1 × 8 Gy at D1 Arm 2: CMP-001 (4 sequential administrations of CMP001 at Day 1 (SC), Day 5 (± 1) (IT), Day 9 (± 1) (IT) and Day 16 (± 1) (IT) + SBRT 1 × 8 Gy at D1	Increase in sTILs, Toxicity of CMP-001 combined with SBRT, pCR, minimal residual cancer, Ki-67 levels, OS, DFS,event-free survival (EFS)
Study of Stereotactic Radiotherapy for Breast Cancer [76]	NCT03043794/ recruiting	Age ≥ 50 years; Invasive ductal carcinoma; T1 N0; Clearly demarcated tumor on magnetic resonance imaging (MRI); ER and/or PR ≥ 10%; HER2 negative; Candidate for BCS + SLNB;	SBRT: 21 Gy followed by standard of care surgery	RCB, pCR, treatment-related toxicity, cosmetic outcome, time to recurrence, QoL
Breast Cancer Study of Stereotactic Body Radiation Therapy (SBRT) Combined Neoadjuvant Treatment (Study to Evaluate the Efficacy and Safety of Stereotactic Body Radiation Therapy (SBRT) Combined Neoadjuvant Treatment for Patients With Triple-negative and Hormone Receptor-positive, HER2-negative Breast Cancer) [23, 77]	NCT05132790/ Active, not-recruiting	Age: 18–75 years; invasive adenocarcinoma of the breast; TNBC patients HER2-neu 0–1 + by IHC or FISH-negative; ER-positive and HER2-negative breast cancer; tumor ≥ 2 cm (mammogram, breast ultrasound, breast MRI); Any nodal status; ECOG 0 -1	Experimental: TNBC (SHR-1316 at a dose 20mg/kg q3w): Combination of SBRT and SHR1316, followed by SHR1316 plus nab-paclitaxel and carboplatin or cisplatin Experimental: HER2-/HR + BC (SHR6390 at a dose of 150mg orally, daily): SHR6390 plus exemestane with/without ovarian function suppression/ ablation (OFS) after SBRT	pCR, RCB, objective response rate (ORR), AE,serious adverse events (SAE)

Table 5 (continued)

	ClinicalTrials.gov ID/ Study status	Inclusion criteria	Study plan	Primary/secondary endpoints
Stereotactic Image-Guided Neoadjuvant Ablative Radiation Then Lumpectomy (SIGNAL 2) [78]	NCT02212860/ Active, not-recruiting	Age ≥ 50 years and postmenopausal; Tumor size < 3 cm; ER positive; Invasive ductal carcinoma or other favorable subtypes (lobular, medullary, papillary, colloid, mucinous, or tubular); cN0; Surgical expectation that a > 2 mm margin can be obtained; Lesion 1 cm or greater from the skin surface; surgery within 14–20 days of radiation therapy; Able to tolerate the prone position	Stereotactic image-guided neoadjuvant ablative radiation (randomized to 1 × 21 Gy or 3 × 10 Gy) followed by lumpectomy	Immune priming, angiogenesis, proliferation, apoptosis, hypoxia, invasion markers level, toxicity
Preoperative Stereotactic Ablative Body Radiotherapy (SABR) for Early-Stage Breast Cancer [79]	NCT03137693/ terminated https://pubmed.ncbi.nlm.nih.gov/34384695/	Age ≥ 50 years; Invasive adenocarcinoma of breast; marker clip in breast; Unifocal tumor = < 2 cm based on contrast-enhanced prone-breast MRI; cN0; candidate for BCS; Able to tolerate the prone position; target lesion at least 10 mm from skin defined on MRI; ER positive; Her-2 negative; No received or planned fof neoadjuvant chemotherapy prior to SABR or surgery; ECOG 0–2	SABR: 28.5 Gy in 3 fractions BCS 6–8 weeks after	pCR
SABR-CaRe in Early Stage Breast Cancer [80]	NCT04959474/ recruiting	Age ≥ 40 years (with TNBC ≥ 50 years); DCIS or invasive breast cancer; BMI > = 21 at time of enrollment; KPS: 70 – 100; Tumor size = < 3.0 cm; Gross disease may be multifocal as long as the total extent of tumor, gross and microscopic, occupies a volume with greatest dimension = < 3 cm; Patient is not being considered for preoperative chemotherapy	Arm I: standard dietary recommendations, SABR every other day for 5 fr, surgery within 4–12 weeks, surgical resection with SLNB) Arm II: caloric restriction diet, SABR every other day for 5 fr, surgery within 4–12 weeks, surgical resection with SLNB	Percent reduction in cellularity of breast tumor
Preoperative Boost Associated With Neoadjuvant Chemotherapy in Luminal B Breast Cancer IBISCO TRIAL [81]	NCT05673304/ recruiting	Age ≥ 18 years; Luminal B BC, cT1-2; Indication for neoadjuvant chemotherapy	SBRT as an anticipated boost with a total dose of 24 Gy (8 Gy × 3 fractions QD) within 2 weeks from the start of neoadjuvant chemotherapy	pCR, acute/late toxicity

Table 5 (continued)

	ClinicalTrials.gov ID/ Study status	Inclusion criteria	Study plan	Primary/secondary endpoints
Three Fraction Radiation to Induce Immuno-Oncologic Response (TRIO) [82]	NCT03978663/ recruiting	Age ≥ 18 years; locally advanced breast cancer defined as stages IIB-III (excluding inflammatory breast cancer). Stage IIA is eligible for TNBC and HER2-positive breast cancers; Invasive mammary carcinoma of any subtype excluding lobular, sarcomatous, or metaplastic subtypes, or with lobular features; Plan to be treated with neoadjuvant chemotherapy; M0	SBRT: 3 fractions administered as an anticipated boost prior to neoadjuvant chemotherapy	pCR, Immune priming, surgical wound healing, LRR
Neo-adjuvant Chemotherapy Combined With Stereotactic Body Radiotherapy to the Primary Tumour + / - Durvalumab, + /- Oleclumab in Luminal B Breast Cancer: (Neo-CheckRay) [83]	NCT03875573/ recruiting	Age ≥ 18 years; luminal B breast cancer subjects candidate for neoadjuvant chemotherapy	Arm I: Experimental: Chemotherapy and pre-operative radiation therapy (boost dose) 3 × 8 Gy Arm II: Experimental: like Arm I plus durvalumab Arm III: Experimental: like Arm I plus durvalumab plus oleclumab	valuation of the immune related or radiation therapy related toxicity, Evaluation of the feasibility of the primary surgery, Phase II: Demonstration of the tumour response in arms 2 or 3 versus arm 1
GammaPod Dose Escalation Radiation for Early Stage Breast Cancer (GCC 1926- Phase Ib Dose Escalation of Single-Fraction Preoperative Stereotactic Partial-Breast Irradiation for Early-Stage Breast Cancer) [84]	NCT04234386/ recruiting	Patients > 45 years; unifocal visible on a CT scan tumor; N0; ER positive; HER2 negative; invasive ductal carcinoma; candidates for BCS; Tumor must not involve the overlying skin or underlying chest wall; Greatest tumor dimension is < 3 cm based on US. MR imaging measurements can be included only if performed before the biopsy; patients weigh < 150 kg; Patients must be able to lie prone position; no lymphovascular invasion on biopsy	single-fraction radiation dose delivered with the GammaPod as a PBI before a lumpectomy Dose Level 1: 21 Gy Dose Level 2: 24 Gy Dose Level 3: 27 Gy Dose Level 4: 30 Gy	Establish the single-fraction radiation dose (MTD), Incidence of Dose-Limiting Toxicities (DLTs), pCR, ipsilateral LRR

Table 5 (continued)

	ClinicalTrials.gov ID/ Study status	Inclusion criteria	Study plan	Primary/secondary endpoints
Single Fraction Preoperative Radiotherapy for Early Stage Breast Cancer CRYSTAL study [51, 85]	NCT04679454/ recruiting	Histologically proven unifocal adenocarcinoma; T1-T2; tumor size up to 2.5 cm; cN0; Age ≥ 18 years old; ECOG 0–2; Planned BCS	phase I dose escalation study to identify the maximum tolerated dose (MTD) delivering 18 Gy, 21 Gy and 24 Gy in single fraction phase II study to evaluate the rate of pathological complete response (pCR) when a dose level is chosen according to the results of the previous phase I study Surgical tumor removal will be scheduled after 4–8 weeks after radioablation. Whole breast radiation therapy without boost will be performed after surgery	Identify the maximum tolerated dose (MTD), pCR, chronic toxicity, Cosmetic outcomes, Post surgery complications, DFS, Local relapse, OS, breast cancer specific survival (BCSS)
Single-dose Preoperative Partial Breast Irradiation in Low-risk Breast Cancer Patients (ABLATIVE-2) [86]	NCT05350722/ recruiting	WHO ≤ 2; Age ≥ 50 years; unifocal cT1N0 breast cancer on MMG, ultrasound and MRI; Patients with an indication for chemotherapy or HER2-targeted therapy are not eligible. Patients with an indication for endocrine therapy are eligible; Tumor size as assessed on MRI; grade 1–2; Non-lobular invasive histological type carcinoma; LCIS or (non-extensive) DCIS is accepted; ER positive; HER2 negative; cN0	PBI with a single dose of 20Gy/15Gy on the GTV and CTV respectively	pCR 12 months after radiotherapy
A Phase I Dose Escalation Study of Single Fraction Ablative Preoperative Partial Breast (S-PBI) for Early Stage Breast Cancer [61]	NCT04040569 /recruiting	Age > / = 18 years old; cT1-T2cN0; Tumor must be unifocal, not involve the overlying skin; must be visible on CT scan and/or preferably marked with clip(s) in tumor; ER/PR positive, Her2 negative	Preoperative single dose escalation study: 30Gy/1fr; 34Gy/1fr; 38Gy/1fr	Dose escalation studyLC, acute/late toxicity/ cosmetic outcomes

Table 5 (continued)

	ClinicalTrials.gov ID/ Study status	Inclusion criteria	Study plan	Primary/secondary endpoints
Phase 2 Surgical Excision vs Neo-adjuvant Radiotherapy + Delayed Surgical Excision of Ductal Carcinoma (NORDIS) [87]	NCT03909282/recruiting	Core needle biopsy demonstrating DCIS; Mammographic or MRI non-mass lesion measuring 4 cm or less in greatest dimension; ER/PR positive or negative DCIS; HER2 positive, negative or unknown DCIS; biopsy marker placed within the tumor bed confirmed on post biopsy imaging and evidence of residual radiographic abnormality; Placement of Savi scout optical reflectance marker in tumor bed area as a wireless guide for surgery and for neoRT treatment planning is preferred; Planned lumpectomy. ECOG: 0, 1, or 2	Active Comparator: Surgical excision of ductal carcinoma Experimental: Neoadjuvant partial breast irradiation delivered once a day for 5 days before surgery. The planned daily dose is 6 Gy	pCR correlation of DCIS subtype with pCR assessment pre and post therapy of tumor grade, atypia, necrosis

et al. revealed that after preoperative PBI the number of Tumor -Infiltrating Lymphocytes (TILs) in tumor tissue decreased, but no differences in numbers of pre irradiation TILs between responders and non-responders were observed [68]. Radiological, biomolecular or genomic biomarkers are searched to identify the group of good responders to radiotherapy for whom surgery could be omitted. In ongoing trials, the Ki67 levels, gene expression and circulating target free DNA are being analyzed as potential predictors of local control response. At the same time, there are reports of the possibility of omitting adjuvant radiotherapy in a group of patients over 65 with early-stage breast cancer with favorable prognostic factors [69]. The trend in de-escalation of breast cancer treatment translating into a reduction in toxicity has been strong in recent years. Perhaps in the future, patients with favorable prognostic factors will be able to choose to use SBRT or BCS as their sole treatment modality.

New technologies

New image-guided radiotherapy (IGRT) technologies are emerging including intra-fractional tracking of tracers placed in the tumor/tumor bed using Cyberknife (Accuray, Palo Alto CA), magnetic resonance-based linear accelerators (MR LINACS), or the Gamma-pod equivalent of Gammaknife for breast cancer treatment which are being used in more trials of preoperative stereotactic radiotherapy [52, 70–72].

Currently ongoing trials

The Table 5 summarizes currently ongoing trials using preoperative stereotactic radiotherapy in the treatment of breast cancer.

Conclusion

Preoperative SBRT is a promising treatment option for breast cancer patients. The precise localization of the irradiated area (targeting the tumor rather than the tumor bed) is a notable feature. Early treatment toxicity is reported to be relatively low. However, the existing data are derived from phase I and II trials focusing on small patient cohorts with limited follow-up, leading to a gap in information regarding late complications or long-term efficacy. Currently, MRI appears to be the optimal imaging modality for planning preoperative SBRT. While various fractionation schemes of SBRT are being explored, there is a lack of comparative studies among them. The key issue seems to be to determine the optimal time interval between the applied radiotherapy and surgery. Given the observed increase in percentage of clinical and pathological CR with the time between radiotherapy and surgery, it seems possible, in future, to select patients who obligatorily require surgical treatment and those in whom surgical treatment can be safely omitted.

Abbreviations

BCS	Breast conserving surgery
BCT	Breast conserving treatment
cN0	Clinically node negative
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTV	Clinical target volume
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
EBRT	External beam radiation therapy
ECOG	Eastern cooperative oncology group
EORTC	European organisation for research and treatment of cancer
ER	Estrogen receptor
FISH	Fluorescence in situ hybridization
GTV	Gross tumor volume
HER2	Human epidermal growth factor receptor 2
IMRT	Intensity modulated radiation therapy
Ki67	A marker for proliferation
LC	Local control
LINAC	Linear accelerator
LVSI	Lymphovascular space invasion
MRI	Magnetic resonance imaging
NA-PBI	Neoadjuvant partial breast irradiation
NSABP	National surgical adjuvant breast and bowel project
NR	Not reported
OARs	Organs at risk
OS	Overall survival
pCR	Pathological complete response
PgR	Progesterone receptor
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PTV	Planning target volume
QoL	Quality of life
RCB	Residual cancer burden
RTOG	Radiation therapy oncology group
SABR	Stereotactic ablative body radiotherapy
SBRT	Stereotactic body radiotherapy
SC	Subcutaneous
SLNB	Sentinel lymph node biopsy
TNBC	Triple negative breast cancer
VMAT	Volumetric modulated arc therapy
WBRT	Whole breast radiotherapy
PBI	Partial breast irradiation
MTD	Maximum tolerated dose
LRR	Local-regional recurrence
DLT	Dose-limiting toxicity
BCSS	Breast cancer-specific survival
MMG	Mammography
US	Ultrasound
RT	Radiotherapy
CR	Complete response
AEs	Adverse events
KPS	Karnofsky performance status

Author contributions

MB: conceptualization, methodology, writing—original draft, formal analysis and data curation, KK-B: writing—original draft and formal analysis, MAZ: writing—review & editing and validation, SC: writing—review & editing, MH: data curation and visualisation, MCL: writing—review & editing, MG: data curation and visualization, AG: data curation, PH: data curation, BAJ-F: writing—review & editing and supervision, JF: writing—review & editing and supervision, ŁK: formal analysis, validation, writing—review & editing and supervision.

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Ethics approval and Consent to participate
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Competing interests
All authors declare that they have no conflicts of interest to disclose.

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