BMC Cancer

RESEARCH

Open Access

Exploring the clinical value of regional nodal irradiation in sentinel lymph node positive breast cancer patients omitting axillary dissection

Yongjin Lu[1], Zhiqiang Shi[1], Qiuchen Zhao[2], Zhao Bi[1], Xiao Sun[1], Chunjian Wang[1], Ruijie Jia[1], Junsheng Zheng[1], Jing Sun[1], Yongsheng Wang[1*] and Pengfei Qiu[1*]

Abstract

Purpose The practice of omitting of axillary lymph node dissection (ALND) in patients with a low tumor burden in sentinel lymph nodes (SLN) has become standard in managing early-stage breast cancer. This study aims to determine the clinical application value of regional lymph node irradiation (RNI) in such patients by analyzing relevant clinical and pathological data and survival outcomes.

Methods We gathered data on 7603 patients from Shandong Cancer Hospital and Institutet between September 2014 and December 2022. Patients identified as SLN-positive who omitted ALND were classified based on whether RNI was included in their radiotherapy target area. Their case data and treatment details were analyzed, followed by regular follow-up assessments. The Kaplan–Meier method was used to compare recurrence and survival differences between the two groups. The primary outcome measured was locoregional recurrence-free survival (LRRFS), and the secondary outcomes were invasive disease-free survival (iDFS) and overall survival (OS).

Results Out of 326 women, they were divided into the RNI group ($n=154$) and no-RNI groups ($n=172$). After a median follow-up of 47 months, the recurrence rate in the no-RNI group was 4.7%. Multivariate Cox proportional hazards analysis identified the triple-negative breast cancer (TNBC) subtype as a strong independent prognostic factor for iDFS ($P<0.001$). Although RNI did not reach statistical significance in univariate analysis, it exhibited a significant protective effect after multivariate adjustment ($P=0.024$). Kaplan–Meier survival analysis further revealed that RNI significantly improved LRRFS and iDFS ($P=0.042$; $P=0.037$, respectively), whereas no OS benefit was observed.

Conclusions As the practice of surgical de-escalation becomes more widely adopted, the precise application of radiotherapy for SLN-positive patients exempt from ALND has become a key area of research. This study supports the use of RNI as crucial adjunctive treatment to enhance locoregional control, particularly for high-risk subgroups.

Keywords Breast cancer, Axillary lymph nodes, Sentinel lymph node biopsy, Regional lymph node irradiation

*Correspondence:
Yongsheng Wang
wangysh2008@aliyun.com
Pengfei Qiu
qiu.pf@outlook.com
Full list of author information is available at the end of the article

With the continuous advancement of systemic therapy and radiotherapy techniques, the approach to surgical treatment for breast cancer has shifted towards more conservative methods. The introduction of sentinel lymph node biopsy (SLNB) in the 1990s has significantly influenced the management of regional lymph nodes in breast cancer, promoting standardization, individualization, and minimally invasive approaches. Since 2012, there has been a notable decline in the overall performance of axillary lymph node dissection (ALND) and an increase in the adoption of SLNB [1, 2]. It is well-established that SLNB offers advantages in terms of safety and effectiveness over ALND for patients with negative sentinel lymph nodes (SLN) [3]. In certain cases, some SLN positive patients may avoid ALND [4–6]. Clinical trials such as ACOSOG Z0011, IBCSG 23–01, and AMAROS have demonstrated that ALND can be safely omitted in early-stage breast cancer patients with low tumor burdens in their SLNs (micro-metastasis or limited macro-metastasis) [4, 6, 7]. However, most trials mainly focused on the optimal surgical approach for these patients and largely neglected the crucial question of whether regional lymph node irradiation (RNI) is necessary after foregoing ALND. The Z0011 trial [7, 8] did not standardize postoperative adjuvant radiotherapy protocols, and the AMAROS trial [4] did not clarify the additional benefits of RNI. The SENOMAC trial [9], despite largely standardizing the radiotherapy strategy (with 83.8% of participants received radiotherapy including lymph node target areas), did not definitively establish the necessity of RNI. This lack of consensus has resulted in an absence of standardized criteria in clinical decision-making regarding the necessity of RNI for SLN positive patients who did not undergo ALND. This study aims to determine the clinical application value of RNI in such patients by analyzing relevant clinical and pathological data and survival prognostic indicators.

Methods

Study design and patients

This single-center, retrospective cohort study included 7,603 female patients with $cT_{1-3}N_0M_0$ invasive breast cancer who underwent SLNB at the cancer hospital in Shandong Province from September 1, 2014, to December 30, 2022. The eligibility criteria were as follows: 1. Female patients aged 18–75 years; 2. Pathologically diagnosed with primary invasive breast cancer before surgery; 3. No distant metastasis; 4. Non-inflammatory breast cancer or bilateral breast cancer. Exclusion criteria included: 1. Patients with breast cancer whose sentinel lymph nodes were all negative; 2. Patients who received neoadjuvant therapy; 3. Patients who underwent ALND; 4. Patients with a previous history of breast cancer; 5. Patients with a history of, or concurrent malignancy who had received systemic adjuvant therapy or radiation therapy to the chest lymphatic drainage area. All patients provided written informed consent for treatment. This study was approved by the Clinical Research Ethics Committee of the Affiliated Cancer Hospital of Shandong First Medical University and adhered strictly to the guidelines provided by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

For patients who met the inclusion criteria of the study, demographic characteristics, pathological data, treatment details, and follow-up information were collected. Patients who tested positive for SLN but did not undergo ALND were classified into two groups based on whether their postoperative adjuvant radiotherapy included lymph node irradiation fields in the internal mammary, axillary, supraclavicular, or infraclavicular (level III axillary) regions: the RNI group and the no-RNI group. Patients who did not receive radiotherapy as part of their postoperative treatment were assigned to the no-RNI group. A series of survival follow-ups were conducted for all enrolled patients. Furthermore, patients were divided into subgroups based on tumor T-stage, type of breast surgery, and molecular tumor classification to further explore the clinical value of RNI in different subgroups.

Surgery, pathology and adjuvant therapy

At our center, all patients who underwent SLNB were intraoperatively assessed using either the blue dye method, the radiotracer method, or a combination of both (dual tracer method). After preoperative dye injection, the surgeon anatomically traced the blue-stained lymphatic vessels to identify the first blue-stained lymph node in the axilla. Subsequently, an intraoperative gamma probe was used to detect lymph nodes with a radioisotope count exceeding 10% of the highest count. Finally, other suspicious lymph nodes were palpated and included as SLNs.

The primary diagnostic method for all SLNs was rapid frozen section pathology, supplemented with imprint cytology to confirm metastasis and guide intraoperative axillary management. Postoperatively, all SLN specimens were subjected to routine pathological examination according to standard procedures. According to the clinical practice guidelines for lymph node pathology, axillary lymph node macrometastasis was defined as a metastatic focus with a diameter >2.0 mm; micrometastasis was defined as a metastatic focus with a diameter ≤ 2.0 mm but >0.2 mm, or a cluster of more than 200 cells. ALND was defined as dissection of axillary level I-II lymph nodes, with the removal of at least 10 lymph nodes.

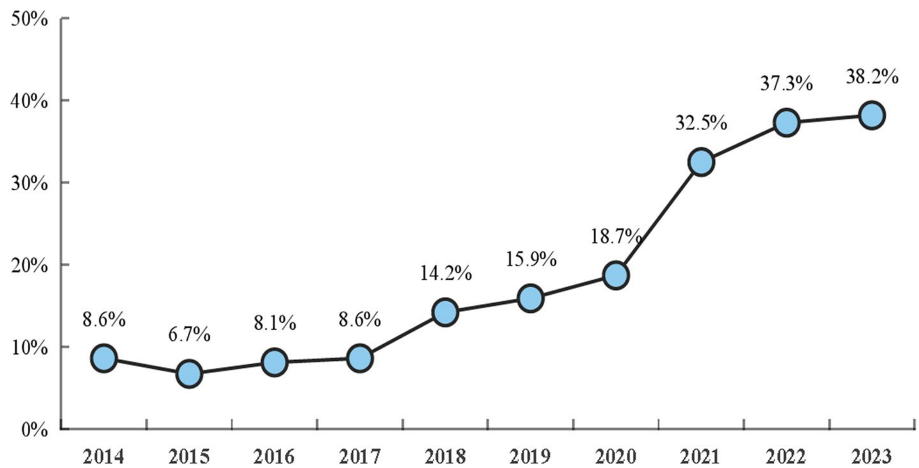

Fig. 1 Trend of ALND omission in SLN low tumor burden patients

The postoperative treatment plan was developed by our institution's multidisciplinary breast cancer team, which consists of experts from various fields, including surgeons, radiation oncologists, pathologists, and radiologists, to ensure comprehensive management.

Follow-up

Follow-up begins on the day of surgery and continues until the last recorded follow-up on March 22, 2025. For the first two years, follow-ups occur every 3–4 months, then semi-annually during years 3–5, and annually thereafter. Follow-up methods included outpatient appointments and telephone calls. The diagnosis of recurrence and metastasis is confirmed based on imaging examinations or pathological biopsy results, with the date of death provided by the patient's family during telephone follow-ups.

Study endpoints

The primary study endpoint is locoregional recurrence-free survival (LRRFS), defined as the time free from recurrence within the ipsilateral chest wall/breast, supraclavicular and infraclavicular regions, axillary area, or internal mammary lymphatic drainage area, encompassing either single or multiple sites. The secondary endpoints include invasive disease-free survival (iDFS), defined as the duration of survival following breast cancer treatment without recurrence of invasive cancer, and overall survival (OS), which assesses the time interval from surgery to breast cancer-related death or the last follow-up.

Statistical analysis

Statistical analysis was performed using SPSS 25.0 and GraphPad Prism 10. The t-test was used to analyze differences in means between continuous variables, while chi-square tests or Fisher's exact test were employed to assess differences between categorical variables. Kaplan–Meier survival curves were used to estimate survival outcomes, with comparisons made using the log-rank test. When no events occurred in one group, the Mantel–Haenszel test was used as an alternative. Univariate and multivariate analyses were conducted using the Cox regression model. A significance level of $\alpha = 0.05$ was used, with $P < 0.05$ considered statistically significant.

Results

Basic characteristics

Between September 1, 2014, and December 31, 2022, a total of 7,603 early-stage breast cancer patients underwent SLNB at our Breast Disease Center. During the study period, the proportion of patients with low tumor burden (1–3 positive SLNs) who were exempted from ALND generally increased over time (Fig. 1). Of the 7,603 patients, 366 met the inclusion criteria for this study. However, 40 patients were excluded due to missing data on the radiation target area, which was a key criterion for group assignment in this study. Follow-up records indicated that some patients received radiotherapy at external institutions, but detailed information on the radiation target area could not be provided by the patients or their families. Ultimately, 326 patients with 1–3 positive SLNs who did not undergo ALND and had complete treatment and follow-up records were included in the analysis (Fig. 2).

Among the 326 patients, the median age was 48 years (range: 23–75). Of these, 265 patients (81.3%) had macrometastasis in the SLN, including 6 cases with additional micrometastasis, while 61 patients (18.7%) had only micrometastasis in the SLN. A total of 167 patients

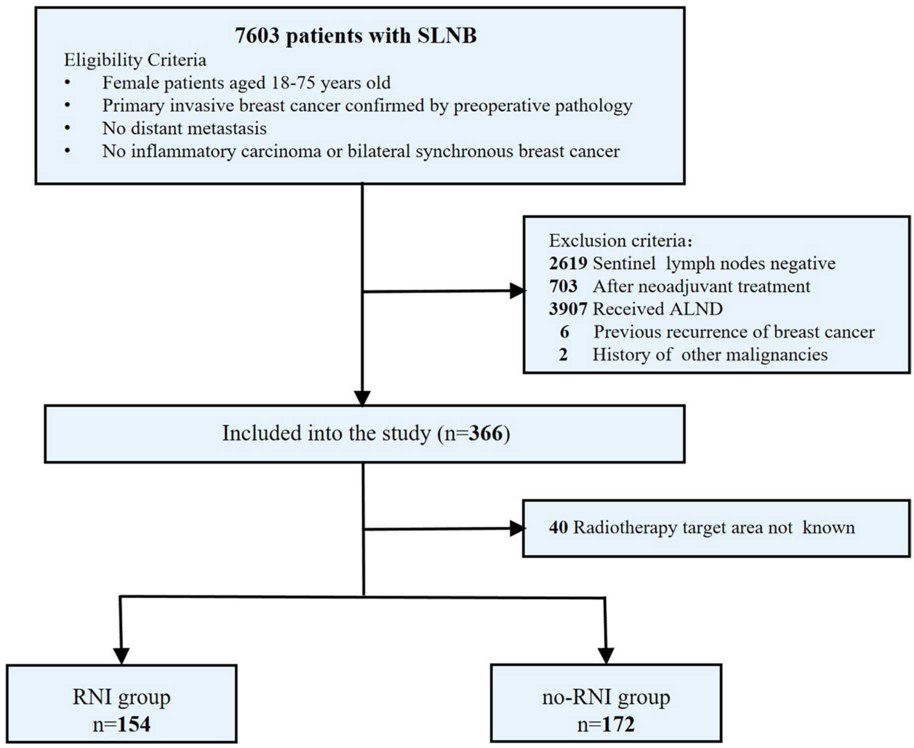

Fig. 2 Study flowchart

(51.2%) underwent breast-conserving surgery (BCS), and 159 patients (48.8%) underwent total mastectomy (TM). Based on the radiation target area, patients were divided into two groups: those receiving RNI and those not receiving RNI, with 154 patients (47.2%) in the RNI group and 172 patients (52.8%) in the no-RNI group. There were 23 patients with only SLN micrometastasis in the RNI group. The two groups were well-balanced in terms of age, body mass index (BMI), menopausal status, tumor laterality, pathological type, histological grade, lymphovascular invasion(LVI) and tumor subtype ($P >$ 0.05), as detailed in Table 1. However, the RNI group exhibited higher tumor burden characteristics, with significantly more positive SLNs ($P =$ 0.003) and a higher T-stage ($P =$ 0.043) compared to the no-RNI group. This may reflect clinical decision-making, where physicians are more likely to administer regional irradiation to higher-risk patients.

Treatment profile

In this study cohort, the rate of postoperative adjuvant chemotherapy was 89.6% (292/326). Further analysis revealed that the chemotherapy implementation rate was significantly higher in the RNI group compared to the no-RNI group (94.2% *vs* 85.5%, $P =$ 0.011). The overall rate of radiotherapy in the cohort was 85.0% (277/326). Among the 277 patients who received radiotherapy, 55.6% (154/277) received RNI. Of the 49 patients who did not receive postoperative radiotherapy, 38.8% (19/49) had SLN micrometastasis, while 61.2% (30/49) had SLN macrometastasis (of which 90% had a single macrometastasis, 27/30; 6.7% had two macrometastases, 2/30; and 3.3% had three macrometastases, 1/30). Notably, in the no-RNI group, 74.4% (128/172) were BCS patients, and 25.6% (44/172) were TM patients. The proportion of patients who received RNI was significantly higher in the TM group (115/159) compared to the BCS group (39/167) (72.3% *vs* 23.4%, $P <$ 0.001). In BCS patients, the radiation target area typically encompasses whole-breast irradiation combined with a tumor bed boost.

Follow-up results

At the time of the study cutoff, the median follow-up time was 47 months (range: 27–126 months), with the RNI group having a median follow-up of 44.5 months (range: 27–123 months) and the no-RNI group having a median follow-up of 49 months (range: 28–126 months). During the follow-up period, a total of 9 recurrence/metastasis events were recorded. The recurrence rate in the no-RNI group was 4.7% (8/172), while the recurrence rate in the RNI group was 0.64% (1/154). The clinical

Table 1 Baseline characteristics of patients by receipt of regional lymph node irradiation

Characteristics	ALL (*N* = 326)	RNI (*n* = 154)	no-RNI (*n* = 172)	*P* value
Age				0.182
Median	48	47	49	
Range	23–75	23–75	27–75	
BMI				0.146
Median	24.36	24.14	24.41	
Range	16.73–38.87	16.73–35.38	17.22–38.87	
Menopause status				0.733
Pre	202(62.0)	97(63.0)	105(61.0)	
Post	124(38.0)	57(37.0)	67(39.0)	
Laterality				0.740
Left	166(50.9)	80(51.9)	86(50.0)	
Right	160(49.1)	74(48.1)	86(50.0)	
T-stage				0.043
1	203(62.3)	87(56.5)	116(67.4)	
2	117(35.9)	62(40.3)	55(32.0)	
3	6(1.8)	5(3.2)	1(0.6)	
Histological type				0.203
Ductal	302(92.6)	146(94.8)	156(90.7)	
Others	24(7.4)	8(5.2)	16(9.3)	
Histologic grade				1.000
II	227(69.6)	107(69.5)	120(69.8)	
III	99(30.4)	47(30.5)	52(30.2)	
LVI				0.238
Yes	75(23.0)	40(26.0)	35(20.3)	
No	251(77.0)	114(74.0)	137(79.7)	
Tumor subtype				0.535
HR +/HER2-	256(78.5)	117(76.0)	139(80.8)	
HER2 +	43(13.2)	22(14.3)	21(12.2)	
TN	27(8.3)	15(9.7)	12(7.0)	
Positive number of SLN				0.003
1	262(80.4)	112(72.7)	150(87.2)	
2	54(16.6)	35(22.7)	19(11.0)	
3	10(3.1)	7(4.5)	3(1.7)	

LVI lymphovascular invasion, *HR+/HER2-* hormone receptor positive/human epidermal growth factor receptor 2 negative, *HER2+* HER2 positive, *TN* triple negative, *SLN* sentinel lymph node

information of the patients with recurrence/metastasis is detailed in Table 2.

Univariate and multivariate Cox proportional hazards regression models were applied to analyze the iDFS in patients with 1–3 positive SLNs who did not undergo ALND (Table 3). The results demonstrated that the iDFS risk for patients with the triple-negative breast cancer (TNBC) subtype was significantly higher than that for those with the HR +/HER2- subtype (multivariate HR =74.066, 95% *CI*: 7.956–689.540, $P<$ 0.001), making it a strong independent prognostic factor. Although RNI did not reach statistical significance in the univariate analysis ($P=$ 0.071), it demonstrated a significant protective effect after multivariate adjustment (HR =0.089, 95% *CI*: 0.011–0.729, $P=$ 0.024). Tumor histological grade was associated with iDFS in the univariate analysis ($P=$ 0.024), but its significance disappeared in the multivariate model ($P=$ 0.731), suggesting that its effect may be confounded by other factors, such as tumor subtype. No significant associations were observed for other variables, including age, surgical type, and so on ($P>$ 0.05).

Kaplan–Meier survival curve analysis (Fig. 3) showed that there was a statistically significant difference between the RNI and no-RNI groups in terms of LRRFS (HR =0.160, 95% *CI*: 0.028–0.933, $P=$ 0.042). Similarly, the RNI group showed superior iDFS compared to the no-RNI group (HR =0.148, 95% *CI*: 0.040–0.549, $P=$ 0.037), demonstrating a substantial survival benefit. However, there was no statistically significant difference between the two groups in OS (HR =0.155, 95% *CI*: 0.003–7.898, $P=$ 0.353).

An exploratory subgroup analysis was further conducted based on clinical and pathological characteristics, including age (≤ 50 *vs* > 50 years), pathological tumor diameter (≤ 2 cm *vs* > 2 cm), histological grade (II *vs* III), molecular subtype (HR +/HER2- *vs* HER2 + *vs* TNBC), and surgical type (BCS *vs* TM). The results showed that patients with tumor diameter >2 cm (HR =0.115, 95% *CI*: 0.020–0.666, $P=$ 0.016), histological grade III (HR =0.165, 95% *CI*: 0.033–0.831, $P=$ 0.029), and molecular subtype TNBC (HR =0.076, 95% *CI*: 0.015–0.393, $P=$ 0.002) may benefit from RNI in terms of iDFS. In the TM subgroup, the difference in iDFS between RNI and no RNI was near significant (HR =0.148, 95% *CI*: 0.018–1.237, $P=$ 0.054). Additionally, patients with tumor diameter >2 cm (HR =0.116, 95% *CI*: 0.016–0.829, $P=$ 0.032) and those with the TNBC molecular subtype (HR =0.070, 95% *CI*: 0.009–0.533, $P=$ 0.010) demonstrated enhanced LRRFS with RNI.

Discussion

ALND has traditionally been the standard axillary treatment for breast cancer patients with SLN positivity, providing comprehensive information on ALN metastasis for staging and guiding subsequent treatment strategies while offering local regional control. However, recent randomized controlled trials such as SENOMAC [4–6, 9] have demonstrated that omitting ALND in early-stage breast cancer patients with low tumor burden or limited metastasis in SLNs followed by adjuvant radiotherapy and systemic treatment is safe, with no significant differences in regional lymph node recurrence risk, disease-free survival (DFS), or OS based on whether ALND is

Table 2 Clinical information of patients with recurrence/metastasis

ID	Tumor subtype	Surgical type	Chemotherapy	Radiotherapy	RNI	Sites of recurrence/metastasis
38#	HER2 +	TM	yes	yes	no	ipsilateral ALNs
84#	TNBC	BCS	yes	yes	no	ipsilateral breast
85#	TNBC	BCS	yes	yes	no	ipsilateral SCLNs
87#	TNBC	BCS	yes	no	no	ipsilateral breast
120#	TNBC	TM	yes	no	no	liver
151#	TNBC	BCS	yes	yes	no	ipsilateral SCLNs/liver/bone
178#	HR +/HER2-	TM	yes	yes	yes	contralateral breast
298#	TNBC	TM	yes	no	no	bone
308#	HER2 +	BCS	yes	yes	no	liver

RNI regional lymph node irradiation, *TM* total mastectomy, *BCS* breast-conserving surgery, *ALN* axillary lymph node, *SCLN* supraclavicular lymph node, *TNBC* triple-negative breast cancer

Table 3 Univariate and multivariate COX analysis of iDFS in patients

Variables	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (≤ 50 *vs* > 50)	0.503 (0.135–1.873)	0.306		
Menopause status (pre *vs* post)	0.508 (0.136–1.892)	0.312		
Lymphovascular invasion (yes *vs* no)	0.516 (0.064–4.147)	0.534		
Laterality (left *vs* right)	0.750 (0201–2.793)	0.668		
Tumor location (lateral *vs* central/medial)	1.053 (0.263–4.211)	0.942		
Histopathologic type (ductal *vs* others)	0.566 (0.071–4.533)	0.592		
Histological grade (II *vs* III)	0.203 (0.051–0.812)	0.024	0.773 (0.178–3.349)	0.731
Pathological size (cm) (≤ 2 *vs* > 2)	0.463 (0.124–1.726)	0.252		
Tumor subtype		< 0.001		< 0.001
HER2 + (*vs* HR +/HER2-)	12.183 (1.105–134.373)	0.041	10.876 (0.909–130.116)	0.059
TN(*vs* HR +/HER2-)	58.478 (7.038–485.866)	< 0.001	74.066 (7.956–689.540)	< 0.001
Positive number of SLN (1 *vs* 2 ~ 3)	0.416 (0.104–1.699)	0.216		
Surgical type (TM *vs* BCS)	0.773 (0.207–2.884)	0.702		
Chemotherapy (yes *vs* no)	23.348 (0.001–468721.034)	0.533		
Radiotherapy (yes *vs* no)	0.401 (0.100–1.609)	0.197		
RNI (yes *vs* no)	0.148 (0.018–1.180)	0.071	0.089 (0.011–0.729)	0.024

performed or not. Consequently, SLNB has supplanted as the standard axillary treatment for breast cancer patients with 1–2 positive SLNs in line with current evidence-based medicine and clinical practice guidelines. It is essential to consider that tumor biology, adjuvant systemic therapy, and radiotherapy are crucial in de-escalating surgical interventions, necessitating a reevaluation and optimization of postoperative axillary management strategies, particularly in selecting regional lymph node radiation, as current clinical trials do not adequately address this issue.

Studies on exempting SLN-positive patients from ALND have shown inconsistent guidelines regarding adjuvant radiotherapy. The Z0011 study, aside from missing some radiotherapy data, also had numerous protocol violations: while the protocol clearly specified whole breast radiotherapy as tangential field irradiation without including the lymphatic drainage area, over half of the patients received high tangential field radiation which includes a greater exposure to the axillary lymph nodes; 18.9% of patients received additional vertical lymph node irradiation atop tangential field irradiation, and 7.9% underwent axillary radiation [8]. The AMAROS study, led by radiation oncologists, with patients similar to those in Z0011, mandated that the SLNB group receive RNI covering all three levels of axilla and the internal mammary lymph node region, while the ALND group received RNI only if four or more positive lymph nodes

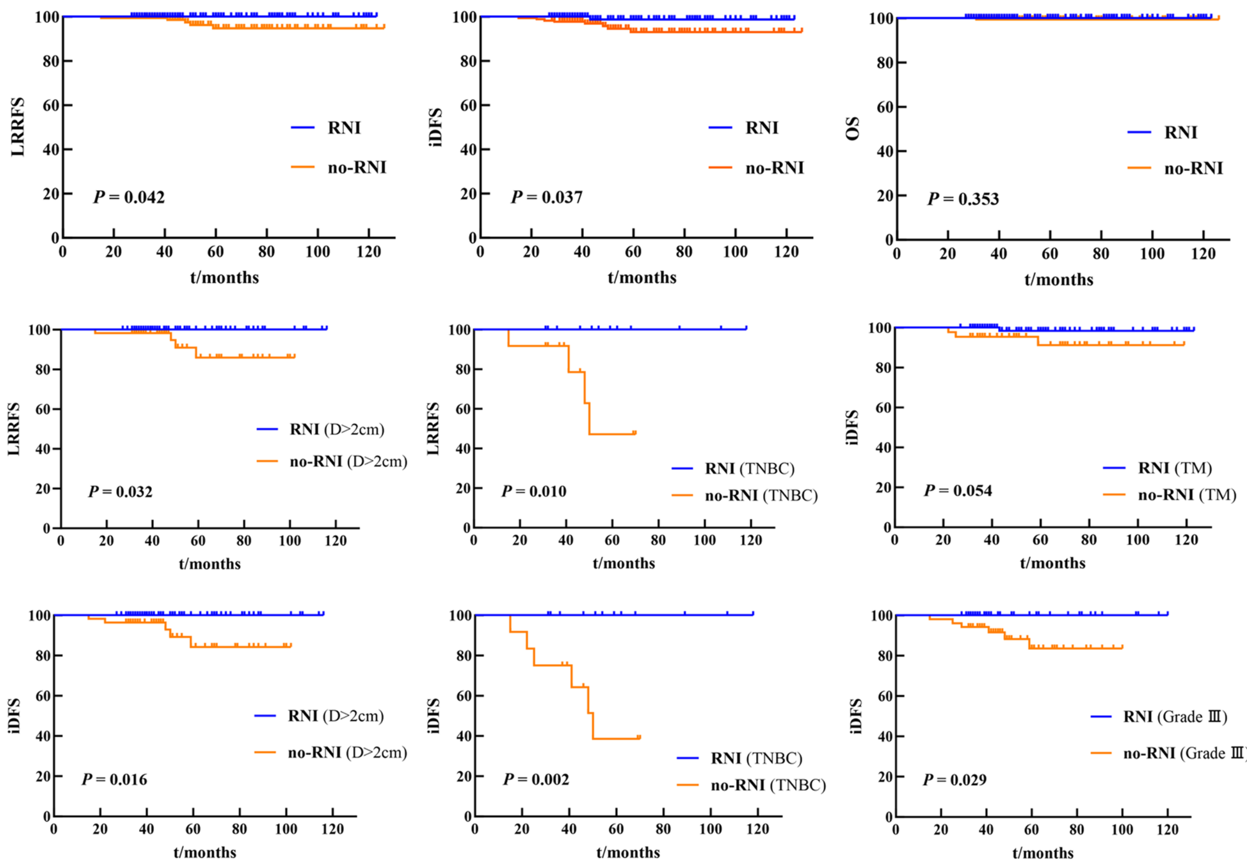

Fig. 3 Kaplan–Meier curves for survival analysis of breast cancer patients based on receipt of RNI. The first row presents the Kaplan–Meier curves comparing the RNI group (blue) and no-RNI group (orange) for all patients, showing LRRFS, iDFS, and OS. The second and third rows display some of the exploratory subgroup analysis results for LRRFS and iDFS across different patient subgroups, including the tumor diameter > 2 cm subgroup (RNI group: blue, $n = 67$; no-RNI group: orange, $n = 56$); the TNBC subgroup (RNI group: blue, $n = 15$; no-RNI group: orange, $n = 12$); the TM subgroup (RNI group: blue, $n = 115$; no-RNI group: orange, $n = 44$); and the histological grade III subgroup (RNI group: blue, $n = 47$; no-RNI group: orange, $n = 52$)

were detected (8% of the total cohort). This evidence raises questions about whether sole whole breast/chest wall radiotherapy is sufficient and how can the selection criteria for RNI be optimized.

Furthermore, studies such as Z0011 [7], IBCSG 23–01 [6], AMAROS [4], and OTOASO [10] predominantly focus on BCS patients (comprising 100%, 91%, 82%, and 84% of the cohorts, respectively); studies focusing on TM patients are largely retrospective analyses [11–13], highlighting the need for further research into the safety of exempting ALND in TM patients and optimization of radiation target areas. Although studies such as SINODAR-ONE [14], SENOMAC [15], and POSNOC [16] have more rigorous research designs, standardizing inclusion criteria and radiotherapy protocols, including mandatory axillary ultrasound screening, the inclusion of only patients with SLN macrometastases, and those undergoing TM, these studies still fail to provide a clear answer to the crucial question of whether patients in this group require RNI. Notably, there has been no direct comparison of the impact on prognosis between RNI administration or omission after ALND exemption, leaving a significant gap in addressing this core issue. As a result, the dilemma regarding radiotherapy decisions in clinical practice remains unresolved. Due to the limitations of the aforementioned studies, the reliance of RNI on the surgical type becomes particularly evident in actual clinical application. For instance, in this study, 23.4% BCS patients received RNI, while the proportion was as high as 72.3% among TM patients. This discrepancy suggests that, in clinical practice, radiotherapy strategies may be significantly influenced by the surgical type. However, the surgical method itself does not accurately reflect the patient's tumor burden and metastasis risk. The selection of radiotherapy target areas should focus more on the patient's tumor biology and the extent of axillary involvement, rather than on the surgical type.

The MA.20 randomized controlled study, which included 1832 BCS patients (with 1–3 lymph node metastases accounting for 85%), demonstrated the benefits of RNI [17]. With a median follow-up of 9.5 years, the study showed that while the addition of RNI to whole breast radiotherapy did not significantly improve OS (82.8% vs. 81.8%, $P = 0.38$), it significantly improved DFS (82% vs. 77%, $p = 0.01$), Locoregional Disease-Free Survival (LRDFS) (95.2% vs. 92.2%, $p = 0.009$), and Distant Metastasis-Free Survival (DMFS) (86.3% vs. 82.4%, $p = 0.03$). These findings are consistent with our study results. The EORTC 22922/10925 study, with a 15.7-year follow-up, demonstrated that RNI significantly reduces breast cancer mortality and recurrence risk but does not show significant improvements in OS, DFS, and DMFS [18]. Similarly, the EBCTCG meta-analysis concluded that adding RNI for lymph node-positive breast cancer patients decreases the risk of distant metastasis and enhances DFS, with no impact on OS [19]. This collective evidence underscores the role of RNI in local–regional control for lymph node-positive patients, generally based on populations who underwent ALND and had accurate lymph node staging without residual positive axillary lymph nodes. Previous research [4–6, 20] indicates that the risk of non-SLN metastasis in patients with 1–2 positive SLNs ranges from approximately 15.9% to 38.6%, indicating that one-third of patients exempted from ALND may have residual positive lymph nodes, potentially leading to upstaging of lymph node status. Therefore, the radiotherapy target volume for SLN-positive patients who do not undergo ALND should match that for pN1 patients who do. However, while RNI has not been shown to improve overall survival, it undoubtedly exposes patients to a higher risk of radiation-induced cardiac and pulmonary damage [21, 22]. Therefore, a major challenge is how to identify high-risk recurrence patients among breast cancer patients who are SLN-positive and exempted from ALND.

The regional lymph node staging plays a crucial role in determining the necessity of RNI. For SLN positive patients exempt from ALND, considering the residual tumor burden is vital. Currently, the most commonly used predictive model is the MSKCC center's model [23, 24], which includes eight indicators such as the presence of frozen section analysis, tumor size, histological type and grade, SLN pathology detection method, number of positive and negative SLNs, vascular invasion, multifocality, and hormone receptor status. It is recommended that additional lymph node interventions (such as RNI or ALND) be implemented for patients at high risk of non-SLN metastasis to reduce the risk of locoregional recurrence. In this study, the non-SLN metastasis risk in patients who experienced recurrence or metastasis ranged from 23% to 52%. Thus, in clinical practice, we cannot solely rely on trials like Z0011. In the current landscape of oncological research, several large-scale randomized clinical trials, such as the T-REX and TAILOR-RT studies, have honed in on the value of regional radiotherapy post-breast cancer surgery. These trials meticulously compare the recurrence risks between cohorts that receive and those that forgo regional radiotherapy, aiming to delineate the effects of tailored local external beam radiation therapy for this patient population. Notably, the TAILOR-RT study has focused its inclusion criteria on patients with low biomarker risk, who are ER positive and HER2 negative. Despite this specific patient selection, the forthcoming results are eagerly anticipated, as they are poised to provide a robust evidence base for the individualization of clinical treatment plans. Prior to the solidification of expert consensus and guideline recommendations, our current clinical practices must take into account the residual burden of regional lymph nodes and the biomarker profile of the tumor. These considerations are essential for determining the optimal radiation therapy target scheme for our patients.

This study demonstrated that RNI significantly improved both LRRFS and iDFS in patients. Despite the fact that patients in the RNI group had higher baseline risks of recurrence and metastasis (such as a greater number of positive SLNs and more advanced T-stage), the prognostic analysis consistently showed better survival outcomes in this group. This suggests that RNI may significantly enhance local–regional control in high-risk populations. Of course, we cannot exclude the possibility that the effect of RNI might be underestimated in certain subtypes of breast cancer with relatively slow progression (such as hormone receptor-positive types) due to the limited follow-up period in this study. However, based on the results of this study, the application of RNI appears to be beneficial, especially in subtypes with larger tumors, higher histological grades, and more aggressive behavior. Moreover, the survival benefit is likely to become more pronounced as follow-up time increases [25].

The limitations of this study include its single-center, retrospective design, small sample size, relatively short follow-up. Breast cancer is recognized as one of the malignancies with a more favorable prognosis, and our study's focus on early-stage patients with low tumor burden in the axillary lymph nodes accounts for the limited number of recurrence and metastasis events observed during follow-up. Additionally, the study did not fully capture the adverse effects associated with RNI, an important consideration in clinical decision-making.

In summary, with effective systemic therapy, the risk of local–regional recurrence has significantly decreased, potentially diminishing the absolute benefits of local–regional treatments. This underscores the increasing importance of individualized"up and down-staging"of surgical and radiation therapy. As more SLN-positive patients are spared from ALND in the era of SLNB, some patients may not receive accurate lymph node staging and adequate local–regional control. Currently, it appears that these patients might benefit from additional RNI in their post-treatment radiation therapy.

Conclusions

Among breast cancer patients with limited SLN positivity who omitted ALND, the addition of RNI significantly improved LRRFS and iDFS, although no benefit in OS was observed. As the omission of ALND becomes increasingly adopted as a standard treatment approach, some patients may not receive accurate axillary lymph node staging. In such scenarios, RNI emerges as a crucial adjunctive treatment, especially for individuals at a higher risk of recurrence. However, as a single-center retrospective study, this research has inherent limitations, and future large-scale, prospective, multi-center studies are needed to validate these findings.

Abbreviations

ALND	Axillary lymph node dissection
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy
TM	Total mastectomy
BCS	Breast-conserving surgery
LRRFS	Locoregional recurrence-free survival
iDFS	Invasive disease-free survival
OS	Overall survival
DFS	Disease-free survival
RNI	Regional lymph node irradiation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14215-8.

Supplementary Material 1.

Authors' contributions

Pengfei Qiu and Yongjin Lu designed the study. Junsheng Zheng, Ruijie Jia, and Jing Sun collected the data, while Chunjian Wang organized the data. Zhiqiang Shi and Xiao Sun conducted a series of statistical analyses, and Yongjin Lu drafted the manuscript. Pengfei Qiu, Yongsheng Wang, Zhao Bi and Qiuchen Zhao made significant revisions to the manuscript. All authors have read and approved the final version of the manuscript for publication.

Funding

This work was supported by the National Natural Science Foundation of China (82172873 W2421095); Jinan Science and Technology Plan (202430063) and the National Health Commission of China's Innovative Drug Post-Marketing Clinical Research Program (WKZX2023 CX050001).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was registered with the Shandong Cancer Hospital Ethics Committee (No.SDTHEC20230324) and approved by the institutional review board of participating center. Written informed consent was obtained from all patients before participation in the study. The study protocol was approved by ethics committees, and the study was undertaken in full accordance with the Declaration of Helsinki.

Competing interests

The authors declare no competing interests.

Author details

[1]Breast Cancer Center, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, Shandong 250117, China. [2]Cancer Research UK Cambridge Centre and Department of Oncology, University of Cambridge, Cambridge CB2 0XZ, UK.

Received: 5 August 2024 Accepted: 23 April 2025
Published online: 13 May 2025

References

1. Poodt IGM, Spronk PER, Vugts G, et al. Trends on Axillary Surgery in Nondistant Metastatic Breast Cancer Patients Treated Between 2011 and 2015: A Dutch Population-based Study in the ACOSOG-Z0011 and AMAROS Era. Ann Surg. 2018;268(6):1084–90.
2. Garcia-Etienne CA, Mansel RE, Tomatis M, et al. Trends in axillary lymph node dissection for early-stage breast cancer in Europe: Impact of evidence on practice. Breast. 2019;45:89–96.
3. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010;11(10):927–33.
4. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981–22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol. 2014;15(12):1303–10.
5. Giuliano AE, Ballman KV, McCall L, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA. 2017;318(10):918–26.
6. Galimberti V, Cole BF, Viale G, et al. International Breast Cancer Study Group Trial 23–01, Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23–01): 10-year follow-up of a randomised, controlled phase 3 trial. Lancet Oncol. 2018;19(10):1385–93.
7. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA. 2011;305(6):569–75.
8. Jagsi R, Chadha M, Moni J, et al. Radiation field design in the ACOSOG Z0011 (Alliance) Trial. J Clin Oncol. 2014;32(32):3600–6.
9. de Boniface J, Filtenborg Tvedskov T, Rydén L, et al. Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases. N Engl J Med. 2024;390(13):1163–75.
10. Sávolt Á, Péley G, Polgár C, et al. Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial. Eur J Surg Oncol. 2017;43(4):672–9.
11. Gao W, Lu S, Zeng Y, et al. Axilla lymph node dissection can be safely omitted in patients with 1–2 positive sentinel nodes receiving mastectomy: a large multi-institutional study and a systemic meta-analysis. Breast Cancer Res Treat. 2022;196(1):129–41.

12. Kim BK, Park B-W, Hur MH, et al. Omission of axillary lymph node dissection in patients who underwent total mastectomy with 1 or 2 metastatic lymph nodes. Ann Surg Treat Res. 2020;98(6):283–90.
13. FitzSullivan E, Bassett RL, Kuerer HM, et al. Outcomes of Sentinel Lymph Node-Positive Breast Cancer Patients Treated with Mastectomy Without Axillary Therapy. Ann Surg Oncol. 2017;24(3):652–9.
14. Tinterri C, Gentile D, Gatzemeier W, et al. Preservation of Axillary Lymph Nodes Compared with Complete Dissection in T1–2 Breast Cancer Patients Presenting One or Two Metastatic Sentinel Lymph Nodes: The SINODAR-ONE Multicenter Randomized Clinical Trial. Ann Surg Oncol. 2022;29(9):5732–44.
15. de Boniface J, Frisell J, Andersson Y, et al. Survival and axillary recurrence following sentinel node-positive breast cancer without completion axillary lymph node dissection: the randomized controlled SENOMAC trial. BMC Cancer. 2017;17(1):379.
16. Goyal A, Mann GB, Fallowfield L, et al. POSNOC-POsitive Sentinel NOde: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy: a randomised controlled trial of axillary treatment in women with early-stage breast cancer who have metastases in one or two sentinel nodes. BMJ Open. 2021;11(12): e054365.
17. Poortmans PM, Struikmans H, Bartelink H. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015;373(19):1879–80.
18. Poortmans PM, Weltens C, Fortpied C, et al. European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups, Internal mammary and medial supraclavicular lymph node chain irradiation in stage I-III breast cancer (EORTC 22922/10925): 15-year results of a randomised, phase 3 trial. Lancet Oncol. 2020;21(12):1602–10.
19. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014;383(9935):2127–35.
20. Yang Z, Lan X, Huang Z, et al. Development and external validation of a nomogram to predict four or more positive nodes in breast cancer patients with one to three positive sentinel lymph nodes. Breast. 2020;53:143–51.
21. Bartelink H. Regional nodal irradiation for early breast cancer; clinical benefit according to risk stratification. Breast. 2019;48(Suppl 1):S65–8.
22. Nitsche M, Temme N, Förster M, et al. Tangential vs defined radiotherapy in early breast cancer treatment without axillary lymph node dissection: a comparative study. Strahlenther Onkol. 2014;190:715–21.
23. Specht MC, Kattan MW, Gonen M, et al. Predicting nonsentinel node status after positive sentinel lymph biopsy for breast cancer: clinicians versus nomogram. Ann Surg Oncol. 2005;12(8):654–9.
24. Van Zee KJ, Manasseh D-ME, Bevilacqua JLB, et al. A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. Ann Surg Oncol. 2003;10(10):1140–51.
25. Lu YJ, Shi ZQ, Li T, et al. Retrospective study on regional lymph node radiotherapy after axillary dissection exemption in breast cancer patients with sentinel lymph node positive status. Chin Oncol. 2025;35(2):228–36.

Publisher's Note