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CLINICAL INVESTIGATION **Breast**

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

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Purpose: To define a subgroup of patients at high risk of locoregional recurrence (LRR) who might be benefit from postmastectomy radiotherapy in invasive breast cancer and tumor size <5 cm with one to three involved axillary lymph nodes (T1–2 N1).

Methods and Materials: Between April 1991 and December 2005, 544 patients with T1–2 N1 invasive breast cancer were treated with modified radical mastectomy. Of the 544 patients, 383 patients (70.4%) had no radiotherapy, and 161 patients (29.6%) received radiotherapy. We retrospectively compared these two patient groups.

Results: With a median follow-up of 40.3 months, LRR occurred in 40 (7.4%) of 544 patients. On univariate analysis, high nuclear grade ($p = 0.04$), negative estrogen receptor (ER) status ($p = 0.001$), presence of lymphovascular invasion (LVI) ($p = 0.003$), and no radiotherapy ($p = 0.0015$) were associated with a significantly higher rate of LRR. Negative ER status (hazard ratio = 5.1) and presence of LVI (hazard ratio = 2.5) were the risk factors for LRR with statistical significance in the multivariate analysis. Radiotherapy reduced the LRR in patients with the following characteristics: age <40 years, T2 stage, high nuclear grade, negative ER status, and presence of LVI. For 41 patients with negative ER and positive LVI status, radiotherapy can reduce LRR from 10 of 25 (40%) to 2 of 16 (12.5%) and increase the 5-year overall survival from 43.7% to 87.1%.

Conclusion: Radiotherapy can reduce LRR and increase survival in T1–2 N1 breast cancer patients with negative ER status and presence of LVI. © 2010 Elsevier Inc.

Invasive breast cancer, T1–2 N1, Locoregional recurrence, Mastectomy, Radiotherapy.

INTRODUCTION

Surgery and radiation share the common goals of controlling the locoregional manifestations of breast cancer (1). For most early-stage breast cancer patients, local therapy of mastectomy alone or lumpectomy in conjunction with radiotherapy to the breast will achieve adequate local control rates with equivalent survival. In certain cases of breast cancer that are associated with a high risk of failure, more aggressive therapy is warranted. Patients treated with mastectomy may harbor occult, microscopic disease beyond the boundaries of the surgical filed, which may not be adequately controlled by adjuvant systemic therapy (1). This may potentially lead to locoregional recurrence (LRR) and increase the risk of distant metastasis. Radiotherapy therefore plays an important role in the locoregional management of some patients treated with mastectomy.

Three randomized trials have shown that adjuvant postmastectomy radiotherapy (PMRT) reduces rates of LRR and can improve overall survival rates in high-risk patients (2–4). There is consensus regarding the routine use of PMRT in breast cancer patients with tumor size >5cm, four or more involved axillary lymph nodes, and invasion of the pectoral muscle or the surgical margins (5–7). The cutoff point of four involved axillary nodes is challenged by Overgaard (8), who demonstrated that the number of involved nodes should not be used as a threshold to prescribe PMRT. The role of PMRT is not clearly defined in breast cancer patients

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with tumor ≤5 cm and one to three positive nodes (T1–2 N1) (1, 6, 8–16). The aim of this study was to investigate our dataset and to determine predictive factors of LRR in T1–2 N1 breast cancer patients and to define a subgroup of patients at high risk of LRR who might benefit from PMRT.

METHODS AND MATERIALS

Study population

Between April 1991 and December 2005, 2849 patients were diagnosed with invasive breast cancer at Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan. Of these patients, 684 patients were found to have invasive cancer and tumor size <5 cm with one to three involved axillary lymph nodes (T1–2 N1 breast cancer) on pathologic examination. Patients treated with neoadjuvant chemotherapy or with previous radiation were excluded. Five hundred forty-four patients received modified radical mastectomy (MRM) and were included in this retrospective study.

The baseline clinical information of this study population included age and date at diagnosis; histology; primary tumor size; number of involved axillary nodes; nuclear grade; lymphovascular invasion (LVI) of primary tumor (prominent LVI defined as three or more vessels or lymphatic ductal invasion by cancer); estrogen receptor (ER) and progesterone receptor (PR) status; and timing and sites of local recurrence or LRR and cause of death. Locoregional recurrence was the evaluation factor for radiotherapy. Institutional board approval and patient's consent for radiotherapy were obtained.

Treatment

All 544 T1–2 N1 breast cancer patients in this study received operation (MRM). Axillary lymph node dissection (at least Level I and II lymph node dissection) was applied to all patients. Adjuvant chemotherapy was recommended to all patients in this study, 2–4 weeks after surgery. The chemotherapy regimens consisted of many combinations, including the following: CMF: cyclophosphamide (600 mg/m^2 body surface area), methotrexate (40 mg/m^2), and 5-fluorouracil (600 mg/m^2); CAF/CEF: cyclophosphamide (500 mg/m^2), doxorubicin (50 mg/m^2) or epirubicin (70 mg/m^2), and 5-fluorouracil (500 mg/m^2); A-CMF: doxorubicin (75 mg/m^2), then cyclophosphamide (600 mg/m^2), methotrexate (60 mg/m^2), and 5-fluorouracil (600 mg/m^2); AC-T: doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2), then paclitaxel (175 mg/m^2); and ATC: doxorubicin (80 mg/m^2), paclitaxel (200 mg/m^2), and cyclophosphamide (800 mg/m^2). The chemotherapy regimen was chosen by the medical oncologists who reviewed the patients on the basis of prognostic factors, such as young age, high nuclear grade, negative ER and PR status, and with prominent LVI (positive LVI).

Postmastectomy radiotherapy was applied with external-beam irradiation 46–50 Gy to the chest wall, internal mammary, and supraclavicular area. The axilla was not included in the PMRT field. Part of Level III of axilla may be included in the field of PMRT for the supraclavicular area. From our previous experience (data not shown), LRR was higher in patients with the following factors: age <40 years, tumor size >2 cm, ER (-) status, LVI (+) status, with extracapsular lymph node invasion and higher nuclear grades (2 or 3). If the T1–2 N1 breast cancer patients had three or more of the above risk factors, PMRT was suggested.

Five-year adjuvant endocrine therapy (with tamoxifen 20 mg/d) was given to patients with positive ER or PR status after chemotherapy and/or radiotherapy completion or 2–4 weeks after surgery if no chemotherapy or radiotherapy was given.

Follow-up

All patients were followed and had their office visits and physical examinations every 3 months for the first 2 years, every 6 months for the third through fifth years, and annually after 5 years. Chest X-ray was performed every 6 months for the first 5 years and then annually, and liver sonography annually. Locoregional recurrence was defined as a tissue-proven lesion in one of the following sites: ipsilateral chest wall, axilla, supraclavicular fossa, and internal mammary chain.

Statistical analysis

Continuous variables were compared using the two-sample Student's t test, whereas categoric variables were compared using Pearson's χ^2 tests or Fisher's exact test (if the patient number was <5). Univariate and multivariate analyses were used to determine prognostic factors. Kaplan-Meier plots and the log–rank test were used to assess the association of treatment group in terms of overall survival and disease-free survival. All p values reported are two-sided. Overall survival was calculated as the time from surgery to death; all deaths regardless of cause were counted as events; patients who were still alive were censored at the date of last contact. Disease-free survival was calculated as the time from surgery to recurrence or death resulting from any cause, whichever occurred first. Patients who were alive without recurrence were classified as censored observations at the time of last follow-up for disease-free survival. Statistical analyses were performed using SAS 9.1.3 statistical software (SAS Institute, Cary, NC).

RESULTS

Clinicopathologic characteristics of the study population

Among the 544 T1–2 N1 breast cancer patients shown in Table 1, mean age at diagnosis was 49.5 years (median, 48 years; range, 26–88 years). Fifty-five percent of patients were younger than 50 years. The majority of these patients had tumor size between 2 and 5 cm (307 of 544, 56.4%). The mean number of dissected axillary lymph nodes was 20 (range, 7–60). Approximately half of the patients (280 of 544, 51.5%) had one axillary lymph node metastasis and poorly differentiated tumors (Grade 3) (288 of 544, 53.4%). Among interpretable cases (some missing cases were excluded), 69.9% (377 of 539) of the whole cohort were ER (+), 64% (345 of 539) were PR (+), and 28% (122 of 436) were Her-2/Neu overexpressed. Most of the patients received systemic chemotherapy (430 of 544, 79%). Radiotherapy was applied to approximately 30% of these patients with T1–2 N1 breast cancer. Endocrine therapy was administered to 72% of patients (392 of 544). Approximately 33% of patients (188 of 544) received systemic chemotherapy and endocrine therapy. One hundred eight (19.9%) of 544 patients received surgery, adjuvant chemotherapy, adjuvant radiotherapy, and endocrine therapy. Eighteen (3.3%) of 544 patients received surgery only and no systemic therapy or radiotherapy.

Predictive factors for LRR in T1–2 N1 breast cancer patients

With a median follow-up of 40.3 months (mean, 57 months; range, 2–178 months), 74 patients died (13.6%).

Table 1. Patient, tumor, and treatment characteristics

Characteristic	*n*	%
Age group (y)		
<35	43	7.9
5–49	260	47.8
50–59	130	23.9
60–69	81	14.9
≥70	30	5.5
Tumor size (cm)		
<0.5	9	1.7
0.5–1	21	3.9
>1–2	207	38
>2–5	307	56.4
Pathology type		
Ductal cancer	492	90.4
Lobular cancer	12	2.2
Others	40	7.4
No. of positive nodes		
1	280	51.5
2	158	29.0
3	106	19.5
Nuclear grade		
1	61	11.3
2	190	35.3
3	288	53.4
Unknown	5	
Estrogen receptor status		
Negative	162	30.1
Positive	377	69.9
Unknown	5	
Progesterone receptor status		
Negative	194	36.0
Positive	345	64.0
Unknown	5	
Her 2/Neu		
Not overexpressed	314	72.0
Overexpressed	122	28.0
Unknown	108	
Lymphovascular invasion		
Absent	225	42.7
Focal	167	31.7
Prominent	135	25.6
Unknown	17	
Chemotherapy		
Not proposed	114	21.0
Proposed	430	79.0
Radiotherapy		
Not proposed	383	70.4
Proposed	161	29.6
Endocrine therapy		
Not proposed	152	27.9
Proposed	392	72.1

Locoregional recurrence happened in 40 (7.4%) of 544 T1–2 N1 patients. The sites of LRR were the chest wall in 28 patients, axilla in 10 patients, supraclavicular area in 14 patients, and internal mammary area in 13 patients. Among 10 axilla-recurrent patients, only 1 patient received PMRT. Twenty patients had LRR at more than one side. The interval between operation and the occurrence of LRR ranged from 5 to 107 months (median, 18.9 months). Distant metastasis occurred in 25 (62.5%) of 40 LRR patients, including lung, liver, bone, and brain metastasis.

Table 2. Characteristics of patients according to locoregional recurrence

	Locoregional recurrence		
Characteristic	No	Yes	*p*
Age (y)			0.031
<40	103	14	
≥40	401	26	
Tumor size			0.14
T1	224	13	
T2	280	27	
Nuclear grade*			0.04
1, 2	239	12	
3	261	27	
Estrogen receptor status*			0.001
Negative	141	21	
Positive	358	19	
Progesterone receptor status*			0.12
Negative	175	19	
Positive	324	21	
Her-2/Neu*			0.17
Not overexpressed	295	19	
Overexpressed	110	12	
LVI*			0.003
Negative	372	20	
Positive	118	17	
Radiotherapy			0.0015
Not proposed	346	37	
Proposed	158	3	
Chemotherapy			0.37
Not proposed	108	6	
Proposed	396	34	
Endocrine therapy			0.08
Not proposed	136	16	
Proposed	368	24	

Abbreviation: LVI = lymphovascular invasion.
* With missing data.

We evaluated the LRR in different subgroups of T1–2 N1 breast cancer patients according to clinicopathologic characteristics (Table 2). On univariate analysis, LRR occurred more frequently in ER (-) patients (21 of 162, 13%) than in ER (+) patients (19 of 377, 5%) (p = 0.001), prominent LVI (defined as positive LVI) patients (17 of 135, 12.6%) than in LVI absence and focal patients (20 of 392, 5.1%) (p = 0.003), and in nuclear Grade 3 patients (27 of 288, 9.4%) than in nuclear Grade 1 or 2 patients (12 of 251, 4.8%) (p = 0.04). Radiotherapy reduced the LRR from 9.7% (37 of 383) to 1.9% (3 of 161) (p = 0.0015), but systemic chemotherapy and endocrine therapy did not reduce LRR in our series.

On multivariate Cox regression analysis, we found that ER status (hazard ratio [HR] = 5.1) and LVI (HR = 2.5) were the prognostic factors for locoregional disease-free survival in these 544 T1–2 N1 breast cancer patients (Table 3).

LRR in different T1–2 N1 breast cancer patients treated with or without PMRT

We analyzed LRR in T1–2 N1 breast cancer patient subgroups with or without PMRT (Table 4). Radiotherapy can

Table 3. Multivariate analysis of predictors for locoregional recurrence in 544 patients with T1 or T2 tumors and one to three positive nodes treated with or without adjuvant postmastectomy radiotherapy

Factor	Hazard ratio	95% confidence interval
Age ≥40 vs. <40 y	0.604	0.304–1.202
Nuclear Grade 1, 2 vs. 3	1.003	0.46–2.188
Estrogen receptor negative vs. positive	4.764	1.812–12.522
Progesterone receptor negative vs. positive	0.641	0.265–1.55
LVI positive vs. negative	2.129	1.066–4.251
T2 vs. T1	1.88	0.966–3.661

Abbreviation: LVI = lymphovascular invasion.

reduce LRR (from 13 of 66 [19.7%] to 1 of 51 [2.9%]) in patients aged <40 years. Radiotherapy decreased LRR (from 13% to 2.1%) in patients with high nuclear grade. For ER (-) breast cancer patients, radiotherapy reduced LRR from 18.3% to 3.5%. For PR (-) patients, radiotherapy lowered LRR from 13.3% to 3%. In PR (+) patients, radiotherapy reduced LRR from 7.9% to 1.1%. For LVI (+) breast cancer patients, radiotherapy can reduce LRR from 16.7% to 4.4%.

Outcome in T1–2 N1 breast cancer patients according to ER and LVI status, treated with or without PMRT

We further analyzed the radiotherapy effect for LRR and outcome for T1–2 N1 breast cancer patients according to LVI and ER status by recursive partitioning analysis (Fig. 1). We found ER status to be the most powerful determinant of LRR. For ER (+) patients, PMRT reduced LRR from 5.7% (15 of 265) to 1% (1 of 100) and increased the 5-year LRR-free survival rate from 93.9% to 98.7% ($p = 0.14$). For ER (-) and LVI (-) patients, PMRT can reduce the LRR from 11.7% (9 of 77) to 0 (0 of 40) and increase the 5-year LRR-free survival rate from 85.5% to 100% ($p = 0.09$). There were 41 ER (-) and LVI (+) patients (7.5% of 544) in our series. In these patients, radiotherapy can reduce the LRR from 40% (10 of 25 LRR without radiotherapy) to 12.5% (2 of 16 LRR with radiotherapy) and increase the 5-year LRR-free survival rate from 53% to 86.7% ($p = 0.038$). The LRR was 5.2% (25 of 482 patients) in the other patient group, which included ER (+) and ER (-) LVI (-) patients. The 1-, 3-, and 5-year LRR disease-free survival rates were 93.3%, 86.7%, and 86.7%, respectively, in the ER (-) LVI (+) with radiotherapy group; 68.3%, 53%, and 53% in the ER (-) LVI (+) without radiotherapy group; and 99.8%, 97.1%, and 93.7% in other patient group ($p < 0.0001$) (Fig. 2). The 1-, 3-, and 5-year overall survival rates were 100%, 87.1%, and 87.1%, respectively, in the ER (-) LVI (+) with radiotherapy group; 88%, 58.3%, and 43.7% in the ER (-) LVI (+) without radiotherapy group; and 98.6%, 94.7%, and 88.7% in the other patient group ($p < 0.0001$) (Fig. 3).

DISCUSSION

We previously reported (17) that age <40 years, T2 classification, tumor size ≥3 cm, ER (-) status, LVI (+) status, and

Table 4. Characteristics of locoregional recurrence according to radiotherapy

Characteristic	Radiotherapy	Locoregional recurrence: No	Locoregional recurrence: Yes	*p*
Age (y)				
<40	No RT	53	13	0.003
	RT	50	1	
≥40 y/o	No RT	293	24	0.03
	RT	108	2	
Tumor size				
T1	No RT	161	11	0.17
	RT	63	2	
T2	No RT	185	26	0.001
	RT	95	1	
Nuclear grade*				
1, 2	No RT	175	11	0.11
	RT	64	1	
3	No RT	167	25	0.001
	RT	94	2	
Estrogen receptor status*				
Negative	No RT	85	19	0.004
	RT	56	2	
Positive	No RT	258	18	0.017
	RT	100	1	
Progesterone receptor status*				
Negative	No RT	111	17	0.014
	RT	64	2	
Positive	No RT	232	20	0.009
	RT	92	1	
Her-2/Neu*				
Not overexpressed	No RT	202	17	0.031
	RT	93	2	
Overexpressed	No RT	71	11	0.043
	RT	39	1	
LVI*				
Negative	No RT	260	19	0.008
	RT	112	1	
Positive	No RT	75	15	0.028
	RT	43	2	

Abbreviations: LVI = lymphovascular invasion; RT = radiotherapy.
* With missing data.

no tamoxifen therapy are the risk factors for LRR of postmastectomy patients with one to three positive axillary lymph nodes without adjuvant radiotherapy. From the present study, we further confirm that PMRT can reduce LRR and increase survival in T1–2 N1 breast cancer patients with ER (-) and LVI (+) status.

The incidence of LRR of breast cancer in patients treated with MRM has been reported to be between 5% and 40% (17–19). For patients with one to three positive axillary lymph nodes, the baseline LRR risk without PMRT is controversial. For T1–2 N1 breast cancer patients, the LRR rates were reported between 8% and 23% when no adjuvant radiotherapy was performed (11–13, 17, 20, 21). The 10-year LRR rate without PMRT was approximately 30% in Danish trials (22, 23) and approximately 20% in the British Columbia trial (24, 25). The 10-year LRR rate reported in pattern-of-failure

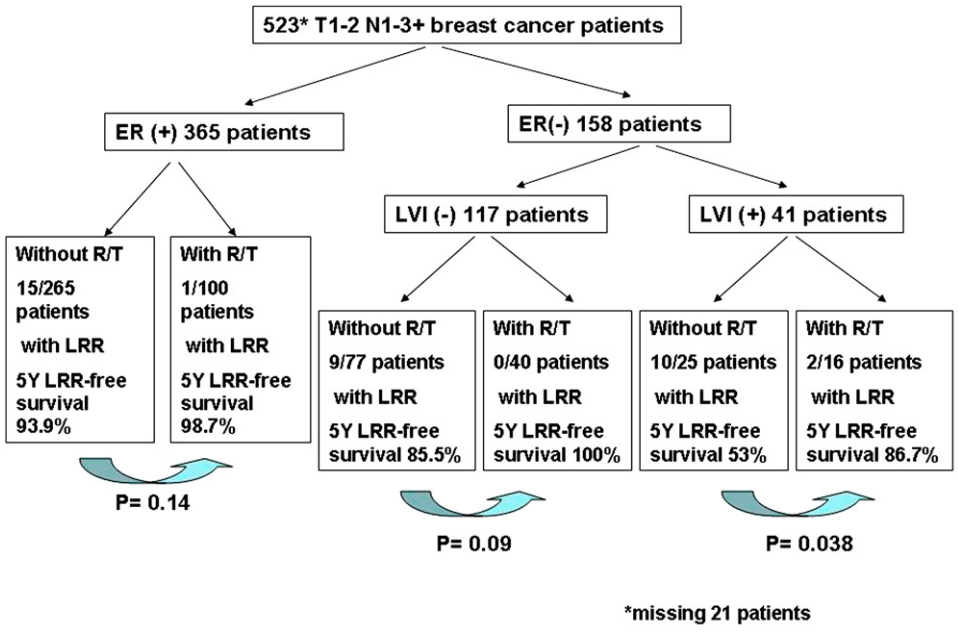

Fig. 1. Results of recursive partitioning analysis of 523 patients (missing 21 patients) treated according to the estrogen receptor (ER) and lymphovascular invasion (LVI) status and with or without postmastectomy radiation. R/T = radiotherapy; LRR = locoregional recurrence.

studies of patients enrolled in adjuvant systemic trials without radiation has been reported to be between 12% and 20% (13, 21, 26, 27). In our series, LRR is approximately 9.7% (37 of 383) in T1–2 N1 breast cancer patients without PMRT. The discrepancies in the reported baseline LRR risk have been attributed to variations in the extent of axillary surgery, yielding different numbers of excised nodes (6, 20, 28). The reason for our lower rate of LRR may be the aggressive axillary clearance. The mean number of dissected axillary lymph nodes was 20 (range, 7–60) in our series. The use of PMRT is largely accepted for preventing of LRR, except for patients at low risk for LRR (i.e., ≤10% at 10 years) (10). From our data, application of PMRT routinely to all T1–2 N1 breast cancer patients is not indicated, and only a subgroup of patients [such as ER (-) LVI (+) patients] may benefit from PMRT.

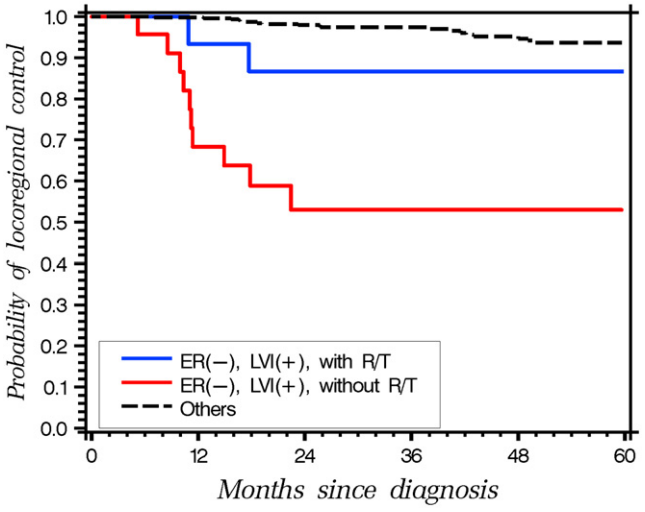

Fig. 2. Locoregional control in patients with T1 or T2 tumors with one to three positive lymph nodes according to estrogen receptor (ER) and lymphovascular invasion (LVI) status and treated with or without radiotherapy (R/T). The rates of freedom from LRR at 5 years were 86.7% of ER (-) LVI (+) patients treated with radiotherapy (n = 16), 53% of ER (-) LVI (+) patients treated without radiotherapy (n = 25), and 93.7% of other patients [ER (+) or ER (-) LVI (-)] treated with or without radiotherapy (n = 482) ($p < 0.0001$).

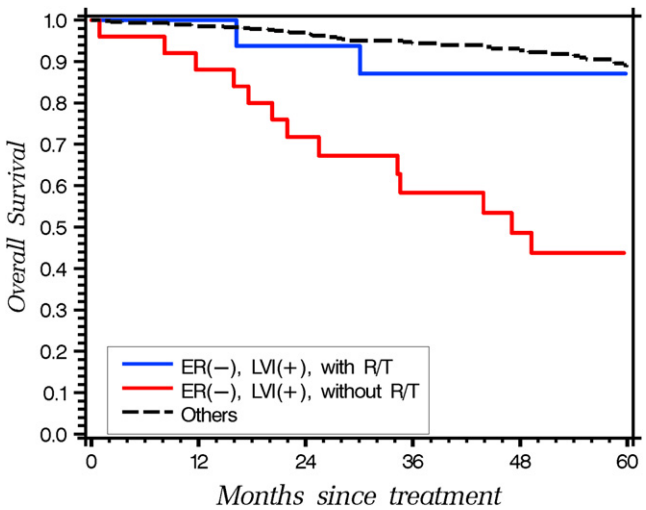

Fig. 3. Overall survival in patients with T1 or T2 tumors with one to three positive lymph nodes according to estrogen receptor (ER) and lymphovascular invasion (LVI) status and treated with or without radiotherapy (R/T). The 5-year overall survival rates were 87.1% in the ER (-) LVI (+) with radiotherapy group (n = 16), 43.7% in the ER (-) LVI (+) without radiotherapy group (n = 25), and 88.7% in the other patients [ER (+) or ER (-) LVI (-)] (n = 482) ($p < 0.0001$).

Several series have demonstrated that the number of involved axillary lymph nodes and primary tumor size are important predictors of LRR after mastectomy and adjuvant systemic therapy in breast cancer patients (19, 27, 29). Some pathologic findings, such as LVI, the presence of multifocal or multicentric disease, involvement of the skin or nipple, pectoralis fascia invasion, and the presence of close or positive surgical margins, increase rates of postmastectomy recurrence (26). For T1–2 N1 breast cancer patients, other groups have reported that no radiation, close or positive surgical margins, gross extracapsular extension, dissection of fewer than 10 nodes, young age, LVI, nuclear grade, ER status, tumor size, and medial tumor location were associated with higher LRR (9, 15, 17, 30, 31). On univariate analysis, we found that high nuclear grade ($p = 0.04$), ER (-) status ($p = 0.001$), presence of LVI ($p = 0.003$), and no radiotherapy ($p = 0.0015$) were associated with a significantly higher rate of LRR in T1–2 N1 breast cancer patients. Negative ER status (HR = 5.1) and presence of LVI (HR = 2.5) were the risk factors for LRR with statistical significance on multivariate analysis. Woodward *et al*. (15) reported that significant predictors of LRR for patients treated with PMRT were higher number and ≥20% positive nodes, larger tumor size, LVI, and ER (-) disease. They also found ER (-) status to be the most powerful discriminator of LRR in irradiated patients. Using recursive partitioning analysis, we found ER status to be the most powerful discriminator of LRR after postmastectomy radiation, followed by presence of LVI in ER (-) status.

Improved locoregional control can also reduce breast cancer mortality (11, 32). Approximately three out of four LRR occur within 5 years after the initial treatment (7). Data from the Early Breast Cancer Trialists' Collaborative Group show that a gain in local control obtained with postoperative radiotherapy of 20% at 5 years will result in an improvement in overall survival at 15 years of 5% (11). However, this meta-analysis also showed that there was a significant excess incidence of contralateral breast cancer and a significant increase in non–breast cancer mortality in irradiated women. The mortality was mainly from heart disease and lung cancer. It may relate to regional (internal mammary) rather than local (chest wall) irradiation. Cardiac irradiation can result in significant pathologic damage to the heart and produce multiple clinical complications, including coronary artery disease, pericarditis, cardiomyopathy, valvular heart disease, and conduction disturbance (33). The number of cardiac-related events will likely decrease with increased use of CT planning of radiation tangents. There is growing level of evidence that PMRT should be offered to all patients with involved axillary nodes (7), but we should be careful about the complications of PMRT.

We acknowledge several limitations to the present study, including its retrospective nature. The sample size of the cohort with irradiated T1–2 N1 breast cancer patients was small and may have limited statistical power. The strategy of systemic chemotherapy in each case was different depending on different medical oncologists in this retrospective study. This may affect the LRR and overall survival in different patient subgroups. Several well-designed large, prospective, randomized clinical trials, such as European Organization for Research and Treatment of Cancer 22922/10925 and National Institute of Canada Clinical Trials Group MA20, aim to determine the advantages and side effects of PMRT for early-stage breast cancer patients (7). Until these results become available, we suggest that PMRT should be applied to those patients with ER (-) and LVI (+) status in T1–2 N1 breast cancer.

In conclusion, PMRT can reduce LRR and increase survival in T1–2 N1 breast cancer patients with ER (-) and LVI (+) status.

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