Research Square

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A Retrospective Single-Center Study on Postoperative Radiotherapy Without Internal Mammary Node Irradiation in pT1–2N1M0 Breast Cancer

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Abstract

Background

Whether internal mammary node irradiation (IMNI) should be routinely included in postoperative radiotherapy for pT1–2N1M0 breast cancer remains controversial. Randomized evidence is inconsistent, while observational data suggest that benefit may be restricted to specific subgroups.

Methods

We conducted a retrospective cohort study of 648 patients treated between January 2010 and December 2015 at a single center. All patients underwent curative surgery (mastectomy or breast-conserving surgery) and received postoperative 3-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT), but without IMNI. The primary endpoint was disease-free survival (DFS); secondary endpoints included overall survival (OS), distant disease-free survival (DDFS), and breast cancer–specific survival (BCSS). Survival was estimated using Kaplan–Meier methods, and prognostic factors were assessed with univariate and multivariable Cox proportional hazards models.

Results

At 10 years, DFS, OS, DDFS, and BCSS were 83.7%, 90.0%, 84.8%, and 93.1%, respectively. In multivariable analyses, triple-negative molecular subtype was the strongest independent adverse factor across endpoints (OS HR = 3.750, P < 0.001; BCSS HR = 3.971, P < 0.001). Age ≤ 40 years (BCSS HR = 0.461, P = 0.027) and lymphovascular invasion positivity (BCSS HR = 2.325, P = 0.010) were independently associated with poorer outcomes. Anthracycline plus taxane–based chemotherapy independently improved OS/DFS/DDFS.

Conclusion

In patients with pT1–2N1M0 breast cancer who did not receive IMNI, triple-negative subtype, age ≤ 40 years, and LVI positivity identify individuals with significantly worse prognosis, supporting individualized IMN decision-making.

1 Introduction

Breast cancer is the most frequently diagnosed malignancy among women worldwide. According to global cancer statistics released by the International Agency for Research on Cancer (IARC), approximately 2.3 million new cases of breast cancer were diagnosed worldwide in 2022, with an estimated 670,000 deaths [1]. Thus, breast cancer has become one of the leading causes of cancer incidence and cancer-related mortality among women. Despite substantial progress in early detection and treatment, the global burden of breast cancer continues to rise and is expected to increase further over the coming decades[2]. In patients with pT1–2N1M0 breast cancer, postoperative whole-breast radiotherapy reduces the risk of ipsilateral breast tumor recurrence(IBTR) to approximately one-third and may improve overall survival[3].

For patients undergoing breast-conserving therapy (BCT) with axillary lymph node involvement, regional lymph node irradiation is recommended[4]. For patients treated with mastectomy, postoperative irradiation of the chest wall and regional lymph nodes is generally recommended when tumors are T3 or higher, when surgical margins are negative, or when there is clear evidence of lymph node metastasis; for patients with T1–2 disease, chest wall and regional lymph node irradiation is recommended only in the presence of certain high-risk features[5]. Although irradiation of the

supraclavicular region has been widely adopted, whether the internal mammary nodes (IMNs) should be routinely included remains controversial.

Therefore, this study aims to evaluate the therapeutic efficacy of postoperative radiotherapy excluding IMN coverage using real-world data.

2 Methods and Materials

This retrospective cohort study was conducted at the Affiliated Cancer Hospital of Xinjiang Medical University. It aimed to evaluate the clinical efficacy of postoperative radiotherapy in patients with pT1–2N1M0 breast cancer who did not receive IMNI. Eligible patients were required to have pathologically confirmed breast cancer and to undergo curative surgical resection, including mastectomy or breast-conserving surgery, irrespective of whether reconstructive surgery was performed. All patients had to receive their first treatment between January 1, 2010 and December 31, 2015. Postoperative pathology must have confirmed pT1–2N1M0 disease, and patients were required to receive 3-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT).

The exclusion criteria were as follows: (1) distant metastasis at diagnosis; (2) prior exposure to thoracic radiotherapy; and (3) coexisting malignancies at other sites or a primary malignancy in the contralateral breast. The primary endpoint was disease-free survival (DFS). Secondary endpoints included overall survival (OS); breast cancer–specific survival (BCSS); and distant disease-free survival (DDFS). First recurrence sites were categorized into three groups: (1) local recurrence within the ipsilateral breast or chest wall; (2) regional lymph node recurrence involving the ipsilateral axillary, supraclavicular, or para-aortic nodal regions; and (3) distant recurrence, defined as metastasis occurring in non-irradiated skin or subcutaneous tissues, bone, lung, liver, or other organs, including recurrence in the contralateral lymph nodes. Clinical, pathological, treatment, and follow-up data were retrospectively collected from the hospital's single-disease institutional database. Data collection was updated through June 30, 2026.

Kaplan–Meier curves were used to estimate DFS, OS, BCSS, and DDFS. Univariate analyses were performed using the log-rank test or the corresponding Cox proportional hazards model. Multivariable analyses were conducted with a Cox proportional hazards regression model to assess the independent prognostic effects of clinical and pathological variables. Based on clinical relevance and previously reported prognostic factors, the following variables at initial presentation were considered for inclusion: age,, laterality, tumor size, molecular subtype, Ki-67 expression, primary tumor location, the number of metastatic lymph nodes, and chemotherapy drug use. To minimize overfitting, the number of covariates was reduced in the multivariable models. Statistical significance was set at a two-sided $P < 0.05$. All statistical analyses were performed using R (version 4.5.3).

3 Results

3.1 Patient characteristics

From January 2010 to December 2015, a total of 648 eligible patients with breast cancer were identified among those treated at the Affiliated Cancer Hospital of Xinjiang Medical University.

Among 648 patients with pT1–2N1M0 breast cancer who received postoperative radiotherapy without IMNI, the median age was 46 years (range, 25–75). Regarding radiotherapy, the median prescribed dose was 5000 cGy (range, 2000–6020 cGy). 14.8% (96 cases) received a tumor bed boost. With respect to T stage, T1 disease was present in 49.2% (319 cases) and T2 disease in 50.8% (329 cases). The number of involved axillary lymph nodes was 1 positive node in 50.6% (328 cases) and 2–3 positive nodes in 49.4% (320 cases). For molecular subtypes, Luminal tumors accounted for 56.5% (366 cases), HER2-overexpressing tumors for 25.0% (162 cases), triple-negative tumors for 13.1% (85 cases). Ki-67 high

expression (≥ 14%) was observed in 67.4% (437 cases), Ki-67 low expression in 17.0% (110 cases). With regard to systemic therapy, 97.5% (632 cases) received chemotherapy. The most common regimen was an anthracycline plus taxane–based regimen (79.3%, 514 cases). Endocrine therapy was administered in 69.9% (453 cases), and anti-HER2 targeted therapy was used in 7.4% (48 cases). The baseline characteristics of the patients are summarized in Table 1.

Table 1
Baseline patient and tumor characteristics

variable	N	%
Age, median (range), y	46.0 (25.0–75.0)	
≤ 40	163	25.20%
40–60	429	66.20%
>60	56	8.60%
Menopause age, median (range), y	49.0 (35.0–58.0)	
postmenopausal	212	32.70%
premenopausal	436	67.30%
T stage		
T1	319	49.20%
T2	329	50.80%
Hypertension		
YES	78	12%
NO	570	88%
Diabetes		
YES	23	3.50%
NO	625	96.50%
Coronary heart disease		
YES	12	1.90%
NO	636	98.10%
Hyperlipidemia		
YES	11	1.70%
NO	637	98.30%
Comorbidity count		
0	553	85.30%
1	71	11%
>2	24	3.70%
Tumor quantity		
Single	602	92.90%
multiple	42	6.50%
Unknown	4	0.60%
Laterality		

variable	N	%
Right	308	47.50%
Left	340	52.50%
Location		
Inner/Central	246	38%
Outer	402	62%
No. of positive nodes		
1	328	50.60%
2	198	30.60%
3	122	18.80%
Histology type		
IDC*	494	76.20%
Others or Unknown	154	23.80%
grade		
1	36	5.60%
2	383	59.10%
3	119	18.40%
Unknown	110	17%
LVI*		
Positive	123	19%
Negative or Unknown	525	81%
PNI*		
positive	38	5.90%
Negative or Unknown	610	94.10%
Molecular subtype		
HR+/HER2–	366	56.50%
HER2+	162	25%
HR–/HER2–	85	13.10%
Unknown	35	5.40%
Ki67		
High	437	67.40%
Low	110	17%
Unknown	101	15.60%
Surgery type		

variable	N	%
Breast-conserving surgery	108	16.70%
Mastectomy	540	83.30%
Ratio of positive/dissected lymph nodes	0.1 (0.0–1.0)	
Chemotherapy		
YES	632	97.50%
NO	16	2.50%
Chemotherapy regimen		
Anthracyclines	56	9%
Taxanes	36	5.70%
Anthracyclines + Taxanes	514	81.30%
Other/Unknown	26	4%
Radiotherapy median, cGy	5000	
Tumor bed boost		
YES	96	14.80%
NO	552	85.20%
AntiHER2		
YES	48	7.40%
NO	600	92.60%
Endocrine		
YES	453	69.90%
NO	195	30.10%

*IDC: Invasive Ductal Carcinoma; *LVI: Lymphovascular Invasion; *PNI: Perineural Invasion; *HR: Hormone Receptor; *HER2: Human Epidermal Growth Factor Receptor 2.

3.2 Survival Analysis

For the 648 patients who did not receive IMNI, the median follow-up time was estimated using the reverse Kaplan–Meier method. The median follow-up durations for DFS, OS, DDFS, and BCSS were 122.3, 122.3, 122.8, and 121.3 months, respectively. At 10 years, the estimated DFS rate was 83.7% (95% CI: 80.7%–86.9%; Fig. 1a). The corresponding OS, DDFS, and BCSS rates at 10 years were 90.0% (95% CI: 87.6%–92.4%), 84.8% (95% CI: 81.9%–87.7%), and 93.1% (95% CI: 91.1%–95.2%), respectively (Fig. 1b–d).

3.3 Univariate Analysis

Univariate Cox regression analyses showed that age 41–60 years (vs ≤ 40 years) was associated with significantly better OS (HR = 0.568, $p = 0.044$) and BCSS (HR = 0.460, $p = 0.017$). T2 stage, two positive lymph nodes, multifocality, LVI positivity, and the triple-negative molecular subtype were all associated with an unfavorable prognosis. Among them, T2 stage was statistically significant across all four endpoints. The triple-negative subtype showed the strongest effects for

OS and BCSS (HR = 3.193 and 3.513, respectively; both $p < 0.001$). An anthracycline plus taxane–based regimen was associated with improved DFS (HR = 0.495, $p = 0.013$) and DDFS (HR = 0.504, $p = 0.020$). Left-sided breast cancer was associated with better OS (HR = 0.592, $p = 0.038$).

For the remaining variables (age > 60 years, three positive lymph nodes, HER2+, taxane-only regimen, tumor location, histologic grade, and Ki-67), no statistically significant associations with any endpoint were observed (Table 2).

3.4 Multivariable Analysis

After multivariable adjustment, age 41–60 years remained an independent protective factor for BCSS (HR = 0.497, $p = 0.048$). Three positive lymph nodes, multifocality, LVI positivity, and the triple-negative molecular subtype were independent risk factors for OS and/or BCSS. Specifically, with three positive nodes, the risks were increased for OS (HR = 2.217, $p = 0.023$) and BCSS (HR = 2.429, $p = 0.034$); with multifocality, BCSS was independently worse (HR = 2.833, $p = 0.030$); for LVI positivity, risks increased for OS (HR = 1.842, $p = 0.048$) and BCSS (HR = 2.714, $p = 0.004$); and for the triple-negative subtype, risks increased for OS (HR = 2.850, $p = 0.002$) and BCSS (HR = 3.175, $p = 0.006$).

An anthracycline plus taxane–based regimen was independently associated with improved DFS, OS, and DDFS (DFS: HR = 0.459, $p = 0.008$; OS: HR = 0.422, $p = 0.027$; DDFS: HR = 0.470, $p = 0.013$). In the multivariable model, T stage, laterality, tumor location, histologic grade, and Ki-67 showed no significant independent effects (Table 3).

Table 2
Univariate analysis of prognostic factors for DFS, OS, DDFS, and BCSS

Variable		DFS		OS		DDFS		BCSS	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	≤ 40 vs.41–60	0.683 (0.442–1.057)	0.087	0.568 (0.328–0.985)	**0.044**	0.654 (0.418–1.021)	0.062	0.460 (0.243–0.872)	**0.017**
	≤ 40 vs.>60	1.607 (0.867–2.978)	0.132	1.894 (0.931–3.856)	0.078	1.389 (0.724–2.665)	0.323	0.974 (0.359–2.646)	0.959
T stage	T1 vs. T2	1.518 (1.026–2.246)	**0.037**	1.982 (1.186–3.314)	**0.009**	1.601 (1.065–2.408)	**0.024**	1.896 (1.012–3.550)	**0.046**
Positive nodes	1 vs. 2	1.202 (0.777–1.858)	0.409	1.779 (1.022–3.097)	**0.042**	1.231 (0.784–1.933)	0.367	2.013 (1.005–4.031)	**0.048**
	1 vs. 3	1.098 (0.654–1.845)	0.724	1.635 (0.862–3.101)	0.133	1.137 (0.666–1.941)	0.638	2.003 (0.920–4.363)	0.080
Tumor quantity	Single vs. Multiple	1.231 (0.599–2.533)	0.572	1.530 (0.661–3.545)	0.321	1.342 (0.651–2.766)	0.426	2.436 (1.028–5.772)	**0.043**
Laterality	Right vs. Left	0.978 (0.666–1.438)	0.912	0.592 (0.360–0.972)	**0.038**	0.877 (0.589–1.305)	0.517	0.640 (0.349–1.173)	0.149
Local	Lateral vs. Medial/Central	0.931 (0.628–1.379)	0.721	0.905 (0.551–1.487)	0.694	0.858 (0.573–1.286)	0.4588	0.926 (0.503–1.707)	0.8062
Grade	1 vs. 2	0.814 (0.35–1.894)	0.633	0.496 (0.191–1.285)	0.149	0.764 (0.328–1.782)	0.533	0.588 (0.175–1.98)	0.392
	1 vs. 3	1.344 (0.553–3.265)	0.514	1.282 (0.483–3.399)	0.618	1.232 (0.503–3.014)	0.648	1.414 (0.406–4.923)	0.586
LVI	Positive vs. Negative	1.367 (0.866–2.158)	0.179	1.746 (1.014–3.008)	**0.044**	1.336 (0.830–2.149)	0.233	2.696 (1.452–5.006)	**0.002**
Ki-67	High vs. Low	1.174 (0.703–1.959)	0.540	1.381 (0.734–2.598)	0.317	1.205 (0.711–2.042)	0.490	1.103 (0.477–2.551)	0.819
Molecular subtype	HR+/HER2−vs. HER2+	0.942 (0.580–1.530)	0.808	1.152 (0.606–2.188)	0.666	0.893 (0.540–1.479)	0.661	1.221 (0.544–2.740)	0.628
	HR+/HER2−vs. **H**R−/HER2−	1.738 (1.043–2.897)	**0.034**	3.193 (1.766–5.774)	**< 0.001**	1.607 (0.943–2.741)	0.081	3.513 (1.677–7.358)	**< 0.001**

Variable		DFS		OS		DDFS		BCSS	
		HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Chemotherapy regimen	Anthracyclines vs. Taxanes	0.497 (0.180–1.369)	0.176	0.848 (0.284–2.534)	0.767	0.424 (0.139–1.288)	0.130	0.612 (0.119–3.162)	0.558
	Anthracyclines vs. Anthracyclines + Taxanes	0.495 (0.283–0.864)	**0.013**	0.493 (0.240–1.014)	0.055	0.504 (0.283–0.897)	**0.020**	0.657 (0.255–1.692)	0.384

Table 3
Multivariable analysis of prognostic factors for DFS, OS, DDFS, and BCSS

Variable		DFS		OS		DDFS		BCSS	
		HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Age	≤ 40 vs.41–60	0.705 (0.447–1.113)	0.133	0.568 (0.315–1.025)	**0.060**	0.687 (0.43–1.098)	0.117	0.497 (0.249–0.993)	**0.048**
	≤ 40 vs.>60	1.363 (0.615–3.021)	0.446	1.213 (0.456–3.226)	0.698	1.245 (0.543–2.855)	0.605	1.188 (0.355–3.978)	0.780
T stage	T1 vs. T2	1.269 (0.837–1.923)	0.261	1.631 (0.941–2.827)	0.081	1.372 (0.892–2.11)	0.150	1.609 (0.829–3.125)	0.160
Positive nodes	1 vs. 2	1.119 (0.692–1.808)	0.647	1.665 (0.895–3.097)	0.108	1.122 (0.683–1.843)	0.650	2.072 (0.985–4.357)	0.055
	1 vs. 3	1.32 (0.767–2.27)	0.316	2.217 (1.115–4.407)	**0.023**	1.306 (0.748–2.279)	0.348	2.429 (1.07–5.513)	**0.034**
Tumor quantity	Single **vs.** Multiple	1.163 (0.541–2.497)	0.699	1.584 (0.631–3.975)	0.328	1.262 (0.584–2.726)	0.554	2.833 (1.105–7.267)	**0.030**
Laterality	Right vs. Left	1.071 (0.716–1.603)	0.738	0.675 (0.4–1.141)	0.142	0.971 (0.642–1.47)	0.891	0.677 (0.362–1.267)	0.223
Local	Lateral vs. Medial/Central	0.967 (0.636–1.47)	0.876	1.058 (0.616–1.82)	0.838	0.91 (0.592–1.398)	0.666	1.021 (0.534–1.952)	0.950
Grade	1 vs. 2	0.862 (0.35–2.122)	0.746	0.693 (0.234–2.047)	0.507	0.815 (0.33–2.011)	0.657	0.933 (0.238–3.651)	0.920
	1 vs. 3	1.441 (0.553–3.752)	0.454	1.718 (0.564–5.232)	0.341	1.356 (0.518–3.549)	0.534	2.014 (0.492–8.249)	0.331
LVI	Positive vs. Negative	1.567 (0.963–2.551)	0.071	1.842 (1.005–3.377)	**0.048**	1.394 (0.853–2.278)	0.184	2.714 (1.371–5.372)	**0.004**
Ki-67	High vs. Low	1.121 (0.624–2.014)	0.703	1.214 (0.565–2.609)	0.619	1.513 (0.912–2.511)	0.109	1.306 (0.502–3.395)	0.584
Molecular subtype	HR+/HER2−vs. HER2+	0.851 (0.499–1.451)	0.554	0.828 (0.401–1.712)	0.611	0.78 (0.448–1.357)	0.379	1.046 (0.442–2.474)	0.918
	HR+/HER2−vs. HR−/HER2−	1.671 (0.957–2.915)	0.071	2.85 (1.469–5.53)	**0.002**	1.5 (0.841–2.674)	0.170	3.175 (1.4–7.203)	**0.006**

Variable		DFS		OS		DDFS		BCSS	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Chemotherapy regimen	Anthracyclines vs. Taxanes	0.441 (0.147–1.328)	0.146	0.648 (0.182–2.309)	0.504	0.378 (0.114–1.254)	0.112	0.367 (0.054–2.509)	0.307
	Anthracyclines vs. Anthracyclines + Taxanes	0.459 (0.258–0.817)	**0.008**	0.422 (0.197–0.905)	**0.027**	0.47 (0.259–0.852)	**0.013**	0.568 (0.208–1.552)	0.271

4 Discussion

In postoperative radiotherapy decisions for pT1–2N1M0 breast cancer, whether the internal mammary lymph node (IMN) region should be included in the radiation field has long remained controversial. Authoritative guidelines, including those from the American Society for Radiation Oncology (ASTRO), generally recommend IMNI for patients with axillary lymph node involvement or with central/medial tumors. However, the strength of these recommendations varies across guidelines issued in different time periods. Before 2016, the NCCN guidelines provided a relatively low recommendation category (category 2B) for IMN irradiation in patients with 1–3 positive axillary lymph nodes. As a result, clinical practice exhibited substantial uncertainty regarding the decision to administer IMNI in this patient subgroup. In the 2016 NCCN guidelines (Version 1), a major update was implemented: the recommendation category for IMN irradiation was increased from 2B to 2A for patients with 1–3 positive lymph nodes, and the guideline explicitly stated that strongly recommending the inclusion of IMNs within the scope of regional nodal irradiation[6]. The most recent NCCN guidelines[7] state that whether IMNs should be included in RNI should be determined based on clinical judgment. Accordingly, the NCCN panel no longer specifies the exact radiation field to be encompassed by RNI, and instead refers to it more broadly as “comprehensive regional nodal irradiation.” The panel emphasizes that patient selection should balance potential risks and benefits, taking into account long-term organ toxicity (including cardiac and pulmonary toxicity), comorbidities, age, and life expectancy. If the radiation volume is expanded to include the internal mammary nodes, a detailed treatment planning process is required, and strict adherence to normal tissue dose constraints is necessary. Given this evolution in guideline recommendations, and to minimize confounding from differences in treatment strategies across periods with differing recommendations, this study included 648 patients with pT1–2N1M0 breast cancer who underwent surgery between January 1, 2010, and December 31, 2015—a period during which NCCN recommendations for IMNI in patients with 1–3 positive nodes were of lower strength—and in whom IMNI was omitted, to evaluate long-term survival and prognostic factors.

Two randomized controlled trials conducted in France and Korea directly compared clinical outcomes between patients receiving and not receiving IMN irradiation. The French trial reported no significant difference in 10-year overall survival between the two groups[8]. Notably, although most participants had T1–2 disease, a substantial proportion were node-negative, and the study used outdated two-dimensional radiotherapy planning techniques. Similarly, the Korean trial failed to demonstrate a statistically significant advantage of IMN irradiation in the overall population[9, 10].

In contrast, observational studies and meta-analyses suggest that IMN irradiation (IMNI) may confer potential benefit. The Danish prospective cohort study (DBCG-IMN1) found improved outcomes in patients treated with IMNI, including overall survival, recurrence-free survival, and distant metastasis rates[11, 12]. In contrast, observational studies and meta-analyses suggest that IMN irradiation (IMNI) may confer potential benefit. The Danish prospective cohort study (DBCG-IMN1) found improved outcomes in patients treated with IMNI, including overall survival, recurrence-free survival,

and distant metastasis rates[13]. A large-scale meta-analysis from China also reported that, among patients with N1 disease, IMNI was associated with an 11% reduction in the overall risk of death and improved recurrence-free survival[14].

Moreover, the MA.20[15] and EORTC 22922/10925[16] studies incorporated IMN regions within broader regional nodal irradiation strategies. Meta-analyses of these trials indicate that such irradiation may reduce recurrence and mortality risks[17]. However, it remains unclear whether the observed benefit is attributable specifically to IMN irradiation or to supraclavicular node irradiation.

In this study, the 10-year DFS, OS, DDFS, and BCSS rates were 83.7%, 90.0%, 84.8%, and 93.1%, respectively. Compared with previous studies, the survival outcomes observed in our non-IMNI group were broadly consistent with historical data from similar patient populations. In the French trial[8], the 10-year OS for the non-IMNI group was 59.3%. In the DBCG-IMN study[11], which included 1,597 patients who did not receive IMNI, the 8-year OS among patients with pN1 disease was 85.5%. In the KROG 08 – 06 trial[9], the 7-year DFS and OS for the non-IMNI group were 81.9% and 88.2%, respectively. A Korean retrospective study[18]reported that the 10-year DFS was 65% in the IMNI group and 57% in the non-IMNI group. The survival rates in our study were slightly better than those reported in the aforementioned studies. This difference may be attributable to several factors. First, all patients in our cohort had pT1–2N1M0 disease, excluding higher N-stage patients. Second, almost all patients (97.5%) received adjuvant chemotherapy, among whom anthracycline plus taxane–based regimens were used in 79.3% of cases. With the increasing use of additional systemic therapies, such as taxane-based chemotherapy and trastuzumab, and the overall shift toward earlier-stage diagnosis, survival outcomes have improved[19]. However, when compared with the best reported outcomes in the IMNI groups—such as the 7-year DFS of 85.3% in the KROG 08 – 06 trial[9] and the 15-year OS of 65.0% in the DBCG-IMN2 study[13] — the survival rates in our study still show a certain gap. This indicates that some high-risk patients may have missed potential survival benefits due to the omission of IMNI. Therefore, accurately identifying high-risk subgroups within the non-IMNI population who may derive benefit from IMNI is crucial for further improving prognosis.

Multivariable analyses demonstrated that the triple-negative molecular subtype was the strongest independent unfavorable prognostic factor (OS: HR = 3.750; BCSS: HR = 3.971). Its effect size was substantially greater than those of T stage and the number of involved lymph nodes, and it was statistically significant across all endpoints. Subgroup analyses from the DBCG-IMN study[11] and the KROG 08 – 06 trial[9] suggested that patients with hormone receptor negativity derived greater benefit from IMNI. However, these analyses did not further stratify by HER2 status, leaving the benefit of IMNI in triple-negative breast cancer insufficiently characterized and warranting further investigation. This notion is also supported by subgroup results from the MA.20 trial[15]. A recent Japanese study[20] reported postoperative radiotherapy outcomes and found that IMN failure was relatively uncommon. Importantly, hormone receptor status was identified as an independent risk factor for IMN recurrence, which is consistent with the conclusions of our study. Collectively, these findings imply that, in the absence of IMNI, the high aggressiveness of triple-negative breast cancer may not be fully compensated by locoregional treatment alone. The higher propensity for distant metastasis suggests that micrometastatic disease may already be present even when IMN involvement is not evident on imaging.

In our study, the anthracycline plus taxane–based regimen demonstrated a consistent protective effect on OS, DFS, and DDFS (with OS: HR = 0.391). A previous Korean retrospective study included patients treated between 1994 and 2002, the majority of whom (86.6%) received CMF (cyclophosphamide, methotrexate, and fluorouracil) or anthracycline-based chemotherapy[18]. Another retrospective analysis from the same institution, which included patients treated with taxane-containing chemotherapy[21], similarly reported a benefit from IMNI. Collectively, these findings suggest that, in patients who do not receive IMNI, intensified systemic therapy may help compensate for the lack of comprehensive locoregional irradiation. For patients who cannot receive IMNI for various reasons, combination chemotherapy should be considered whenever feasible to better control potential micrometastases in the IMN region.

It is noteworthy that T stage lost statistical significance in the multivariable analysis, and the independent prognostic effect of the number of involved lymph nodes was limited to OS and BCSS. This suggests that, in patients who did not receive IMNI, prognostic outcomes are predominantly driven by biological and treatment-related factors—particularly chemotherapy regimens—rather than traditional anatomic staging. The prognostic differences associated with the primary tumor size and lymph node burden may be partially attenuated by adjuvant systemic therapy and regional radiotherapy. When IMNs are not irradiated, control of distant metastasis is likely to rely more heavily on systemic treatment efficacy and tumor biological behavior. Therefore, in clinical practice, the decision to accept or omit IMNI should not be based solely on TNM stage, but should integrate biological features such as molecular subtype and treatment factors including chemotherapy regimen.

Age demonstrated a non-linear association with prognosis. The 41–60 years group showed an independent protective effect for OS and BCSS, whereas patients aged > 60 years did not differ significantly. In contrast, patients aged ≤ 40 years had the poorest outcomes, with a BCSS risk approximately two-fold higher than that of the 41–60 years group. This pattern may be related to the higher proportion of aggressive molecular subtypes among younger breast cancer patients. Evidence indicates that women with breast cancer younger than 40 years have a 12%–18% probability of carrying BRCA1 or BRCA2 gene mutations[22–24]. Additionally, younger patients generally tolerate radiotherapy better, suggesting that they may represent a priority subgroup potentially benefiting from IMNI.

Lymphovascular invasion (LVI) remained an independent adverse factor only for BCSS (HR = 2.325), suggesting that LVI may contribute to breast cancer–specific mortality by promoting hematogenous dissemination. The underlying molecular mechanisms are not yet fully elucidated. However, one study reported that in breast cancers with LVI positivity, KRT6A expression is upregulated. KRT6A may promote tumor metastasis through the Wnt/β-catenin signaling pathway[25]. As a result, even after systemic therapy, patients with LVI-positive disease may continue to face an elevated risk of breast cancer–related death. A potential explanation is that patients with higher KRT6A expression may exhibit reduced chemosensitivity. Specifically, the IC50 values of multiple chemotherapeutic agents commonly used in metastatic breast cancer were found to be markedly higher in the KRT6A-high subgroup, indicating an association between increased KRT6A levels and decreased sensitivity to chemotherapy[25]. Therefore, LVI-positive breast cancer patients may derive benefit from IMNI.

The lack of statistical significance for laterality and multifocality in the multivariable model may be due to limited sample size and/or residual confounding. The 20-year results of EORTC 22922 suggest that the breast cancer–specific mortality benefit of IMNI observed earlier may be offset in the long term by an increase in non–breast cancer–related deaths. Notably, this trial was conducted using older radiotherapy techniques. With modern IMRT and advanced techniques such as deep inspiration breath-hold, the cardiac and pulmonary dose to organs at risk has been substantially reduced, making IMNI safer in contemporary practice. In our cohort, none of the patients received IMNI, thereby avoiding potential cardiopulmonary toxicity; however, high-risk patients may have paid a survival price[16].

The limitations of this study include its retrospective design, potential follow-up bias, and the inability to reconstruct the IMN radiation dose. In addition, the median follow-up time of approximately 10 years may be insufficient to comprehensively evaluate the risk of late cardiotoxicity. The study also included patients treated during an earlier period (2010–2015), during which radiotherapy and systemic treatment techniques differed from those currently used. Furthermore, we did not perform a separate analysis of the neoadjuvant chemotherapy subgroup; the results of NSABP B-51 suggest that patients with ypN0 may be eligible to omit RNI. Despite these limitations, our study clearly identified triple-negative subtype, age ≤ 40 years, and LVI positivity as high-risk factors among pT1–2N1M0 patients who did not receive IMNI. These factors can help select patients who may derive advantage from IMNI. Future research should integrate radiomics and pathomics to precisely identify subgroups that are most likely to benefit from IMNI, thereby enabling more individualized regional nodal irradiation.

Abbreviations

Internal mammary nodes (IMNs); Internal mammary node irradiation (IMNI); Disease-free survival (DFS); Overall survival (OS); Distant disease-free survival (DDFS); Breast cancer–specific survival (BCSS); 3-Dimensional conformal radiotherapy (3D-CRT); Intensity-modulated radiotherapy (IMRT); International Agency for Research on Cancer (IARC); Breast-conserving therapy (BCT); Ipsilateral breast tumor recurrence (IBTR); the American Society for Radiation Oncology (ASTRO).

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Shaya Nazihan , Chen Junxiao and Wang Yihai. The first draft of the manuscript was written by Shaya Nazihan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets generated and analyzed during the current study are not publicly available due to institutional data protection regulations and patient privacy restrictions but are available from the corresponding author on reasonable request and with permission of the institutional review board.

Ethics approval

This retrospective study was approved by the ethics committee of the Tumor Hospital of Xinjiang Medical University. All experimental protocols were approved by this committee.As the study did not involve private patient information,the requirement for ethical approval was satisfied in accordance with the committee's regulations.

Accordance

This study was conducted in accordance with the Declaration of Helsinki and followed the relevant national guidelines for retrospective clinical research.

Consent to participate

The need for informed consent was waived by the Ethics Committee of the Tumor Hospital of Xinjiang Medical University, because this was a retrospective study using medical records obtained during previous clinical diagnosis and treatment

and did not involve biological specimens (secondary use of research cases/biological specimens).

Consent to publish

Not applicable.

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Clinical trial number

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Figures

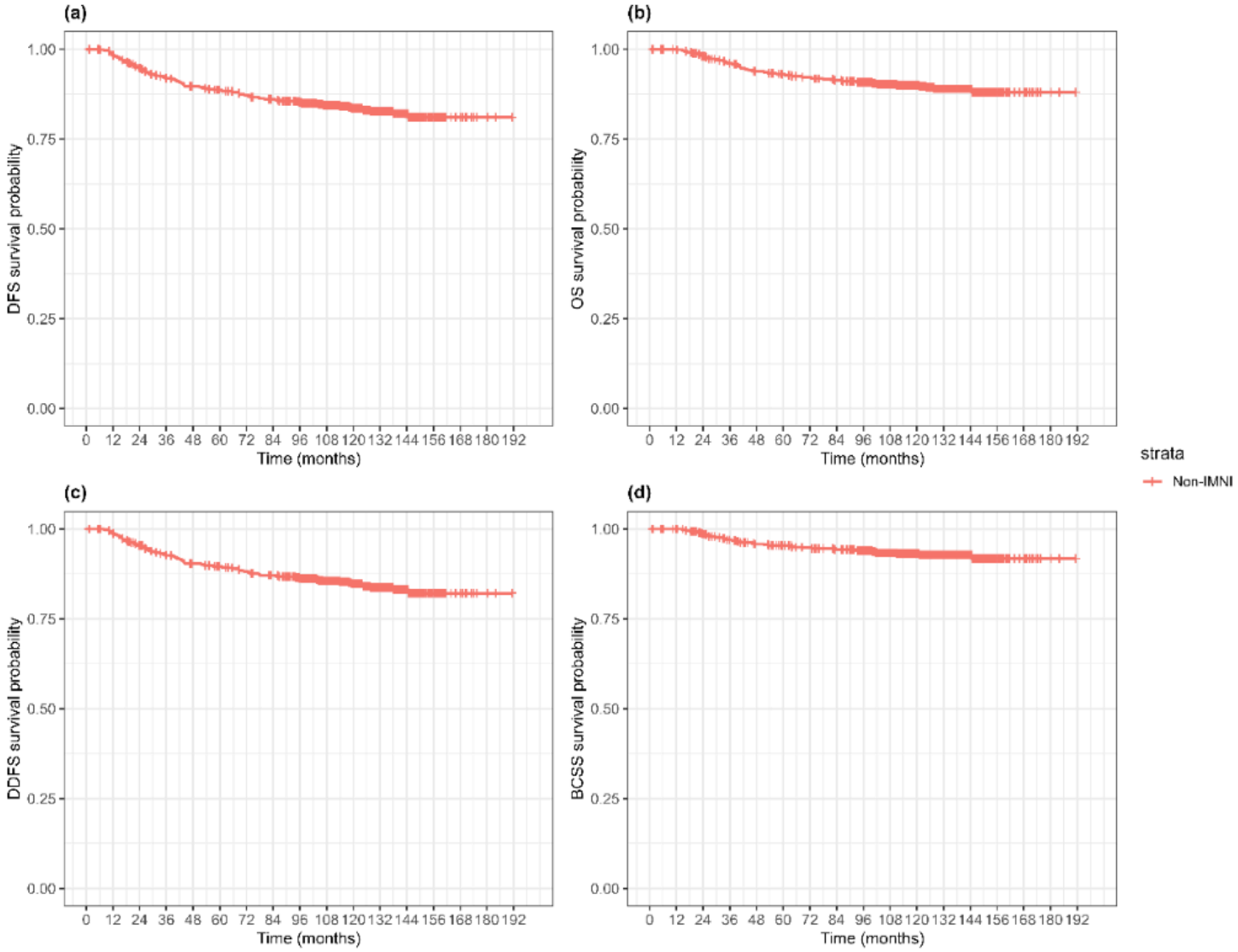


Figure 1

Kaplan–Meier survival curves.

(a) Disease-free survival (DFS): time from the date of initial treatment to disease recurrence, metastasis, or death from any cause. (b) Overall survival (OS): time from the date of initial treatment to death from any cause. (c) Distant disease-free survival (DDFS): time from the date of initial treatment to distant metastasis or death from any cause. (d) Breast cancer–specific survival (BCSS): time from the date of initial treatment to death attributable to breast cancer.