NEW APPROACHES TO BREAST CANCER RADIOTHERAPY

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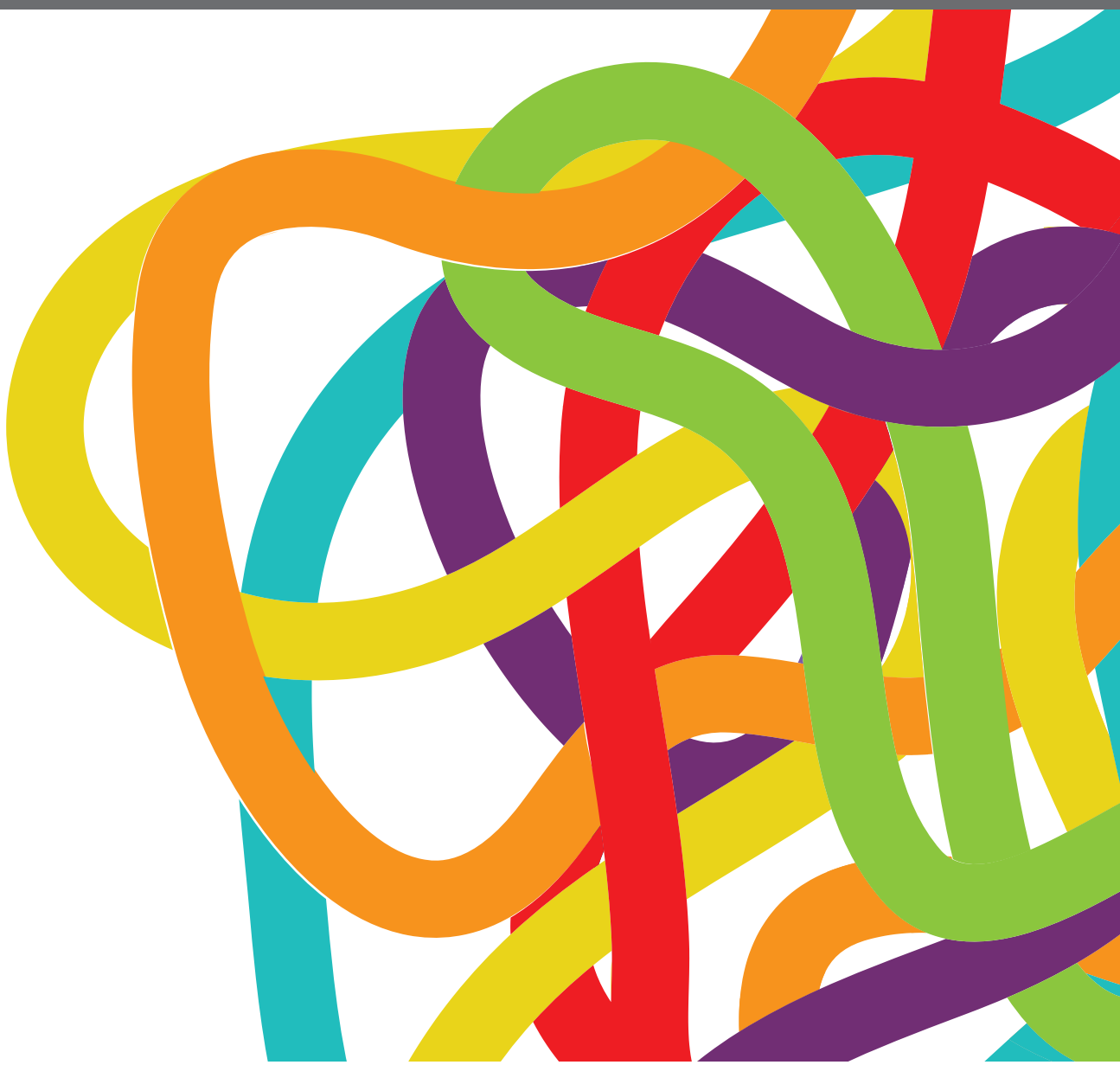

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NEW APPROACHES TO BREAST CANCER RADIOTHERAPY

Topic Editors:
Geraldine Meerbott Jacobson, West Virginia University, United States
Cristiane Takita, University of Miami Health System, United States

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EDITORIAL
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Editorial: New Approaches to Breast Cancer Radiotherapy

Geraldine Meerbott Jacobson[1]* *and Cristiane Takita*[2]

[1] Department of Radiation Oncology, WVU Cancer Institute, West Virginia University, Morgantown, WV, United States,
[2] Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL, United States

Keywords: neoadjuvant radiation therapy, partial breast irradiation, MR-guided radiotherapy, boost radiation, stereotactic body radiotherapy, oligometastases, distant metastases

Editorial on the Research Topic

New Approaches to Breast Cancer Radiotherapy

Multiple randomized clinical trials have confirmed the efficacy of radiation therapy in reducing local recurrence of breast cancer (1). For decades the predominant approach was six weeks of whole breast radiotherapy followed by a boost. This "one size fits all" paradigm has been questioned based on the identification of molecular markers, genomic profiling, and other prognostic factors that indicate recurrence risk for individual patients.

Breast cancer survival has improved in developed countries with almost 80% of patients surviving at least 10 years. Long-term survival reveals the late toxicity of all treatment modalities and provides an incentive to develop effective treatments that maintain quality of life. In the field of radiation oncology, we have the opportunity to tailor our treatments for each patient to improve progression free survival, minimize normal tissue toxicity and functional impairment, and respect our patient's resources and time constraints.

We have seen a de-escalation of the surgical approach to breast cancer and the development of a more personalized targeted approach to the selection of systemic therapy. Technical innovations in radiotherapy delivery provide the opportunity to treat patients with greater precision and fewer treatments.

Radiation delivery can be modified by altering volume, dose, timing, number and overall duration of treatment consistent with optimal medical outcome and quality of life. Hypofractionation, which reduces the number and overall treatment duration, has become the recommended approach to whole breast RT (2, 3). The concept of APBI (accelerated partial breast irradiation) which minimizes volume, treatment number and duration, has been demonstrated to be appropriate for low-risk patients (4–7). Clinical trials have explored more efficient fractionation for whole breast RT (8, 9) and novel approaches to APBI. Technical progress in radiation image guidance, planning, and treatment delivery has fostered the development of SBRT (stereotactic body radiotherapy) and stereotactic ablative radiotherapy (SABR) as an ablative treatment for primary and metastatic cancer.

In this Research Topic, New Approaches to Breast Cancer Radiotherapy, we have included original research and review articles that describe SBRT for primary and metastatic breast cancer, MR-guided RT for neoadjuvant local treatment, aggressive local management of breast cancer with synchronous metastases, and a new look at the breast boost.

The article by Lee et al. describes the first experience in Korea of stereotactic partial breast irradiation. While accelerated partial breast irradiation (APBI) has been demonstrated in randomized trials to be non-inferior to whole breast radiation in selected patients with low-risk

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Edited and reviewed by:
Timothy James Kinsella, Warren Alpert Medical School of Brown University, United States

***Correspondence:**
Geraldine Meerbott Jacobson
gmjacobson@hsc.wvu.edu

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tumors, the technique has been rarely used in Korea. Reasons include the younger age distribution of Korean breast cancer patients and smaller breast volumes that limit many APBI techniques. This article demonstrates the safety and feasibility of fractionated SBRT using Cyber knife with robotic tracking and implanted fiducials. This technique offers a non-invasive APBI modality that may be well suited to small volume breasts.

The concept of oligometastatic disease proposed in the 1990's, is that a limited number of metastases (≤5) may be amenable to ablative treatments resulting in prolonged disease-free interval or improved survival. SBRT and SABR can provide a non-invasive ablative treatment for oligometastases. The randomized phase II SABR-COMET trial demonstrated an improvement in overall survival in the SABR arm for multiple disease site, of which 20% were breast cancer (10). The role of SBRT/SABR for oligometastatic breast cancer has not been well defined. This may change with the results of NRG-BR002, an ongoing randomized study of ablative therapy for oligometastatic breast cancer. The Weykamp et al. article is a single institutional review of extracranial SBRT for oligometastatic or oligoprogressive breast cancer, which evaluates outcome and prognostic factors in this cohort of patients. As such, it contributes to the growing body of literature on the role of ablative treatment for oligometastases in breast cancer.

The rising number of breast cancer cases and the decrease in mortality from improvements in breast cancer treatment have resulted in a growing number of breast cancer survivors that experience late treatment-related toxicity. Despite the advances in radiotherapy treatment duration and oncologic outcomes with APBI (4–6), improvements in late toxicity are still needed (6, 9). Few single institutional studies have evaluated the use of neoadjuvant partial breast irradiation (PBI) treating smaller target volumes compared to adjuvant PBI, potentially reducing RT-related toxicity and improving quality of life (11–13). The evolution of Magnetic Resonance (MR)-guided RT systems has provided significant improvement in image-guided RT, with better target and normal tissue visualization. In this review paper, Groot Koerkamp et al. discuss MR-guided RT to deliver neoadjuvant PBI, outlining the steps from breast treatment planning, contouring and treatment delivery, including optimization for the use of this technique and workflow for clinical implementation.

The benefit in local control by adding a boost dose after whole breast radiotherapy has been studied in randomized trials (14, 15). However, higher radiation dose is also associated with worse cosmesis and higher cost related to additional treatment. Several guidelines have been proposed to delineate who should receive a boost, including younger patients, high grade tumors, and positive surgical margin. In this review paper, Gulstene and Raziee discuss the lack of consensus guidelines for the use of boost after hypofractionated whole breast RT and in close surgical margins, two common clinical scenarios. The authors discuss the trend in lower rates of utilization of boost after hypofractionated RT compared to conventional treatment, including the data of similar cosmetic outcomes when boost is used independent of fractionation of whole breast. The management of patients with close surgical margin has changed since ASTRO-SSO consensus guidelines recommendation of re-excision only for positive margins, resulting in significant practice variations in regard to boost for close surgical margins. The authors recommend future prospective studies to address these questions.

About 6% of newly diagnosed breast cancer patients present with Stage IV disease and an intact primary tumor. Improvements in systemic therapies including chemotherapy, HER2-target therapy, and immunotherapy have improved prognosis of this small subset of patients. The use of locoregional therapy, including surgery and/or radiotherapy has been controversial, after the results of four randomized trials showing no benefit in survival with addition of locoregional therapy (16–19). Lian et al. investigate the effect of local therapy on survival in this population using SEER database. The authors noted a decrease in the number of patients receiving surgery alone and an increase in radiotherapy alone over time. Local therapy was an independent prognostic factor for breast cancer-specific survival (BCSS). Surgery combined with radiotherapy had better BCSS compared with surgery alone and radiotherapy alone. Identification of a selected group of patients with De Novo Stage IV disease that benefit of locoregional therapy is still to be defined.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version. The individual authors added separate comments for the manuscripts they edited.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10801 women in 17 randomised trials. *Lancet* (2011) 378:1707–16. doi: 10.1016/S0140-6736(11)61629-2
2. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomized controlled trials. *Lancet Oncol* (2013) 14:1086–94. doi: 10.1016/S1470-2045(13)70386-3
3. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* (2010) 362:513–20. doi: 10.1056/NEJMoa0906260
4. Whelan TJ, Julian JA, Berrang TS, Kim DH, Germain I, Nichol AM, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. *Lancet* (2019) 394:2165–72. doi: 10.1016/S0140-6736(19)32515-2
5. Vicini FA, Cecchini RS, White JR, Arthur DA, Julian TB, Rabinovitch RA, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: randomized, phase 3, equivalent trial. *Lancet* (2019) 394:2155–64. doi: 10.1016/S0140-6736(19)32514-0

6. Meattini I, Marrazzo L, Saieva C, Desideri I, Scotti V, Simontacchi G, et al. Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: long-term results of the randomized phase III APBI-IMRT-Florence trial. *J Clin Oncol* (2020) 38:4175–83. doi: 10.1200/JCO.20.00650
7. Bhattacharya IS, Haviland JS, Kirby AM, Kirwan CC, Hopwood P, Yarnold JR, et al. Patient-reported outcomes over 5 years after whole- or partial-breast radiotherapy: longitudinal analysis of the IMPORT LOW (CRUK/06/003) phase III randomized controlled trial. *J Clin Oncol* (2018) 37:305–17. doi: 10.1200/JCO.18.00982
8. Brunt AM, Haviland JS, Sydenham M, Agrawal RK, Algurafi H, Alhasso A, et al. Ten-year results of FAST: a randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. *J Clin Oncol* (2020) 38:3261–72. doi: 10.1200/JCO.19.02750
9. Brunt AM, Haviland JS, Wheatley DA, Sydenham M, Alhasso A. Hypofractionated breast radiotherapy for 1 weeks versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from multicentre, non-inferiority, randomised, phase 3 trial. *Lancet* (2020) 395:1613–26. doi: 10.1016/S0140-6736(20)30932-6
10. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET Phase II randomized trial. *J Clin Oncol* (2020) 38:2830–8. doi: 10.1200/JCO.20.00818
11. Van der Leij F, Bosma SCJ, Vijver MJVD, Wesseling J, Vreeswijk S, Rivera S, et al. First Results of preoperative acerated partial breast irradiation trial. *Rad Oncol* (2015) 114(3):322–7. doi: 10.1016/j.radonc.2015.02.002
12. Nichols E, Kesmodel SB, Bellavance E, Drogula C, Tkaczuk K, Cohen RJ, et al. Pre-operative Accelerated Partial Breast Irradiation for early-stage breast cancer: preliminary results of a prospective, phase 2 trial. *IJROBP* (2017) 97 (4):747–53. doi: 10.1016/j.irobp.2016.11.030
13. Horton JK, Blitzblau RC, Yoo S, Geradts J, Chang Z, Baker JA, et al. Preoperative single-fraction partial breast radiation therapy: a novel phase 1 dose-escalation protocol with radiation response modifiers. *IJROBP* (2015) 92:846–55. doi: 10.1016/j.ijrobp.2015.03.007
14. Vrieling C, Werkhoven EV, Maingon P, Poortmans P, Weltens C, Rodenhuis CC, et al. Prognostic factors for local control in breast cancer after a long-term follow up in the EORTC boost vs no boost trial: a randomized clinical trial. *JAMA Oncol* (2017) 3(1):42–8. doi: 10.1001/jamaoncol.2016.3031
15. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer:20-year follow-up of a randomized phase 3 trial. *Lancet Oncol* (2015) 16(1):47–56. doi: 10.1016/S1470-2045(14)71156-8
16. Badwe R, Hawaldar R, Nair N, Kaushik R, Parmar PV, Siddique S, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. *Lancet Oncol* (2015) 16(13):1380–8. doi: 10.1016/S1470-2045(15)00135-7
17. Soran A, Ozmen V, Ozbas S, Karanlik H, Muslumanoglu M, Igci A, et al. Randomized Trial Comparing Resection of Primary Tumor with No Surgery in Stage IV Breast Cancer at Presentation: Protocol MF07-01. *Ann Surg Oncol* (2018) 25(11):3141–9. doi: 10.1245/s10434-018-6494-6
18. Fitzal F, Bjelic-Radisic V, Knauer M, Steger G, Hubalek M, Balic M, et al. Impact of Breast Surgery in Primary Metastasized Breast Cancer: Outcomes of the Prospective Randomized Phase III ABCSG-28 POSYTIVE. *Trial Ann Surg* (2019) 269(6):1163–9. doi: 10.1097/SLA.0000000000002771
19. Khan SA, Zhao F, Solin LJ, Goldstein LJ, Cella D, Basik M, et al. A randomized phase III trial of systemic therapy plus early local therapy versus systemic therapy alone in women with de novo stage IV breast cancer: A trial of the ECOGACRIN Research Group (E2108). *J Clin Oncol* (2020) 38(18_suppl): LBA2–2. doi: 10.1200/JCG.2020.38.18_suppl.LBA2

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ORIGINAL RESEARCH
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First Experience in Korea of Stereotactic Partial Breast Irradiation for Low-Risk Early-Stage Breast Cancer

*Won Hee Lee[1], Jee Suk Chang[1], Min Jung Kim[2], Vivian Youngjean Park[2], Jung Hyun Yoon[2], Se Young Kim[1], Jee Ye Kim[3], Hyung Seok Park[3], Seung Il Kim[3], Young Up Cho[3], Byeong Woo Park[3] and Yong Bae Kim[1]**

[1] Department of Radiation Oncology, Breast Cancer Center, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea, [2] Department of Radiology, Breast Cancer Center, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea, [3] Department of Surgery, Breast Cancer Center, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Purpose: Accelerated partial breast irradiation (A-PBI) in Korean women has been considered impracticable, owing to small breast volume and lack of high-precision radiotherapy experience. We present the first experience of stereotactic-PBI (S-PBI) with CyberKnife M6 to investigate feasibility of use and early toxicities in Korean women with early breast cancers.

Materials and Methods: A total of 104 breasts receiving S-PBI at our institution between September 2017 and October 2018 were reviewed. Patients were selected based on the American Society for Radiation Oncology (ASTRO), American Brachytherapy Society, American Society of Breast Surgeons, and Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology guidelines. A dose of 30 Gy in 5 fractions (NCT01162200) was used. Gold fiducials were routinely inserted near the tumor bed for tracking. Constraints regarding organs-at-risk followed the NSABP-B39/RTOG 0413 protocol.

Results: Median follow-up was for 13 months. Patients were categorized as "suitable" (71.2%) or "cautionary" (28.8%) according to 2017 the ASTRO guidelines. No tracking failure of inserted gold fiducials occurred. Median planning target volume (PTV) and PTV-to-whole breast volume ratio was 73.6 mL (interquartile range, 58.8–103.9 mL) and 17.0% (13.3–19.1%), respectively. Median PTV $V_{95\%}$, PTV D_{max}, and ipsilateral breast $V_{50\%}$ were 97.8% (96.2–98.8%), 105.3% (104.2–106.4%), and 35.5% (28.3–39.8%), respectively. No immediate post-S-PBI toxicity $\geq$ grade 2 was reported, except grade 2 induration in three breasts. All patients remain disease-free to date.

Conclusion: The first use of S-PBI in Korean women was feasible and safe for selected early breast cancer. Based on these results, we have initiated a prospective study (NCT03568981) to test S-PBI in whole-breast irradiation for low-risk early breast cancer.

Keywords: stereotactic partial breast irradiation, accelerated partial breast irradiation, breast cancer, Korean, feasibility studies, dosimetric outcomes, early toxicity

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Geraldine Meerbott Jacobson, West Virginia University, United States

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Jonathan Haas, Winthrop University Hospital, United States
Miriam Knoll, Hackensack University Medical Center, United States

***Correspondence:**
Yong Bae Kim
ybkim3@yuhs.ac

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INTRODUCTION

Accelerated partial breast irradiation (A-PBI) has emerged as an alternative to whole- breast irradiation (WBI). Previous studies in patients with low-risk early-stage breast cancer show that rates of local recurrence after A-PBI are extremely low, and most cases are limited to the vicinity of the original tumor bed (1, 2). Several prospective randomized trials demonstrated that A-PBI is associated with a non-inferior ipsilateral breast tumor recurrence (IBTR) rate, excellent cosmesis, and low treatment-related toxicity compared to WBI; however, there are some variabilities in outcomes owing to use of different radiation techniques and patient selection criteria (3–6). However, while A-PBI has been widely adopted worldwide for low-risk early breast cancer patients, A-PBI adoption remains limited in South Korea. The "Patterns of practice" study revealed that the use of A-PBI is far from widespread in South Korea (7).

With advancements in high-precision radiotherapy techniques, stereotactic body radiation therapy has become an emerging option for early breast cancer, in the form of stereotactic A-PBI (S-PBI). Several Western institutions have shown that S-PBI is a safe and feasible treatment in patients with early breast cancer who meet strict criteria (8–10).

Given this background, we have implemented A-PBI in Korean women, and report here our first experience in South Korea of using S-PBI for low-risk early breast cancer. Our aim was to investigate the feasibility and early treatment toxicity profile of S-PBI in Korean women.

MATERIALS AND METHODS

Patient Selection

We reviewed patients treated with S-PBI using CyberKnife M6 (Accuray Incorporated, Sunnyvale, CA, USA) at our institution between September 2017 and October 2018. Patients referred for radiotherapy after breast-conserving surgery for breast cancer were screened by radiation oncologists for suitability for S-PBI, based on consensus guidelines of the American Society for Radiation Oncology (ASTRO), American Brachytherapy Society (ABS), American Society of Breast Surgeons (ASBS), and Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) (11–14). Patients with invasive lobular carcinoma were eligible for S-PBI, as ASBS and ABS guidelines accept all invasive subtypes, whereas ASTRO and GEC-ESTRO guidelines accept invasive lobular carcinoma as "cautionary" and "intermediate risk," respectively. In our institution, invasive lobular carcinoma with no multiplicity found in preoperative image and surgical pathology, and satisfying other criteria in the guidelines were eligible for S-PBI. Low risk breast cancer patients in this study were defined as patients satisfying the criteria of all of the above guidelines. These low risk patients were preferentially selected for S-PBI. Physicians explained expected benefits and risks of S-PBI in contrast to conventional WBI to these selected patients, and S-PBI was given to those only who agreed the treatment. Updates to guidelines during the course of the study were applied immediately (15, 16). Ultimately, patients categorized as "suitable" as well as "cautionary" according to ASTRO guidelines were included in the study.

Patients who experienced surgical complications, had positive resection margins, were younger than 45 years, or had multicentric tumors were ineligible for S-PBI. Only patients who had a follow-up period of longer than 6 months were included in this study. All patients diagnosed with breast cancer were evaluated preoperatively using breast magnetic resonance imaging (MRI), ultrasonography, and mammography.

Fiducial Insertion and Simulation

S-PBI performed with CyberKnife M6 tracked gold fiducials inserted near the tumor bed as fiducial markers. At commencement of the study in September 2017, the gold fiducials were routinely inserted, with three gold fiducials inserted into patients' breasts at a 1 cm margin from the postoperative tumor cavity under ultrasonographic guidance. Upon insertion, the fiducials were placed in a non-coplanar position with respect to the radiographic orthogonal images of the CyberKnife M6, and the greatest possible extent of angular separation was aimed for. Mammography was performed immediately after insertion to confirm the presence of the gold fiducials, and simulation computed tomography (CT) was carried out at least 1 week later to minimize the effect of fiducial migration (17). Non-contrast 1 mm cut CT images were obtained, with the surgical scar marked by a radiopaque angiocatheter. Vac-Lok (CIVCO Radiotherapy, Coralville, IA, USA) devices were used to immobilize patients in the supine position with arms placed overhead (**Figure S1**).

Treatment Planning

Ct images were imported into MIM software (MIM Software Inc., Cleveland, OH, USA) for target delineation. The surgical tumor cavity was identified based on pre- and postoperative images, surgical clips, and the incisional scar. The clinical target volume (CTV) was defined as a uniform 1 cm margin expansion from the tumor cavity, excluding the skin and chest wall. A margin of at least 5 mm from the breast skin surface was required. Chest wall structures, such as the pectoralis muscle or ribs, were excluded from the CTV. We defined the planning target volume (PTV) as equal to the CTV, using a robotic stereotactic tracking system capable of real-time respiratory tracking. The ipsilateral breast, contralateral breast, skin, chest wall, both lungs, heart, left anterior descending coronary artery, esophagus, thyroid, and spinal cord were delineated as organs-at-risk. The contoured PTV and ipsilateral whole-breast volume were measured using MIM software. The PTV-to-whole-breast ratio (PTV/WB) was calculated for each breast. An example of target delineation for S-PBI is shown in **Figure 1**.

The prescribed dose was 30 Gy in 5 fractions, identical to that used in work reported by the University of Texas Southwestern (UTSW), which proved safe and feasible in their phase I study (NCT01162200) (10). Following this regimen, radiotherapy was delivered every other day. The S-PBI was planned such that the PTV receiving 95% of the prescribed dose ($V_{95\%}$) would be over 95% of the total PTV, and the maximum point dose

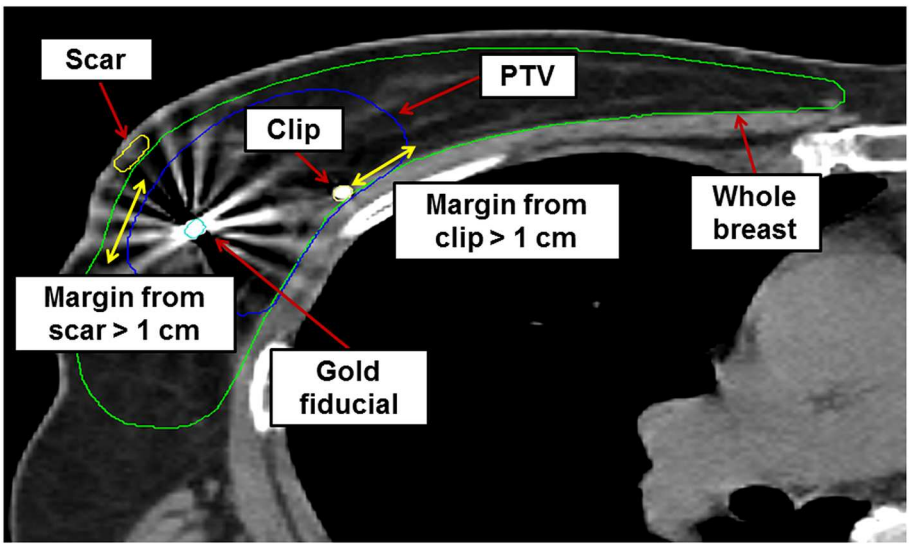

FIGURE 1 | Example of axial cut image showing target delineation for stereotactic accelerated partial breast irradiation in a sample patient. PTV, planning target volume.

(D_{max}) allowed for the PTV was <107%. Constraints to organs-at-risk mostly followed those of the NSABP B-39/RTOG 0413 protocol: ipsilateral breast $V_{50\%} < 60\%$, contralateral breast $D_{max} < 1$ Gy, ipsilateral lung $V_{30\%} < 15\%$, heart (right-sided lesions) $V_{5\%} < 5\%$, and heart (left-sided lesions) $V_{5\%} < 40\%$. Doses to the contralateral lung, skin, chest wall, and thyroid were also considered according to the NSABP B-39/RTOG 0413 protocol.

Treatment and Follow-Up

Robotic stereotactic radiotherapy using the CyberKnife M6 with fiducial tracking was used in all patients. Before every treatment, orthogonal X-ray images (from 45 and 135° angles with respect to the surface) were acquired after patient setup to visualize and align the fiducials with those in the original orthogonal X-ray images. If only two fiducials were detectable, treatment required authorization from a radiation oncologist.

Patients were interviewed and examined by the treating physician during the course of therapy, followed by routine visits every 6–12 months after S-PBI. Routine surveillance consisted of medical interviews, breast examinations, and mammography, in addition to optional breast ultrasonography and MRI. Toxicity assessment was performed using the Harvard scale, and mainly included breast skin change and induration assessments. In addition, skin thickness was measured by assessing ultrasound images obtained before surgery and 6–12 months after radiotherapy (if available). Both the skin above the tumor bed and the skin of the opposite quadrant of the ipsilateral breast (at least 5 cm away from the tumor bed) were measured at each time point.

For this study, we selected a cohort of 237 breasts that received WBI during the same period that the S-PBI was undertaken, for comparison of patient characteristics, toxicity, and skin thickness. All these breasts exhibited pathologically Tis or T1, node-negative breast cancers that received WBI of 40.05 Gy in 15 fractions, combined with a simultaneously integrated boost of 48 Gy in 15 fractions to the tumor bed by intensity-modulated radiation therapy (IMRT) after breast-conserving surgery.

Ethical Statement

The hospital's institutional review board approved the retrospective review of S-PBI patients for this study (4-2019-0054). The necessity of written informed consent was waived due to the retrospective nature of the study, and the S-PBI patients in this study were not based on a protocol-based prospective study.

RESULTS

Patient Characteristics

Between September 2017 and October 2018, 911 patients (922 breasts) were referred for radiotherapy after undergoing breast-conserving surgery. After screening, 103 patients (104 breasts; 11.3% of total referred breasts) received S-PBI. The median follow-up was 13 months (range, 6–21 months). The patient characteristics are summarized in **Table 1**. Among the total of 103 patients, the median age was 60 years (range, 46–85 years). Of the total of 104 breasts, 75 (72.1%) had invasive ductal carcinoma, with a median tumor size of 1.0 cm (range, 0.1–2.5 cm). Three patients had metastatic lymph nodes (1–2 sentinel lymph node metastases with no perinodal extension). The tumor grade was 1 or 2 in 97 breasts (93.3%). None of the tumors had lymphovascular invasion, and all had clear resection margins. All tumors except 1 were estrogen receptor-positive. The breasts were categorized as "suitable" (71.2%) or "cautionary" (28.8%) according to the updated 2017 ASTRO guidelines. The most common reason for classification as "cautionary" was extensive intraductal carcinoma of <3 cm (18 breasts). Compared to the pathologically Tis or T1, node negative WBI cohort, the S-PBI

TABLE 1 | Patient characteristics (per breast).

Characteristic	*N*	%
Age (years; median, range)	60 (46–85)	
Pathologic type		
DCIS	15	14.4
IDC	75	72.1
Other	14	13.5
Tumor size (cm; median, range)	1.0 (0.1–2.5)	
N stage		
N0	101	97.1
N1	3	2.9
RM		
Negative	104	100.0
Close or Positive	0	0.0
Grade		
Grade 1	53	51.0
Grade 2	44	42.3
Grade 3	7	6.7
LVI		
No	103	99.0
Yes	1	1.0
EIC		
No	86	82.7
Yes	18	17.3
ER		
No	1	1.0
Yes	103	99.0
ASTRO guideline category		
Suitable	74	71.2
Cautionary	30	28.8
Unsuitable	0	0.0

DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; N stage, nodal stage; RM, resection margin; LVI, lymphovascular invasion; EIC, extensive intraductal carcinoma; ER, estrogen receptor; ASTRO, American Society for Radiation Oncology.

TABLE 2 | Treatment characteristics.

Characteristic	*N*	%
Number of tracked gold fiducials (among inserted)		
3 fiducials	81	77.9
2 fiducials	23	22.1
Treatment time (min; median, range)	33 (25-45)	

TABLE 3 | Dosimetric outcomes of stereotactic partial breast irradiation.

Dosimetric parameters	Median (interquartile range)
PTV $V_{95\%}$	97.8% (96.2–98.8%)
PTV D_{max}	105.3% (104.2–106.4%)
Ipsilateral breast $V_{50\%}$	35.5% (28.3–39.8%)
Contralateral breast D_{max}	0.8 Gy (0.6–1.1 Gy)
Ipsilateral lung V_{20Gy}	0.1% (0.0–0.3%)
Ipsilateral lung V_{10Gy}	2.2% (1.5–3.0%)
Contralateral lung $V_{1.5Gy}$	0.0% (0.0–0.0%)
Heart mean dose (left-sided lesions)	0.7 Gy (0.5–1.2 Gy)
Heart mean dose (right-sided lesions)	0.4 Gy (0.3–0.5 Gy)
Skin D_{max}	26.6 Gy (25.5–28.0 Gy)
Chest wall D_{max}	29.8 Gy (29.2–30.5 Gy)

$V_{x\%}$, percentage of volume receiving X% of the prescribed dose; V_{xGy}, percentage of volume receiving X Gy; D_{max}, maximum point dose.

patients had younger age ($p < 0.01$), lower tumor grade ($p < 0.01$), less lymphovascular invasion ($p < 0.01$), and more estrogen receptor positivity ($p < 0.01$) (**Table S1**). The WBI cohort had trend toward more positive resection margin, larger tumor size, and more extensive intraductal component, although not statistically significant.

Technical Feasibility of S-PBI

All 104 breasts had real-time tracking with inserted gold fiducials. All three inserted fiducials were trackable in 83 breasts (75.5%), and two of the three were trackable in 27 breasts (24.5%). There was no treatment interruption, reinsertion of fiducials, or re-simulation owing to tracking failure. The median treatment time was 33 min (range, 25–45 min) (**Table 2**).

Dosimetric Outcomes

The median whole-breast volume was 481.1 mL [interquartile range (IQR), 375.1–646.4 mL], while the median PTV was 73.6 mL (IQR, 58.8–103.9 mL). The median PTV/WB was 17.0% (IQR, 13.3–19.1%). The dosimetric parameters for S-PBI in this study are shown in **Table 3**, while the PTV and PTV/WB in this study are compared to those found in other similar S-PBI studies in **Table S2**. The median PTV $V_{95\%}$ was 97.8% (IQR, 96.2–98.8%), and PTV D_{max} was 105.3% (IQR, 104.2–106.4%). The median ipsilateral breast $V_{50\%}$, ipsilateral lung V_{10Gy}, and contralateral lung $V_{1.5Gy}$ were 35.5% (IQR, 28.3–39.8%), 2.2% (IQR, 1.5–3.0%), and 0.0% (IQR, 0.0–0.0%), respectively. The median skin and chest wall D_{max} were 26.6 Gy (IQR, 25.5–28.0 Gy) and 29.8 Gy (IQR, 29.2–30.5 Gy), respectively. The mean dose for the heart was a median of 0.7 Gy (IQR, 0.5–1.2 Gy) and 0.4 Gy (IQR, 0.3–0.5 Gy), for left- and right-sided lesions, respectively. **Figure 2** shows an example of an isodose line and dose-volume histogram of an S-PBI plan that successfully satisfied all dosimetric goals.

Physician-Rated Early Toxicity and Change in Breast Skin Thickness

After a median follow-up of 13 months, no IBTR, regional recurrence, or distant metastasis was detected in any of the patients. **Figure 3** shows the toxicity data at the end of each follow-up period. Immediately after S-PBI, 87 breasts (83.7%) had no breast skin color change, and 66 (63.4%) had no palpable induration. No grade 2 or higher breast color change was reported, and grade 2 induration was observed in 3 breasts, which had persisted threesince immediately after the completion of surgery. After 6 months of follow-up, grade 1 color change and grade 1 palpable induration were noted in

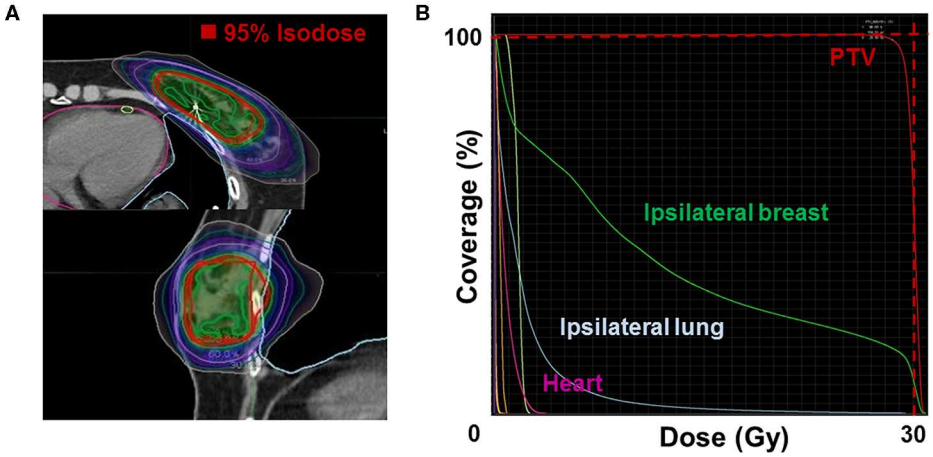

FIGURE 2 | Example of **(A)** an isodose line (upper: axial; lower: sagittal) and **(B)** dose-volume histogram of a stereotactic accelerated partial breast irradiation plan that satisfies all dosimetric goals. PTV, planning target volume.

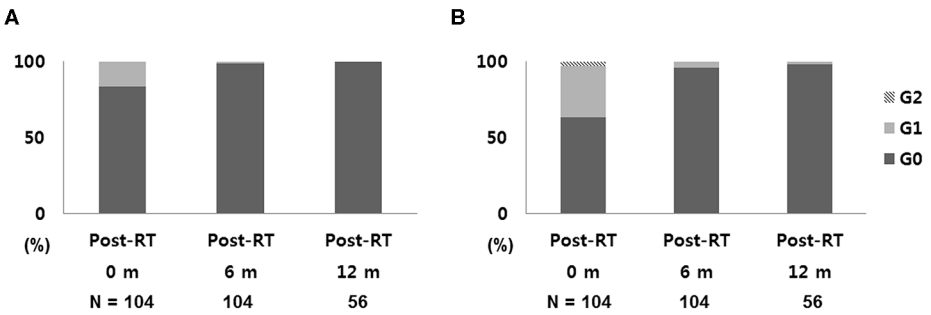

FIGURE 3 | Early toxicity outcomes: **(A)** skin change and **(B)** breast induration after S-PBI. S-PBI, stereotactic partial breast irradiation; m, months.

one and four breasts, respectively. Among the 56 breasts where follow-up of 1 year was reached, none showed color change and only one showed grade 1 induration. The WBI cohort showed similar results after 1 year of follow-up (135 breasts), as all except two breasts with grade 1 color change showed no color change, and two breasts had grade 1 induration. In terms of other treatment-related toxicities after S-PBI, one breast had grade 1 breast edema, and one breast had grade 2 breast cellulitis which was successfully managed with oral antibiotics. No rib fracture or radiation pneumonitis was noted after S-PBI.

The change in skin thickness from before surgery to 6–12 months after radiotherapy was compared in the skin above the tumor bed and the skin of the opposite quadrant of the tumor bed (**Figure 4**). In S-PBI breasts, the median increase in skin thickness above the tumor bed was 800 μm (range, −600 to +3,200 μm), while skin of the opposite quadrant of the tumor bed in the ipsilateral breast increased by a median of 100 μm (range, −600 to +1,100 μm). In WBI breasts, the median increase in skin thickness above the tumor bed was 1,000 μm (range, −200 to +5,200 μm), while in the opposite quadrant of the tumor bed in the ipsilateral breast it increased by a median of 400 μm (range, −300 to +3,300 μm). Changes in skin thickness of the opposite quadrant were significantly smaller in the S-PBI group compared to the WBI group ($p < 0.01$).

DISCUSSION

Our first experience of S-PBI revealed that it is a feasible and safe treatment in low-risk early breast cancer in Korean women. The high-precision radiotherapy technique showed excellent fiducial tracking abilities, with excellent dosimetric outcomes and minimal early toxicity, despite the relatively small breast volumes. To our knowledge, this is the first experience of S-PBI use in Korean women.

Over the last three decades, prospective trials using various techniques have demonstrated that A-PBI is non-inferior to WBI (3–6). However, only 4.7% of total radiation oncology facilities in South Korea use A-PBI (7). This could be due to several reasons. First, patient selection is limited, owing to the younger age distribution of breast cancer in South Korea compared to the Western hemisphere (18). In addition, even though many radiation oncologists have sufficient clinical experience in high-precision radiotherapy, they usually feel that it is unnecessary

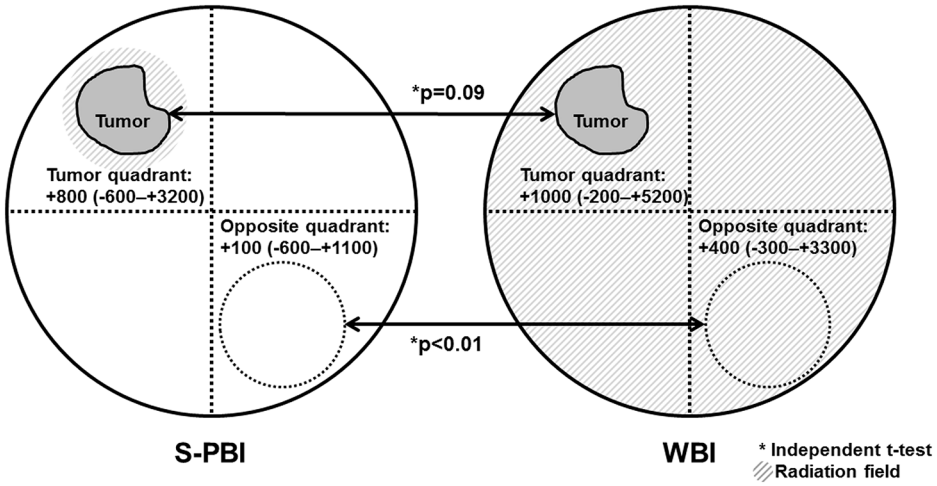

FIGURE 4 | Changes in skin thickness after surgery followed by stereotactic partial breast irradiation (S-PBI) or whole-breast irradiation (WBI). Changes in skin thickness are defined as breast skin thickness before surgery, subtracted from breast skin thickness at 1 year after radiation. Values are presented in micrometers (range).

to apply such techniques because of the relatively small breast volumes and favorable clinical outcomes with conventional techniques. Lastly, but most practically, the Korean National Health Insurance (KNHI) program's reimbursement system, based on fraction number, has been a major obstacle to use of A-PBI.

Radical advances in IMRT and image guidance have provided a potential breakthrough for A-PBI, as shown in an Italian prospective trial (19). S-PBI, a further developed form of high-precision IMRT, has the potential to circumvent the limitations in Korean women. While A-PBI using conventional IMRT may carry risks owing to respiratory motion uncertainty, the novel high-precision technique of S-PBI addresses this with real-time motion tracking via fiducial markers, allowing minimal PTV margin expansion. We believe that S-PBI could provide a breakthrough for A-PBI in South Korea.

Our S-PBI was performed after careful patient selection. We considered all available A-PBI guidelines for selecting the patients. Only 6.2% of total breasts referred for radiotherapy were selected for S-PBI, and none were categorized as "unsuitable" according to the ASTRO guidelines. The results of strict patient selection are well described in **Table S1**, showing S-PBI patients bearing much more favorable clinicopathologic features. We were especially cautious when selecting patients aged 45–50 years, the gray zone among different guidelines (11–16). In this age group, only those without any relative contraindications were selected. As a result, despite the young age at which breast cancer frequently occurs in South Korea, as mentioned previously (18), we successfully managed to select an optimal group of Korean women for S-PBI.

We have also shown the technical feasibility of S-PBI in low-risk patients with early breast cancer. S-PBI was highly successful in terms of fiducial utilization, as no tracking failure occurred with routine gold fiducial insertion. All patients deemed eligible for A-PBI successfully underwent the procedure after fiducial insertion. The safety and efficacy of gold fiducial insertion for A-PBI has been well established by the UTSW, whose methods we followed (17). Moreover, the treatment time per fraction remained reasonable, compared to the UTSW S-PBI study (10). Each S-PBI treatment may be relatively longer than that for WBI, but the substantially shortened treatment total fraction ultimately saves both time and costs. Our first attempt at S-PBI in South Korea successfully proved that it is technically feasible in Korean women.

The dosimetric analyses in this study showed that S-PBI with minimal PTV expansion resulted in excellent dosimetric parameters in Korean women. During our initial S-PBI setup, we intended to set dose-volume constraints and define PTV based on the NSABP B-39/RTOG 0413 protocol, which establishes PTV as a uniform 1 cm expansion of CTV. However, we believed that modification of the definition of PTV was necessary, considering poor dosimetric outcomes in the ipsilateral breast in the Korean Radiation Therapy Oncology Group (KROG) 0804 study (20). Based on the high precision of S-PBI with successful fiducial tracking, and the preference of our surgeons for cavity shave margins over inked margins, we chose a much smaller PTV definition than that of the NSABP B-39/RTOG 0413 protocol.

As a result, not only were the ipsilateral breast dosimetric goals successfully satisfied in all breasts in our study, but the median ipsilateral breast $V_{50\%}$ in our study was 35.8%, much lower than that of the KROG study (20). Compared to the Western A-PBI reports (**Table S2**), the ipsilateral breast $V_{50\%}$ in our patients was as low as those in Western S-PBI studies (9, 21, 22), and dramatically lower than in A-PBI studies using three-dimensional conformal radiation therapy (3D-CRT), ranging from 42 to 49% (23–26). This could be explained by the substantial PTV margin expansion mandated by respiratory and setup uncertainties in 3D-CRT. Likewise, our delicate S-PBI

planning achieved consistent dosimetric profiles compared to those observed in Western S-PBI studies in other organs-at-risk, without compromising PTV coverage or creating PTV hot spots (9, 21, 22). These results demonstrated that S-PBI could overcome the disadvantage of relatively small breast volumes in Korean women.

Early toxicities after S-PBI were minimal in our study. Although a few grade 1 or 2 palpable indurations due to surgery were observed, most patients did not experience any breast color change or palpable induration immediately after S-PBI. Any minimal color change or palpable induration had mostly recovered by the first follow-up visit after S-PBI, similar to the WBI group. Breast skin thickness is well known for its relationship with palpable induration, and radiotherapy is a well-known cause of thickening (27). In our study, the change in skin thickness after S-PBI appears to be limited to the tumor bed, in contrast to the diffuse skin thickening observed after WBI. These favorable toxicity profiles are comparable to those of the UTSW's identical dose cohort (10). They are also remarkably more favorable than those observed in prospective 3D-CRT A-PBI trials (6, 28, 29). In contrast to widespread concerns about hypofractionated radiotherapy in South Korea, S-PBI proved to be safe in terms of early toxicities in Korean women, despite small breast volumes.

Despite these promising findings, the KNHI reimbursement system still acts as a major barrier to S-PBI. The unreasonably low total income from S-PBI compared to WBI would ultimately prevent adoption of any form of A-PBI in Korean hospitals, even with sufficient proof of the technical feasibility and safety of S-PBI. Given the rapid developments in high-precision radiotherapy, the reimbursement system based on fraction size as a new parameter is a solution that should be actively considered (30). This could motivate hospitals to reduce loadings for patients, and ultimately provoke widespread use of A-PBI in Korean women.

Limitations of our study are its retrospective, single-institution nature, the limited number of patients, and the relatively short follow-up period. Longer follow-up may reveal whether these promising dosimetric outcomes and minimal early toxicity would translate into rare late toxicities and excellent cosmesis. However, we firmly believe that our first experience of S-PBI in Korean women will act as a cornerstone for widespread use of A-PBI in this population.

In conclusion, the first experience of S-PBI in Korean women demonstrated that it is a feasible and safe treatment for low-risk early breast cancer patients. Despite smaller breast volumes, outstanding dosimetric outcomes and successful fiducial tracking were achieved, with rare early toxicities. Based on this first experience in South Korea, we have initiated a prospective study (NCT03568981) to test S-PBI in terms of cosmesis and quality of life compared to WBI in early breast cancer.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Human Reasearch Protection Center, Severance Hospital, Yonsei University Health System. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

WL and JC contributed to data collection. WL wrote the initial manuscript with YK. YK had a huge role in setting up S-PBI in our department, with help from breast surgeons, who are JK, HP, SIK, YC, and BP. The breast surgeons, JK, HP, SIK, YC, and BP contributed to the discussion part where surgical margin and acute toxicity is described. VP, JY, and MK contributed in fiducial insertion during S-PBI in our institution and actively participated in the manuscript by giving ideas to measure skin thickness as an outcome for this study. SYK was the main dosimetrist of our S-PBI. Not only she created plans that successfully satisfied dosimetric goals, but also participated in setting up the CT-simulation and treatment process.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.00672/full#supplementary-material

Figure S1 | Example of simulation of stereotactic partial breast irradiation using Vac-Lok (CIVCO Radiotherapy, Coralville, IA, USA) for immobilization in supine position with arms placed overhead.

Table S1 | Patient characteristics compared between stereotactic partial breast irradiation (S-PBI) and the whole breast irradiation (WBI) cohort[a] (per breast).

Table S2 | Comparison of PTV, PTV-to-whole-breast ratio, and irradiated ipsilateral breast volume among published studies of external beam accelerated partial breast irradiation.

REFERENCES

1. Fisher ER, Sass R, Fisher B, Gregorio R, Brown R, Wickerham L. Pathologic findings from the National Surgical Adjuvant Breast Project (protocol 6). II. Relation of local breast recurrence to multicentricity. *Cancer.* (1986) 57:1717–24.
2. Veronesi U, Marubini E, Mariani L, Galimberti V, Luini A, Veronesi P, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma:

long-term results of a randomized trial. *Ann Oncol.* (2001) 12:997–1003. doi: 10.1023/A:1011136326943
3. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet.* (2014) 383:603–13. doi: 10.1016/s0140-6736(13)61950-9
4. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet.* (2016) 387:229–38. doi: 10.1016/s0140-6736(15)00471-7
5. Vargo JA, Verma V, Kim H, Kalash R, Heron DE, Johnson R, et al. Extended (5-year) outcomes of accelerated partial breast irradiation using MammoSite balloon brachytherapy: patterns of failure, patient selection, and dosimetric correlates for late toxicity. *Int J Radiat Oncol Biol Phys.* (2014) 88:285–91. doi: 10.1016/j.ijrobp.2013.05.039
6. Julian TB, Costantino JP, Vicini FA, White JR, Winter KA, Arthur DW, et al. Early toxicity results with 3-D conformal external beam therapy (CEBT) from the NSABP B-39/RTOG 0413 Accelerated Partial Breast Irradiation (APBI) Trial. *Int J Radiat Oncol Biol Phys.* (2011) 81:S7. doi: 10.1016/j.ijrobp.2011.06.014
7. Park HJ, Oh DH, Shin KH, Kim JH, Choi DH, Park W, et al. Patterns of practice in radiotherapy for breast cancer in Korea. *J Breast Cancer.* (2018) 21:244–50. doi: 10.4048/jbc.2018.21.e37
8. Haas JA, Witten MR, Cotrutz C, Blacksburg SR, Catell D, Clancey O, et al. Stereotactic body radiation therapy for early-stage breast cancer using a robotic linear accelerator. *Int J Radiat Oncol Biol Phys.* (2017) 99:S7. doi: 10.1016/j.ijrobp.2017.06.033
9. Obayomi-Davies O, Kole TP, Oppong B, Rudra S, Makariou EV, Campbell LD, et al. Stereotactic accelerated partial breast irradiation for early-stage breast cancer: rationale, feasibility, and early experience using the cyberknife radiosurgery delivery platform. *Front Oncol.* (2016) 6:129. doi: 10.3389/fonc.2016.00129
10. Rahimi A, Thomas K, Spangler A, Rao R, Leitch M, Wooldridge R, et al. Preliminary results of a phase 1 dose-escalation trial for early-stage breast cancer using 5-fraction stereotactic body radiation therapy for partial-breast irradiation. *Int J Radiat Oncol Biol Phys.* (2017) 98:196–205.e2. doi: 10.1016/j.ijrobp.2017.01.020
11. Smith BD, Arthur DW, Buchholz TA, Haffty BG, Hahn CA, Hardenbergh PH, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys.* (2009) 74:987–1001. doi: 10.1016/j.ijrobp.2009.02.031
12. Shah C, Vicini F, Wazer DE, Arthur D, Patel RR. The American Brachytherapy Society consensus statement for accelerated partial breast irradiation. *Brachytherapy.* (2013) 12:267–77. doi: 10.1016/j.brachy.2013.02.001
13. American Society of Breast Surgeons. *Consensus Statement on Accelerated Partial Breast Irradiation*. Columbia, MD: American Society of Breast Surgeons (2018). Available online at: https://www.breastsurgeons.org/about/statements/PDF_Statements/APBI.pdf (accessed July 22, 2018).
14. Polgar C, Van Limbergen E, Potter R, Kovacs G, Polo A, Lyczek J, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence 2009. *Radiother Oncol.* (2010) 94:264–73. doi: 10.1016/j.radonc.2010.01.014
15. Correa C, Harris EE, Leonardi MC, Smith BD, Taghian AG, Thompson AM, et al. Accelerated partial breast irradiation: executive summary for the update of an ASTRO Evidence-Based Consensus Statement. *Pract Radiat Oncol.* (2017) 7:73–9. doi: 10.1016/j.prro.2016.09.007
16. Shah C, Vicini F, Shaitelman SF, Hepel J, Keisch M, Arthur D, et al. The American Brachytherapy Society consensus statement for accelerated partial-breast irradiation. *Brachytherapy.* (2018) 17:154–70. doi: 10.1016/j.brachy.2017.09.004
17. Seiler S, Rahimi A, Choudhery S, Garwood D, Spangler A, Cherian S, et al. Ultrasound-guided placement of gold fiducial markers for stereotactic partial-breast irradiation. *AJR Am J Roentgenol.* (2016) 207:685–8. doi: 10.2214/AJR.15.14771
18. Kweon SS. Updates on cancer epidemiology in Korea, 2018. *Chonnam Med J.* (2018) 54:90–100. doi: 10.4068/cmj.2018.54.2.90
19. Livi L, Meattini I, Marrazzo L, Simontacchi G, Pallotta S, Saieva C, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer.* (2015) 51:451–63. doi: 10.1016/j.ejca.2014.12.013
20. Jeong JU, Yoon JH, Park MH, Yoon MS, Song JY, Nam TK, et al. A phase I/II trial to evaluate the technical feasibility of partial breast irradiation with three-dimensional conformal radiation therapy in Korean women with stage I breast carcinoma: an initial report of the korean radiation therapy oncology group (KROG) Study 0804. *Cancer Res Treat.* (2015) 47:18–25. doi: 10.4143/crt.2013.202
21. Lozza L, Fariselli L, Sandri M, Rampa M, Pinzi V, De Santis MC, et al. Partial breast irradiation with CyberKnife after breast conserving surgery: a pilot study in early breast cancer. *Radiat Oncol.* (2018) 13:49. doi: 10.1186/s13014-018-0991-4
22. Vermeulen SS, Haas JA. CyberKnife stereotactic body radiotherapy and CyberKnife accelerated partial breast irradiation for the treatment of early breast cancer. *Transl Cancer Res.* (2014) 3:295–302. doi: 10.3978/j.issn.2218-676X.2014.07.06
23. Hepel JT, Tokita M, MacAusland SG, Evans SB, Hiatt JR, Price LL, et al. Toxicity of three-dimensional conformal radiotherapy for accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys.* (2009) 75:1290–6. doi: 10.1016/j.ijrobp.2009.01.009
24. Jagsi R, Ben-David MA, Moran JM, Marsh RB, Griffith KA, Hayman JA, et al. Unacceptable cosmesis in a protocol investigating intensity-modulated radiotherapy with active breathing control for accelerated partial-breast irradiation. *Int J Radiat Oncol Biol Phys.* (2010) 76:71–8. doi: 10.1016/j.ijrobp.2009.01.041
25. Chen PY, Wallace M, Mitchell C, Grills I, Kestin L, Fowler A, et al. Four-year efficacy, cosmesis, and toxicity using three-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys.* (2010) 76:991–7. doi: 10.1016/j.ijrobp.2009.03.012
26. Formenti SC, Truong MT, Goldberg JD, Mukhi V, Rosenstein B, Roses D, et al. Prone accelerated partial breast irradiation after breast-conserving surgery: preliminary clinical results and dose-volume histogram analysis. *Int J Radiat Oncol Biol Phys.* (2004) 60:493–504. doi: 10.1016/j.ijrobp.2004.04.036
27. Wratten CR, O'Brien P C, Hamilton CS, Bill D, Kilmurray J, Denham JW. Breast edema in patients undergoing breast-conserving treatment for breast cancer: assessment via high frequency ultrasound. *Breast J.* (2007) 13:266–73. doi: 10.1111/j.1524-4741.2007.00420.x
28. Rabinovitch R, Moughan J, Vicini F, Pass H, Wong J, Chafe S, et al. Long-term update of NRG oncology RTOG 0319: a Phase 1 and 2 trial to evaluate 3-dimensional conformal radiation therapy confined to the region of the lumpectomy cavity for stage I and II breast carcinoma. *Int J Radiat Oncol Biol Phys.* (2016) 96:1054–9. doi: 10.1016/j.ijrobp.2016.08.042
29. Olivotto IA, Whelan TJ, Parpia S, Kim DH, Berrang T, Truong PT, et al. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. *J Clin Oncol.* (2013) 31:4038–45. doi: 10.1200/JCO.2013.50.5511
30. Yoon WS. Fraction size: a new paradigm for radiotherapy payment. *J Korean Med Sci.* (2019) 34:e94. doi: 10.3346/jkms.2019.34.e94

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Extracranial Stereotactic Body Radiotherapy in Oligometastatic or Oligoprogressive Breast Cancer

Fabian Weykamp[1,2,3], *Laila König*[1,2,3], *Katharina Seidensaal*[1,2,3], *Tobias Forster*[1,2,3], *Philipp Hoegen*[1,2,3], *Sati Akbaba*[1,2,3], *Stephan Mende*[1,2,3], *Stefan E. Welte*[1,2,3], *Thomas M. Deutsch*[4], *Andreas Schneeweiss*[3], *Jürgen Debus*[1,2,3,5,6,7] and *Juliane Hörner-Rieber*[1,2,3,6]*

[1] Department of Radiation Oncology, Heidelberg University Hospital, Heidelberg, Germany, [2] Heidelberg Institute of Radiation Oncology (HIRO), Heidelberg, Germany, [3] National Center for Tumor Diseases (NCT), Heidelberg, Germany, [4] Department of Obstetrics and Gynecology, Heidelberg University Hospital, Heidelberg, Germany, [5] Department of Radiation Oncology, Heidelberg Ion-Beam Therapy Center (HIT), Heidelberg University Hospital, Heidelberg, Germany, [6] Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany, [7] German Cancer Consortium (DKTK), Partner Site Heidelberg, Heidelberg, Germany

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Edited by:
Geraldine Meerbott Jacobson, West Virginia University, United States

Reviewed by:
Jon Cacicedo, Cruces University Hospital, Spain
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***Correspondence:**
Juliane Hörner-Rieber
juliane.hoerner-rieber@med.uni-heidelberg.de

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Purpose/Objective: Oligometastatic disease (OMD) and oligoprogressive disease (OPD) describe tumor states with a limited metastasization. In contrast to other disease states, treatment of OMD or OPD has not yet become common for breast cancer. We sought to understand the outcomes and toxicities of this treatment paradigm.

Material/Methods: We retrospectively analyzed female breast cancer patients with OMD (≤3 metastases) or OPD (1 progressive lesion) who received stereotactic body radiotherapy (SBRT) for their respective extracranial metastatic lesions between 01/2002 and 07/2019. Survival analysis was performed using the Kaplan-Meier method with log-rank test being used for evaluation of significance. Cox regression was used to detect prognostic outcome factors. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE v. 5.0).

Results: Forty-six patients (70% OMD; 30% OPD) with 58 lesions met criteria for inclusion. The majority of treatments (34 out of 58; 58.6%) were delivered from 2017 to 2018. Treatment sites were bone, liver, lung [$n = 19$ (33%) for each site], and adrenal gland [$n = 1$ (1%)]. Median biologically effective dose (BED at $\alpha/\beta = 10$) was 81.6 Gy (range: 45–112.5 Gy) and median planning target volume was 36.60 mL (range: 3.76–311.00 mL). At 2 years, local control (LC) was 89%, distant control (DC) was 44%, progression free survival (PFS) was 17% and overall survival (OS) was 62%. Multivariate analysis identified the diagnosis of a solitary metastasis as an independent prognostic factor for superior DC (HR = 0.186, CI [0.055; 0.626], $p = 0.007$) and PFS (HR = 0.363, CI [0.152; 0.863], $p = 0.022$). OS was independently inferior for patients treated at a higher age (HR = 5.788, CI [1.077; 31.119] $p = 0.041$). Nine (15.5%) grade I° and one (1.7%) grade II° toxicities were recorded, with no grade III° or higher toxicities.

Conclusion: Extracranial SBRT in breast cancer patients with OMD or OPD was well-tolerated with excellent LC. SBRT should especially be offered to younger OMD and OPD breast cancer patients with only one metastasis. The increase in utilization since 2017 points toward a growing acceptance of SBRT for OMD and OPD in breast cancer.

Keywords: oligometastatic, oligoprogression, stereotactic body radiotherapy (SBRT), breast cancer, local control, progression free survival, distant control, overall survival

BACKGROUND AND PURPOSE

The concept of oligometastatic disease (OMD) was first described by Weichselbaum and Hellman during the 1990s (1). Up to 10% of patients with metastatic breast cancer are thought to belong to this category (2). Recent studies defined OMD as a maximum of five present metastases (3–5). A few years after the initial description of OMD, surgical metastasectomy emerged as a promising treatment modality (6). A non-invasive alternative to treat limited metastases is stereotactic body radiotherapy (SBRT), which has been proven effective and well-tolerated during the last decade (7–10). SBRT allows to deliver high ablative radiation doses, while sparing surrounding normal tissue. Two recently published randomized controlled Phase-II trials, one of them including 20% breast cancer patients (SABR-COMET trial), could demonstrate, that local therapy of metastases in patients with OMD leads to a prolonged progression free survival (PFS) and even increases overall survival (OS) (11, 12). Moreover, Wong et al. demonstrated in a study with a similar design (61 patients; 12% breast cancer histology), that breast cancer histology was the strongest positive prognostic factor for local control (LC), PFS and OS (13). It was already shown during the first pilot studies in this field, that breast cancer patients benefit significantly better from ablative radiation of their oligometastases than any other primary tumor (14).

On the contrary, the concept of oligoprogressive disease (OPD) describes a widespread tumor stage, where usually up to five metastases are progressive after systemic therapy. In times of emerging targeted therapies and immunotherapies the concept of OPD gains importance as few resistant subclones leading to progression of solitary metastases are observed more frequently (15). OMD and OPD are not well-established as disease concepts for breast cancer patients, in contrast to other tumor entities. On the contrary, the recent 8th edition of the TNM classification of lung cancer describes a M-subgroup for patients with OMD (16). There is no such subclassification in breast cancer patients with OMD (17). This is a surprising fact, considering a 10 year OS of up to 75% in breast cancer patients with single bone metastases which surmounts the OS of many other tumors, even in their early stage (4). A survey of Canadian medical oncologists revealed that 65% would rather start systemic therapy in breast cancer patients with OMD, than even consider a SBRT at all (18). As SBRT for oligometastatic breast cancer patients is a relatively new disease concept, most studies in this area only include a small number of patients and mostly consist of only one specific (5) or predominant (19–21) location of metastases. Additionally, OPD patients are not represented in these studies.

The aim of the study was therefore to evaluate outcome and prognostic factors following SBRT in oligometastatic and oligoprogressive breast cancer patients.

METHODS

Patient and Treatment Characteristics

We retrospectively analyzed female breast cancer patients treated with ablative SBRT for their extracranial metastases in the Department of Radiation Oncology at Heidelberg University Hospital from 01/2002 to 07/2019. Patients were excluded from the study if they were not treated with SBRT, but with palliative intent or palliative doses. SBRT was defined as an ablative dose with single fraction doses > 4 Gy and number of fractions < 10.

SBRT was performed if patients were either classified inoperable, technically or medically, or refused surgical resection. At our center, patients with brain metastases are only treated with SBRT for extracranial metastases under special circumstances (e.g., excellent performance status and completed whole brain radiotherapy).

A 4D computed tomography (CT) scan with 3 mm slice thickness was used for treatment planning except for bone metastases. Furthermore, contrast-enhanced CT scans were applied for target delineation in all patients except for the ones who were treated with SBRT for bone metastases. When available, diagnostic magnetic resonance (MR) images or positron emission tomography (PET) scans were additionally used for target volume delineation. For lesions in the lower lung, an abdominal compression device was used. Patients were positioned in an individually shaped vacuum mattress. Number of fractions and single-fraction doses were adjusted to size and location of the metastases. Lung metastases were classified to be peripheral or central according to the RTOG definition (22, 23). Before 2012, lung SBRT was performed with a single fraction of 24–30 Gray (Gy) prescribed to the 90–95% isodose line. From 2012 on, peripheral lung metastases were treated with three fractions of 15–18 Gy, prescribed to the minimum 65% isodose covering at least 95% of the PTV. Central lesions received eight fractions of 7.5 Gy prescribed to the minimum 80% isodose line covering at least 95% of the PTV and very central lesions (<2 cm distance to main bronchus) 10 fractions of 5 Gy to the 95% isodose. The same fractionation schemes were applied to liver and adrenal metastases. Bone metastases received three fractions of 9 Gy, prescribed to the minimum 80% isodose covering at least 95% of the PTV. Before 2012, a single fraction of 24 Gy was used,

TABLE 1 | Analysis of patient characteristics at initial diagnosis.

Estrogen positive	35	76.0%
Progesterone positive	29	63.0%
Her2/neu rich	8	20.5% ($n = 39$)
"Triple negative"	3	7.7% ($n = 39$)
Well-differentiated (G1)	2	4.9% ($n = 41$)
Moderately differentiated (G2)	25	61.0% ($n = 41$)
Poorly differentiated (G3)	14	34.1% ($n = 41$)
Histology		
Ductal	15	39.5% ($n = 38$)
Lobular	6	15.8% ($n = 38$)
Ductolobular	1	2.6% ($n = 38$)
Not otherwise specified	16	42.1% ($n = 38$)
UICC stage at initial diagnosis		
Early stage (I–II)	22	47.8%
Locally advanced (III)	9	19.6%
Metastatic disease (IV)	15	32.6%
Initial chemotherapy	33	71.7%
- Neoadjuvant	18	54.5%
- Adjuvant	15	32.6%
- Anthracycline/cyclophosph-amide/taxane based	18	54.5%
- Plus anti Her2/neu agent	7	21.2%
Initial surgery	46	100%
Breast conserving surgery	24	52.2%
Mastectomy	22	47.8%
Axillary dissection	34	73.9%

TABLE 2 | Analysis of patient characteristics at time of or after SBRT.

Median age	55 years	Range 27–82 years
Median Karnofsky Score	90%	Range 70–100%
Median time from initial diagnosis to metastasization*	43 months	Range 5.4–265.0 months
≤3 metastases in total (=oligometastatic)	32	70.0%
≥3 metastases in total, but 1 progressive (=oligoprogressive)	14	30.0%
Any metastases in other organs	16	34.8%
- Bone	9	56.3%
- Liver	4	25.0%
- Brain	1	6.3%
- Bone, liver, brain	1	6.3%
- Bone, liver, lung, lymphatic	1	6.3%
Chemotherapy within 4 weeks before SBRT	8	17.4%
Chemotherapy within 4 weeks after SBRT	7	15.2%
Number of SBRT lesions		
One	37	80.4%
Two	8	17.4%
Three	1	1.7%

SBRT, stereotactic body radiotherapy.
**excluding patients with synchronous metastasization.*

prescribed to the minimum 80% isodose covering at least 95% of the PTV.

The biologically effective dose (BED) was used to compare treatment schemes with the clinical result. An α/β ratio of 10 Gy was assumed for the metastases. BED was calculated using the linear-quadratic model (24).

$$\mathbf{BED\,(Gy)} = \mathbf{fractional\ dose} \times \mathbf{number\ of\ fractions}\left(1+\frac{\mathbf{fractional\ dose}}{\boldsymbol{\alpha/\beta}}\right)$$

Endpoints and Statistical Methods

LC, distant control (DC), PFS and OS were calculated starting from the last day of SBRT. In this study, LC refers to the high dose area surrounding the irradiated metastases. Recurrences anywhere else where classified as distant failure. LC was calculated based on each lesion. DC, PFS and OS were calculated per patient. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE v. 5.0).

First follow-up was performed 6 to 8 weeks after completion of the SBRT with a clinical examination as well as a contrast fluid CT or MRI scan of the irradiated area. Further follow-up was done according to German guidelines and regularly included a contrast-enhanced CT scan of the thorax/abdomen every 3 months.

LC, DC, PFS and OS were estimated using the Kaplan-Meier method. Survival curves were compared between groups in an univariate analysis applying the log-rank test or cox regression analysis. Multivariate cox models were performed including all variables with p ≤0.1 from univariate analysis. A $p \leq 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS software (IBM SPSS Version 24.0).

This retrospective study was approved by the Ethics committee of the University Hospital Heidelberg (Reference number: S-855/2019).

RESULTS

Most patients had early stage breast cancer at primary diagnosis (47.8%) and received neoadjuvant or adjuvant chemotherapy (71.7%), mainly anthracycline/cyclophosphamide/taxane based regimes. All patients had a controlled or recently resected primary tumor, with adequate adjuvant radiotherapy of the breast or chest wall according to current national guidelines (25–27). Further patient characteristics are shown in **Table 1**. **Table 2** illustrates patient characteristics at time of the respective SBRT. Median age at time of SBRT was 55 years (range 27–82), with a median time from primary diagnosis to development of metastases of 43.0 months (range 5.4–265.0). The majority of patients had oligometastatic disease (70%), with a maximum of three present and therefore irradiated metastases in this subgroup. Oligoprogressive patients (30%) had had one progressive lesion which was treated with SBRT. Lung, liver and bone were equally represented as SBRT organs (each 33%), with a single case of a metastasis in the adrenal gland (1%). All 14 OPD patients also had stable metastases in further organs, and two OMD patients received SBRT in two different organs. In

TABLE 3 | Analysis of the SBRT lesions.

Localization of SBRT lesion		
- Bone	19	32.8%
- Lung	19	32.8%
- Liver	19	32.8%
- Adrenal gland	1	2.0%
Histological sample taken from metastasis	3	5.2%
SBRT lesions progressive in planning CT scan	6	10.3%
Median prescribed total dose	28 Gy	Range 24–60 Gy
Median fractions	3	Range 1–10
Median dose inhomogeneity	80%	Range 65–100%
Median EQD2 ($\alpha/\beta = 10$)	68.8 Gy	Range 40.0–93.4 Gy
Median BED ($\alpha/\beta = 10$)	81.6 Gy	Range 45–112.5 Gy
BED ($\alpha/\beta = 10$) >100 Gy	25	43.1%
PTV volume	median 36.6 mL	Range 3.8–311.0 mL
Result in first follow-up		
Complete remission	1	1.7%
Partial remission	21	36.2%
Stable disease	34	58.6%
Progressive disease	2	3.4%
Toxicity CTC I°	9	15.5%
Toxicity CTC II°	1	1.7%

BED, biologically effective dose; CTC, Common Terminology Criteria; PTV, planning target volume; SBRT, stereotactic body radiotherapy.

total, 16 patients (34.8%; **Table 2**) had metastases in more than one organ. Within 4 weeks prior to SBRT, 27 patients (58.7%) received endocrine therapy, nine patients (19.5%) received anti-Her2/neu treatment and eight patients (17.4%) received chemotherapy (taxan $n = 3$; vinca alkaloid $n = 2$; capecitabine, pegylated liposomal doxorubicin, carboplatin/gemcitabine, each $n = 1$). Within 4 weeks after SBRT, 26 patients (56.5%) received endocrine therapy, nine patients (19.5%) received anti-Her2/neu treatment and seven patients (15.2%) received chemotherapy (vinca alkaloid $n = 3$; capecitabine, pegylated liposomal doxorubicin, carboplatin/gemcitabine, carboplatin, each $n = 1$). No significant difference in terms of acute toxicity was found in patients, who had received chemotherapy prior to or after SBRT ($p = 0.823$). **Table 3** describes details of the SBRT treatment and toxicities. Median prescribed total dose was 28 Gy (range 24–60) applied in a median of three fractions (range 1–10) resulting in a median biologically effective dose of 81.6 Gy (range 45.0–112.5 Gy). Overall response rate was 96.6%, with two progressive SBRT lesions (3.4%) in the first follow-up. Nine (15.5%) grade I° toxicities were documented after first follow-up, namely pneumonitis ($n = 4$), reflux esophagitis, abdominal pain, nausea, fatigue and liver edema (each $n = 1$). One (1.7%) grade II° pneumonitis was described. No grade III° or higher toxicities were reported. Toxicity as well as LC, DC, PFS, and OS were not significantly different before the year 2012, when single dose SBRT was used ($p > 0.05$).

Median clinical follow-up was 21 months (range 2.4–93.0). During the analyzed period from 01/2002 to 07/2019, the majority of patient (58.6%) was treated recently, beginning in the year 2017 (**Figure 1**).

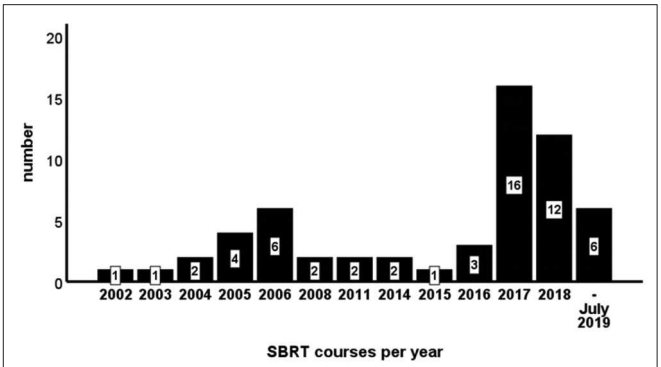

FIGURE 1 | Stereotactic body radiotherapy (SBRT) courses per year.

Local Control

Four out of 58 lesions (6.9%) recurred during follow-up period with 1 and 2 year LC of 92.2% and 88.5% (**Figure 2A**). Univariate analysis (**Table 4**) revealed Karnofsky Performance Score (KPS) (HR = 0.840, CI [0.721; 0.977], $p = 0.024$) and estrogen receptor positivity (HR = 0.098, CI [0.010; 0.946], $p = 0.045$; **Figure 3A**) as positive prognostic factors, whereas OPD was associated with worse local control (HR = 11.234, CI [1.159; 108.877], $p = 0.037$; **Figure 3B**) as well as chemotherapy 4 weeks before or after SBRT (HR = 14.149, CI [1.461;137.050], $p = 0.022$). After adjusting for potential confounding variables on multivariate analysis, none of the aforementioned variables stayed significant (**Table 5**).

Distant Control

Twenty out of 46 patients (43.5%) were diagnosed with progression distant to the SBRT lesion during follow-up. One and 2 year DC rates were 68.6% and 43.9% (**Figure 2B**). KPS (HR = 0.932, CI [0.884; 0.990], $p = 0.020$) and bone metastases as the SBRT treating site (HR = 0.225, CI [0.065; 0.775], $p = 0.018$; **Figure 3C**) appeared to be significant favorable prognostic factors in univariate analysis (**Table 4**), with the overall number of one metastasis at borderline significance level (HR = 0.371, CI [0.134; 1.025], $p = 0.056$). Patients with higher KPS (HR = 0.918, CI [0.850; 0.992], $p = 0.030$) and a solitary metastasis (HR = 0.186, CI [0.055; 0.626], $p = 0.007$; **Figure 3D**) were at significantly lower risk of developing distant progression in multivariate analysis (**Table 5**).

Progression Free Survival

During follow-up, 28 progressions or deaths occurred (60.9%). One and 2 year PFS rates were 54.3 and 16.6% (**Figure 2C**). KPS (HR = 0.932, CI [0.888; 0.977], $p = 0.004$), estrogen receptor positivity (HR = 0.449, CI [0.204; 0.985], $p = 0.046$) and bone metastases as SBRT lesions (HR = 0.172, CI [0.051; 0.573], $p = 0.004$) were shown to be positive prognostic factors in univariate analysis, with single metastasis at borderline significance level (HR = 0.491, CI [0.219; 1.101], $p = 0.084$) and a higher BED as a significant unfavorable factor (HR = 1.019, CI [1.001; 1.036], $p = 0.035$). In multivariate analysis, only bone metastases as SBRT target (HR = 0.022, CI [0.001; 0.351, $p = 0.007$; **Figure 4A**) and

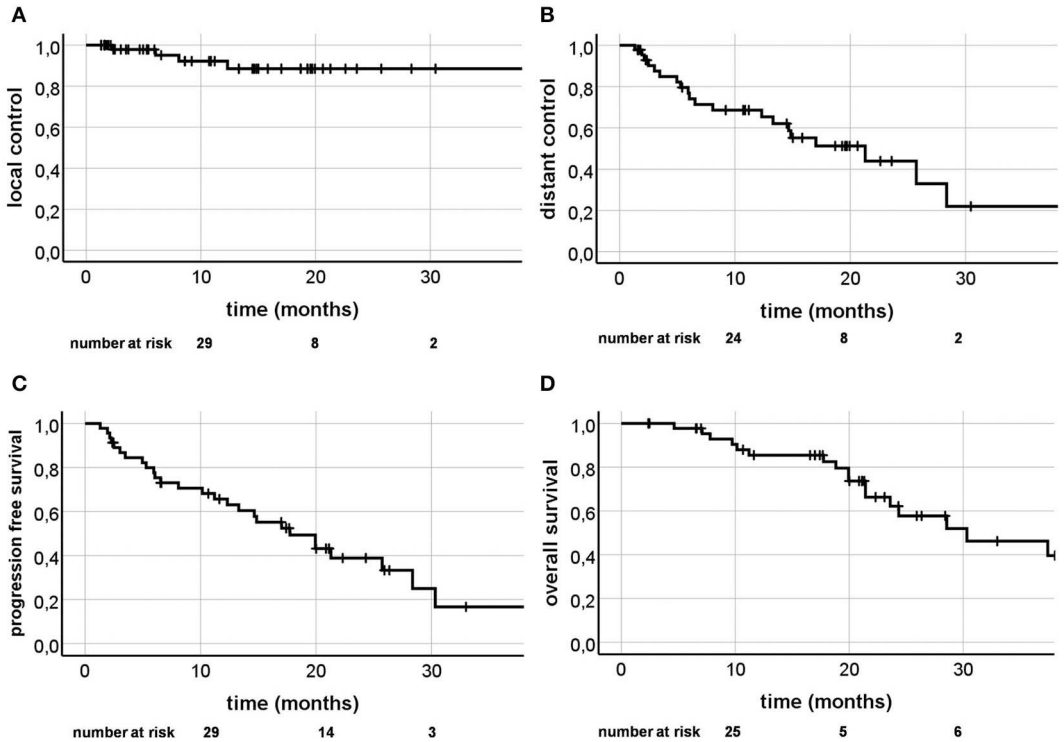

FIGURE 2 | Kaplan-Meier curves; Local control **(A)**, distant control **(B)**, progression free survival **(C)**, and overall survival **(D)**.

TABLE 4 | Univariate analysis of prognostic factors influencing LC, DC, PFS, and OS.

	LC			DC			PFS			OS		
Factors	**HR**	**95%-CI**	***p***	**HR**	**95%-CI**	***p***	**HR**	**95%-CI**	***p***	**HR**	**95%-CI**	***p***
Age above 55 years	0.358	[0.000; 80.068]	*0.358*	2.370	[0.962; 5.840]	***0.061***	1.803	[0.823; 3.949]	*0.141*	2.618	[1.030; 6.653]	***0.043***
Karnofsky Performance Score	0.840	[0.721; 0.977]	***0.024***	0.932	[0.884; 0.990]	***0.020***	0.932	[0.888; 0.977]	***0.004***	0.962	[0.910; 1.017]	*0.170*
Estrogen receptor positive	0.098	[0.010; 0.946]	***0.045***	0.384	[0.140; 1.049]	***0.062***	0.449	[0.204; 0.985]	***0.046***	0.587	[0.242; 1.426]	*0.239*
Her2/neu receptor rich	3.812	[0.533; 27.256]	*0.182*	1.969	[0.669; 5.798]	*0.219*	1.878	[0.669; 5.274]	*0.232*	0.158	[0.020; 1.270]	***0.083***
Grading G3	1.294	[1.204; 11.623]	*0.872*	1.556	[0.580; 4.173]	*0.380*	1.775	[0.757; 4.163]	*0.187*	3.751	[1.169; 12.044]	***0.026***
SBRT target = bone metastasis	0.019	[0.000; 66.083]	*0.341*	0.225	[0.065; 0.775]	***0.018***	0.172	[0.051; 0.573]	***0.004***	0.117	[0.015; 0.886]	***0.038***
Number of metastases=1	0.019	[0.000; 71.124]	*0.347*	0.371	[0.134; 1.025]	***0.056***	0.491	[0.219; 1.101]	***0.084***	0.916	[0.378; 2.223]	*0.847*
Oligoprogressive disease	11.234	[1.159; 108.877]	***0.037***	1.644	[0.656; 4.118]	*0.289*	1.806	[0.813; 4.011]	*0.146*	1.834	[0.753; 4.467]	*0.182*
BED ($\alpha/\beta = 10$)	1.010	[0.971; 1.049]	*0.630*	1.076	[0.997; 1.035]	*0.109*	1.019	[1.001; 1.036]	***0.035***	1.025	[1.000; 1.051]	***0.046***
PTV volume at least 37mL	1.618	[0.226; 11.590]	0.887	0.392	[0.572; 3.383]	*0.466*	1.583	[0.724; 3.460]	*0.250*	3.199	[1.157; 8.847]	***0.025***
Chemotherapy within 4 weeks before or after SBRT	14.149	[1.461; 137.050]	**0.022**	1.534	[0.553;4.252]	*0.411*	1.625	[0.679;3.883]	0.275	0.644	[0.214; 1.941]	0.434

BED, biologically effective dose; CI, confidence interval; DC, distant control; HR, hazard ratio; LC, local control; OS, overall survival; PFS, progression free survival; PTV, planning target volume; SBRT, stereotactic body radiotherapy. The variables BED ($\alpha/\beta = 10$) and Karnofsky Performance Score were continuous variables, all other were analyzed as categorical variables. For Her2/neu receptor rich, data was missing for 7 patients and 5 patients had missing data on Grading G3. Bold and italic values indicate $p < 0.1$. Bold, italic, and underlined values indicate $p < 0.05$.

a solitary metastasis (HR = 0.363, CI [0.152; 0.863], $p = 0.022$; **Figure 4B**) remained as significant favorable factors (**Table 5**).

Overall Survival

Twenty-two patients (47.8%) died during follow-up time. One and 2 year OS were 85.4 and 62.1% (**Figure 2D**). Univariate analysis revealed age over 55 years (HR = 2.618, CI [1.030; 6.653], $p = 0.043$), tumor grading G3 (HR = 3.751, CI [1.169; 12.044], $p = 0.026$; **Figure 4C**), higher BED (HR = 1.025, CI [1.000; 1.051], $p = 0.046$), and PTV volume ≥37mL (HR = 3.199, CI [1.157; 8.847], $p = 0.025$) as significant unfavorable factors influencing OS. Bony lesions as SBRT target was identified a favorable prognostic factor (HR = 0.117, CI [0.015; 0.886], $p = 0.038$; **Figure 4D**). In multivariate analysis, only age over 55 years

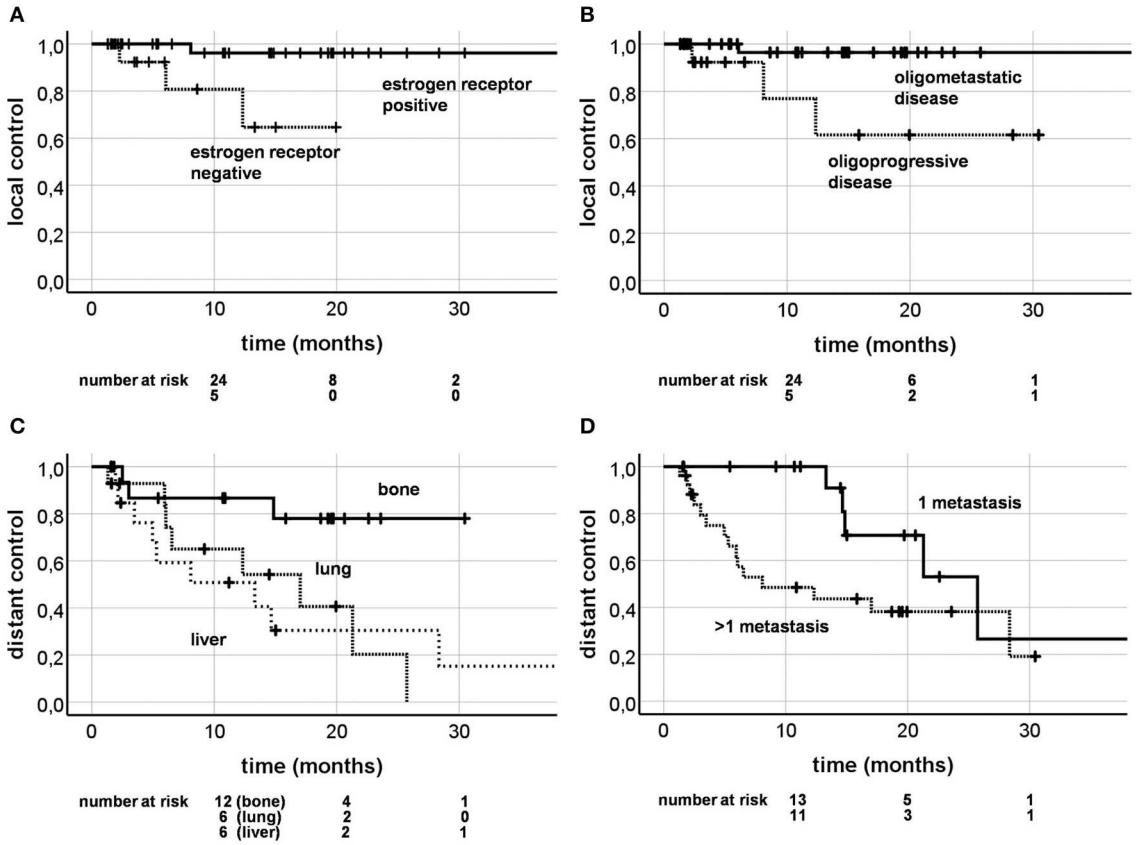

FIGURE 3 | Kaplan-Meier curves; local control depending on estrogen receptor positivity (**A**; $p = 0.045$) and oligoprogressive disease (**B**; $p = 0.037$); distant control depending on the irradiation site (**C**; $p = 0.018$) and present metastases (**D**; $p = 0.056$).

TABLE 5 | Multivariate analysis of prognostic factors influencing LC, DC, PFS, and OS.

	LC			DC			PFS			OS		
Factors	**HR**	**95%-CI**	***p***	**HR**	**95%-CI**	***p***	**HR**	**95%-CI**	***p***	**HR**	**95%-CI**	***p***
Age above 55 years				2.627	[0.970; 7.118]	***0.057***				5.788	[1.077; 31.119]	***0.041***
Karnofsky Performance Score	0.985	[0.774; 1.253]	*0.900*	0.918	[0.850; 0.992]	***0.030***	0.950	[0.891; 1.012]	*0.112*			
Estrogen receptor positive	0.198	[0.009; 4.308]	*0.303*	1.838	[0.524; 6.440]	*0.342*	2.005	[0.688; 5.848]	*0.203*			
Her2/neu receptor rich										1.090	[0.096; 12.437]	*0.944*
Grading G3										1.321	[0.328; 5.320]	*0.695*
SBRT target = bone metastasis				0.272	[0.072; 1.030]	**0.055**	0.022	[0.001; 0.351]	***0.007***	0.849	[0.057; 12.585]	*0.905*
Number of metastases = 1				0.186	[0.055; 0.626]	***0.007***	0.363	[0.152; 0.863]	***0.022***			
Oligoprogressive disease	3.044	[0.210; 44.028]	*0.414*									
BED ($\alpha/\beta = 10$)							0.965	[0.923; 1.008]	*0.112*	1.023	[0.966; 1.083]	*0.438*
PTV volume at least 37 mL										3.493	[0.846; 14.425]	***0.084***
Chemotherapy within 4 weeks before or after SBRT	6.904	[0.377; 126.476]	*0.193*									

BED, biologically effective dose; CI, confidence interval; DC, distant control; HR: hazard ratio; LC, local control; OS, overall survival; PFS, progression free survival; PTV, planning target volume; SBRT, stereotactic body radiotherapy. The variables BED ($\alpha/\beta = 10$) and Karnofsky Performance Score were continuous variables, all other were analyzed as categorical variables. For Her2/neu receptor rich, data was missing for 7 patients and 5 patients had missing data on Grading G3. Bold and italic values indicate $p < 0.1$. Bold, italic, and underlined values indicate $p < 0.05$.

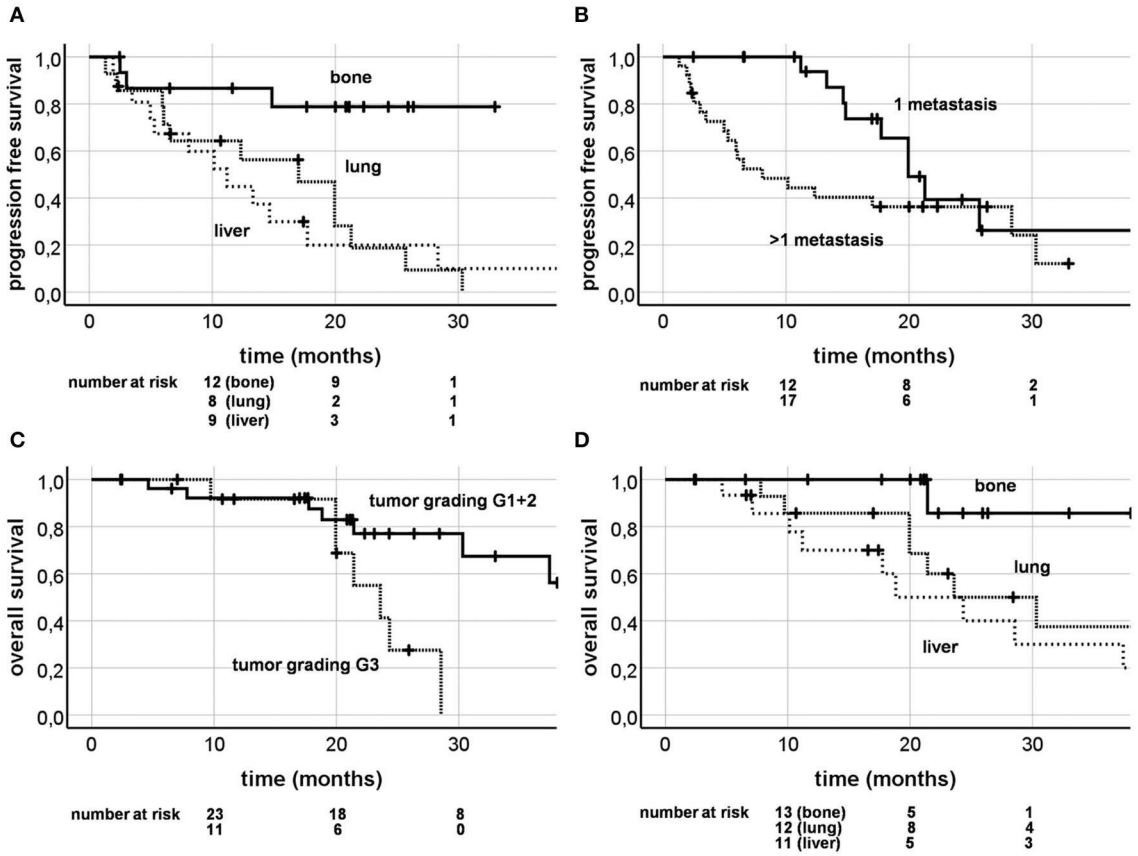

FIGURE 4 | Kaplan-Meier curves; progression free survival depending on the irradiation site (**A**; $p = 0.004$) and present metastases (**B**; $p = 0.084$); overall survival depending on tumor grading (**C**; $p = 0.026$) and on irradiation site (**D**; $p = 0.038$).

stayed significant (HR = 5.788, CI [1.077; 31.119], $p = 0.041$; **Table 5**).

DISCUSSION

In this retrospective study consisting of 46 patients who received ablative SBRT for their 58 extracranial metastases, we sought to describe outcome patterns in comparison to the resulting toxicity and searched for prognostic factors. Our findings resemble the statement concluded in a review by Dorota Kwapisz, that the ideal patients for SBRT in oligometastatic or oligoprogressive breast cancer are young, have a good performance status and a low tumor burden (28) (**Tables 4**, **5**).

In our study, the dominant failure pattern was distant, with 1 and 2 year LC of 92 and 89% vs. DC of 69 and 44%. **Table 6** illustrates the most important further studies analyzing SBRT in the treatment of OMD patients. LC at 2 years was shown to be excellent in our study (89%) and comparable to other studies (88–100%; **Table 6**) (3, 5, 19, 20, 29, 30). In our study, patients with OPD or chemotherapy within 4 weeks before or after SBRT, had significantly less local control rates (**Table 4**; **Figure 3B**). This fact has already been described for lung cancer patients treated with SBRT, who showed inferior LC if they had received systemic therapy before (31). This may be due to the changes in tumor biology through systemic treatment, selecting resistant clones (15). Patients with previous systemic therapies might require higher doses to overcome this effect. Furthermore, prior chemotherapy as a negative prognostic factor for local control has also been reported in a large cohort of patients treated with hepatic SBRT ($n = 452$ lesions) (32). Interestingly, 56 breast cancer patients were included in the cohort and also showed inferior LC after the admission of prior chemotherapy. In our study, DC at 2 years (44%) was comparable to the only other study (50%) that analyzed this outcome factor (29). Yet, 2 year PFS and OS in our study were rather low (17% and 62%). This might be due to the fact, that 30% patients had OPD and therefore were more likely to show further disease progression shortly after SBRT. On the other hand, the rather low PFS and OS could also be explained by the high proportion of lung and liver metastases (66%) and consequently lower proportion of bone metastases (33%). Bone metastases are, in contrast to lung and liver metastases, a positive prognostic factor for OS (4), which was also shown in our study (**Table 4**). Moreover, PFS and OS at 2 years were highest in the study population by David et al. with bone only metastases (65 and 100%) (30) and lowest in the study population by Onal et al. with liver only metastases (8 and 57%) (5).

TABLE 6 | Prospective and retrospective studies investigating ablative, stereotactic radiotherapy for oligometastastic breast cancer.

	Patients, design, characteristics	Treated lesions	Gy @ isodose	Significant prognostic factors in multivariate analysis	CTC toxicity	2 y. LC	2 y. DC	2 y. PFS	2 y. OS
Milano et al. (29)	$n = 40$; ≤5 mets; KPS ≥70 Prospective pilot study OMD: 100%	$n = 85$ 17% bone 22% lung 39% liver 18% lymph node	10 × 5 @ 80%*	Negative: GTV (*patient* LC)	III°: $n = 1$ pleural/peri-cardial effusion ≥IV°: 0%*	80% (4 y.)	50%	44%	76%
Yoo et al. (19)	$n = 50$; ≤5 mets retrospective OMD: 100%	$n = n/a$ 100% bone	"median dose 30 Gy (range 20–60)"	Positive: hormone receptor positivity (OS) and single bone metastasis (OS)	n/a	70% (3 y.)	n/a	n/a	85%
Scorsetti et al. (20)	$n = 33$; ≤5mets (lung/liver); ECOG ≤2 observational study OMD: 100%	$n = 43$ 100% lung or liver	3 × 18.75–25 Gy @ 95% 4 × 12 Gy@ 95%	None	I–II°: 18% ≥III°: 0%	90%	n/a	27%	66%
Onal et al. (5)	$n = 22$; ≤5 mets retrospective OMD: 100%	$n = 29$ 100% liver	3 × 18 Gy @ 90%	None	III°: $n = 2$ (rib fracture, duodenal ulcer) ≥IV°: 0%	88%	n/a	8%	57%
Trovo et al. (3)	$n = 54$; ≤5 mets; ECOG ≤1; prospective, multicenter phase II trial FDG-PET/CT staging OMD: 100%	$n = 92$ 66% bone 25% lymph node 5% liver 4%lung	3 × 10–15 Gy (isodose n/a) 25 × 2,4 Gy IMRT	None	II°: $n = 2$ (pain/fatigue) ≥III°: 0%	97%	n/a	53%	95%
David (30)	$n = 15$; ≤3 bone only mets; ECOG ≤2 prospective Na-18-F-PET/CT staging OMD: 100%	$n = 19$ 100% bone	1 × 20 Gy @ 80%	Not tested	I°: 67% II°: 27% ≥III°: 0%	100%	n/a	65%	100%
Weykamp et al. (present study)	$n = 46$; KPS ≥70 retrospective OMD: 70% (≤3 mets) OPD: 30% (1 met progressive)	$n = 58$ bone 33% lung 33% liver 33% adrenal 1%	1 × 24–30 @ 90–95% 3 × 15–18 @ 65% 8 × 7.5 @ 80% 10 × 5 @ 90% (bone: 1 × 24 @ 80% or 3 × 9 @ 80%)	Positive: overall present mets ≤ 1 (DC; PFS), KPS (DC); bone metastasis as SBRT target (PFS) Age ≥55 (OS)	I°: 16% II°: 2% ≥III°: 0%	89%	44%	17%	62%

**not mentioned in the cited paper, "10 × 5 Gy" was obtained from a different citation investigating additional other primary tumors (14).*

CTC, Common Terminology Criteria; DC, distant control; ECOG, Eastern Cooperative Oncology Group Performance Status; FDG, fluoro-deoxy-glucose; Gy, Gray; LC, local control; Mets, metastases; n/a, not available; Na-18-F, natriumfluoride-18; OMD, oligometastatic disease; OPD, oligoprogressive disease; OS, overall survival; PET, positron emission tomography; PFS, progression free survival; y, years.

Significant positive prognostic factors for PFS in multivariate analysis were overall number of metastases ($n = 1$) and bone metastases as the SBRT target (**Table 5**; **Figures 4A,B**), the latter was already shown by Yoo et al. (19). Furthermore, patients with one metastastic lesion were already reported to have a more favorable outcome (29). A higher BED as a prognostic factor for superior OS has been described by Hong et al. (33) in 361 patients (16% breast cancer) treated with SBRT for their oligometastases. Surprisingly, in our study, univariate analysis described a higher BED as a negative prognostic factor for PFS and OS (**Table 4**). This is probably caused by the fact that bone metastases had a better outcome with less radiation dose. Accordingly, BED did not remain a significant factor in multivariate analysis.

Furthermore, patients who received SBRT for their bone metastases showed a significantly longer OS in our univariate analysis. However, this did not persist in multivariate analysis, after adjusting for age. As Milano et al. had described before,

breast cancer patients with bone metastases are more likely to be of young age (4). A PTV volume of at least 37 mL was a negative prognostic factor for OS in univariate analysis, which might reflect a higher tumor burden. Similar results were shown by Milano et al. describing a higher GTV negatively influencing LC (**Table 6**) (29). As expected, tumor grading G3 had a negative impact on OS in univariate analysis (**Table 4**), reflecting a more aggressive disease.

Interestingly, the KPS was a significant positive prognostic factor for LC, DC and PFS (**Table 4**) and stayed significant for DC in multivariate analysis (**Table 5**). The above mentioned two prospective studies on SBRT for oligometastatic breast cancer by Milano et al. and David et al. used a certain performance index threshold for inclusion into the respective study (29, 30). Similarly, our cohort consists of patients with a relatively high KPS, with a median of 90% and a range of 70–100%.

Recently, Murano et al. reported that SBRT in oligometastatic breast cancer patients resulted in an increase or even new appearance of polyfunctional CD4+ and CD8+ T-cells against breast cancer antigens (34). Since SBRT is thought to promote immunogenic cell death, it may also lead to a treatment benefit not only in local control of the irradiated lesion, but also in distant control (35, 36). This might be caused by the so called "abscopal effect," which describes a "response at a distance from the irradiated volume" (37). However, breast cancer is so far not considered a typical immunogenic cancer (38). Nonetheless, especially triple negative or Her2/neu rich breast cancer seems to show a high proportion of tumor infiltrating immune cells (39, 40). Results of a recently published Phase-III trial could show a prolonged disease free survival in metastasized breast cancer patients when adding Atezolizumab to Nab-Paclitaxel chemotherapy (41). SBRT is thought to be less affected by a high mutation load, which leads to the interesting concept to use SBRT to postpone a change of systemic therapy (15). For patients with oligoprogressive lung, renal cell or prostate cancer, several recent studies have already investigated the role of additional local treatment to the progressive lesions (31, 42–44). To date, there has been no dedicated study published for breast cancer patients with OPD which goes beyond the plane description of the progression pattern (45).

To our knowledge, our study is the first in the field to also include and analyze oligoprogressive patients with widespread metastatic disease. Patients with OMD had a maximum of three present metastases, compared to a maximum of one progressive lesion in patients with OPD, pointing toward a more cautious and stricter definition of limited metastatic disease in case of oligoprogressive disease. Patients with OPD showed an inferior, yet satisfying local control after SBRT, which may be due to a higher mutation burden in these patients. A dose escalation concept could be investigated to overcome this suspected higher radioresistance. Interestingly, DC, PFS and OS were not significantly different in OPD patients, which would have been expected otherwise due to their worse prognosis from the outset (45). Moreover, though nearly a third of our study population consists of OPD patients, outcome was still comparable to other studies in the field only including oligometasatic breast cancer patients (**Table 6**). Consequently, SBRT should also be investigated in OPD patients in further studies. In future, SBRT for a few progressive metastases in widespread metastatic disease could help to postpone a change in systemic therapy and hence help to change a fatal cancer state into a chronic disease.

The main limitation of this study is its retrospective design. Unlike other, prospective studies, patients did not receive fluoro-deoxy-glucose (FDG) positron emission tomography (PET) or natirumfluoride-18 (Na-18-F) PET scan as initial staging (3, 30). Hence, those patients with less favorable outcome in our study might have had more metastases than detected during contrast enhanced CT scan staging.

The above mentioned survey of Canadian medical oncologists revealed a high proportion of doubt considering SBRT for oligometastastic breast cancer (18). Studies investigating high dose chemotherapy for metastatic breast cancer were mainly conducted when Weichselbaum and Hellman developed their theory of OMD in the 1990s (1, 46). Compared to standard dose chemotherapy, little benefit could be achieved with this approach, at the cost of higher toxicity (46). These experiences may have led to the perception, that therapy escalation for (oligo)metastatic breast cancer patients in general is rather harmful. A certain amount of skepticism due to the lack of phase III studies for SBRT in oligometastatic breast cancer is understandable. Moreover, the SABR-COMET trial, which can be considered one of the most important studies addressing the concept of ablative therapies in OMD in general, revealed a risk of CTC V° toxicities (4.5%; each $n = 1$ radiation pneumonitis, pulmonary abscess and subdural hemorrhage after surgery due to the SBRT). To our best knowledge, no grade IV or higher toxicity was described in the aforementioned studies on SBRT in breast cancer patients with OMD (**Table 6**), with only very few grade III toxicities. In consistence with other studies in the field, our study demonstrates SBRT as a well-tolerated ablative therapy. The growing acceptance of OMD and even OPD as a disease concept is reflected by our recently increasing treatment sessions (**Figure 1**).

Based on the promising results of the SABR-COMET trial, future prospective studies need to focus on OMD and OPD in breast cancer to evaluate the benefit of SBRT added to systemic treatment. The German OLIGOMA study will address this particular topic in near future and includes breast cancer patients with up to five metastases (47). The NRG BR002 study was commenced in 2016 and investigates additional SBRT or surgery in breast cancer patients with OMD compared to standard therapy alone (48). Nonetheless, robust data on the expected benefit of local ablative therapy in breast cancer patients with OMD and OPD will take years to be available. Until then, SBRT in oligometastastic or oligoprogressive breast cancer patients should be strongly considered as a highly effective treatment option to eradicate local metastases with only mildest toxicity. As shown in our retrospective study with an equal proportion of the three most common metastatic organs (bone, liver, and lung), SBRT provides excellent local control and is

safe outside a clinical trial. Moreover, in times of more and more expensive systemic therapy options, SBRT offers a cost effective treatment approach compared to other local ablative treatments (49–51).

CONCLUSION

Extracranial SBRT in breast cancer patients with OMD or OPD is well-tolerated with excellent LC. The ideal patient is of young age, has only one metastasis and reaches an excellent performance score. The increase in utilization since 2017 points toward a growing acceptance of SBRT for OMD and OPD in breast cancer. Future trials are highly needed to consolidate the role of local ablative treatment in both oligometastatic and oligoprogressive breast cancer patients.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Heidelberg University Faculty of Medicine. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FW carried out the data collection, performed the statistical analysis, and drafted the manuscript. LK, KS, TF, PH, SA, SM, and SW helped with data collection as well as figure and table preparation. FW, LK, KS, SA, and JH-R were involved in patient treatment. TD and AS contributed the gynecological knowledge of the manuscript and were involved in pre-radiotherapy treatment. JH-R and JD participated in the study design and helped to draft the manuscript. All the authors were responsible for data interpretation, participated in manuscript revisions, and approved the final manuscript.

REFERENCES

1. Weichselbaum R, Hellman S. Oligometastases. *J Clin Oncol*. (1995) 13:8–10. doi: 10.1200/JCO.1995.13.1.8
2. Hanrahan EO, Broglio KR, Buzdar AU, Theriault RL, Valero V, Cristofanilli M, et al. Combined-modality treatment for isolated recurrences of breast carcinoma: update on 30 years of experience at the University of Texas MD Anderson Cancer Center and assessment of prognostic factors. *Cancer Interdisc Int J Am Cancer Soc*. (2005) 104:1158–71. doi: 10.1002/cncr.21305
3. Trovo M, Furlan C, Polesel J, Fiorica F, Arcangeli S, Giaj-Levra N, et al. Radical radiation therapy for oligometastatic breast cancer: results of a prospective phase II trial. *Radiother Oncol*. (2018) 126:177–80. doi: 10.1016/j.radonc.2017.08.032
4. Milano MT, Katz AW, Zhang H, Huggins CF, Aujla KS, Okunieff P. Oligometastatic breast cancer treated with hypofractionated stereotactic radiotherapy: some patients survive longer than a decade. *Radiother Oncol*. (2019) 131:45–51. doi: 10.1016/j.radonc.2018.11.022
5. Onal C, Guler OC, Yildirim BA. Treatment outcomes of breast cancer liver metastasis treated with stereotactic body radiotherapy. *Breast*. (2018) 42:150–6. doi: 10.1016/j.breast.2018.09.006
6. Bartlett EK, Simmons KD, Wachtel H, Roses RE, Fraker DL, Kelz RR, et al. The rise in metastasectomy across cancer types over the past decade. *Cancer*. (2015) 121:747–57. doi: 10.1002/cncr.29134
7. Hong JC, Salama JK. The expanding role of stereotactic body radiation therapy in oligometastatic solid tumors: what do we know and where are we going? *Cancer Treat Rev*. (2017) 52:22–32. doi: 10.1016/j.ctrv.2016.11.003
8. Rieber J, Streblow J, Uhlmann L, Flentje M, Duma M, Ernst I, et al. Stereotactic body radiotherapy (SBRT) for medically inoperable lung metastases—a pooled analysis of the German working group "stereotactic radiotherapy". *Lung Cancer*. (2016) 97:51–8. doi: 10.1016/j.lungcan.2016.04.012
9. Sterzing F, Brunner TB, Ernst I, Baus WW, Greve B, Herfarth K, et al. Stereotactic body radiotherapy for liver tumors: principles and practical guidelines of the DEGRO Working Group on Stereotactic Radiotherapy. *Strahlenther Onkol*. (2014) 190:872–81. doi: 10.1007/s00066-014-0714-1
10. Andratschke N, Alheid H, Allgäuer M, Becker G, Blanck O, Boda-Heggemann J, et al. The SBRT database initiative of the German Society for Radiation Oncology (DEGRO): patterns of care and outcome analysis of stereotactic body radiotherapy (SBRT) for liver oligometastases in 474 patients with 623 metastases. *BMC Cancer*. (2018) 18:283. doi: 10.1186/s12885-018-4191-2
11. Gomez DR, Tang C, Zhang J, Blumenschein GR, Hernandez M, Lee JJ, et al. Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non–small-cell lung cancer: long-term results of a multi-institutional, phase ii, randomized study. *J Clin Oncol*. (2019) 37:1558–65. doi: 10.1200/JCO.19.00201
12. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet*. (2019) 393:2051–8. doi: 10.1016/S0140-6736(18)32487-5
13. Wong AC, Watson SP, Pitroda SP, Son CH, Das LC, Stack ME, et al. Clinical and molecular markers of long-term survival after oligometastasis-directed stereotactic body radiotherapy (SBRT). *Cancer*. (2016) 122:2242–50. doi: 10.1002/cncr.30058
14. Milano MT, Katz AW, Muhs AG, Philip A, Buchholz DJ, Schell MC, et al. A prospective pilot study of curative-intent stereotactic body radiation therapy in patients with 5 or fewer oligometastatic lesions. *Cancer Interdisc Int J Am Cancer Soc*. (2008) 112:650–8. doi: 10.1002/cncr.23209
15. Patel P, Palma D, McDonald F, Tree A. The Dandelion dilemma revisited for oligoprogression: treat the whole lawn or weed selectively? *Clin Oncol*. (2019) 31:824–33. doi: 10.1016/j.clon.2019.05.015
16. Dias M, Antunes A, Campainha S, Conde S, Barroso A. Prognostic impact of M descriptors of the 8th edition of TNM classification of lung cancer. *J Thorac Dis*. (2017) 9:685. doi: 10.21037/jtd.2017.03.106
17. Wang M, Chen H, Wu K, Ding A, Zhang M, Zhang P. Evaluation of the prognostic stage in the 8th edition of the American Joint Committee on Cancer in locally advanced breast cancer: an analysis based on SEER 18 database. *Breast*. (2018) 37:56–63. doi: 10.1016/j.breast.2017.10.011
18. Donovan E, Dhesy-Thind S, Mukherjee S, Kucharczyk M, Swaminath A. Attitudes and beliefs toward the use of stereotactic body radiotherapy in oligometastatic breast cancer: a commentary on a survey of Canadian Medical Oncologists. *Breast J*. (2019) 25:1222–4. doi: 10.1111/tbj.13435
19. Yoo GS, Yu JI, Park W, Huh SJ, Choi DH. Prognostic factors in breast cancer with extracranial oligometastases and the appropriate role of radiation therapy. *Radiat Oncol J*. (2015) 33:301–9. doi: 10.3857/roj.2015.33.4.301
20. Scorsetti M, Franceschini D, De Rose F, Comito T, Villa E, Iftode C, et al. Stereotactic body radiation therapy: a promising chance for oligometastatic breast cancer. *Breast*. (2016) 26:11–7. doi: 10.1016/j.breast.2015.12.002
21. Scorsetti M, Franceschini D, De Rose F, Comito T, Franzese C, Masci G, et al. The role of SBRT in oligometastatic patients with liver metastases from breast cancer. *Rep Pract Oncol Radiother*. (2017) 22:163–9. doi: 10.1016/j.rpor.2016.07.008

22. Timmerman R, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol*. (2006) 24:4833–9. doi: 10.1200/JCO.2006.07.5937
23. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA*. (2010) 303:1070–6. doi: 10.1001/jama.2010.261
24. Park C, Papiez L, Zhang S, Story M, Timmerman RD. Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. *Int J Radiat Oncol Biol Phys*. (2008) 70:847–52. doi: 10.1016/j.ijrobp.2007.10.059
25. Wöckel A, Stüber T, editors. *S3-Leitlinie "Interdisziplinäre Früherkennung, Diagnose, Therapie und Nachsorge des Mammakarzinoms". Forum*. Basel: Springer (2019).
26. Liedtke C, Jackisch C, Thill M, Thomssen C, Müller V, Janni W, et al. AGO recommendations for the diagnosis and treatment of patients with early breast cancer: update 2018. *Breast Care*. (2018) 13:196–208. doi: 10.1159/000489329
27. Thill M, Liedtke C, Müller V, Janni W, Schmidt M, Committee AB. AGO recommendations for the diagnosis and treatment of patients with advanced and metastatic breast cancer: update 2018. *Breast Care*. (2018) 13:209–15. doi: 10.1159/000489331
28. Kwapisz D. Oligometastatic breast cancer. *Breast Cancer*. (2019) 26:138–46. doi: 10.1007/s12282-018-0921-1
29. Milano MT, Zhang H, Metcalfe SK, Muhs AG, Okunieff P. Oligometastatic breast cancer treated with curative-intent stereotactic body radiation therapy. *Breast Cancer Res Treat*. (2009) 115:601–8. doi: 10.1007/s10549-008-0157-4
30. David S. Stereotactic ablative body radiotherapy (SABR) for bone only oligometastatic breast cancer: a prospective clinical trial. *Breast*. (2019) 49:55–62. doi: 10.1016/j.breast.2019.10.016
31. Lara TM, Helou J, Poon I, Sahgal A, Chung HT, Chu W, et al. Multisite stereotactic body radiotherapy for metastatic non-small-cell lung cancer: delaying the need to start or change systemic therapy? *Lung Cancer*. (2018) 124:219–26. doi: 10.1016/j.lungcan.2018.08.005
32. Klement RJ, Guckenberger M, Alheid H, Allgäuer M, Becker G, Blanck O, et al. Stereotactic body radiotherapy for oligo-metastatic liver disease – influence of pre-treatment chemotherapy and histology on local tumor control. *Radiother Oncol*. (2017) 123:227–33. doi: 10.1016/j.radonc.2017.01.013
33. Hong JC, Ayala-Peacock DN, Lee J, Blackstock AW, Okunieff P, Sung MW, et al. Classification for long-term survival in oligometastatic patients treated with ablative radiotherapy: a multi-institutional pooled analysis. *PloS ONE*. (2018) 13:e0195149. doi: 10.1371/journal.pone.0195149
34. Muraro E, Furlan C, Avanzo M, Martorelli D, Comaro E, Rizzo A, et al. Local high-dose radiotherapy induces systemic immunomodulating effects of potential therapeutic relevance in oligometastatic breast cancer. *Front Immunol*. (2017) 8:1476. doi: 10.3389/fimmu.2017.01476
35. Bhalla N, Brooker R, Brada M. Combining immunotherapy and radiotherapy in lung cancer. *J Thorac Dis*. (2018) 10(Suppl. 13):S1447. doi: 10.21037/jtd.2018.05.107
36. Ko EC, Raben D, Formenti SC. The integration of radiotherapy with immunotherapy for the treatment of non–small cell lung cancer. *Clin Cancer Res*. (2018) 24:5792–806. doi: 10.1158/1078-0432.CCR-17-3620
37. Dagoglu N, Karaman S, Caglar HB, Oral EN. Abscopal effect of radiotherapy in the immunotherapy era: systematic review of reported cases. *Cureus*. (2019) 11:e4103. doi: 10.7759/cureus.4103
38. Miglietta F, Griguolo G, Guarneri V, Dieci MV. Programmed cell death ligand 1 in breast cancer: technical aspects, prognostic implications, and predictive value. *Oncologist*. (2019) 24:e1055–69. doi: 10.1634/theoncologist.2019-0197
39. Savas P, Salgado R, Denkert C, Sotiriou C, Darcy PK, Smyth MJ, et al. Clinical relevance of host immunity in breast cancer: from TILs to the clinic. *Nat Rev Clin Oncol*. (2016) 13:228. doi: 10.1038/nrclinonc.2015.215
40. Stanton SE, Adams S, Disis ML. Variation in the incidence and magnitude of tumor-infiltrating lymphocytes in breast cancer subtypes: a systematic review. *JAMA Oncol*. (2016) 2:1354–60. doi: 10.1001/jamaoncol.2016.1061
41. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. (2018) 379:2108–21. doi: 10.1056/NEJMoa1809615
42. Qiu B, Liang Y, Li Q, Liu G, Wang F, Chen Z, et al. Local therapy for oligoprogressive disease in patients with advanced stage non–small-cell lung cancer harboring epidermal growth factor receptor mutation. *Clin Lung Cancer*. (2017) 18:e369–73. doi: 10.1016/j.cllc.2017.04.002
43. Triggiani L, Alongi F, Buglione M, Detti B, Santoni R, Bruni A, et al. Efficacy of stereotactic body radiotherapy in oligorecurrent and in oligoprogressive prostate cancer: new evidence from a multicentric study. *Br J Cancer*. (2017) 116:1520. doi: 10.1038/bjc.2017.103
44. Santini D, Ratta R, Pantano F, De Lisi D, Maruzzo M, Galli L, et al. Outcome of oligoprogressing metastatic renal cell carcinoma patients treated with locoregional therapy: a multicenter retrospective analysis. *Oncotarget*. (2017) 8:100708. doi: 10.18632/oncotarget.20022
45. Kelly P, Ma Z, Baidas S, Moroose R, Shah N, Dagan R, et al. Patterns of progression in metastatic estrogen receptor positive breast cancer: an argument for local therapy. *Int J Breast Cancer*. (2017) 2017:1367159. doi: 10.1155/2017/1367159
46. Gianni L. High-dose chemotherapy for breast cancer: any use for it? *Ann Oncol*. (2002) 13:650–2. doi: 10.1093/annonc/mdf232
47. Krug D, Fabian A, Pyschny F, Blanck O, Dellas K, Maass N, et al. Strahlentherapie bei Patientinnen mit oligometastasiertem Mammakarzinom. *Der Gynäkol*. (2019) 52:918–26. Available online at: https://www.springermedizin.de/mammakarzinom/mammakarzinom/strahlentherapie-bei-patientinnen-mit-oligometastasiertem-mammak/17122456
48. Chmura SJ, Winter KA, Al-Hallaq HA, Borges VF, Jaskowiak NT, Matuszak M, et al. NRG-BR002: a phase IIR/III trial of standard of care therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical ablation for newly oligometastatic breast cancer (NCT02364557). *J Clin Oncol*. (2019) 37(Suppl. 15):TPS1117. doi: 10.1200/JCO.2019.37.15_suppl.TPS1117
49. Possanzini M, Greco C. Stereotactic radiotherapy in metastatic breast cancer. *Breast*. (2018) 41:57–66. doi: 10.1016/j.breast.2018.06.011
50. Sher DJ, Wee JO, Punglia RS. Cost-effectiveness analysis of stereotactic body radiotherapy and radiofrequency ablation for medically inoperable, early-stage Non-small cell lung cancer. *Int J Radiat Oncol*. (2011) 81:e767–74. doi: 10.1016/j.ijrobp.2010.10.074
51. Bijlani A, Aguzzi G, Schaal D, Romanelli P. Stereotactic radiosurgery and stereotactic body radiation therapy cost-effectiveness results. *Front Oncol*. (2013) 3:77. doi: 10.3389/fonc.2013.00077

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Radiation Boost After Adjuvant Whole Breast Radiotherapy: Does Evidence Support Practice for Close Margin and Altered Fractionation?

Stephanie Gulstene[1] *and Hamid Raziee*[2]*

[1] Department of Radiation Oncology, University of Western Ontario, London, ON, Canada, [2] Department of Radiation Oncology, BC Cancer Surrey, University of British Columbia, Vancouver, BC, Canada

Adding a boost to whole breast radiation (WBI) following breast-conserving surgery (BCS) may help improve local control, but it increases the total cost of treatment and may worsen cosmetic outcomes. Therefore, it is reserved for patients whose potential benefit outweighs the risks; however, current evidence is insufficient to support comprehensive and consistent guidance on how to identify these patients, leading to a potential for significant variations in practice. The use of a boost in the setting of close margins and hypofractionated radiotherapy represents two important areas where consensus guidelines, patterns of practice, and current evidence do not seem to converge. Close margins were previously routinely re-excised, but this is no longer felt to be necessary. Because of this recent practice change, good long-term data on the local recurrence risk of close margins with or without a boost is lacking. As for hypofractionation, although there is guidance recommending that the decision to add a boost be independent from the whole-breast fractionation schedule, it appears that patterns-of-practice data may show underutilization of a boost when hypofractionation is used. The use of a boost in these two common clinical scenarios represents important areas of future study for the optimization of adjuvant breast radiation.

Keywords: boost radiation, hypofractionated, close margins, radiation therapy (radiotherapy), breast cancer, breast malignancy, breast carcinoma (BC)

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Cristiane Takita, University of Miami Health System, United States

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Maria Carmen De Santis, Istituto Nazionale dei Tumori (IRCCS), Italy
Laure Marignol, Trinity College Dublin, Ireland

***Correspondence:**
Hamid Raziee
Hamid.Raziee@bccancer.bc.ca

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BACKGROUND

A considerable proportion of patients with early-stage breast cancer are treated with breast-conserving surgery (BCS) followed by whole breast radiation (WBI). In this group, an additional dose of radiation—a boost—can be delivered in order to reduce the risk of local recurrence (1–8). There is variation of boost dose, planning technique, radiation modality, and sequence, but in general, in addition to WBI, a few additional fractions of radiation are delivered to the lumpectomy site (including postoperative seroma and surgical clips) in addition to a margin, using various radiation modalities including photon or electron beams (9).

However, studies have shown that the higher radiation dose associated with the addition of a boost may lead to worse cosmetic outcomes (10–12). In a recent Cochrane review, adding a boost led to worse cosmesis when scored by a review panel (OR 1.41, 95% CI 1.07–1.85), but no difference in cosmetic outcomes when scored by a physician (OR 1.58, 0.93–2.69) (10).

Immink et al. (11) assessed long-term cosmetic outcomes of 348 patients enrolled in the European Organization for Research and Treatment of Cancer (EORTC) boost vs. no boost trial. At 3 years, there was no significant difference between the patients that received a boost and those who did not; however, over longer-term follow-up it became clear that addition of a boost increased the degree of fibrosis (11). Another, larger analysis that included over 3,000 patients from this same trial found similar results (12). Specifically, they found that after a 10-year follow-up, the addition of a boost led to increased rates of moderate or severe fibrosis (12). In an older study that included just over 100 patients, addition of a boost was linked to other long-term side effects such as telangiectasis and depigmentation (13). Beyond cosmetic outcomes, use of a boost adds to the cost of radiation therapy. Lanni et al. (14) estimated that the cost of WBI was US$11,725 using opposed tangents and US$20,637 with 3D-CRT/IMRT. With the addition of a boost, this increased to $13,829 and $22,130, respectively (14).

Therefore, radiation boost should be reserved for patients whose potential benefit from additional radiation outweighs the risks and justifies the additional costs. Younger patients have consistently been shown to be at higher risk for local recurrence, with age acting as an independent risk factor (1–3, 5, 7, 15). Given this, they would be expected to benefit more from a boost, and this is what the EORTC boost vs. no boost trial demonstrated. In this study, following whole breast radiation (50 Gy/25 fractions), patients were randomized to receive a boost of 16 Gy to the tumor bed or no boost (1). In younger patients, the addition of a boost translated into a significantly higher absolute risk reduction in comparison to older patient groups (1). For patients ≤40 and 41–50 years of age, the absolute reduction in risk of local recurrence was 11.6 and 5.9%, as compared to 2.9 and 3.0% for patients 51–60 and >60 years of age, respectively (1). As far as side effect profile is concerned, rates of fibrosis were higher in the boost group for all age groups except for patients ≤40 (1). Hazard ratios for fibrosis by age group were 1.02 (99% CI 0.17–6.22, $p = 0.98$), 3.51 (1.16–10.55, $p < 0.003$), 3.15 (1.49–6.65, $p < 0.001$), and 2.55 (1.24–5.27, $p < 0.001$) for patients age ≤40, 41–50, 51–60, and > 60.

The benefit of boost in younger patients is appropriately reflected in the pattern-of-practice data, where age exerts a strong influence on the decision to add a boost (16–18), as well as in the guideline recommendations from collaborative groups and national agencies (**Table 1**). Within these guidelines, age is the most consistently cited factor, with most using a cut-off of 50 years. However, beyond age, other determinants of boost utilization such as tumor grade, presence of lymphovascular invasion (LVI), hormone receptor status, and presence of positive margins are not supported by high-level evidence, creating the potential for variation in recommendations and practice, as reflected in the available guidelines (**Table 1**).

This review will focus on two other important factors for boost decision-making, namely, close surgical resection margin status and fractionation schedule. We will review the available evidence as well as the patterns-of-practice data surrounding each.

TABLE 1 | Summary of guidelines and expert recommendations on the indications for adding boost radiation.

Organization	Recommendations
ASTRO (American Society for Radiation Oncology)—(19)	Boost is recommended for: • ≤50 years old • 51–70 years old with high-grade tumor • Positive margins Omitting boost is recommended for: • >70 years old with low or intermediate grade, hormone positive tumor that was excised with a widely negative margin (≥2 mm) Boost and fractionation schedule: • Use of a boost should be independent of the whole breast fractionation scheme.
GEC-ESTRO Breast Cancer Working Group—(20)	Boost may be omitted for: • ≥50 years old with a ≤3-cm unicentric, unifocal tumor with no nodal involvement that was resected with a widely negative margin (≥2 mm), with no LVI or no EIC (extensive intraductal component) and not triple negative Boost with dose escalation (above 16 Gy EQD2) is recommended for: • ≤40 years old with close margins, EIC or triple negative disease • Positive margins Boost with or without dose escalation is recommended for: • ≤40 years old and do not meet criteria for boost with dose escalation • 40–50 years old • >50 years old with any of the following risk factors (close margins, tumor >3 cm, extensive intraductal component, LVI, node involvement, multicentric or multifocal disease, triple negative disease, or residual disease after neoadjuvant chemotherapy)
Consensus from 15th St. Gallen Expert Conference, ESMO (21)	Boost may be omitted for: • >60 years old with low-grade tumor and/or favorable tumor biology who will be receiving adjuvant endocrine therapy.
ESMO (European Society for Medical Oncology)—(22)	Boost is recommended for: • <50 years old • Grade 3 • Extensive DCIS • LVI • Focally positive margin
SSO-ASTRO Consensus Guideline (23)	Boost is not necessarily recommended for: • Close margins. More specifically, use of a boost should be based on "a priori estimation of IBTR [ipsilateral breast tumor recurrence] risk and should not be determined, in isolation, by the width of the surgical margin"
National comprehensive cancer network (NCCN)—(24)	Boost is recommended for: • Patient at higher risk of recurrence Boost with consideration of dose escalation is recommended for: • Microscopically focally positive margins, in the absence of EIC

MARGIN STATUS, CLOSE

Surgical margin is the width of non-cancerous tissue surrounding the tumor when resected, with a general concern that a narrow

(close) but negative margin might correlate with increased risk of recurrence. The exact definition of close margins for breast cancer resected with BCS has been variable; however, the most commonly used definition for close margins in invasive breast cancer is <2 mm (25).

Management of patients with close margins in invasive breast cancer has undergone a recent shift in practice. Previously, re-excision was recommended for both close and positive margins; however, recent evidence has demonstrated that once there is no "tumor on ink," increasing the margin width does not correlate with reduction in local recurrence, and therefore, consensus practice has moved to reserving re-excision for positive margins only (5, 25–27).

In light of this, guidelines by Society of Surgical Oncology—American Society for Radiation Oncology (SSO-ASTRO) recommended that the decision to deliver a boost be based on overall assessment of the risk of local recurrence and that the width of margins is not, in and of itself, an indication for a boost (23). To date, there is no new evidence since the SSO-ASTRO recommendations in 2014 that convincingly suggests that width of negative margins should dictate the decision to add a boost when treating invasive breast cancer.

Looking closer at the available literature, a meta-analysis by Houssami et al. (27) which investigated the effect of margin status and width on cancer outcomes found that after addressing differing rates of boost as a possible confounder, the width of the negative margin did not significantly affect local control ($p = 0.86$). This analysis included 33 separate studies reporting on a combined 32,363 patients (27). Comparable results were found in a recent analysis by Vrieling et al. of the EORTC boost vs. no boost trial (28). For inclusion in this trial patients were required to have a negative margin (i.e., no tumor on ink) as assessed by a local pathologist. However, 1,616 patients, or 30% of the study population, then underwent a central pathology review which re-assessed margin status (28, 29). In Vrieling et al. (28), margins confirmed as negative on pathology review were divided by width of the negative margin (≤5, 3–4, or ≤2mm). The rate of boost in each margin category was roughly similar, with a boost used in 52% (497/950), 49% (91/187), and 48% (146/306), for ≥5, 3–4, and ≤2-mm (28). Over a median follow-up of 18.2 years the rate of local relapse as first event was 10% (95/950), 11% (20/187), and 9% (29/306) for ≤5, 3–4, and ≤2 mm (28). These rates were not significantly different with a hazard ratio for local relapse by margin statuses of 1 (reference), 1.10 (95% CI 0.68–1.78), and 0.97 (0.64–1.47), for ≥5, 3–4, and ≤2 mm (28). Here, each group received a boost at similar frequencies and demonstrated similar rates of local recurrence over long-term follow-up, which supports the idea that the use of a boost is not a confounding factor in the excellent local control rates seen in close margin resections that do not undergo re-excision and that therefore close margins are not an indication for a boost.

The data from Vrieling et al. (28) also showed that the addition of a boost provided a similar reduction in risk of local recurrence for negative margin widths of ≥5 vs. 3–4 mm or ≤2 mm ($p = 0.63$). However, in an earlier analysis of the same data, Jones et al. (29) found that addition of a boost significantly reduced local recurrence in patients with negative margins >2 mm (HR 0.47, $p = 0.0004$), but not for patients with negative margins <2 mm or positive margins ($p = 0.65$). This study grouped <2-mm and positive margins together; however, there were relatively few patients with positive margins (29). Nevertheless, this may offer an explanation for the difference between Vrieling et al. (28) and Jones et al. (29). Additionally, Jones et al. (29) had a shorter median follow-up time of 10 years and it is possible that, with the shorter follow-up time, the effect of boost could not reach statistical significance for the <2-mm and positive margin group, which was roughly 4-fold smaller than the >2-mm group.

Next, turning to patterns-of-practice, the available data is somewhat limited. Ceilley et al. (30) surveyed 1,137 physicians and found that, among active physicians of ASTRO and ESTRO, there was a significantly increased likelihood to add a boost for close margins. Among the 702 American physicians surveyed, 85% gave a boost in patients with negative margins compared to 98% for patients with close margins ($p < 0.001$) (30). Data from European physicians was similar with 75% giving a boost in cases of negative margins vs. 94% for close margins (30). However, this survey data was collected in 2002, which is prior to the shift away from re-excision for close margins (30). Looking at more recent studies, Nguyen et al. (17) surveyed 388 radiation oncologists in Australia and New Zealand, receiving responses from 156 of them. They found significant division in opinion around close margins as an indication for a boost. 35.2% felt that a margin <2 mm was an absolute indication for a boost, 38.7% felt it was a relative indication, and 26.1% felt it was not an indication (17). Although limited, available data does suggest that significant variations in practice exist with regards to a boost for close margins.

FRACTIONATION SCHEDULE

The most recent ASTRO consensus guidelines support the use of hypofractionated whole breast radiation (40 Gy/15 fractions or 42.5 Gy/16 fractions) for the vast majority of patients. Specifically, they support its use for any age group, in combination with any chemotherapy regimen, and for patients with any stage of disease, provided that they do not require coverage of regional lymph nodes (19). However, pattern-of-practice studies show an interesting trend toward far lower rates of boost utilization when using hypofractionation vs. conventional fractionation. Stokes et al. (16) analyzed patterns of practice for patients with early-stage breast cancer treated between 2004 and 2014 using the US National Cancer Database (NCDB), identifying a total of 423,500 patients. They found that those managed with hypofractionation received a boost significantly less frequently (OR 0.15, 95% CI 0.15–0.16, $p < 0.001$). Another analysis of the NCDB by Zhong et al. (18) which included 356,160 patients showed similar results, with a boost being given in 88.9% of the cases following conventional fractionation vs. 52.2% of the time after hypofractionation ($p < 0.001$).

Looking at the evidence for addition of boost with hypofractionation vs. conventional fractionation, there does

not appear to be significant differences in clinical outcomes. Addressing long-term cosmetic outcomes first, the addition of a boost appears to lead to worse cosmetic results regardless of fractionation schedule (31, 32). De Santis et al. (32) compared toxicity outcomes following hypofractionated WBI with 42.4 Gy in 16 fractions with or without a boost and on univariant analysis boost was a significant predictor of late toxicity ($p < 0.001$). This is similar to the trend toward worse cosmetic outcomes with addition of a boost within conventional fractionation (10–12).

More importantly, cosmetic outcomes are similar when a boost is used in combination with hypofractionated vs. conventional WBI (33–39). In their 120-patient study comparing addition of a boost to conventional fractionation (50 Gy/25 fractions) vs. hypofractionation (42.5 Gy/16 fractions), De Felice et al. (34) found no difference in long-term breast fibrosis. Median follow-up in this study was 16 months (34). Similarly, in their 287-patient study, Shaitelman et al. (36) found no difference in any $\geq$ grade 2 or $\geq$ grade 3 toxicity, hyperpigmentation, skin induration, dermatitis, telangiectasia, fibrosis, or breast edema, at 6 months post-radiation with conventional WBI plus boost vs. hypofractionated WBI plus boost. Furthermore, a systematic review and meta-analysis by Valle et al. (39) found no significant difference (RR 0.95, 95% CI 0.81–1.12) in the rates of poor cosmetic outcomes between hypofractionation vs. conventional fractionation.

Next, with regards to cancer control, conventional and hypofractionation regiments have been shown to produce similar outcomes (33). Within conventional fractionation, the improved local control provided by a boost is well-documented (40). However, there is insufficient data specifically assessing the addition of a boost to hypofractionated WBI. From the UK START trial, a *post-hoc* analysis showed that in patients who received a boost, the rate of local–regional relapse was not significantly different between those treated with hypofractionated vs. conventional WBI (HR 0.99, 95% CI 0.76–1.29) (41). This suggests that the boost effect was similar in both dosing schedules. An older study by Romestaing et al. (8) using an alternative dosing schedule of 50 Gy in 20 fractions given over 5 weeks also showed decreased local recurrence with the addition of a boost. The dosing schedule used here is different from both conventional and hypofractionation schedules used today; however, it does support the assumption that a boost will provide improved local control regardless of the whole breast dosing schedule it is combined with.

Returning to the patterns-of-practice data, an important caveat to interpreting the results previously discussed is that patient characteristics may not have be similar between the groups treated with hypofractionated vs. conventional radiation. Using the same National Cancer Database (NCDB) as Stokes et al. (16) and Zhong et al. (18), Hasan et al. (42) found that hypofractionation was used more commonly in older patients (2.6% age <40 vs. 19.5% age >80; RR 8.40, 95% CI 5.01–14.09), those with node-negative disease (9.8% pN0 vs. 3.3% pN1; RR 0.38, 0.36–0.40), smaller tumors (9.5% $\leq$2.0 cm vs. 5.9% 2.1–5.0 cm; RR 0.78, 0.75–0.81), and lower-grade cancers [10.9% Grade 1 vs. 9.1% Grade 2 (RR 0.87, 0.85–0.90) vs. 5.8% Grade 3 (RR 0.79, 0.76–0.83)]. However, a survey of 2,150 randomly selected members of the American Society for Radiation Oncology suggests that the decision to forgo boost may still be made solely on the basis of WBI fractionation schedule. They reported that 94.4% of physicians used a boost after conventional fractionation in more than two thirds of their patients, compared to 14.4% after hypofractionation (43). Moreover, 69.7% indicated never using a boost after hypofractionation compared to 0% after conventional fractionation (43). This variation in the use of a boost based on fractionation schedule is in opposition to the most recent guideline by ASTRO which recommends that the decision to add a boost should be independent of the whole breast fractionation scheme (19).

DISCUSSION

Addition of a boost is an established technique for improving local control in higher-risk patients. However, improved local control can come at the cost of worse cosmetic outcomes (1, 4, 6, 7, 10–12). There is a lack of consensus between published guidelines on exactly which patients benefit from a boost, and largely, the decision is left to the discretion of individual physicians with or without the guidance of institutional policies and guidelines.

Here we have discussed the differences between consensus guidelines, patterns of practice, and current evidence surrounding use of a boost with regards to close margins and WBI fractionation. Due to the recent practice changes around re-excision for close margins, there is not good long-term data on the local recurrence of close margins with or without a boost. The overall consensus of guidelines indicate that close margins are not, by themselves, an absolute indication for a boost; however, in at least some of the recent guidelines, they do appear to be an important consideration in decision-making (19, 20, 23). As to how this is being implemented in day-to-day practice, this is unclear since our pattern-of-practice data is very limited. However, it is easy to imagine that there is a strong potential for practice variation.

In order to minimize these variations in guidance and practice, we will eventually need more long-term data assessing local recurrence with and without a boost for patients with close margins preferably from prospective studies, also incorporating our modern understanding of tumor biology, particularly as we move into a time when close margins are not routinely re-excised. In the meantime, studies to understand the practice pattern for boost utilization with close margins could offer insight into how these patients are being managed.

With the current state of evidence, however, it is perhaps most reasonable to follow the guidance in Moran et al. (23) and not to use close margins as a sole indication for a boost, but to base the decision on an overall assessment of the risk of local recurrence. This unfortunately is somewhat vague. Moreover, the current status of evidence leaves the possibility that close margins may exert a more significant effect on the gestalt impression of risk of recurrence than is truly warranted, especially since current data suggests that patients with close margins have excellent

local control rates similar to those with wide negative margins, regardless of the use of a boost.

As for hypofractionation, although there is specific guidance indicating that the addition of a boost be independent from the whole breast fractionation schedule (19), it appears that patterns of practice may not entirely follow consensus guidelines. Instead, the data shows that a boost is used far less frequently in cases of hypofractionation, at least at some jurisdictions. The reason for lower utilization of a boost in hypofractionation could be from concern about inferior cosmesis. However, the current evidence shows similar toxicity profile and benefit for a boost with conventional vs. hypofractionated WBI. Therefore, the lower rates of boost utilization with hypofractionation represent an area of potential future research focus to support practice. Further studies specifically on the effect of adding a boost to hypofractionation will help elucidate this issue, but it will take years for relevant outcomes data to become available. In the meantime, it seems most reasonable to make decisions on addition of a boost independent from fractionation schedule.

AUTHOR CONTRIBUTIONS

HR provided supervision and guidance to SG, who was responsible for the literature review and drafting of this article.

REFERENCES

1. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol*. (2015) 16:47–56. doi: 10.1016/S1470-2045(14)71156-8
2. Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot JC, Jager JJ, et al. Can patient-, treatment- and pathology-related characteristics explain the high local recurrence rate following breast-conserving therapy in young patients? *Eur J Cancer*. (2003) 39:932–44. doi: 10.1016/S0959-8049(03)00123-0
3. Polgár C, Fodor J, Orosz Z, Major T, Takácsi-Nagy Z, Csaba Mangel L, et al. Electron and high-dose-rate brachytherapy boost in the conservative treatment of stage I-II breast cancer: first results of the randomized Budapest boost trial. *Strahlentherapie Onkol*. (2002) 178:615–23. doi: 10.1007/s00066-002-1053-1
4. Van Werkhoven E, Hart G, Van Tinteren H, Elkhuizen P, Collette L, Poortmans P, et al. Nomogram to predict ipsilateral breast relapse based on pathology review from the EORTC 22881-10882 boost versus no boost trial. *Radiother Oncol*. (2011) 100:101–7. doi: 10.1016/j.radonc.2011.07.004
5. Bosma SCJ, Van Der Leij F, Van Werkhoven E, Bartelink H, Wesseling J, Linn S, et al. Very low local recurrence rates after breast-conserving therapy: analysis of 8485 patients treated over a 28-year period. *Breast Cancer Res Treat*. (2016) 156:391–400. doi: 10.1007/s10549-016-3732-0
6. Kindts I, Laenen A, Peeters S, Janssen H, Depuydt T, Neven P, et al. Evaluation of a breast cancer nomogram to predict ipsilateral breast relapse after breast-conserving therapy. *Radiother Oncol*. (2016) 119:45–51. doi: 10.1016/j.radonc.2016.01.023
7. Livi L, Borghesi S, Saieva C, Fambrini M, Iannalfi A, Greto D, et al. Benefit of radiation boost after whole-breast radiotherapy. *Int J Radiat Oncol Biol Phys*. (2009) 75:1029–34. doi: 10.1016/j.ijrobp.2008.12.038
8. Romestaing P, Lehingue Y, Carrie C, Coquard R, Montbarbon X, Ardiet JM, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol*. (1997) 15:963–8. doi: 10.1200/JCO.1997.15.3.963
9. van Mourik AM, Elkhuizen PHM, Minkema D, Duppen JC, van Vliet-Vroegindeweij C. Multiinstitutional study on target volume delineation variation in breast radiotherapy in the presence of guidelines. *Radiother Oncol*. (2010) 94:286–91. doi: 10.1016/j.radonc.2010.01.009
10. Kindts I, Laenen A, Depuydt T, Weltens C. Tumour bed boost radiotherapy for women after breast-conserving surgery. *Cochrane Database Syst Rev*. (2017) 11:CD011987. doi: 10.1002/14651858.CD011987.pub2
11. Immink JM, Putter H, Bartelink H, Cardoso JS, Cardoso MJ, Van der Hulst-Vijgen MHV, et al. Long-term cosmetic changes after breast-conserving treatment of patients with stage I-II breast cancer and included in the EORTC "boost versus no boost" trial. *Ann Oncol*. (2012) 23:2591–8. doi: 10.1093/annonc/mds066
12. Collette S, Collette L, Budiharto T, Horiot JC, Poortmans PM, Struikmans H, et al. Predictors of the risk of fibrosis at 10 years after breast conserving therapy for early breast cancer - a study based on the EORTC trial 22881-10882 "boost versus no boost." *Eur J Cancer*. (2008) 44:2587–99. doi: 10.1016/j.ejca.2008.07.032
13. Pezner RD, Patterson MP, Lipsett JA, Odom-Maryon T, Vora NL, Wong JYC, et al. Factors affecting cosmetic outcome in breast-conserving cancer treatment - objective quantitative assessment. *Breast Cancer Res Treat*. (1991) 20:85–92. doi: 10.1007/BF01834638
14. Lanni T, Keisch M, Shah C, Wobb J, Kestin L, Vicini F. A cost comparison analysis of adjuvant radiation therapy techniques after breast-conserving surgery. *Breast J*. (2013) 19:1688–97. doi: 10.1111/tbj.12075
15. Voogd AC, Nielsen M, Peterse JL, Blichert-Toft M, Bartelink H, Overgaard M, et al. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. *J Clin Oncol*. (2001) 19:162–7. doi: 10.1200/JCO.2001.19.6.1688
16. Stokes WA, Jackson MW, Kounalakis N, Kabos P, Rabinovitch RA, Rusthoven CG, et al. Disparities and patterns of care in boost utilization for early-stage breast cancer. *Int J Radiat Oncol*. (2017) 99:2. doi: 10.1016/j.ijrobp.2017.06.1598
17. Nguyen K, Mackenzie P, Allen A, Dreosti M, Morgia M, Zissiadis Y, et al. Breast interest group faculty of radiation oncology: Australian and New Zealand patterns of practice survey on breast radiotherapy. *J Med Imaging Radiat Oncol*. (2017) 61:508–16. doi: 10.1111/1754-9485.12566
18. Zhong J, Kandula S, Liu X, Cassidy RJ, Gillespie TW, Liu Y, et al. Patterns of radiation therapy boost administration in 356,160 breast cancer patients treated with hypofractionated versus conventional whole-breast irradiation. *Int J Radiat Oncol*. (2016) 96:2. doi: 10.1016/j.ijrobp.2016.06.600
19. Smith BD, Bellon JR, Blitzblau R, Freedman G, Haffty B, Hahn C, et al. Radiation therapy for the whole breast: executive summary of an american society for radiation oncology (ASTRO) evidence-based guideline. *Pract Radiat Oncol*. (2018) 8:145–52. doi: 10.1016/j.prro.2018.01.012
20. Polo A, Polgár C, Hannoun-Levi JM, Guinot JL, Gutierrez C, Galalae R, et al. Risk factors and state-of-the-art indications for boost irradiation in invasive breast carcinoma. *Brachytherapy*. (2017) 16:552–64. doi: 10.1016/j.brachy.2017.03.003
21. Curigliano G, Burstein HJ, Winer EP, Gnant M, Dubsky P, Loibl S, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. *Ann Oncol*. (2017) 28:1700–12. doi: 10.1093/annonc/mdx308
22. Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. (2015) 26:v8–30. doi: 10.1093/annonc/mdv298
23. Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *J Clin Oncol*. (2014) 32:14. doi: 10.1200/JCO.2013.53.3935
24. NCCN. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer. Version 3.2019*. Plymouth Meeting, PA (2019).

25. Tyler S, Truong PT, Lesperance M, Nichol A, Baliski C, Warburton R, et al. Close margins less than 2 mm are not associated with higher risks of 10-year local recurrence and breast cancer mortality compared with negative margins in women treated with breast-conserving therapy. *Int J Radiat Oncol Biol Phys*. (2018) 101:661–70. doi: 10.1016/j.ijrobp.2018.03.005
26. Kaufmann M, Morrow M, Von Minckwitz G, Harris JR. Locoregional treatment of primary breast cancer: consensus recommendations from an international expert panel. *Cancer*. (2010) 116:1184–91. doi: 10.1002/cncr.24874
27. Houssami N, Macaskill P, Luke Marinovich M, Morrow M. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. *Ann Surg Oncol*. (2014) 21:717–30. doi: 10.1245/s10434-014-3480-5
28. Vrieling C, Van Werkhoven E, Maingon P, Poortmans P, Weltens C, Fourquet A, et al. Prognostic factors for local control in breast cancer after long-term follow-up in the EORTC boost vs no boost trial: a randomized clinical trial. *JAMA Oncol*. (2017) 3:42–8. doi: 10.1001/jamaoncol.2016.3031
29. Jones HA, Antonini N, Hart AAM, Peterse JL, Horiot JC, Collin F, et al. Impact of pathological characteristics on local relapse after breast-conserving therapy: a subgroup analysis of the EORTC boost versus no boost trial. *J Clin Oncol*. (2009) 27:4939–47. doi: 10.1200/JCO.2008.21.5764
30. Ceilley E, Jagsi R, Goldberg S, Grignon L, Kachnic L, Powell S, et al. Radiotherapy for invasive breast cancer in North America and Europe: results of a survey. *Int J Radiat Oncol Biol Phys*. (2005) 61:365–73. doi: 10.1016/j.ijrobp.2004.05.069
31. Chan EK, Tabarsi N, Tyldesley S, Khan M, Woods R, Speers C, et al. Patient-reported long-term cosmetic outcomes following short fractionation whole breast radiotherapy with boost. *Am J Clin Oncol*. (2016) 39:473–8. doi: 10.1097/COC.0000000000000084
32. De Santis MC, Bonfantini F, Di Salvo F, Dispinzieri M, Mantero E, Soncini F, et al. Factors influencing acute and late toxicity in the era of adjuvant hypofractionated breast radiotherapy. *Breast*. (2016) 29:90–5. doi: 10.1016/j.breast.2016.07.013
33. Lee SW, Kim YJ, Shin KH, Kim K, Chie EK, Han W, et al. A comparative study of daily 3-Gy hypofractionated and 1.8-Gy conventional breast irradiation in early-stage breast cancer. *Medicine*. (2016) 95:e3320. doi: 10.1097/MD.0000000000003320
34. De Felice F, Ranalli T, Musio D, Lisi R, Rea F, Caiazzo R, et al. Relation between hypofractionated radiotherapy, toxicity and outcome in early breast cancer. *Breast J*. (2017) 23:563–8. doi: 10.1111/tbj.12792
35. Reddy JP, Lei X, Huang SC, Nicklaus KM, Fingeret MC, Shaitelman SF, et al. Quantitative assessment of breast cosmetic outcome after whole-breast irradiation. *Int J Radiat Oncol Biol Phys*. (2017) 97:894–902. doi: 10.1016/j.ijrobp.2016.12.021
36. Shaitelman SF, Schlembach PJ, Arzu I, Ballo M, Bloom ES, Buchholz D, et al. Acute and short-term toxic effects of conventionally fractionated vs hypofractionated whole-breast irradiation : a randomized clinical trial. *JAMA Oncol*. (2015) 1:931–41. doi: 10.1001/jamaoncol.2015.2666
37. Hopwood P, Haviland JS, Sumo G, Mills J, Bliss JM, Yarnold JR. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. *Lancet Oncol*. (2010) 11:231–40. doi: 10.1016/S1470-2045(09)70382-1
38. Youssef A, Stanford J. Hypofractionation radiotherapy vs. conventional fractionation for breast cancer: a comparative review of toxicity. *Cureus*. (2018) 10:e3516. doi: 10.7759/cureus.3516
39. Valle LF, Agarwal S, Bickel KE, Herchek HA, Nalepinski DC, Kapadia NS. Hypofractionated whole breast radiotherapy in breast conservation for early-stage breast cancer: a systematic review and meta-analysis of randomized trials. *Breast Cancer Res Treat*. (2017) 162:409–17. doi: 10.1007/s10549-017-4118-7
40. James ML, Lehman M, Hider PN, Jeffery M, Hickey BE, Francis DP. Fraction size in radiation treatment for breast conservation in early breast cancer. *Cochrane Database Syst Rev*. (2010) 10:CD003860. doi: 10.1002/14651858.CD003860.pub3
41. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol*. (2013) 14:1086–94. doi: 10.1016/S1470-2045(13)70386-3
42. Hasan Y, Waller J, Yao K, Chmura SJ, Huo D. Utilization trend and regimens of hypofractionated whole breast radiation therapy in the United States. *Breast Cancer Res Treat*. (2017) 162:317–28. doi: 10.1007/s10549-017-4120-0
43. Hoopes DJ, Kaziska D, Chapin P, Weed D, Smith BD, Hale ER, et al. Patient preferences and physician practice patterns regarding breast radiotherapy. *Int J Radiat Oncol Biol Phys*. (2012) 82:674–81. doi: 10.1016/j.ijrobp.2010.11.077

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Optimizing MR-Guided Radiotherapy for Breast Cancer Patients

Maureen L. Groot Koerkamp[1†], Jeanine E. Vasmel[1*†], Nicola S. Russell[2], Simona F. Shaitelman[3], Carmel N. Anandadas[4], Adam Currey[5], Danny Vesprini[6], Brian M. Keller[6], Chiara De-Colle[7], Kathy Han[8], Lior Z. Braunstein[9], Faisal Mahmood[10,11], Ebbe L. Lorenzen[10], Marielle E. P. Philippens[1], Helena M. Verkooijen[12], Jan J. W. Lagendijk[1], Antonetta C. Houweling[1], H. J. G. Desiree van den Bongard[1] and Anna M. Kirby[13]* on behalf of the Breast Tumor Site Group of the International MR-Linac Atlantic Consortium*

[1] Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, Netherlands, [2] Department of Radiotherapy, The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, [3] Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, United States, [4] Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom, [5] Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI, United States, [6] Department of Radiation Oncology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [7] Department of Radiation Oncology, University Hospital and Medical Faculty, Eberhard Karls University Tübingen, Tübingen, Germany, [8] Department of Radiation Oncology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada, [9] Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, United States, [10] Department of Oncology, Odense University Hospital, Odense, Denmark, [11] Research Unit for Oncology, Department of Clinical Research, University of Southern Denmark, Odense, Denmark, [12] Imaging Division, University Medical Center Utrecht, Utrecht, Netherlands, [13] Department of Radiotherapy, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton, United Kingdom

Current research in radiotherapy (RT) for breast cancer is evaluating neoadjuvant as opposed to adjuvant partial breast irradiation (PBI) with the aim of reducing the volume of breast tissue irradiated and therefore the risk of late treatment-related toxicity. The development of magnetic resonance (MR)–guided RT, including dedicated MR-guided RT systems [hybrid machines combining an MR scanner with a linear accelerator (MR-linac) or ^{60}Co sources], could potentially reduce the irradiated volume even further by improving tumour visibility before and during each RT treatment. In this position paper, we discuss MR guidance in relation to each step of the breast RT planning and treatment pathway, focusing on the application of MR-guided RT to neoadjuvant PBI.

Keywords: breast cancer, neoadjuvant radiation therapy, partial breast irradiation, MR-guided radiotherapy, hybrid machine, MR-linac, magnetic resonance imaging (MRI)

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***Correspondence:**
Maureen L. Groot Koerkamp
m.l.grootkoerkamp-3@umcutrecht.nl
Jeanine E. Vasmel
j.e.vasmel@umcutrecht.nl
Anna M. Kirby
anna.kirby@rmh.nhs.uk

†These authors share first authorship

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INTRODUCTION

The combination of a worldwide rising incidence of breast cancer together with decreasing mortality following breast cancer treatment has resulted in increasing numbers of breast cancer survivors living with late treatment-related toxicity (1–3). In recent decades, this has led to prioritization of treatment de-escalation aiming to reduce treatment-related toxicity without impeding survival (4). Studies comparing adjuvant whole breast irradiation (WBI) vs. adjuvant partial breast irradiation (PBI) in women with lower-risk breast cancers have demonstrated that PBI is as effective as WBI in terms of 5-years local recurrence rates and survival but with lower rates of late patient-reported and clinician-reported toxicity (5–8). Nonetheless, late treatment-related toxicity remains an issue in a significant proportion of patients (6, 8).

With neoadjuvant PBI, smaller target volumes can be irradiated compared to conventional adjuvant PBI, potentially resulting in less radiotherapy (RT)–related toxicity and therefore a higher quality of life (9–11). This is because, for neoadjuvant PBI, the gross target volume (GTV) is tumour rather than tumour bed, presenting a smaller, more easily definable target. Furthermore, the breast tissue at risk of local relapse remains in the closest possible proximity to the GTV, thereby reducing uncertainty around location of the clinical target volume (CTV). This is increasingly important in the current era of oncoplastic surgery in which the tissue that was adjacent to the tumour, the edge of which is usually marked by titanium surgical clips, may be mobilized and placed at some distance from its original location in order to ensure a good cosmetic result. This can lead to a larger CTV in the adjuvant setting than would have been necessary in the neoadjuvant setting. One problem with irradiating tumours in the neoadjuvant setting using the current standard computed tomography (CT)–based RT planning pathway, however, is that primary breast cancers can be difficult to see on a standard non–contrast-enhanced RT planning CT scan.

The development of magnetic resonance (MR)–guided RT has greatly improved the possibilities for image-guided RT and greater sparing of healthy tissue by providing excellent soft tissue visualization. MR–guided RT can refer to treatment on a conventional linear accelerator (linac) with the use of additional imaging on an MR scanner to plan treatment or to treatment on a hybrid machine. A hybrid machine is an MR scanner combined with a linac (MR-linac, Unity Elekta and MRIdian linac, ViewRay) or with ^{60}Co sources (MRIdian, ViewRay) (12–15). For breast cancer patients, MR-guided RT is expected to be most beneficial in the neoadjuvant setting treating *in situ* tumours, which can be more clearly visualized on MR images than on CT, both at the time of RT planning and during RT treatment. The latter would facilitate reduction in setup error margins in both the neoadjuvant and adjuvant setting. In addition, administering MR-guided RT on a hybrid machine could reduce the radiation exposure associated with the daily cone-beam CT (CBCT) required during treatment on a conventional linac.

In this position paper, we discuss MR guidance in relation to each step of the breast RT planning and treatment pathway from simulation to contouring, to treatment planning, and then delivery. We review what is already known, what is under evaluation, and potential obstacles to clinical implementation, highlighting where optimization of techniques and/or workflow is still required (**Table 1**).

SIMULATION

Patient Setup

The main challenge for patient setup in treatment position for breast RT in a magnetic resonance imaging (MRI) scanner or a hybrid machine is the limited MRI bore size (60–70 cm) compared to the CT bore size of 80 to 90 cm (16–18). This limits the size and inclination of a positioning device, as well as the number of possible positions for patient setup.

For patients treated in supine position with arms raised above their head, the elbow span in combination with an inclined position can be problematic. A solution for this is to put the arms closer together and/or to use either a wedge with smaller inclination or no wedge at all. Placement of an anterior receiver coil on a patient in supine position could lead to deformation of the breast (19). However, coil bridges can be used as support for the coil to prevent deformation (**Figure 1**) (9, 20–22).

In the prone position, the proportion of patients who can fit into the MR scanner bore is limited by the space needed for a pendulous breast to hang freely without touching the table top in combination with the requirement to place an additional receiver coil on the back of the patient (**Figure 2**). The additional receiver coil is necessary as the full body contour is needed for RT planning purposes, which is not a requirement for diagnostic prone breast imaging.

Standard RT immobilization equipment may not necessarily be MR-compatible, and standard MR equipment (e.g., the dedicated prone breast coil) is not designed for setup reproducibility. Therefore, it is necessary to develop dedicated RT immobilization equipment that is MR-compatible (i.e., non-conductive, low-density material). This equipment must also fit inside the MR bore and leave room for the MR receiver coils (e.g., flexible receiver coils in a prone breast board), while not degrading image quality (17, 22). Because of the electron stream effect (ESE), further discussed in *Treatment Planning for a Hybrid Machine*, simulation should include the chin and upper abdominal region.

Image Quality

For optimal quality of MR images, the receiver coil should be placed close to the target volume. Therefore, a strategic setup for the additional coils should be chosen, specific to the selected patient position (e.g., supine or prone). Because RT immobilization devices, such as the supine and prone breast boards and coil bridges, increase the gap between the patient and the receiver coils (i.e., the distance to the posterior coil located in the scanner table and to the anterior coil on top of the patient), it was initially thought that the positioning requirements for breast cancer RT might have a negative impact on MR image quality. However, multiple studies have reported good quality of MR images for breast RT in both supine and prone treatment positions acquired at 1.5- and 3.0-T MR scanners (19, 21, 22).

Another factor that might impair MR image quality is organ motion, including respiratory and cardiac motion, during scanning. Imaging in prone position has the advantage of minimizing breast motion due to respiration and may also minimize motion artefacts (19). Batumalai et al. (22) found no significant effect of the breathing artefacts on image quality in both prone and supine position by instructing their volunteers to maintain shallow breathing and choosing a right–left phase encoding direction in their MRI scans. Additionally, to preventing the motion, artefact reduction (e.g., gating or triggering) or motion correction (e.g., MR navigators) techniques can be used to minimize motion effects on MRI scans. However, it is important to realize how the anatomy relates to the breathing state during RT (18). To prevent step-like displacements in

TABLE 1 | Overview of challenges for the implementation of MR-guided radiotherapy on a hybrid machine for breast cancer patients.

Challenge	Effect	Potential solution
SIMULATION		
Patient positioning inside the MR bore	Prone: breast deformation on table and fitting of receiver coil (**Figure 2**)	Development of a thinner coil or a dedicated MR-linac breast coil
	Supine: difficulties fitting arms inside bore in standard RT position	Use a minimal or no inclined wedge support, move arms closer together above the head
Deformation of body contour by receiver coil	Disturbed body contour	Use coil bridges to support the coil (**Figure 1**)
Body contour visibility in prone position	With dedicated prone breast coil, body contour and OARs not visible further away from coil	Use an additional coil placed on top of the patient
Electron stream effect	Irradiation dose outside the treatment field in an inferior-to-superior direction (**Figure 4**)	Include chin, arm, and abdominal region in the simulation plan
Breathing and cardiac motion during scanning	Motion artefacts	Use a 3D sequence, signal averaging, and left–right phase encoding in protocol design, or use triggering or breath-hold for acquisition
CONTOURING		
Surgical clip and/or marker visualization on MRI	Magnetic field distortion and artefacts impeding contouring of target volume (**Figure 3**)	1. Use or develop markers or clips with smaller artefacts 2. No marker insertion (only possible in the neoadjuvant setting if no further surgery is required)
SIMULATION AND PLANNING		
Geometric accuracy (gradient nonlinearities) in combination with lateral target volumes	Reduced geometric accuracy, increasing with distance from isocenter	1. Use distortion correction software on scanner 2. Position target as close to scanner isocenter as possible (e.g., shift patient on the table) 3. Include remaining inaccuracy in PTV margin
Geometric accuracy (magnetic field inhomogeneities and patient-induced distortions)	Reduced geometric accuracy, especially near tissue–air interfaces	1. Use high bandwidth acquisition 2. Acquisition of B0 map to assess patient-induced distortion.
PLANNING		
Electron return effect	Possible skin dose, chest wall, or lung dose increase (dose increase at tissue–air interfaces)	Pay attention to skin, chest wall, and lung dose constraints in planning, carefully choose beam setup (e.g., use enough beams)
Electron stream effect	Irradiation dose outside the treatment field in an inferior-to-superior direction (**Figure 4**)	Use of bolus material to shield irradiation outside of field
Missing electron density information in MR-only workflow	Inaccurate dose calculation without correct electron density assignments	Development of methods for synthetic CT generation from MRI
High-density treatment couch material	Unpredictable dose effects by daily replanning	Avoid beam angles passing through the treatment couch edges
TREATMENT		
Irradiation through coil	No irradiation through MR receiver coils, only through dedicated hybrid machine coils. Dedicated prone breast coil cannot be used	1. Try to fit the dedicated MR-linac coil on top of prone patient (only for smaller patients) 2. Design a thinner, more flexible coil for the hybrid system 3. Design a new prone coil for the hybrid system
Fixed treatment couch	Interfractional changes in position cannot be corrected by moving the treatment couch	Use online plan adaptation strategies to account for interfractional changes in anatomy
Motion during treatment	Geographical miss during treatment or increased PTV margins	Use online gating or tracking when available, e.g., only beam-on when the target volume is within pre-specified boundaries

MRI, magnetic resonance imaging; MR, magnetic resonance; OAR, organ at risk; PTV, planning target volume; CT, computed tomography; RT, radiotherapy.

different slices in the scan volume caused by motion during scanning, a three-dimensional (3D) sequence can be used, although motion in a 3D scan will lead to blurring (23).

In studies that evaluated prone breast MRI for RT, a dedicated breast coil is usually used (19, 22, 24). While this coil provides optimal image quality for the breasts, it cannot capture the full body contour and all organs at risk (OARs) with adequate quality (**Figure 2**). However, for MR-guided RT on a conventional linac, this may be sufficient, provided that enough anatomical landmarks are visible to register the MR scan to the planning CT scan. Scanning with an additional receiver coil on top of the patient could help to overcome this issue, but may not be possible in all patients because of the limited MR bore size.

In case of RT treatment on a hybrid MR-guided RT system, it is not possible to irradiate through the standard dedicated prone breast coils that are used in diagnostic MRI. For that reason, the receiver coils dedicated to hybrid machines have a "window" through which irradiation is possible (15, 25). Because these dedicated coils have different properties to the standard receiver coils (i.e., fewer coil arrays, which restricts acceleration

of imaging) and are not breast specific, the image quality can be inferior. Another restriction is that the coil cannot be placed too closely to the patient because of the electron return effect (ERE; see *Treatment Planning for a Hybrid Machine*), which restricts the signal-to-noise ratio of the imaging. In general, a higher field strength gives a better signal-to-noise ratio, which may place a 1.5-T hybrid system in favour over a 0.35-T system. However, experiences with the 0.35-T hybrid system show that patient setup and online tracking for breast cancer could be performed successfully based on imaging at this lower magnetic field strength (26). To ensure appropriate image quality, the MRI sequences and image quality for breast imaging on the hybrid systems should therefore be tested and optimized for the use of the dedicated coil and each system specifically.

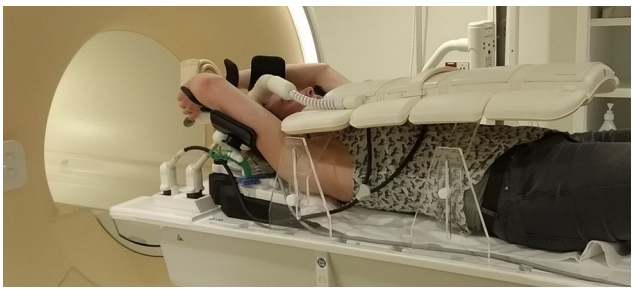

FIGURE 1 | Supine patient setup for MRI simulation. In this setup, a 5-degree inclined wedge is used. Height-adjustable coil bridges are used as support for the anterior receiver coil to prevent deformation of the body contour.

Geometric Accuracy

The impact of geometric distortions on MR-based contouring and planning should be taken into account when optimizing image quality and MRI sequences for RT on a hybrid machine (18, 27). The effect of distortions on image quality is described in this section, whereas the effect of distortions on dose distributions is described in *Treatment Planning for a Hybrid Machine*.

Distortions arise from system-related factors (i.e., main magnetic field inhomogeneity and gradient nonlinearities) and patient-related factors (i.e., chemical shift and susceptibility effects) and depend on the specific scanner and sequence parameters (18, 28–31).

System-related distortions due to gradient non-linearities increase with increasing distance of the target volume from the MRI isocenter and can range up to 12 mm (25, 27, 28, 30, 32). For the Elekta MR-linac (1.5 T), maximum displacements of 2.0 mm were found within 17.5 cm from the isocenter (25). For the ViewRay ^{60}Co-system (0.35 T), this was 1.9 mm, but larger distortions were observed further from the central axis (33). To minimize the effect of image distortion by gradient non-linearities, the target volume should be positioned as close to the scanner isocenter as possible (17), which may be challenging for

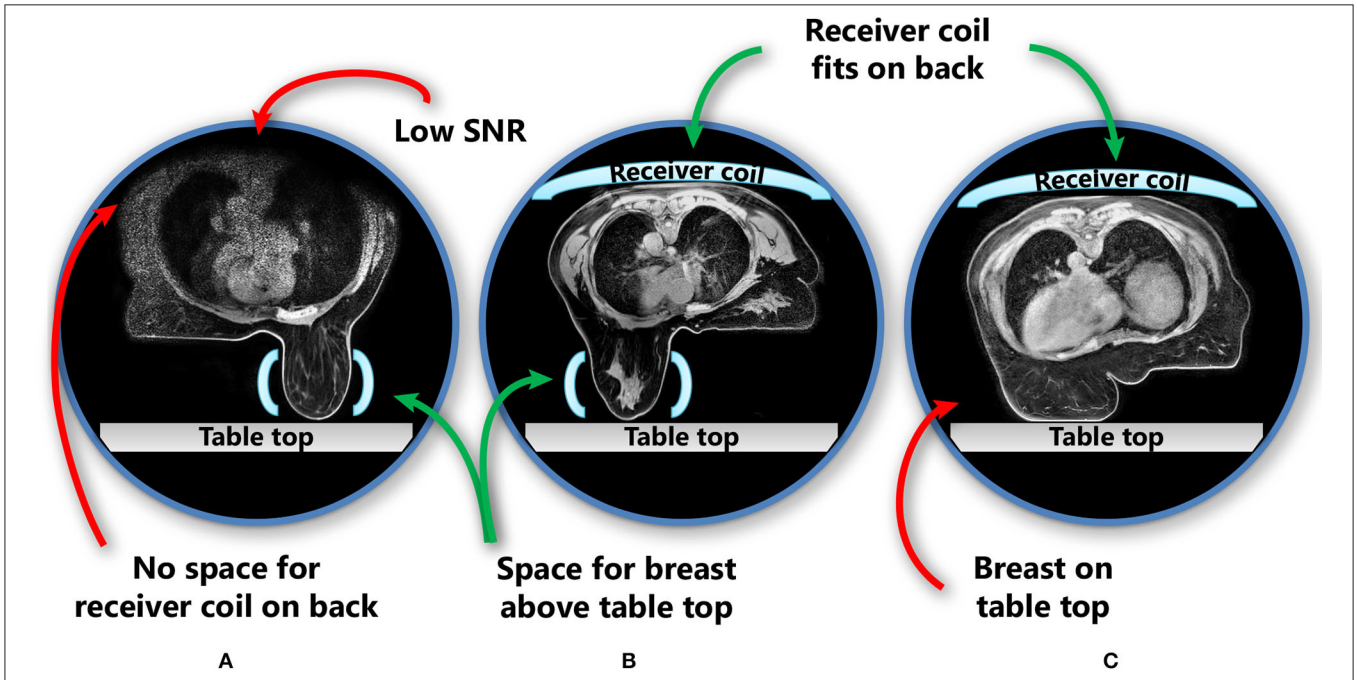

FIGURE 2 | Patient and receiver coil positioning in prone position, including challenges in this position. The images show three different patients. **(A)** No space for the receiver coil on the back of the patient if the breast hangs freely without touching the scanner table; **(B)** the receiver coil fits above the patient while also the breast hangs freely; **(C)** when the receiver coil is fitted in the MRI bore above the patient, the breast touches the table top and is deformed. Light blue shapes represent the receiver coils (horizontal: receiver coil array; vertical: single flex coil). SNR, signal-to-noise ratio.

laterally located target volumes, such as lateral breast tumours. A possible solution may be to shift the patient on the scanner table toward the contralateral side such that the ipsilateral breast moves closer to the machine isocenter, if this is possible within the limited space inside the bore. Furthermore, to minimize system-related distortions, it is also important to always use the scanner's software for gradient non-linearity correction (23, 30). By using a 3D scan, the gradient non-linearity correction can be applied in all directions.

Distortions caused by main magnetic field inhomogeneities and by susceptibility effects induced by the patient's presence in the scanner also need to be corrected for. Distortion caused by patient-induced susceptibility can be particularly large, especially at the tissue–air interface, with mean maximum distortions at 3.0 T having been found to increase from 1.4 to 3.7 mm in a phantom to 3.7 to 11.3 mm in patients (including setup uncertainties) (29). Susceptibility effects scale with the main magnetic field strength (31). A lower field strength or a high receiver bandwidth can help to reduce both main magnetic field inhomogeneity and patient-induced susceptibility, but reduces signal-to-noise ratio (30, 31). Patient-specific correction methods (e.g., using the B0 map) may be helpful to correct for these distortions (18, 30).

Choice of MR Image Contrast

Several MRI sequences have been recommended for MR-guided RT. For use of MRI in the adjuvant breast RT setting, use of T1-weighted 3D sequences without fat suppression resulted in the best visualization of surgical clips, whereas T1-weighted images with fat suppression (e.g., mDixon) best enabled differentiation between glandular breast tissue and seroma (9, 20, 34). Two-dimensional or 3D T2-weighted MRI with fat suppression [e.g., Short inversion time inversion recovery (STIR) or water selective excitation] or without fat suppression was preferred for visualization of lumpectomy cavity and associated seroma and for discrimination between glandular breast tissue and tumour bed (17, 19, 21, 22, 24).

In the neoadjuvant setting, the use of T1-weighted fat-suppressed contrast-enhanced MRI is recommended for optimal tumour and tumour spiculae visualization, because differences

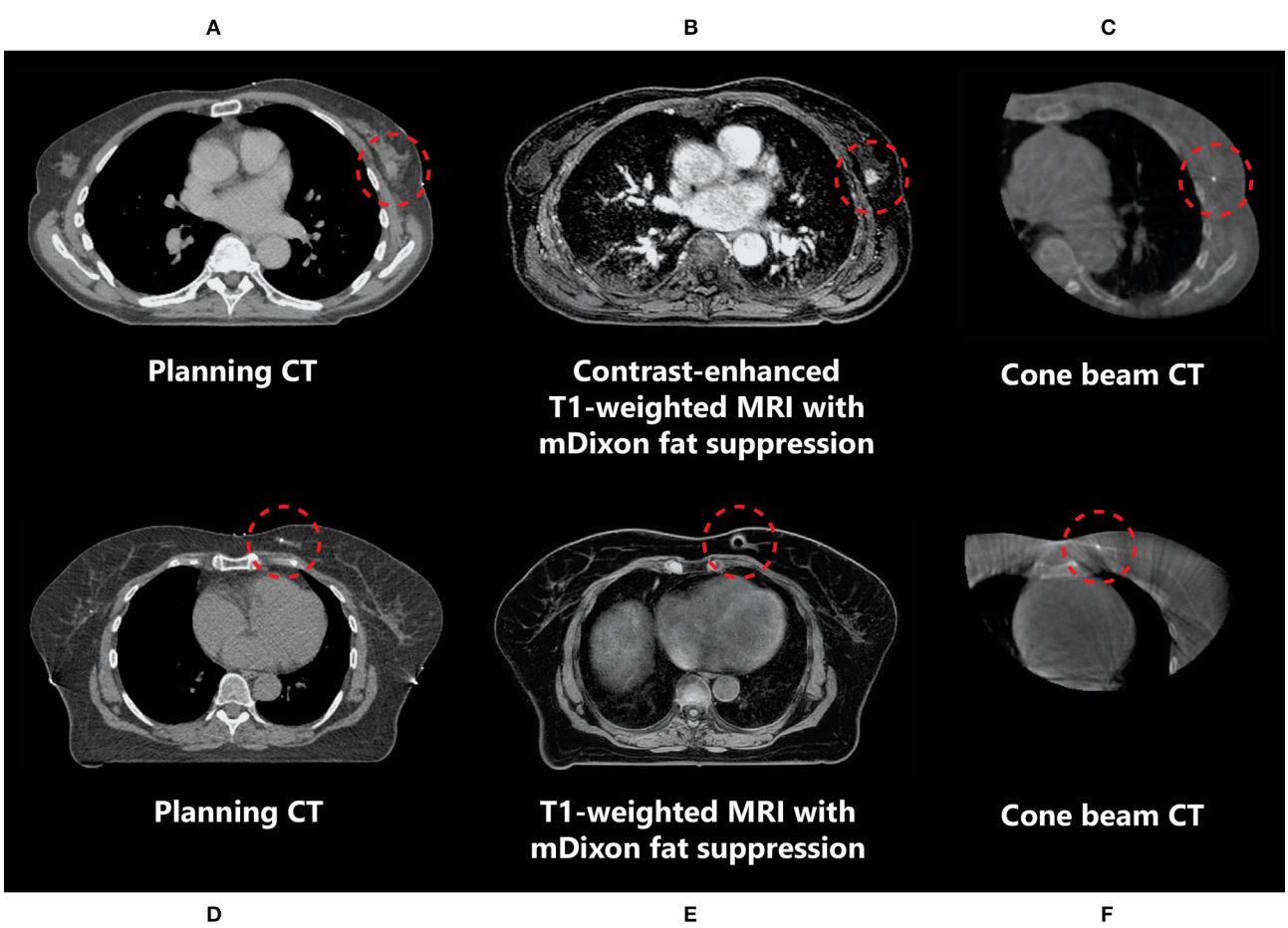

FIGURE 3 | Imaging of a primary breast tumour on CT **(A,D)**, (contrast-enhanced) MRI **(B,E)**, and CBCT **(C,F)** scans indicating the difference in tumour visibility (inside the red circle) between these modalities in two different patients (**A–C** and **D–F**). **(D–F)** The marker inserted in the tumour medial in the left breast is observed as a void on MRI (indicated by the red circles).

in contrast uptake provide a clear distinction between tumour and glandular breast tissue (**Figure 3**) (35–38). Additionally, T2-weighted images might aid in the differentiation between tumour and postbiopsy changes (35). mDixon fat suppression methods proved to be reliable and are recommended because they are relatively insensitive to main magnetic field inhomogeneities (39, 40). Use of diffusion-weighted imaging (DWI) was described in only one study, where it was used in the context of response evaluation after RT and not for target delineation (35). Use of DWI for RT could help in differentiation between benign and malignant lesions, but magnetic susceptibility-induced geometric distortions make it more suitable for diagnostic imaging than for MR-guided RT (41, 42). All studies presented above used fusion of MRI with a planning CT scan on which the OARs were delineated. Therefore, no recommendations focusing on OAR visualization on different MRI sequences have been published. Based on expert opinion, OARs are clearly visualized on any of the sequences mentioned above, except for DWI. All sequences described were acquired on stand-alone MRI scanners. Hybrid treatment machines may come with only a fixed set of available MRI sequences in clinical mode (15, 43). Therefore, not all sequences described may be available on these machines during treatment. A summary of online available MRI sequences on hybrid machines is presented in **Table 2**.

CONTOURING

With regard to target volume delineation in the adjuvant PBI setting, delineation of the tumour bed on CT should, according to guidelines, include visible seroma and representative surgical clips and the tumour location on preoperative imaging and take into account the microscopic tumour free margins (44–47). The added value of MRI to a standard planning CT scan for delineation in the adjuvant setting is disputed for several reasons (48, 49). First, surgical clips lead to voids on MRI, potentially leading to less accurate target volume definition (34). Second, studies have shown both a significant increase as well as a decrease in the target volume when either a preoperative or postoperative MRI scan was available for delineation in addition to a postoperative planning CT (20, 21, 34, 50). Third, in three separate studies, MRI did not lead to a reduction in interobserver variation (20, 24, 50). However, in a more recent larger study, a significant reduction in interobserver variation was reported for delineation on MRI in patients without surgical clips (51). Therefore, the added value of using MRI for contouring in the adjuvant setting seems likely to be limited to those patients in whom tumour bed clips have not been placed.

In the context of neoadjuvant PBI, given that this is not yet a standard of care in breast cancer management, delineation of *in situ* breast tumours is a relatively new concept to most radiation oncologists, and new guidelines are needed. Guidelines for the delineation of primary breast tumours on MRI for use in neoadjuvant PBI setting have recently been developed by the Breast Tumor Site Group of the International MR-Linac Atlantic Consortium (36). These recommend the use of contrast-enhanced MRI, which, because of increased contrast uptake in tumours compared to the surrounding glandular breast tissue, allows for better visualization of breast tumours than using

TABLE 2 | Overview of recommended MR sequences and commercial online availability for clinical breast cancer treatment on hybrid machines.

Type of MR sequence	Advantages (+) and disadvantages (-)	Availability on Unity (Elekta AB)	Availability on MRIdian® (ViewRay®)
Postoperative			
T1-weighted with fat suppression (9, 20, 34)	+ Differentiation between glandular breast tissue and seroma	Not available*	Not available
T1-weighted without fat suppression (9, 20, 34)	+ Best visualization of surgical clips	3D T1-weighted FFE	3D T2/T1-weighted TRUFI
T2-weighted with or without fat suppression (17, 19, 21, 22, 24)	+ Visualization of lumpectomy cavity and seroma + Differentiation between glandular breast tissue and seroma	3D T2-weighted TSE without fat suppression*	3D T2/T1-weighted TRUFI
DWI (35)	+ Differentiation between malignant and benign tissue in case of irradical resection – Susceptible to geometric distortions	Not available*	Not available*
Preoperative			
T1-weighted contrast-enhanced with fat suppression (35–38)	+ Visualization of tumour and tumour spiculae – Injection of and irradiation with contrast agent	No standard contrast injection available	No standard contrast injection available
T2-weighted with or without fat suppression (35)	+ Differentiation between tumour and post-biopsy changes	3D T2 TSE without fat suppression*	3D T2/T1-weighted TRUFI
DWI (35)	+ Differentiation between malignant and benign tissue – Susceptible to geometric distortions	Not available*	Not available*

*TSE, turbo spin echo (fast spin echo); FFE, fast field echo (spoiled gradient echo); TRUFI, true fast imaging with steady state precession (balanced steady state free precession). *Not available in online treatment setting. Acquiring DWI and MR sequences with fat suppression is possible offline—outside online treatment setting mode.*
This table does not provide an exhaustive overview of all imaging possibilities but only refers to MR sequences mentioned in this article and currently commercially available imaging options.

CT (**Figure 3**) (9, 38). Contrast-enhanced MRI has been used for the delineation of target volumes in several recent studies of neoadjuvant PBI (37, 52). In these studies, insertion of an additional fiducial marker by a radiologist was necessary both to help localize the tumour for subsequent surgical resection in case of tumour downstaging and for tumour position verification because the tumour cannot be visualized on CBCT in most patients. These markers cause artefacts on MRI, which can be observed as voids (**Figure 3**). The size of these artefacts depends on the material and geometry of the marker. As the artefact can obscure tumour tissue, the void of a marker should be included in the target volume. If omission of surgery after an ablative dose RT becomes clinically feasible, insertion of a fiducial marker in the tumour might not be necessary anymore. This would be beneficial for both target volume definition and follow-up imaging, as well as patient satisfaction (53).

TREATMENT PLANNING FOR A HYBRID MACHINE

For MR-guided RT on a conventional linac, treatment planning is performed according to the standard practice. This includes registering the MRI scan to the planning CT scan used for delineation and producing a dose distribution using a standard treatment planning system. However, when treatment is to be delivered on a MR-guided hybrid machine, several additional factors need to be considered, all of which will be incorporated into the dedicated treatment planning systems. These factors are inherently related to the design of the hybrid machines. First, given that the magnetic field influences the path of secondary electrons, the ERE and the ESE in air have to be taken into account. Second, the influence of geometric accuracy of the MR images on treatment planning must be considered. Third, there are some restrictions for planning to bear in mind.

Electron Return Effect

The Lorentz force acting on moving charged particles in a magnetic field causes several effects during irradiation in a magnetic field (54–59). One of these is the ERE, which refers to the fact that the path of electrons is bent in the presence of a magnetic field, resulting in exit electrons re-entering the body after a helical path in air (55). Studies have shown that skin dose is increased for patients undergoing WBI in a magnetic field due to the ERE (60, 61). According to van Heijst et al. (60), the mean skin dose increased from 29.5 Gy at 0 T to 32.3 Gy at 0.35 T and to 33.2 Gy at 1.5 T for 2-beam WBI. For 7-beam WBI, the mean skin dose increased from 27.9 Gy at 0 T to 30.2 Gy at 0.35 T and to 29.8 Gy at 1.5 T. Given these findings, WBI is not thought to be a good indication for treatment on a hybrid machine, irrespective of the field strength. Although van Heijst et al. found that the mean skin dose for PBI also increased, from 5.2 Gy at 0 T to 5.6 Gy at 0.35 T and 5.8 Gy at 1.5 T, the absolute mean skin dose was small compared to WBI. Therefore, the increase in skin dose for PBI in a magnetic field would be highly unlikely to translate into a higher risk of radiation dermatitis. Furthermore, it has been reported that increasing the number of beam angles helps in decreasing the skin dose (60, 62). Therefore, although PBI is a good indication for breast RT on a hybrid machine, one should remain aware of the risk of increased skin dose and use more rather than fewer beams. Because the ERE effect is also present at the lung–tissue interface, it is also important to check the maximum lung and chest wall dose (57, 62). Previous planning studies concluded that the effects of the magnetic field on OARs, other than the skin, are generally negligible, and doses were within clinical constraints (60, 62, 63).

Electron Stream Effect

The second effect that should be kept in mind for breast cancer treatment on a hybrid machine is the ESE in air, which can lead to dose being deposited in tissues well outside the irradiated field (**Figure 4**). This was first observed and evaluated by Park et al. (64), who, in the context of accelerated PBI delivered on the 0.35 T ^{60}Co ViewRay system, observed an electron stream in air extending toward the head and ipsilateral arm. This ESE is caused by electrons generated inside the body that, instead of scattering in random directions when leaving the body, start spiraling along the magnetic field (65). If unobstructed, this electron stream would reach the chin and arm, causing unwanted irradiation of the skin in these areas. In an extreme case, the maximum dose measured was as high as 16.1% of the prescribed dose (64). Dose to the skin outside the treatment field was highest in patients with tumours located in the cranial part of the breast. Depending on the location of the high-dose region in the breast, this electron stream can also be directed toward the feet (**Figure 4**). Studies on phantoms and early clinical experiences suggest that the treatment planning system is able to fully describe the ESE and that the use of bolus material to shield the body parts located in the electron stream showed effective reduction of the dose in these regions (64–66).

Impact of Geometric Distortions

Because the breast is located peripherally in the body and geometric distortions increase with distance from the isocenter and susceptibility effects arise near tissue–air interfaces (as described in *Simulation*), the effects of these distortions on dosimetry for breast RT may be significant (27, 30). The system-specific distortions together with patient-related distortions may result in unacceptable dosimetric variations, as has already been shown for WBI (29). This issue still requires investigation in the context of PBI, such as investigation of the impact of distortion at the edges of the breasts, which would lead to inaccurate assignment of air vs. tissue electron density and therefore inaccurate dose calculations when these are based on the MRI. Geometric distortions inside the target region should be carefully considered in choosing adequate planning target volume (PTV) margins in the context of breast RT on an hybrid machine (33).

Planning Restrictions

Technical specifications such as the magnetic field strength, beam energy, source-to-axis distance, and maximum field size are system-specific and are accounted for in the treatment planning systems (13–15). However, there are some specific issues to highlight that will be different from treatment planning for breast

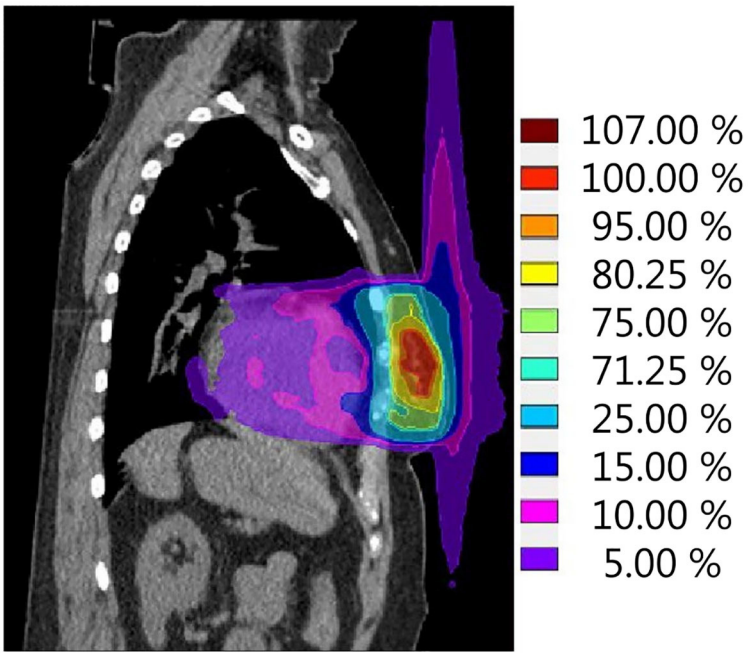

FIGURE 4 | Simulation of a single fraction neoadjuvant PBI treatment plan (ABLATIVE trial approach, 1 × 20 Gy to GTV) for the 1.5-T MR-linac. The calculated dose distribution shows the electron stream effect in air resulting in dose outside of the treatment field in both cranial and caudal directions. Scale is set to 100% reference dose = 20 Gy.

irradiation on a conventional linac. First, for the ViewRay MR-linac system angles between 30 and 33° are not available, whereas for the Elekta system 8 to 18° degrees need to be avoided because of the cryostat pipe (15, 67). Furthermore, some beam angles commonly used for breast RT on conventional systems should preferably not be used on the Elekta system, that is, angles around 130–150° and 210–230°, with exact angles depending on the tumour location (66, 67). This is because of high-density material in the treatment couch edges that may cause unwanted dose effects during daily plan adaptation. Because of the design of the hybrid machines, rotations of the table with respect to the gantry angle and therefore irradiation with non-coplanar beams are not possible. No problems are expected because of this because good plan quality for PBI can be achieved with coplanar IMRT (26, 63, 68).

With respect to the methods currently used for dose calculation, co-registration of the planning CT to the pre-treatment and/or online MR images or bulk density assignment are currently used for electron density information for both the ViewRay and Elekta hybrid machines (15, 67, 69). Strategies for creating a synthetic CT directly from an MRI scan, such as atlas-based, voxel intensity–based, or deep learning approaches, are in development (70, 71). However, data on the use of synthetic CT for the breast or thoracic region are limited. Recent data have shown encouraging results for synthetic CT generation for the thoracic region based on (a combination of) voxel intensity– and atlas-based approaches, with a mean absolute error <50 HU in the body and dosimetric differences ≤1.7% inside lung tumour PTVs (72, 73). Inclusion of bone density information, specifically the spine in this study on lung tumour treatment plans, proved to be important to reduce local hot spots in the differences between the simulated dose distributions on CT and synthetic CT (73). Ahunbay et al. (74) proposed to continue using a planning CT scan for each patient. Their approach with inclusion of bone density and the use of deformably registered lung density, both of which may be necessary for breast RT treatment planning as well, may enable accurate full online replanning on the daily anatomy. In an online workflow, options may be limited by the specific system, but aforementioned issues should be taken into account, as well as speed of synthetic CT generation.

TREATMENT ON A HYBRID MACHINE

For MR-guided RT on a conventional linac, the treatment and position verification can be performed according to the current standard RT workflow. Using a hybrid machine with daily online MRI both before and during treatment, new opportunities become available for daily setup and positioning accuracy, online adaptive RT based on daily anatomy, and intrafraction motion management.

Daily Setup and Positioning Accuracy

Experiences from hospitals that have treated breast cancer patients in the adjuvant setting with the 0.35 T ^{60}Co system have shown that initial patient setup verification based on location of lumpectomy cavity and online motion monitoring could be beneficial for PBI patients in terms of reducing the CTV to PTV margin and therefore irradiated volume and thereby the

risk of late toxicity (26, 43, 69, 75). A >52% reduction in treatment volume was achieved by applying no PTV margin for the lumpectomy cavity with the help of online MRI for setup (26, 75). Although a 0-mm PTV margin neglects correction of other uncertainties that would normally be incorporated in the CTV to PTV margin (e.g., mechanical equipment and dosimetric uncertainties) (76), this illustrates that online MRI for setup may help to reduce the PTV margin compared to treatment on a conventional linac. With the aid of an online motion monitoring approach, a mean difference of <1% between planned and delivered dose to 95% of the target volume was achieved (26). For treatment in the neoadjuvant setting, patient setup and positioning accuracy on a hybrid machine are still to be evaluated.

Online Adaptive RT

On hybrid machines, a new treatment plan can be made during each fraction based on online MRI. Depending on the specific system, different strategies are available. These range from dose recalculation on the new patient anatomy to full online recontouring and replanning (15, 77, 78). Requirements for online replanning are somewhat different than for pretreatment planning. In particular, the time available for target and OAR redelineation and plan optimization is much reduced because the patient is on the treatment table. The choice of plan adaptation strategy will therefore depend on a trade-off between plan quality and speed of plan adaptation. In general, it is expected that a full reoptimization plan adaptation method will lead to improved dosimetry in most patients, especially in the case of deformations in the tumour or OARs, but will take more time (78, 79). In the group reporting on adjuvant PBI on a ^{60}Co system, where online MRI proved beneficial for setup and PTV margin reduction, no online plan adaptation was performed, and yet retrospective comparison of planned vs. delivered dose showed adequate coverage, suggesting that, in the context of PBI, use of a simpler plan adaptation strategy may be reasonable (26, 43). Currently, injection of contrast agent is not performed during treatment on a hybrid machine, although it could help to recontour the tumour volume in case of neoadjuvant PBI. However, gadolinium chelates, the most commonly used contrast agent for breast cancer, could have a radiosensitizing effect (80). Because of the uncertainty of the effect and safety of irradiation when a contrast agent has been injected and concern about stability and toxicity of irradiated gadolinium, it is not recommended to use contrast-enhanced sequences for imaging during treatment.

Intrafraction Motion Management

Generally three types of intrafraction motion can be distinguished: (1) regular breathing motion, (2) irregular transient motion, and (3) non-transient bulk motion. Breast intrafraction motion evaluated on 2D and 3D MR images (2- to 20-minutes duration) has been reported to be generally regular and limited to <3 mm (26, 81). Larger displacements have been observed, but these were mostly transient. Acharya et al. (26) calculated that a mean PTV margin of 0.7 mm would be sufficient to cover 90% of the lumpectomy cavity for 90% of the treatment time for a mean fraction duration of 12.7 minutes. However, intrafraction displacement seemed to differ substantially between patients, reaching a mean displacement range of 6 mm in anterior-posterior direction for one patient. One possibility to handle intrafraction displacement might be to individualize the PTV margin based on cine MR data from simulation. Larger whole-body shifts of up to 14 mm over a 21-minutes duration have been observed infrequently, although for the majority of patients motion evaluated up to 20 minutes was generally regular and small (81). The impact of intrafraction motion on current standard hypofractionated treatment is therefore likely to be limited. However, for extremely hypofractionated treatment schedules (one to two fractions) delivered on hybrid machines, treatment times will increase significantly because of the online delineation and planning procedure and because of increased beam on time because of a lower dose rate of the hybrid machines and use of IMRT compared to volumetric modulated arc therapy (68, 82, 83). This will increase the risk of systematic non-transient patient displacement both before and during treatment and may also negatively affect patient comfort. Although not yet available, real-time plan adaptation during RT delivery will be the ultimate goal to account for intrafraction motion management (84). Henke et al. (43) noted that online motion tracking and gating on the lumpectomy cavity were beneficial for accelerated PBI treatment with regard to reduction of the PTV margin (26, 43). A disadvantage of gating is that, although it is a solution for intrafraction motion management, it will even further increase the treatment time. Solutions for online monitoring and management of intrafraction motion such as cine MRI-based gated irradiation are not yet implemented for the 1.5-T Elekta MR-linac.

First Clinical Experiences

Several publications have reported on neoadjuvant MR-guided PBI on a conventional linac including favourable toxicity profiles (35, 37, 85). However, no patients have yet been treated with neoadjuvant PBI on a hybrid machine. A planning study has shown that neoadjuvant PBI in a single fraction in prone or supine position on the 1.5-T Elekta MR-linac would be dosimetrically feasible with adequate target coverage and within predefined constraints for OAR (63).

Experiences with adjuvant PBI on a hybrid system have been published. For patients treated on the 0.35-T ^{60}Co Viewray system with single-fraction adjuvant PBI, up to 12 months' follow-up is available, and no local recurrences have been reported. The first clinical results showed good tolerability, low toxicity with a maximum of grade 2 toxicity, and good to excellent cosmetic outcome assessed by both patients and physician (86, 87). Usage of this system resulted in benefits for initial patient setup on lumpectomy cavity and online motion monitoring by which the PTV margin was diminished to 0 mm, which led to a large reduction in treatment volume of 52% (26, 43, 69, 75). The first patient has also been successfully treated with adjuvant PBI in 15 fractions on a 1.5-T Elekta MR-linac, which led to only grade 1 toxicity of the breast with adequate protection of the chin to prevent unwanted irradiation due to the ESE (66).

Patients are currently being recruited for several studies on MR-guided PBI. On ClinicalTrials.gov, two trials are registered aiming to treat patients in the adjuvant setting on a hybrid machine, looking primarily at either reproducibility of treatment or cosmetic outcome (88, 89). Three other trials are being conducted to further explore the effect of neoadjuvant MR-guided PBI on a conventional linac (90–92). The primary outcomes of these trials are postoperative complication rate, reproducibility of treatment, and pathologic response, respectively.

CONCLUSION

The addition of MR guidance to the breast RT planning pathway facilitates target volume delineation in the neoadjuvant PBI setting, whereas treatment on a hybrid MR and linac or ^{60}Co machine could lead to reduced CTV to PTV margins in the neoadjuvant and adjuvant PBI settings through clearer visualization of the target volume during treatment. Although challenges for treatment of breast cancer patients on these systems remain (**Table 1**), the first breast cancer patients have been treated successfully with adjuvant PBI on a hybrid system, and studies of MR-guided neoadjuvant PBI will open shortly, through which technical approaches and workflow are likely to be further refined.

ETHICS STATEMENT

Written informed consent was obtained from the patients and volunteers for the publication of any potentially identifiable images or data included in this article. Medical images presented in this work were from subjects participating in the ABLATIVE trial (ClinicalTrials.gov identifier: NCT02316561) and were used with permission from the ABLATIVE trial team. The ABLATIVE protocol was approved by the Institutional Review Board of the University Medical Center Utrecht, Utrecht, the Netherlands.

AUTHOR CONTRIBUTIONS

AK, HB, AH, MG, and JV contributed to conception and design of this work. MG and JV wrote the first draft of the manuscript. All authors contributed to data interpretation, critical manuscript revision, read, and approved the submitted version.

REFERENCES

1. van Maaren MC, de Munck L, de Bock GH, Jobsen JJ, van Dalen T, Linn SC, et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. *Lancet Oncol.* (2016). 17:1158–70. doi: 10.1016/S1470-2045(16)30067-5
2. Aalders KC, van Bommel ACM, van Dalen T, Sonke GS, van Diest PJ, Boersma LJ, et al. Contemporary risks of local and regional recurrence and contralateral breast cancer in patients treated for primary breast cancer. *Eur J Cancer.* (2016) 63:118–26. doi: 10.1016/j.ejca.2016.05.010
3. American Cancer Society. *Cancer Facts & Figures 2020*. Atlanta: American Cancer Society (2020). Available online at: https://www.cancer.org/research/cancer-facts-statistics.html
4. Curigliano G, Burstein HJ, Winer EP, Gnant M, Dubsky P, Loibl S, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. gallen international expert consensus conference on the primary therapy of early breast cancer 2017. *Ann Oncol.* (2017) 28:1700–12. doi: 10.1093/annonc/mdx308
5. Coles CE, Griffin CL, Kirby AM, Titley J, Agrawal RK, Alhasso A, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial):5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet.* (2017) 90:1048–60. doi: 10.1016/S0140-6736(17)31145-5
6. Bhattacharya I, Haviland JS, Kirby AM, Kirwan CC, Hopwood P, Yarnold JR, et al. Patient-Reported outcomes over 5 years after whole- or partial-breast radiotherapy: longitudinal analysis of the IMPORT LOW (CRUK/06/003) phase III randomized controlled trial. *J Clin Oncol.* (2019) 37:305–17. doi: 10.1200/JCO.18.00982
7. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a ran. *Lancet.* (2016). 387:229–38. doi: 10.1016/S0140-6736(15)00471-7
8. Whelan TJ, Julian JA, Berrang TS, Kim D-H, Germain I, Nichol AM, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. *Lancet.* (2019) 394:2165–72. doi: 10.1016/S0140-6736(19)32515-2
9. Den Hartogh MD, Philippens MEP, van Dam IE, Kleynen CE, Tersteeg RJHA, Pijnappel RM, et al. MRI and CT imaging for preoperative target volume delineation in breast-conserving therapy. *Radiat Oncol.* (2014) 9:1–9. doi: 10.1186/1748-717X-9-63
10. van der Leij F, Elkhuizen PHM, Janssen TM, Poortmans P, van der Sangen M, Scholten AN, et al. Target volume delineation in external beam partial breast irradiation: less inter-observer variation with preoperative- compared to postoperative delineation. *Radiother Oncol.* (2014) 110:467–70. doi: 10.1016/j.radonc.2013.10.033
11. Lightowlers SV, Boersma LJ, Fourquet A, Kirova YM, Offersen BV, Poortmans P, et al. Preoperative breast radiation therapy: indications and perspectives. *Eur J Cancer.* (2017) 82:184–92. doi: 10.1016/j.ejca.2017.06.014
12. Lagendijk JJW, Raaymakers BW, Raaijmakers AJE, Overweg J, Brown KJ, Kerkhof EM, et al. MRI/linac integration. *Radiother Oncol.* (2008) 86:25–9. doi: 10.1016/j.radonc.2007.10.034
13. Raaymakers BW, Jürgenliemk-Schulz IM, Bol GH, Glitzner M, Kotte ANTJ, Van Asselen B, et al. First patients treated with a 1.5 T MRI-Linac: clinical proof of concept of a high-precision, high-field MRI guided radiotherapy treatment. *Phys Med Biol.* (2017) 62:L41–50. doi: 10.1088/1361-6560/aa9517
14. Mutic S, Dempsey JF. The viewray system: magnetic resonance–guided and controlled radiotherapy. *Semin Radiat Oncol.* (2014) 24:196–9. doi: 10.1016/j.semradonc.2014.02.008
15. Klüter S. Technical design and concept of a 0.35 T MR-Linac. *Clin Transl Radiat Oncol.* (2019) 18:98–101. doi: 10.1016/j.ctro.2019.04.007
16. Dundas K, Pogson EM, Batumalai V, Delaney GP, Boxer MM, Yap ML, et al. The impact of imaging modality (CT vs MRI) and patient position (supine vs prone) on tangential whole breast radiation therapy planning. *Pract Radiat Oncol.* (2018) 8:e87–e97. doi: 10.1016/j.prro.2017.07.007
17. Paulson ES, Erickson B, Schultz C, Allen Li X. Comprehensive MRI simulation methodology using a dedicated MRI scanner in radiation oncology for external beam radiation treatment planning. *Med Phys.* (2015) 42:28–39. doi: 10.1118/1.4896096
18. Schmidt MA, Payne GS. Radiotherapy planning using MRI. *Phys Med Biol.* (2015) 60:R323–61. doi: 10.1088/0031-9155/60/22/R323
19. Ahn KH, Hargreaves BA, Alley MT, Horst KC, Luxton G, Daniel BL, et al. MRI guidance for accelerated partial breast irradiation in prone position: imaging

protocol design and evaluation. *Int J Radiat Oncol Biol Phys.* (2009) 75:285–93. doi: 10.1016/j.ijrobp.2009.03.063
20. Giezen M, Kouwenhoven E, Scholten AN, Coerkamp EG, Heijenbrok M, Jansen WPA, et al. MRI- versus CT-based volume delineation of lumpectomy cavity in supine position in breast-conserving therapy: an exploratory study. *Int J Radiat Oncol Biol Phys.* (2012) 82:1332–40. doi: 10.1016/j.ijrobp.2011.05.008
21. Jolicoeur M, Racine ML, Trop I, Hathout L, Nguyen D, Derashodian T, et al. Localization of the surgical bed using supine magnetic resonance and computed tomography scan fusion for planification of breast interstitial brachytherapy. *Radiother Oncol.* (2011) 100:480–4. doi: 10.1016/j.radonc.2011.08.024
22. Batumalai V, Liney G, DeLaney GP, Rai R, Boxer M, Min M, et al. Assessment of MRI image quality for various setup positions used in breast radiotherapy planning. *Radiother Oncol.* (2016) 119:57–60. doi: 10.1016/j.radonc.2016.02.024
23. Liney GP, Moerland MA. Magnetic resonance imaging acquisition techniques for radiotherapy planning. *Semin Radiat Oncol.* (2014) 24:160–8. doi: 10.1016/j.semradonc.2014.02.014
24. Pogson EM, Delaney GP, Ahern V, Boxer MM, Chan C, David S, et al. Comparison of magnetic resonance imaging and computed tomography for breast target volume delineation in prone and supine positions. *Int J Radiat Oncol Biol Phys.* (2016) 96:905–12. doi: 10.1016/j.ijrobp.2016.08.002
25. Tijssen RHN, Philippens MEP, Paulson ES, Glitzner M, Chugh B, Wetscherek A, et al. MRI commissioning of 1.5T MR-linac systems – a multi-institutional study. *Radiother Oncol.* (2019) 132:114–20. doi: 10.1016/j.radonc.2018.12.011
26. Acharya S, Fischer-Valuck BW, Mazur TR, Curcuru A, Sona K, Kashani R, et al. Magnetic resonance image guided radiation therapy for external beam accelerated partial-breast irradiation: evaluation of delivered dose and intrafractional cavity motion. *Int J Radiat Oncol Biol Phys.* (2016) 96:785–92. doi: 10.1016/j.ijrobp.2016.08.006
27. Prott F-J, Haverkamp U, Eich H, Resch A, Micke O, Fischedick A-R, et al. Effect of distortions and asymmetry in MR images on radiotherapeutic treatment planning. *Int J Cancer.* (2000) 90:46–50. doi: 10.1002/(SICI)1097-0215(20000220)90:1<46::AID-IJC6>3.0.CO;2-6
28. Fransson A, Andreo P, Pötter R. Strahlentherapie und onkologie aspects of MR image distortions in radiotherapy treatment planning. *Strahlentherapie und Onkol.* (2001) 177:59–73. doi: 10.1007/PL00002385
29. Walker A, Metcalfe P, Liney G, Batumalai V, Dundas K, Glide-Hurst C, et al. MRI geometric distortion: impact on tangential whole-breast IMRT. *J Appl Clin Med Phys.* (2016) 17:7–19. doi: 10.1120/jacmp.v17i5.6242
30. Walker A, Liney G, Metcalfe P, Holloway L. MRI distortion: considerations for MRI based radiotherapy treatment planning. *Australas Phys Eng Sci Med.* (2014) 37:103–13. doi: 10.1007/s13246-014-0252-2
31. Das IJ, McGee KP, Tyagi N, Wang H. Role and future of MRi in radiation oncology. *Br J Radiol.* (2019) 91:1–14. doi: 10.1259/bjr.20180505
32. Tijssen RHN, Crijns SPM, Bluemink JJ, Hackett SS, De Vries JHW, Kruiskamp MJ, et al. OC-0257: comprehensive MRI acceptance testing & commissioning of a 1.5T MR-linac: guidelines and results. *Radiother Oncol.* (2017) 123:S130–1. doi: 10.1016/S0167-8140(17)30700-4
33. Ginn JS, Agazaryan N, Cao M, Baharom U, Low DA, Yang Y, et al. Characterization of spatial distortion in a 0.35 T MRI-guided radiotherapy system. *Phys Med Biol.* (2017) 62:4525–40. doi: 10.1088/1361-6560/aa6e1a
34. Kirby AM, Yarnold JR, Evans PM, Morgan VA, Schmidt MA, Scurr ED, et al. Tumor bed delineation for partial breast and breast boost radiotherapy planned in the prone position: what does MRI add to X-ray CT localization of titanium clips placed in the excision cavity wall? *Int J Radiat Oncol Biol Phys.* (2009) 74:1276–82. doi: 10.1016/j.ijrobp.2009.02.028
35. Horton JK, Blitzblau RC, Yoo S, Geradts J, Chang Z, Baker JA, et al. Preoperative single-fraction partial breast radiation therapy: a novel phase 1, dose-escalation protocol with radiation response biomarkers. *Int J Radiat Oncol Biol Phys.* (2015) 92:846–55. doi: 10.1016/j.ijrobp.2015.03.007
36. Vasmel JE, Groot Koerkamp ML, Kirby AM, Russell NS, Shaitelman SF, Vesprini D, et al. Consensus on contouring primary breast tumors on MRI in the setting of neoadjuvant partial breast irradiation in trials. *Pract Radiat Oncol.* (in press). doi: 10.1016/j.prro.2020.03.011
37. Guidolin K, Yaremko B, Lynn K, Gaede S, Kornecki A, Muscedere G, et al. Stereotactic image-guided neoadjuvant ablative single-dose radiation, then lumpectomy, for early breast cancer: the SIGNAL prospective single-arm trial of single-dose radiation therapy. *Curr Oncol.* (2019) 26:1–7. doi: 10.3747/co.26.4479
38. Mouawad M, Biernaski H, Brackstone M, Lock M, Yaremko B, Sexton T, et al. Reducing the dose of gadolinium-based contrast agents for DCE-MRI guided SBRT: the effects on inter and intra observer variability for preoperative target volume delineation in early stage breast cancer patients. *Radiother Oncol.* (2019) 131:60–5. doi: 10.1016/j.radonc.2018.11.020
39. Glover GH. Multipoint dixon technique for water and fat proton and susceptibility imaging. *J Magn Reson Imaging.* (1991) 1:521–30. doi: 10.1002/jmri.1880010504
40. Van Heijst TCF, Van Asselen B, Pijnappel RM, Cloos-van Balen M, Lagendijk JJW, Van den Bongard D, et al. MRI sequences for the detection of individual lymph nodes in regional breast radiotherapy planning. *Br J Radiol.* (2016) 89:20160072. doi: 10.1259/bjr.20160072
41. Partridge SC, Nissan N, Rahbar H, Kitsch AE, Sigmund EE. Diffusion-weighted breast MRI: Clinical applications and emerging techniques. *J Magn Reson Imaging.* (2017) 45:337–55. doi: 10.1002/jmri.25479
42. Leibfarth S, Winter RM, Lyng H, Zips D, Thorwarth D. Potentials and challenges of diffusion-weighted magnetic resonance imaging in radiotherapy. *Clin Transl Radiat Oncol.* (2018) 13:29–37. doi: 10.1016/j.ctro.2018.09.002
43. Henke LE, Contreras JA, Green OL, Cai B, Kim H, Roach MC, et al. Magnetic resonance image-guided radiotherapy (MRIgRT): a 4.5-year clinical experience. *Clin Oncol.* (2018) 30:720–7. doi: 10.1016/j.clon.2018.08.010
44. Major T, Gutiérrez C, Guix B, van Limbergen E, Strnad V, Polgár C. Recommendations from GEC ESTRO breast cancer working group (II): target definition and target delineation for accelerated or boost partial breast irradiation using multicatheter interstitial brachytherapy after breast conserving open cavity surgery. *Radiother Oncol.* (2016) 118:199–204. doi: 10.1016/j.radonc.2015.12.006
45. Offersen B V., Boersma LJ, Kirkove C, Hol S, Aznar MC, Biete Sola A, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. *Radiother Oncol.* (2015) 114:3–10. doi: 10.1016/j.radonc.2014.11.030
46. Strnad V, Hannoun-Levi J-M, Guinot J-L, Lössl K, Kauer-Dorner D, Resch A, et al. Recommendations from GEC ESTRO breast cancer working Group (I): target definition and target delineation for accelerated or boost partial breast irradiation using multicatheter interstitial brachytherapy after breast conserving closed cavity surgery. *Radiother Oncol.* (2015) 115:342–8. doi: 10.1016/j.radonc.2015.06.010
47. Boersma LJ, Janssen T, Elkhuizen PHM, Poortmans P, van der Sangen M, Scholten AN, et al. Reducing interobserver variation of boost-CTV delineation in breast conserving radiation therapy using a pre-operative CT and delineation guidelines. *Radiother Oncol.* (2012) 103:178–82. doi: 10.1016/j.radonc.2011.12.021
48. Mast M, Coerkamp E, Heijenbrok M, Scholten A, Jansen W, Kouwenhoven E, et al. Target volume delineation in breast conserving radiotherapy: are co-registered CT and MR images of added value? *Radiat Oncol.* (2014) 9(Lc):65. doi: 10.1186/1748-717X-9-65
49. Christopherson KM, Smith BD. How does MR imaging help care for my breast cancer patient? Perspective of a radiation oncologist. *Magn Reson Imaging Clin N Am.* (2018) 26:295–302. doi: 10.1016/j.mric.2017.12.007
50. Den Hartogh MD, Philippens MEP, Van Dam IE, Kleynen CE, Tersteeg RJHA, Kotte ANTJ, et al. Post-lumpectomy CT-guided tumor bed delineation for breast boost and partial breast irradiation: can additional pre- and postoperative imaging reduce interobserver variability? *Oncol Lett.* (2015) 10:2795–801. doi: 10.3892/ol.2015.3697
51. Al-Hammadi N, Caparrotti P, Divakar S, Riyas M, Chandramouli SH, Hammoud R, et al. MRI reduces variation of contouring for boost clinical target volume in breast cancer patients without surgical clips in the tumour bed. *Radiol Oncol.* (2017) 51:160–8. doi: 10.1515/raon-2017-0014
52. Charaghvandi RK, van Asselen B, Philippens MEP, Verkooijen HM, van Gils CH, van Diest PJ, et al. Redefining radiotherapy for early-stage breast cancer with single dose ablative treatment: a study protocol. *BMC Cancer.* (2017) 17:181. doi: 10.1186/s12885-017-3144-5

53. Seely JM, Hill F, Peddle S, Lau J. An evaluation of patient experience during percutaneous breast biopsy. *Eur Radiol.* (2017) 27:4804–11. doi: 10.1007/s00330-017-4872-2
54. Raaymakers BW, Raaijmakers AJE, Kotte ANTJ, Jette D, Lagendijk JJW. Integrating a MRI scanner with a 6 MV radiotherapy accelerator: dose deposition in a transverse magnetic field. *Phys Med Biol.* (2004) 49:4109–18. doi: 10.1088/0031-9155/49/17/019
55. Raaijmakers AJE, Raaymakers BW, Lagendijk JJW. Integrating a MRI scanner with a 6 MV radiotherapy accelerator: dose increase at tissue-air interfaces in a lateral magnetic field due to returning electrons. *Phys Med Biol.* (2005) 50:1363–76. doi: 10.1088/0031-9155/50/7/002
56. Raaijmakers AJE, Raaymakers BW, Van Der Meer S, Lagendijk JJW. Integrating a MRI scanner with a 6 MV radiotherapy accelerator: impact of the surface orientation on the entrance and exit dose due to the transverse magnetic field. *Phys Med Biol.* (2007) 52:929–39. doi: 10.1088/0031-9155/52/4/005
57. Raaijmakers AJE, Raaymakers BW, Lagendijk JJW. Magnetic-field-induced dose effects in MR-guided radiotherapy systems: dependence on the magnetic field strength. *Phys Med Biol.* (2008) 53:909–23. doi: 10.1088/0031-9155/53/4/006
58. Oborn BM, Metcalfe PE, Butson MJ, Rosenfeld AB. High resolution entry and exit monte carlo dose calculations from a linear accelerator 6 MV beam under the influence of transverse magnetic fields. *Med Phys.* (2009) 36:3549–59. doi: 10.1118/1.3157203
59. Oborn BM, Metcalfe PE, Butson MJ, Rosenfeld AB. Monte carlo characterization of skin doses in 6 MV transverse field MRI-linac systems: effect of field size, surface orientation, magnetic field strength, and exit bolus. *Med Phys.* (2010) 37:5208–17. doi: 10.1118/1.3488980
60. van Heijst TCF, den Hartogh MD, Lagendijk JJW, van den Bongard HJGD, van Asselen B. MR-guided breast radiotherapy: feasibility and magnetic-field impact on skin dose. *Phys Med Biol.* (2013) 58:5917–30. doi: 10.1088/0031-9155/58/17/5917
61. Esmaeeli AD, Mahdavi SR, Pouladian M, Monfared AS, Bagheri S. Improvement of dose distribution in breast radiotherapy using a reversible transverse magnetic field linac-MR unit. *Med Phys.* (2013) 41:011709. doi: 10.1118/1.4845175
62. Kim A, Lim-Reinders S, Mccann C, Ahmad SB, Sahgal A, Lee J, et al. Magnetic field dose effects on different radiation beam geometries for hypofractionated partial breast irradiation. *J Appl Clin Med Phys.* (2017) 18:62–70. doi: 10.1002/acm2.12182
63. Charaghvandi KR, Van't Westeinde T, Yoo S, Houweling AC, Rodrigues A, Verkooijen HM, et al. Single dose partial breast irradiation using an MRI linear accelerator in the supine and prone treatment position. *Clin Transl Radiat Oncol.* (2019) 14:1–7. doi: 10.1016/j.ctro.2018.09.001
64. Park JM, Shin KH, Kim J in, Park SY, Jeon SH, Choi N, et al. Air–electron stream interactions during magnetic resonance IGRT: skin irradiation outside the treatment field during accelerated partial breast irradiation. *Strahlentherapie und Onkol.* (2018) 194:50–9. doi: 10.1007/s00066-017-1212-z
65. Malkov VN, Hackett SL, Wolthaus JWH, Raaymakers BW, van Asselen B. Monte carlo simulations of out-of-field surface doses due to the electron streaming effect in orthogonal magnetic fields to. *Phys Med Biol.* (2019) 64:115029. doi: 10.1088/1361-6560/ab0aa0
66. Nachbar M, Mönnich D, Boeke S, Gani C, Weidner N, Heinrich V, et al. Partial breast irradiation with the 1.5 T MR-Linac: First patient treatment and analysis of electron return and stream effects. *Radiother Oncol.* (2019) 145:30–5. doi: 10.1016/j.radonc.2019.11.025
67. Werensteijn-Honingh AM, Kroon PS, Winkel D, Aalbers EM, van Asselen B, Bol GH, et al. Feasibility of stereotactic radiotherapy using a 1.5 T MR-linac: multi-fraction treatment of pelvic lymph node oligometastases. *Radiother Oncol.* (2019) 134:50–4. doi: 10.1016/j.radonc.2019.01.024
68. Yoo S, Blitzblau R, Yin FF, Horton JK. Dosimetric comparison of preoperative single-fraction partial breast radiotherapy techniques: 3D CRT, noncoplanar IMRT, coplanar IMRT, and VMAT. *J Appl Clin Med Phys.* (2015) 16:5126. doi: 10.1120/jacmp.v16i1.5126
69. Fischer-Valuck BW, Henke L, Green O, Kashani R, Acharya S, Bradley JD, et al. Two-and-a-half-year clinical experience with the world's first magnetic resonance image guided radiation therapy system. *Adv Radiat Oncol.* (2017) 2:485–93.
70. Johnstone E, Wyatt JJ, Henry AM, Short SC, Sebag-Montefiore D, Murray L, et al. Systematic review of synthetic computed tomography generation methodologies for use in magnetic resonance imaging–only radiation therapy. *Int J Radiat Oncol Biol Phys.* (2018) 100:199–217. doi: 10.1016/j.ijrobp.2017.08.043
71. Han X. MR-based synthetic CT generation using a deep convolutional neural network method. *Med Phys.* (2017). 44:1408–19. doi: 10.1002/mp.12155
72. Su K, Friel HT, Kuo J, Al Helo R, Baydoun A, Stehning C, et al. UTE-mDixon-based thorax synthetic CT ceneration. *Med Phys.* (2019) 46(8):3520–31. doi: 10.1002/mp.13574
73. Freedman JN, Bainbridge H, Nill S, Collins DJ, Kachelriess M, Leach MO, et al. Synthetic 4D-CT of the thorax for treatment plan adaptation on MR-guided radiotherapy systems. *Phys Med Biol.* (2019) 64:115005. doi: 10.1088/1361-6560/ab0dbb
74. Ahunbay EE, Thapa R, Chen X, Paulson E, Li XA. A technique to rapidly generate synthetic computed tomography for magnetic resonance imaging–guided online adaptive replanning: an exploratory study. *Int J Radiat Oncol Biol Phys.* (2019) 103:1261–70. doi: 10.1016/j.ijrobp.2018.12.008
75. Jeon SH, Shin KH, Park S-Y, Kim J, Park JM, Kim JH, et al. Seroma change during magnetic resonance imaging-guided partial breast irradiation and its clinical implications. *Radiat Oncol.* (2017) 12:103. doi: 10.1186/s13014-017-0843-7
76. International Commission on Radiation Units Measurements. Prescribing, recording, reporting photon-beam intensity-modulated radiation therapy (IMRT). ICRU report 83. *J ICRU.* (2010) 10:1–106. doi: 10.1093/jicru/ndq002
77. Winkel D, Bol GH, Kiekebosch IH, Van Asselen B, Kroon PS, Jürgenliemk-Schulz IM, et al. Evaluation of online plan adaptation strategies for the 1.5T MR-linac based on "First-In-Man" treatments. *Cureus.* (2018) 10:1–7. doi: 10.7759/cureus.2431
78. Acharya S, Fischer-Valuck BW, Kashani R, Parikh P, Yang D, Zhao T, et al. Online magnetic resonance image guided adaptive radiation therapy: first clinical applications. *Int J Radiat Oncol Biol Phys.* (2016) 94:394–403. doi: 10.1016/j.ijrobp.2015.10.015
79. Winkel D, Kroon PS, Werensteijn-Honingh AM, Bol GH, Raaymakers BW, Jürgenliemk-Schulz IM. Simulated dosimetric impact of online replanning for stereotactic body radiation therapy of lymph node oligometastases on the 1.5T MR-linac. *Acta Oncol (Madr).* (2018) 57:1705–12. doi: 10.1080/0284186X.2018.1512152
80. Taupin F, Flaender M, Delorme R, Brochard T, Mayol JF, Arnaud J, et al. Gadolinium nanoparticles and contrast agent as radiation sensitizers. *Phys Med Biol.* (2015) 60:4449–64. doi: 10.1088/0031-9155/60/11/4449
81. van Heijst TCF, Philippens MEP, Charaghvandi RK, den Hartogh MD, Lagendijk JJW, van den Bongard HJGD, et al. Quantification of intra-fraction motion in breast radiotherapy using supine magnetic resonance imaging. *Phys Med Biol.* (2016) 61:1352–70. doi: 10.1088/0031-9155/61/3/1352
82. van Herk M, McWilliam A, Dubec M, Faivre-Finn C, Choudhury A. Magnetic resonance imaging–guided radiation therapy: a short strengths, weaknesses, opportunities, and threats analysis. *Int J Radiat Oncol Biol Phys.* (2018) 101:1057–60. doi: 10.1016/j.ijrobp.2017.11.009
83. Park JM, Wu HG, Kim HJ, Choi CH, Kim JI. Comparison of treatment plans between IMRT with MR-linac and VMAT for lung SABR. *Radiat Oncol.* (2019) 14:1–8. doi: 10.1186/s13014-019-1314-0
84. Kontaxis C, Bol GH, Stemkens B, Glitzner M, Prins FM, Kerkmeijer LGW, et al. Towards fast online intrafraction replanning for free-breathing stereotactic body radiation therapy with the MR-linac. *Phys Med Biol.* (2017) 62:7233–48. doi: 10.1088/1361-6560/aa82ae
85. Vasmel JE, Charaghvandi RK, Houweling AC, Philippens MEP, van Asselen B, Vreuls CPH, et al. Tumor response following neoadjuvant MR-guided single ablative dose partial breast irradiation. *Int J Radiat Oncol.* (2020) 106:821–9. doi: 10.1016/j.ijrobp.2019.11.406
86. Zoberi I, Thomas MA, Ochoa LL. Evaluation of single fraction high-gradient partial breast irradiation as the sole method of radiation therapy for low-risk stage 0 and i breast cancer—early results of a single institution prospective clinical trial. *Int J Radiat Oncol Biol Phys.* (2017) 99:E61. doi: 10.1016/j.ijrobp.2017.06.736

87. Kennedy WR, Thomas MA, DeBroeck KR, Ochoa LL, Atkinson AR, Green OL, et al. Postoperative single-fraction partial breast irradiation for low-risk stage 0 and i breast carcinomas: results of a prospective clinical trial. *Int J Radiat Oncol Biol Phys*. (2018) 102:S227–8. doi: 10.1016/j.ijrobp.2018.07.159
88. Anderson B. *Real-time MRI-Guided 3-Fraction Accelerated Partial Breast Irradiation in Early Breast Cancer (Clinical Trials.gov Identifier NCT03936478).* (2019)
89. Gani C. *Feasibility of Online MR-Guided Radiotherapy on a 1.5T MR-Linac (Clinical trials.gov Identifier NCT04172753).* (2019).
90. Currey A. *MRI-Based Preoperative Accelerated Partial Breast Irradiation (Clinical trials.gov Identifier NCT02728076*). (2016).
91. White JR. *Intensity Modulated Accelerated Partial Breast Irradiation Before Surgery in Treating Older Patients With Hormone Responsive Stage 0-I Breast Cancer (Clinical trials.gov Identifier NCT02186470).* (2014).
92. van den Bongard HJGD. *MRI-Guided Single Dose Preoperative Radiotherapy in Low-risk Breast Cancer (Clinical trials.gov Identifier NCT03863301).* (2019).

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Aggressive Local Treatment Improves Survival in Stage IV Breast Cancer With Synchronous Metastasis

Chen-Lu Lian[1†], Li-Yi Guo[2†], Lei Zhang[3†], Jun Wang[1], Jian Lei[4], Li Hua[4], Zhen-Yu He[3] and San-Gang Wu[1*]*

[1] Department of Radiation Oncology, Cancer Hospital, The First Affiliated Hospital of Xiamen University, Xiamen, China, [2] The Sixth People's Hospital of Huizhou, Affiliated Huiyang Hospital of Southern Medical University, Huizhou, China, [3] Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China, [4] Department of Obstetrics and Gynecology, The First Affiliated Hospital of Xiamen University, Xiamen, China

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***Correspondence:**
Zhen-Yu He
hezhy@sysucc.org.cn
San-Gang Wu
unowu12345@hotmail.com

[†]These authors have contributed equally to this work

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Introduction: To investigate the effect of local treatment strategy on survival outcome in *de novo* stage IV breast cancer patients who received chemotherapy.

Methods: We identified stage IV breast cancers that presented with synchronous metastasis from the Surveillance, Epidemiology, and End Results database. Binomial logistic regression, Kaplan–Meier survival curves, propensity score matching (PSM), and multivariate Cox regression model were used for statistical analyses.

Results: We identified 5,374 patients in total, including 2,319 (43.2%), 2,137 (39.8%), and 918 (17.1%) patients who received surgery alone, surgery+radiotherapy, and radiotherapy alone, respectively. The probability of patients receiving surgery alone decreased over time, and the probability of patients receiving radiotherapy alone increased over time. However, no significant difference was observed in the probability of patients receiving postoperative radiotherapy ($P = 0.291$). The 3-year breast cancer-specific survival (BCSS) in patients treated with surgery alone, radiotherapy alone, and surgery+radiotherapy was 57.1, 35.9, and 63.9%, respectively ($P < 0.001$). The local treatment strategy was the independent prognostic factor related to BCSS. Using surgery alone as the reference, radiotherapy alone was related to lower BCSS ($P < 0.001$), while additional radiotherapy after surgery improved BCSS ($P < 0.001$). Similar results were observed using PSM.

Conclusions: Compared to radiotherapy alone, surgery to the primary site may confer a survival benefit in stage IV breast cancer with synchronous metastasis, and additional postoperative radiotherapy further improves outcome after primary tumor removal. Local treatment can only be an option in highly selected patients with *de novo* stage IV disease in the treatment guidelines. More prospective studies are needed to investigate the role of local management for this patient subset.

Keywords: breast cancer, distant metastasis, treatment, prognosis, radiotherapy

BACKGROUND

Breast cancer remains the leading cause of malignancy in women worldwide, with approximately two million new cases diagnosed in 2018 (1). About 3–5% of newly diagnosed breast cancer cases are stage IV disease with synchronous metastasis (*de novo* stage IV disease) (2–4). Although related to poor outcomes, advances in systemic therapies against breast cancer such as taxane-based chemotherapy, targeted therapies, and endocrine therapy have improved the survival outcomes of stage IV patients (5). Two recent studies have indicated that the prognosis has improved over the past three decades in this patient subset (6, 7).

Traditional management in this patient subset comprises systemic therapy, with additional surgery or radiotherapy to control locoregional symptoms. However, four recent randomized trials that investigated prognosis after surgery in *de novo* stage IV breast cancer reported conflicting results (8–11). Several retrospective studies have shown a survival advantage with locoregional treatment, including surgery or radiotherapy to the primary site (12–21). The rationale for proceeding with additional surgery or radiotherapy includes the possibility of increasing the effectiveness of chemotherapy, reducing the total tumor burden, restoring immunity, eliminating breast cancer stem cells, and decreasing the likelihood of resistant disease, which may lower the metastatic potential of the primary tumor (22–24). These observations suggest that locoregional intervention to primary tumors may improve outcome in stage IV breast cancer with synchronous metastasis.

In current clinical practice, approximately half of the patients with *de novo* stage IV disease were treated with local surgery, because it was associated with better local control and longer survival times in retrospective studies (19, 25, 26). The consensus from the Third International Consensus Conference for Advanced Breast Cancer suggests that surgery to the primary site can be considered in selected patients, particularly to improve the quality of life (27). However, the survival benefit of radiotherapy in these patients has been rarely investigated (13, 20, 21). In addition, it is worth speculating whether postoperative radiotherapy could improve survival, as this has shown conflicting results in the past (13, 18, 19, 21). Therefore, we explored the existing real-world data from the Surveillance, Epidemiology, and End Results (SEER) program to assess the outcomes of different local treatment strategies including surgery alone, radiotherapy alone, and surgery+radiotherapy for patients with stage IV breast cancer with synchronous metastasis.

METHODS AND MATERIALS

Patients

Patient data were selected from the SEER database that includes patient information regarding clinical cancer incidence, demographics, clinicopathological characteristics, the first course of treatment including surgery, radiotherapy, and chemotherapy, and vital status from 18 registries, which represents approximately 28% of the population of the United States (28). We identified *de novo* stage IV breast cancer patients treated with surgery alone, radiotherapy alone, or surgery and radiotherapy in addition to chemotherapy, between 2004 and 2012. The following patients were excluded: those with no pathologic diagnosis, those with non-invasive ductal carcinoma or invasive lobular carcinoma, those that did not undergo external beam radiation, and those with unavailable data regarding ethnicity, grade, tumor size, nodal status, estrogen receptor (ER), and progesterone receptor (PR) status. The Institutional Review Board waived the need for informed consent because anonymized patient data from the SEER database was used.

Measures

We identified the following variables of interest: age, ethnicity, grade, histology, T stage, N stage, ER status, PR status, and local treatment procedures. T and N category was determined based on the seven edition of the UICC/AJCC staging system. The primary outcome of this study was breast cancer-specific survival (BCSS), which was calculated as the time from the initial diagnosis to the date of breast cancer-specific death or last follow-up.

Statistical Analysis

The distribution differences among locoregional treatment procedures and patient information were compared using the chi-square test. Predictors of receipt of locoregional treatment procedures were analyzed using binomial logistic regression. A 1:1 propensity score matching (PSM) method was performed by logistic regression to balance the above patient demographic and clinicopathological characteristics to reduce the potential baseline selection bias. The BCSS rate was assessed using the Kaplan–Meier method, and the effect of locoregional treatment procedures on BCSS was analyzed using the log-rank test. The independent prognostic indicators associated with BCSS were determined using multivariate Cox regression models with Backward Wald. IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses, and a $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Patient Characteristics

We identified 5,374 patients from the SEER database in this study. A flow-chart of patient selection is shown in **Figure 1**. Of these patients, 93.2% (n = 5,006) had invasive ductal carcinoma, 81.6% (n = 4,387) had node-positive disease, 76.3% (n = 4,102) were aged <65 years, 64.3% (n = 3,454) had ER-positive disease, 62.1% (n = 3,339) were non-Hispanic White, and 60.8% (n = 3,272) had poorly differentiated/undifferentiated disease. In addition, approximately 50% of patients had stage T3-4 disease. A total of 4,456 patients underwent surgical treatment, and 48.0% (n = 2,137) of them were treated with postoperative radiotherapy, while 918 patients received radiotherapy alone. The patient baseline characteristics are listed in **Table 1**.

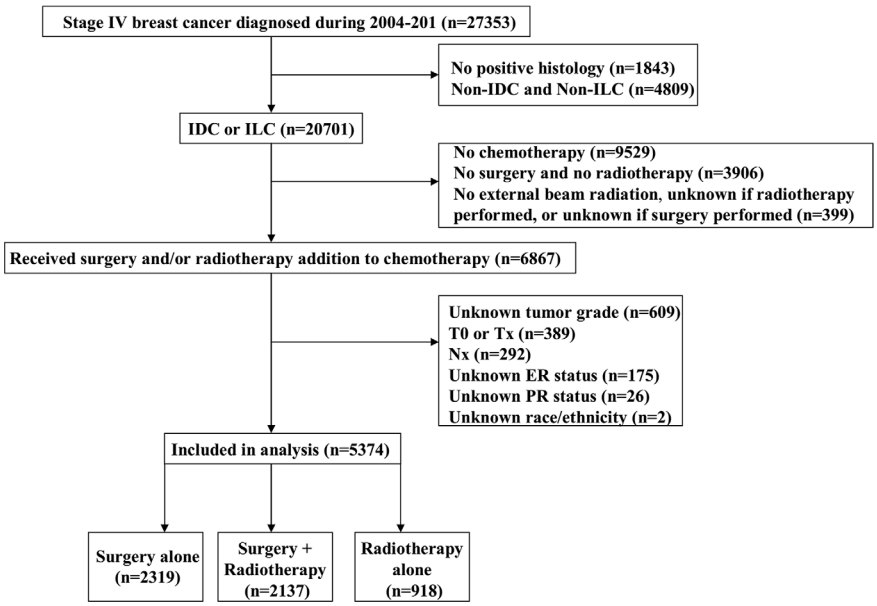

FIGURE 1 | The patient selection flowchart of the study.

TABLE 1 | Patients' baseline characteristics.

Variables	n	S alone (%)	RT alone (%)	S + RT (%)	P
Age (years)					
<65	4,102	1,707 (73.6)	691 (75.3)	1,704 (79.7)	<0.001
≥65	1,272	612 (26.4)	227 (24.7)	433 (20.3)	
Ethnicity					
Non-Hispanic White	3,339	1,465 (63.2)	521 (56.8)	1,353 (63.3)	0.008
Non-Hispanic Black	946	405 (17.5)	193 (21.0)	348 (16.3)	
Hispanic (all ethnicities)	641	272 (11.7)	115 (12.5)	254 (11.9)	
Other	448	177 (7.6)	89 (9.7)	182 (8.5)	
Grade					
Well-differentiated	285	118 (5.1)	57 (6.2)	110 (5.1)	<0.001
Moderately differentiated	1,817	711 (30.7)	374 (40.7)	732 (34.3)	
Poorly/undifferentiated	3,272	1,490 (64.3)	487 (53.1)	1,295 (60.6)	
Histology					
IDC	5,006	2,148 (92.6)	866 (94.3)	1,992 (93.2)	0.219
ILC	368	171 (7.4)	52 (5.7)	145 (6.8)	
Tumor stage					
T1	774	361 (15.6)	115 (12.5)	298 (13.9)	<0.001
T2	1,916	913 (39.4)	211 (23.0)	792 (37.1)	
T3	991	448 (19.3)	154 (16.8)	389 (18.2)	
T4	1,693	597 (25.7)	438 (47.7)	658 (30.8)	
Nodal status					
N0	987	451 (19.4)	223 (24.3)	313 (14.6)	<0.001
N1	2,105	865 (37.3)	450 (49.0)	790 (37.0)	
N2	1,029	468 (20.2)	94 (10.2)	467 (21.9)	
N3	1,253	535 (23.1)	151 (16.4)	567 (26.5)	
ER status					
Negative	1,920	918 (39.6)	322 (35.1)	680 (31.8)	<0.001
Positive	3,454	1,401 (60.4)	596 (64.9)	1,457 (68.2)	
PR status					
Negative	2,702	1,235 (53.3)	464 (50.5)	1,003 (46.9)	<0.001
Positive	2,672	1,084 (46.7)	454 (49.5)	1,134 (53.1)	

IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; N, nodal; PR, progesterone receptor; RT, radiotherapy; S, surgery; T, tumor.

Trends of Local Treatment Receipt

The use of surgery alone decreased from 45.7% in 2004 to 39.8% in 2012 (P < 0.001). However, no significant difference was observed in the probability of patients receiving postoperative radiotherapy (41.6% in 2004 *vs.* 39.5% in 2012, P = 0.291). Moreover, the probability of receiving radiotherapy alone showed an increase over time, from 12.8% in 2004 to 21.1% in 2012 (P < 0.001). **Figure 2** shows the probability of receiving different local treatments over time.

Predictors for Receipt of Local Treatment

Using binomial logistic regression (**Table 2**), we found that ethnicity, grade, T stage, and N stage were independent predictors of radiotherapy receipt. Patients with non-Hispanic Black and other ethnicities, lower tumor grade, larger tumor size, and node-negative disease were more likely to be treated with radiotherapy alone. In addition, age, T stage, N stage, and ER status were independent predictors of postoperative radiotherapy receipt. Patients with younger age, T4 stage, and node-positive and ER-positive disease were more likely to receive postoperative radiotherapy.

Survival and Prognostic Analyses

With a median follow-up of 37 months (range, 0–143 months), a total of 3,727 patients died, including 3,317 patients who died with breast cancer. The 3- and 5-year BCSS was 56.3 and 40.2%, respectively. The 3-year BCSS in patients that underwent surgery alone, radiotherapy alone, and surgery+radiotherapy was 57.1, 35.9, and 63.9%, respectively, with a median survival time of 45, 25, and 55 months, respectively (P < 0.001) (**Figure 3**).

In the multivariate Cox regression analysis (**Table 3**), local treatment strategy also served as an independent prognostic factor related to BCSS. Using surgery alone as the reference, radiotherapy alone was related to lower BCSS (hazard ratio [HR]: 1.966, 95% confidence interval [CI]: 1.788–2.162, P < 0.001), while additional radiotherapy after surgery improved BCSS (HR: 0.829, 95% CI: 0.767–0.896, P < 0.001). In addition, age, ethnicity, grade, histology, T stage, N stage, and hormone receptor status were the prognostic factors related to BCSS.

Using PSM, a total of 792 pairs were completely matched between the surgery ± radiotherapy and radiotherapy alone cohorts. In addition, 1,469 pairs were completely matched between surgery alone and surgery+radiotherapy cohorts. After adjustment of age, ethnicity, grade, histology, T stage, N stage, and hormone receptor status, the results confirmed that patients who received radiotherapy alone had lower BCSS than those who were treated with surgery ± radiotherapy (HR: 2.135, 95% CI: 1.889–2.412, P < 0.001) (Model 1) (**Table 4**). Moreover, patients who received postoperative radiotherapy had better BCSS than those treated with surgery alone (HR: 0.814, 95% CI: 0.742–0.893, P < 0.001) (Model 2) (**Table 4**). The survival curves in the two cohorts are shown in **Figure 4**.

DISCUSSION

In the current study, we used the SEER database to investigate whether aggressive local treatment improves survival in stage IV breast cancer with synchronous metastasis. Our results showed that local surgery was related to better BCSS than radiotherapy alone, and additional postoperative radiotherapy further improved BCSS than surgery alone.

De novo stage IV breast cancer is a relatively rare disease, and most patients were treated with systemic therapy only. The efficacy of local treatment, such as surgery and/or radiotherapy remains controversial. Thus, there were significant differences in the distribution regarding local treatment strategies in these patients. In a study by Choi et al. that included 245 patients, 82 patients received locoregional treatment and systemic therapy, and 32.9, 11.0, and 56.1% of them received surgery alone, radiotherapy alone, and surgery+radiotherapy, respectively (18). Another study from the British Columbia Cancer Agency (n = 378) indicated that surgery was the most common treatment procedure (78.3%), with only 13.9% (n = 41)

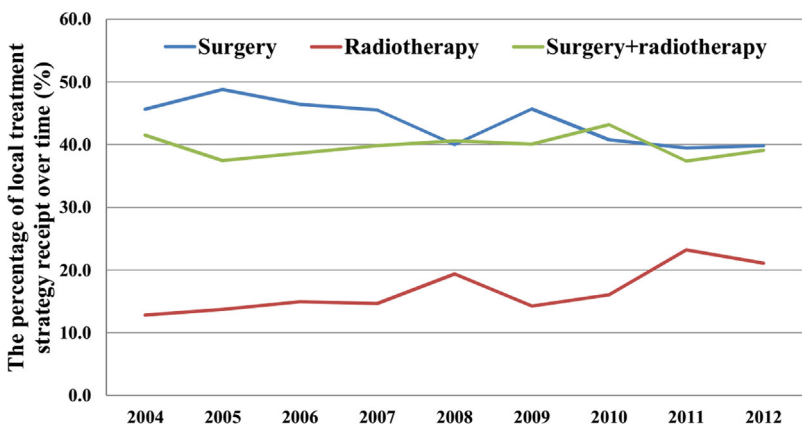

FIGURE 2 | The probability of receiving different local treatment strategies over time.

TABLE 2 | Predictive factors for receipt of local treatment.

Variables	RT alone *vs.* S ± RT			S + RT *vs.* S alone		
	OR	95% CI	P	OR	95% CI	P
Age (years)						
<65	1			1		
≥65	1.057	0.889–1.257	0.532	0.698	0.606–0.804	<0.001
Ethnicity						
Non-Hispanic White	1			1		
Non-Hispanic Black	1.367	1.129–1.654	0.001	0.905	0.767–1.068	0.237
Hispanic (All ethnicities)	1.188	0.944–1.495	0.143	0.98	0.811–1.184	0.834
Other	1.332	1.027–1.726	0.031	1.055	0.845–1.318	0.636
Grade						
Well-differentiated	1			1		
Moderately differentiated	0.982	0.712–1.356	0.914	1.032	0.775–1.374	0.830
Poorly/undifferentiated	0.635	0.462–0.873	0.005	0.907	0.680–1.210	0.506
Histology						
IDC	1			1		
ILC	0.796	0.578–1.097	0.163	0.847	0.664–1.081	0.182
Tumor stage						
T1	1			1		
T2	0.852	0.663–1.095	0.212	0.995	0.828–1.196	0.960
T3	1.367	1.039–1.797	0.025	0.982	0.795–1.212	0.863
T4	2.726	2.140–3.472	<0.001	1.296	1.066–1.577	0.009
Nodal status						
N0	1			1		
N1	0.776	0.640–0.941	0.010	1.24	1.038–1.481	0.018
N2	0.282	0.216–0.370	<0.001	1.366	1.121–1.665	0.002
N3	0.372	0.292–0.472	<0.001	1.482	1.223–1.796	<0.001
ER status						
Negative	1			1		
Positive	1.013	0.820–1.252	0.903	1.427	1.259–1.617	<0.001
PR status						
Negative	1			1		
Positive	0.941	0.770–1.150	0.551	1.040	0.883–1.226	0.637

CI, confidence interval; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; N, nodal; OR, odds ratio; PR, progesterone receptor; RT, radiotherapy; S, surgery; T, tumor.

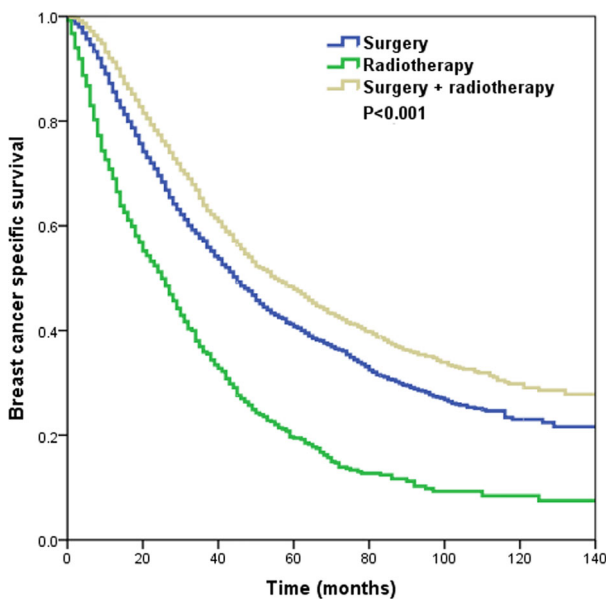

FIGURE 3 | The Kaplan–Meier curves of breast cancer-specific survival by different local treatment strategies before propensity score matching.

patients receiving radiotherapy in the surgery cohort and 21.7% patients receiving radiotherapy alone (19). However, another study from Le Scodan et al. that included 320 patients treated with locoregional treatment showed that 78% (n = 249) received radiotherapy alone, 71 (22.2%) received surgery, and 57.7% had additional radiotherapy (13). In our study, the distribution of the types of local treatment was 43.2, 17.1, and 38.8 in the surgery alone, radiotherapy alone, and surgery+radiotherapy, respectively. There was no consensus regarding the locoregional treatment in this patient subset. Therefore, the different distribution of locoregional treatment might reflect the different clinical practices in various institutions.

To our best knowledge, no study has so far assessed changes to local treatment patterns in *de novo* stage IV breast cancer over time. In this study, we additionally investigated the relationship between the patterns of local treatment and the time of diagnosis. Our results showed that from 2004 to 2012, patients who received surgery alone decreased by 5.9% (45.7 *vs.* 39.8%), while those that received radiotherapy alone increased by 8.3% (12.8 *vs.* 21.1%). The main reason for the changing trends of local treatment remains unclear. A possible explanation is that systemic treatments for breast cancer patients, including chemotherapy, targeted therapy, and endocrine therapy, have made significant progress, and the outcomes have improved (5),

TABLE 3 | Multivariate analysis on prognostic indicators associated with breast cancer-specific survival before propensity score matching.

Variables	HR	95% CI	P
Age (years)			
<65	1		
≥65	1.171	1.081–1.269	<0.001
Ethnicity			
Non-Hispanic White	1		
Non-Hispanic Black	1.321	1.208–1.444	<0.001
Hispanic (all ethnicities)	1.023	0.917–1.140	0.686
Other	0.816	0.714–0.933	0.003
Grade			
Well-differentiated	1		
Moderately differentiated	1.120	0.937–1.338	0.214
Poorly/undifferentiated	1.418	1.188–1.693	<0.001
Histology			
IDC	1		
ILC	1.187	1.033–1.363	0.015
Tumor stage			
T1	1		
T2	1.180	1.051–1.326	0.005
T3	1.360	1.196–1.546	<0.001
T4	1.565	1.390–1.761	<0.001
Nodal status			
N0	1		
N1	0.881	0.798–0.974	0.013
N2	0.955	0.820–1.076	0.436
N3	1.064	0.954–1.187	0.267
ER status			
Negative	1		
Positive	0.752	0.683–0.827	<0.001
PR status			
Negative	1		
Positive	0.712	0.648–0.782	<0.001
Treatment			
Surgery alone	1		
Radiotherapy alone	1.966	1.788–2.162	<0.001
Surgery + radiotherapy	0.829	0.767–0.896	<0.001

CI, confidence interval; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; HR, hazard ratio; N, nodal; PR, progesterone receptor; RT, radiotherapy; S, surgery; T, tumor.

which may have reduced the use of aggressive treatments, including surgery.

Although an improvement in median survival was observed with upfront local surgery for *de novo* stage IV breast cancer in the MF07-01 trial (9), there were three randomized trials, including TATA memorial study, E2108 trial, and ABCSG-28 POSYTIVE trial, which investigated local therapy for *de novo* stage IV breast cancer and indicated that additional local therapy to optimal systemic therapy did not improve survival outcomes than those treated with optimal systemic therapy alone (8, 10, 11). In the current clinical practice, approximately half of patients with *de novo* stage IV breast cancer were treated with local therapy (15, 16, 19, 21, 25, 26). Therefore, according to our findings, if the clinicians decide to use local treatment in select cases, it appears that surgery+radiotherapy is better than those with radiotherapy or surgery alone.

Results regarding the predictive factors of receipt of radiotherapy alone were contradictory. A study by Le Scodan et al. included patients who received radiotherapy alone or no local treatment, patients with small tumor size, lower nodal stage, non-visceral metastases, and received a combination of endocrine treatment and chemotherapy were more likely to received radiotherapy (13). Another study from the Institut Gustave Roussy Breast Cancer Database showed that patients with large tumor size, higher tumor grade, advanced nodal stage, and higher tumor burden were more likely to be included in the radiotherapy alone than surgery ± radiotherapy cohort (21). Our results also showed that patients with favorable prognostic factors, including lower tumor grade and node-negative disease were more likely to received radiotherapy alone. However, patients with larger tumor size also had a higher chance of receiving radiotherapy alone compared to surgery cohort. The results from a meta-analysis showed that patients with larger tumor size were less likely to undergo surgery (20). Thus, locoregional radiotherapy might be a reasonable choice for patients with larger tumor size if locoregional management was to be performed. However, our study showed that radiotherapy alone had the worst survival.

Although the efficacy of local treatment in these patients showed contradictory results in prospective studies (8–11), current retrospective studies with large cohorts had suggested that local treatment could improve the survival of this patient subset (12–21). However, most studies are mainly based on surgical treatment, and there are currently no prospective studies to compare the role of radiotherapy and surgery. A study by Le Scodan et al. showed that patients in the radiotherapy cohort had better 3-year overall survival (OS) (43.4 *vs.* 26.7%, $P < 0.001$) than patients who did not undergo any local treatment (13). They suggested that locoregional radiotherapy may be an effective alternative to surgery. However, more patients who are treated with radiotherapy alone had smaller tumor size, lower nodal burden, bone-only metastases, and less visceral organ involvement, and more received endocrine therapy (13). Two recent studies from the Institut Gustave Roussy Breast Cancer Database and the British Columbia Cancer Agency showed comparable survival outcomes between surgery ± radiotherapy and radiotherapy-alone cohorts when adjusted for prognostic factors (19, 21). However, patients who received surgery ± radiotherapy were less likely to be treated with systemic therapies (55 *vs.* 99% in surgery ± radiotherapy *vs.* radiotherapy alone, respectively) (21), which may limit the representative value of the study. The study by Choi et al. included 245 patients, wherein 90% were treated with chemotherapy, and patients with surgery ± radiotherapy had significantly higher locoregional-free survival (LRFS) and OS rates than the radiotherapy-only cohort (5-year LRFS: surgery+ radiotherapy [70%], surgery only [53%], and radiotherapy only [27%]; 5-year OS: surgery+radiotherapy [77%], surgery only [70%], and radiotherapy only [44%]). Moreover, 63.0% of patients received postoperative radiotherapy in the surgery cohort (18). In our large cohort study, all patients were treated with chemotherapy, and patients in the surgery ± radiotherapy cohorts had significantly higher BCSS than those treated with radiotherapy alone before and after PSM, which was similar to Choi et al.'s results (18). Our study indicated that surgery is an

TABLE 4 | Multivariate analysis on prognostic indicators associated with breast cancer-specific survival after propensity score matching.

Variables	Model 1			Model 2		
	HR	95% CI	P	HR	95% CI	P
Age (years)						
<65	1			1		
≥65	1.160	1.002–1.343	0.047	1.035	0.919–1.167	0.570
Ethnicity						
Non-Hispanic White	1			1		
Non-Hispanic Black	1.302	1.118–1.517	0.001	1.511	1.334–1.711	<0.001
Hispanic (all ethnicities)	1.132	0.930–1.377	0.217	1.059	0.904–1.240	0.477
Other	0.727	0.565–0.936	0.013	0.890	0.727–1.091	0.264
Grade						
Well-differentiated	1			1		
Moderately differentiated	1.219	0.866–1.714	0.256	1.597	1.110–2.296	0.012
Poorly/undifferentiated	1.393	0.987–1.965	0.059	2.083	1.445–3.004	<0.001
Histology						
IDC	1			1		
ILC	0.913	0.608–1.371	0.660	1.647	1.291–2.101	<0.001
Tumor stage						
T1	1			1		
T2	1.158	0.931–1441	0.187	1.011	0.863–1.185	0.892
T3	1.139	0.880–1.423	0.361	1.309	1.095–1.564	0.003
T4	1.373	1.117–1.688	0.003	1.545	1.311–1.820	<0.001
Nodal status						
N0	1			1		
N1	0.859	0.733–1.007	0.061	0.905	0.783–1.045	0.173
N2	0.984	0.776–1.246	0.892	0.979	0.833–1.151	0.797
N3	1.054	0.860–1.293	0.611	1.138	0.975–1.328	0.102
ER status						
Negative	1			1		
Positive	0.663	0.558–0.789	<0.001	0.822	0.717–0.944	0.005
PR status						
Negative	1			1		
Positive	0.734	0.622–0.866	<0.001	0.721	0.629–0.827	<0.001
Treatment						
Surgery ± radiotherapy	1			—		
Radiotherapy	2.135	1.889–2.412	<0.001	—	—	—
Treatment						
Surgery	—			1		
Surgery + radiotherapy	—	—	—	0.814	0.742–0.893	<0.001

CI, confidence interval; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; HR, hazard ratio; N, nodal; PR, progesterone receptor; RT, radiotherapy; S, surgery; T, tumor.

acceptable alternative to radiotherapy alone in appropriately selected patients.

There were still large differences in the recommendation for postoperative radiotherapy, ranging from 18.9 to 63.0% (12, 18, 19, 25, 29). Several previous studies have shown comparable LRFS or OS between patients treated with surgery alone and surgery+radiotherapy (18, 19, 25, 29). Our study further indicated that postoperative radiotherapy could improve BCSS in the surgical cohort. The potential interpretation of our results may be with respect to higher tumor burden, including larger tumor size, advanced nodal stage, and higher tumor grade that may have a significant correlation with subsequent locoregional recurrence and distant metastasis. Therefore, postoperative radiotherapy may be an important option, together with local surgical treatment for these patients. Studies from non-metastatic breast cancer have also shown that postoperative radiotherapy can improve locoregional control, distant recurrence, and OS in patients with node-positive lymph nodes (30–32).

Our study has some limitations. First, as with any retrospective study, there exists a possible selection bias with limits any conclusions of direct causative relationships. In addition, we were unable to include targeted therapy and endocrine therapy, given that it was not recorded in the SEER database. Third, the sequence of chemotherapy and local treatment, the timing of local treatment, the evaluation of tumor response to chemotherapy, the recurrence, and distant patterns after local treatment are not recorded in the SEER program. Finally, the dose and target volume of locoregional radiotherapy was also not recorded in the SEER database. The primary strength of this study was that we used a large database series to determine the optimal additional local treatment strategy in *de novo* stage IV breast cancer treated with chemotherapy.

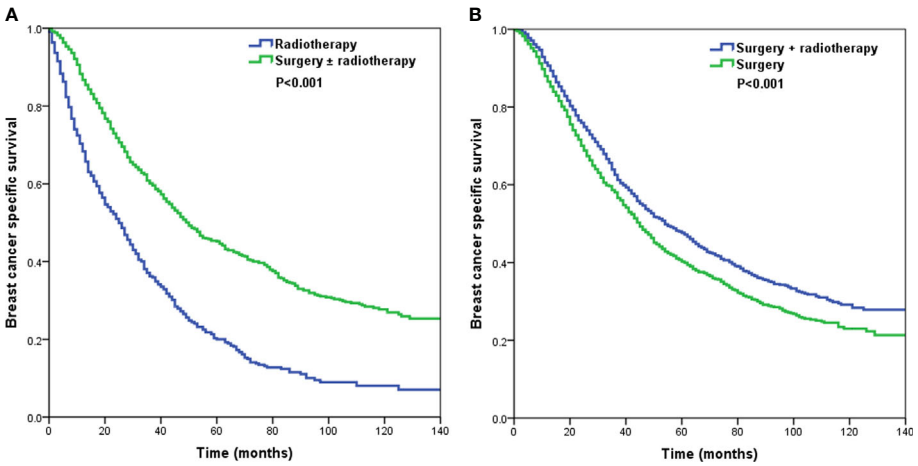

FIGURE 4 | The Kaplan–Meier curves of breast cancer-specific survival by different local treatment strategies after propensity score matching **(A)** surgery ± radiotherapy *vs.* radiotherapy alone; **(B)** surgery+radiotherapy *vs.* surgery alone).

CONCLUSION

In conclusion, our study suggests that surgery to primary sites may offer better survival benefit than radiotherapy alone in patients with *de novo* stage IV breast cancer. Additionally, additional postoperative radiotherapy further improves outcomes after primary tumor removal. However, due to lack of important information regarding tumor biology, systemic treatments, and site of metastasis. This study does not provide reliable data on the real impact of local treatments for this patient subset. According to the guidelines from the European School of Oncology and European Society for Medical Oncology (33), local treatment can only be an option in highly selected patients. Therefore, more prospective studies are needed to investigate the role of local management in patients with *de novo* stage IV breast cancer.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: www.seer.cancer.gov.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

C-LL, L-YG, LZ, Z-YH, and S-GW are lead authors who participated in data collection, manuscript drafting, table/figure creation, and manuscript revision. S-GW and Z-YH aided in data collection. JL, LH, and JW are senior authors who aided in drafting the manuscript and manuscript revision. Z-YH and S-GW are the corresponding authors who initially developed the concept and drafted and revised the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* (2018) 68(6):394–424. doi: 10.3322/caac.21492
2. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Sauer AG, et al. Breast cancer statistics, 2019. *CA Cancer J Clin* (2019) 69(6):438–51. doi: 10.3322/caac.21583
3. Jung KW, Won YJ, Kong HJ, Oh CM, Shin A, Lee JS. Survival of Korean adult cancer patients by stage at diagnosis, 2006-2010: national cancer registry study. *Cancer Res Treat* (2013) 45(3):162–71. doi: 10.4143/crt.2013.45.3.162

4. Li J, Zhang BN, Fan JH, Pang Y, Zhang P, Wang SL, et al. A nation-wide multicenter 10-year (1999-2008) retrospective clinical epidemiological study of female breast cancer in China. *BMC Cancer* (2011) 11:364. doi: 10.1186/1471-2407-11-364
5. Harbeck N, Gnant M. Breast cancer. *Lancet* (2017) 389(10074):1134–50. doi: 10.1016/S0140-6736(16)31891-8
6. Mariotto AB, Etzioni R, Hurlbert M, Penberthy L, Mayer M. Estimation of the Number of Women Living with Metastatic Breast Cancer in the United States. *Cancer Epidemiol Biomarkers Prev* (2017) 26(6):809–15. doi: 10.1158/1055-9965.EPI-16-0889
7. Thomas A, Khan SA, Chrischilles EA, Schroeder MC. Initial Surgery and Survival in Stage IV Breast Cancer in the United States, 1988-2011. *JAMA Surg* (2016) 151(5):424–31. doi: 10.1001/jamasurg.2015.4539
8. Badwe R, Hawaldar R, Nair N, Kaushik R, Parmar V, Siddique S, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. *Lancet Oncol* (2015) 16(13):1380–8. doi: 10.1016/S1470-2045(15)00135-7
9. Soran A, Ozmen V, Ozbas S, Karanlik H, Muslumanoglu M, Igci A, et al. Randomized Trial Comparing Resection of Primary Tumor with No Surgery in Stage IV Breast Cancer at Presentation: Protocol MF07-01. *Ann Surg Oncol* (2018) 25(11):3141–9. doi: 10.1245/s10434-018-6494-6
10. Fitzal F, Bjelic-Radisic V, Knauer M, Steger G, Hubalek M, Balic M, et al. Impact of Breast Surgery in Primary Metastasized Breast Cancer: Outcomes of the Prospective Randomized Phase III ABCSG-28 POSYTIVE Trial. *Ann Surg* (2019) 269(6):1163–9. doi: 10.1097/SLA.0000000000002771
11. Khan SA, Zhao F, Solin LJ, Goldstein LJ, Cella D, Basik M, et al. A randomized phase III trial of systemic therapy plus early local therapy versus systemic therapy alone in women with de novo stage IV breast cancer: A trial of the ECOG-ACRIN Research Group (E2108). *J Clin Oncol* (2020) 38(18_suppl):LBA2–2.
12. Rapiti E, Verkooijen HM, Vlastos G, Fioretta G, Neyroud-Caspar I, Sappino AP, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. *J Clin Oncol* (2006) 24(18):2743–9. doi: 10.1200/JCO.2005.04.2226
13. Le Scodan R, Stevens D, Brain E, Floiras JL, Cohen-Solal C, De La Lande B, et al. Breast cancer with synchronous metastases: survival impact of exclusive locoregional radiotherapy. *J Clin Oncol* (2009) 27(9):1375–81. doi: 10.1200/JCO.2008.19.5396
14. Kim YJ, Jung SY, Kim K. Survival benefit of radiotherapy after surgery in de novo stage IV breast cancer: a population-based propensity-score matched analysis. *Sci Rep* (2019) 9(1):8527. doi: 10.1038/s41598-019-45016-2
15. Co M, Ng J, Kwong A. De-novo metastatic breast cancers with or without primary tumor resection - A 10-year study. *Cancer Treat Res Commun* (2019) 19:100118. doi: 10.1016/j.ctarc.2019.100118
16. Lane WO, Thomas SM, Blitzblau RC, Plichta JK, Rosenberger LH, Fayanju OM, et al. Surgical Resection of the Primary Tumor in Women With De Novo Stage IV Breast Cancer: Contemporary Practice Patterns and Survival Analysis. *Ann Surg* (2019) 269(3):537–44. doi: 10.1097/SLA.0000000000002621
17. Li X, Huang R, Ma L, Liu S, Zong X. Locoregional surgical treatment improves the prognosis in primary metastatic breast cancer patients with a single distant metastasis except for brain metastasis. *Breast* (2019) 45:104–12. doi: 10.1016/j.breast.2019.03.006
18. Choi SH, Kim JW, Choi J, Sohn J, Kim SI, Park S, et al. Locoregional Treatment of the Primary Tumor in Patients With De Novo Stage IV Breast Cancer: A Radiation Oncologist's Perspective. *Clin Breast Cancer* (2018) 18(2):e167–78. doi: 10.1016/j.clbc.2017.06.002
19. Nguyen DH, Truong PT, Alexander C, Walter CV, Hayashi E, Christie J, et al. Can locoregional treatment of the primary tumor improve outcomes for women with stage IV breast cancer at diagnosis? *Int J Radiat Oncol Biol Phys* (2012) 84(1):39–45. doi: 10.1016/j.ijrobp.2011.11.046
20. Xiao W, Zou Y, Zheng S, Hu X, Liu P, Xie X, et al. Primary tumor resection in stage IV breast cancer: A systematic review and meta-analysis. *Eur J Surg Oncol* (2018) 44(10):1504–12. doi: 10.1016/j.ejso.2018.08.002
21. Bourgier C, Khodari W, Vataire AL, Pessoa EL, Dunant A, Delaloge S, et al. Breast radiotherapy as part of loco-regional treatments in stage IV breast cancer patients with oligometastatic disease. *Radiother Oncol* (2010) 96(2):199–203. doi: 10.1016/j.radonc.2010.02.028
22. Fehm T, Sagalowsky A, Clifford E, Beitsch P, Saboorian H, Euhus D, et al. Cytogenetic evidence that circulating epithelial cells in patients with carcinoma are malignant. *Clin Cancer Res* (2002) 8(7):2073–84.
23. Ali D, Le Scodan R. Treatment of the primary tumor in breast cancer patients with synchronous metastases. *Ann Oncol* (2011) 22(1):9–16. doi: 10.1093/annonc/mdq301
24. Dean M, Fojo T, Bates S. Tumour stem cells and drug resistance. *Nat Rev Cancer* (2005) 5(4):275–84. doi: 10.1038/nrc1590
25. Gnerlich J, Jeffe DB, Deshpande AD, Beers C, Zander C, Margenthaler JA. Surgical removal of the primary tumor increases overall survival in patients with metastatic breast cancer: analysis of the 1988-2003 SEER data. *Ann Surg Oncol* (2007) 14(8):2187–94. doi: 10.1245/s10434-007-9438-0
26. Khan SA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? *Surgery* (2002) 132(4):620–626; discussion 626-7. doi: 10.1067/msy.2002.127544
27. Untch M, Augustin D, Ettl J, Haidinger R, Harbeck N, Lück HJ, et al. ABC3 Consensus Commented from the Perspective of the German Guidelines: Third International Consensus Conference for Advanced Breast Cancer (ABC3), Lisbon, 07.11.2015. *Geburtshilfe Frauenheilkd* (2016) 76(2):156–63. doi: 10.1055/s-0042-101168
28. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database. *Incidence - SEER 18 Regs Custom Data (with chemotherapy recode), Nov 2015 Sub (2000-2013) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2014 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released July 2016, based on the November 2015 submission.*
29. Ruiterkamp J, Ernst MF, van de Poll-Franse LV, Bosscha K, Tjan-Heijnen VC, Voogd AC. Surgical resection of the primary tumour is associated with improved survival in patients with distant metastatic breast cancer at diagnosis. *Eur J Surg Oncol* (2009) 35(11):1146–51. doi: 10.1016/j.ejso.2009.03.012
30. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* (1997) 337(14):949–55. doi: 10.1056/NEJM199710023371401
31. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* (1999) 353(9165):1641–8. doi: 10.1016/S0140-6736(98)09201-0
32. Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Jackson SM, Wilson KS, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. *J Natl Cancer Inst* (2005) 97(2):116–26. doi: 10.1093/jnci/dji217
33. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). *Ann Oncol* (2018) 29(8):1634–57. doi: 10.1093/annonc/mdy192

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