

Effectiveness of Neck Lymph Node Dissection for Breast Cancer Patients with Isolated Supraclavicular Nodal Recurrence

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Background: Isolated supraclavicular nodal recurrence (ISNR) is a rare form of recurrence and is regarded as a precursor of a poor prognosis. The surgical removal of ISNR is typically neglected in multimodal therapy.

Patients and Methods: Among 5279 consecutive patients who underwent primary breast cancer surgery at a single hospital between 1977 and 2011, INSR was observed in 77 patients (1.5%). Two INSR patients whose fate was unknown were excluded from the present analysis. Therefore, 75 patients with ISNR treated with (n=58) or without (n=17) neck lymph node dissection (NLND) were evaluated.

Results: Overall survival rates were significantly higher in the NLND group than in the no-NLND group ($p = 0.0027$). Five- and 10-year survival rates were 64.8 and 47.2%, respectively, in the NLND group and 35.3 and 11.7%, respectively, in the no-NLND group. In a Cox proportional hazards regression (stepwise selection) analysis in which the time interval from the primary surgery to ISNR was excluded, the T factor (T2, 3 vs. T1, hazard ratio 2.26) and NLND (yes vs. no, hazard ratio 0.41) were identified as significant factors affecting OS rates. When the time interval from primary surgery to ISNR was included, the interval from the primary surgery to ISNR (>2 years) and NLND were identified as significant factors for long OS (HR 0.21, HR 0.39).

Conclusion: ISNR is type of a loco-regional recurrence, and NLND needs to be considered in multimodal (radiation and systemic chemo-) therapy.

Keywords: breast cancer, isolated supraclavicular nodal recurrence, neck lymph node dissection

Introduction

Breast cancer is the most common malignant disease and is characterized by simultaneous local progression and systemic general metastasis.

Supraclavicular lymph node metastasis (SNM) is one of the predictors of a poor prognosis. In the treatment of primary breast cancer, synchronous ipsilateral SNM is defined as M1 in the 5th edition of the American Joint Committee on Cancer (AJCC). Brito et al¹ showed that patients with isolated SNM had a better prognosis than those with distant metastasis; therefore, in 2002, the 6th staging guidelines of AJCC reclassified breast cancer with SNM to N3c and stage IIIC,² which is operable.

Isolated supraclavicular nodal recurrence (ISNR) is a rare form of recurrence and is regarded as a precursor of distant recurrence with a poor prognosis. The surgical removal of ISNR is generally neglected in multimodal therapy because it is categorized as a near systemic disease with inconsistent survival benefits from surgical treatment.

The Japanese Breast Cancer Guidelines³ has addressed the surgical resection of ISNR as a future research question, stating that “the surgical resection of supraclavicular lymph node recurrence is generally not recommended for ISNR”.

ISNR has recently been regarded as a type of regional nodal recurrence, including the axillary or internal mammary nodes, and is associated with favorable outcomes.^{4,5} However, few studies have investigated the outcomes of surgery for ISNR and long-term survival.^{4,6}



In our institute, we perform neck lymph node dissection (NLND) for breast cancer patients with ISNR. Therefore, we retrospectively investigated the effectiveness of NLND for these patients, with a focus on its impact on overall survival (OS).

Patients and Methods

Among 5279 consecutive patients who underwent primary breast surgery at Oomoto Hospital (No. 0111442, Medical Corporation Hospital, Okayama, Japan) between February 1977 and December 2011 (from the Oomoto Hospital Breast Cancer Database) using the database created by Yamamoto (one of the authors), INSR was observed in 77 patients (1.5%). Patients with metachronous isolated SNM within 6 months after the primary surgery or those with ISNR concomitant with local regional or distant recurrence were excluded from this study. In 77 patients, two INSR patients whose fate was unknown were excluded from the present analysis. Therefore, we retrospectively analyzed 75 patients with ISNR who detected from 6 months after the primary surgery.

Patients who underwent NLND for ISNR in addition to chemotherapy and/or radiation therapy (RT) were assigned to the NLND group (n=58), whereas those who received only chemotherapy and/or RT were assigned to the no-NLND group (n=17). NLND involved radical neck dissection in 45 patients and selective positive node dissection in 13. The decision of whether to perform NLND was dependent on the clinician's judgment and preference. OS was defined as the time from the date of the primary surgery to death or the last follow-up. The last follow-up was December 2024.

All statistical analyses were performed using 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).⁷ More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. OS curves and breast cancer-specific survival curves were plotted using the Kaplan-Meier method. *P*-values <0.05 by Fisher's exact test, the unpaired *t*-test, Log rank test, and Cox regression proportional hazards model were considered to be significant.

Results

Clinicopathological Factors in the NLND and No-NLND Groups

Table 1 shows clinicopathological factors in the NLND (n=58 patients) and no-NLND (n=17 patients) groups.

At the primary treatment for breast cancer, all patients were women with an average age of 52.7 years in the NLND group and 50.6 years in no-NLND group ($p = 0.419$). The mean number of positive resected axillary lymph nodes was 10.3 (minimum 0 - maximum 44) in the NLND group and 14.6 (0–56) in the no-NLND group ($p = 0.282$). Regarding treatments, 96.6, 62.1, and 0% of patients in the NLND group and 88.2, 64.7, and 0% in the no-NLND group received chemotherapy, hormone therapy, and RT, respectively.

The average time interval from the primary surgery to ISNR was 4.0 years in the NLND group and 2.8 years in the no-NLND group, with no significant difference ($p = 0.208$).

NLND involved radical neck dissection in 45 patients and selective positive nodes dissection in 13. The average number of positive cervical lymph nodes was 10.3, with 15.2 in the radical method and 2.8 in the selective method.

Chemotherapy, hormone therapy and RT were performed in 72.4, 56.9, and 81.0% of the patients in the NLND group and in 70.6, 70.6, and 88.2% of the patients in no-NLND group.

Univariate Analysis of Survival Rates (Log Rank Test) According to Clinical Factors in Patients with ISNR

Table 2 shows the results of a univariate analysis of survival rates (Log rank test) according to the clinical factors of patients with ISNR. In relation to the primary treatment for breast cancer, the T factor (T2, 3 vs. T1) and number of positive axillary lymph nodes (>10 vs. ≤10) were identified as significant factors affecting OS rates ($p = 0.0004$ and $p = 0.0009$, respectively), whereas postoperative adjuvant chemotherapy and hormone therapy were not.

The time interval from the primary surgery to ISNR was also identified as a significant factor affecting OS rates (≤2 years vs. >2 years, $p < 0.001$).



Table 1 Clinicopathological Factors in Patients with Isolated Supraclavicular Nodal Recurrence (ISNR) Treated with or without Neck Lymph Node Dissection (NLND)

Factor	Group	Neck Lymph Node Dissection (NLND)	No NLND	p-Value
n		58	17	
Sex (%)	Female	58 (100)	17 (100)	1
	Male	0	0	
Primary treatment for breast cancer				
Age	Mean (SD) Years	52.7 (8.7)	50.6 (13.0)	0.419
Side (%)	Right	27 (46.6)	7 (41.2)	0.419
	Left	31 (53.4)	10 (58.8)	
Subsites (%)	Nipple	4 (6.9)	1 (5.9)	
	Central portion	7 (12.1)	2 (11.8)	0.942
	Upper-inner quadrant	11 (19.0)	3 (17.6)	
	Lower-outer quadrant	2 (3.4)	1 (5.9)	
	Upper-outer quadrant	28 (48.3)	7 (41.2)	
Tumor (%)	Lower-outer quadrant	6 (10.3)	3 (17.6)	
	T1	27 (46.6)	4 (23.5)	0.113
	T2	20 (34.5)	11 (64.7)	
	T3	11 (19.0)	2 (11.8)	
Operative procedure (%)	BP	6 (10.3)	1 (5.9)	1
	BT	52 (89.7)	16 (94.1)	
Number of positive resected LN (Ax)	Mean (sd) Number (minimum -maximum)	10.3 (12.3) (0–44)	14.6 (17.4) (0–56)	0.282
ER (%)	Positive	29 (50.0)	7 (41.2)	0.819
	Negative	26 (44.8)	9 (52.9)	
	Unknown	3 (5.2)	1 (5.9)	
PR (%)	Positive	21 (36.2)	5 (29.4)	0.911
	Negative	32 (55.2)	11 (64.7)	
	Unknown	5 (8.6)	1 (5.9)	
HER2 (%)	Positive	3 (5.2)	2 (11.8)	0.394
	Negative	13 (22.4)	2 (11.8)	
	Unknown	42 (72.4)	13 (76.5)	
Chemotherapy (postoperative) (%)	Yes	56 (96.6)	15 (88.2)	0.219
	No	2 (3.4)	2 (3.4)	
Hormone therapy (postoperative) (%)	Yes	36 (62.1)	11 (64.7)	1
	No	22 (37.9)	6 (35.3)	

(Continued)

Table 1 (Continued).

Factor	Group	Neck Lymph Node Dissection (NLND)	No NLND	p-Value
Radiation therapy (postoperative) (%)	Yes	0	0	1
	No	58 (100)	17 (100)	
Time interval from the primary surgery to ISNR	Mean (SD) Years	4.0 (3.5)	2.8 (2.8)	0.208
	≤2 years	24 (41.4)	9 (52.9)	0.42
	>2 years	34 (58.6)	8 (47.1)	
Treatment for ISNR				
NLND (%)	Radical	45 (77.6)	0	1
	Selective positive LN dissection	13 (22.4)	0	
Number of positive cervical LN	Mean positive nodes (95% confidence interval)	10.3 (7.1–13.5)		
Radical	Mean (sd) positive nodes	15.2 (13.1)		0.001
Selective positive LN dissection	Mean (sd) positive nodes	2.8 (1.8)		
Chemotherapy (%)	Yes	42 (72.4)	12 (70.6)	1
	No	16 (27.6)	5 (29.4)	
Hormone therapy (%)	Yes	33 (56.9)	12 (70.6)	0.403
	No	25 (43.1)	5 (29.4)	
Radiation therapy (%)	Yes	47 (81.0)	15 (88.2)	0.72
	No	11 (19.0)	2 (11.8)	
Total observation period	Mean (SD) Years	9.0 (7.0)	5.0 (3.8)	0.025

Abbreviations: NLND, Neck lymph node dissection; ISNR, Isolated supraclavicular nodal recurrence; BP, Partial mastectomy; BT, Total mastectomy; LN, Lymph nodes; Ax, Axillary.

Table 2 Univariate Analysis of Survival Rates (Log-Rank Test) According to Clinical Factors in Patients with Isolated Supraclavicular Nodal Recurrence (ISNR)

Factor	Median Survival Time (Year)	p-value (Log-Rank Test)
Primary treatment for breast cancer		
T1 (n=31) vs. T2, 3 (n=44)	11.5 vs. 3.9	0.004
Positive lymph node (Ax) ≤10 (n=47) vs. >10 (n=28)	10.5 vs. 3.5	0.009
Time interval from the primary surgery to ISNR		
≤2 years (n=33) vs. >2 years (n=42)	2.8 vs 11.4	< 0.001
Treatment for ISNR		
Neck lymph node dissection (NLND) No (n=17) vs. yes (n=58)	3.5 vs. 7.2	0.003
Chemotherapy No (n=21) vs. Yes (n=54)	7.2 vs. 4.4	0.971
Hormone therapy No (n=30) vs. Yes (n=45)	6.4 vs. 6.9	0.475
Radiation therapy No (n=62) vs. Yes (n=13)	4.3 vs 6.9	0.493

Table 3 Cox proportional hazards regression (stepwise selection) analysis of overall survival rates of patients with isolated supraclavicular nodal recurrence (ISNR)

A Time interval from the primary surgery to ISNR excluded			
Factor		Hazard Ratio	p-value
T	T2, 3 vs T1	2.26 (1.28 - 4.01)	0.005
Neck lymph node dissection	Yes vs no	0.41 (0.22 - 0.75)	0.004
B Time interval from the primary surgery to ISNR included			
Factor		Hazard Ratio	p-value
Time interval from primary surgery to ISNR	≤2 years vs. >2 years	0.21 (0.12 - 0.37)	<0.0001
Neck lymph node dissection	No vs. Yes	0.39 (0.21 - 0.72)	0.0029

OS rates were significantly higher in the NLND group than in the no-NLND group ($p = 0.003$).

No significant differences were observed in the effects of chemotherapy, hormone therapy, or RT on the OS rate of ISNR patients.

Cox Proportional Hazards Regression (Stepwise Selection) Analysis of OS Rates of Patients with ISNR

When the time interval from the primary surgery to ISNR was excluded, the Cox proportional hazards regression (stepwise selection) analysis of the OS rates of patients with ISNR identified the T factor (T2, 3 vs. T1, hazard ratio 2.26) and NLND (yes vs. no, hazard ratio 0.41) as significant factors affecting the OS rate (Table 3).

When the time interval from the primary surgery to ISNR was included, the time interval from the primary surgery to ISNR (≤2 years vs. > 2 years, hazard ratio 0.21) and NLND (yes vs. no, hazard ratio 0.39) were identified as significant factors affecting OS rates (Table 3).

Cumulative Survival Curves of Patients with ISNR

Figure 1 shows the cumulative survival curves of patients with ISNR. OS rates were significantly higher in the NLND group than in the no-NLND group ($p = 0.0027$). Five- and 10-year survival rates were 64.8 and 47.2%, respectively, in the NLND group and 35.3 and 11.7%, respectively, in the no-NLND group.

Figure 2 shows the cumulative survival curves of patients with ISNR according to the method of NLND performed. Survival rates were higher with the selective positive node dissection than with radical neck dissection.

Figure 3 shows cumulative survival curves after recurrence in patients with ISNR. Five-year survival rates were 42.0% in the NLND group and 6.9% in the no-NLND group.

Discussion

The present study investigated the utility of NLND for patients with ISNR. Patients with ipsilateral SNM at or before the primary treatment are categorized as N3c and stage IIIC or M1, respectively. Therefore, ISNR is defined as local recurrence.

Previous studies reported the usefulness of RT as a treatment for ISNR,^{8–10} whereas few have demonstrated the utility of surgical treatment.^{4,6} The treatment of ISNR generally varies depending on whether RT is administered to the supraclavicular lymph nodes at the time of the initial treatment. During the study period (1977–2011), no patient received postoperative RT after the primary surgery in our hospital.

Since the incidence of ISNR is low at 0.5–2% (1.5% in the present study), the study period is typically long in many studies. In addition, with advances in anti-cancer drugs, such as the development of anti-HER2 drugs in 1998, survival

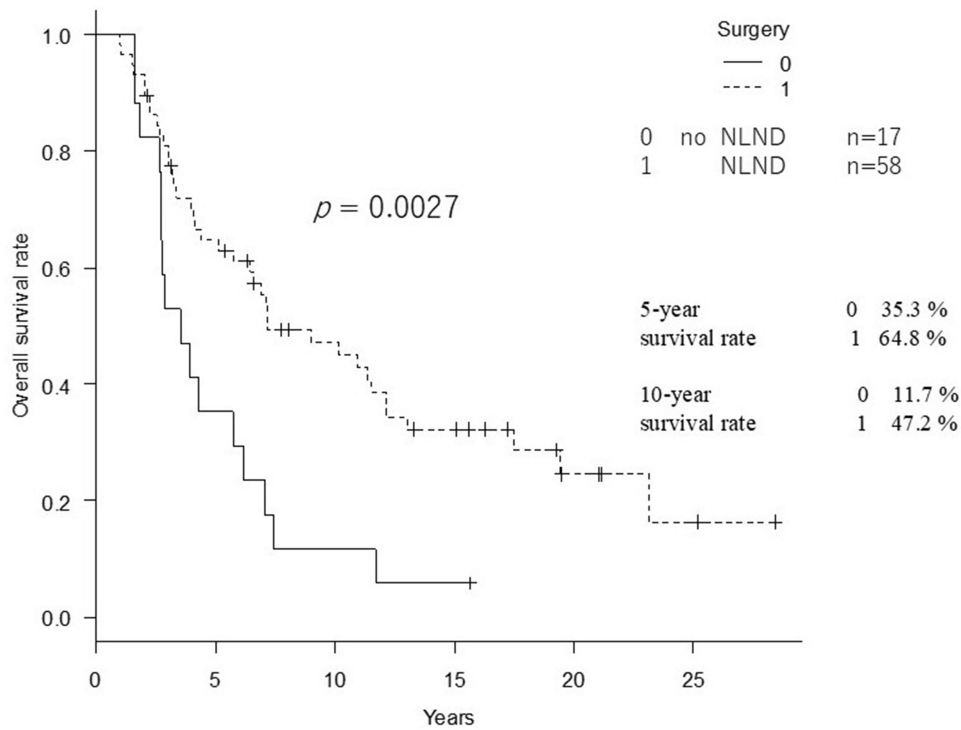


Figure 1 Cumulative survival curves of patients with Isolated supraclavicular nodal recurrence (ISNR) after primary surgery. OS rates were significantly higher in the NLND group than in the no-NLND group.

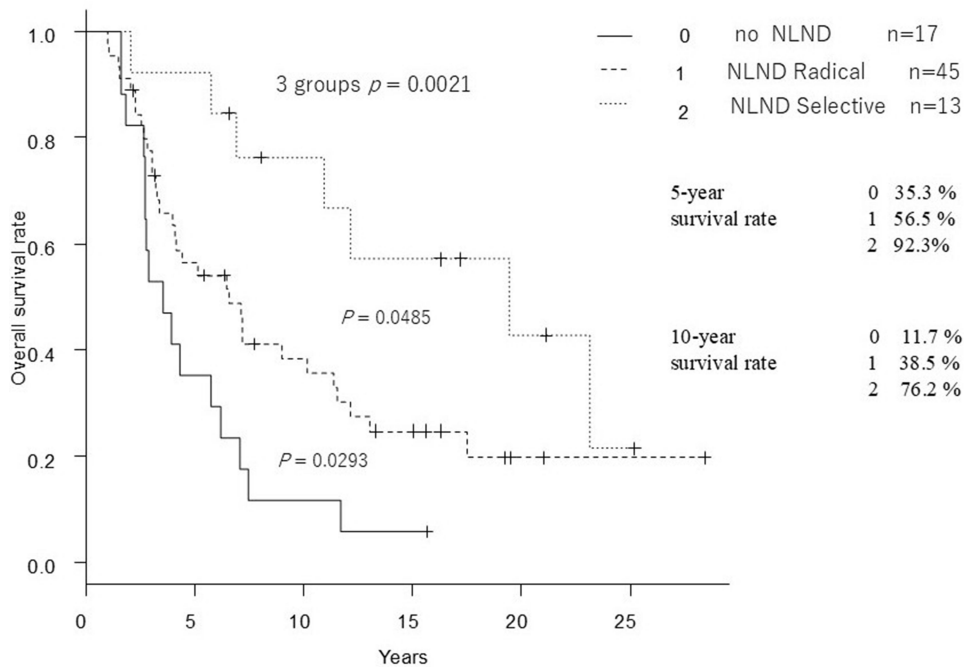


Figure 2 Cumulative survival curves of patients with ISNR after primary surgery according to the method of NLND performed. Survival rates were higher with the selective positive nodes dissection than with radical neck dissection.

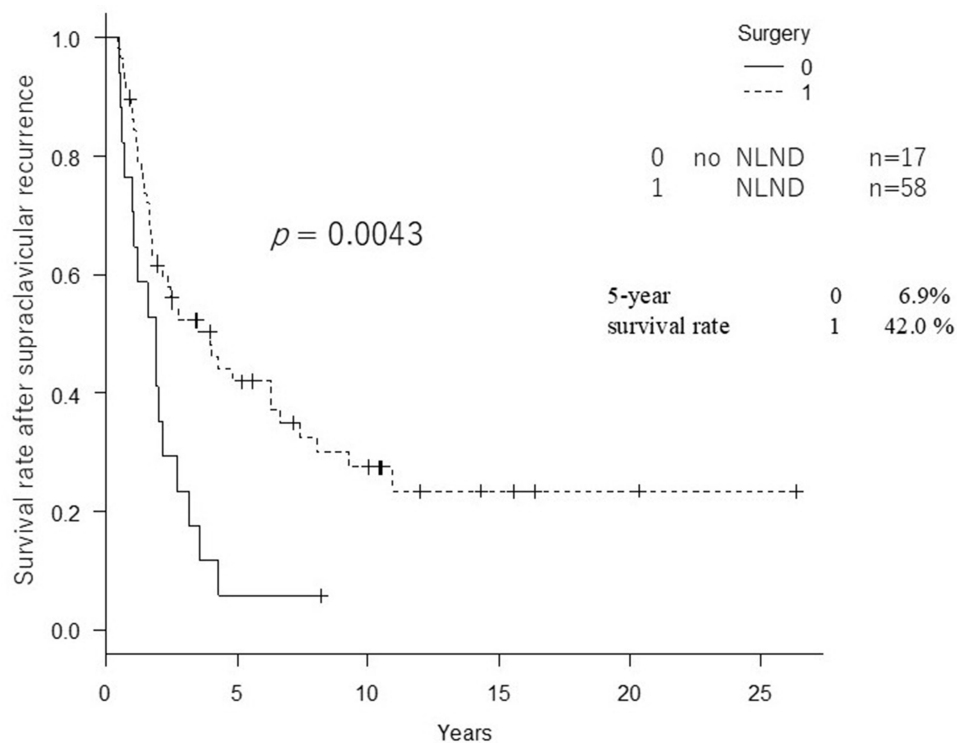


Figure 3 Cumulative survival curves after ISNR.

rates have varied over time. So, we analyzed the impact on survival rate of clinicopathological factors at the time of primary surgery and the period from primary surgery to the onset of ISNR in this study.

In 2003, van der Sangen et al⁸ reported the outcomes of ISNR in 42 patients (0.9%, 42/4669) (1984–1994). Surgery (NLND) was performed on 19% (6/42), while 60% (25/42) received RT. The distant disease-free survival rate was higher in the 25 patients who received RT for ISNR than in 17 who did not ($p = 0.06$); this difference became more pronounced after the exclusion of 8 patients who had received RT for the primary tumor ($p = 0.002$). The 5-year survival rate after ISNR was 38% in their study. They concluded that involved field RT played an important role in the treatment of supraclavicular recurrence.

In 2005, Pergolizzi et al⁹ conducted a prospective multicenter study on the effects of chemotherapy combined with RT in 44 patients with ISNR (1995–2002). Surgery (NLND) was performed on 11% (5/44), while 89% (39/44) received RT. The 5-year survival rate after ISNR was 33% in their study. They concluded that a curative course of intravenous chemotherapy and radical irradiation was feasible for patients with ISNR.

In 2010, Pedersen et al¹¹ reported the largest series of 305 (0.67%, 305/45854) patients with ISNR from the Danish Breast Cancer Cooperative Group treatment database (1977–2003). Surgery (NLND) was performed on 29%, while 43% received RT. In a multivariate analysis, salvage therapy and the malignancy grade remained as independent factors affecting survival. The 5-year survival rate after ISNR was 24% in their study. They concluded that although the prognosis of ISNR was generally poor, it appeared to be a curable condition with salvage therapy (local and systemic).

In 2020, Ma et al¹⁰ reported the outcomes of ISNR in 99 patients (0.7%, 99/13,847) (2009–2019). Surgery (NLND) was performed on 27% (27/99), while 43% (43/99) received RT. Ninety-nine patients were divided into two groups: a systemic therapy group ($n=43$) and combined group ($n=56$). In the combined group, patients were further divided into systemic therapy plus the following: 1) Group A; RT, 2) Group B; surgery, and 3) Group C; RT and surgery. Progression-free survival (PFS) and OS were significantly longer in the combined group than in the systemic group. PFS was significantly longer in Group A ($n=29$) than in Groups B ($n=13$) and C ($n=14$) ($p = 0.007$). Neck RT was an independent parameter affecting OS ($p = 0.002$).

The 3-year survival rate after ISNR was 76.8% in their study. They concluded that systemic therapy combined with local therapy improved PFS and OS. Based on systemic therapy, the effects of RT on survival were superior to those of surgery.

The present study investigated the effects of surgery (NLND) on ISNR. To the best of our knowledge, only two studies have examined this issue: Chen et al⁶ and the present study.

In 2021, Chen et al.⁶ analyzed 139 (1.7%, 139/8129) patients with ISNR at a single medical center (1990–2008). Sixty-one (43.9%) patients underwent surgery (NLND). Five-year OS (from the primary surgery to the last follow-up) rates were 68.9% in the NLND group and 57.7% in the no-NLND group ($p = 0.001$). No NLND and the time interval from the primary surgery to neck relapse ≤ 24 months were the only significant risk factors identified in the multivariate analysis of OS. Multimodal therapy, including neck dissection, significantly improved the distant metastasis-free survival (DMFS) and OS of patients with ISNR. They concluded that improvements in survival after the control of ISNR by intensive surgical treatment suggested that ISNR was not distant metastasis.

The present study examined 75 (1.4%, 75/5279) patients with ISNR at a single medical center (1977–2011). Fifty-eight (77.7%) patients underwent NLND. Five-year OS (the primary surgery to the last follow-up) rates were 64.8% in the NLND group and 35.3% in the no-NLND group ($p = 0.0027$).

The univariate analysis of survival rates (Log rank test) according to clinical factors identified the T factor (T1 vs. T2, 3) and N factor (positive lymph node (Ax) ≤ 10 vs. >10) at the primary surgery, the time interval from the primary surgery to ISNR (≤ 2 years vs. > 2 years), and NLND as significant factors affecting the OS of ISNR patients.

A Cox proportional hazards regression (stepwise selection) analysis, in which the time interval from the primary surgery to ISNR was excluded, identified the T factor (T2, 3 vs. T1, hazard ratio 2.26) and NLND (yes vs. no, hazard ratio 0.41) as significant factors affecting OS; however, when the time interval from the primary surgery to ISNR was included, the interval from the primary surgery to ISNR (>2 years) and NLND were identified as significant factors for long OS (HR 0.21, HR 0.39).

Uni- and multivariate analyses also identified the primary tumor size (T2,3 vs. T1) as a significant factor affecting the OS of ISNR patients in the present study. However, the primary tumor size (≤ 20 mm vs >20 mm) did not affect OS in the Danish Breast Cancer Cooperative Group treatment database,¹¹ or was an independent prognostic factor for synchronous SNM patients.¹² Although the reason for this difference is unknown, one factor may be that patients in this study did not receive RT as the initial treatment.

The univariate analysis identified the N factor (positive lymph nodes (Ax) ≤ 10 vs. >10) at the primary surgery as a significant factor affecting the OS of ISNR patients in the present study. In previous studies,^{4,11–13} the number of positive nodes of the axilla affected OS. Inari et al¹³ demonstrated that patients with internal mammary recurrence and/or ISNR without distant metastasis who had no clinical or pathological axillary LNs at the primary surgery had a favorable prognosis.

The time interval from the primary surgery to ISNR (≤ 2 years vs. >2 years) affected OS in the Danish Breast Cancer Cooperative Group treatment database [11]. In this study, proportional hazards regression analysis identified the same factors (time interval <2 years and no NLND) as significant factors affecting OS in ISNR patients. However, as the time interval itself is a period that included in OS; therefore, we also performed a Cox multivariate analysis excluding the time interval. Fast-growing tumors are considered to develop ISNR within 2 years, while slow-growing tumors recur after 2 years, and the rate of tumor growth continues to affect survival rates.

Uni- and multivariate analyses identified NLND as a significant factor affecting OS in ISNR patients in the present study, as reported by Chen et al⁶ Among patients who underwent NLND in the present study, survival rates were higher in the selective positive nodes dissection group than in the radical dissection group. Therefore, the necessity of radical neck dissection as a surgical treatment for INSR remains unclear. In some patients, it may be sufficient to simply remove metastatic lymph nodes for supraclavicular loco-regional metastases. The selective positive node dissection group may have had more indolent cancers than the radical group. However, the rate of recurrence within 2 years was 55.6% (25/45) in the radical group and 69.2% (9/13) in the pick-up group ($p = 0.526$), which was not significantly different (data not shown in the Results).

ISNR was confirmed to be a type of loco-regional recurrence in the present study, as described in the NCCN Guidelines Version 4.2025.¹⁴ According to the NCCN Panel, “mastectomy-treated patients should undergo surgical resection of the local recurrence (if it can be accomplished with limited morbidity) and involved-field RT to the chest

wall and supraclavicular area. (if the chest wall was not previously treated or if additional RT may be safely administered)". Therefore, NLND needs to be considered as a local control method for ISNR patients and more actively performed. NLND was only significant factor for survival period after ISNR in this study by a Cox multivariate analysis (data not shown). The surgical complications of NLND included nerve or vessel injury, shoulder function impairment, and, rarely, chylous leaks. However, most of these complications are manageable by surgical techniques and post-operative care.

Since the study by Grill et al¹⁵ in 2003, regional nodal irradiation, including the supraclavicular lymph nodes, has been recommended for patients with four or more positive axillary lymph nodes. After 2012, we treated breast cancer according to the breast cancer treatment guidelines and performed RT. Since then, the number of early detected breast cancer patients has increased and the number of patients with ISNR has decreased.

In conclusion, the present study reported the development of ISNR in breast cancer patients who did not receive RT as the primary treatment, and the effectiveness of surgical treatment for ISNR. The results obtained herein revealed that many cases of ISNR were local recurrence without distant metastasis for which surgical removal was an effective and reliable treatment. Furthermore, the findings of the CALOR trial¹⁶ showed that after complete resection in patients with isolated loco-regional recurrence, adjuvant chemotherapy improved DFS and OS. Therefore, the excision of ISNR combined with postoperative RT and general adjuvant chemotherapy is essential for ISNR patients.

The limitations of this study need to be addressed. This was a retrospective study with small number, not a randomized trial. Furthermore, the study period covered a long period of 34 years, during which time treatment medications changed. There were also many deaths and medical records were discarded; therefore, it was not possible to investigate the means by which ISNR or DMFS was detected and assessed. Nevertheless, the present results are consistent with the findings reported by Chen et al,⁶ and are valuable data showing the effectiveness of surgical treatment for ISNR.

In conclusion, INSR is type of a loco-regional recurrence, and NLND needs to be considered in multimodal (radiation and systemic chemo-) therapy for ISNR patients.

Data Sharing Statement

The datasets used and/or analyzed of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the ethics committee of Oomoto Hospital (12 members) in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and all subsequent revisions. Informed consents to participate for the analysis of anonymous data of National Clinical Database and/or Oomoto hospital database were obtained through our institutional form.

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Disclosure

The authors declare no competing interests in this work.

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