Suggestion for the omission of post-mastectomy chest wall radiation therapy in patients who underwent skin-sparing/ nipple-sparing mastectomy

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ABSTRACT

Aim: Both skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM) have been widely adopted. Although postmastectomy radiation therapy (PMRT) can improve clinical outcomes, it can worsen cosmesis following reconstruction. Therefore, identifying risk factors of ipsilateral breast tumor recurrence (IBTR) could help de-escalate PMRT after NSM/SSM in patients with pT1-2 disease.

Methods: We retrospectively reviewed patients treated with SSM (N = 400) and NSM (N = 156) in patients with pT1-2N0-1 disease between 2009 and 2016. Seventy-four patients received PMRT with 50–50.4 Gy in 25–28 fractions. The Cox proportional hazards model was used to analyze the prognostic factors of IBTR.

Results: With a median follow-up of 66.2 months, 17 IBTR events were observed, with 5-year IBTR-free rate of 97.2%. Although only one IBTR was observed after PMRT, there was no statistical difference in the 5-year IBTR-free rate (PMRT vs. no PMRT, 98.6% vs. 97.0%, p = 0.360). Multivariable analyses demonstrated that age ≤ 45 years and lymphovascular invasion (LVI) were adverse features of IBTR. The low-risk group (0 risk factor) showed a better 5-year IBTR-free rate than the high-risk group (>1 risk factor) (100.0% vs. 95.8%, p = 0.003). In the high-risk group, PMRT slightly improved 5-year IBTR-free rate compared with no PMRT (98.6% vs. 95.2%, p = 0.166). In addition, PMRT increased 5-year cumulative incidence of reconstruction failure (10.0% vs. 2.8%, p = 0.001).

Conclusion: We identified risk factors (age and LVI) related to IBTR following upfront SSM/NSM with pT1-2 disease. As a hypothesis-generating study, de-escalation of PMRT by omitting chest wall irradiation in selective patients could improve reconstruction-related complications without compromising oncologic outcomes.

1. Introduction

Relatively conservative mastectomies, such as skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM), have been widely adopted recently with increasing interest in improved cosmetic outcomes and immediate breast reconstruction [1, 2]. With regard to post-mastectomy radiation therapy (PMRT), the indications for PMRT were revisited through recent guidelines and studies, including patients with intermediate-risk factors [3–7]. Therefore, adjuvant radiation therapy (RT) following reconstruction has become a common practice [8]. However, the integration of PMRT and reconstruction contributed to poor patient satisfaction from cosmetic outcomes, increased toxicities of capsular contracture (2.2–51%), and even increased failures of reconstruction (6.4–40.0%) [9, 10].

Based on the low rate of local recurrence (<5%) following SSM or NSM in pT1-2 disease, de-escalating PMRT by omitting chest wall irradiation could minimize possible toxicities [11]. However, few data are available to show the possible risk factors for recurrences limited to the...
ipsilateral chest wall/skin following SSM or NSM [12–15]. Furthermore, there has been no attempt of omitting chest wall RT in the pT1-2N0-1 disease. We hypothesized that identifying the risk factors related to recurrence could categorize potential candidates for omitting chest wall RT. In this context, we aimed to comprehensively analyze the prognostic factors related to local recurrence of T1-2 breast cancer following upfront SSM or NSM.

2. Materials and methods

2.1. Study population

We retrospectively reviewed 816 patients who underwent SSM or NSM between January 2009 and December 2016 at Samsung Medical Center. The exclusion criteria were as follows: (a) diagnosis of ductal carcinoma in situ or phyllodes tumor (N = 107), (b) receiving neo-adjuvant chemotherapy (N = 53), (c) pT3Nx stage (N = 31), and (d) positive resection margin (N = 4). We identified and included 556 patients: 482 were treated without PMRT (no PMRT group) and 74 were treated with PMRT (PMRT group). This study was approved by the institutional review board (No. 2020-10-175).

2.2. Surgery

Overall, 400 (71.9%) and 156 (28.1%) patients underwent SSM and NSM, respectively. Most patients (N = 543, 97.7%) underwent reconstruction with subpectoral insertion: immediate reconstruction in 124 patients (22.3%), two-stage reconstruction in 415 patients (74.6%), and delayed reconstruction in four patients (0.7%). At the time of PMRT, tissue expander was irradiated in 59 patients, and autologous tissue was irradiated in 11 patients. Regarding complete reconstruction, 441 patients received implant-based reconstruction, and 102 patients received autologous tissue-based reconstruction. For 393 patients with cN0 disease, sentinel lymph node biopsy was performed with a median number of dissected lymph nodes of 5 (interquartile range [IQR] 4–7); 163 patients underwent upfront axillary node dissection with a median number of dissected lymph nodes of 18 (IQR, 13–22).

2.3. Radiation therapy

Overall, PMRT was performed at median 6.8 months (IQR, 6.4–7.2) following surgery. Based on institutional policy, PMRT was considered in pN1 disease with two or more risk factors such as >1 positive lymph nodes, lymphovascular invasion (LVI, either focal or extensive), extra-nodal extension, and involvement of axillary level II or III [16]. Also, patients with pT2N0 disease was treated PMRT due to close margin (≤2 mm) [17,18]. Chest wall and axillary level II-III were covered by PMRT planning. Tissue expander was fully inflated before PMRT. Supravacular node irradiation was performed when pN1 disease with 4 or more predictive index scores (Supplementary Table 1) [19]. Internal mammary node irradiation was not performed. All PMRT planning was performed using three-dimensional conformal RT planning with 6 MV photons. A dose of 50–50.4 Gy in 25–28 fractions over 5 weeks was prescribed.

2.4. Follow-up evaluation

Ipsilateral breast tumor recurrence (IBTR) was defined as a local recurrence in the skin, nipple-areola complex, or chest wall muscles. IBTR was confirmed through a needle or excisional biopsy. Reconstruction-related failure was evaluated when implant/expander/flap removal was recommended due to complications.

2.5. Statistical analysis

Differences between the PMRT and no PMRT groups were analyzed using the Pearson chi-square or Fisher’s exact test (categorical variables) and the Mann–Whitney U test (continuous variables). The primary endpoint of this study was the IBTR-free rate, and the secondary endpoints were disease-free survival (DFS), overall survival (OS), and reconstruction failure rate. DFS was calculated from the date of surgery to the date of any event (locoregional recurrence or distant metastasis), death, or last follow-up. The Kaplan–Meier method was used to estimate the IBTR-free rate, DFS, and OS using the log-rank test for comparison. The failure rate of reconstruction from surgery was estimated using the cumulative incidence method and compared using Gray’s test, which considered death and IBTR as competing risks. The Cox proportional hazards model was used to analyze the significance of prognostic factors that were statistically significant in univariable analyses for IBTR, DFS, and OS. Recursive partitioning analysis (RPA) was performed to stratify patients according to their risk of IBTR using the R-package, “rpart.” Propensity score matching (PSM) analysis was carried out to minimize the effects of selection biases and potential confounders using the R-package, “MatchIt.” Propensity scores were obtained using a multivariate logistic regression model including age, tumor location (lateral vs. central/medial), grade, molecular subtype, number of positive axillary lymph nodes, and LVI. Patients were matched 1:1 nearest matching with a caliper distance of 0.05, standard deviations of the logit of the propensity score. McNemar’s test and Wilcoxon signed-rank test were used to compare categorical and continuous variables after PSM. A two-sided P-value of < 0.05 was considered significant. All statistical analyses were performed using the R software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics

The baseline characteristics of the cohort before and after PSM are summarized in Table 1. Patients in the PMRT group were younger (age ≤45 years, 68.9% vs. 53.7%, p = 0.020), and had frequent intermediate/high-grade tumors (90.6% vs. 73.5%, p = 0.005), a more advanced stage (N1, 90.5% vs. 24.3%, p < 0.001), and frequent LVI (81.1% vs. 24.3%, p < 0.001) compared to those in the no PMRT group. After PSM, there were 31 patients in each group with well-balanced baseline characteristics.

3.2. Clinical outcomes

With a median follow-up of 66.2 months (IQR, 58.5–80.4), there were 17 (3.1%) IBTR events: 16 (3.3%) and one (1.4%) in the no PMRT and PMRT groups, respectively. Details regarding patterns of failure are summarized in Supplementary Table 2. Specifically, most IBTR events occurred in the subcutaneous area (N = 12), followed by pectoralis muscle (N = 3), and cutaneous area (N = 2). In addition, 11 IBTR events were located in ventral to implant, followed by the periareolar area (N = 4), medial to implant (N = 1), and dorsal to free flap (N = 1). There was no IBTR in dorsal part of implant. There was no difference in regional recurrence, distant metastasis, and death according to PMRT. The 5-year IBTR-free, DFS, and OS rates for all patients were 97.2%, 92.8%, and 98.5%, respectively. Patients in the PMRT group exhibited a 5-year IBTR-free rate comparable to those in the no PMRT group (98.6% vs. 97.0%, p = 0.360; Fig. 1). After PSM, there was only 1 IBTR (1.6%) in the matched cohort and 5-year IBTR-free rates were comparable between PMRT and no PMRT group (100.0% vs. 96.8%, p = 0.320, Fig. 1B).

Regarding the results of the Cox proportional hazards model, age ≤45 years and LVI were associated with frequent IBTR events (Table 2). Based on this result, RPA resulted in three terminal nodes: group 1 (age >45 years, LVI-negative), group 2 (age >45 years, LVI-positive), and group 3 (age ≤45 years) (Supplementary Fig. 1).

The 5-year IBTR-free rates for groups 1, 2, and 3 were 100.0%,...
Table 1
Baseline characteristics.

|                | Before matching |          |          |          |          |          |          |
|----------------|-----------------|----------|----------|----------|----------|----------|----------|
|                | N = 482         | N = 74   |          | N = 467  | N = 70   |          |          |
| Age (years)    |                 |          |          |          |          |          |          |
| Age ≤45        | 259 (53.7)      | 51 (68.9)| 0.020    | 365 (76.5)| 7 (9.5) | <0.001   |          |
| Age >45        | 223 (46.3)      | 23 (31.1)|          | 117 (24.3)| 60 (81.1)| <0.001   |          |
| Laterality     |                 |          |          |          |          |          |          |
| Left           | 244 (50.6)      | 39 (52.7)| 0.835    | 252 (52.3)| 50 (67.6)|          |          |
| Right          | 238 (49.4)      | 35 (47.3)|          | 225 (47.7)| 81 (55.3)|          |          |
| Location       |                 |          |          |          |          |          |          |
| Lateral        | 167 (34.6)      | 25 (33.8)| 0.989    | 64 (13.3)| 5 (6.8) |          |          |
| Central/Medial | 315 (65.4)      | 49 (66.2)|          | 262 (54.7)| 1 (1.4) |          |          |
| Multicentricity| 113 (23.4)      | 25 (33.8)| 0.076    | 170 (35.9)| 14 (19.4)| 0.384    |          |
| Multilocality  | 232 (48.1)      | 36 (48.6)| 1.000    | 367 (75.7)| 7 (9.5) | <0.001   |          |
| Pathology      |                 |          |          |          |          |          |          |
| IDC            | 421 (87.3)      | 69 (93.2)| 0.205    | 305 (65.4)| 49 (68.9)|          |          |
| ILC            | 19 (3.9)        | 3 (4.1) |          | 27 (5.6) | 3 (4.1) |          |          |
| Others         | 42 (8.7)        | 2 (2.7) |          | 10 (2.1) | 1 (1.4) |          |          |
| Grade          | 128 (26.6)      | 7 (9.5) | 0.005    | 136 (28.8)| 7 (9.5) | <0.001   |          |
| Intermediate   | 252 (52.3)      | 50 (67.6)|          | 18 (3.9) | 2 (2.7) |          |          |
| High           | 102 (21.2)      | 17 (23.0)|          | 5 (1.0) | 1 (1.4) |          |          |
| subareolar     | 113 (23.4)      | 25 (33.8)|          | 25 (5.0) | 2 (2.7) |          |          |
| DCIS           | 232 (48.1)      | 36 (48.6)| 1.000    | 367 (75.7)| 7 (9.5) | <0.001   |          |
| SA extension   | 197 (40.9)      | 37 (50.0)| 0.176    | 197 (40.9)| 37 (50.0)|          |          |
| SA extension   | 197 (40.9)      | 37 (50.0)| 0.176    | 197 (40.9)| 37 (50.0)|          |          |
| Rate           | 197 (40.9)      | 37 (50.0)| 0.176    | 197 (40.9)| 37 (50.0)|          |          |
| Resection margin| 252 (52.3)   | 50 (67.6)|          | 18 (3.9) | 2 (2.7) |          |          |
| Close (<2 mm)  | 230 (47.7)      | 43 (58.1)|          | 170 (35.9)| 49 (68.9)|          |          |
| Reconstruction failure | 225 (47.7) | 81 (55.3) | 0.391 | 113 (23.4) | 35 (47.3) | 0.989 | 0.835 |
| Fat necrosis   | 230 (47.7)      | 43 (58.1)|          | 113 (23.4) | 35 (47.3) | 0.989 | 0.835 |
| Nodularity     | 225 (47.7)      | 81 (55.3) | 0.391 | 113 (23.4) | 35 (47.3) | 0.989 | 0.835 |
| LN metastasis  | 365 (75.7)      | 7 (9.5) | <0.001   | 365 (75.7)| 7 (9.5) | <0.001   |          |
| LN dissection  | 381 (79.0)      | 12 (16.2)| <0.001   | 381 (79.0)| 12 (16.2)| <0.001   |          |
| Adjuvant treatment | 101 (21.0) | 62 (83.8) | 0.019     | 101 (21.0) | 62 (83.8) | 0.019     |          |
| Anthracycline  | 204 (42.3)      | 62 (83.8)| <0.001   | 204 (42.3)| 62 (83.8)| <0.001   |          |
| Taxane         | 218 (45.2)      | 62 (83.8)| <0.001   | 218 (45.2)| 62 (83.8)| <0.001   |          |
| Trastuzumab    | 70 (14.5)       | 12 (16.2)| 0.836    | 70 (14.5) | 12 (16.2)| 0.836    |          |
| Endocrine therapy| 384 (79.7) | 68 (91.9) | 0.019     | 384 (79.7) | 68 (91.9) | 0.019     |          |

** Values are presented as patient (%) or median [interquartile range].

Abbreviations: PMRT, postmastectomy radiation therapy; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; LN, lymph node; LVI, lymphovascular invasion; SA, subareolar; DCIS, ductal carcinoma in situ; SSN, skin-sparing mastectomy; NSN, nipple-sparing mastectomy; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

96.5%, and 95.7%, respectively (p < 0.05, group 1 vs. 2 and group 1 vs. 3; Supplementary Fig. 2). Groups 2 and 3, which had similar IBTR-free rates, were merged and classified as the “high-risk” group (N = 367) and group 1 was classified as the “low-risk” group (N = 189). The patterns of failure according to the risk group are summarized in Supplementary Table 3. The high-risk group showed a significantly lower 5-year IBTR-free rate (95.8% vs. 95.0%, p = 0.003; Fig. 2) and 5-year DFS rate (91.0% vs. 96.3%, p = 0.014; Supplementary Fig. 3A) than the low-risk group, with a comparable 5-year OS rate (99.4% vs. 96.8%, p = 0.120; Supplementary Fig. 3B).

In the subgroup analyses, there was no significant difference in the effects of PMRT according to the risk groups (Fig. 3A–B). However, the 5-year IBTR-free rate in the high-risk group was slightly improved in the PMRT group compared to that in the no PMRT group (98.6% vs. 95.2%, p = 0.166; Fig. 3B).

Additionally, there was no significant difference in DFS and OS according to PMRT (Supplementary Figs. 4A–B). Multivariable analysis demonstrated that PMRT was associated with the outcomes of DFS along with LVI, whereas none was associated with OS outcomes (Supplementary Tables 4 and 5).

3.3. Reconstruction-related complications

Among the 543 patients who underwent reconstruction, 162 (29.8%) experienced any grade of reconstruction-related toxicities after surgery (Table 3): 136/473 (28.8%) and 26/70 (37.1%) in the no PMRT and PMRT groups, respectively (p = 0.196). Wound-related complications (N = 46, 8.5%) were frequently observed, followed by fat necrosis (N = 44, 8.1%), contracture (N = 33, 6.1%), and rippling (N = 32, 5.9%). Among them, 40 patients (7.4%) were surgically treated or hospitalized because of toxicities. Patients in the PMRT group showed a higher rate of reconstruction failure than those in the no PMRT group (11.4% vs. 3.0%, p = 0.004). In addition, the 5-year cumulative incidence of reconstruction failure was higher in the PMRT group than in the no PMRT group (10.0% vs. 2.8%, p = 0.001; Supplementary Fig. 5).

4. Discussion

Over the past decades, both SSM and NSM have gained increased acceptance in parallel with an increased interest in quality of life and cosmetic outcomes for patients with breast cancer. However, PMRT involving chest wall RT can lead to poor cosmetic outcomes and increased toxicities [10]. Therefore, identifying the risk factors of IBTR
could stratify patients for whom chest wall RT can be omitted. Although previous studies have shown a low IBTR rate of 5%, little data regarding the risk factors of IBTR following SSM/NSM exists [11]. In the current study, we identified a favorable 5-year IBTR-free rate of 97.2% in 556 patients after SSM or NSM in pT1-2N0-1 disease. PMRT did not significantly improve IBTR-free rate both before PSM and after PSM. We also found that age ≤45 years and LVI were independent factors for IBTR. Notably, the 5-year IBTR-free rate was 100% in patients with none of these risk factors and 95.8% in patients with at least one of these risk factors.

A recent meta-analysis including 3365 patients from 19 studies demonstrated 3.5% and 5.2% IBTR after SSM and NSM for mostly early-stage breast cancer, respectively (Table 4) [11]. Despite wide range of adopting PMRT, overall IBTR events after SSM/NSM were infrequent (about 5%, Table 4). Regarding risk factors, several previous series of SSM/NSM suggested high-grade as an adverse feature related to IBTR events [14,15,20,21]. Cont et al. also reported no IBTR events in patients who received PMRT [13]. To our knowledge, the current study was the first to focus specifically on the incidence of and risk factors associated with IBTR with a long-term follow-up period (median follow-up of 66

Revised Figure 1. Ipsilateral breast tumor recurrence (IBTR)-free rate according to postmastectomy radiation therapy (PMRT) (A) before propensity score matching (PSM), and (B) after PSM.

Table 2
Prognostic factors for ipsilateral breast tumor recurrence.

| Variables | (Ref. vs.) | Univariable analysis | Multivariable analysis |
|-----------|------------|----------------------|-----------------------|
| PMRT      | (No vs. Yes) | 0.40 (0.05-3.04) 0.279 | 0.20 (0.03-1.55) 0.124 |
| Age (years) | (<45 vs. ≤45) | 5.87 (1.34-25.69) 0.019 | 5.06 (1.14-22.40) 0.033 |
| Location  | (Lateral vs. Central/Medial) | 1.74 (0.57-5.33) 0.334 | 1.35 (0.18-10.35) 0.772 |
| Multicentricity | (No vs. Yes) | 0.88 (0.29-2.69) 0.819 | |
| Multilocularity | (No vs. Yes) | 1.25 (0.48-3.25) 0.645 | |
| Grade     | (Low/Intermediate vs. High) | 1.56 (0.55-4.44) 0.402 | |
| Subtype   | (HR positive vs. HER2 positive) | 1.58 (0.45-5.55) 0.474 | |
| High Ki67 (≥20) | (No vs. Yes) | 1.57 (0.61-4.07) 0.353 | |
| pT stage  | (pT1 vs. pT2) | 1.11 (0.42-2.93) 0.825 | |
| pN stage  | (N0 vs. N1) | 0.58 (0.19-1.79) 0.348 | |
| LVI       | (No vs. Yes) | 3.13 (1.19-8.23) 0.021 | 3.37 (1.25-9.04) 0.016 |
| Subareolar extension | (No vs. Yes) | 0.36 (0.12-1.12) 0.078 | |
| Resection margin | (Negative vs. Closea) | 1.72 (0.49-5.98) 0.395 | |
| Surgery   | (SSM vs. NSM) | 1.03 (0.36-2.93) 0.954 | |
| Taxane    | (No vs. Yes) | 0.51 (0.14-1.76) 0.284 | |

Abbreviations: HR, hazard ratio; PMRT, postmastectomy radiation therapy; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; LVI, lymphovascular invasion; SSM, skin-sparing mastectomy; NSM, nipple-sparing mastectomy; CI, confidence interval.

a Close margin refers to margin width ≤2 mm.
months) and modern systemic chemotherapy following NSM/SSM. In the current study, we found that both age and LVI were associated with IBTR.

In contrast, a growing pile of evidence exists regarding IBTR following conventional total mastectomy (Table 4). Similar to the SSM/NSM series, previous studies regarding total mastectomy have described comparably low rates of chest wall recurrence, from 1.2% to 4.1%, in the absence of PMRT for pT1-2N0-1 disease [29–34]. Regarding local recurrence following no PMRT, several risk factors, including age, pT stage, hormonal receptor status, and LVI have been reported [29,30,32,34]. Focusing on IBTR in the chest wall following no PMRT, a multi-institutional study including 3224 patients reported IBTR rates of 1.7% and 2.8% in patients with pT1-2N0 and pT1-2N1 disease [32]. They also found that age (<35 years), LVI, and hormone receptor status were found to be related to IBTR. Given <5% of 10-year IBTR, Chang et al. suggested the necessity of chest wall RT needs to be re-considered balancing between toxicities (to the lung, heart, or contralateral breast) and possible risks from IBTR events [32]. Despite the lack of a definite cutoff value (35–45 years) for young age through previous reports,

Table 3
Details of reconstruction-related complications.

| Total | No PMRT | PMRT | P-value |
|-------|---------|------|---------|
| Complication | N = 543 | N = 473 | N = 70 | 0.196 |
| Contracture | (29.8) | (28.8) | (37.1) |
| Rippling | (32.5) | (28.5) | (5.7) |
| Wound-related | (46.8) | (34.7) | (12.1) |
| Fat necrosis | (44.8) | (42.8) | (2.9) |
| Implant rupture | (7.1) | (6.1) | (1.4) |
| CTCAE grade | 0.122 |
| Grade 1 | (5.7) | (28.5) | (4.3) |
| Grade 2 | (91.6) | (78.6) | (13.6) |
| Grade 3 (surgical procedure) | (40.7) | (30.6) | (10.1) |
| Failure of reconstruction | (22.4) | (14.3) | (8.1) |

** Values are presented as patient (%). 
Abbreviations: PMRT, postmastectomy radiation therapy; CTCAE, Common Terminology Criteria for Adverse Events.

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Fig. 2. Ipsilateral breast tumor recurrence (IBTR)-free rate according to risk group stratified by age (45 years) and lymphovascular invasion. Footnotes: High-risk group, 1 or 2 risk factors; low-risk group, 0 risk factors.

Fig. 3. Impact of postmastectomy radiation therapy (PMRT) on ipsilateral breast tumor recurrence (IBTR)-free rate according to subgroups based on risk factors. Footnotes: High-risk group, 1 or 2 risk factors; low-risk group, 0 risk factor.
Table 4
Literature review for rates of ipsilateral breast tumor recurrence (IBTR) stratified by surgery.

| First Author | Yr | No. | FU (months) | PMRT (%) | IBTR, N (%) | Prognostic factors related to IBTR |
|--------------|----|-----|-------------|-----------|-------------|----------------------------------|
| SSM/NSM      |    |     |             |           |             |                                  |
| Franco [13]   | 2001 | 173 | 73         | 7.5       | 8           | Grade, stage, subtype            |
| Vaughan [14]  | 2007 | 206 | 59         | 20.0      | 11          | Grade, stage                     |
| Romics [21]   | 2012 | 253 | 119        | 47.1      | 6           | Grade, stage                     |
| Petit [22]    | 2012 | 934 | 50         | 3.2       | 34          | Grade, subtype                   |
| Liang [22]    | 2013 | 249 | 53         | 12.9      | 5           |                                  |
| Sakurai [23]  | 2013 | 788 | 78         | 0.0       | 65          |                                  |
| Stanec [24]   | 2014 | 361 | 63         | NA        | 15          |                                  |
| Agusti [25]   | 2016 | 249 | 101        | 28.0      | 11          |                                  |
| Frey [26]     | 2016 | 319 | 31         | 12.7      | 1           | (0.3)                            |
| Park [27]     | 2016 | 189 | 66         | 10.1      | 7           | (3.7)                            |
| Cont [28]     | 2017 | 518 | 33         | 18.1      | 14          | (2.7)                            |
| Lee [29]      | 2018 | 1032| 94         | 8.5       | 35          | (3.4)                            |
| Wu [30]       | 2019 | 944 | 85         | NA        | 39          | Multifocality, subtype, grade, EIC |
| Current study | 2022 | 556 | 66         | 13.3      | 17          | Age (45 years), LVI              |
| Meta-analysis | 2021 | 4797| NA         |          | 108 (5.2)   | - NSM 49 (3.5) - SSM             |
| Total mastectomy |     |     |             |           |             |                                  |
| No PMRT      |    |     |             |           |             |                                  |
| Sharma [32]  | 2010 | 1019| 90         | 0.0       | 12          | Age (40 years)                    |
| Lai [33]     | 2016 | 293 | 83         | 0.0       | 5           | Age (40 years), size, EIC        |
| Park [34]    | 2017 | 1382| 71         | 0.0       | 39          | (2.8)                            |
| Chang [35]   | 2018 | 3224| 72         | 0.0       | 70          | Age (35 years), LVI, subtype      |
| Park [36]    | 2018 | 133 | 57         | 0.0       | 3           | (3.1)                            |
| Zhao [37]    | 2020 | 2042| 63         | 0.0       | 83          | Age (45 years), T2, location, subtype |
| PMRT         |    |     |             |           |             |                                  |
| Yang [38]    | 2010 | 544 | 40         | 29.6      | 28          | (5.1)                            |
| Su [39]      | 2014 | 207 | 60         | 39.1      | 12          | (5.8)                            |
| Kim [40]     | 2017 | 714 | 69         | 18.2      | 7           | (1.0)                            |
| Muhsen [41]  | 2018 | 1087| 132        | 14.9      | 37          | (3.4)                            |
| Zeiden [42]  | 2018 | 684 | 108        | 49.0      | 16          | (2.3)                            |
| Abi [43]     | 2020 | 1633| 132        | 57.6      | 53          | (3.2)                            |
| Jaoude [44]  | 2020 | 379 | 62         | 53.8      | 3           | (0.8)                            |
| Gilmore [45] | 2020 | 1474| 93         | 45.0      | 25          | (1.7)                            |

Abbreviations: Yr, year; FU, median follow-up; PMRT, postmastectomy radiation therapy; SSM, skin-sparing mastectomy; NSM, nipple-sparing mastectomy; EIC, extensive intraductal component; LVI, lymphovascular invasion; NA, not available.
patients in the PMRT group had more risk factors than those in the no PMRT group, the protective effect of PMRT for IBTR could be underestimated. Although we performed PSM analysis to minimize potential confounders and found no significant benefit of PMRT in these patients, lack of IBTR event could lead to statistical insignificance. In addition, a longer follow-up time (>66 months) might be required to accurately evaluate the true IBTR-free rates and reconstruction-related complications. Cruz et al. reported that weighted average of IBTR after NSM was 11.4% for studies with >5 years of follow-up compared with 5.4% for studies with <3 years of follow-up [51]. Therefore, long-term follow-up should be warranted to verify the oncologic safety of omitting chest wall RT. Finally, prospective randomized studies are warranted to safely omit chest wall irradiation in the setting of PMRT.

In conclusion, a favorable IBTR-free rate of less than 5% was observed in patients who underwent SSN or NSM. Since patients without risk factors, such as age ≤45 years and LVI, showed an excellent IBTR-free rate of 100%, chest wall RT could be omitted in the setting of PMRT. As a hypothesis-generation study, we cautiously suggest that selective omission of chest wall RT in the setting of PMRT could bring promise of fewer reconstruction-related complications and lifelong adverse events.

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Ethics approval and informed consent
The requirement for informed consent was waived because of the retrospective nature of this study.

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

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.09.004.

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