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ORIGINAL ARTICLE

The effect of radiotherapy on patients with pathological stage IIB breast cancer after breast-conserving surgery or mastectomy: A cohort study

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Abstract

Background: Breast cancer is one of the most common cancers in women, and treatment options include surgery, systemic therapies, and radiotherapy (RT). While postoperative RT plays an important role in reducing local recurrence rates and improving survival outcomes, its exact impact on patients with pathological stage IIB breast cancers remains unidentified.

Methods: In this retrospective cohort study, patients with newly diagnosed pathological stage IIB breast cancer who underwent surgery and postoperative RT were included. The data were collected from medical records, and survival outcomes were assessed using the Kaplan-Meier method, log-rank tests, and Cox regression models.

Results: In total, 350 patients participated in this study. Overall survival, locoregional recurrence-free survival, event-free survival, and distant metastasis-free survival rates did not significantly differ between those who received RT and those who did not. Multivariate analyses revealed that patients who received anthracycline or taxane chemotherapy had better survival outcomes.

Conclusion: Our findings demonstrated that postoperative RT had no significant effect on overall survival, locoregional recurrence, event-free survival, or distant metastasis rates in patients with pathological stage IIB breast cancer. However, anthracycline- and taxane-based chemotherapies were associated with improved outcomes. These findings demonstrated the complexities of treating such patient populations with multimodal therapies. Further research is needed to ensure optimal postoperative RT in patients with pathological stage IIB breast cancer. Clinicians must consider individual patient characteristics and incorporate comprehensive treatment approaches to ensure successful outcomes in this population.

Keywords: Breast cancer; Mastectomy; Radiotherapy

1. INTRODUCTION

Breast cancer is the most common type of cancer in women worldwide. In Taiwan, it is the most common cancer in women, accounting for approximately 13% of all new cases.[1] Breast cancer management is a complex process influenced by several factors, including disease stage, patient age, and overall health. Treatment options include surgery, systemic therapies such as chemotherapy, hormonal therapy, targeted therapy, and radiotherapy (RT).[2] Postoperative RT, including whole breast or chest wall irradiation and regional nodal irradiation (RNI), plays a crucial role in reducing the risk of local recurrence in patients with breast cancer.[3] It aims to improve survival rates and minimize the risk of recurrence by targeting residual cancer cells in the breast or regional lymph nodes after surgery.[4] It is particularly beneficial for patients with high-risk characteristics such as larger tumor size, lymph node involvement, or a more advanced pathological stage.

Pathological stage IIB breast cancer is typically characterized by a tumor larger than 2 cm but not exceeding 5 cm (T2) with involvement of one to three axillary lymph nodes (N1) or a tumor larger than 5 cm (T3) with no lymph node involvement (N0).[2] Although it is widely assumed to be in its early stages, some research classifies it as locally advanced breast cancer.[5,6] Previous studies have investigated the impact of postoperative RT on overall survival (OS), local recurrence, and distant metastasis (DM). In 2005, 2011, and 2014, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted meta-analyses comparing RT to no-RT after surgery. These analyses revealed a reduced risk of breast cancer recurrence and mortality when RT was applied.[3,7,8] However, the reported effects of RT were not limited to patients with stage IIB breast cancer. Furthermore, a randomized trial initiated in 1976 found no significant differences in disease-free survival, distant disease-free survival, or OS.[9] Consequently, further investigation is necessary to determine the optimal use of postoperative RT in cases of pathological stage IIB breast cancer.

As the clinical strategy for pathological stage IIB breast cancer is rather ambiguous, we aimed to investigate the effects of postoperative RT on the survival outcomes of patients and determine which subgroup of patients might benefit from postoperative RT owing to some risk factors.

2. METHODS

2.1. Study population and data source

In this study, a retrospective population-based cohort was constructed by reviewing our hospital's medical records. Patients with

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newly diagnosed breast cancer who were treated at our hospital between January 1, 2007, and December 31, 2016, were included in this study. The main inclusion criteria were proven invasive breast carcinoma with pathological stage IIB, including breast cancer with pathological stage T2 (tumor larger than 2 cm but not exceeding 5 cm) and N1 (involvement of one to three axillary lymph nodes) (pT2N1) and breast cancer with pathological stage T3 (tumor larger than 5 cm) and N0 (no lymph node involvement) (pT3N0) according to the tumor, node and metastasis staging system of the American Joint Committee on Cancer classification system 8th edition, and receiving primary treatment with surgery and postoperative RT. Patients with a history of other primary cancers, missing cancer stage or RT information, or who had neoadjuvant chemotherapy for breast cancer were excluded from this study. The current analysis was based on follow-up information through October 31, 2022. The protocol for this study was approved by the Institutional Review Board of Taipei Veterans General Hospital (IRB no. 2021-02-006AC).

2.2. Study variables and covariates

The primary outcomes were OS and event-free survival (EFS). Secondary outcomes were locoregional recurrence-free survival (LRRFS) and DM-free survival (DMFS). The times to these endpoints were all calculated from the date of surgery. EFS events included the first recurrence at a local, regional, or distant site, as well as death without evidence of cancer, as determined by clinical evidence from imaging or a pathology report. A first locoregional recurrence included relapse in the ipsilateral breast, chest wall, or regional nodal sites such as the axillary, supraclavicular, or internal mammary nodes. Recurrences at other locations, such as the bone, liver, lung, or central nervous system, were classified as distant metastases. Covariates included status of RT and RNI (including irradiation of axillary, supraclavicular, or internal mammary nodal region), RNI region, patient age at the time of surgery, and tumor site. Pathologic information included the surgical method for the primary tumor (total mastectomy and lumpectomy) and lymph node (sentinel lymph node biopsy and axillary lymph node dissection), histologic grade, lymphovascular invasion, surgical margin status (R0, R1 resection), Ki-67 index (%), extranodal extension status (ENE), and immunohistochemical staining of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2). Furthermore, data on the adjuvant chemotherapy regimen, as well as the status of hormonal therapy and target therapy, were retrieved from the medical records.

For the policy of RT in our hospital, according to the previous studies,[3,7,8] whole breast irradiation is indicated for patients status post breast-conserving surgery, whereas chest wall irradiation is for mastectomized patients having primary tumor of pT3 and beyond. RNI is indicated for patients of more than three positive lymphadenopathies (pN2 and beyond). For patients with 1 to 3 positive lymph nodes, however, the clinical management varies and is at radiation oncologist's discretion. All patients had 3D-conformal RT using standard or high tangential fields with 45 to 50.4 Gy in 25 to 28 fractions. For additional tumor bed boost the typical doses are 10 to 16 Gy in 4 to 8 fractions.

2.3. Statistical analysis

Categorical variables were compared using Fisher exact test, and continuous variables were compared using Student's *t* test or Mann-Whitney *U* test. The Kaplan-Meier method was used to estimate survival functions, and the log-rank test was used to compare survival distributions between groups in univariate analysis. Cox regression was used for multivariate analysis to assess the effect of multiple covariates on the hazard ratio [HR] of the event of interest. Overall, these methods were used to assess the relationship between various predictors and survival outcomes in the study population. A $p < 0.05$ was considered statistically significant, with no adjustment for multiple testing. All analyses were conducted using R software, Version 4.3.0.

3. RESULTS

Between December 2016 and January 2007, 350 patients were recruited. The baseline characteristics of patients in both study groups were comparable (Table 1). The majority of patients had

Table 1

Patients' characteristics

	RT (n = 117)	No-RT (n = 233)	*p*[a]
Median age (range), y	50 (29-82)	60 (30-87)	0.01
Stage, n (%)			1.00
pT2N1	109 (93.2)	218 (93.6)	
pT3N0	8 (6.8)	15 (6.4)	
Site, n (%)			0.45
Central/ medial	33 (28.2)	80 (34.3)	
Lateral	50 (42.7)	96 (41.2)	
Overlapping/multifocal/unspecified	34 (29.1)	57 (24.5)	
Primary tumor surgical method, n (%)			0.01
BCS	68 (58.1)	6 (2.6)	
Mastectomy	49 (41.9)	227 (97.4)	
Lymph node surgical method, n (%)			0.01
ALND	84 (71.8)	215 (92.3)	
SLNB	18 (15.4)	14 (6)	
Nil	15 (12.8)	4 (1.7)	
Surgical margin, n (%)			0.01
R0	87 (74.4)	216 (92.7)	
R1, close margin, unknown	30 (25.6)	17 (7.3)	
KI-67, n (%)			0.90
KI <35%	41 (35)	76 (32.6)	
KI ≥35%	39 (33.3)	82 (35.2)	
Unknown	37 (31.6)	75 (32.2)	
Hormone receptor status, n (%)			0.15
ER+ or PR+, with HER2−	74 (63.2)	150 (64.4)	
HER2+	25 (21.4)	62 (26.6)	
Triple-negative	18 (15.4)	21 (9)	
ENE, n (%)			0.01
+	25 (21.4)	69 (29.6)	
−	76 (65)	153 (65.7)	
Unknown	16 (13.7)	11 (4.7)	
Grade, n (%)			0.05
1	8 (7)	4 (1.7)	
2	60 (52.6)	134 (58)	
3	46 (40.4)	93 (40.3)	
LVI, n (%)			0.02
+	66 (56.4)	117 (50.2)	
−	42 (35.9)	110 (47.2)	
Unknown	9 (7.7)	6 (2.6)	
Chemotherapy, n (%)			0.01
Anthracycline-taxane-based therapy	86 (73.5)	125 (53.6)	
Anthracycline or taxane only	12 (10.3)	44 (18.9)	
Non or unknown	13 (11.1)	56 (24)	
Others[b]	6 (5.1)	8 (3.4)	
Hormonal therapy, n (%)			0.90
+	83 (70.9)	168 (72.1)	
−	34 (29.1)	65 (27.9)	
HER2-directed agent, n (%)			0.31
+	23 (19.7)	53 (22.7)	
−	93 (79.5)	180 (77.3)	
Unknown	1 (0.9)	0 (0)	

ALND = axillary lymph node dissection; BCS = breast-conserving surgery; ENE = extranodal extension; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; LVI = lymphovascular invasion; PR = progesterone receptor; pT2N1 = breast cancer with pathological stage T2 (tumor larger than 2 cm but not exceeding 5 cm) and N1 (involvement of one to three axillary lymph nodes); pT3N0 = breast cancer with pathological stage T3 (tumor larger than 5 cm) and N0 (no lymph node involvement); RT = radiotherapy; SLNB = sentinel lymph node biopsy.

[a]Fisher exact tests were used for numerical variables, and Mann-Whitney *U* tests were used for categorical variables.

[b]Cisplatin, carboplatin, methotrexate.

pT2N1-stage cancer (93.2% in the RT group and 93.6% in the no-RT group). Estrogen receptor/progesterone receptor-positive disease predominated (63.2% in the RT group and 64.4% in the no-RT group). The majority of patients (73.5% of the RT group and 53.6% of the no-RT group) received anthracycline-taxane-based chemotherapy. Patients who received RT had mostly breast-conserving surgery (58.1%), while those who did not have mostly mastectomy (97.4%). Patients were divided into RNI and no-RNI groups, and their baseline characteristics are summarized in Supplementary Table 1, http://links.lww.com/JCMA/A227. There was a high level of collinearity between the RNI region and the RNI. To avoid nonconvergence, the RNI region was not included in the subsequent multivariate analysis. The median follow-up at the time of this analysis was 8.9 years.

3.1. Overall survival

The OS in relation to RT and RNI is depicted in Fig. 1. The 10-year survival rates were 85.9% in the RT group and 78.2% in the no-RT group (HR = 0.742, 95% CI, 0.426-1.293, p = 0.290; Fig. 1A). In terms of RNI, the 10-year survival rates were 83.8% in the RNI group and 79.9% in the no-RNI group (HR = 0.765, 95% CI, 0.399-1.466, p = 0.418; Fig. 1B). There was no significant difference in OS between the groups studied. The HRs for death were also not statistically significant, indicating that neither RT nor RNI had a significant impact on patient survival in this dataset.

The Cox proportional hazards regression (Fig. 2) analysis revealed that patients who received anthracycline- and taxane-based chemotherapy had significantly better survival outcomes (p

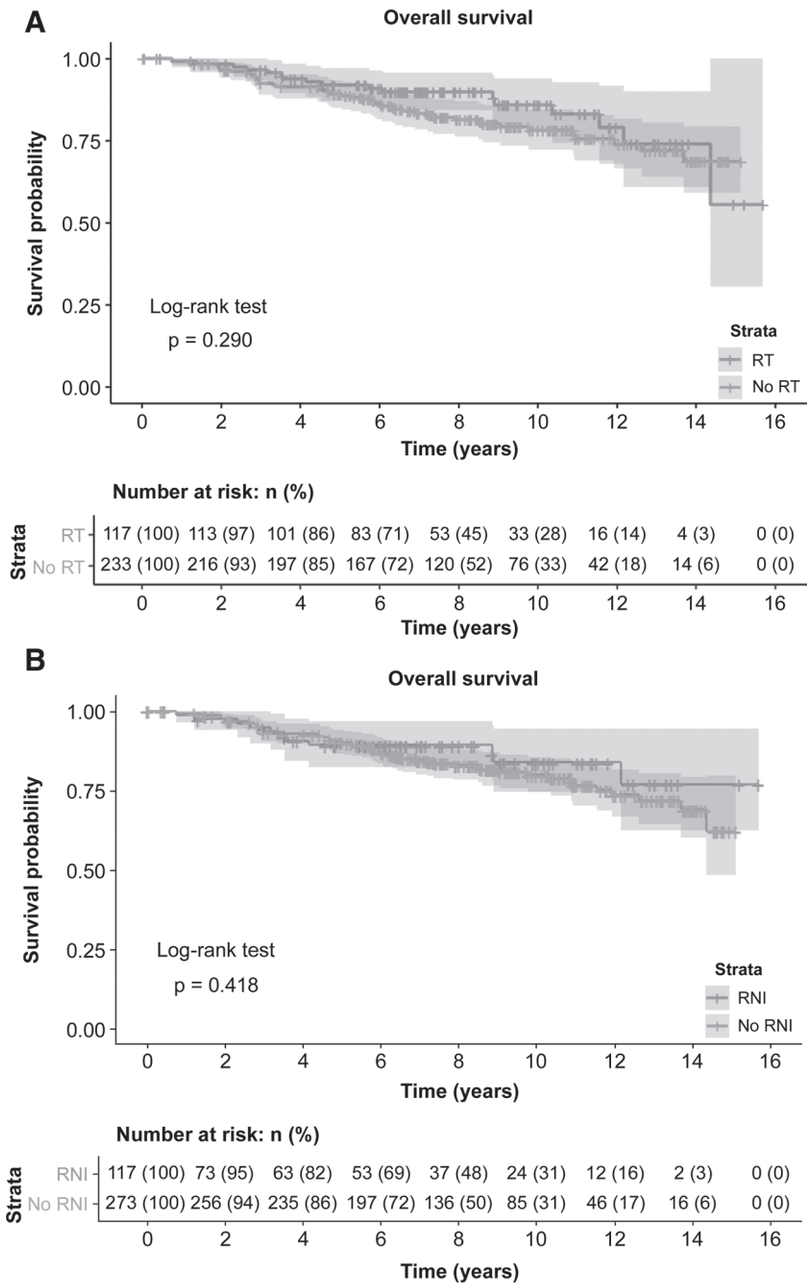

Fig. 1 Kaplan-Meier estimates of overall survival according to (A) RT and (B) RNI. RNI = regional nodal irradiation; RT = radiotherapy.

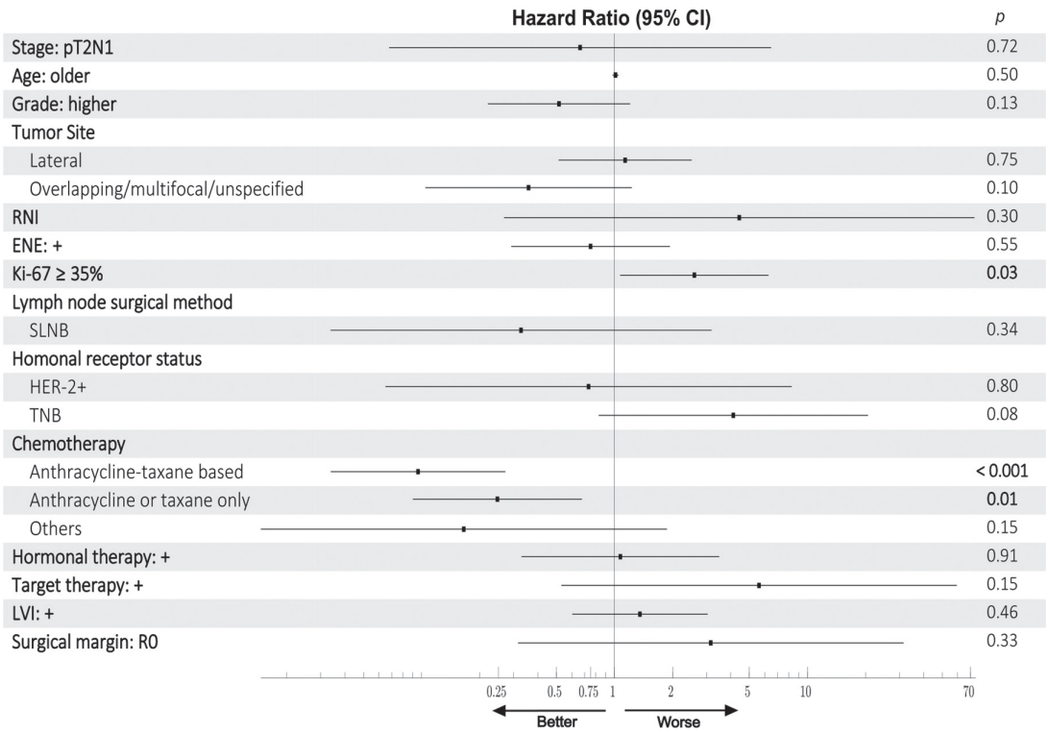

Fig. 2 The overall survival hazard ratio based on multivariate analyses. ENE = extranodal extension status; HER2 = human epidermal growth factor receptor 2; LVI = lymphovascular invasion; R0 = microscopically margin-negative resection; RNI = regional nodal irradiation; SLNB = sentinel lymph node biopsy; TNB = Triple-negative breast cancer.

< 0.001), while those who received only anthracycline or taxane had slightly better outcomes (p = 0.010). High Ki-67 expression greater than 35% indicated worse survival (p = 0.03). On the other hand, RT was beneficial to patients with pT2N1 or Ki-67 expression of 35% or higher (Supplementary Table 2, http://links.lww.com/JCMA/A228). The results are detailed in Fig. 2. If the CI for a covariate was not bounded, it was not included in the forest plot.

3.2. Event-free survival

The event was defined as the occurrence of either LRR or DM events. Data on patient event in relation to RT and RNI revealed no significant differences in EFS between the groups studied. The 10-year EFS rates were 78.9% for the RT group and 77.7% for the no-RT group (HR = 0.917, 95% CI, 0.556-1.511, p = 0.732; Fig. 3A). Additionally, the 10-year EFS rates were 86.3% for the RNI group and 76.1% for the no-RNI group (HR = 0.660, 95% CI, 0.347-1.253, p = 0.200; Fig. 3B).

The multivariate analyses (Fig. 4) revealed that RNI was associated with a marginally lower risk of event (HR = 0.11, p = 0.06). The tumor site was also associated with event, with patients with overlapping, multifocal, or unspecified tumors having a lower risk of event (HR = 0.25, p = 0.02). In addition, patients who received anthracycline- and taxane-based chemotherapy had significantly better survival outcomes (p = 0.03). No other variables were found to be significantly associated with event. Overall, RNI was associated with a lower risk of event in both univariate and multivariate Cox proportional hazards regression analyses.

3.3. Local recurrence-free survival

In terms of locoregional recurrence in relation to RT and RNI, there were no significant differences in LRRFS between the groups studied. The 10-year LRRFS rates were 75.9% for the RT group and 72.1% for the no-RT group (HR = 0.886, 95% CI, 0.542-1.448, p = 0.629; Fig. 5A). Additionally, the 10-year LRRFS rates were 79.9% for the RNI group and 71.4% for the no-RNI group (HR = 0.663, 95% CI, 0.358-1.230, p = 0.190; Fig. 5B). The analysis indicated that neither RT nor RNI had a statistically significant influence on LLR in this dataset.

According to the multivariate analysis, the following factors were found to be significantly associated with a lower risk of LRR: overlapping, multifocal, or unspecified sites (HR = 0.30, p = 0.03), adjuvant hormonal therapy (HR = 0.22, p = 0.01), targeted therapy (HR = 0.05, p < 0.001) and anthracycline- and taxane-based chemotherapy (HR = 0.25, p = 0. 01). Ki-67 expression of 35% or higher was marginally associated with a higher risk of recurrence (HR = 2.35, p = 0.07). Patients with HER2-positive breast cancer had a significantly higher risk of LRR (HR = 8.42, p < 0.001). The results are presented in Fig. 6.

3.4. DM-free survival

Neither RT nor RNI had a statistically significant impact on DMFS. The 10-year DMFS rates were 82.8% for the RT group and 80.3% for the no-RT group (HR = 0.995, 95% CI, 0.557-1.777, p = 0.987; Fig. 7). In addition, the 10-year DMFS rates were 89.0% for the RNI group and 78.9% for the no-RNI group (HR = 0.652, 95% CI, 0.307-1.386, p = 0.263; Fig. 8).

Multivariate analyses revealed that anthracycline- and taxane-based chemotherapy (HR = 0.25, p = 0.02) and older age (HR = 0.95, p = 0.003) were associated with a significantly lower risk of DM. Furthermore, RNI was associated with a lower risk of DM (HR = 0.23, p = 0.24; Fig. 8).

4. DISCUSSION

This study investigated the impact of a number of factors on patients' OS, disease events, and DM rates in pathological stage

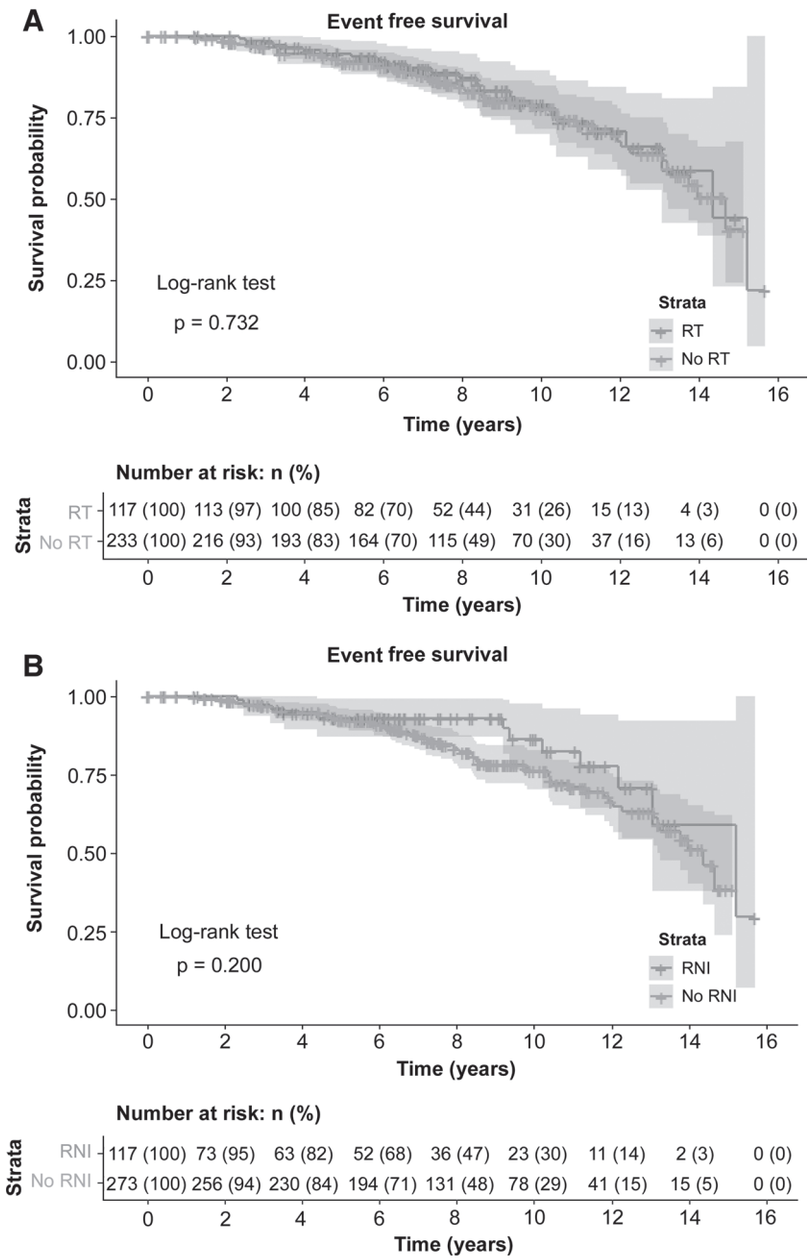

Fig. 3 Kaplan-Meier estimates of event-free survival according to (A) RT and (B) RNI. RNI = regional nodal irradiation; RT = radiotherapy.

IIB breast cancer. The long-term outcomes of patients who received RT or RNI were compared to those who did not. The log-rank univariate analysis revealed that the survival rates did not differ significantly between cohorts. Multivariate analyses revealed an association between RNI and a reduced risk of disease events, LRR, or DM. Cox regression analyses revealed that patients who received adjuvant chemotherapy regimens based on anthracycline and taxane, or any of these, had better outcomes in all categories. Ki-67 expression of 35% or higher was associated with worse OS rates. Patients who received adjuvant hormonal or targeted therapy had better locoregional outcomes, but those who tested positive for the hormonal receptor subtype HER2 had poorer outcomes. Patients with older ages had favorable DMFS rates. These findings provide a comprehensive picture of the impact of RT on breast cancer at this stage.

The purpose of this study was to gain insight into the effects of postoperative RT on patients with pathological stage IIB breast cancer who had not received neoadjuvant chemotherapy. The EBCTCG meta-analysis in 2005 revealed that RT improved OS when adjuvant RT was added.[3] Furthermore, an EBCTCG meta-analysis conducted in 2011 reported a modest but statistically significant reduction in breast cancer deaths.[7] Both studies, however, did not provide a specific breakdown of the various stages in patients with early-stage breast cancer. Moreover, Kaplan et al[10] distinguished this study as being from the modern era due to general advancements in surgical technique, RT, or hormonal therapy. Furthermore, while the randomized study NSABP B-06 found a lower 20-year cumulative recurrence rate on the ipsilateral side in patients who received irradiation following lumpectomy compared

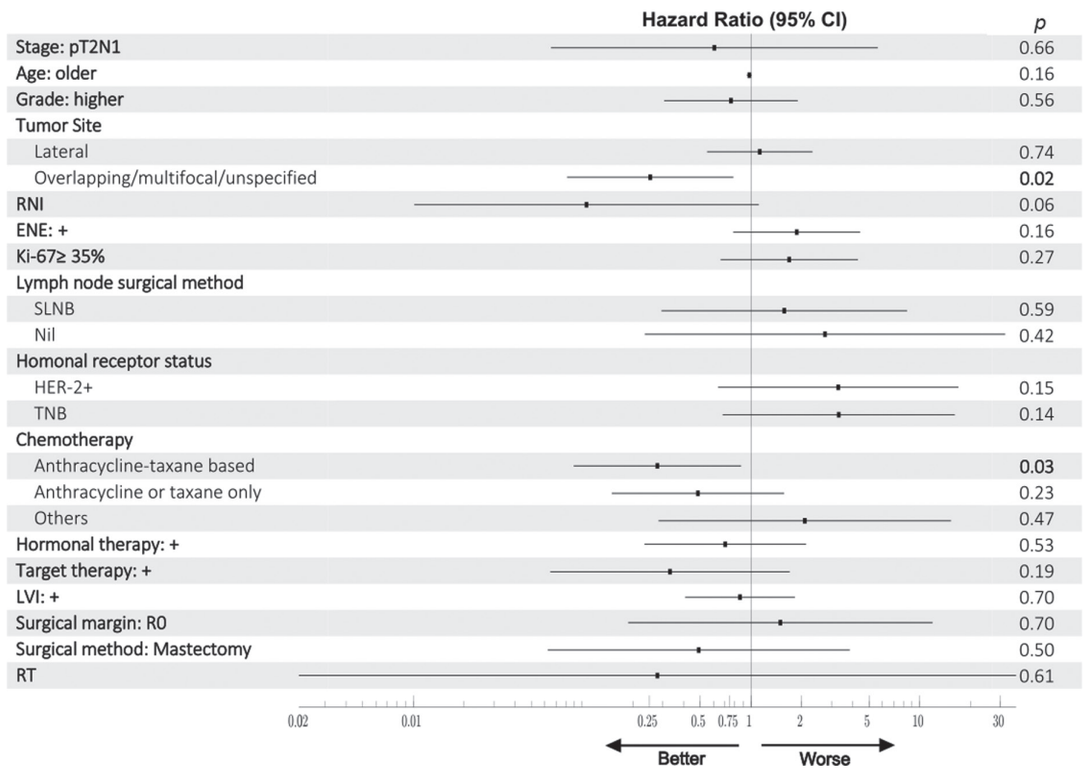

Fig. 4 The event-free survival hazard ratio based on multivariate analyses. ENE = extranodal extension status; HER2 = human epidermal growth factor receptor 2; LVI = lymphovascular invasion; R0 = microscopically margin-negative resection; RNI = regional nodal irradiation; RT = radiotherapy; SLNB = sentinel lymph node biopsy; TNB = Triple-negative breast cancer.

to those who did not (14.3% vs 39.2%, p = 0.001), there was no difference in disease-free, distant disease-free, or OS rates.[9] The definition of recurrence varies depending on the study. When analyzing disease-free survival in NSABP B-06, for example, the occurrence of a tumor on the ipsilateral side of the breast following a lumpectomy was not considered an event. This was because women who had total mastectomy as their assigned treatment were not at risk of such an event. Therefore, the appearance of a recurrent lump in the breast ipsilateral to the lumpectomy was deemed a cosmetic failure in this trial. Despite the fact that the evidence was strong and the conclusion was well established, the findings of these studies are ambiguous due to a wide range of inconsistencies.

A number of studies have investigated the effectiveness of RNI after surgery for patients with pT2N1 breast cancer. A randomized controlled trial found that adding nodal radiation to regional irradiation reduced regional recurrence and improved disease-free life expectancy.[11] However, there is disagreement about the impact of RNI on OS.[12] In a previous analysis, there was no difference between patients who received nodal radiation and those who did not.[13] In fact, our study revealed that RNI was associated with a reduced risk of disease events, LRR, and DM. Chest wall irradiation, on the other hand, is an important part of treatment for women with pT3N0 pathological breast cancer. It is designed to reduce the risk of local recurrence and eliminate any residual tumor cells that may remain in the chest wall following mastectomy.[14] The effect of chest wall irradiation after mastectomy on patients with pT3N0 breast cancer has been extensively studied.[15] A meta-analysis revealed a significant decrease in local recurrences with chest wall irradiation.[16] It has also been linked to improved disease-free life expectancy in this patient group.[17] The impact of RT on OS remains a matter of debate.[18] Due to the small number of pT3N0 cases in our database (only 6%) and the low incidence of this disease, it was not possible to conduct additional analysis of the benefits of chest wall RT postoperatively on this subgroup. The group that would benefit from RT or RNI has yet to be determined. However, our data were insufficiently powered to assess the benefits of different subgroups. The p values for subgroup analyses were also not adjusted for multiple testing. In addition, interaction terms were included in the analysis of subgroup differences. The results were not statistically significant, but they did show that RT was preferred in patients with Ki-67 expression greater than 35% or only receiving sentinel lymph node biopsy, as detailed in the Supplementary Section.

Our multivariate results were consistent with the findings of previous research. Our findings revealed that, among all covariates tested, HER2 was associated with significantly lower LRRFS rates. Overexpression of this receptor protein has been linked to aggressive tumor behavior and an increased risk of recurrence in multiple studies.[19,20] For patients with early breast cancer, sequential administration of taxanes and anthracyclines has been common. The combined regimens consistently improved disease-free and OS when compared to anthracycline or taxane chemotherapy alone.[21–23] Our study's findings also supported this conclusion. ENE, or extracapsular expansion, has been identified as an independent predictor of poor prognosis in breast cancer, even after adjusting for other clinicopathological variables.[24,25] However, as with lymphovascular space invasion, the present study found a weak, nonsignificant correlation between ENE and worse EFS.

The study has some limitations. First, our dataset was not linked to the National Death Registry, which could have provided additional information, such as breast cancer-specific

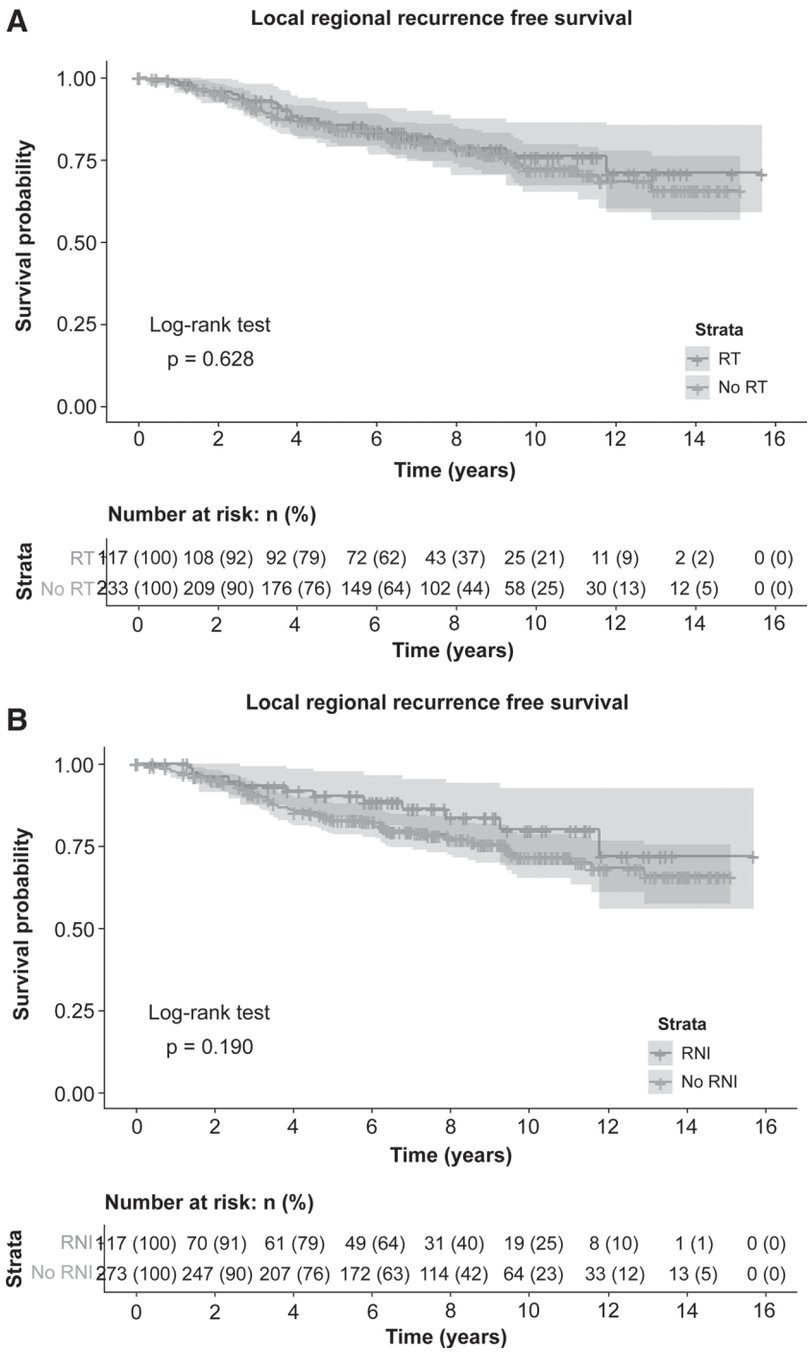

Fig. 5 Kaplan-Meier estimates of locoregional recurrence-free survival according to (A) RT and (B) RNI. RNI = regional nodal irradiation; RT = radiotherapy.

mortality, to allow for a more precise study on the effects of RT and RNI. Second, this was a retrospective analysis with a relatively small number of patients (n = 350), and there were missing data in the medical records (eg, ambiguous documentation regarding the status of surgical margins, ENEs, regimens of adjuvant systemic treatment, latest follow-up dates, and so on). Third, only patients who were at a certain stage and had not received neoadjuvant chemotherapy were included. However, the effectiveness of RT and RNI may be more definite in other circumstances. Besides, the side effects of these therapies should also be reviewed and evaluated. Last, we had performed sensitivity analysis to compare the propensity of receiving treatment between the two groups. It turns out the lack of covariate overlap is indeed a challenge for comparing the two groups (RT vs no-RT group). In order to solve this issue, we had already input surgical types into our multivariable regression.[26] However, this sort of confounding by indication cannot be entirely managed by statistical methods and need more patient data (eg, the numbers of patients who receive postmastectomy radiotherapy). Therefore, based on the associated risk factors found in our current study, we should perform causal inference analysis in the future. (eg, comparison of RT

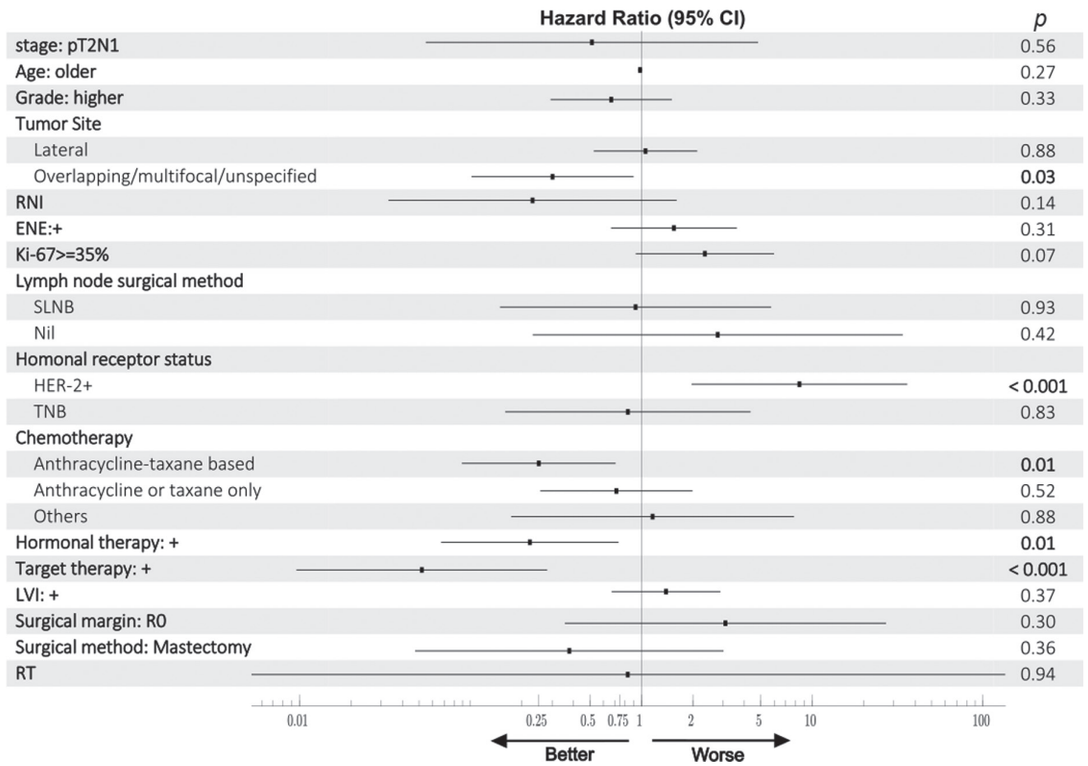

Fig. 6 The locoregional recurrence-free survival hazard ratio based on multivariate analyses. ENE = extranodal extension status; HER2 = human epidermal growth factor receptor 2; LVI = lymphovascular invasion; R0 = microscopically margin-negative resection; RNI = regional nodal irradiation; RT = radiotherapy; SLNB = sentinel lymph node biopsy; TNB = Triple-negative breast cancer.

vs no-RT within patients receiving either breast-conserving surgery [BCS] or mastectomy only.) Moreover, the findings of our investigation have stimulated subsequent research endeavors aimed at enhancing data collection methodologies with the goal of augmenting generalizability.

The present study reevaluated postoperative RT for patients with pathological stage IIB breast cancer and found that RNI after surgery could reduce local recurrence as well as DM. To provide stronger evidence, future research should focus on large-scale prospective studies that are well-designed and follow standardized treatment protocols. To guide treatment decisions, it is important to carefully consider the benefits and side effects of each treatment modality in relation to individual patient characteristics and preferences. Furthermore, postoperative RT, including chest wall/whole breast radiation and RNI, should be used with caution in patients with pathological stage IIB breast cancer.

In conclusion, this study provides valuable insights into the impact of RT on patients with pathological stage IIB breast cancer. The findings suggest that RT or RNI did not significantly influence overall, event-free, or LRRFS. However, anthracycline- and taxane-based chemotherapy showed favorable survival outcomes. High Ki-67 expression was associated with worse OS. These results contribute to our understanding of the optimal use of postoperative RT in pathological stage IIB breast cancer patients and underscore the importance of personalized treatment approaches. Herein, RT did not have a significant impact on OS or disease events in pathological stage IIB breast cancer patients following breast-conserving surgery or mastectomy. However, further research is needed to validate these findings and determine the optimal treatment strategies for this specific subgroup of patients.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A227 and http://links.lww.com/JCMA/A228.

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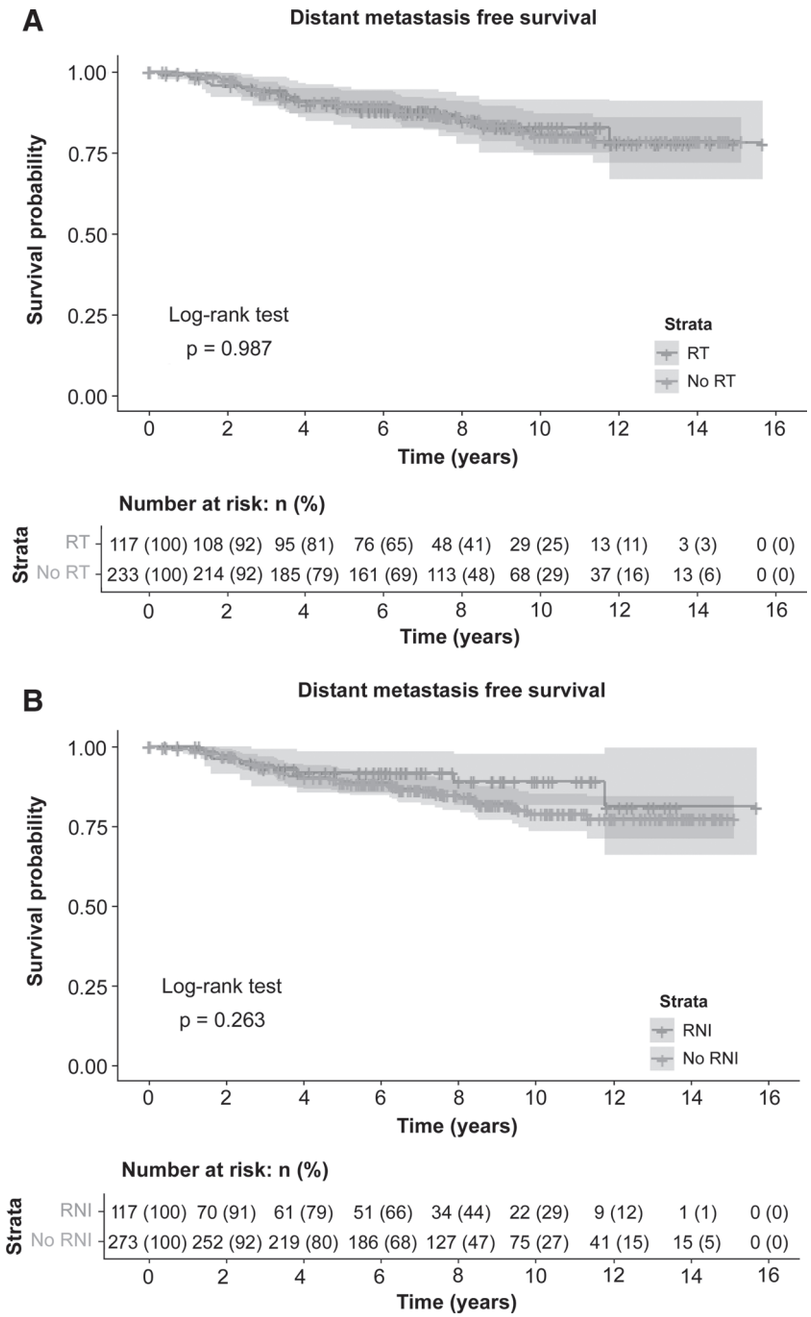

Fig. 7 Kaplan-Meier estimates of distant metastasis-free survival according to (A) RT and (B) RNI RNI = regional nodal irradiation; RT = radiotherapy.

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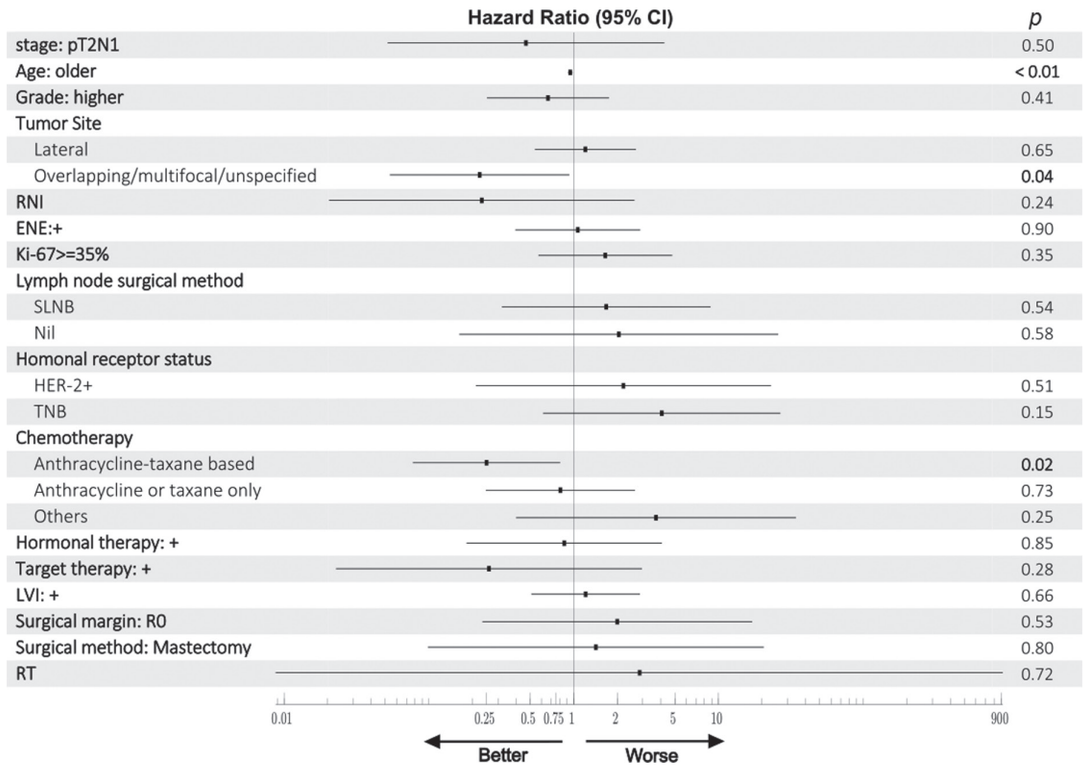

Fig. 8 The distant metastasis-free survival hazard ratio based on multivariate analyses. ENE = extranodal extension status; HER2 = human epidermal growth factor receptor 2; LVI = lymphovascular invasion; R0 = microscopically margin-negative resection; RNI = regional nodal irradiation; RT = radiotherapy; SLNB = sentinel lymph node biopsy; TNB = Triple-negative breast cancer.

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