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Original Article

Effectiveness of Postoperative Irradiation in Patients with cN0 Early Breast Cancer Treated with Sentinel Lymph Node Surgery

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To evaluate the effectiveness of postoperative irradiation (POI) for patients with cN0 early breast cancer, we retrospectively analyzed the cases of 650 consecutive breast cancer patients who underwent sentinel lymph node (SLN)-guided surgery (2005-2022) at our hospital. In this cohort, 53% (278/521) of the patients who underwent breast conservative surgery (BCS) and 96% (124/129) of those treated with mastectomy did not receive POI. The patients who underwent BCS were treated with POI using opposing tangential field irradiation. A false negative (FN) SLN was retrospectively defined as a negative metastasis in SLN plus positive recurrence in the axillary lymph nodes. Recurrence was detected in 83 patients. A logistic regression analysis revealed that the nuclear grade (odds ratio [OR] 1.69), POI (OR 0.41), and postoperative hormone therapy (OR 0.40) were each significantly related to recurrence. The 26.1% (12/46) FN rate of the non-POI patients decreased to 5.8% (1/17) compared to those treated with POI. The rate of axillary recurrence was significantly lower in the POI group (0.4%) versus the non-POI group (2.7%) ($p=0.0355$). The rate of locoregional recurrence was also significantly lower in the POI group (2.0%) versus the non-POI group (13.4%) ($p<0.0001$). No significant difference was observed in the rate of distant recurrence between the POI (4.0%) and non-POI (3.3%) ($p=0.831$) groups. These results indicated that the postoperative opposing tangential field irradiation of conserved breast tissue inhibited recurrence in the axillary lymph nodes.

Key words: breast cancer, postoperative irradiation, radiation therapy, sentinel lymph nodes, recurrence

Surgical and postoperative treatments for early breast cancer with no clinically detectable lymph node metastasis are being standardized based on the findings of many pivotal studies [1-6]. Partial mastectomy with a sentinel lymph node (SLN) biopsy (SLNB) is generally performed for patients with T1-T2 early breast cancer and clinically negative lymph node metastasis. When SLNs are positive for metastasis, if there are ≤2 metastatic lymph nodes, the axillary lymph node dissection (ALN) may be omitted and patients may be effectively treated using radiation therapy alone [7]. After chemotherapy, patients with hormone-positive invasive breast cancer receive postoperative hormone therapy, if necessary, for 5-10 years [8, 9].

However, since irradiation is associated with adverse effects including dermatitis, fatigue, and radiation pneumonitis that may occur during or several months after the completion of radiation therapy after breast surgery, some patients decline to undergo postoperative radiation therapy. The inhibitory effects of radiation therapy on postoperative locoregional recurrence were demonstrated in an overview of randomized trials [10], but a limited amount of information is currently available on the actual clinical usefulness of radiation therapy. The possibility of avoiding postoperative radi-

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ation therapy has been investigated [11,12]. Indeed, several now-retired surgeons at our hospital did not recommend postoperative radiation therapy for their patients based on their professional opinion or when patients refused irradiation, and thus many patients with early-stage breast cancer were not treated with postoperative radiation therapy.

We conducted the present study to clarify the clinical outcomes of patients with cN0 early breast cancer who underwent sentinel lymph node (SLN)-guided surgery at our hospital followed or not followed by irradiation. We also investigated the inhibitory effects of postoperative radiotherapy on regional lymph node recurrence in this cohort.

Patients and Methods

A total of 650 consecutive breast cancer patients who underwent an SLN-guided mastectomy at our hospital during the period 2005-2022 and were followed up for ≥2 years were enrolled in this retrospective study. The following operative procedures were performed: partial mastectomy (n=521 patients), total mastectomy (n=96), skin-sparing mastectomy (n=6), and nipple sparing mastectomy (n=27). In this cohort, 53% (278/521) of the patients underwent breast conservative surgery and 96% (124/129) of those treated with a mastectomy did not receive postoperative irradiation. Of the 541 patients with estrogen receptor (ER)-positive breast cancer (83.2% of all patients), 77% received hormone therapy. The date of recurrence was recorded in the patients' medical records.

We categorized recurrences as (*i*) axillary lymph node (LN) or internal mammary LN, (*ii*) axillary LN + conserved breast, (*iii*) axillary LN + Other(s), (*iv*) conserved breast (including skin), or (*v*) other organ(s) (distant), *i.e.*, brain, bone, liver, lung, others.

SLN dissection was performed using blue dye. In most of the patients, 5 mL of indigocarmine was injected into the subareolar or periareolar region 10-15 min before surgery. We examined one maximum cut surface of each SLN in the present study, which is the standard procedure at our hospital.

A rapid pathological diagnosis was conducted using frozen SLN sections in 132 of the 650 patients, and ALN dissection was performed on 10 patients because their SLN results were positive for metastasis. In the remaining 518 patients, SLNs were examined after surgery using formalin-fixed paraffin-embedded (FFPE) sections. Among the 32 patients with one or more metastasis-positive SLNs, three underwent ALN dissection as a second procedure on the postoperative day.

The accuracy of the SLN dissection was retrospectively defined as follows: *True positive:* positive metastasis in stained LNs including nearby dissected LNs harvested as SLN (SLNs). *False negative (retrospective):* negative metastasis in SLNs plus positive recurrence in the axillary or internal mammary lymph nodes, without recurrence conserved breast tissue during the follow-up period. Thirteen patients with recurrence in axillary (regional) LNs were classified as false negatives: recurrence in axillary LN(s) (n=10), internal mammary LN(s) (n=1), axillary LN(s) and bone (n=1), or axillary LN(s) and kidney(n=1). *False positive:* positive metastasis in SLN(s) on frozen sections but not FFPE sections in the same patient. *True negative (retrospective):* negative metastasis in SLNs and in principle negative recurrence in the axillary or internal mammary LNs during the follow-up period. Three patients with recurrence both axillary LN(s) and conserved breast tissue were classified as true negatives, because of the possibility of LN metastasis from the recurrent conserved breast cancer.

Statistical analyses. Overall survival curves for the two groups were plotted using the Kaplan-Meier method. Probability (p)-values < 0.05 by Fisher's exact test, the unpaired t-test, logistic regression, and the Log-rank test were considered significant. The statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [13]. More precisely, EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

This study was approved by the Ethics Committee of Oomoto Hospital in accord with the ethical standards laid down in the 1964 Declaration of Helsinki and all subsequent revisions.

Results

Clinicopathological factors of the patients with negative or positive recurrence. Recurrence was detected in 83 (12.76%) of the 650 patients. Table 1 summarizes the clinicopathological factors of the

Table 1 Clinicopathological factors of patients with negative and positive recurrence

Factor	Group	Negative recurrence	Positive recurrence	*P*-value
n		567	83	
Sex (%)	Female	565 (99.6)	83 (100.0)	1
	Male	2 (0.4)	0 (0.0)	
Age	Mean (SD) Years	61.4 (12.1)	59.4 (14.3)	0.168
Body mass index	BMI (SD)	22.6 (4.3)	22.6 (4.3)	0.987
Side (%)	Right	283 (49.9)	50 (60.2)	0.099
	Left	284 (50.1)	33 (39.8)	
Subsites (%)	Nipple	3 (0.5)	0 (0.0)	
	Central portion	48 (8.5)	7 (8.4)	
	Upper-inner quadrant	131 (23.1)	18 (21.7)	
	Lower-outer quadrant	51 (9.0)	7 (8.4)	
	Upper-outer quadrant	262 (46.2)	34 (41.0)	
	Lower-outer quadrant	69 (12.2)	16 (19.3)	
	Axillary tail	3 (0.5)	1 (1.2)	
Tumor (%)	Tis	90 (15.9)	15 (18.1)	0.007
	T1	409 (72.1)	47 (56.6)	
	T2	66 (11.6)	21 (25.3)	
	T3	2 (0.4)	0 (0.0)	
Operative procedure (%)	BP	457 (80.6)	64 (77.1)	
	BT	89 (15.7)	7 (8.4)	
	BT (SSM)	4 (0.7)	2 (2.4)	
	BT (NSM)	17 (3.0)	10 (12.0)	
LN metastasis (%)	pN0	524 (92.4)	76 (91.6)	0.825
	pN1	43 (7.6)	7 (8.4)	
ER (%)	Positive	475 (83.9)	66 (79.5)	0.343
	Negative	91 (16.1)	17 (20.5)	
PgR (%)	Positive	421 (74.5)	56 (67.5)	0.183
	Negative	144 (25.5)	27 (32.5)	
HER2 (%)	Positive	70 (14.7)	13 (19.1)	0.366
	Negative	407 (85.3)	55 (80.9)	
Nuclear grade (%)	I	341 (71.5)	36 (52.9)	0.006
	II	99 (20.8)	21 (30.9)	
	III	37 (7.8)	11 (16.2)	
Resected margin cancer involvement (%)	Positive	112 (19.8)	28 (33.7)	0.006
	Negative	455 (80.2)	55 (66.3)	
Chemotherapy (postoperative) (%)	Yes	145 (25.6)	28 (33.7)	0.143
	No	455 (80.2)	55 (66.3)	
Radiation therapy (postoperative) (%)	Yes	233 (41.1)	15 (18.1)	<0.001
	No	334 (58.9)	68 (81.9)	
Hormone therapy (postoperative) (%)	Yes	383 (67.5)	40 (48.2)	0.001
	No	184 (32.5)	43 (51.8)	
Location of Recurrence (%)	No recurrence	567 (100.0)	0 (0.0)	
	Axillary or internal mammary LN		12 (14.5)	
	Axillary LN + conserved breast		4 (4.8)	
	Axillary LN + Others		1 (1.2)	
	Conserved breast (including skin)		42 (50.6)	
	Other organs (distant)		24 (28.9)	
	Brain		0	
	Bone		10	
	Liver		6	
	Lung		7	
	Other		1	
Observation period	Mean (SD) Years	7.1 (2.9)	8.4 (3.2)	<0.001

BP, partial mastectomy; BT, total mastectomy; BT (SSM), skin sparing mastectomy; BT (NSM), nipple sparing mastectomy; LN, lymph nodes.

patients with negative or positive recurrence. A univariate analysis revealed significant differences in the following factors: the tumor status, nuclear grade, resected margin cancer involvement, radiation therapy (postoperative), and hormone therapy (postoperative).

The logistic regression analysis (with backward stepwise selection) showed that the nuclear grade (nuclear grade 1 to 2-3, odds ratio [OR] 1.69), postoperative radiation therapy (yes or no, OR 0.41), and postoperative hormone therapy (yes or no, OR 0.40) were significant factors related to positive recurrence after SLN-guided surgery for early breast cancer (Table 2).

Among the 541 patients with ER-positive breast cancer, the positive recurrence rate was significantly lower in the patients who received postoperative hormonal therapy (9.1%, 38/417) compared to those who did not (22.6%, 28/124) ($p=0.00015$).

Retrospective assessment of SLN dissection according to postoperative radiotherapy. The false negative rate was lower in the patients who underwent postoperative irradiation (POI) (5.8%, 1/17) compared to those who did not (26.1%, 12/46) ($p=0.0939$) (Table 3).

The type of recurrence in relation to postoperative irradiation. Table 4 shows the incidence of the types of recurrence with or without POI. The rate of recurrence in the axillary (regional) LNs was significantly lower in the POI group (0.4%) versus the non-POI group (2.7%) ($p=0.0355$). The rate of locoregional recurrence was also significantly lower in the POI group (2.0%) versus the no POI group (13.4%) ($p<0.0001$). No significant difference was observed in the rate of distant recurrence between the POI (4.0%) and non-POI (3.3%) groups ($p=0.831$).

Disease-free survival curves and overall survival curves according to irradiation. The 10-year disease-free survival rate was significantly lower in the non-POI group (79.6%) compared to those treated with POI (90.3%) ($p=0.00136$) (Fig. 1), but the 10-year overall survival rate was similar in the non-POI (97.3%) and POI (96.3%) groups (Fig. 2).

Table 2 Logistic regression analysis of positive recurrence (stepwise selection)

Factor	Odds ratio	*P*-value
(Intercept)	0.15 (0.06–0.39)	0.00007
NG1.NG2-3	1.69 (0.95–2.99)	0.0373
Radiation therapy (postoperative)	0.41 (0.22–0.76)	0.00314
Hormone therapy (postoperative)	0.40 (0.23–0.68)	0.00083

Table 3 Retrospective assessment of sentinel lymph node dissection according to postoperative irradiation

Irradiation (postoperative)	Yes	No
True positive	16 (6.5)	34 (8.5)
False negative (retrospective)	1 (0.4)	12 (3.0)
False positive	1 (0.4)	0
True negative (retrospective)	230 (92.7)	356 (88.6)

Fisher's test *p*-value 0.027.

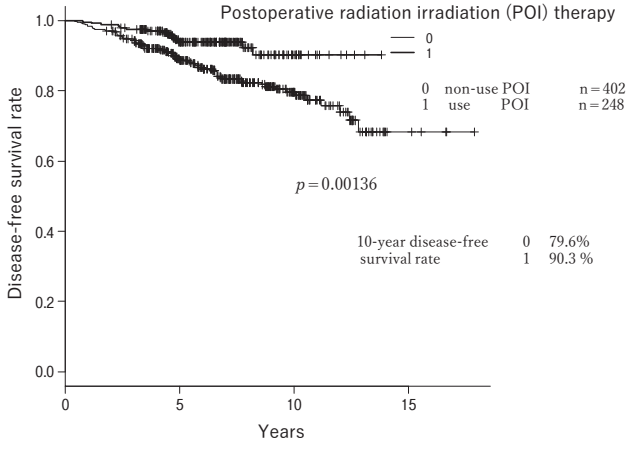

Fig. 1 The disease-free survival rate according to the use or non-use of postoperative irradiation (POI) therapy.

Table 4 Type of recurrence in relation to postoperative irradiation

Irradiation (postoperative)	Yes	No	
Number	248	402	
Axillary (regional) recurrence*	1 (0.4%)	11 (2.7%)*	$p=0.0355$
Locoregional recurrence	5 (2.0%)	54 (13.4%)	$p<0.0001$
Distant recurrence	10 (4.0%)	14 (3.3%)	$p=0.831$

*including recurrence in one internal mammary lymph node.

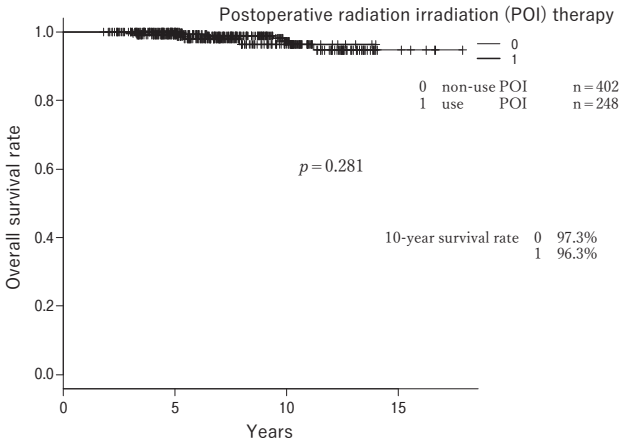

Fig. 2 The overall survival rate according to the use or non-use of POI.

Discussion

In this retrospective cohort, 53% (278/521) of the patients who underwent breast conservative surgery and 96% (124/129) of those who underwent a mastectomy did not receive postoperative irradiation (POI). Of the 541 patients with ER-positive breast cancer (83.2% of all patients), 77% received hormone therapy. The logistic regression analysis revealed that the nuclear grade (OR 1.69), use of POI (OR 0.41), and use of postoperative hormone therapy (OR 0.40) were significant factors related to positive recurrence after SLN-guided surgery for early breast cancer.

The nuclear grade was the only preoperative risk factor for recurrence identified in this study, and it was also one of the significant prognostic factors reported in other investigations [14, 15].

A meta-analysis revealed that adjuvant endocrine therapy with tamoxifen for positive hormone receptors reduced the 15-year breast cancer recurrence and mortality rates; the recurrence rate decreased (RR 0.53) in the first 10 years [8]. Another study demonstrated that the recurrence and mortality rates were approx. 30% and 15% lower, respectively, when aromatase inhibitors were used compared to the use of tamoxifen [9]. Our present analyses showed that the recurrence rate was 22.6% in the ER-positive breast cancer patients who did not receive postoperative hormone therapy, thus demonstrating the importance of this treatment.

A large-scale meta-analysis of the effects of POI concluded that "After breast-conserving surgery, radiotherapy to the conserved breast remaining halves the rate at which the disease recurs and reduces the breast cancer death rate by about a sixth." [16].

In the present study's relatively small cohort, we specifically focused on the inhibitory effects of POI on lymph node recurrence. This study is the first to employ a methodology for a retrospective assessment of the accuracy of SLNs at first operation. In this assessment, the false negative rate without POI was as high as 26%. In a meta-analysis of 69 studies [17], the false negative rates ranged between 0% and 29%, with the generally acceptable false negative rate at ≤ 10%. Our false negative rate was very high, but it decreased to 6% when POI was performed, which we attributed to the effects of irradiation. We suggest the following reasons for this high false negative rate: (*i*) the dye-only method used; (*ii*) the dye injection site was limited to the subareolar region [18] and thus was not injected around the tumor; and (*iii*) unlike many other large-scale studies that followed the ASCO guidelines [19] of the lymph node search width not being thicker than 2 mm, we examined one maximum cut surface of each SLN in the present study. Based on these results, we are now searching for 2-mm-width of SLNs. A more preferable method may be to use radiocolloid technetium [18], but this is not available at our hospital and many other institutions. We are also planning to use indocyanine green fluorescence [20] instead of indigocarmine as the dye and inject it into the subareolar region and around the tumor.

Our findings once again highlight the increased risk of local recurrence after surgery in patients who are not treated with postoperative radiation therapy. The rate of locoregional recurrence was as high as 13.4% in our patients with breast cancer without irradiation and 2.0% in those treated with irradiation. Significant differences were thus observed in the locoregional recurrence and 10-year disease-free survival rates (90.3 and 79.6%) between the patients treated or not treated with POI. However, no significant differences were noted in the distant recurrence (4.0 and 3.3%) or 10-year overall survival (96.3 and 97.3%) rates between patients treated or not treated with POI. These results are consistent with previous findings [11].

The rate of recurrence in the axillary (regional) lymph nodes was 0.4% (1/248) in the present patients who received POI, which is consistent with reported in the Z0011 [21], AMAROS [4], OTOASOR [5], and

SENOMAC [6] trials at 0.5%, 1.19%, 0.43%, and 0.4%, respectively.

Our analyses revealed that the application of POI significantly suppressed axillary (regional) lymph node recurrence in addition to local recurrence.

In this cohort, POI after breast conservation surgery consisted only of opposing tangential field irradiation of the conserved breast, and it did not specifically include axillary or supraclavicular nodal radiation.

In the Z0011 trial [3, 21], only opposing tangential field irradiation of the conserved breast was performed, similar to the present cohort. In the AMAROS trial [4], in addition to irradiation of the conserved breast, "Axillary radiotherapy included the contents of all three levels of the axilla and the medial part of the supraclavicular fossa." In the OTOASOR trial [5], whole breast plus regional nodal irradiation (RNI, 3 levels of the axilla and the supraclavicular fossa) was performed. In the recent SENOMAC trial [6], whole-breast irradiation and radiation therapy to the regional lymph nodes was conducted in accord with the national guidelines of each participating institution, which led to a high percentage of patients receiving nodal field irradiation.

We observed a low recurrence rate (0.4%) in the patients who received POI, and as described in the Z0011 trial [21, 22], this suggests that when opposing tangential field irradiation is performed, most of the level I axilla and part of the level II axilla are included in the irradiation field. However, in the NCIC Clinical Trails Group MA. 20 trial [23], which compared whole-breast irradiation with whole-breast irradiation + RNI in high-risk patients with positive or negative SLN results who underwent an ALN dissection, the disease-free survival was significantly longer in the patients for whom RNI was added compared to those for whom only whole-breast irradiation was performed. The addition of RNI is thus beneficial for patients who are at a high risk of recurrence.

Based on the results of our analyses, we suggest that postoperative irradiation therapy of conserved breast is necessary for patients who undergo a partial mastectomy with an SLNB regardless of the presence or absence of SLN metastasis. Moreover, axillary recurrence was detected in five of the 129 patients who underwent a total mastectomy. The breakdown of clinical factors in these five patients was as follows: T2 (n = 4 patients) and T1 (n = 1); nuclear grade III (n = 4) and I (n = 1); ER-positive (n = 4) and ER-negative (n = 1); postoperative chemotherapy, yes (n = 3) and no (n = 2); postoperative hormone therapy, yes (n = 3) and no (n = 2); no radiation therapy (postoperative); BT(nipple-sparing mastectomy) (n = 4) and BT (n = 1). Therefore, for high risk patients who undergo a total mastectomy and an SLNB (for example, for patients with stage T2-3 and nuclear grade III breast cancer), postoperative radiation therapy may be considered in order to prevent axillary lymph node recurrence.

According to the Japanese guidelines, postoperative radiation therapy after a mastectomy is indicated for patients with lymph node metastasis or ≥ T3 cancer. We will follow these guidelines and use our present findings as a reference to consider the suitability of radiation therapy for each individual patient.

In conclusion, postoperative opposing tangential field irradiation of the conserved breast inhibited axillary (regional) lymph node recurrence as well as local recurrence in patients with cN0 early breast cancer.

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