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Comparison of Clinical Outcome of Breast Cancer Patients with T1-2 Tumor and One to Three Positive Nodes with or without Postmastectomy Radiation Therapy

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Objective: The value of postmastectomy radiation therapy for breast cancer patients with T1-2 tumor and one to three positive nodes remains controversial. The purpose of this retrospective study was to compare the clinical outcomes of breast cancer patients with T1-2 and one to three positive nodes with and without postmastectomy radiation therapy.

Methods: Between May 1990 and June 2008, of 318 breast cancer patients with T1-2 and one to three positive nodes who had undergone modified radical mastectomy, 163 received postmastectomy radiation therapy and 155 did not. The clinico-pathologic characteristics were analyzed for clinical outcomes including loco-regional recurrence, distant metastasis, disease-free survival and overall survival.

Results: During the median follow-up period of 102 months, the clinical outcomes in postmastectomy radiation therapy versus no-postmastectomy radiation therapy groups were as follows: loco-regional recurrence rate (3.1 versus 11.0%, $P = 0.006$); distant metastasis rate (20.9 versus 27.7%, $P = 0.152$); 10-year disease-free survival rate (73.8 versus 61.3%, $P = 0.001$); and 10-year overall survival rate (82.1 versus 76.1%, $P = 0.239$). Through a multivariate analysis, a positive nodal ratio of $\geq$25% (hazard ratio = 4.571, $P = 0.003$) and positive lymphovascular invasion (hazard ratio = 2.738, $P = 0.028$) were found to be independent poor prognostic predictors of loco-regional recurrence. The reduction in loco-regional recurrence (hazard ratio = 0.208, $P = 0.004$) by postmastectomy radiation therapy was found to be significant.

Conclusions: On the basis of our results, postmastectomy radiation therapy is highly recommended for breast cancer patients with T1-2 and one to three positive nodes, especially for high-risk subgroups with a positive nodal ratio of $\geq$25% and positive lymphovascular invasion, not only for reducing loco-regional recurrence but also for improving disease-free survival.

Key words: breast cancer – postmastectomy radiation therapy – positive 1-3 axillary nodes – loco-regional recurrence – distant metastasis – disease-free survival – overall survival

INTRODUCTION

The basis for a decision on postmastectomy radiation therapy (PMRT) for breast cancer (BC) patients with T1-2 and positive one to three lymph nodes (T1-2N1) is one of most debatable issues for breast surgeons and radiation oncologists (1–3). Many randomized clinical trials have shown that PMRT in locally advanced BC patients not only reduces the risk of loco-regional recurrence (LRR) but also improves disease-free survival (4). In general, the indications for PMRT include a tumor size of >5 cm, presence of more than three positive lymph nodes or positive surgical margins (5). However, according to the NCCN 2011 practice guidelines in oncology for T1-2N1 BC patients, PMRT is highly recommended.

The clinical randomized trials carried out by the Danish Breast Cancer Cooperative Group (DBCG 82 b and c) demonstrated that PMRT changes the failure patterns in high-risk BC patients (2). However, the value of PMRT in BC patients with intermediate risk of T1-2N1 is uncertain. The MRC Selective Use of Post-Mastectomy Radiotherapy (SUPREMO) trial BIG 2-04 is an ongoing randomized study for assessment of the role of adjuvant chest wall irradiation in 'intermediate-risk' operable BC following mastectomy (6). The optimal treatment for such patients remains controversial.

Several studies have reported that younger age (<35 years old), negative estrogen receptor (ER) status, positive nodal number or positive nodal ratio, lymphovascular invasion (LVI) and higher nuclear grade are considered high-risk factors for LRR (7,8). A decision on PMRT for intermediate-risk BC patients with T1-2N1 was usually based on the discrepancy in prognostic factors considered by radiation oncologists. In our hospital, systemic chemotherapy is routinely administered for patients with T1-2N1 BC after modified radical mastectomy (MRM). PMRT is usually opted for on a case-to-case basis, taking into account the patient's family, and at the discretion of the radiation oncologist, after explaining the benefits and the risks to the patient.

The aim of this retrospective study was to compare the clinical outcomes of BC patients with T1-2N1 with and without PMRT and to identify the risk factors for LRR and distant metastases (DM).

PATIENTS AND METHODS

Patient Population

From May 1990 to June 2008, 385 BC patients with pathologically proven T1-2 and 1–3 positive axillary lymph nodes were treated with MRM at Kaohsiung Medical University Hospital. Sixty-seven patients were excluded from the study because of bilateral BCs, previous surgical treatment at other hospitals and incomplete treatment, or did not attend the follow-up. Eventually, 318 patients constituted the cohort of this study. We had reviewed their pathology reports and the stage was based on 2002 AJCC cancer staging. The mean age of these patients was 48.5 years (range 27–81 years).

The median follow-up period was 102 months (range 36–254 months). In order to compare the clinical outcomes and evaluate the impact of PMRT, the patients were divided into two groups: 163 patients, who underwent PMRT (PMRT group), and the remaining 155 patients, who did not (no-PMRT group).

Clinico-pathologic Characteristics

The distribution patterns of clinico-pathologic characteristics for the PMRT and no-PMRT groups were determined separately and compared by means of the χ^2 test as shown in Table 1. The clinico-pathologic characteristics were as follows: age (<50 and ≥50 years); location (lateral, medial and central); laterality (left and right); primary tumor size (≤2 and >2 cm); excised lymph node number; number of involved lymph nodes; positive nodal ratio (positive nodes number/total excised node number <25 or ≥25%); pathologic cell grade (I, II and III); histology (invasive ductal carcinoma, lobular carcinoma, mucinous carcinoma and others); lymphovascular invasion (LVI); ER status; and progesterone receptor (PR) status.

Surgical and Systemic Treatment

All the 318 patients underwent MRM with dissection of Level I and II axillary lymph nodes and preservation of the pectoralis major and minor muscles. The median number of the dissected lymph nodes was 12.5 (range 3–40). All the patients underwent adjuvant systemic chemotherapy with six cycles of 5-fluorourcil, doxorubicin (Endoxan) and cyclophosphamide (FEC) or four cycles of FEC and four cycles of taxane-based chemotherapy. After completion of systemic chemotherapy, 232 patients with positive ER or PR received adjuvant hormone therapy with tamoxifen or aromatase inhibitors.

Radiation Therapy

After the completion of systemic chemotherapy, most of the patients were referred to the radiation oncology department for evaluation of PMRT. As already mentioned, the decision on PMRT was taken on a case-to-case basis, taking into account the patient's family, and at the discretion of the radiation oncologist, after explaining the benefits and the risks to the patient. Among them, 163 patients underwent PMRT and 155 patients did not.

The patients undergoing PMRT were immobilized with a breast board. For most of the patients, two tangential fields were used to deliver the prescribed dose to the chest wall. A bolus was used to cover the entire chest wall and on alternate days in some patients. A direct anterior–posterior field was used to treat the supraclavicular and the infraclavicular nodes. Internal mammary lymph nodes were irradiated in those patients with inner located BC. After December 2007, seven patients underwent PMRT through the intensity-modulated radiation therapy technique. The total

Table 1. Characteristics of the 318 breast cancer patients with T1-2 and one to three positive nodes receiving modified radical mastectomy and chemotherapy

	RT ($n = 163$)	No-RT ($n = 155$)	P value
Age (years)			
Mean	49.1	48.0	0.292
Range	31–74	27–81	
<50	98 (60.1%)	100 (64.5%)	0.419
≥50	65 (39.9%)	55 (35.5%)	
Location			
Lateral	122 (74.8%)	119 (76.8%)	0.761
Medial	30 (18.4%)	24 (15.5%)	
Central	11(6.7%)	12 (7.7%)	
Laterality			
Right	89 (54.6%)	78 (50.3%)	0.445
Left	74 (45.4%)	77 (49.7%)	
Histology			
Invasive ductal carcinoma	144 (88.3%)	135 (87.1%)	0.671
Invasive lobular carcinoma	13 (8.0%)	10 (6.5%)	
Medullary carcinoma	2 (1.2%)	4 (2.6%)	
Others	4 (2.5%)	6 (3.9%)	
Cell grade			
1	21 (12.9%)	22 (14.2%)	0.720
2	86 (52.8%)	74 (47.7%)	
3	54 (33.1%)	42 (27.1%)	
Unknown	2 (1.2%)	17 (11.0%)	
Pathologic tumor size (cm)			
≤2	48 (29.4%)	42 (27.1%)	0.642
>2	115 (70.6%)	113 (72.9%)	
Excised lymph node number			
<10	57 (35.0%)	55 (35.5%)	0.924
≥10	106 (65.0%)	100 (64.5%)	
Number of positive nodes			
1	77 (47.2%)	108 (69.7%)	<0.001
2	54 (33.1%)	32 (20.6%)	
3	32 (19.6%)	15 (9.7%)	
Positive nodal ratio			
<25%	130(79.8%)	137(88.4%)	0.036
≥25%	33(20.2%)	18 (11.6%)	
Estrogen receptor status			
Positive	82 (50.3%)	76 (49.0%)	0.921
Negative	63 (38.7%)	57 (36.8%)	
Unknown	18 (11.0%)	22 (14.2%)	
Progesterone receptor status			
Positive	65 (39.9%)	62 (40.0%)	0.509
Negative	67 (41.1%)	54 (34.8%)	
Unknown	31 (19.0%)	39 (25.2%)	
Lymphovascular invasion			
Positive	38 (23.3%)	40 (25.8%)	0.652
Negative	105 (64.4%)	98 (63.2%)	
Unknown	20 (12.3%)	17 (11.0%)	
Loco-regional recurrence			
No	158 (96.9%)	138 (89.0%)	0.007
Yes	5 (3.1%)	17 (11.0%)	
Distant metastasis			
No	129 (79.1%)	112 (72.3%)	0.152
Yes	34 (20.9%)	43 (27.7%)	

RT, radiation therapy.

dose of radiation to the chest wall and to the loco-regional nodes ranged from 48 to 54 Gy (median: 50 Gy).

Follow-up

All the patients were regularly followed up at our clinic every 3 months for the first 3 years and then every 6 months after 3 years. After PMRT, all the patients received generalized work-ups every 3–6 months including physical examinations, biochemical laboratory examinations, tumor markers (CA-153 and carcino-embryonal antigen), chest X-rays, abdominal sonography and TC-99 bone scintigraphy.

The diagnosis of LRR was corroborated by biopsy. The diagnosis of distant metastases was carried out by examinations of bone scan, chest X-ray or chest computer tomography or other associated imaging studies, and by surgical excision in some cases.

Statistical Analysis

Determination of the risk factors for LRR and distant metastasis was the aim of this study. The risk factors for LRR including age, primary tumor location, laterality, tumor size, histology, cell grade, ER or PR, positive nodal number, excised nodal number, positive nodal ratio, LVI and PMRT were analyzed by means of the χ^2 test or Fisher's exact test. Disease-free survival (DFS) and overall survival (OS) were calculated using the Kaplan–Meier methods. A multivariate analysis of the prognostic factors for DFS and OS was performed through using the Cox proportional hazards survival regression analysis. The statistical significance was defined as $P < 0.05$. All the statistical analyses were performed using the SPSS software (version 18, SPSS Inc., Chicago, IL, USA). The research was approved by the Kaohsiung Medical University Hospital research ethics boards.

Table 2. Univariate analyses for risk factors of loco-regional recurrence (LRR)

Variable	No LRR ($n = 296$)	LRR ($n = 22$)	P value
Age (years)			
<50	186 (62.8%)	12 (54.5%)	0.439
≥50	110 (37.2%)	10 (45.5%)	
Location			
Lateral	222 (75.0%)	19 (86.4%)	0.271
Medial	53 (17.9%)	1 (4.5%)	
Central	21 (7.1%)	2 (9.1%)	
Laterality			
Right	154 (52.0%)	13 (59.1%)	0.522
left	142 (48.0%)	9 (40.9%)	
Histology			
Invasive ductal carcinoma	259 (87.5%)	20 (90.9%)	0.836
Invasive lobular carcinoma	22 (7.4%)	1 (4.5%)	
Medullary carcinoma	6 (2.0%)	0 (0%)	
Others	9 (3.0%)	1 (4.5%)	
Cell grade			
I	41 (13.9%)	2 (9.1%)	0.064
II	152 (51.4%)	8 (36.4%)	
III	84 (28.4%)	12 (54.5%)	
Unknown	19 (6.4%)	0 (0%)	
Pathologic tumor size (cm)			
≤2	84 (28.4%)	6 (27.3%)	0.912
>2	212 (71.6%)	16 (72.7%)	
Excised lymph node number			
<10	102 (34.5%)	10 (45.5%)	0.298
≥10	194 (65.5%)	12 (54.5%)	
Number of positive nodes			
1	170 (57.4%)	15 (68.2%)	0.573
2	82 (27.7%)	4 (18.2%)	
3	44 (14.9%)	3 (13.6%)	
Positive nodal ratio			
<25%	252 (85.1%)	15 (68.2%)	0.037
≥25%	44 (14.9%)	7 (31.8%)	
Estrogen receptor status			
Positive	151 (51.0%)	7 (31.8%)	0.024
Negative	106 (35.8%)	14 (63.6%)	
Unknown	39 (13.2%)	1 (4.6%)	
Progesterone receptor status			
Positive	121 (40.9%)	6 (27.3%)	0.075
Negative	108 (36.5%)	13 (59.1%)	
Unknown	67 (22.6%)	3 (13.6%)	
Lymphovascular invasion			
Positive	66 (22.3%)	12 (54.5%)	0.003
Negative	193 (65.2%)	10 (45.5%)	
Unknown	37 (12.5%)	0 (0%)	
Radiation therapy			
No	138 (46.6%)	17 (77.3%)	0.006
Yes	158 (53.4%)	5 (22.7%)	

RESULTS

The median follow-up period was 102 months for the PMRT group and 106 months for the no-PMRT group ($P = 0.541$). The distribution patterns of clinico-pathologic characteristics for the PMRT and the no-PMRT groups are presented in Table 1. There was no statistical difference between the two groups regarding age, tumor location, laterality, primary tumor size, nuclear grade, histology, pathologic stage, LVI status, excised nodal number and ER/PR status except for the number of positive lymph nodes and for a positive nodal ratio of ≥25%. Patients with more positive nodes (3 versus 1 and 2, $P < 0.001$) or with a nodal ratio of ≥25% ($P = 0.036$) would more likely undergo PMRT.

Furthermore, we analyzed recurrent patterns of LRR and DM. Twenty-two patients (6.9%, 22/318) had LRR and 77 patients (24.2%, 77/318) had DM. The median interval from mastectomy to tumor recurrence was 33 months (range, 5–191 months). The distribution of LRR sites was 20 chest wall recurrences and 2 axillary nodal recurrences. The incidence of LRR was 3.1% (5/163) for the PMRT group and 11.0% (17/155) for the no-PMRT group ($P = 0.006$). The negative ER status ($P = 0.024$), positive LVI ($P = 0.003$), positive nodal ratio ≥25% ($P = 0.037$) and no PMRT ($P = 0.006$) were associated with higher risk of LRR as shown in Table 2.

The incidence of distant metastasis was 20.9% (34/163) for the RT group and 27.7% (43/155) for the no-PMRT group ($P = 0.152$). The distribution of the first presentation of 77 patients with DM was as follows: bone, 33 (42.9%, 33/77); lung and pleura, 9 (11.6%, 9/77); liver, 6 (7.8%, 6/77); bone and lung, 7 (10%, 7/77); bone and liver, 6 (7.8%, 6/77); lung and liver, 2 (2.6%, 2/77); bone, lung and liver, 4 (5.2%, 4/77); and others, 10 (12.9%, 10/77). Through a univariate analysis, an age of ≥50 years was found to be a poor prognostic factor of distant metastases ($P = 0.007$) as shown in Table 3.

Through the multivariate Cox regression analysis, a positive nodal ratio of ≥25% [hazard ratio (HR) = 4.571, 95% confidence interval (CI) 1.706–12.252, $P = 0.003$] and LVI (HR = 2.738, 95% CI 1.112–6.741, $P = 0.028$) were found to be the significant risk factors for LRR as shown in

Table 3. Univariate analyses for risk factors of distant metastases

Variable	No distant metastases ($n = 241$)	Distant metastases ($n = 77$)	P value
Age (years)			
Mean	48.3	49.2	0.497
<50	160 (66.4%)	38 (49.4%)	0.007
≥50	81 (33.6%)	39 (50.6%)	
Location			
Lateral	188 (78.0%)	53 (68.8%)	0.261
Medial	37 (15.4%)	17 (22.1%)	
Central	16 (6.6%)	7 (9.1%)	
Laterality			
Left	112 (46.5%)	39 (50.6%)	0.523
Right	129 (53.5%)	38 (49.4%)	
Histology			
Invasive ductal carcinoma	209 (86.7%)	70 (90.9%)	0.562
Invasive lobular carcinoma	20 (8.3%)	3 (3.9%)	
Medullary carcinoma	5 (2.1%)	1 (1.3%)	
Others	7 (2.9%)	3 (3.9%)	
Cell grade			
I	32 (13.3%)	11 (14.3%)	0.543
II	126 (52.3%)	34 (44.2%)	
III	70 (29.0%)	26 (33.8%)	
Unknown	13 (5.4%)	6 (7.8%)	
Excised lymph node number			
<10	84 (34.9%)	28 (36.4%)	0.809
≥10	157 (65.1%)	49 (63.6%)	
Number of positive nodes			
1	142 (58.9%)	43 (55.8%)	0.893
2	64 (26.6%)	22 (28.6%)	
3	35 (14.5%)	12 (15.6%)	
Positive nodal ratio			
<25%	205 (80.5%)	62 (80.5%)	0.344
≥25%	36 (19.5%)	15 (14.9%)	
Pathologic tumor size (cm)			
≤2	70 (29.0%)	20 (26.0%)	0.602
>2	171 (71.0%)	57 (74.0%)	
Estrogen receptor status			
Positive	125 (51.9%)	33 (42.9%)	0.259
Negative	88 (36.5%)	32 (41.6%)	
Unknown	28 (11.6%)	12 (15.5%)	
Progesterone receptor status			
Positive	101 (41.9%)	26 (33.8%)	0.844
Negative	95 (39.4%)	26 (33.8%)	
Unknown	45 (18.7%)	25 (32.4%)	
Lymphovascular invasion			
Positive	56 (23.2%)	22 (28.6%)	0.429
Negative	155 (64.3%)	48 (62.3%)	
Unknown	30 (12.5%)	7 (9.1%)	
Radiation therapy			
No	112 (46.5%)	43 (55.8%)	0.152
Yes	129 (53.5%)	34 (44.2%)	

Table 4. The LRR was reduced significantly by PMRT (HR = 0.208, 95% CI = 0.071–0.609, $P = 0.004$). A patient age of ≥50 years had an increased risk for DM (HR = 2.129, 95% CI 1.241–3.652, $P = 0.006$), but the lateral tumor location might reduce the risk of DM (HR = 0.545, 95% CI 0.301–0.988, $P = 0.045$).

We present the multivariate Cox regression analyses of DFS and OS done in this study in Table 5. The patients with PMRT had better survival benefit on DFS (HR = 0.445, 95% CI 0.274–0.722, $P = 0.001$), but not significantly on OS (HR = 0.695, 95% CI 0.380–1.273, $P = 0.239$). A patient age of ≥50 years (HR = 1.995, CI 1.253–3.177, $P = 0.004$) and a positive nodal ratio of ≥25% (HR = 2.026, 95% CI 1.142–3.592, $P = 0.016$) were found to be the poor prognostic factors for DFS. Simultaneously, an age of ≥50 years (HR = 1.901, 95% CI = 1.044–3.462, $P = 0.036$) and a positive nodal ratio of ≥25% (HR = 2.329, 95% CI = 1.158–4.687, $P = 0.018$) were found to be associated with poor prognosis of OS as well. In contrast with the aforementioned factors, the lateral tumor location was shown as a better prognostic predictor for DFS (HR = 0.506, 95% CI = 0.327–0.967, $P = 0.037$) and OS (HR = 0.456, 95% CI 0.232–0.894, $P = 0.022$).

Further analyses of the survival status revealed 5-year LRR-free survival rates of 97.2 and 92.5% for the PMRT group and the no-PMRT group ($P = 0.004$) as shown in Figure 1, and 5-year DM-free survival rates of 86.5 and 80.4% ($P = 0.074$) as shown in Figure 2, respectively. The 5-year DFS rate was 84.2% for the PMRT group and 72.2% for the no-PMRT group; the 10-year DFS rate was 73.8 and 61.3% ($P = 0.001$) as shown in Figure 3. The 5-year OS rate was 91.5 versus 87.0% and the 10-year OS rate was 82.1 versus 76.1% ($P = 0.239$) for the PMRT versus the no-PMRT group, respectively, as shown in Figure 4.

DISCUSSION

In this study, PMRT reduced the LRR ($P = 0.004$) for the BC patients with T1-2N1 and improved the DFS

Table 4. Multivariate analysis of LRR and distant metastasis in 318 breast cancer patients with T1-2 and one to three positive nodes

Variable	Loco-regional recurrence		Distant metastasis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Radiation therapy (yes versus no)	0.208 (0.071–0.609)	0.004	0.612 (0.357–1.049)	0.074
Age (≥50 versus <50 years)	1.431 (0.586–3.491)	0.431	2.129 (1.241–3.652)	0.006
Tumor size (≤2 versus >2 cm)	0.707 (0.259–1.929)	0.498	0.984 (0.538–1.798)	0.957
Histologic grade (III versus II and I)	1.900 (0.767–4.712)	0.166	1.130 (0.645–1.981)	0.669
Estrogen receptor (positive versus negative)	0.525 (0.200–1.376)	0.190	0.900 (0.525–1.543)	0.701
Positive nodal ratio (≥25 versus <25%)	4.571 (1.706–12.252)	0.003	1.402 (0.695–2.827)	0.346
Location (lateral versus medial/central)	0.972 (0.267–3.544)	0.966	0.545 (0.301–0.988)	0.045
Lymphovascular invasion (yes versus no)	2.738 (1.112–6.741)	0.028	1.382 (0.800–2.386)	0.246

CI, confidence interval.

Table 5. Cox's regression multivariate analyses of disease-free survival and overall survival

Variable	Disease-free survival		Overall survival	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Radiation therapy (yes versus no)	0.445 (0.274–0.722)	0.001	0.695 (0.380–1.273)	0.239
Age (≥ 50 years versus <50 years)	1.995 (1.253–3.177)	0.004	1.901 (1.044–3.462)	0.036
Tumor size (≤2 versus >2 cm)	0.932 (0.552–1.575)	0.793	1.149 (0.568–2.326)	0.699
Histologic grade (III versus II and I)	1.266 (0.782–2.049)	0.337	0.940 (0.504–1.751)	0.845
Estrogen receptor (positive versus negative)	0.686 (0.426–1.106)	0.122	0.629 (0.343–1.151)	0.132
Positive nodal ratio (≥25 versus <25%)	2.026 (1.142–3.592)	0.016	2.329 (1.158–4.687)	0.018
Location (lateral versus medial/central)	0.563 (0.327–0.967)	0.037	0.456 (0.232–0.894)	0.022
Lymphovascular invasion (yes versus no)	1.552 (0.971–2.479)	0.066	1.133 (0.601–2.136)	0.699

($P = 0.001$). However, the improvement in DM ($P = 0.074$) and OS ($P = 0.239$) was not significant.

As already mentioned, PMRT was found to reduce LRR in BC patients with pathologic tumor size more than 5 cm or more than four positive lymph nodes (5). However, the value of PMRT to reduce LRR and total mortality in the intermediate-risk subgroup of BC patients with T1-2N1 remained uncertain (3,9). During the past decade, there has been a lack of definitive data from randomized trials to enable any conclusions to be drawn about delivering PMRT to the intermediate-risk subgroup of T1-2N1 BC patients. Consequently, there was a worldwide discrepancy in the clinical practice of PMRT for T1-2N1 BC patients among radiation oncologists, and one survey reported that only 40.7% (285/702) and 36.1% (157/435) of respondents would use PMRT in patients with one to three positive lymph nodes in North America and Europe, respectively (10,11). An NIH consensus statement insisted that there be formed a set of international standard guidelines for the clinical use of PMRT in T1-2N1 BC patients (12). There is an ongoing study of SUPREMO trial in the UK to investigate whether chest wall irradiation may or not reduce LRR and improve survival (6).

The LRR rate in patients with positive nodes treated by MRM and chemotherapy without PMRT ranged from 8 to 42% (13,14). For T1-2N1 BC patients, the LRR rate was reported between 8 and 30% (13,15). Comparing the LRR rate of the PMRT and no-PMRT groups, Cosar et al. (16) reported 3 versus 17% and Ragaz et al. (17) 10 versus 21%, respectively. Our study revealed a similar result in LRR rate: 3.1 versus 11.0%. The relative risk reduction in the LRR rate by PMRT was 72.7% and absolute risk reduction (ARR) was 8% in our study.

From previous randomized trials, Fowble had reviewed the clinical benefits on the reduction of the risk of LRR by PMRT in BC patients and the results had a wide range: the ARR ranged from 10 to 28% for patients with four or more positive nodes and from 3 to 23% for patients with one to three nodes (1). According to an overview report published by the Early Breast Cancer Trials Collaboration Group

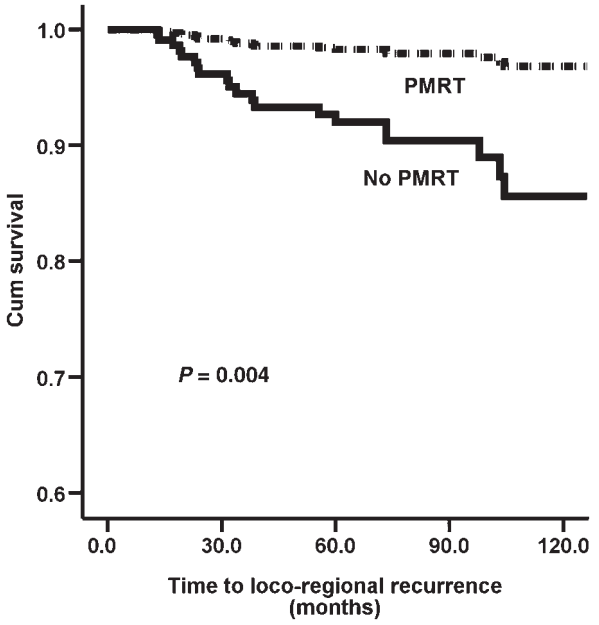

Figure 1. The Kaplan–Meier curve of loco-regional recurrence (LRR)-free survival [5-year LRR-free survival: postmastectomy radiation therapy (PMRT) group 97.2% and no-PMRT group 92.5%, $P = 0.004$, hazard ratio (HR) = 0.208, 95% confidence interval (CI) 0.071–0.609].

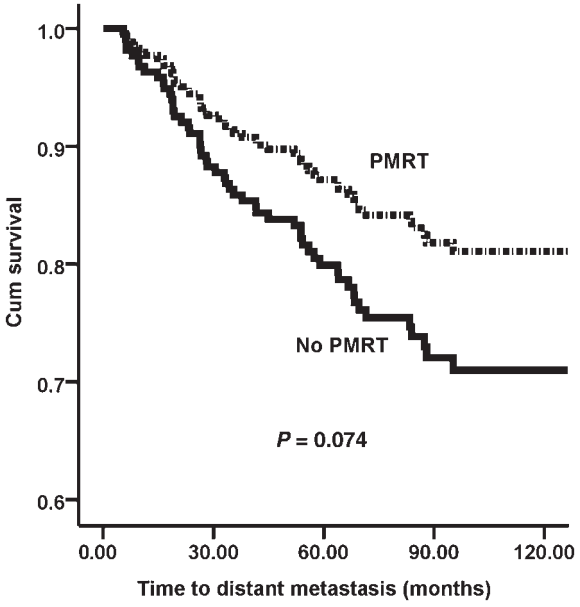

Figure 2. The Kaplan–Meier curve of DM-free survival (5-year DM-free survival: PMRT group 86.5% and no-PMRT group 80.4%, HR = 0.612, 95% CI 0.357–1.049; $P = 0.074$).

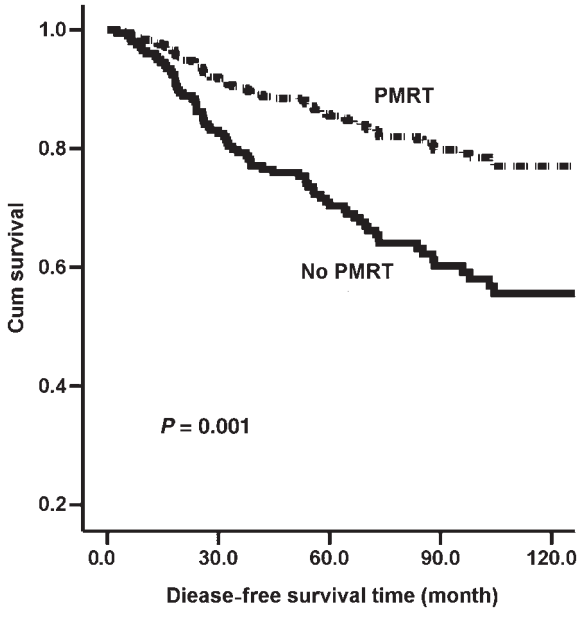

Figure 3. The Kaplan–Meier curve of disease-free survival (5-year DFS: PMRT group 84.2% and no-PMRT group 72.2%, HR = 0.445, 95%CI 0.274–0.722, $P = 0.001$).

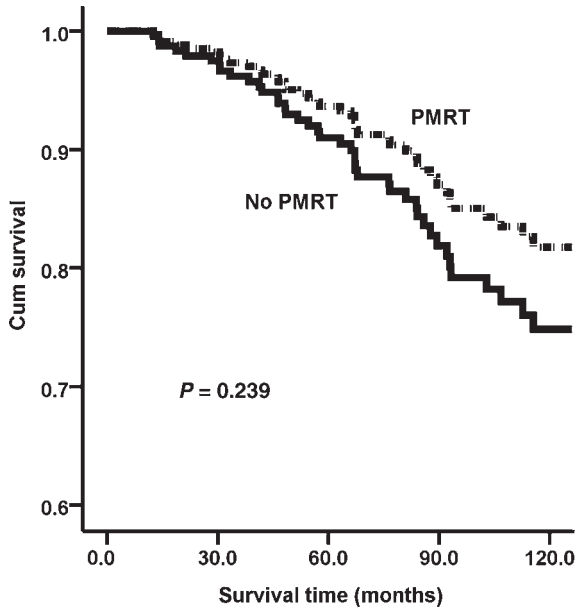

Figure 4. The Kaplan–Meier curve of overall survival (5-year OS: PMRT group 91.5% and no-PMRT group 87%; 10-year OS: PMRT group 82.1% and no-PMRT group 76.1%, HR = 0.695, 95% CI 0.380–1.273, $P = 0.239$).

(EBCTCG), local treatment including nodal radiotherapy and mastectomy with or without systemic chemotherapy produced an ARR of ≥10% in 5-year local recurrence (4). Truong et al. (18) also reported that nodal PMRT significantly reduced LRR (HR = 0.59, $P = 0.02$). Our study showed the benefits of PMRT related to a reduction in LRR.

PMRT improves loco-regional control and subsequently might reduce the occurrence of DM. Our results showed that 163 patients with PMRT had a lower DM rate (20.9%) as against 155 patients without PMRT (27.7%), although it was not statistically significant ($P = 0.152$). Cosar et al. (16) reported that PMRT significantly improved the DM rate between the PMRT and no-PMRT groups (12 versus 42%, $P = 0.004$), but that study consisted of a relatively small number of patients ($n = 90$). We found that the elder patients aged over 50 years had an increased risk of DM. In fact, as seen from Table 3, the mean age of DM patients was 49.2

[standard deviation (SD) = 9.3] years, while the mean age of patients without DM was 48.3 (SD = 9.4) years. The two-group impendent *t*-test was not significant ($P = 0.497$). The available data on this aspect are scanty. Further research into this topic is needed.

'Does PMRT increase survival rates of BC patients with T1-2N1?' According to the results of our retrospective study, comparing the PMRT and no-PMRT groups, the irradiation after mastectomy and systemic chemotherapy significantly improved 5-year LRR-free survival rate (97.2 versus 92.5%, HR = 0.208, $P = 0.004$) and DFS (84.2 versus 72.2%, HR = 0.445, $P = 0.001$). The impact of PMRT on 5-year OS (91.5 versus 87%) and 10-year OS (82.1 versus 76.1%) showed improvement in survival, but was not significant ($P = 0.239$) in this study. EBCTCG 2005 reported a significant survival benefit (5.4% at 15 years) in BC women with positive nodes treated by PMRT (4), which was similar to our result.

Several previous studies have shown the benefits of radiotherapy related to the OS of intermediate-risk BC patients after surgery or chemotherapy. The result of the British Columbia randomized trial showed that loco-regional radiation therapy has a 7% gain in 20-year OS in BC patients with one to three positive nodes after adjuvant chemotherapy (PMRT versus no-PMRT: 57 versus 50%, $P = 0.009$) (17). The data of three EORTC (European organization for research and treatment of cancer)-BC group trial showed that adjuvant radiotherapy after mastectomy was associated with significantly improved survival rates with a risk reduction ratio of 48% (relative risk = 0.48, $P < 0.001$) (19). There were 9% survival benefits at 10-year follow-up from PMRT (45 versus 36%, $P = 0.03$) in high-risk post-menopausal BC (with tumor $\geq$5 cm and $\geq$4 positive lymph nodes) patients with chemotherapy (20). The DBCG 82 b and c trial in 3083 pre- and post-menopausal BC patients showed that 15-year survival benefit after RT significantly improved in both the patients groups: a 9% survival improvement in patients with one to three positive nodes (57 versus 48%, $P = 0.03$) and the same benefit in patients with 4+ nodes (21 versus 12%, $P = 0.03$) (21). However, our result of a comparison between the PMRT and the no-PMRT groups revealed only 4.5% survival improvement (91.5 versus 87%, $P = 0.239$) in 5-year OS and 6% benefit (82.1 versus 76.1%) at 10-year OS. PMRT was an independent good prognostic factor for LRR ($P = 0.004$) and DFS ($P = 0.001$) according to the findings of our study.

It is also important to identify the prognostic factors that affect disease recurrence in BC T1-2N1 patients after surgery. In our trial, through the multivariate Cox regression analysis, it was found that an age of $\geq$50 years, a positive nodal ratio of $\geq$25% and LVI were the statistically significant risk factors for LRR, while an age of $\geq$50 years and medial–central location were the adverse predictors for DM. An analysis of prospective data from the post-mastectomy randomized trial at British Columbia (22) and the MD Anderson cancer center (23) showed that the presence of >20% positive nodes was associated with high LRR risk. Vinh-Hung et al. (24) pointed out that the lymph node ratio should be considered an alternative to pN staging to predict the survival of node-positive BC. It meant that the percentage of positive nodes was a stronger poor prognostic factor for LRR compared with the absolute number of nodes involved. Fortin et al. (25) also identified the percentage of positive nodes to be significantly associated with LRR. Yildirim and Berberoglu (26) reported that the ratio of positive nodes and the presence of local recurrence were the most important predictors of distant recurrence in intermediate-risk BC patients.

An age of <50 years, Grade III histology and LVI were the other adverse predictors for higher LRR as revealed by the multivariate analysis in other studies (1,7,27). In one recent Canadian study, Truong et al. (18) also reported that patients with one to three positive nodes and young age, Grade III histology or ER-negative disease have a high LRR risk of 15–20%.

Tumor location is generally not included as a prognostic factor. Several studies have reported that medial or inner sites had a higher LRR rate and poor survival in node-negative BC (28–30). Vinh-Hung et al. (24) demonstrated that the medial location was not a poor prognostic factor for BC mortality among 1829 patients with node-positive BC. Chen et al. (7) showed no correlation of medial location with LRR. Otherwise, Shen et al. (31) reported that medially located tumors were associated with higher risk of axillary lymph node recurrence. Truong et al. (32) also demonstrated that the medial location of tumor was associated with a high risk of LRR. Our study had a similar result. It may be due to the lymphatic drainage of medial tumor more often to the internal mammary nodes.

LVI might be strongly related to the presence of lymph node metastases and predict poor prognosis (7,27,33). Through a multivariate analysis, Cosar et al. (16) reported LVI, a positive nodal ratio of $\geq$25% and PMRT being independent significant factors for improving OS. Yang et al. (34) reported that PMRT can reduce LRR in pT1-2N1 BC patients with the following characteristics: an age of <40 years, T2 stage, high nuclear grade, negative ER status and positive LVI status. Similarly, our result emphasized the importance of the negative ER status and the positive LVI status correlated with LRR.

he limitations of this study included its retrospective nature and the selection bias. The decision on PMRT was at the discretion of the oncologists. The sample size was relatively small compared with large randomized clinical trials. The techniques used in the chemotherapy and radiotherapy might change from time to time and from oncologist to oncologist. The indication of irradiated internal mammary chain is controversial among radiation oncologists. These factors may affect the outcomes in different subgroups. Of course, we need a large randomized and prospective trial to evaluate the value of PMRT on LRR, survival, morbidity and even on the quality of life in pT1-2N1 BC patients. As we know, the ongoing SUPREMO randomized clinical trial in the UK may provide answers to many such

questions and improved measures in the management of intermediate-risk BC patients, making the research a promising for future studies (6).

CONCLUSIONS

According to our results, PMRT is highly recommended for BC patients with T1-2 tumor and one to three positive axillary lymph nodes, especially for subgroups with poor prognostic factors, such as a positive nodal ratio of >25% and LVI, not only for reducing local–regional recurrence but also for improving DFS.

Authors' Contributions

C.-J.H. and S.-F.L. coordinated the entire study. Clinical data collection was done by C.-J.H., M.-F.H., M.-Y.H., O.-Y.F., F.-M.C., S.-F.L. and S.-L.L. Data analysis was done by H.-Y.C. The manuscript was prepared by C.-J.H., M.-F.H. and S.-F.L. Corrections and/or improvements were suggested by S.-F.L. Major revisions were done by C.-J.H. and S.-F.L. All authors read and approved the final manuscript.

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Conflict of interest statement

None declared.

References

1. Fowble B. Postmastectomy radiation in patients with one to three positive axillary nodes receiving adjuvant chemotherapy: an unresolved issue. *Semin Radiat Oncol* 1999;9:230–40.
2. Recht A, Gray R, Davidson NE, et al. Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: experience of the Eastern Cooperative Oncology Group. *J Clin Oncol* 1999;17:1689–700.
3. Olivotto IA, Truong PT, Chua B. Postmastectomy radiation therapy: who needs it? *J Clin Oncol* 2004;22:4237–9.
4. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2006;366:2087–106.
5. NCCN Practice Guideline in Oncology. *NCCN 2011 Practice Guidelines in Oncology for Breast Cancer*, 2011. p. BINV3, New York, USA.
6. Kunkler IH, Canney P, van Tienhoven G, Russell NS. Elucidating the role of chest wall irradiation in 'intermediate-risk' breast cancer: the MRC/EORTC SUPREMO trial. *Clin Oncol (R Coll Radiol)* 2008;20:31–4.
7. Cheng JC, Chen CM, Liu MC, et al. Locoregional failure of postmastectomy patients with 1–3 positive axillary lymph nodes without adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys* 2002;52:980–8.
8. Huang EH, Tucker SL, Strom EA, et al. Predictors of locoregional recurrence in patients with locally advanced breast cancer treated with neoadjuvant chemotherapy, mastectomy, and radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;62:351–7.
9. Abrams JS. Adjuvant therapy for breast cancer—results from the USA consensus conference. *Breast Cancer* 2001;8:298–304.
10. Ceilley E, Jagsi R, Goldberg 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.
11. The National Institutes of Health Consensus Development Conference: adjuvant therapy for breast cancer. Bethesda, Maryland, USA. November 1–3, 2000. Proceedings. *J Natl Cancer Inst Monogr* 2001:1–152.
12. Eifel P, Axelson JA, Costa J, et al. National Institutes of Health Consensus Development Conference Statement: adjuvant therapy for breast cancer, November 1–3, 2000. *J Natl Cancer Inst* 2001;93:979–89.
13. Sartor CI, Peterson BL, Woolf S, et al. Effect of addition of adjuvant paclitaxel on radiotherapy delivery and locoregional control of node-positive breast cancer: cancer and leukemia group B 9344. *J Clin Oncol* 2005;23:30–40.
14. Blichert-Toft M, Nielsen M, During M, et al. Long-term results of breast conserving surgery versus mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. *Acta Oncol* 2008;47:672–81.
15. Overgaard M, Hansen PS, Overgaard J, 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;337:949–55.
16. Cosar R, Uzal C, Tokatli F, et al. Postmastectomy irradiation in breast in breast cancer patients with T1-2 and 1-3 positive axillary lymph nodes: is there a role for radiation therapy? *Radiat Oncol* 2011;6:28.
17. Ragaz J, Olivotto IA, Spinelli JJ, 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;97:116–26.
18. Truong PT, Jones SO, Kader HA, et al. Patients with t1 to t2 breast cancer with one to three positive nodes have higher local and regional recurrence risks compared with node-negative patients after breast-conserving surgery and whole-breast radiotherapy. *Int J Radiat Oncol Biol Phys* 2009;73:357–64.
19. van der Hage JA, Putter H, Bonnema J, Bartelink H, Therasse P, van de Velde CJ. Impact of locoregional treatment on the early-stage breast cancer patients: a retrospective analysis. *Eur J Cancer* 2003;39:2192–9.
20. Overgaard M, Jensen MB, Overgaard J, 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;353:1641–8.
21. Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. *Radiother Oncol* 2007;82:247–53.
22. Truong PT, Woodward WA, Thames HD, Ragaz J, Olivotto IA, Buchholz TA. The ratio of positive to excised nodes identifies high-risk subsets and reduces inter-institutional differences in locoregional recurrence risk estimates in breast cancer patients with 1–3 positive nodes: an analysis of prospective data from British Columbia and the M. D. Anderson Cancer Center. *Int J Radiat Oncol Biol Phys* 2007;68:59–65.
23. Strom EA, Woodward WA, Katz A, et al. Clinical investigation: regional nodal failure patterns in breast cancer patients treated with mastectomy without radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;63:1508–13.

24. Vinh-Hung V, Verkooijen HM, Fioretta G, et al. Lymph node ratio as an alternative to pN staging in node-positive breast cancer. *J Clin Oncol* 2009;27:1062–8.
25. Fortin A, Dagnault A, Blondeau L, Vu TT, Larochelle M. The impact of the number of excised axillary nodes and of the percentage of involved nodes on regional nodal failure in patients treated by breast-conserving surgery with or without regional irradiation. *Int J Radiat Oncol Biol Phys* 2006;65:33–9.
26. Yildirim E, Berberoglu U. Local recurrence in breast carcinoma patients with T(1-2) and 1–3 positive nodes: indications for radiotherapy. *Eur J Surg Oncol* 2007;33:28–32.
27. Matsunuma R, Oguchi M, Fujikane T, et al. Influence of lymphatic invasion on locoregional recurrence following mastectomy: indication for postmastectomy radiotherapy for breast cancer patients with one to three positive nodes. *Int J Radiat Oncol Biol Phys* 2011 (ahead of print).
28. Colleoni M, Zahrieh D, Gelber RD, et al. Site of primary tumor has a prognostic role in operable breast cancer: the international breast cancer study group experience. *J Clin Oncol* 2005;23:1390–400.
29. Shahar KH, Buchholz TA, Delpassand E, et al. Lower and central tumor location correlates with lymphoscintigraphy drainage to the internal mammary lymph nodes in breast carcinoma. *Cancer* 2005;103:1323–9.
30. Sarp S, Fioretta G, Verkooijen HM, et al. Tumor location of the lower-inner quadrant is associated with an impaired survival for women with early-stage breast cancer. *Ann Surg Oncol* 2007;14:1031–9.
31. Shen SC, Liao CH, Lo YF, et al. Favorable outcome of secondary axillary dissection in breast cancer patients with axillary nodal relapse. *Ann Surg Oncol* 2012;19:1122–8.
32. Truong PT, Olivotto IA, Kader HA, Panades M, Speers CH, Berthelet E. Selecting breast cancer patients with T1-T2 tumors and one to three positive axillary nodes at high postmastectomy locoregional recurrence risk for adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;61:1337–47.
33. Wallgren A, Bonetti M, Gelber RD, et al. Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. *J Clin Oncol* 2003;21:1205–13.
34. Yang PS, Chen CM, Liu MC, et al. Radiotherapy can decrease locoregional recurrence and increase survival in mastectomy patients with T1 to T2 breast cancer and one to three positive nodes with negative estrogen receptor and positive lymphovascular invasion status. *Int J Radiat Oncol Biol Phys* 2010;77:516–22.