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ORIGINAL ARTICLE

Risk factors for complications among breast cancer patients treated with post-mastectomy radiotherapy and immediate tissue-expander/permanent implant reconstruction: a retrospective cohort study

Mami Ogita[1,2] · Naomi Nagura[3] · Jiro Kawamori[1] · Reika In[3] · Atsushi Yoshida[3] · Hideko Yamauchi[3] · Junko Takei[3] · Naoki Hayashi[3] · Yoshiko Iwahira[4] · Sachiko Ohde[5] · Shoko Fukushima[1] · Kenji Sekiguchi[1,6]

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Abstract

Background The use of post-mastectomy radiotherapy (PMRT) following immediate breast reconstruction has increased recently, and its safety is becoming a major concern. We aimed to evaluate the complication rates of PMRT to immediate tissue-expander/permanent implant (TE/PI)-based reconstructions for breast cancer and its association with radiotherapy timing (irradiation to TE or PI).

Methods We retrospectively reviewed the cases of breast cancer patients who underwent mastectomy, immediate TE/PI reconstruction, and PMRT between January 2003 and December 2014. The rates of complications including reconstruction failure, re-operation, and infection were estimated by Kaplan–Meier analysis. The risk factors including radiotherapy timing were analyzed by log-rank test and multivariate Cox proportional hazard model.

Results A total of 81 patients were included. Median follow-up was 32 months (range 2–120 months). Radiotherapy consisted of 50 Gy to the reconstructed breast and supraclavicular region in most cases. Total reconstruction failure, re-operation, and infection rates were 12.3, 13.6, and 11.1%, and 5-year cumulative reconstruction failure, re-operation, and infection rates were 16.7, 16.6, and 12.2%, respectively. No significant differences were observed in complication rates with respect to radiotherapy timing. In multivariate analysis, age 55 years and older was a significant risk factor for complications ($P < 0.05$).

Conclusion There were no significant differences in rates of reconstruction failure, re-operation, or infection with regard to radiotherapy timing. PMRT to reconstructed breasts of older patients aged 55 years or over can be expected to result in more complications than in younger patients.

Keywords Breast cancer · Post-mastectomy radiotherapy · Prosthetic reconstruction · Breast implant

This study was approved by the institutional review board at our institution (IRB code: 15-R089).

✉ Mami Ogita
mamiogi@luke.ac.jp

[1] Department of Radiation Oncology, St. Luke's International Hospital, 9-1, Akashi-cho, Chuo-ku, Tokyo 104-8560, Japan

[2] Department of Radiology, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyoku, Tokyo 113-8655, Japan

[3] Department of Breast Surgical Oncology, St. Luke's International Hospital, 9-1, Akashi-cho, Chuo-ku, Tokyo 104-8560, Japan

[4] Breast Surgery Clinic, 2-21-43, Takanawa, Minato-ku, Tokyo 108-0074, Japan

[5] Center for Clinical Epidemiology, St. Luke's International University, 3-6-2, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

[6] Sonoda-kai Radiation Oncology Clinic, 3-4-19, Hokima, Adachi-ku, Tokyo 121-0064, Japan

Introduction

The recent increase in the mastectomy rate for breast cancer has resulted in a concomitant increase in breast reconstruction [1–3]. Breast reconstruction can improve cosmetic outcome and thus increases patient satisfaction after mastectomy [4]. Simultaneously, the indication of post-mastectomy radiotherapy (PMRT) has expanded. PMRT is known to reduce breast cancer mortality in breast cancer patients with four or more positive axillary lymph nodes [5]. The results of the updated Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis showed that PMRT reduces breast cancer mortality as well as reducing

both loco-regional and distant recurrence in breast cancer patients with one-to-three positive lymph nodes [6]. Based on this EBCTCG result, the guidelines in the United States (the National Comprehensive Cancer Network: NCCN) and Europe (the European Society for Medical Oncology: ESMO) now strongly consider PMRT for patients with one-to-three positive nodes [7, 8]. Consequently, the number of patients receiving PMRT after breast reconstruction has increased [9].

Among breast reconstruction techniques, tissue-expander/permanent implant (TE/PI)-based reconstruction is a major procedure [2]. There are basically two timings of radiotherapy with immediate TE/PI reconstruction: PMRT during TE insertion or PMRT after exchange to PI. The application of radiotherapy to a TE/PI-based reconstructed breast is known to increase complications [10]. Meta-analysis and a recent study suggested that PMRT applied to a tissue expander (TE) caused more complications than when applied to a permanent implant [11, 12]. However, the optimal timing and type of reconstructive surgery in the setting of PMRT remain controversial [13]. Therefore, we aimed to evaluate the complication rate of PMRT applied to the implant-based reconstructed breast as treatment for breast cancer and its association with radiotherapy timing.

Patients and methods

Patients

From January 2003 to December 2014, breast cancer patients undergoing reconstruction by the immediate tissue-expander/permanent implant (TE/PI) method together with PMRT at St. Luke's international hospital in Tokyo, Japan were included in this study. Each patient's medical records were retrospectively reviewed. Inclusion criteria were: female breast cancer patients who underwent mastectomy (skin-sparing mastectomy or nipple-sparing mastectomy), immediate tissue-expander/permanent implant (TE/PI) reconstruction, and PMRT. Patients who received radiotherapy for local breast cancer recurrence after implant-based reconstruction and/or patients with autologous breast reconstruction were excluded. Two patients who could not complete PMRT because of distant metastasis were also excluded. The reconstructed breast and supraclavicular region were treated to a total dose of 50 Gy in 25 fractions over 5 weeks in most cases. The 3D-conformal technique with 4 or 6 MV photon beam was used. Patients were divided into two groups: one with PMRT to a TE (TE group) and another with PMRT to PI (PI group). Our basic treatment flow was as follows: patients treated with neoadjuvant chemotherapy received PMRT to a TE after mastectomy. Subsequently, the TE was exchanged to a PI after completion of TE inflation. In patients treated with adjuvant chemotherapy, the TE was exchanged to a PI after chemotherapy, and then, PMRT was administered to the PI.

This study was approved by the institutional review board at our institution (IRB code: 15-R089).

Outcome

Primary outcome was reconstruction failure rate. The definition of reconstruction failure was permanent removal of the TE or PI without replacement, or conversion to autologous reconstruction. Secondary outcomes were re-operation, infection, and disease recurrence. Re-operation was defined as unplanned removal or exchange of the TE or PI. The definition of infection was based on the Centers for Disease Control and Prevention (CDC) and National Healthcare Safety Network (NHSN) surveillance definitions for specific types of infections. Breast infection must meet at least one of the following criteria: (1) positive culture of the affected breast tissue or fluid; (2) breast abscess or other evidence of infection on gross anatomic or histopathologic exam; and (3) fever (> 38.0 °C) and local inflammation of the breast, and initiation of antimicrobial therapy by physician within 2 days of onset or worsening of symptoms [14].

Variables including age, body mass index (BMI), smoking history, clinical stage, chemotherapy (neoadjuvant or adjuvant), axillary lymph node dissection (AxLND), TE size, radiotherapy timing (TE/PI), supraclavicular radiotherapy (Sc-RT), internal mammary node radiotherapy (IMN-RT), boost, bolus, radiation dermatitis were also collected. Clinical stage was classified based on the Union for International Cancer Control (UICC) staging system 7th edition. Dermatitis was graded based on Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.03.

Statistical analysis

Kaplan–Meier analysis and log-rank test were used to assess the event rate and the difference between the TE and PI groups. The multivariate Cox proportional hazard model was used to assess the differences adjusted for clinical covariates. The Chi-square test was used to assess the trend of events according to year. All statistical analyses were performed using the SPSS ver.22 software (IBM Corporation, Armonk, NY, USA).

Results

Baseline characteristics

Eighty-one patients were included in this study. The baseline clinical characteristics are shown in Table 1. Three patients

Table 1 Baseline clinical characteristics

	All ($n = 81$)		TE ($n = 32$)		PI ($n = 49$)		P value
	N	%	N	%	N	%	
Age, years							
25–34	8	9.9	3	9.4	5	10.2	0.46
35–44	33	40.7	10	31.3	23	46.9	
45–54	29	35.8	13	40.6	16	32.7	
55–64	11	13.6	6	18.8	5	10.2	
Median (range), years	44 (29–64)		46.5 (29–63)		44 (29–64)		0.48
BMI, kg/m^2							
< 25	72	88.9	30	93.8	42	85.7	0.47
≥ 25	8	9.9	2	6.3	6	12.2	
Unknown	1	1.2	0	0	1	2	
Median (range)	20.7 (17.0–27.9)		20.7 (17.6–27.4)		20.8 (17.0–27.9)		0.81
Smoking history							
Yes	16	19.8	6	18.8	10	20.4	0.86
No	65	80.2	26	81.3	39	79.6	
Clinical stage							
0	3	3.7	2	6.3	1	2	0.003
I	6	7.4	1	3.1	5	10.2	
II	41	50.6	9	28.1	32	65.3	
III	30	37	19	59.4	11	22.4	
IV	1	1.2	1	3.1	0	0	
Chemotherapy							
NAC	36	44.4	28	87.5	8	16.3	< 0.001
Adj	43	53.1	3	9.4	40	81.6	
NAC and adj	1	1.2	0	0	1	2	
Non	1	1.2	1	3.1	0	0	
AxLND							
Yes	77	95.1	32	100	45	91.8	0.097
No	4	4.9	0	0	4	8.2	
TE size, mL							
Median (range), mL	387.5 (150–650)		350(150–550)		400 (200–650)		0.51
Radiotherapy							
Dose, Gy							
50	76	93.8	30	93.8	46	93.9	0.66
60	4	4.9	2	6.3	2	4.1	
Unknown	1	1.2			1	2	
Energy, MV							
4	38	46.9	14	50	24	49	0.9
6	38	46.9	16	43.8	22	44.9	
Unknown	5	6.2	2	6.3	3	6.1	
Sc							
Yes	77	95.1	1	3.1	2	4.1	0.7
No	3	3.7	31	96.9	46	93.9	
Unknown	1	1.2			1	2	
IMN							
Yes	16	19.8	10	31.3	6	12.2	0.086
No	64	79	22	68.8	42	85.7	
Unknown	1	1.2			1	2	
Boost							
Yes	3	3.7	2	6.3	1	2	0.45

Table 1 (continued)

	All ($n = 81$)		TE ($n = 32$)		PI ($n = 49$)		*P* value
	N	%	*N*	%	*N*	%	
No	77	95.1	30	93.8	47	95.9	
Unknown	1	1.2			1	2	
Bolus							
Yes	7	8.6	6	18.8	1	2	0.009
No	69	85.2	24	75	45	91.8	
Unknown	5	6.2	2	6.3	3	6.1	
Dermatitis, grade							
1	72	88.9	28	87.5	44	89.8	0.54
2	5	6.2	3	9.4	2	4.1	
Unknown	4	4.9	1	3.1	3	6.1	

TE tissue expander, *PI* permanent implant, *BMI* body mass index, *NAC* neoadjuvant chemotherapy, *Adj* adjuvant chemotherapy, *AxLND* axillary lymph node dissection, *Sc* supraclavicular radiotherapy, *IMN* internal mammary node radiotherapy

received mastectomy and immediate reconstruction at other institutions. Five patients received radiotherapy at other hospitals. Median follow-up duration (from the initiation of radiotherapy to the last follow-up) was 32 months (range 2–120), and median age of patients was 44 years (range 29–64). AxLND was performed in 77 patients (95.1%). Median TE size was 387.5 mL (range 150–650). Three patients (3.7%) received PMRT only to the reconstructed breast because of a positive margin with no or microlymph node metastasis. IMN-RT was given to 16 patients (20%). Three patients (3.7%) received boost with electron beam for an additional 10 Gy in 5 fractions. Bolus was used in 7 patients (8.6%). Thirty-two patients (40%) received PMRT to the TE, and 49 patients (60%) received PMRT to the PI. Higher number of patients in the TE group received neoadjuvant chemotherapy compared with PI group (87.5 vs 16.3%). More patients in TE group had stage III disease than PI group (59.4 vs 22.4%). The other clinical characteristics were similar between TE and PI groups.

In the TE group, the median interval between operation (mastectomy and TE insertion) and radiotherapy was 51 days (range 20–243), and the median interval between radiotherapy completion and implant insertion was 248 days (range 170–447). In the PI group, the median interval between implant insertion and radiotherapy was 29 days (range 10–180).

Incidence of complications

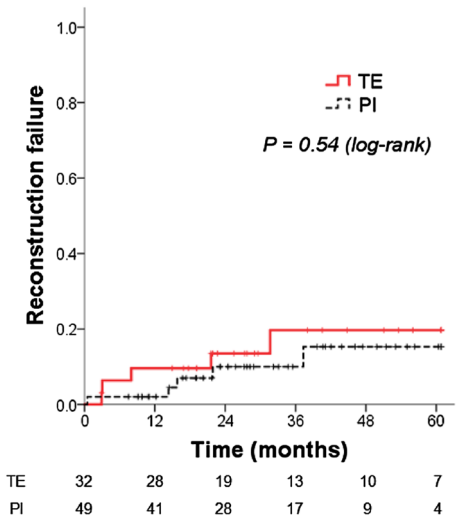
Rates of total reconstruction failure, re-operation, and infection were 12.3% (10/81), 13.6% (11/81), and 11.1% (9/81), respectively. Five patients in TE group (15.6%) and 5 patients in PI (10.2%) had reconstruction failure. The most frequent reason for reconstruction failure was infection (7/10) followed by implant exposure (2/10) and capsular contracture (1/10). The median duration between PMRT and reconstruction failure, re-operation, and infection were 452 days (range 14–1120), 474 days (range 14–825), and 223 days (range 9–654), respectively. Rates of reconstruction failure, re-operation, and infection decreased over time ($P = 0.023$, 0.048, 0.001, respectively).

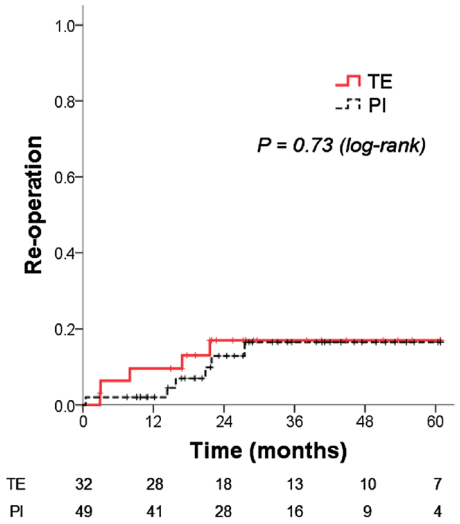
Risk factors

There were no significant differences in the rates of reconstruction failure, re-operation, or infection between TE and PI groups (Fig. 1).

In univariate analysis, age ≥ 55 years was a significant factor for re-operation and infection. A similar tendency was observed in reconstruction failure, but the difference was not statistically significant (Fig. 2). When analyzed according to age group, the re-operation rate was increased in older age groups ($P = 0.027$) (Fig. 3). No reconstruction failure was observed in the 25–34 age group. No significant differences were observed in reconstruction failure, re-operation, or infection rates based on BMI ≥ 25 ($P = 0.77$, 0.22, 0.79), smoking history ($P = 0.87$, 0.98, 0.21), clinical stage ($P = 0.48$, 0.66, 0.38), chemotherapy (neoadjuvant vs adjuvant) ($P = 0.22$, 0.37, 0.09), AxLND ($P = 0.46$, 0.45, 0.50), TE size > 400 ml ($P = 0.16$, 0.09, 0.43), Sc-RT ($P = 0.21$,0.26, 0.17), IMN-RT ($P = 0.81$, 0.77, 0.45), boost ($P = 0.54$, 0.51, 0.56), bolus ($P = 0.99$, 0.96, 0.13), and radiation dermatitis ($P = 0.44$, 0.41, 0.44), respectively.

In multivariate analysis, age ≥ 55 years was not statistically significant for reconstruction failure {$P = 0.08$, hazard ratio (HR) [95% confidence interval (CI)] 3.47 (0.85–14.2)}. However, age ≥ 55 years was statistically significant for re-operation [$P = 0.02$, HR (95% CI): 4.64 (1.27–16.9)] and infection [$P = 0.04$, HR (95% CI): 4.6 (1.08–19.5)] (Table 2).





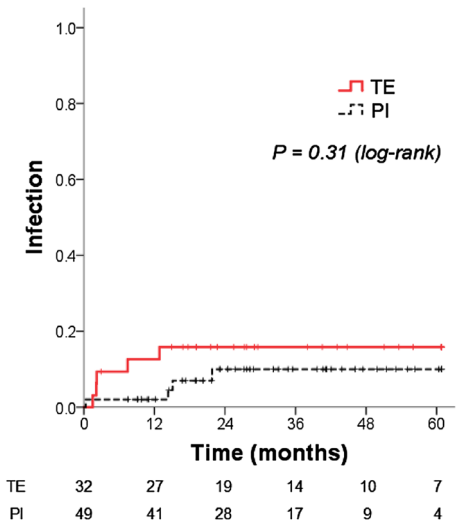


Fig. 1 Reconstruction failure, re-operation, and infection rates of tissue-expander (TE)/permanent implant (PI) reconstruction and post-mastectomy radiotherapy (PMRT) by radiotherapy timing; PMRT to a TE or a PI. The numbers below each part of the figure show the number of patients at risk

Breast cancer recurrence

Seven patients (8.6%) experienced disease recurrence during the follow-up period. All recurrences were distant metastases, and no local and/or regional recurrences were observed. Three patients (3.7%) died of recurrent disease.

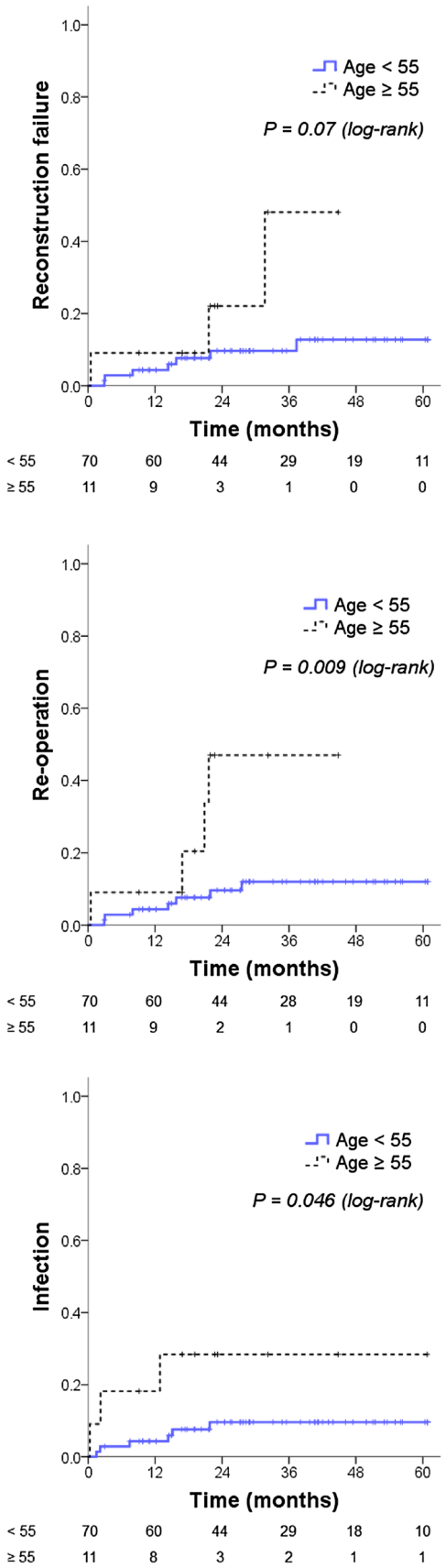
Discussion

Our reconstruction failure rate was 12.3% which was relatively low compared with the past reported studies (14–20%) [12, 15–17]. Follow-up periods were comparable (24–45.6 months), but each study used slightly different definition of reconstruction failure. Nava et al. and Fowble et al. used almost the same definition as ours. Cordeiro et al. did not report whether conversion to autologous reconstruction was included or not. Baschnagel et al. included removal or replacement of the TE or PI in their definition, making it closer to the definition of re-operation in our study. Taking into account the differences in definitions, our reconstruction failure rate is still relatively low.

Although BMI was not a risk factor in our study, some studies have suggested that obesity increases the complication rates among TE/PI patients, and most of whom did not receive radiotherapy [18–21]. Our patients were mostly thin Japanese women with the median BMI of 20. There were no obese women (BMI > 30) and only eight overweight patients (BMI ≥ 25), which may explain relatively low complication rates.

Age has not been identified as a risk factor for complications among irradiated patients with TE/PI-based breast reconstruction in the previous studies. Older age was a risk factor among TE/PI-based reconstructed patients in some previous studies, even though most received no radiotherapy [18–21]. Age could, therefore, be a common risk factor in TE/PI-based reconstructed patients with or without radiotherapy. Older patients may have comorbidities or other biological changes which negatively affect breast reconstruction. Patient age of 55 years and older was a risk factor in our study. The peak age for diagnosis of breast cancer in Asia is late forties, which is younger than in Western countries, where it is around sixty [22]. In addition to low BMI, younger age might have resulted in lower complication rates.

A meta-analysis reported that radiotherapy to a TE increased the risk of reconstruction failure more than that to a PI; however, this conclusion was largely lead by a single



◂**Fig. 2** Reconstruction failure, re-operation, and infection rates of tissue-expander (TE)/permanent implant (PI) reconstruction and post-mastectomy radiotherapy (PMRT) by age < 55 or ≥ 55 years. The numbers below each part of the figure show the number of patients at risk

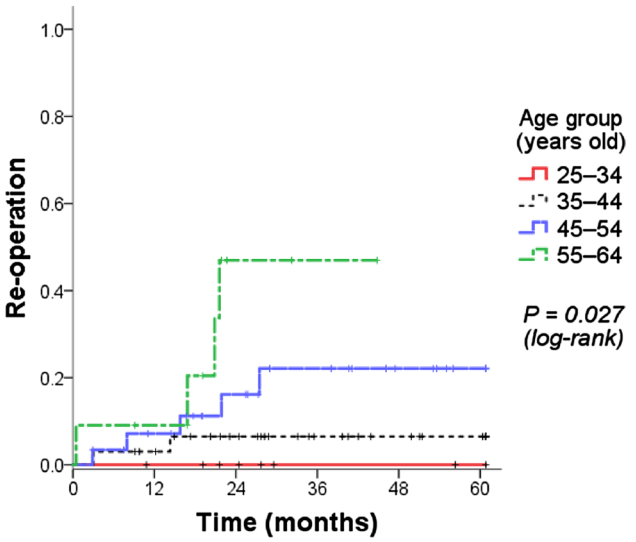


Fig. 3 Re-operation rate of tissue-expander (TE)/permanent implant (PI) reconstruction and post-mastectomy radiotherapy (PMRT) by age group

Table 2 Multivariate analysis of risk factors for complications

	HR (95% CI)	*P* value
Reconstruction failure		
Age ≥ 55	3.47 (0.85–14.2)	0.08
Smoking history	1.40 (0.28–6.90)	0.68
BMI ≥ 25	1.24 (0.15–9.95)	0.84
Re-operation		
Age ≥ 55	4.64 (1.27–16.9)	0.02
Smoking history	1.37 (0.28–6.78)	0.70
BMI ≥ 25	2.40 (0.51–11.2)	0.27
Infection		
Age ≥ 55	4.60 (1.08–19.5)	0.04
Smoking history	3.10 (0.73–13.2)	0.13
BMI ≥ 25	1.14 (0.14–9.10)	0.90

HR hazard ratio, *CI* confidence interval, *BMI* body mass index

study of Nova et al. [11, 15]. Their reconstruction rate of 40% in TE was more than twice as high as the other previous reports. Recent studies have reported that there were no differences in the rates of reconstruction failure between irradiation to a TE or a PI (Table 3) [12, 17, 23–26]. Although our relatively small sample size may not have enough power to

Table 3 Comparison of reconstruction failure (RF) rates in post-mastectomy radiotherapy to tissue expander (TE) vs permanent implant (PI)

	TE		PI		*P*
	No. of patients	RF rate (%)	No. of patients	RF rate (%)	
Anderson et al. [24]	62	4.8	12	0	0.21
Nava et al. [15]	50	40	109	6.4	NA
Collier et al. [25]	32	6.3	22	4.5	1
Fowble et al. [17]	86	19.8	13	7.7	NA
Cordeiro et al. [12]	94	18.1	210	12.4	NS
Yan et al. [26]	41	12.2	11	0	0.57
Santosa et al. [23]	104	11.5	46	8.7	0.9
Present study 2017	32	15.6	49	10.2	0.47

N/A not available, *NS* not significant

detect a difference, there were no statistically significant differences between the reconstruction failure rates of TE group (15.6%) and that of PI group (10.2%). Most previous studies have an imbalance in the sample size between the two timing groups, whereas our study had a relatively balanced sample size. There might be other outcome differences between the irradiation to a TE and a PI. A study showed that capsular contracture might occur more frequently when a PI is irradiated compared to a TE [12], whereas another study showed that the result, evaluated by shape and symmetry assessment and the patients' opinion, was better after irradiation to a PI [15]. Therefore, the timing of radiotherapy should be chosen carefully, considering each aspect of the outcome.

The reconstruction failure rate has decreased over time with higher complication in older time. This may be a result of the shorter follow-up period in the more recent cases, or could be explained by improved infection control management during surgery over time.

Several previous studies have investigated recurrence after breast reconstruction [27–30]. Nedumpara et al. and a meta-analysis by Gieni et al. showed that immediate breast reconstruction did not have any effect on breast cancer recurrence or survival [30, 31]. Some studies have shown that an internal metallic port in the TE impacted on radiation dose distribution. A high atomic number metallic port made radiation dose calculation difficult and reduced transmission near the magnet [32, 33]. Local recurrence near the metallic port might, therefore, be a concern. Although a longer follow-up will be required to detect all recurrences, so far, all recurrences were distant metastases, and no local and/or regional recurrence was observed in our study.

A bolus was used among a few patients in the early period of our study. We currently do not use a bolus for the reconstructed breast. However, a bolus was applied to the reconstructed breast in some previous studies [12, 16, 17]. A bolus is used to increase skin dose in PMRT, but there is no clinical evidence that this technique is useful. Even for cases of PMRT without breast reconstruction, the use of a bolus varied significantly through the region [34]. In a survey in the US, 36.7% of radiation oncologists did not use a bolus to treat patients with a TE [35]. Another worldwide survey showed that 40% of radiation oncologists never used a bolus for a breast reconstruction [36]. There is still no standard method of bolus use on reconstructed breast and we need further studies to clarify its utility.

There are some limitations to our study, including the retrospective nature, limited sample size, racial imbalance, and no specific cosmetic evaluation; however, this is one of few retrospective studies examining PMRT in TE/PI in the Asian population. Reconstruction failure was a relatively solid outcome and hard to be missed even in a retrospective study.

For the next step, we are conducting a retrospective study to compare irradiated and non-irradiated patients with implant-based reconstruction to evaluate the risk of radiation on reconstructed breasts.

Conclusion

The overall rate of reconstruction failure was 12% among breast reconstructed patients who received PMRT at our institution. Although there were no significant differences in reconstruction failure, re-operation, and infection rates with radiotherapy timing, the timing of radiotherapy must be carefully planned. Re-operation and infection rates increased among patients aged 55 years or over. We need to pay careful attention to the indication of reconstruction for older patients.

Compliance with ethical standards

Conflict of interest All authors have declared no conflicts of interest. No funding was received for this article.

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