

Efficacy and Survival Analysis of Radiotherapy for Internal Mammary Lymph Nodes After Modified Radical Mastectomy for T₁₋₃N₃M₀ the Lateral Quadrant Breast Cancer

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Purpose: This study aimed to investigate the efficacy and survival analysis of internal mammary lymph nodes (IMLNI) radiotherapy after modified radical mastectomy for T₁₋₃N₃M₀ The lateral quadrant breast cancer.

Materials and Methods: A total of 124 patients who underwent adjuvant radiotherapy after modified radical mastectomy for breast cancer in the First Affiliated Hospital of Bengbu Medical University were included. The patients were divided into the internal mammary lymph node (IMLN) irradiation group, and sixty-two patients received postoperative chest wall + upper and infraclavicular lymph nodes + IMLNI, sixty-two patients in the non-IMLN irradiation group received postoperative radiotherapy to the chest wall + upper and infraclavicular lymph nodes. The radiotherapy dose was 45–50GY, The disease-free survival rate (DFS), survival rate (OS), local recurrence rate (LRR), distant metastasis rate (DM), and adverse radiation reactions were analyzed.

Results: Median follow-up was 56 months (range 12–96). The 5-year OS in the IMLNI group and the non-IMLNI group were 80.6% and 79.8% ($P>0.05$), DFS was 62.9% and 59.7% ($P>0.05$), LRR was 22.6 and 21.0% ($P>0.05$), and DM was 25.8% and 33.9% ($P>0.05$), respectively. Multifactorial showed that T stage, PR status, vascular cancer embolism, it was an independent prognostic factor affecting the 5-year OS of patients, and PR expression status ($P=0.038$) was an independent prognostic factor affecting the 5-year LRR.

Conclusion: For breast cancer patients located in the outer quadrant and more than 9 axillary lymph node positives, increasing IMNI failed to improve the 5-year prognosis of the patients, and for patients with late N stage, PR receptor-negative, and vascularity cancer thrombosis positive, the 5-year OS of breast cancer postoperative patients could be reduced, and the PR receptor positivity could reduce the 5-year LRR of patients. There was no significant difference in 5-year late radiation adverse effects between the IMLNI and non-IMLNI groups.

Keywords: breast cancer, internal mammary lymph node irradiation, radiotherapy, survival rate, retrospective study

Introduction

In recent years, female breast cancer incidence has surpassed lung cancer, it has become the most common tumor among female malignant tumor patients in China, ranking first in the incidence of breast cancer in most countries.¹⁻³ There are many pathological types of breast cancer, and in addition to histological types, molecular alteration patterns can also guide the treatment of breast cancer, such as the expression of estrogen receptor (ER) and progesterone receptor (PR), gene amplification of human epidermal growth factor 2 (HER-2), and protein overexpression.⁴ Breast cancer is composed of at least four distinct clinically relevant molecular subtypes: luminal type A, luminal type B, HER-2 overexpressing

type, and triple-negative type. The main treatment modalities include surgery, chemotherapy, radiotherapy, targeting, immunization, and Endocrine therapy.⁵ The most common site of breast cancer is the outer upper quadrant, followed by the inner upper quadrant, and the outer lower quadrant and the lower inner quadrant the third place.⁶ Relevant studies have shown that internal mammary lymph node and axillary lymph nodes (ALN) are the first echelons of breast cancer metastasis.⁷⁻⁹ The pathological status of the internal mammary lymph node is also one of the important bases for the staging of breast cancer. Due to the small size and deep anatomical position of the internal mammary lymph nodes, it is difficult to perform surgical dissection, so most hospitals do not routinely perform internal mammary lymph node dissection. In patients at risk of internal mammary lymph node metastasis, postoperative radiotherapy to internal mammary lymph nodes has been controversial. The 2022 national Comprehensive Cancer Network(NCCN) guidelines point out that patients with axillary lymph node metastases after modified radical mastectomy for breast cancer ≥ 4 are recommended as category 1, that is, radiotherapy with whole breast + all regional lymph nodes (upper and lower clavicle area, internal mammary lymph node and axillary lymph node irradiation) is strongly recommended; 1 ~ 3 patients with positive axillary lymph nodes are recommended for category 2A, that is, all regional lymph node radiotherapy is recommended; Radiation therapy to all regional lymph nodes is recommended for primary tumors located in the inner quadrant or central region with high-risk factors (pathologic T3 tumors or pathologic T2 tumors with the following high-risk features: grade 3, extensive lymphovascular invasion, or estrogen receptor-negative).¹⁰

Therefore, there is still a lack of strong evidence on whether postoperative internal mammary lymph node irradiation (IMLNI) can improve the prognosis when the local advanced tumor is located in the lateral quadrant. In addition, internal mammary lymph node irradiation (IMLNI) will increase the radiation dose to the heart and lungs, causing heart and lung damage to patients. As a result, the adverse effects of radiotherapy may be outweighed by the benefits of radiotherapy. Given the lateral quadrant, there is still controversy about whether to undergo radiotherapy with internal mammary lymph nodes after surgery for N3 breast cancer. The purpose of this study was to compare 124 patients with breast cancer with stage T1-3N3M0, all patients who underwent postoperative irradiation for chest wall + upper and infraclavicular lymph nodes area $\pm$ internal mammary lymph node irradiation after radical mastectomy, and preliminarily explore the efficacy analysis of IMLN, the main endpoints were disease-free survival (DFS), survival (OS), local recurrence rate (LRR) and distant metastasis rate (DM), and adverse radiation reactions. Provide data support for the selection of clinical treatment decisions.

Materials and Methods

Inclusion Criteria

1. All patients underwent tumor puncture and biopsy to confirm breast cancer before treatment; 2. Female breast cancer patients aged ≥ 18 years and ≤ 75 years old; 3. Primary tumors located in the outer quadrant and axillary lymph node positive ≥ 10 ; 4. The radiotherapy target range of all patients includes chest wall + upper and infraclavicular lymph nodes area $\pm$ IMNI, and the radiotherapy dose is 45–50GY) during the treatment period.

Exclusion Criteria

1. Have bilateral breast cancer or distant metastases, or have a history of other malignancies; 2. Evidence of supraclavicular lymph node or IMN involvement at the time of diagnosis; 3. Have severe concomitant diseases (liver and kidney failure); 4. Radiotherapy was not completed after surgery and was lost to follow-up; 5. Clinical data are incomplete.

Clinical Data

The clinical and pathological data of patients who underwent adjuvant radiotherapy after modified radical mastectomy for breast cancer in the First Affiliated Hospital of Bengbu Medical University from January 2016 to June 2021 were collected. Including the age, gender, tumor size, location, clinical stage, molecular classification, number of axillary positive lymph nodes, previous treatment, and side effects during treatment. The clinical stage was determined by

mammography, ultrasound, computed tomography(CT), breast magnetic resonance imaging (MRI), and whole-body emission computed tomography(ECT). The molecular typing of tumors was divided into four types immunohistochemistry (IHC), ER, PR, HER-2 expression status, and Ki67 index. All patients with HER-2 (2+) underwent fluorescence in situ hybridization (FISH) to determine the HER-2 expression status. 124 patients were enrolled. According to whether they received IMLN grouping, 62 patients who underwent postoperative irradiation chest wall + upper and infraclavicular lymph nodes + internal mammary lymph node radiation therapy were divided into IMLN irradiation group, and 62 patients who underwent postoperative chest wall + upper and infraclavicular lymph nodes radiation therapy were divided into non-IMLN irradiation group. The radiotherapy dose was 45–50GY, which was 50GY/25F for conventional radiotherapy versus 45.22/17F for hyperfractionated radiation therapy(HRT). The patient generally takes the supine position, the upper body is exposed, and the hands are placed on the top of the head. Fixation device: body film and styrofoam are preferred, parameters Scan range is upper edge of C1 - lower edge of L2 vertebral body. The scanning layer thickness is 5mm. Transmit the image: Transmit the scanned image to the TPS system radiotherapy techniques for enrolled patients include electron beam irradiation, intensity-modulated intensity-modulated (IMRT), volumetric rotational intensity-modulated (VMAT), and tomotherapy (TOMO). Clinical target volume (CTV) includes chest wall + upper and infraclavicular lymph nodes area + $\pm$ internal mammary lymph node irradiation. The planning target volume (PTV) is the area that is released based on the clinical target area taking into account the movement of the irradiated organs and the error of the positioning position. 1.0 cm in the direction of the head and feet, 0.5–1.0 cm in other directions, not in the skin direction, limited to 0.3–0.5 cm under the skin. Organs at risk (OAR) include the heart, bilateral lungs, spinal cord, contralateral mammary gland, humeral head, thyroid gland. To evaluate the accuracy of the clinical target area (CTV) and the delineation of the organ in crisis. Evaluate the uniformity and conformability of the dose, whether the angle and number of fields cover the target area, and whether the limit value of the crisis organ meets the optimal, and evaluate the limit of crisis organs by DVH chart, The quality control process includes calibration, positioning, regular image verification, and whether the two-way plan needs to be changed according to the deformation.

Assessment of Baseline Clinical Characteristics

Collecting from the electronic medical record system patients the age, gender, tumor size, location, clinical stage, molecular classification, number of axillary positive lymph nodes, previous treatment, menopause, neoadjuvant therapy, and side effects during treatment.

Collecting ER, PR, HER-2 expression status, and Ki67 index by immunohistochemistry (IHC). All patients with HER-2 (2+) underwent fluorescence in situ hybridization (FISH) to determine the HER-2 expression status, thrombosis of vascular cancer, and nerve invasion.

Survival Analysis Evaluation Indicators

The follow-up data were obtained through a combination of outpatient clinics, admission reviews, and telephone follow-up. The evaluation indicators mainly included the following aspects 5-year overall survival (OS), disease-free survival (DFS), local recurrence rate (LRR) and distant metastasis (DM). OS is defined as the time from the date of diagnosis of breast cancer to death. DFS is the time until recurrence, metastasis, or death. LRR is defined as the recurrence of lymph nodes in the chest wall, ipsilateral axilla, medial mammary region, and supraclavian region after surgery. DM is defined as the presence of metastases from other sites other than eceregions. The adverse reactions of the skin, bilateral lungs, and heart were evaluated according to the grading criteria for late adverse radiation reactions of the Radiation Therapy Oncology Group (RTOG) of the United States. Acute adverse reactions occurred within 90 d of the start of radiotherapy. Late adverse reactions were adverse reactions occurring 90 d after the start of radiotherapy (See the [Supplementary Table 1](#)).

Statistical Analysis

SPSS27.0 software was used for statistical analysis with a significance level of 0.05 for two-sided tests. The clinical characteristics and pathological characteristics of patients were compared by chi-square test or Fisher's exact test, and survival analyses and confidence intervals were estimated using the Kaplan–Meier method, and OS, DFS, LRR, and DM

were assessed and compared by the log-rank method. Log-rank was used for univariate analysis, and the COX proportional hazards regression model was used for subgroup and multivariate analysis. Survival plots were drawn using GraphPad Prism 9.

Results

Baseline Characteristics of Patients

From January 2016 to June 2021 were included in this research. To balance the clinical characteristics and pathological characteristics of the two groups of patients, propensity score matching (PSM) was used to balance the baseline of the two groups according to 1:1 matching, and a total of 124 patients were enrolled after matching, all whom were patients with T1-3N3M0 and the primary tumor in the outer quadrant, of which 62 (50%) underwent IMNI radiotherapy and 62 (50%) did not undergo IMNI radiotherapy. Estrogen receptor and progesterone receptor-positive patients were 77 (62.1%), 61 (49.2%), endocrine therapy for 5 years or more, 45 (36.6%) HER-2 over expression, and all received trastuzumab or pertuzumab for HER2-positive patients. 19 patients (15.3%) had received 4 to 8 cycles of neoadjuvant therapy. Compared the age, tumor location, tumor quadrant, T stage, ER receptor, PR receptor, vascular cancer receptor, nerve invasion, and menopause, neoadjuvant therapy, and the choice of radiotherapy technique ($P > 0.05$) (see [Table 1](#) for details).

The Survival Rate, Recurrence, and Metastasis

The prognosis analysis of 124 patients enrolled was performed. The last follow-up was June 2024, with a median follow-up of 56 (12–96) months. The follow-up time was up to 5 years, and there were 25 deaths, all of which were due to tumor progression, 27 cases of local recurrence, 37 cases of distant metastasis, and the 5-year OS, DFS, LRR, and DM were 79.8%, 61.3%, 21.8%, and 29.8%, respectively. (see [Table 2](#)).

Comparative Analysis of Survival Between the IMLNI Group and the Non-IMLNI Group

In the IMLNI group and non-IMLNI group, respectively (see [Table 2](#)). The 5-year OS was 80.6% and 79.8% ($p = 0.647$, $P > 0.05$, [Figure 1a](#)), DFS was 62.9% and 59.7% ($p = 0.980$, $P > 0.05$, [Figure 1b](#)), LRR was 22.6 and 21.0% ($p = 0.585$, $P > 0.05$, [Figure 1c](#)), and DM was 25.8% and 33.9% ($p = 0.627$, $P > 0.05$, [Figure 1d](#)). There were no significant differences in 5-year OS, DFS, LRR, DM in subgroups of patients of different ages, T stage, tumor quadrant and tumor location ($P > 0.05$) (see [Supplementary Tables 2–5](#)).

Univariate Analysis of the Effects of OS, DFS, LRR, and DM in Enrolled Patients for 5 Years

Univariate analysis of age, tumor quadrant, tumor location, T stage, ER, PR, HER-2 expression status, vascular cancer thrombus, nerve invasion, menopausal status, and other factors by log-rank method showed that T stage, ER, PR, and vascular cancer thrombosis status were related to the 5-year OS of the patients ($P < 0.05$), PR status was associated with the 5-year DFS and LRR of the patients ($P < 0.05$), and the ER and PR status were related to the five-year DM ($P < 0.05$). There were no significant differences in 5-year OS, DFS, LRR, and DM in age, tumor quadrant, tumor location, HER-2 expression status, nerve invasion, and menopause ($P > 0.05$) (see [Table 3](#), [Figure 2a–h](#), and for details).

Multivariate Analysis of Influencing Factors of OS, DFS, LRR, DM in the 5th Year of Enrollment

The Cox regression model was used to further incorporate the factors of $P < 0.1$ into the multivariate analysis, and the results showed that T stage ($P = 0.008$, $HR = 0.224$, 95% $CI = 0.074–0.675$), PR status ($P = 0.040$, $HR = 0.237$, 95% $CI = 0.060–0.937$), vascular cancer thrombosis ($P = 0.012$, $HR = 3.089$, 95% $CI = 1.282–9.441$), PR expression status ($P = 0.038$, $HR = 3.14$, 95% $CI = 0.106–0.935$) was an independent prognostic factor affecting 5-year LRR ([Tables 4 and 5](#)). There were no significant 5-year differences in OS, DFS, LRR, and DM among the other factors ($P > 0.05$).

Table 1 Comparison of Basic Clinical Data of Breast Cancer Patients [Cases (%)]

Characteristics	IMNI Radiotherapy(n=62)	No IMNI Radiotherapy(n=62)	χ^2/Z	P
Age(year)			1.679	0.195
≤52	42(67.7%)	35(56.5%)		
>52	20(32.3%)	27(43.5%)		
Tumor location			1.166	0.280
Left	36 (58.1%)	30 (48.4%)		
Right	26 (41.9%)	32 (51.6%)		
Tumor quadrant			0.000	1.000
Outside	39 (62.9%)	39 (62.9%)		
Outside down	23 (37.1%)	23 (37.1%)		
T stage			3.200	0.202
T1	12 (19.4%)	18 (29.0%)		
T2	38 (61.3%)	38 (61.3%)		
T3	12 (19.4%)	6 (9.7%)		
ER status			3.426	0.064
Positive	33 (53.2%)	44 (71.0%)		
Negative	29 (46.8%)	18 (29.0%)		
PR status			2.065	0.151
Positive	26 (41.9%)	35 (56.5%)		
Negative	36 (58.1%)	27 (43.5%)		
HER-2 status			1.256	0.262
Positive	26 (41.9%)	19 (30.6%)		
Negative	36 (58.1%)	43 (69.4%)		
Vasculatogenic cancer thrombus			0.688	0.407
Positive	18 (29.0%)	13 (21.0%)		
Negative	44 (71.0%)	49 (79.0%)		
Nerve involvement			0.479	0.489
Positive	6 (9.7%)	3 (4.8%)		
Negative	56 (90.3%)	59 (95.2%)		
Menopause			1.582	0.208
Yes	28 (45.2%)	36 (58.1%)		
No	34(54.8%)	26 (41.9%)		
Neoadjuvant therapy			3.046	0.081
Yes	13 (21.0%)	6 (9.7%)		
No	49 (79.0%)	56 (90.3%)		

Abbreviations: ER, Estrogen receptor; PR, Progesterone receptor; HER-2, Human epidermal growth factor receptor 2; IMLNI, Internal mammary lymph node irradiation, Non-internal mammary lymph node irradiation.

Radiotherapy-Related Toxicity and Side Effects

There was no statistical difference in the incidence of grade 1–2 advanced skin, lung, and cardiac adverse radioactive reactions in the IMLNI group and the non-IMLNI group ($P>0.05$) ($P<0.05$), and there was no grade 3 advanced adverse radiation reaction in both groups (see [Table 6](#) for details). The results showed that there was no statistically significant difference in the adverse reactions of left-sided and right-sided breast cancer in the IMLNI group ($P>0.05$) (see [Table 7](#)).

Discussion

Petrov et al used clinical data and lymphatic scintigraphy results to calculate the probability of breast cancer (BC) invasion of internal mammary lymph node s (IMLN), and clinical studies showed that the number of ALN-positive patients was positively correlated with internal mammary lymph node metastasis, and the rates of internal mammary lymph node metastasis in ALN-negative and positive breast cancer patients were 7.8% and 38.1%, respectively.¹¹ Huang O, Wang L, Shen K et al reported the relationship between the number of ALN positivity and the rate of Breast cancer subpopulation with high risk of internal mammary lymph nodes metastasis, the study showed that with the increase in the

Table 2 Comparison of Survival Between the IMLNI Group and Non-IMLNI Group[Cases (%)]

Survival Indicators	IMLNI Group (n=62)	Non-IMLNI Group (n=62)	Statistical Value X ² /Z	P
5 years of OS			0.210	0.647
Finale	12 (19.4%)	13 (20.2%)		
Censoring	50 (80.6%)	49 (79.8%)		
5 years of DFS			0.001	0.980
Finale	23 (39.1%)	25 (40.3%)		
Censoring	39 (62.9%)	37 (59.7%)		
5 years of LRR			0.299	0.585
Finale	14 (22.6%)	13 (21.0%)		
Censoring	48 (77.4%)	49 (79.0%)		
5 years of DM			0.237	0.627
Finale	16 (25.8%)	21 (33.9%)		
Censoring	46 (74.2%)	41 (66.1%)		

Abbreviations: OS, Overall survival; DFS, Disease-free survival; LRR, Local recurrence rate; DM, distant metastasis rate; IMLNI, Internal mammary lymph node irradiation, Non-internal mammary lymph node irradiation.

number of axillary lymph nodes, the rate of internal mammary lymph nodes metastasis was significantly lower in tumors located in the lateral quadrant compared with medial and central tumors.¹² In recent years, the decision to radiotherapy to the internal mammary lymph nodes (IMNI) has been a controversial topic. In the 2014 EBCTCG meta-analysis, 22 clinical trials were included, and 8135 patients with positive axillary lymph nodes were treated with postoperative radiotherapy to the affected chest wall and regional lymph nodes (including internal mammary lymph nodes), and the 10-year recurrence rate and 20-year mortality rate of patients were followed-up, and the results showed that it could improve local recurrence, overall recurrence and breast cancer-related mortality in patients.¹³ The DBCG-IMN study collected 3089 patients with a median follow-up of 8.9 years to evaluate the effect of internal mammary lymph node

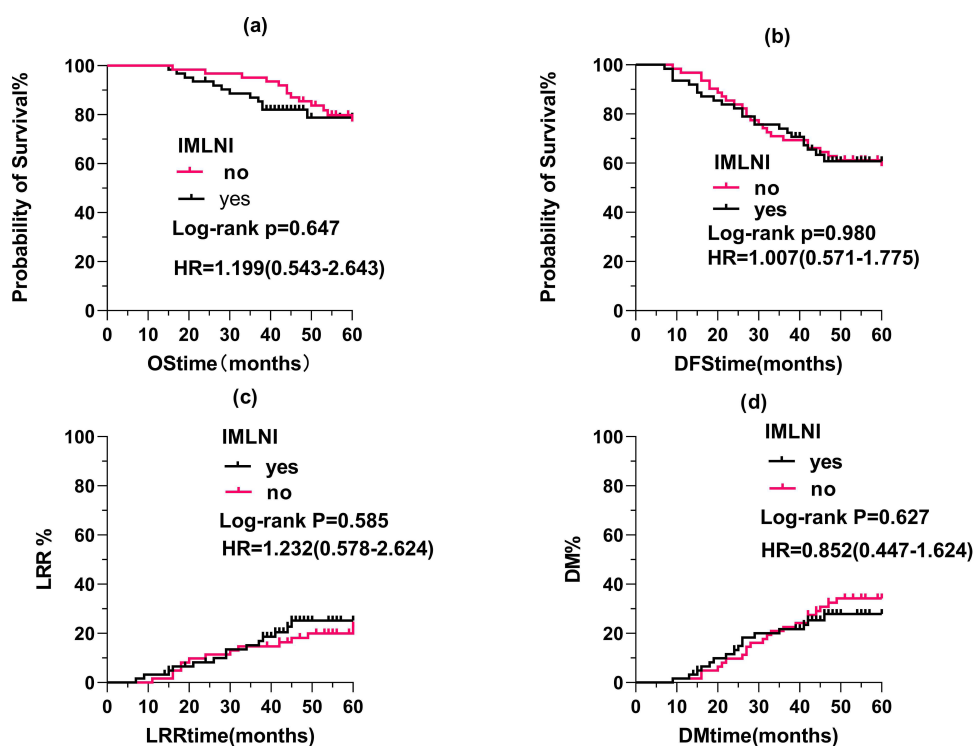


Figure 1 (a) OS of IMLNI and non-IMLNI patients; (b) DFS of IMLNI and non-IMLNI patients; (c) LRR of IMLNI and non-IMLNI patients; (d) DM of IMLNI and non-IMLNI patients.

Table 3 Univariate Analysis of Influencing Factors of OS, DFS, LRR, and DM in 5 Years of Enrolled Patients [Case (%)]

Influencing factors	OS		DFS		LRR		DM	
	X ² /Z	P	X ² /Z	P	X ² /Z	P	X ² /Z	P
Age(year)	0.120	0.729	0.694	0.405	0.051	0.821	0.008	0.927
Tumor location	0.834	0.361	0.256	0.213	0.098	0.754	0.798	0.372
Quadrant	0.033	0.856	0.092	0.762	0.000	0.984	0.037	0.911
T stage	11.150	0.004	3.067	0.216	4.020	0.134	0.237	0.888
ER status	5.144	0.023	2.906	0.088	3.695	0.055	4.668	0.031
PR status	5.723	0.017	4.569	0.033	7.234	0.007	6.354	0.012
HER-2 status	0.642	0.423	0.340	0.560	0.900	0.343	0.346	0.556
Vasculatogenic cancer thrombus	4.024	0.045	0.258	0.612	0.052	0.820	0.948	0.330
Nerve invasion	0.133	0.715	0.575	0.448	0.363	0.547	0.886	0.347
Menopause	0.282	0.595	0.407	0.523	0.025	0.874	0.119	0.730

Abbreviations: ER, Estrogen receptor; PR, Progesterone receptor; HER-2, Human epidermal growth factor receptor 2; OS, Overall survival; DFS, Disease-free survival; LRR, Local recurrence rate; DM, distant metastasis rate.

radiotherapy in patients with early-stage axillary node-positive breast cancer. In this study, 1492 patients were enrolled in the internal mammary lymph node radiotherapy group and 1597 patients were enrolled in non- internal mammary lymph node lymph nodes, and the results showed that patients who received postoperative internal mammary lymph node radiotherapy had an 8-year OS benefit (75.9% vs 72.2%, HR=0.82, 95% confidence interval 0.72–0.94, P=0.005). The results of the irradiation group showed that internal mammary lymph node irradiation significantly improved the overall survival rate of patients, and reduced the mortality rate and distant recurrence risk of breast cancer.¹⁴ EORTC22922/1092 is a multicenter randomized controlled trial (RCT), which included patients with stage I–III breast cancer, and the patients were randomly divided into regional lymph node irradiation group (internal mammary lymph node + supraclavicular lymph node) and non-regional lymph node irradiation group, a total of 4004 patients were included in the study, and the 10-year follow-up data showed that the overall survival rate of patients receiving regional lymph node irradiation was The disease-free survival rate and distant metastasis-free survival rate were improved, and the mortality rate of breast cancer was reduced.¹⁵ These three prospective randomized clinical studies have shown that postoperative radiation therapy to regional lymph nodes for breast cancer can improve patient outcomes.

However, the following results differ from the 2020 EORTC22922 / 10925 study published 15-year follow-up results: 15-year overall survival did not improve in the regional node exposure group; breast cancer recurrence and breast cancer mortality in the regional node exposure group than the non-regional node exposure group,disease-free survival and distant.¹⁶ The NCICMA.20 study released its 10-year follow-up data. The study 2000–2007,1832 patients of breast cancer after breast-conserving surgery and breast surgery + regional lymph node radiotherapy, regional lymph node irradiation range of internal lymph nodes + supraclavicular lymph nodes + axillary lymph nodes, 10-year follow-up data showed that regional lymph node irradiation group can improve disease-free survival, reduce distant metastasis, but can not improve mortality and OS.¹⁷ These two prospective randomized clinical studies have different survival benefits depending on the follow-up duration. In addition, the KROG08-06 trial included 735 breast cancer patients for post-operative radiotherapy, of which 373 patients were included in the non- internal mammary lymph node node irradiation group and 362 patients were included in the internal mammary lymph node node irradiation group. There was no significant difference in the 7-year progression-free survival rate between the two groups. However, subgroup analysis showed that only patients with tumor lesions located in the central area had a higher progression-free survival rate than those with non-inner breast lymph node irradiation, and breast cancer mortality was improved in the inner breast irradiation group. The study confirmed that internal mammary lymph node irradiation does not significantly improve progression-free survival in patients with node-positive breast cancer and that this exposure may yield benefits in patients with tumors located in the inner quadrant / central zone.¹⁸ In a 2013 French randomized study including 1334 breast cancer patients (inclusion criteria: age <75 years, positive axillary lymph nodes or lesions in central/medial breast with or

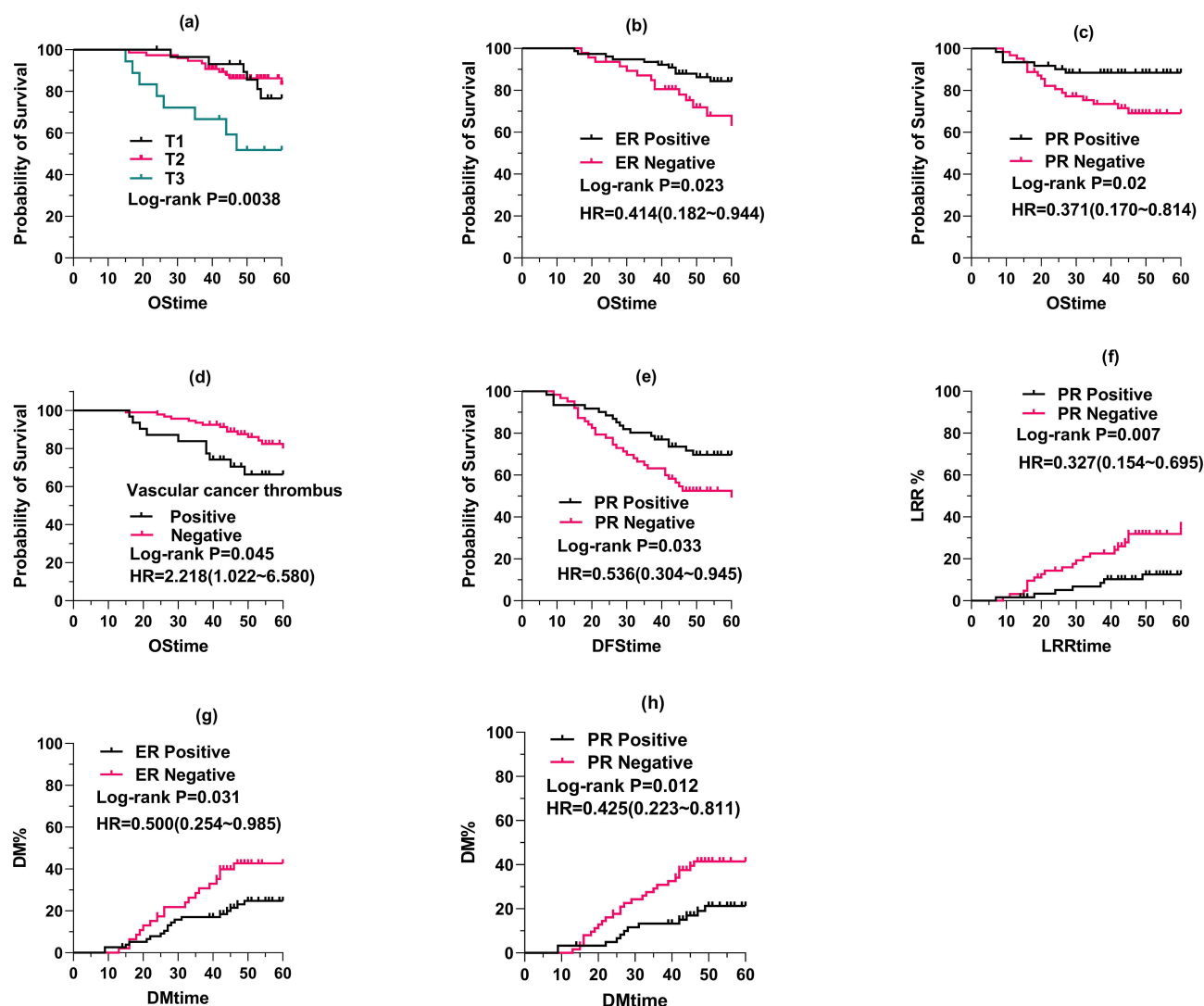


Figure 2 (a) OS of different T stages patients; (b) OS of ER status patients; (c) OS of PR status patients; (d) OS of vascular cancer thrombosis patients; (e) DFS of PR status patients; (f) LRR of PR status patients; (g) DM of ER status patients; (h) DM of PR status patients.

without positive lymph nodes), all patients received postoperative radiotherapy and were randomly divided into internal mammary lymph node irradiation group and non-internal mammary lymph node lymph node irradiation group. There was no significant difference in the 10-year survival rate and disease-free survival rate between the two groups. The negative study results may be caused by the lack of assessment of the target dose and the patients enrolled in the trial including many low-risk patients (axillary node-negative patients).¹⁴ In a retrospective analysis, a total of 99 patients were included, including 23 (23.2%) who underwent IMLNI. IMLNI and non-IMLNI 5-year OS were 78.3% and 81.6% ($P > 0.05$), respectively, DFS 56.5% and 72.4% ($P > 0.05$), LRR 13.0% and 9.2% ($P > 0.05$), and DM 31.4% and 22.4% ($P > 0.05$), respectively. After prognosis analysis in subgroups of patients of different age groups, T stage, N stage, and quadrants, IMLNI showed statistically significant differences in 5-year OS, DFS, and DM in patients aged 50 ($P < 0.05$). No significant difference in 5-year DFS for patients with tumors in the inner/central quadrant ($P < 0.05$) and no significant differences in 5-year OS, DFS, LRR, and DM for the other subgroups ($P > 0.05$).¹⁹ In the above studies, the outcome bias caused by the radiation between the lymph node group and the non-lymph node radiotherapy group may be due to the different clinical baseline characteristics, pathological characteristics, systemic treatment regimen and radiotherapy equipment. The results of patients with stage N3 breast cancer in the lateral quadrant showed no 5-year OS, DFS, LRR, and DM in the non-IMLNI radiotherapy group in the IMLNI radiotherapy group. It may be because the short

Table 4 Results of Multivariate Analysis of Influencing Factors of OS and DFS in 5 Years of Enrolled Patients

Influencing Factors	OS	DFS	P
	HR (95% CI) P	HR (95% CI)	
Age(year)	–	–	–
Tumor location	–	–	–
Quadrant	–	–	–
T stage	0.224(0.074–0.675) 0.008	–	–
ER status	0.949 (0.289–3.119) 0.932	0.959 (0.427–2.156)	0.919
PR status	0.23 (0.060–0.937) 0.040	0.552 (0.240–1.269)	0.162
HER-2 status	–	–	–
Vasculatogenic cancer thrombus	3.089(1.282–9.441) 0.012	–	–
Nerve invasion	–	–	–
Menopause	–	–	–

Table 5 Results of Multivariate Analysis of Influencing Factors of LRR and DM in 5 Years in Enrolled Patients

Influencing Factors	LRR	DM	P
	HR (95% CI) P	HR (95% CI)	
Age(year)	–	–	–
Tumor location	–	–	–
Quadrant	–	–	–
T stage	–	–	–
ER status	1.05 (0.404–2.745) 0.915	0.875 (0.349–2.194)	0.776
PR status	0.314 (0.106–0.935) 0.038	0.469 (0.176–1.249)	0.130
HER-2 status	–	–	–
Vasculatogenic cancer thrombus	–	–	–
Nerve invasion	–	–	–
Menopause	–	–	–

Notes: – represents $P > 0.1$ in univariate analysis, and was not included in multivariate analysis.

Abbreviations: HR, hazard ratio; CI, confidence interval; ER, Estrogen receptor; PR, Progesterone receptor; HER-2, Human epidermal growth factor receptor 2.

Table 6 Comparison of Late Radiation Adverse Reactions Between the IMLNI Group and the Non-IMLNI Group[Cases (%)]

		IMLNI group(n=62)			Non-IMLNI group(n=62)			Z	P
Adverse effects	Level 0	Level 1–2	Level 3	Level 0	Level 1–2	Level 3			
Skin	49(79%)	13(21%)	0 (0%)	51 (82.3%)	11 (17.7%)	0 (0%)	0.207	0.649	
Lung	52 (83.9%)	10 (16.1%)	0 (0%)	55 (88.7%)	7 (11.3%)	0 (0%)	0.614	0.443	
Heart	56 (90.3%)	6 (9.7%)	0 (0%)	58 (93.5%)	4 (6.5%)	0 (0%)	0.435	0.510	

Abbreviations: IMLNI, Internal mammary lymph node irradiation, Non-internal mammary lymph node irradiation.

Table 7 Comparison of Advanced Cardiac Radiation Adverse Reactions Between Left and Right Breast Cancer in the IMLNI Group[Cases (%)]

Survival Indicators	Left Mammary Gland (n=36)	Right Mammary Gland (n=26)	χ^2	P
Cardiac response			0.782	0.376
Finale	5 (13.9%)	1 (3.8%)		
Censoring	31 (86.1%)	25 (96.2%)		

follow-up time, late N stage, and local advanced stage lead to poor overall survival status, which counteracts the survival benefit of internal mammary lymph node radiotherapy and biases the results. These results should be obtained and further examined in a multicenter study.

Fowble et al showed that the incidence of pulmonary fibrosis in the IMLNI group was 1.9% higher than that in the no IMNI group (2.8% vs 0.9%, $P < 0.001$). The incidence of pneumonia and dyspnea IMNI increased by 0.6% over no IMNI (0.7% vs 0.1%, $P = 0.0007$; 0.7% vs 0.1%, $P = 0.0012$).²⁰ In Darby et al, 2168 patients with breast cancer radiotherapy were included to evaluate the effect of radiotherapy on the coronary artery. The average cardiac dose of patients was 4.9 Gy, and the average cardiac dose was linearly related to the occurrence of coronary artery disease. For every 1 Gy increase in the average cardiac dose, the incidence of coronary artery disease increased by 7.4% and 11.8%. MA.20 results suggested significantly increased grade 3 acute reactions (radiation dermatitis and radiation pneumonia) and late reactions (lymphedema, skin telangiectasia and subcutaneous fibrosis) in the regional lymph node irradiation group; cardiovascular events were not differentiated due to short follow-up.²¹ The results of the EORTC22922 / 10925 trial provided some guidance for internal mammary lymph node radiotherapy, and the 15-year follow-up data showed that any cardiac event was 2.7% higher than the control group, and pulmonary fibrosis was 2.8% higher than the control group. Most patients had no significant difference in grade 1–2 cardiac or pulmonary adverse events. The incidence of cardiotoxicity events caused by internal milk lymph node irradiation, the occurrence of second malignancy, the occurrence of contralateral breast cancer, and cardiovascular-related death were not associated with the tumor site (left / right). In addition, the KROG08-06 test also confirmed that internal mammary lymph node irradiation did not increase cardiotoxic effects and radiation pneumonia, but the follow-up time of the study was short, and long-term follow-up data have not been published. The five-year follow-up results of this study showed no statistical difference between the IMLNI group and the non-IMLNI group ($P > 0.05$). No patients in both groups had > 3 late RT and there was no statistical difference in the left and right breast cancer subgroups in the IMLNI group ($P > 0.05$). With the progress of radiotherapy technology, studies have shown IMTRT, VMRT, proton beam radiotherapy, radiation Angle optimization, and the use of multi-leaf grating collimator. Can maximize the protection of the surrounding normal tissue.^{22,23} In addition, studies have shown that breathing gating, deep inhalation and breath holding, and changing the position to a prone position can increase the distance between the heart and the target of radiotherapy, thus reducing the dose of heart and lung irradiation during radiotherapy.^{24,25} In this way, we can develop individualized radiotherapy programs so that the patients can benefit the most. The results of the univariate analysis in this study showed that T stage, ER, PR, and vascular cancer thrombus status were related to five-year OS ($P < 0.05$), PR status was related to five-year DFS and LRS ($P < 0.05$), and ER and PR status were related to five-year DM ($P < 0.05$). The multivariate results showed that, T stage ($P = 0.008$, HR=0.224, 95% CI=0.074–0.675), PR status ($P = 0.040$, HR=0.237, 95% CI=0.060–0.937), Vascular cancer plug ($P = 0.012$, HR=3.089, 95% CI=1.282–9.441), Is an independent prognostic factor affecting 5-year OS in breast cancer patients, PR expression status ($P = 0.038$, HR=3.14, 95% CI=0.106–0.935) is an independent prognostic factor affecting 5-year LRR. The remaining factors are not statistically different from the 5-year prognosis. Prem Chand et al showed that the incidence of axillary lymph node (ALN) positivity was higher with the increasing size of breast tumors and tumors located in the outer quadrant of the breast. Radiotherapy has significantly improved survival in patients with lesions greater than 5cm or 4 positive axillary lymph nodes (ALNs).²⁶ The current NCCN guidelines recommend adjuvant endocrine therapy for patients with hormone receptor positive.²⁷ Prolonged endocrine therapy in ER-positive, HER-2-negative breast cancer patients report reported reduced recurrence risk and overall mortality after 2 years of treatment with tamoxifen or aromatase inhibitors (aromatase inhibitor, AI).²⁸ Amelia B. Zelnak et al also showed that for patients with early and advanced HR + breast cancer, adjuvant endocrine significantly improved prognosis.^{29–31} In recent years, the results of several studies showed that a positive vascular cancer thrombus is associated with local recurrence, distant metastasis, and poor prognosis in breast cancer patients. In 2014, Munzone et al found in their study that for patients with node-positive breast cancer, vascular cancer embolism caused an increased risk of local recurrence, but did not affect the overall prognostic level of breast cancer.³² The study presented in this paper suggests that hormone receptor-positive patients may benefit from IMNI and that positive vascular cancer thrombolysis may be associated to distant metastasis in breast cancer patients. This still needs to be verified by further clinical trials. In the era of precision therapy, we need to find out the population suitable for IMNI, especially for patients with hormone receptor-positive

results. More prospective studies and clinical retrospective studies are needed to verify whether adding IMNI can benefit such patients.

In conclusion, the limitations of this study are as follows: (1) the study was retrospective with a small number of samples; (2) Due to the short follow-up time, long-term DFS, OS, LRR, DM, and long-term adverse effects due to radiotherapy cannot be obtained; (3) In this study, a shorter follow-up period was not possible to evaluate the long-term cardiotoxicity and efficacy of IMNI + anthracycline + trastuzumab in triple-negative and her-2-positive patients. The following studies may indicate these deficiencies. A 10-year prospective study comparing cardiotoxicity in node-positive breast cancer patients on radiotherapy (Radiotherapy, RT) versus adjuvant chemotherapy alone observed no significant difference in cardiotoxicity risk.³³ According to the results of the EBCTCG meta-analysis, chemotherapy including anthracycline and taxane species can reduce breast cancer mortality by 1 / 3 at 10 years.³⁴ In the Slamon D, Eiermann W, Robert Net al et al study, 27% of patients combined with anthracycline and trastuzumab had cardiac dysfunction and symptomatic heart failure in 16%, compared with 8% and 3% of anthracycline patients without trastuzumab.³⁵ Therefore, a large number of multicenter prospective clinical trials need longer follow-up to clarify the prognosis and adverse effects.

Conclusion

1. This study concluded that: after bias score matching, breast cancer patients located in the lateral quadrant and positive axillary lymph nodes of more than 9, increasing IMNI failed to improve the 5-year prognosis of patients, still requiring more large clinical trial evidence to support;
2. Late N stage, negative PR receptor, and positive vascular cancer embolism can reduce the 5-year OS of breast cancer patients after breast cancer surgery, and positive PR receptor can reduce the 5-year LRR of patients;
3. There was no significant difference in 5-year late radiation adverse effects in the IMLNI group and non-IMLNI group.

Data Sharing Statement

The data supporting the results in the manuscript can be obtained from the corresponding author based on reasonable request.

Ethics Approval and Consent to Participate

This retrospective study approved by the Institutional Review Board of The First Affiliated Hospital of Bengbu Medical University (approval number: 2020123). Given that this study was conducted relying on retrospective data collected as part of routine clinical practice, ethical committee waived the consent, and individual informed consent was not obtained. In this retrospective study, no patient identifiers were used and data were anonymized. This study followed the Declaration of Helsinki (2013 revision).

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Disclosure

The authors report no conflicts of interest in this work.

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