Table 1 Characteristics in all patients

Characteristics	All patients $n = 1994$	Locoregional recurrence $n = 306$ (15.3%)	Univariate Log-rank p
Median follow-up time	112 months (0-231)		
Age (%)			
Average 52.11 ± 10.42			0.014
≦49	885	121 (13.7)	
≧50	1109	185 (16.7)	
T-stage (%)			
T1	306	25 (8.2)	<0.001
T2	1255	166 (13.2)	
T3	401	109 (27.2)	
Unknown	32	6 (18.8)	
Lymphatic invasions			
ly−	1090	105 (9.6)	<0.001
ly+	508	82 (16.1)	
ly++	396	119 (30.1)	
Number of positive lymph nodes (%)			
1−3	1086	91 (8.4)	<0.001
4−9	480	81 (16.9)	
≧10	428	134 (31.3)	
ER*(%)			
Positive	671	75 (11.2)	<0.001
Negative	1167	197 (16.9)	
Unknown	156	34 (21.8)	
PgR* (%)			
Positive	921	115 (12.5)	
Negative	904	155 (17.1)	
Unknown	169	36 (21.3)	
Histology (%)			
IDC	1839	277 (15.1)	0.193
Mucinous Ca	19	4 (21.0)	
Lobular Ca	93	20 (21.5)	
Other	43	5 (11.6)	

Abbreviations: IDC = invasive ductal carcinoma; % = locoregional recurrence rate.

* Refenece because these were valued at Enzyme Immuno Assay.

on any slides; ly+ (low ly), where one to nine areas of ly were detected; and ly++ (high ly), where 10 or more areas of ly were detected. LRR was compared among patients classified by ly grade to evaluate the relationship between LRR and ly status. Based on the results of this evaluation, we sought to identify the subgroup of patients for whom PMRT might be indicated among all patients with one to three positive nodes (n1−3 group).

Locoregional recurrence was defined as local recurrence, including isolated relapse in the regional lymph node areas (axillary, supraclavicular, infraclavicular, or parasternal). In assessing locoregional recurrences, we ensured that they were first relapses. Patients with only node-negative tumors have been shown to have low LRRs in earlier studies (16, 17) and were therefore excluded.

Statistical analyses were undertaken using Dr SPSS II for Windows Version 11.0.1 J (SPSS Japan, Tokyo, Japan). LRRs were estimated by the Kaplan-Meier method and compared with a two-sided log rank test. Multivariate analysis was performed using the Cox proportional hazards model for four risk factors of locoregional recurrence: ly grade, number of positive lymph nodes, tumor size, and patient age. Intergroup comparisons were carried out using χ^2 test or Fisher's exact test (Excel; Microsoft). All p values were two-tailed; a p value of 0.05 or less was considered significant. In the present study, complete anonymity of patients and medical record numbers was maintained.

Results

The median follow-up period for the 1,994 patients was 112 months, with locoregional recurrence in 306 (15.3%) patients. Larger tumor size, more extensive ly, and greater number of positive lymph nodes were associated with higher LRRs, with LRR surpassing 30% in patients with ly++ or 10 or more positive nodes. Univariate analysis revealed that T stage, ly status, and number of positive nodes were particularly strong risk factors ($p < 0.001$) (Table 1). Although significant difference was detected for ER status and PgR status, those receptor status data lacked accuracy, as they were reference data obtained from enzyme immunoassay and were "unknown" (*i.e.*, not available or not evaluable) for approximately 8% of patients (ER "unknown," 156/1,994 patients; PgR "unknown," 169/1,994 patients).

The Kaplan-Meier estimated LRRs for all patients with positive lymph nodes were compared among different ly status groups; the log rank test detected a significant difference ($p < 0.001$), indicating a particularly high LRR for the ly++ subgroup (Fig. 1). Multivariate analysis incorporating the number of positive nodes, T stage, and age showed that ly++ status ($p < 0.001$) was as strong a factor for chest wall recurrence and LRR as number of positive nodes, T3 stage, and age (≥50) (Table 2). Regarding overall survival (OS), having a higher number of positive lymph nodes, which was associated with higher risk of distant metastasis, was the strongest risk factor, while ly++ status fell short of showing significant difference (relative risk [RR] = 1.182, 95% confidence interval [CI], 0.974−1.436, $p = 0.091$). When the group with $n \geq 10$ was excluded, however, ly status was found to affect survival (RR = 1.430; 95% CI, 1.100−1.859; $p = 0.008$) (Table 2).

Data in Fig 2 were prepared and examined. For both the n1−3 group and the n ≥4 group, the ly++ level was associated with a very high LRR, with the ly++ subgroup of n1−3 patients showing a higher LRR than the ly− subgroups of n ≥4 patients. Limited to the n1−3 group, multivariate analysis identified ly++ status as the sole risk factor for chest wall recurrence (RR = 3.018; 95% CI, 1.472−6.190; $p = 0.003$) and locoregional recurrence (RR = 3.132; 95% CI, 1.753−5.596; $p < 0.001$) (Table 2). As for OS, the presence of three positive lymph nodes was the strongest risk factor (RR = 1.780; 95% CI, 1.303−2.432; $p < 0.001$), rendering ly status a less influential factor for the n1−3 group (RR = 1.231; 95% CI, 0.815−1.857; $p = 0.323$) (Table 2).

Discussion

The utility of PMRT has been established, including evidence of the Danish clinical trial in 1997 (2) and meta-analysis by the Early Breast Cancer Trialists' Collaborative Group in 2005 (7). In the United States and Europe, the value of PMRT is a time-proven treatment. In Japan, postoperative irradiation tended to remain uncommon for some time, in response to very low LRRs reported

Table 2 Cox regression analysis of chest wall recurrence free survival, locoregional recurrence free survival and overall survival in all patients with positive lymph nodes and patients with positive lymph nodes (1–3)

	Chest wall recurrence free survival			Locoregional recurrence free survival			Overall survival			Overall survival Patients with node-positive (lto9) (N.1566)*		
All patients (n = 1994)	p value	RR	95% CI	p value	RR	95% CI	p value	RR	95% CI	p value	RR	95% CI
ly												
ly−		1.000			1.000			1.000			1.000	
ly+	0.002	1.731	1.215–2.464	0.000	1.703	1.246–2.295	0.462	1.072	0.890–1.291	0.821	0.973	0.771–1.229
ly++	0.000	2.548	1.795–3.617	0.000	2.665	1.989–3.570	0.091	1.182	0.974–1.436	0.008	1.430	1.100–1.859
Number of positive nodes												
1–3		1.000			1.000			1.000			1.000	
4–9	0.000	2.325	0.953–2.489	0.000	2.157	1.608–2.892	0.000	2.605	1.323–1.947	0.000	1.551	1.274–1.888
≥10	0.000	2.028	1.394–2.950	0.000	2.206	1.622–2.999	0.000	3.322	2.737–4.033	–	–	–
T-stage												
T1		1.000			1–000			1.000			1.000	
T2	0.137	1.491	0.881–2.523	0.116	1.405	0.920–2.145	0.651	1.056	0.834–1.336	0.551	1.087	0.826–1.433
T3	0.000	2.968	1.712–5.145	0.000	2.778	1.780–4.336	0.000	1.743	1.347–2.255	0.000	1.901	1.380–2.618
Age												
≤49		1.000			1.000			1.000			1.000	
≥50	0.000	1.712	1.289–2.275	0.000	1.616	1.276–2.046	0.000	1.352	1.162–1.572	0.022	1.254	1.033–1.523
Patients with node-positive (l to 3) (n = 1086)												
ly												
ly−		1.000			1.000			1.000				
ly+	0.040	1.845	1.027–3.314	0.032	1.701	1.047–2.765	0.565	0.913	0.671–1.243			
ly++	0.003	3.018	1.472–6.190	0.000	3.132	1.753–5.596	0.323	1.231	0.815–1857			
Number of positive nodes												
n:1		1.000			1.000			1.000				
n:2	0.609	1.171	0.639–2.146	0.078	1.540	0.953–2.489	0.688	1.064	0.787–1.437			
n:3	0.096	1.724	0.909–3.270	0.078	1.644	0.946–2.856	0.000	1.780	1.303–2.432			
T-stage												
T1		1.000			1.000			1.000				
T2	0.859	1.063	0.543–2.078	0.847	0.949	0.558–1.614	0.899	1.021	0.741–1.406			
T3	0.236	1.679	0.712–3.958	0.295	1.454	0.722–2.927	0.112	1.411	0.923–2.157			
Age												
≤49		1.000			1.000			1.000				
≥50	0.043	1740	1.019–2.972	0.052	1.538	0.996–2.373	0.025	1339	1.036–1.730			

Abbreviation: RR = Relative risk.

* Overall survival in patients with positive lymph nodes (1–9).

Table 3 LRR (locoregional recurrence rate) in patients not received PMRT on other reports

Authors	Journal	No. of patients	Follow up	N1-3 LRR	$n \geqq 4$ LRR
Overgaard M *et al* (1997)	N Engl J Med	1708	10y	30%	42%
Ragaz J *et al* (1997)	N Engl J Med	318	15y	33%	46%
Overgaard M *et al* (1999)	Lancet	1375	10y	31%	46%
Taghian A *et al* (2004)	J Clin Oncol	5758	10y	8.1%	15.5–18.8%
Ragaz J *et al* (2005)	J Natl Cancer Inst	318	20y	21%	41%
Clarke M *et al* (2005) (EBCTCG)	Lancet	8500	5y	16%	26%
Overgaard M *et al* (2007)	Radiother Oncol	1152	15y	27%	51%
Present study (2010)		1994	10y	8.4%	23.7%

in the US (12, 18). In the 1990s at our hospital, PMRT was not a standard therapy; therefore, we had a number of breast cancer cases untreated with radiotherapy even in the presence of four or more positive lymph nodes. During that period, against such a backdrop, institutional review board approval was not necessarily required for implementation of PMRT in clinical research.

Our study yielded three major findings. First, for patients with positive nodes, ly++ status was associated with an LRR as great as that of the number of positive nodes (Fig. 1, Table 2). Second, within the n1–3 group, ly++ status was associated with particularly high LRR, indicating the need for consideration of PMRT for this subgroup (Table 2). Third, PMRT might not have to be done positively, as the risk of locoregional recurrence is low in the n1–3 group if tumor diameter is 5 cm or more, not ly++ (Table 2). Some previous studies reported that PMRT needed to be considered for breast cancer patients involving tumors >5 cm (13, 14, 19). The present study showed that breast tumors >5 cm affected locoregional recurrence only when patients with four or more positive lymph nodes were included (Table 2). In the n1–3 group, locoregional recurrence was unaffected by T stage (Table 2).

Regarding patient age, the present study showed that age 50 years or older was associated with higher LRRs, while conflicting information is available: some studies found only a nonsignificant relationship between age and LRR (17, 18), whereas others reported stronger association of younger ages with higher LRRs (2, 16). We performed additional analyses of LRR in the 35-year-old and younger group and the 35-year-old and older group. In that analysis, contrary to the aforementioned analysis of patients below or above 50 years old, we found that the younger age group exhibited higher LRR but not with a significant difference (log-rank, $p = 0.1391$; multivariate analysis, RR = 0.951; 95% CI, 0.596–1.517; $p = 0.833$).

We undertook multivariate analysis incorporating ER and PgR status. In an analysis of all patients, each receptor status was a risk factor for both chest wall recurrence and locoregional recurrence but was not as strong a factor as other risk factors for those recurrences. For the n1–3 group, ER and PgR status were not risk factors. ly++ status was shown to be the sole risk factor for locoregional recurrence (Table 4). As mentioned above, however, these findings should be followed only as reference data. In this multivariate analysis, ER and PgR status had only minimal impact on the finding that ly++ was the risk factor for LRR. Given the results of this analysis, it seems possible to predict that ER-negative and PgR-negative status are associated with higher LRRs.

The definition of ly used in the present study may raise a question concerning the applicability of our findings to cases at other institutions. Because the criteria of ly status vary depending on institution, differences in the criteria need to be taken into consideration. Another possible point of consideration is that in the present study, the entire tissue from each postmastectomy patient was not subjected to histologic examination, which could have affected the number of sections in which ly status was detected. It is our view, however, that the use of entire dissected tissue for ly status assessment would not have resulted in any significant discrepancy from the results (frequencies of ly–, ly+, and ly++) we obtained, because ly were found in peritumoral lesions as usual (20).

According to earlier reports, LRR seems to differ widely among reported series of patients. For example, LRR varies from 8.1% to 33% in postmastectomy patients with one to three positive nodes who were assessed in several studies to which we referred (Table 3). While time to treatment from diagnosis may affect LRR in certain cases, or other undetected selection factors may also account for the reported LRR in this series, the quality of surgery is deemed critical in any case. The LRR of 8.4% at our hospital appears to reflect satisfactorily high quality of surgery offered here.

Regarding a threshold for the indication of PMRT, it should be judged based on treatment outcomes at each site as LRR varies substantially among institutions (Table 3). Data in Fig. 2 show that at our hospital, when the presence of four or more positive lymph nodes is assumed to be the indication for PMRT as a standard treatment, the n1–3 plus ly++ subgroup will be able to indicate PMRT. Therefore, because the LRR of the n1–3 plus ly++ subgroup was 16.3% at 10 years, the threshold for PMRT indication in our hospital is around 15%.

Because PMRT was initially developed as a local therapy for the chest wall, it may be more rational to discuss this therapy in the context of chest wall recurrence, rather than locoregional recurrence, which includes isolated relapse in the regional lymph node areas. In the present study we based our assessment mainly on LRR, as in many earlier studies. We also performed a secondary assessment that was based on chest wall recurrence and found tendencies similar to those in the LRR-based evaluation (Table 2): the ly++ status in all patients was a risk factor for chest wall recurrence (RR = 2.548; 95% CI, 1.795–3.617; $p < 0.001$); and that of the n1–3 group was also similar (RR = 3.018; 95% CI, 1.472–6.190; $p = 0.003$).

Regarding OS, multivariate analysis showed that ly++ status only nonsignificantly affected OS in the entire node-positive patient group, and the n1–3 group, as opposed to the n1–9 group, for which ly++ as well as higher number of positive lymph nodes, was found to be a significant factor in OS (Table 2). It is suspected that the $n \geq 10$ group has a poorer prognosis because of problems other than locoregional recurrences, distant metastases, for example, and that many cases in the n1–9 group are associated

Table 4 Cox regression analysis including ER and PgR of chest wall recurrence free survival locoregional recurrence free survival and overall survival in all patients and patients with positive lymph nodes (1–3)

All patients (n = 1994)	Chest wall recurrence free survival			Locoregional recurrence free survival			Overall survival		
	p value	RR	95% CI	p value	RR	95% CI	p value	RR	95% CI
ly									
ly−		1.000			1.000			1.000	
ly+	0.028	1.555	1.050–2.305	0.004	1.614	1.169–2.228	0.406	1.086	0.894–1.320
ly++	0.001	1.971	1.341–2.897	0.000	2.217	1.616–3.042	0.066	1.208	0.988–1.477
Number of positive nodes									
1–3		1000			1.000			1.000	
4–9	0.000	2.770	1.798–4.269	0.000	2.167	1.545–3.040	0.000	1.670	1.362–2.047
≧10	0.000	4.300	2.771–6.672	0.000	3.677	2.611–5.179	0.000	3.421	2.788–4.197
T-stage									
T1		1.000			1.000			1.000	
T2	0.110	1.711	0.886–3.303	0.127	1.457	0.899–2.362	0.980	1.003	0.783–1.285
T3	0.001	3.242	1.647–6.381	0.000	2.675	1.616–4.428	0.000	1.636	1.249–2.141
Age									
≦49		1.000			1.000			1.000	
≧50	0.008	1.531	1.115–2.100	0.002	1.503	1.163–1.941	0.001	1.300	1.107–1.526
ER									
Positive		1.000			1.000			1.000	
Negative	0.019	1.559	1.077–2.256	0.025	1.393	1.042–1.862	0.426	1.074	0.901–1.279
PgR									
Positive		1.000			1.000			1.000	
Negative	0.201	1.240	0.892–1.723	0.164	1.207	0.926–1.575	0.002	1.302	1.103–1.536
Patients with node-positive (1 to 3) (n = 1086)									
ly									
ly−		1.000			1.000			1.000	
ly+	0.088	1.925	0.906–4.090	0.061	1.722	0.976–3.040	0.731	0.943	0.677–1.315
ly++	0.139	2.168	0.779–6.035	0.005	2.762	1.359–5.616	0.411	1.210	0.769–1.904
Number of positive nodes									
n:1		1.000			1.000			1.000	
n:2	0.526	0.760	0.324–1.778	0.263	1.384	0.784–2.444	0.991	0.998	0.716–1.391
n:3	0.303	1.528	0.682–3.421	0.245	1.471	0.767–2.818	0.000	1.813	1.302–2.524
T-stage									
T1		1.000			1.000			1.000	
T2	0.750	1.159	0.468–2.875	0.781	0.914	0.487–1.716	0.629	0.919	0.653–1.294
T3	0.187	2.095	0.698–6.285	0.369	1.448	0.645–3.248	0.265	1.292	0.823–2.028
Age									
≦49		1.000			1.000			1.000	
≧50	0.494	1.269	0.641–2.511	0.428	1.225	0.741–2.025	0.085	1.274	0.967–1.679
ER									
Positive		1.000			1.000			1.000	
Negative	0.464	1.316	0.631–2.741	0.574	1.164	0.686–1.973	0.610	0.928	0.697–1.236
PgR									
Positive		1.000			1.000			1.000	
Negative	0.806	1.092	0.541–2.205	0.455	0.819	0.485–1.383	0.768	1.044	0.784–1.390

Abbrevations: ER = Estrogen receptor; RR = relative risk; PgR = progesterone receptor. ER, PgR evaluated at Enzyme Immuno Assay.

with worse survival rates due to locoregional recurrences. In the n1–3 group alike, survival rates can be decreased similarly, owing to locoregional recurrences; it may be that difference in the OS were not detected because of insufficient length of follow-up and inadequate number of events analyzed. Data are available to indicate that locoregional recurrences eventually affected OS in the n1–3 group (5, 11). Extension of follow-up may result in the detection of differences in OS.

Our results showed LRR was strongly associated with ly status as well as with the number of positive lymph nodes or T stage, with ly++ being an especially strong risk factor; LRR was notably high in ly++ patients in the n1–3 group; whereas in the n1–3 group, T3 was not a risk factor for LRR, even with tumor size of 5cm or more.

The hypothesis that PMRT targets and eradicates or reduces residual tumor cells in regional lymphatics needs to be validated in

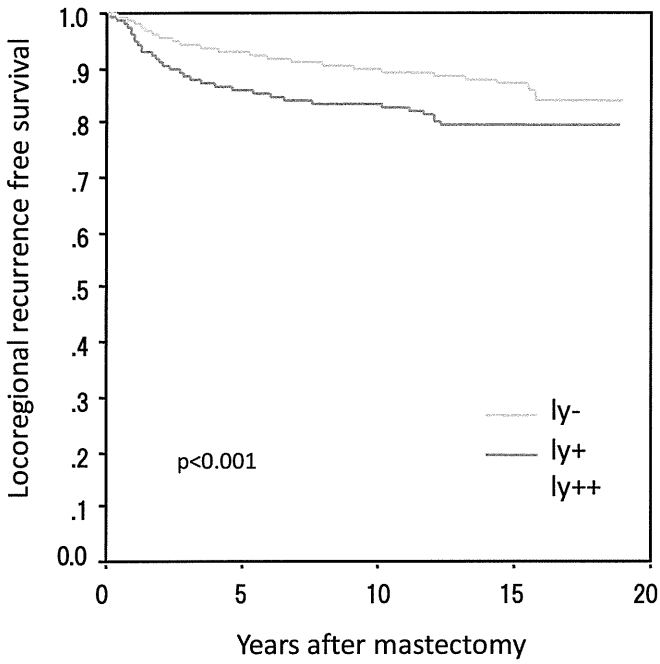

Fig. 1. Kaplan-Meier locoregional recurrence-free survival is shown according to ly status in all patients with positive lymph nodes.

clinical studies with patients assigned to either a PMRT group or a non-PMRT group based on ly status.

Conclusions

Postmastectomy patients with one to three positive lymph nodes showed a particularly high LRR in the presence of extensive ly. This subgroup seems to require local therapy regimens similar to those for patients with four or more positive nodes and should be considered for the indication of PMRT. In postmastectomy patients with one to three positive lymph nodes, because the risk of locoregional recurrence is low even if it is T3, not ly++, PMRT could be considered negatively.

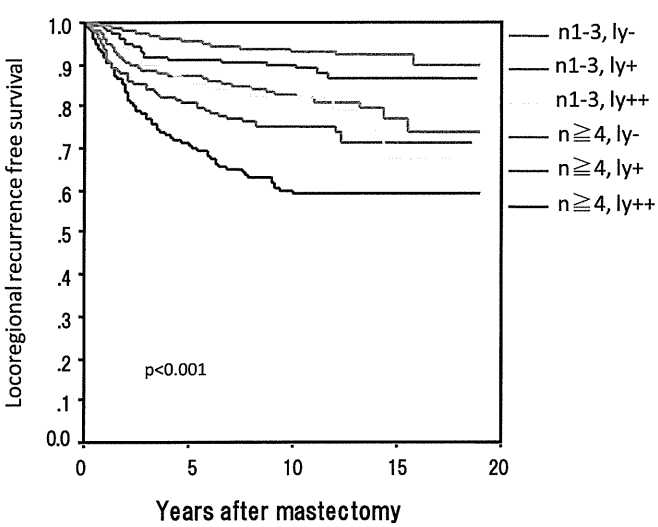

Fig. 2. Kaplan-Meier locoregional recurrence-free survival is shown according to each group in node-positive patients includingly status.

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