Impact of Post-Mastectomy Radiation Therapy for Sentinel Lymph Node Micrometastases in Early-Stage Breast Cancer Patients

Hua Luo*
Ou Ou Yang*
Jun Ling He
Tian Lan

* Hua Luo and Ou Ou Yang contributed equally to this work

Corresponding Authors:
Tian Lan, e-mail: lan_tian_lt@163.com, Hua Luo, e-mail: luohua0313@163.com

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Background: The association of radiotherapy with breast cancer survival in patients who underwent a mastectomy and had micrometastases in the sentinel lymph node is unclear.

Material/Methods: The survival benefit of radiotherapy was examined in patients with T0/1-T2N1mi breast cancer undergoing mastectomy plus sentinel lymph node biopsy (SLNB). Kaplan-Meier curves were employed for survival analysis and competing risk analysis, and a propensity score matching (PSM) cohort was enrolled to investigate whether such patients benefit from radiotherapy.

Results: We identified 2864 patients in the SEER database from 2004 to 2015. All eligible patients were divided into the radiotherapy and no-radiotherapy cohorts. With the median follow-up of 53 months, 5-year breast cancer-specific survival (BCSS) was 94.4% vs 95.2% (P=0.135), and 5-year overall survival (OS) was 91.2% vs 90.1% (P=0.466) in the radiotherapy cohorts and no-radiotherapy cohorts, respectively. The results of the competing risk analysis showed a comparable 5-year cumulative incidence of breast cancer-specific death (BCSD) in the radiotherapy and no-radiotherapy groups (5.5% vs 4.7%, P=0.107) but a higher 5-year cumulative incidence of other causes of death (OCD) in the no-radiotherapy cohort (3.3% vs 5.3%, P=0.011). No significant difference was observed for BCSS or OS in the PSM cohort.

Conclusions: Radiotherapy has no benefit for patients with T0/1-T2 breast cancer undergoing mastectomy with N1mi disease on SLNB. This analysis provides evidence that radiotherapy may safely be omitted in this group of patients.

Keywords: Breast Neoplasms • Mastectomy • Neoplasm Micrometastasis • Radiotherapy • Sentinel Lymph Node

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Background

Axillary lymph node status is one of the most important prognostic factors for breast cancer survival [1]. Axillary lymph node dissection (ALND) was the criterion standard in patients with regional nodal metastasis in past decades. An axillary lymph node examination dissected by the largest diameter was based on hematoxylin and eosin (H&E) staining. However, when lymph node slices are thicker than 2 mm, micrometastases of cancer within the slice can be missed and underestimate the risk of lymph node involvement [2-10].

Sentinel lymph node biopsy (SLNB) has replaced ALND as the surgical standard staging procedure for breast cancer patients clinically considered to be node-negative over the last decade [11]. Since the introduction of SLNB, a more comprehensive examination of a smaller number of sentinel lymph nodes, routine use of a step-sectioning procedure, and immunohistochemistry resulted in increased detection of micrometastases [7]. Although several prospective studies have been published suggesting that ALND can be safely omitted in breast-conserving surgery patients with micrometastases in the sentinel lymph node (SLN), these studies included only a few patients who underwent mastectomy surgery [12-14].

The role of radiation therapy in post-mastectomy patients with micrometastases in the SLN is uncertain. The question remains whether further axillary radiotherapy is indicated in patients with micrometastases in the SLN of T0/1-T2 tumors who underwent a mastectomy.

The present study aimed to determine whether radiation therapy had any impact on the breast cancer-specific survival (BCSS) and overall survival (OS) of breast cancer patients undergoing mastectomy with SLN micrometastases in whom a completion ALND was omitted, based on data from the Surveillance, Epidemiology, and End Results (SEER) database.

Material and Methods

Data Source and Cohort Selection

Data were obtained from the SEER 18-regions database (Incidence-SEER 18 Regs Research Data [with additional treatment fields], Nov 2018 Sub [1975-2016 varying]) using SEER*Stat version 8.3.9 (http://seer.cancer.gov/seerstat). The SEER registries routinely collect data on patient demographics, age at diagnosis, primary tumor size, stage at diagnosis, survival months, and follow-up vital status. The International Classification of Diseases for Oncology and histology codes identified women older than 18 and under 80 years diagnosed with primary breast cancer from 2004 to 2015.

Patients were included based on the following criteria: historically diagnosed with staged T0/1-T2 breast cancer who had a mastectomy, unilateral early breast cancer as the first primary tumor, evaluation of lymph node status determined by SLN as pN1mi, M0, the number of SLN examined <6 involved, and primary surgical procedure with mastectomy plus SLN without completion ALND. The SEER database also provides information regarding chemotherapy and radiotherapy; thus, these data are also included. Information regarding the HER2 status and molecular subtypes was only available after 2010 and was excluded from our analysis. Patients were excluded if they underwent ALND (with or without SLNB), did not undergo a lymph node evaluation, or did not undergo primary surgery.

Clinicopathological Variables

The following clinicopathological variables were collected: age at diagnosis, race, marital status, median household income, T stage, nuclear grade, estrogen-receptor (ER) status, progesterone-receptor (PR) status, and results of SLNB pathological examination, as well as administration of chemotherapy and radiotherapy. Age was categorized as ≤50 or >50 years. Ethnicity was classified into White or non-White. Patients were divided into married, single, or divorced, and widowed were combined as unmarried based on marital status. Socioeconomic status was divided into Quartile 1 (<$52,620), Quartile 2 ($52,621-$60,260), Quartile 3 ($60,261-$74,610), and Quartile 4 (> $74,610). Tumor grade was classified into I-II and III. T staging was classed as T0/1 or T2, and micro-metastatic disease (staged as pN1mi) was defined as deposits >0.2 to ≤2.0 mm according to the 6th edition of the American Joint Committee on Cancer (AJCC). Chemotherapy was categorized as “yes” or “no/unknown.” For the reasons previously stated, information concerning hormone therapy and anti-HER2 treatment was not collected.

The primary surgical procedure included a total mastectomy and SLNB, and patients were further categorized into 2 groups by whether they received radiotherapy (radiotherapy group) or not (no-radiotherapy group).

Statistical Analyses

Continuous variables were compared using the t test, and the chi-square test or Fisher’s exact test were used to compare categorical variables to describe the patients’ and tumors’ characteristics. The primary aim of this study was to compare patients with staged T0/1-T2 breast cancer undergoing mastectomy plus SLNB to determine if there was any benefit in BCSS and OS when N1mi patients received radiotherapy. Survival probabilities for BCSS and OS were carried out by plotting survival curves using the Kaplan-Meier method for various patients. The log-rank test was used to analyze associations between
clinopathologic variables and survival of groups based on whether they received radiotherapy or not in N1mi patients. Subgroup analyses were also performed to determine whether radiotherapy could benefit different groups.

Univariable and multivariable Cox proportional hazards regression models were performed to assess clinical-pathological features. A log-rank test was used for univariate comparison; variables with a statistically significant $P$ value in the univariable model were included in the multivariable model. The Cox proportional hazards regression model was applied to assess the relative risk of death according to radiotherapy. Hazard ratios (HRs) with 95% CIs were calculated as estimated risks of death.

PSM can minimize selection bias and mimic randomized controlled trials [15]. To balance patient characteristics between radiotherapy and no-radiotherapy groups, PSM was performed using 1: 1 nearest-neighbor matching with a caliper of 0.01. Patient cohorts were matched for marital status, age, race, median household income, grade, T stage, ER status, PR status, and chemotherapy. In addition, we use a competing risk model that treated deaths without evidence of breast cancer recurrences as the competing risk, and cumulative risk curves of different outcomes were plotted by cumulative incidence function (CIF).

All statistical tests were two-sided, statistical significance was set at the 0.05 level for all tests, and R software (version 4.0.3, https://www.r-project.org/) was used to conduct all statistical analyses. R packages, including tableone, rms, survival, survminer, ggplot2, cmprsk, and Matchit, were used.

### Results

#### Descriptive Statistics

In the present study, based on the eligibility criteria, 2864 patients diagnosed with T0/1-T2 breast cancer were treated with a mastectomy who had node micrometastases determined by SLNB were available for analysis from 2004 to 2015. Of these patients, the radiotherapy and no-radiotherapy cohorts included 588 (20.5%) and 2276 (79.5%) patients, respectively. There were a series of significant differences between the groups. Patients in the no-radiotherapy group vs the radiotherapy group were more likely to be older (mean age, 58 vs 53.9 years, respectively). Among the subgroups of age, there was also a significant difference in age <50 or >50 years between the groups; patients in the radiotherapy group were more likely to be <50 years (40.6% vs 31.0%, $P<0.001$). A higher proportion of patients with radiotherapy had more T2 tumors compared to those without radiotherapy (57.8% vs 42.4%, $P<0.001$), while the no-radiotherapy group had fewer grade III tumors (27.5% vs 33.5%, $P<0.001$). In the no-radiotherapy group, 79.9% were PR-positive, compared to 75.5% in the radiotherapy group ($P=0.024$). In terms of adjuvant chemotherapy, 69.2% of patients in the radiotherapy group received chemotherapy compared to only 45.1% in the no-radiotherapy group ($P<0.001$). After propensity score matching, a total of 1120 patients (radiotherapy 560 [50.0%] versus no-radiotherapy 560 [50.0%]) were matched. All variables were balanced between the radiotherapy group and the no-radiotherapy group. The baseline characteristics of the patients before and after propensity score matching are summarized in Table 1.

#### Effects of Radiotherapy on BCSS and OS Before PSM

After a median follow-up of 53 months (ranging from 0 to 155 months, 44 and 53 months in the radiotherapy and no-radiotherapy cohorts, respectively), the BCSS and OS of patients with T0/1-T2N1mi breast cancer treated with a mastectomy who had node micrometastases determined by SLNB were assessed using Kaplan-Meier analysis.

There were 34 (5.78%) breast cancer-related death events observed in the radiotherapy group and 124 (5.44%) in the no-radiotherapy group. The 5-year cancer-specific survival was 94.4% in the radiotherapy group and 95.2% in the no-radiotherapy group ($P=0.135$). Kaplan-Meier analysis showed that patients who received radiotherapy had a similar BCSS compared with those who did not; the log-rank test $P$ value was 0.13 (Figure 1A). No significant differences in 5-year OS were observed between the groups, with the 5-year OS was 91.2% vs 90.1% in the radiotherapy group compared to those with no-radiotherapy, respectively ($P=0.466$). Kaplan-Meier analysis showed that patients with radiotherapy had similar outcomes as patients without radiotherapy; the log-rank test $P$ value was 0.47 (Figure 1B).

In consideration of competing risks (death from other causes), we constructed cumulative incidence plots in the overall population, indicating comparable 5-year cumulative incidence of breast cancer-specific death (BCSD) in the radiotherapy and no-radiotherapy groups (5.5% vs 4.7%, $P=0.107$). However, there was a higher 5-year cumulative incidence of other causes of death (OCD) in the no-radiotherapy cohort compared to the radiotherapy cohort (5.3% vs 3.3%, $P=0.011$) (Figure 2A).

#### Univariable Cox and Multivariate Cox Analysis

The results of the univariable Cox analyses revealed that radiotherapy was not associated with improved BCSS ($P=0.135$) (Table 2) or OS ($P=0.466$) (Table 3). In addition, the univariate analysis demonstrated that marital status, T stage, tumor grade, ER, and PR status were significantly associated with BCSS (Table 2) and OS (Table 3) (all $P<0.05$). Moreover, our univariate analysis showed that older age, median household...
| Characteristics | Before PSM | After PSM | P | Before PSM | After PSM | P |
|-----------------|------------|-----------|---|------------|-----------|---|
| Age (mean (SD)) | 58.00 (13.59) | 53.93 (13.11) | <0.001 | 55.08 (12.77) | 54.46 (13.01) | 0.423 |
| Age <50 | 705 (31.0) | 239 (40.6) | <0.001 | 215 (38.4) | 215 (38.4) | 1.000 |
| Age >50 | 1571 (69.0) | 349 (59.4) | 345 (61.6) | 345 (61.6) | 345 (61.6) | 345 (61.6) | 345 (61.6) | 1.000 |
| Marital status | | | | | | |
| Married | 1438 (63.2) | 389 (66.2) | 0.197 | 378 (67.5) | 376 (67.1) | 0.949 |
| Unmarried | 838 (36.8) | 199 (33.8) | 182 (32.5) | 184 (32.9) | 184 (32.9) | 184 (32.9) | 184 (32.9) | 1.000 |
| Race | | | | | | |
| Non White | 424 (18.6) | 105 (17.9) | 0.711 | 95 (17.0) | 96 (17.1) | 1.000 |
| White | 1852 (81.4) | 483 (82.1) | 465 (83.0) | 464 (82.9) | 464 (82.9) | 464 (82.9) | 464 (82.9) | 464 (82.9) | 1.000 |
| Median household income | | | | | | |
| Quartile 1 | 537 (23.6) | 136 (23.1) | 0.560 | 132 (23.6) | 133 (23.8) | 0.997 |
| Quartile 2 | 521 (22.9) | 121 (20.6) | 121 (21.6) | 118 (21.1) | 118 (21.1) | 118 (21.1) | 118 (21.1) | 1.000 |
| Quartile 3 | 578 (25.4) | 162 (27.6) | 148 (26.4) | 148 (26.4) | 148 (26.4) | 148 (26.4) | 148 (26.4) | 1.000 |
| Quartile 4 | 640 (28.1) | 169 (28.7) | 159 (28.4) | 161 (28.7) | 161 (28.7) | 161 (28.7) | 161 (28.7) | 1.000 |
| Tumor size | 35.85 (123.31) | 34.90 (97.95) | 0.862 | 34.79 (108.29) | 35.05 (100.35) | 0.967 |
| T stage | | | | | | |
| T0/1 | 1311 (57.6) | 248 (42.2) | <0.001 | 245 (43.8) | 246 (43.9) | 1.000 |
| T2 | 965 (42.4) | 340 (57.8) | 315 (56.2) | 314 (56.1) | 314 (56.1) | 314 (56.1) | 314 (56.1) | 1.000 |
| Grade | | | | | | |
| I+II | 1649 (72.5) | 391 (66.5) | 0.005 | 389 (69.5) | 379 (67.7) | 0.562 |
| III | 627 (27.5) | 197 (33.5) | 171 (30.5) | 181 (32.3) | 181 (32.3) | 181 (32.3) | 181 (32.3) | 1.000 |
| ER status | | | | | | |
| Negative | 252 (11.1) | 79 (13.4) | 0.127 | 59 (10.5) | 73 (13.0) | 0.228 |
| Positive | 2024 (88.9) | 509 (86.6) | 501 (89.5) | 487 (87.0) | 487 (87.0) | 487 (87.0) | 487 (87.0) | 1.000 |
| PR status | | | | | | |
| Negative | 458 (20.1) | 144 (24.9) | 0.024 | 116 (20.7) | 132 (23.6) | 0.280 |
| Positive | 1818 (79.9) | 444 (75.5) | 444 (79.3) | 428 (76.4) | 428 (76.4) | 428 (76.4) | 428 (76.4) | 1.000 |
| Chemotherapy | | | | | | |
| No/unknown | 1250 (54.9) | 181 (30.8) | <0.001 | 179 (32.0) | 179 (32.0) | 1.000 |
| Yes | 1026 (45.1) | 407 (69.2) | 381 (68.0) | 381 (68.0) | 381 (68.0) | 381 (68.0) | 381 (68.0) | 1.000 |
income in Quartile 1, and did not receive chemotherapy were significantly associated with shorter OS (Table 3) (all \(P<0.05\)).

The multivariate analysis results were consistent with the result of the univariate analysis, except for chemotherapy. In multivariate Cox regression analysis, radiotherapy did not significantly improve the BCSS (HR=1.28, 95% CI=0.87-1.9, \(P=0.212\)) or OS (HR=1.07, 95% CI=0.78-1.45, \(P=0.686\)) for breast cancer patients, but chemotherapy improved the OS (HR=0.55, 95% CI=0.43-0.7, \(P<0.001\)). All subgroup analyses are summarized in Tables 2 and 3.

After matching, the univariate analysis of BCSS showed similar results with before matching, except for marital status. The multivariate analysis indicated that a T2 tumor, ER, and PR-negative were poor prognosticators for BCSS (Table 2). Furthermore, a T2 tumor, ER-negative, and no-chemotherapy administration remained poor prognosticators for OS (Table 3).

**Effects of Radiotherapy on BCSS and OS After PSM**

After 1:1 PSM, the standardized difference (SD) of all baseline features was less than 0.1, which indicated a good agreement between the no-radiotherapy and radiotherapy groups. The 5-year BCSS was 94.6% in the radiotherapy group and 96.4% in the no-radiotherapy group (\(P=0.115\)). Kaplan-Meier analysis showed that patients who received radiotherapy had a similar BCSS compared with those who did not receive radiotherapy,
Table 2. Univariate and multivariate analyses of breast cancer-specific survival in unmatched and matched cohort.

| Characteristics          | Before PSM | Univariate | Multivariate |
|--------------------------|------------|------------|--------------|
|                          |            | 5 year BCSS |              |
|                          |            | Chisq      | HR | 95%CI | P   |
| Age                      |            |            |    |      |     |
| <50                      | 0.96       |            |    |      |     |
| >50                      | 0.946      |            | 1.17 | 0.81-1.7 | 0.397 |
| Marital status           |            |            |    |      |     |
| Married                  | 0.957      |            |    |      |     |
| Unmarried                | 0.939      |            | 1.46 | 1.06-2.02 | 0.02  |
| Race                     |            |            |    |      |     |
| Non White                | 0.955      |            |    |      |     |
| White                    | 0.95       |            | 1.32 | 0.83-2.1 | 0.247 |
| Median household income  |            | 6.27       |    | 0.999 |      |
| Quartile 1               | 0.94       |            |    |      |     |
| Quartile 2               | 0.966      |            | 1.01 | 0.74-1.37 | 0.968 |
| Quartile 3               | 0.946      |            | 1.08 | 0.78-1.49 | 0.653 |
| Quartile 4               | 0.953      |            | 0.63 | 0.45-0.89 | 0.008 |
| T stage                  |            | 21.9       |    | <0.001 |      |
| T0/1                     | 0.968      |            |    |      |     |
| T2                       | 0.929      |            | 1.89 | 1.37-2.62 | <0.001 |
| Grade                    |            | 42.439     |    | <0.001 |      |
| I+II                     | 0.97       |            |    |      |     |
| III                      | 0.903      |            | 1.80 | 1.27-2.56 | 0.001 |
| ER status                |            | 63.363     |    | <0.001 |      |
| Negative                 | 0.831      |            |    |      |     |
| Positive                 | 0.968      |            | 0.67 | 0.42-1.07 | 0.09  |
| PR status                |            | 70.351     |    | <0.001 |      |
| Negative                 | 0.869      |            |    |      |     |
| Positive                 | 0.974      |            | 0.44 | 0.29-0.68 | <0.001 |
| Radiation                |            | 2.234      |    | 0.135 |      |
| None/unknown             | 0.952      |            |    |      |     |
| Yes                      | 0.944      |            | 1.28 | 0.87-1.9 | 0.212 |
| Chemotherapy             |            | 1.876      |    | 0.171 |      |
| No/unknown               | 0.957      |            |    |      |     |
| Yes                      | 0.945      |            | 0.94 | 0.66-1.34 | 0.742 |
Table 2 continued. Univariate and multivariate analyses of breast cancer-specific survival in unmatched and matched cohort.

| Characteristics          | 5 year BCSS | Univariate Chisq | P   | Multivariate HR | 95%CI     | P   |
|--------------------------|------------|------------------|-----|-----------------|----------|-----|
| Age                      |            | 0.244            | 0.622 |                 |          |     |
| <50                      |            |                  |      |                 |          |     |
| >50                      |            | 0.949            | 0.622 |                 |          |     |
| Marital status           | Reference  | 0.397            | 0.529 |                 |          |     |
| Married                  | Reference  |                  |      |                 |          |     |
| Unmarried                |            | 0.948            | 0.622 |                 |          |     |
| Race                     |            | 2.055            | 0.152 |                 |          |     |
| Non White                | Reference  |                  |      |                 |          |     |
| White                    |            | 0.955            | 2.48 | 0.96-6.39       | 0.06     |     |
| Median household income  | Reference  | 5.659            | 0.129 |                 |          |     |
| Quartile 1               | Reference  |                  |      |                 |          |     |
| Quartile 2               | Reference  | 0.956            | 0.70 | 0.41-1.17       | 0.171    |     |
| Quartile 3               | Reference  | 0.962            | 1.16 | 0.68-1.99       | 0.579    |     |
| Quartile 4               | Reference  | 0.98             | 0.64 | 0.36-1.13       | 0.121    |     |
| T stage                  | Reference  | 12.22            | <0.001 |                |          |     |
| T0/1                     | Reference  |                  |      |                 |          |     |
| T2                       | Reference  | 0.935            | 3.47 | 1.89-6.37       | <0.001   |     |
| Grade                    | Reference  | 11.19            | 0.001 |                |          |     |
| I+II                     | Reference  |                  |      |                 |          |     |
| III                      | Reference  | 0.931            | 1.26 | 0.69-2.3        | 0.442    |     |
| ER status                | Reference  | 30.08            | <0.001 |               |          |     |
| Negative                 | Reference  |                  |      |                 |          |     |
| Positive                 | Reference  | 0.973            | 0.41 | 0.17-0.97       | 0.043    |     |
| PR status                | Reference  | 22.29            | <0.001 |               |          |     |
| Negative                 | Reference  |                  |      |                 |          |     |
| Positive                 | Reference  | 0.975            | 0.45 | 0.21-0.97       | 0.042    |     |
| Radiation                | Reference  | 2.488            | 0.115 |                |          |     |
| None/unknown             | Reference  |                  |      |                 |          |     |
| Yes                      | Reference  | 0.946            | 1.46 | 0.87-2.48       | 0.155    |     |
| Chemotherapy             | Reference  | 1.394            | 0.238 |                |          |     |
| No/unknown               | Reference  |                  |      |                 |          |     |
| Yes                      | Reference  | 0.947            | 1.04 | 0.54-2          | 0.913    |     |

BCSS – breast cancer-specific survival; PSM – propensity score matching; HR – hazard ratio; CI – confidence interval.
Table 3. Univariate and multivariate analyses of overall survival in unmatched and matched cohort.

| Characteristics                | Before PSM | Univariate | Multivariate |
|--------------------------------|------------|------------|--------------|
|                                |            | 5 year OS  | Chisq        | P            |
|                                |            |            | HR           | 95%CI        | P            |
| Age                            |            | 50.288     | <0.001       |
| >50                            | 0.954      | Reference  |              |
| Marital status                 |            | 79.005     | <0.001       |
| Married                        | 0.938      | Reference  |              |
| Unmarried                      | 0.84       | 2.22       | 1.78-2.77    | <0.001       |
| Race                           |            | 0.803      | 0.37         |
| Non White                      | 0.915      | Reference  |              |
| White                          | 0.901      | 1.09       | 0.8-1.48     | 0.603        |
| Median household income        |            | 8.782      | 0.032        |
| Quartile 1                     | 0.861      | Reference  |              |
| Quartile 2                     | 0.919      | 0.87       | 0.7-1.07     | 0.197        |
| Quartile 3                     | 0.91       | 1.15       | 0.92-1.43    | 0.212        |
| Quartile 4                     | 0.92       | 0.86       | 0.68-1.08    | 0.188        |
| T stage                        |            | 25.135     | <0.001       |
| T0/1                           | 0.925      | Reference  |              |
| T2                             | 0.876      | 1.69       | 1.35-2.11    | <0.001       |
| Grade                          |            | 17.861     | <0.001       |
| I+II                           | 0.917      | Reference  |              |
| III                            | 0.867      | 1.44       | 1.12-1.84    | 0.005        |
| ER status                      |            | 25.656     | <0.001       |
| Negative                       | 0.788      | Reference  |              |
| Positive                       | 0.919      | 0.77       | 0.54-1.09    | 0.141        |
| PR status                      |            | 45.864     | <0.001       |
| Negative                       | 0.814      | Reference  |              |
| Positive                       | 0.928      | 0.60       | 0.44-0.8     | 0.001        |
| Radiation                      |            | 0.531      | 0.466        |
| None/unknown                   | 0.901      | Reference  |              |
| Yes                            | 0.912      | 1.07       | 0.78-1.45    | 0.686        |
| Chemotherapy                   |            | 31.872     | <0.001       |
| No/unknown                     | 0.877      | Reference  |              |
| Yes                            | 0.929      | 0.55       | 0.43-0.7     | <0.001       |
### Table 3 continued. Univariate and multivariate analyses of overall survival in unmatched and matched cohort.

| Characteristics          | 5 year OS | Univariate |       | HR | 95%CI | P        | Multivariate |       | HR | 95%CI | P     |
|--------------------------|----------|------------|-------|----|-------|----------|--------------|-------|----|-------|-------|
| Age                      | 8.045    | 0.005      |       |    |       |          | Reference    |       |    |       |       |
| <50                      | 0.944    | Reference  |       |    |       |          | 1.39         | 0.87-2.22  | 0.168 |
| >50                      | 0.918    |           | 1.39  | 0.87-2.22  | 0.168 |
| Marital status           | 9.054    | 0.003      |       |    |       |          | Reference    |       |    |       |       |
| Married                  | 0.942    |           | Reference    |       |       |          | 1.48         | 0.98-2.22  | 0.061 |
| Unmarried                | 0.896    | 1.48       | 0.98-2.22  | 0.061 |
| Race                     | 1.47     | 0.225      |       |    |       |          | Reference    |       |    |       |       |
| Non White                | 0.936    | Reference  |       |    |       |          | 1.43         | 0.75-2.71  | 0.277 |
| White                    | 0.925    |           | 1.43  | 0.75-2.71  | 0.277 |
| Median household income  | 12.242   | 0.007      |       |    |       |          | Reference    |       |    |       |       |
| Quartile 1               | 0.862    | Reference  |       |    |       |          | 1.39         | 0.92-2.08  | 0.115 |
| Quartile 2               | 0.931    |           | 1.39  | 0.92-2.08  | 0.115 |
| Quartile 3               | 0.953    |            | Reference    |       |       |          | 0.86         | 0.55-1.34  | 0.503 |
| Quartile 4               | 0.954    |            | 0.86  | 0.55-1.34  | 0.503 |
| T stage                  | 15.59    | <0.001     |       |    |       |          | Reference    |       |    |       |       |
| T0/1                     | 0.964    | Reference  |       |    |       |          | 2.78         | 1.79-4.31  | <0.001 |
| T2                       | 0.897    |           | 2.78  | 1.79-4.31  | <0.001 |
| Grade                    | 7.583    | 0.006      |       |    |       |          | Reference    |       |    |       |       |
| I+II                     | 0.94     | Reference  |       |    |       |          | 1.37         | 0.87-2.16  | 0.169 |
| III                      | 0.899    |           | 1.37  | 0.87-2.16  | 0.169 |
| ER status                | 21.061   | <0.001     |       |    |       |          | Reference    |       |    |       |       |
| Negative                 | 0.785    | Reference  |       |    |       |          | 0.44         | 0.22-0.87  | 0.018 |
| Positive                 | 0.946    | 0.44       | 0.22-0.87  | 0.018 |
| PR status                | 16.306   | <0.001     |       |    |       |          | Reference    |       |    |       |       |
| Negative                 | 0.858    | Reference  |       |    |       |          | 0.66         | 0.37-1.17  | 0.154 |
| Positive                 | 0.947    | 0.66       | 0.37-1.17  | 0.154 |
| Radiation                | 13.056   | 0.304      |       |    |       |          | Reference    |       |    |       |       |
| None/unknown             | 0.939    | Reference  |       |    |       |          | 1.27         | 0.85-1.89  | 0.243 |
| Yes                      | 0.912    | 1.27       | 0.85-1.89  | 0.243 |
| Chemotherapy             | 13.02    | <0.001     |       |    |       |          | Reference    |       |    |       |       |
| No/unknown               | 0.914    |            | Reference    |       |       |          | 0.41         | 0.26-0.62  | <0.001 |
| Yes                      | 0.933    | 0.41       | 0.26-0.62  | <0.001 |

OS – overall survival; PSM – propensity score matching; HR – hazard ratio; CI – confidence interval.
and the log-rank test $P$ value was 0.11 (Figure 3A). The 5-year OS was 91.2% in the radiotherapy group and 93.9% in the no-radiotherapy group ($P=0.304$); Kaplan-Meier analysis showed that patients with radiotherapy had similar outcomes as patients without radiotherapy; the log-rank test $P$ value was 0.3 (Figure 3B).

After using this approach, we observed that radiotherapy did not decrease BCSD or OCD in patients with T0/1-T2N1miM0 breast cancer treated with mastectomy and who had micrometastases in SLNB. The 5-year cumulative incidences of BCSD were 5.3% and 3.5% ($P=0.115$) in the radiotherapy and no-radiotherapy cohorts, respectively. No significant difference was observed in the 5-year cumulative incidence of OCD between the 2 cohorts (3.5% vs 2.6%, $P=0.745$) (Figure 2B).

We conducted an exploratory subgroup analysis in the matched cohort to identify the patient or tumor features that may benefit from radiotherapy among a specific population. There were no significant BCSS benefits to radiotherapy seen for subgroups with high risk (age <50 years, staging T2, grade III, ER-negative, PR-negative, and receiving chemotherapy) (log-rank $P>0.05$ for all) (Figure 4A-4F) in survival analysis. Notably, a significantly shorter BCSS was identified when radiotherapy was administered in ER-positive patients (log-rank $P=0.022$) (Figure 4E) and PR-positive patients (log-rank $P=0.022$) (Figure 4F). The stratified survival analysis also showed a close to statistically significantly decreased BCSS for the radiotherapy group among married (log-rank $P=0.051$) and grade I+II patients (log-rank $P=0.067$).

**Discussion**

Macro-metastasis in SLN is associated with worse disease-free survival [16], and current guidelines recommend further axillary surgery or radiotherapy when there are macro-metastases in the SLN [17]. With the increasing use of SLNB, identification rates of micrometastases in sentinel nodes have increased, but the prognostic significance and clinical management remain controversial [18,19].

Several studies have demonstrated that micrometastases in sentinel nodes are associated with a worse prognosis [20-28], and other studies found that the presence of sentinel node micrometastases in breast cancer patients was not significantly associated with a more inferior OS or DFS compared to node-negative disease [29-35]. For those patients undergoing breast-conserving surgery who have SLN micrometastases, whole-breast irradiation was administered to the breast, in which the dose is delivered to the lower part of the axilla and helps control this region [36-38]. Based on the results of the ACOSOG Z0011 [17] and IBCSG 23-01 trials [12], supplemental ALND has been abandoned for breast-conserving patients only with micrometastases in the SLN in some centers, but in patients who underwent a mastectomy, it was not comprehensively analyzed. Whether radiotherapy can be safely omitted in patients with micrometastases in the SLN who undergo mastectomy without a completion dissection remains unclear. Less than 10% of patients undergoing mastectomy had positive SLNs in the randomized prospective data. In the Z0011 trial, which randomized patients with positive SLNs to ALND vs no further surgery, approximately 40% of...
Figure 4. Breast cancer-specific survival for breast cancer patients according to radiotherapy in subgroups stratified by age (A), grade (B), T staging (C), chemotherapy (D), ER status (E), and PR status (F) after PSM.
patients had micrometastases in the SLNs, but only patients who received breast-conserving therapy were included [17]. The International Breast Cancer Study Group (IBCSG) 23-01 trial randomized 934 patients with T1-T2 tumors with isolated tumor cells and micrometastases in lymph nodes to SLNB or ALND, but only 9% underwent mastectomy [12]. The AATRM trial similarly randomized 233 patients with micrometastases to SLNB or ALND, but only 8% underwent mastectomy [13]. Wu et al performed a retrospective study based on The National Cancer Database (NCDB) identified, in which 14 019 patients diagnosed with pT1-2N1mi breast cancer between 2004 and 2014 were treated with mastectomy [39]. The study aimed to investigate the impact of post-mastectomy radiation therapy (PMRT) on OS for patients with early-stage breast cancer post-mastectomy with micrometastases in the axillary nodes, leaving 2043 patients for subset analyses in those patients who only received an SLNB without ALND, with 1490 patients in the SLNB alone arm and 553 patients in the SLNB+PMRT arm. In this subgroup, there was a trend to better OS in the SLNB+PMRT arm compared with the SLNB alone arm, with 2 (0.9%) deaths in the SLNB+PMRT arm vs 21 (2.9%) deaths in the SLNB-alone arm (log-rank P=0.053). As the authors mentioned, the work lacks LRR information, and it did not evaluate the effect of radiation on BCSS, which would be a more effective measure than OS for the cancer patient population [40]. Some previous studies have mentioned the prognostic impact of radiotherapy for breast cancer and sentinel node micrometastases on patients after mastectomy, but the number of patients is small. Of the 566 patients with breast cancer and micrometastases in the SLNs for analysis in the SENOMIC trial, only 67 (30.9%) patients who underwent mastectomy were treated with radiation to the chest wall and/or regional lymph nodes [41]. In the SERC trial, 134 PMRT was delivered in 82.7% (134/162) of patients, but only 34/55 (61.8%) for ITC lymph nodes [41]. In the SERC trial, 134 PMRT was delivered in 82.7% (134/162) of patients, but only 34/55 (61.8%) for ITC lymph nodes [41]. In the SERC trial, 134 PMRT was delivered in 82.7% (134/162) of patients, but only 34/55 (61.8%) for ITC lymph nodes [41]. In the SERC trial, 134 PMRT was delivered in 82.7% (134/162) of patients, but only 34/55 (61.8%) for ITC lymph nodes [41]. In the SERC trial, 134 PMRT was delivered in 82.7% (134/162) of patients, but only 34/55 (61.8%) for ITC lymph nodes [41]. In the SERC trial, 134 PMRT was delivered in 82.7% (134/162) of patients, but only 34/55 (61.8%) for ITC lymph nodes [41]. 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In the SERC trial, 134 PMRT was delivered in 82.7% (134/162) of patients, but only 34/55 (61.8%) for In summary, the current findings demonstrated that in patients with T0/1-T2 breast cancer undergoing mastectomy with N1mi disease found on SLNB, no differences in BCSS or
OS were found between patients with and without radiotherapy. This study supports the recommendation that radiotherapy for this specific group of the population should be individualized. Furthermore, according to the risk stratification, individualized radiotherapy strategies should be further investigated in the subgroup with lower-risk populations.

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Declaration of Figures’ Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Reference:

1. Ribelles N, Perez-Villa L, Jerez JM, et al. Pattern of recurrence of early breast cancer is different according to intrinsic subtype and proliferation index. Breast Cancer Res. 2013;15:R98
2. Viale G, Maiorano E, Mazzaolin G, et al. Histologic detection and clinical implications of micrometastases in axillary sentinel lymph nodes for patients with breast carcinoma. Cancer. 2001;92:1378-84
3. den Bakker MA, van Weeszenberg A, de Kanter AV, et al. Non-sentinel lymph node involvement in patients with breast cancer and sentinel node micrometastasis; Too early to abandon axillary clearance. J Clin Pathol. 2002;55:912-35
4. Jakub JW, Diaz NM, Ebert MD, et al. Completion axillary lymph node dissection minimizes the likelihood of false negatives for patients with invasive breast carcinoma and cytokeratin positive sentinel lymph node nodules. Am J Surg. 2002;184:302-6
5. Cserni G. Complete sectioning of axillary sentinel nodes in patients with breast cancer. Analysis of two different step sectioning and immunohistochemistry protocols in 246 patients. J Clin Pathol. 2002;55:926-31
6. Dowlatshahi K, Fan M, Anderson JM, Bloom KJ. Occult metastases in sentinel nodes of 200 patients with operable breast cancer. Ann Surg Oncol. 2001;8:675-81
7. Cserni G, Amendoeira I, Apostolikas N, et al. Pathological work-up of sentinel lymph nodes in breast cancer. Review of current data to be considered for the formulation of guidelines. European journal of cancer (Oxford, England, 1990). 2003;39:1654-67
8. Tjan-Heijnen VC, Buit P, de Widt-Evert LM, et al. Micro-metastases in axillary lymph nodes: an increasing classification and treatment dilemma in breast cancer due to the introduction of the sentinel lymph node procedure. Breast Cancer Res Treat. 2001;70:81-88
9. Houvenaeghel G, Nos C, Mignotte H, et al. Micrometastases in sentinel lymph node in a multicentric study: Predictive factors of nonsentinel lymph node involvement – Groupe des Chirurgiens de la Federation des Centres de Lutte Contre le Cancer. J Clin Oncol. 2006;24:1814-22
10. Forissier V, Tallet A, Cohen M, et al. Is post-mastectomy radiation therapy contributive in pN0-1mi breast cancer patients? Results of a French multicentric cohort. Eur J Cancer (Oxford, England, 1990). 2017;87:47-57
11. Lyman GH, Giuliano AE, Somerset MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol. 2005;23:7703-20
12. Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): A phase 3 randomised controlled trial. Lancet Oncol. 2013;14:297-305
13. Solà M, Albero JA, Fraile M, et al. Complete axillary lymph node dissection versus clinical follow-up in breast cancer patients with sentinel node micrometastasis: Final results from the multicenter clinical trial AATRM 048/13/2000. Ann Surg Oncol. 2013;20:120-27
14. de Boer M, van Deurzen CMM, van Dijk IAM, et al. Micrometastases or isolated tumor cells and the outcome of breast cancer. Ann Surg. 2009;361:653-63
15. Shah BR, Bergkvist L, Frisell J, de Boniface J. Do clinical trials truly mirror their target population? An external validity analysis of national registries versus trial data from the Swedish prospective SENOMIC trial on sentinel node micrometastases in breast cancer. Breast Cancer Res Treat. 2019;177:469-75
16. Houvenaeghel G, El Hajj H, Barroz J, et al. External validation of the SERC trial population: Comparison with the multicenter French cohort, the Swedish and SENOMIC trial populations for breast cancer patients with sentinel node micro-metastasis. Cancers. 2020;12:2924
17. Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in women with invasive breast cancer and sentinel node metastasis: A randomized clinical trial. JAMA. 2011;305:569-75
18. Andersson Y, Bergkvist L, Frisell J, de Boniface J. Do clinical trials truly mirror their target population? An external validity analysis of national registries versus trial data from the Swedish prospective SENOMIC trial on sentinel node micrometastases in breast cancer. Breast Cancer Res Treat. 2019;177:469-75
19. Houvenaeghel G, El Hajj H, Barroz J, et al. External validation of the SERC trial population: Comparison with the multicenter French cohort, the Swedish and SENOMIC trial populations for breast cancer patients with sentinel node micro-metastasis. Cancers. 2020;12:2924
20. Andersson Y, Bergkvist L, Frisell J, de Boniface J. Do clinical trials truly mirror their target population? An external validity analysis of national registries versus trial data from the Swedish prospective SENOMIC trial on sentinel node micrometastases in breast cancer. Breast Cancer Res Treat. 2019;177:469-75
21. Kahn HI, Hanna WM, Chapman JW, et al. Biological significance of occult micrometastases in histologically negative axillary lymph nodes in breast cancer patients using the recent American Joint Committee on Cancer breast cancer staging system. Breast J. 2006;12:294-301
22. Fournier K, Schiller A, Perry RR, Laronga C. Micrometastasis in the sentinel lymph node of breast cancer does not mandate completion axillary dissection. Ann Surg. 2004;239:859-63, discussion 863-65
23. Susnik B, Fkovic-Graziol S, Bracko M. Occult micrometastases in axillary lymph nodes predict subsequent distant metastases in stage I breast cancer: A case-control study with 15-year follow-up. Ann Surg Oncol. 2004;11:568-72
24. Querzoli P, Pedriali M, Rinaldi R, et al. Axillary lymph node nanometastases are prognostic factors for disease-free survival and metastatic relapse in breast cancer patients. Clin Cancer Res. 2006;12:6696-701
25. de Mascarel I, Bonichon F, Coindre JM, Trojani M. Prognostic significance of breast cancer axillary lymph node micrometastases assessed by two special techniques: Reevaluation with longer follow-up. Br J Cancer. 1992;66:523-27
26. Rosen PP, Saijo PE, Braun DW, et al. Axillary micro- and macrometastases in breast cancer: Prognostic significance of tumor size. Ann Surg. 1981;194:585-91
27. Andersson Y, Bergkvist L, Frisell J, de Boniface J. Long-term breast cancer survival in relation to the metastatic tumor burden in axillary lymph nodes. Breast Cancer Res Treat. 2018;171:559-69
28. Houvenaeghel G, Sabatier R, Reyal F, et al. Axillary lymph node micrometastases decrease triple-negative early breast cancer survival. Br J Cancer. 2016;115:1024-31
29. Colleoni M, Rotmensz N, Peruzzi G, et al. Size of breast cancer metastases in axillary lymph nodes: Clinical relevance of minimal lymph node involvement. J Clin Oncol. 2005;23:1379-89
30. Gobardhan PD, Elias SG, Madsen EVE, et al. Prognostic value of micrometastases in sentinel lymph nodes of patients with breast carcinoma: A cohort study. Ann Oncol. 2009;20:41-48
31. Hansen NM, Grube B, Ye X, et al. Impact of micrometastases in the sentinel node of patients with invasive breast cancer. J Clin Oncol. 2009;27:4679-84
32. de Boer M, van Dijk IAM, Buit P, et al. Breast cancer prognosis and occult lymph node metastases, isolated tumor cells, and micrometastases. J Natl Cancer Inst. 2010;102:410-25
33. Weaver DL, Ashikaga T, Krag DN, et al. Effect of occult metastases on survival in node-negative breast cancer. New Engl J Med. 2011;364:412-21
34. Houvenaeghel G, Classe J-M, Garbay J-R, et al. Prognostic value of isolated tumor cells and micrometastases of lymph nodes in early-stage breast cancer: A French sentinel node multicenter cohort study. Breast (Edinburgh, Scotland). 2014;23:561-66

35. Houvenaeghel G, de Nonneville A, Cohen M, et al. Lack of prognostic impact of sentinel node micro-metastases in endocrine receptor-positive early breast cancer: Results from a large multicenter cohort. ESMO open. 2021;6:100151

36. Reed DR, Lindsley SK, Mann GN, et al. Axillary lymph node dose with tangential breast irradiation. Int J Radiat Oncol Biol Phys. 2005;61:358-64

37. Fisher B, Redmond C, Poisson R, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. New Engl J Medicine. 1989;320:822-28

38. Ribeiro GG, Dunn G, Swindell R, et al. Conservation of the breast using two different radiotherapy techniques: Interim report of a clinical trial. Clin Oncol (R Coll Radiol). 1990;2:27-34

39. Wu SP, Tam M, Shaikh F, et al. Post-mastectomy radiation therapy in breast cancer patients with nodal micrometastases. Ann Surg Oncol. 2018;25:2620-31

40. Fu J, Wu L, Ge C, et al. De-escalating chemotherapy for stage II colon cancer? Therap Adv Gastroenterol. 2019;12:1756284819867553

41. Andersson Y, Bergkvist L, Frisell J, de Boniface J. Omitting completion axillary lymph node dissection after detection of sentinel node micrometastases in breast cancer: First results from the prospective SENOMIC trial. Br J Surg. 2021;108:1105-11

42. Houvenaeghel G, Cohen M, Raro P, et al. Overview of the pathological results and treatment characteristics in the first 1000 patients randomized in the SERC trial: Axillary dissection versus no axillary dissection in patients with involved sentinel node. BMC Cancer. 2018;18:1153