

Post-mastectomy radiation therapy without usage of a bolus may be a reasonable option

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ABSTRACT

To clarify the efficacy and toxicity of post-mastectomy radiation therapy (PMRT) without usage of a bolus, we identified 129 consecutive patients who received PMRT at the National Cancer Center Hospital East between 2003 and 2012. Seven of the 129 patients who received breast reconstruction before PMRT were excluded. All patients received PMRT of 6 MV photons, without usage of a bolus. The median follow-up duration for all eligible patients was 47.7 months (range: 4.0–123.2). Local, locoregional and isolated locoregional recurrence was found in 12 (9.8%), 14 (11%) and 5 patients (4.1%), respectively. The 3- and 5-year cumulative incidence of local recurrence, locoregional recurrence and isolated locoregional recurrence was 9.2 and 10.7%, 10.8 and 12.4%, and 4.3 and 4.3%, respectively. Although Grade 2 dermatitis was found in 11 patients (9.0%), no Grade 3–4 dermatitis was found. On univariate analysis, only a non-luminal subtype was a significant predictor for local recurrence ($P < 0.001$). On multivariate analysis, a non-luminal subtype remained as an independent predictor for local recurrence ($P = 0.003$, odds ratio: 10.9, 95% confidence interval: 2.23–53.1). In conclusion, PMRT without usage of a bolus resulted in a low rate of severe acute dermatitis without an apparent increase in local recurrence. PMRT without usage of a bolus may be reasonable, especially for patients with a luminal subtype.

KEYWORDS: breast cancer, radiotherapy, post-mastectomy radiotherapy, bolus, local recurrence

INTRODUCTION

Post-mastectomy radiotherapy (PMRT) has been proven to increase both locoregional control and survival in breast cancer patients with a large tumor and/or lymph node metastases [1–4]. However, the optimal PMRT regimen, including the total dose, fraction size, use of a boost and usage of a bolus remains unknown.

Most local recurrences after mastectomy occur on the chest wall skin and subcutaneous tissues [5]. According to previous surveys, more than 90% of institutions use a tissue-equivalent bolus to maximize the dose to the chest wall skin in order to decrease the risk of local recurrence [6–8]. However, there are no prospective data supporting evidence regarding the link between dose to the chest wall

skin and local recurrence. On the contrary, the usage of a bolus possibly increases the risk of severe skin toxicity. Considering this background, our institution does not use a bolus when we deliver PMRT.

The purpose of this study was to clarify the efficacy and toxicity of PMRT without usage of a bolus.

MATERIALS AND METHODS

Patient identification

We identified 129 consecutive patients who received PMRT at the National Cancer Center Hospital East between 2003 and 2012. Seven of the 129 patients who received breast reconstruction before

PMRT were excluded, and the remaining 122 patients were included in the analysis. We defined subtypes of breast cancer according to the status of the estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor (HER)-2, and Ki-67 index. Luminal A was defined as luminal type (ER-positive and/or PgR-positive), HER-negative, and Ki-67 < 20%. Luminal B was defined as luminal type other than luminal A. HER-2-enriched was defined as non-luminal type (ER-negative and PgR-negative) and HER-2-positive. Triple-negative was defined as non-luminal type and HER-2-negative. With the approval of our Institutional Review Board, we performed a retrospective chart review of patient characteristics, treatments and clinical outcomes.

Treatments

All patients received total mastectomy. Almost all patients (98%) received axillary lymph node dissection, whereas two (1.6%) received only sentinel node biopsy.

Eighty-five patients (70%) received preoperative chemotherapy, whereas 27 (22%) received postoperative chemotherapy. Of those, all but two patients received an anthracycline-based regimen. Eighty-six patients (77%) received an anthracycline and cyclophosphamide (AC) followed by taxane regimen, 12 (11%) received an 5FU, epirubicin, and cyclophosphamide (FEC) followed by taxane regimen, 7 (6%) received AC, 3 (3%) received FEC, and 4 (4%) received other regimens. Ten patients (8.2%) did not receive chemotherapy before PMRT. Of 27 patients who had breast cancer and who were HER-2-positive, 21 (78%) received trastuzumab concurrently with pre- or postoperative chemotherapy. Of 76 patients who had breast cancer with the luminal type, 73 received adjuvant endocrine therapy.

All patients received PMRT without usage of a bolus. The 3D conformal technique with 6-MV X-rays was used in all patients. The clinical target volume typically included the chest wall and supra and infraclavicular nodes. The total irradiated dose for the initial target volume was 50 Gy at 2 Gy per fraction in all patients. Eleven patients (9.0%) received a 10-Gy boost at 2 Gy per fraction for possible residual lesions.

Endpoints and statistical analysis

As clinical outcomes, the rates of local recurrence, locoregional recurrence, isolated locoregional recurrence, breast cancer-specific death, and adverse effects were evaluated. Local recurrence was defined as recurrence in the chest wall, whereas regional recurrence was defined as regional lymph node recurrence, including the ipsilateral axilla, supraclavicular fossa, and parasternal region. Isolated locoregional recurrence was defined as local or regional recurrence that occurred without any distant metastases. Adverse effects were graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. We used EZR version 1.27 for statistical analysis [9]. Time analysis was calculated from the day when PMRT began. In the analysis of isolated locoregional recurrence, patients were censored when they had distant metastases, died, or were lost to follow-up. In the analysis of cumulative local or locoregional recurrence, local or locoregional recurrences that occurred at any time were counted as events. Univariate analysis by Fisher's

exact test and multivariate logistic regression analysis were used to examine the potential associations between local recurrence and patient characteristics, including age (≤ 50 or > 50), histology (ductal carcinoma or other), subtype (luminal or non-luminal), clinical and/or pathological T4 factor (yes or no), number of pathological lymph node metastases (0–3 or ≥ 4), lymphatic invasion status (0–1, 2–3), usage of chemotherapy (yes or no), and total irradiated dose (50 or 60 Gy). Differences were deemed significant when two-tailed *P*-values were less than 0.05.

RESULTS

Patient characteristics

All patients were diagnosed pathologically with T3–4 and/or N2–3 disease or clinically with T3–4 disease and/or ≥ 4 positive axillary lymph node metastases before preoperative chemotherapy. The patient characteristics are summarized in Table 1.

Recurrence and survival

The median follow-up duration for all eligible patients was 47.7 months (range: 4.0–123.2). Throughout the follow-up period, local, locoregional, and isolated locoregional recurrence was found in 12 (9.8%), 14 (11%) and 5 patients (4.1%), respectively. Among ten patients who did not receive chemotherapy, local, locoregional,

Table 1. Patient characteristics

Factor		Number
Age		Median 53 years (30–79)
Histology	Ductal carcinoma	109 (89%)
	Lobular carcinoma	9 (7%)
	Other	4 (3%)
Subtype	Luminal A	44 (36%)
	Luminal B	30 (25%)
	HER-2-enriched	15 (12%)
	Triple-negative	31 (25%)
	Unknown	2 (2%)
With T4 components (clinical and/or pathological)	No	66 (54%)
	Yes	56 (46%)
Number of pathologically metastatic lymph nodes	0	23 (19%)
	1–3	29 (24%)
	4–9	44 (36%)
	10 or more	26 (21%)
Lymphatic invasion status	0–1	86 (70%)
	2–3	33 (27%)
	Unknown	3 (2%)

and isolated locoregional recurrence was found in 0 (0%), 0 (0%) and one patient (10%), respectively. Eleven of 12 local recurrences and all five isolated locoregional recurrences occurred within 1 year. The 3- and 5-year cumulative incidences of local recurrence, locoregional recurrence, and isolated locoregional recurrence were 9.2 and 10.7%, 10.8 and 12.4%, and 4.3 and 4.3%, respectively (Fig. 1a, b and c). The 3- and 5-year cumulative incidences of breast cancer-specific death was 16.9 and 21.3%, respectively (Fig. 1d).

Adverse effects

Grade 2 dermatitis was found in 11 patients (9.0%) during or within 2 weeks after PMRT. However, no Grade 3–4 dermatitis was found.

Other Grade 2 adverse effects were found in 4 patients (arm edema: 2, nausea: 1, pneumonitis: 1). Grade 3 or severer adverse effects were not found.

Predictors for local recurrence

On univariate analysis, only a non-luminal subtype was a significant predictor for local recurrence ($P < 0.001$) (Table 2). On multivariate analysis, a non-luminal subtype remained an independent predictor for local recurrence ($P = 0.003$, odds ratio: 10.9, 95% confidence interval: 2.23–53.1) (Table 2). The incidence of local recurrence according to the subtype was 0 (0%) in luminal A, 2 (6.7%) in luminal B, 2 (13%) in HER-2-enriched, and 8 (26%) in triple-negative (Table 3).

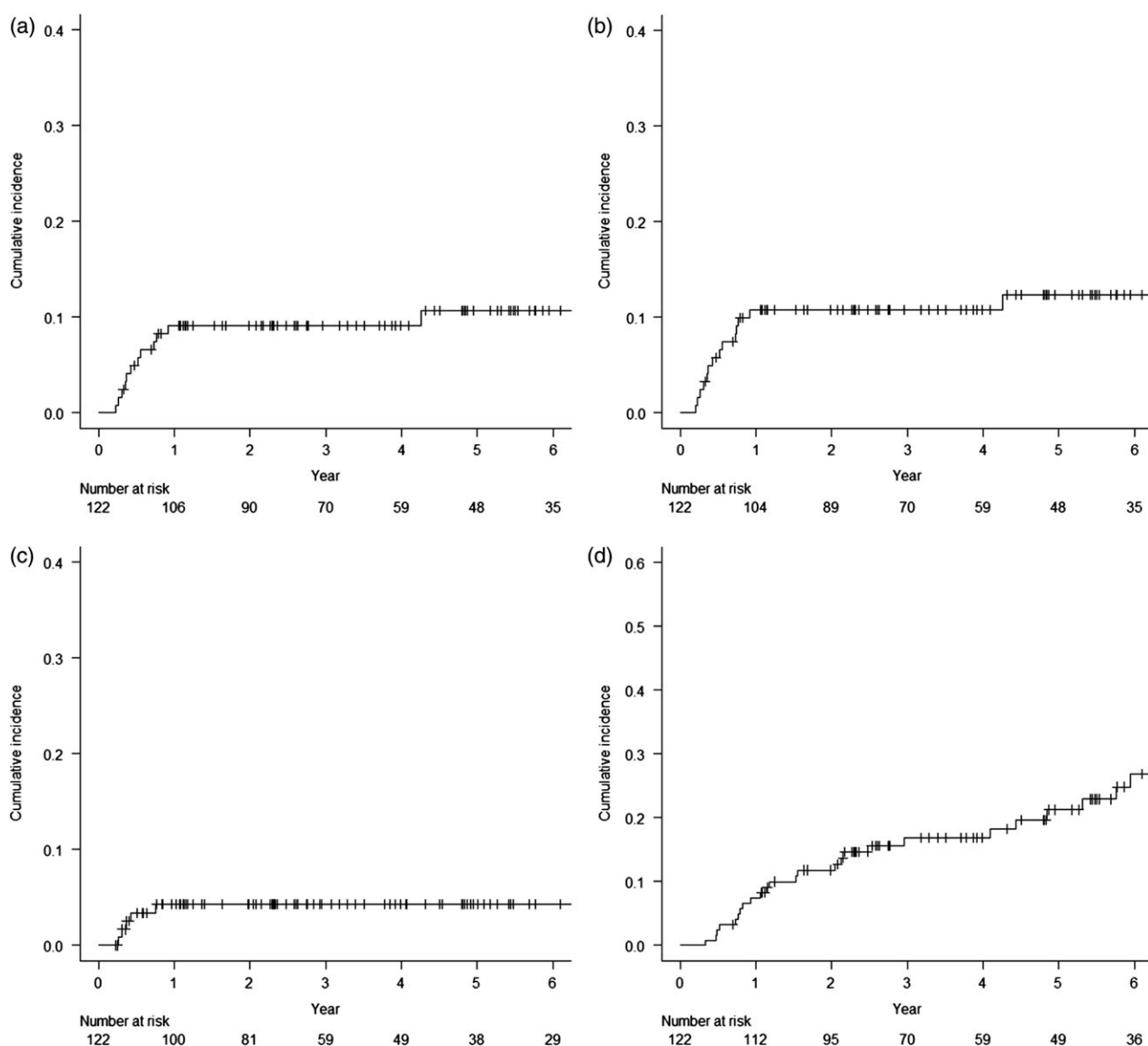


Fig. 1. The cumulative incidence of local recurrence (a), locoregional recurrence (b), isolated locoregional recurrence (c) and breast cancer-specific death (d).

Table 2. Univariate and multivariate analysis of predictors of local recurrence

Factor		Incidence	<i>P</i> -value
Univariate analysis			
Age	≤50 years	13%	0.537
	>50 years	8.1%	
Histology	Ductal carcinoma	10%	1
	Other	7.7%	
Subtype	Luminal	2.6%	< 0.001
	Non-luminal	22%	
With T4 components (clinical and/or pathological)	No	6.1%	0.142
	Yes	14%	
Number of pathologically metastatic lymph nodes	0–3	9.6%	1
	4 or more	10%	
Lymphatic invasion status	0–1	10%	1
	2–3	9.1%	
Chemotherapy	No	0%	0.596
	Yes	11%	
Total irradiated dose	50 Gy	9.0%	0.295
	60 Gy	18%	
Multivariate analysis			
Subtype	Luminal	1.00	0.003
	Non-luminal	10.9 (2.23–53.1)	
T4 (clinical and/or pathological)	No	1.00	0.12
	Yes	2.89 (0.77–10.9)	

P-values in boldface type indicate a significant difference.

DISCUSSION

There is little evidence that the application of a bolus significantly reduces local recurrence in patients receiving PMRT. Uematsu *et al.* retrospectively reviewed 309 patients who received PMRT [10]. Of those, 214 patients (69%) used a bolus, usually every other day. At a median follow-up of 130 months, the incidence of local recurrence was 5% in patients treated with a bolus and 4% in those treated without usage of a bolus.

A recent meta-analysis that confirmed the efficacy of PMRT used isolated locoregional recurrence as a primary indicator [4]. The meta-analysis showed 5-year isolated locoregional recurrence in 10.7% of high-risk patients. Although the meta-analysis included various PMRT regimens, including bolus usage, and the relatively

Table 3. The incidence of local recurrence according to subtype

Subtype	Number of patients	Incidence of local recurrence
Luminal A	44	0 (0%)
Luminal B	30	2 (6.7%)
Her-2-enriched	15	2 (13%)
Triple-negative	31	8 (26%)
Unknown	2	0 (0%)

old-fashioned chemotherapy regimens like CMF (cyclophosphamide, methotrexate, and 5FU) used in the cohort may be associated with the higher incidence of locoregional recurrence, we suggest that the incidence of isolated locoregional recurrence in our study (4.3%) was not worse than the standard outcome.

We found Grade 2 dermatitis in 9% of our patients and no Grade 3–4 dermatitis. Thus, severe acute dermatitis was much less common compared with in previous reports on PMRT using a bolus (Grade 2–4: 80–98%, Grade 3–4: 8.2–47%) [11–13].

A non-luminal subtype was found to be a predictor of local recurrence in our study, which is compatible with the findings in previous reports [14–16]. Considering the low incidence rate of local recurrence and severe acute dermatitis, PMRT without usage of a bolus may be a reasonable option for patients with a luminal subtype. On the contrary, stronger treatment, including bolus use, may be considered for the purpose of decreasing local recurrence for patients with a non-luminal subtype.

Despite the evidence and guideline recommendation to encourage PMRT [1–4, 17, 18], an underuse of PMRT has been reported [19, 20]. Although the actual reason underlying the underuse of PMRT may be multifactorial, the complexity of the treatment planning and delivery may be part of the explanation. PMRT without usage of a bolus is less complex and less toxic, which may contribute to its prominence in clinical use.

This study is inevitably limited by its single institutional and retrospective nature. Furthermore, the relatively short follow-up period may have affected the clinical outcomes, including locoregional recurrence.

In conclusion, PMRT without usage of a bolus resulted in a low rate of severe acute dermatitis, without an apparent increase in local recurrence. PMRT without usage of a bolus may be reasonable, especially for patients with a luminal subtype.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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