Postmastectomy Radiation Therapy can Improve Survival for Breast Cancer Patients with 1-3 Positive Axillary Lymph Nodes: A Retrospective Cohort Study Using SEER Database

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Abstract

Postmastectomy radiation (PMRT) is an important adjuvant treatment for high-risk breast cancer. However, evidence concerning the efficacy of PMRT on survival for breast cancer patients with 1-3 positive axillary lymph nodes remains insufficient. We identified 57,793 patients from the Surveillance, Epidemiology, and End Results database, including 15,126 cases of beam radiation and 42,667 cases of none/unknown radiation. All patients were diagnosed during 2010–2015. Kaplan–Meier curve was utilized to compare the survival of the two groups. We used univariate and multivariate Cox proportional hazard models to identify independent prognostic factors with Hazard Ratio and 95% Confidence Intervals. Patients were stratified according to lymph node status, tumor size and molecular subtypes to perform subgroup analysis. The PMRT group shows more aggressive clinicopathological features, including higher grade ($p<0.001$), larger tumor size ($p<0.001$), more lymph nodes ($p<0.001$), younger age ($p<0.001$), more ER absence ($p<0.001$), more PR absence ($p<0.001$), and more HER2 overexpression ($p<0.001$). In addition, the PMRT group received more radical surgery ($p<0.001$) and more chemotherapy ($p<0.001$). In the multivariable Cox proportional hazard regression analysis, the PMRT group presented improved survival in terms of breast cancer specific survival (BCSS) (HR, 0.739; 95% CI, 0.679–0.805; $p<0.001$) and overall survival (OS) (HR, 0.721; 95% CI, 0.670–0.777; $p<0.001$). After stratified according to positive axillary lymph nodes, the PMRT group showed improved BCSS and OS in the LN 1 to 3 subgroup (HR, 0.738, 95% CI, 0.639–0.853, $p<0.001$ and HR, 0.684, 95% CI, 0.604–0.776, $p<0.001$, respectively). For patients with 1-3 positive axillary lymph nodes and T1-2 tumors, the PMRT group still showed improved survival in terms of BCSS and OS (HR, 0.826, 95% CI, 0.688–0.992, $p=0.04$ and HR, 0.751, 95% CI, 0.643–0.878, $p<0.001$, respectively). In the subgroup analysis, PMRT remained a significant favorable prognostic factor in T2 and Her2-/HR+ subtype ($p<0.05$). This study suggests that even in the era of modern therapy, PMRT can confer a survival benefit to breast cancer patients with 1-3 positive axillary lymph nodes. Furthermore, for patients with 1-3 positive axillary lymph nodes and T1-2 tumors, PMRT can still provide survival benefits.

Introduction

Postmastectomy radiation therapy (PMRT) can eliminate the microscopic residual disease in the chest wall and regional lymph nodes, which may become the source of locoregional recurrence (LRR) and distant metastasis. It was recommended for patients with four or more positive axillary lymph nodes, but not for negative axillary lymph node by some guidelines [1-5]. However, the effect of PMRT for patients with 1-3 positive axillary lymph nodes remains controversial and was not firmly recommended by these guidelines. There were some prospective clinical trials focusing on this group of patients. The MA25 study was designed to randomize patients with 1-3 positive axillary lymph nodes to receive radiotherapy or not after mastectomy. Unfortunately, this trial was closed. The European SUPREMO trial was opened to assess the effect of PMRT on intermediate risk patients. This trial randomized patients to local regional radiotherapy or no radiotherapy after mastectomy. However, it will take years before the definitive result is obtained [6].

Despite the lack of data from randomized controlled trials, there have been some retrospective studies regarding this question. Marie Overgaard et al. conducted a subgroup analysis of the DBCG 82b and c randomized trials and only included 1152 patients with eight or more axillary lymph nodes removed [7]. The 15-year LRR was 10% and 51% for PMRT group and no PMRT group ($p<0.001$) for patients with four or more positive lymph nodes, 4% and 27% ($p<0.001$) for patients with 1-3 positive lymph nodes, respectively. Similarly, the PMRT group demonstrated significant improved 15-year OS for both patients with four or more positive lymph nodes (21% vs. 12%, $p=0.03$) and patients with 1-3 lymph nodes (57% vs. 48%, $p=0.03$). In 2014, McGale P et al. published a landmark meta-analysis of individual data including 8135 patients from 22 trials between 1964 and 1986[8]. For 700 patients without positive axillary lymph node, PMRT had no significant effect on LRR or breast cancer mortality. For 1772 patients with four or more axillary lymph nodes, PMRT reduced locoregional recurrence (from 32.1% to 13.0% at 10 years, $p<0.0001$), overall recurrence (from 75.1% to 66.3% at 10 years, $2p=0.0003$) and breast cancer mortality (from 80.0% to 70.7% at 20 years, $2p=0.04$). Notably, for 1314 patients with 1-3 axillary lymph nodes, PMRT significantly reduced the locoregional recurrence first (from 20.3% to 3.8% at 10 years, $2p<0.00001$), overall recurrence (from 45.7% to 34.2% at 10 years, $2p=0.00006$) and breast cancer mortality (from 50.2% to 42.3% at 20 years, $2p=0.01$). Even for the 1133 patients with 1-3 positive axillary lymph nodes who received systemic therapy, PMRT significantly reduce the locoregional recurrence, overall recurrence and breast cancer mortality. Since accumulating evidences in favor of PMRT for patients with 1-3 axillary lymph nodes, the National Comprehensive Cancer Network guidelines ‘strongly consider radiation therapy to chest wall and infraclavicular region, supraclavicular area, internal mammary nodes, and any part of the axillary bed at risk’ for this group of patients(evidence category Ⓐ) [9].

However, these studies have some limitations. These trials were started decades ago. For example, the patients in the DBCG 82b and c trials were treated in the 1970s or 80s, and the patients included in the 2014 EBCTCG meta-analysis were treated between 1964 and 1986. Firstly, they could not reflect the state-of-the-art treatment. From that time, there have been a lot of improvements in detection, surgical technique, pathological review and systemic therapy regimen. First, most patients received the cyclophosphamide-methotrexate-fluorouracil (CMF) chemotherapy, but more intensive anthracycline and/or taxane-based regimens are widely used in the present day. Second, some studies applied no or less intensive endocrine therapy. For example, in the DBCG 82 b and c trials, endocrine therapy was given based on postmenopausal status rather than ER positive. Additionally, in the DBCG 82 c trial, postmenopausal patients were given tamoxifen 30mg for 1 year, while these patients will receive aromatase inhibitor for 5 years or longer in the present days. Third, for HER2 positive patient, the contemporary therapy contains targeted therapy (for example, Herceptin). Since these improvements in adjuvant therapy can reduce LRR and improve survival, PMRT may not be necessary any more. On the other hand, radiation technology has improved a lot, which can improve patients’ survival [10]. Secondly, these trials did not contain some important clinicopathological factors such as ER and/or PR, HER2, hence it may bring some bias into the retrospective analyses.

Since whether breast cancer patients with 1-3 lymph nodes in the modern days can benefit from PMRT remains uncertain, we performed a population-based study to compare the prognosis of breast cancer patients with 1-3 positive axillary lymph nodes with or without PMRT utilizing the Surveillance, Epidemiology, and End Results (SEER) database. We present the article in accordance with the STROBE reporting checklist

Materials And Methods

Patients: We signed the Data-Use Agreement for the Surveillance, Epidemiology, and End Results (SEER) Program Research Data (1973–2015) custom database (<http://www.seer.cancer.gov>). The SEER 18 database contains data from Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, rural Georgia, and the Alaska Native Tumor Registry and the registries of greater California, Kentucky, Louisiana, New Jersey, and greater Georgia. SEER collects demographic and clinical information for patients and makes them available for analysis through custom databases on request. The SEER*Stat (version 8.3.5) was used to download data from the SEER 18 registries custom database. This database contains data in the SEER 18 registries research database in addition to the radiotherapy and chemotherapy information. We selected female breast cancer patients according to the following criteria: 1) patients were histologically confirmed as breast cancer; 2) the histologic subtype is invasive ductal cancer (according to ICD-O-3); 3) patients were diagnosed between 2010 and 2015; 4) breast cancer is the patient's first and only tumor; 5) patients without metastasis and received mastectomy. In total, 72442 patients were primarily included. We exclude 2447 cases of radiotherapy recommended, but unknown if administered, 158 cases of radiation but method or source not specified. We excluded 6 cases of radioisotope, 66 cases of radioactive implants and 20 cases of combination of beam with implant or isotopes. We excluded 366 cases of radiotherapy not after surgery, including beam radiation and intraoperative radiation, radiation before and after surgery, radiation prior to surgery, surgery both before and after radiation, sequence unknown, intraoperative radiation with other radiation before/after surgery. We excluded 11,586 cases with missing data on one or more covariates. Finally, 57,793 patients were eligible in this study, including 15,126 cases of beam radiation and 42,667 cases of none/unknown radiation (Fig. 1). This article does not contain any studies with human participants or animals performed by any of the authors. The informed consent was not required because this was a population-based retrospective study and personal information was not involved.

Construction of variables

All the variables were extracted from SERR records. In this study, we included radiation (PRMT or no PMRT), race (white, black or other), grade(I, II, III or IV), tumor size(T1, T2, T3 or T4), lymph nodes(0, 1–3, 4 or more), diagnosis year(2010–2011, 2012–2013 or 2014–2015), age at diagnosis(15–34, 35–39, 40–49, 50–59, 60–69, 70–79 or 80–100), ER status (positive or negative), PR status(positive or negative), HER2 status(positive or negative), surgery (Subcutaneous mastectomy and simple mastectomy, modified radical mastectomy and radical mastectomy and extended radical mastectomy) and chemotherapy (yes

or No/Unknown). PMRT was defined as beam radiation, no PMRT was defined as No/Unknown radiation. ER and PR borderline were classified as positive, while HER2 borderline was classified as missing data. We focus on Breast cancer specific survival (BCSS) and overall survival (OS). BCSS was defined as the time from diagnosis to death from breast cancer, while OS was defined as the time from diagnosis to death due to any cause. Loss of follow-up were censored.

Statistical analysis

We Chi-squared test was used to compare the baseline characteristics of two groups. The Kaplan-Meier method and log-rank test was performed to compare the distribution of survival between two groups. The univariate and multivariate Cox proportional hazard regression models were utilized to calculate the hazard ratio (HR) and 95% confidence interval. Subgroup analysis was used to compare the distribution of survival between two groups after stratified by different covariates. In each subgroup, the multivariate Cox proportional hazard regression model was utilized to calculate the hazard ratio (HR) and 95% confidence interval. All subgroup analyses were presented with forest plots.

We performed all statistical analyses with R (version 3.2.4, R project for Statistical Computing, Austria). All statistical analyses were 2-sided and $p < 0.05$ was defined as statistically significant.

Results

Baseline patient characteristics

Table I shows demographic and clinicopathological characteristics of patients in this study. The follow-up time ranges from 0 to 71 months, with a median time if 31 months. There were 4288 deaths or 2905 deaths caused by breast cancer during follow-up. The two groups have significantly different distribution of clinicopathological characteristics. Compared with the no PMRT group, tumors in the PMRT group were more aggressive. Specifically, PMRT group shows higher grade (III and IV, 55.4% vs. 41.0%, $p < 0.001$), larger tumor size (T2, 3, 4, 76.5% vs. 42.9%, $p < 0.001$), more lymph nodes (LN positive, 78.6% vs. 29.2%, $p < 0.001$), more absence of ER (26.2% vs. 21.6%, $p < 0.001$) and PR (37.4% vs. 32.1%, $p < 0.001$), HER2 overexpression (23.8% vs. 20.5%, $p < 0.001$) and younger age (15–59, 68.5% vs. 56.5%, $p < 0.001$). In addition, the PMRT group received more radical surgery (MRM, RM and ERM, 61.3% vs. 30.9%, $p < 0.001$) and more chemotherapy (87.2% vs. 44.4%, $p < 0.001$).

Comparison of survival between the PMRT and no PMRT groups

We performed Kaplan–Meier analysis to compare the survival between the PMRT and no PMRT groups. The PMRT group had significantly shorter survival in comparison of the no PMRT group both in BCSS (HR, 1.975, 95% CI, 1.835–2.126, $p < 0.001$) and OS (HR, 1.378, 95% CI, 1.293–1.468, $p < 0.001$) (Fig. 2). The five-year BCSS rates were 85.2% (95% CI, 84.3–86.1%) and 92.4% (95% CI, 92.0–92.8%) in the PMRT group and no PMRT group, respectively. Similarly, OS rates were 82.7% (95% CI, 81.7–83.6%) and 87.5% (95% CI, 87.0–88.0%) in the two groups, respectively.

In the univariate model, radiation, race, grade, tumor size, lymph node status, diagnosis year (2012–2013), age group (40–49, 50–59, 60–69 and 80–99), ER status, PR status, HER2 status, surgery, and chemotherapy were significantly associated with BCSS (Table II). In the multivariate model, radiation, race, grade, tumor size, lymph nodes, age group (70–79, 80–99), ER status, PR status, HER2 status, surgery and chemotherapy remained significantly related to BCSS after controlling the above factors. Compared with the no PMRT group, the PMRT group had longer BCSS (HR, 0.739, 95% CI, 0.679–0.805, $p < 0.001$). Several characteristics, including radiation, race, tumor size, lymph node status, diagnosis year (2014–2015), age group (40–49, 70–79 and 80–99), ER status, PR status, HER2 status and surgery were significantly related to OS in the univariate model (Table III). And in the multivariate model, radiation, race, grade, tumor size, lymph nodes, age group (60–69, 70–79, 80–99), ER status, PR status, HER2 status, surgery and chemotherapy remained significantly related to OS. It is noteworthy, PMRT was a significant better prognostic predictor for OS (HR, 0.721, 95% CI, 0.670–0.777, $p < 0.001$).

Comparison of survival between the PMRT and no PMRT groups based on LN subgroups

We stratified all patients into three subgroups based on positive axillary lymph nodes. As presented in Fig. 3 and Fig. 4, the PMRT group showed improved BCSS and OS in the LN 1 to 3 subgroup (HR, 0.738, 95% CI, 0.639–0.853, $p < 0.001$ and HR, 0.684, 95% CI, 0.604–0.776, $p < 0.001$, respectively) and LN ≥ 4 subgroup (HR, 0.635, 95% CI, 0.563–0.717, $p < 0.001$ and HR, 0.623, 95% CI, 0.558–0.696, $p < 0.001$, respectively) except for LN 0 subgroup (HR, 1.146 95% CI, 0.925–1.419, $p = 0.211$ and HR, 1.035, 95% CI, 0.868–1.234 $p = 0.704$, respectively).

Comparison of survival between the PMRT and no PMRT groups in the LN 1–3 and T1-2 subgroup

In the univariate model, PMRT, grade, race, age group (80–99), ER status, PR status, HER2 status, surgery and chemotherapy were significantly related to BCSS (Table IV). After controlling the above factors, beam radiation, race (other race), grade, age group (80–99), ER status, PR status, HER2 status and surgery remained significantly related to BCSS in the multivariate model. The PMRT group had better BCSS (HR, 0.826, 95% CI, 0.688–0.992, $p = 0.040$) compared with the no PMRT group. Some characteristics, including radiation, race, grade, age group (60–69, 70–79, 80–99), ER status, PR status, HER2 status, surgery and chemotherapy were significantly related to OS in the univariate model, as is shown in Table IV. In the multivariate model, radiation, race (other race), grade, age group (70–79, 80–99), ER status, PR status, HER2 status, surgery and chemotherapy remained significantly related to OS. Specially, PMRT was a significant better prognostic predictor for OS (HR, 0.751, 95% CI, 0.643–0.878, $p < 0.001$).

Subgroup analysis of patients with 1–3 lymph nodes and T1-2 based on T stage and molecular subtype

Since the effect on survival of PMRT may be different in different T stages and molecular subtypes, subgroup analyses of survival by stratifying T stage and molecular subtype were performed. When stratified by T stage, PMRT can significantly improve BCSS in T2 stage (HR, 0.773, 95% CI, 0.629–0.949, $p = 0.014$) and T4 stage (HR, 0.605, 95% CI, 0.415–0.882, $p = 0.009$), but not in T1 stage (HR, 0.841, 95% CI, 0.565–1.253, $p = 0.395$) and T3 stage (HR, 0.789, 95% CI, 0.583–1.069, $p = 0.127$) (Fig. 5). In terms of

OS, PMRT can significantly improve survival in T2 (HR, 0.710, 95% CI, 0.594–0.848, $p < 0.001$), T3 (HR, 0.737, 95% CI, 0.561–0.969, $p = 0.029$) and T4 (HR, 0.550, 95% CI, 0.392–0.773, $p = 0.001$) stages except T1 stage (HR, 0.744, 95% CI, 0.535–1.033, $p = 0.078$) (Fig. 6).

As presented in Figs. 7 and 8, the PMRT group showed improved BCSS and OS in the HER2-/HR+ subtype (HR, 0.722, 95% CI, 0.548–0.953, $p = 0.021$ and HR, 0.648, 95% CI, 0.518–0.811, $p < 0.001$, respectively), while there was no significant difference in the HER2+/HR+ (HR, 1.253, 95% CI, 0.673–2.331, $p = 0.477$ and HR, 0.971, 95% CI, 0.572–1.647, $p = 0.912$, respectively), HER2+/HR- (HR, 0.831, 95% CI, 0.415–1.662, $p = 0.600$ and HR, 0.651, 95% CI, 0.344–1.233, $p = 0.188$, respectively) and triple-negative (HR, 0.863, 95% CI, 0.646–1.153, $p = 0.320$ and HR, 0.843, 95% CI, 0.646–1.100, $p = 0.209$, respectively) subtypes.

Discussion

In our study, we found the PMRT group showed improved survival in terms of BCSS after controlling confounding variables. For patients with 1–3 positive axillary lymph nodes, PMRT had both improved BCSS and OS. Among these patients, those had T1-2 tumors or T2 tumors with Her2-/HR+ subtype also benefit from PMRT.

There are many studies regarding whether PMRT can improve survival of high-risk breast cancer patients, including three well-conducted randomized controlled trials [11–14]. The DBCG 82b trial enrolled 1708 high-risk premenopausal patients with breast cancer after modified radical mastectomy between 1982 and 1989 [12]. The patients were randomized to cyclophosphamide-methotrexate-fluorouracil (CMF) chemotherapy alone or chemotherapy with PMRT to the chest wall and regional lymph nodes. With 114-month median follow-up, the chemotherapy and PMRT group demonstrated statistically reduction in locoregional recurrence (9% vs. 32%, $p < 0.001$) and improvement in OS (54% vs. 45%, $p < 0.001$). The DBCG 82c trial randomized 1375 postmenopausal high-risk patients after modified radical mastectomy to tamoxifen for one year or with concurrent PMRT to the chest wall and regional lymph nodes between 1982 and 1989. With 10 years median follow up, the tamoxifen and PMRT group demonstrated statistically significant lower LRR (8% vs. 35%, $p < 0.001$) and improved OS (45% vs. 36%, $p = 0.03$). The British Columbia Trial (14) enrolled 318 node-positive premenopausal patients with breast cancer between 1978 and 1986. All the subjects were randomized to CMF chemotherapy alone or CMF chemotherapy with PRMT to the chest wall and regional lymph nodes after modified radical mastectomy. After a 15 years median follow-up, the CMF chemotherapy and PRMT group demonstrated statistically significant lower LRR (13% vs. 33%, $p = 0.003$) and improved OS (54% vs. 46%, $p = 0.07$). The 20-year results was consistent with the previous report showing that the CMF chemotherapy and PRMT group had statistically significant improved survival free of isolated locoregional disease (90% vs. 74%, $p = 0.002$) and OS (47% vs. 37%, $p = 0.03$) [11]. These studies and the following EBCTCG meta-analysis demonstrated that PMRT in addition to decrease risk of local-regional recurrence also improve survival for patients with high-risk breast cancer [15]. In our study, these results were consistent with the previous studies. Since the PMRT group contained more high-risk patient, they demonstrated inferior cumulative six-year survival. However, after controlling the potential confounders, PMRT can significantly improve

BCSS and OS. Interestingly, the HR for OS does not differ significantly between these studies, even with decades of improvement in diagnosis and treatment. It means that in the era of modern adjuvant therapy algorithm, such as anthracycline and/or taxane-based chemotherapy, targeted therapy and modern endocrine therapy, PMRT can also confer a similar survival benefit for breast cancer patients.

Whether patients with 1–3 positive lymph nodes can benefit from PMRT is a hot topic and continues to be controversial. There are some studies supporting PMRT for patients with 1–3 positive lymph nodes [7, 8, 12], however, some studies have come to the opposite conclusion [11, 14, 16]. The inconsistent results may due to disparity in criteria for patient selection, different therapy strategies, the small number of patients involved and lack of some important prognostic factors such as ER, PR and HER2. In the present study, we conducted a population-based study utilizing the SEER 18 registries custom database, which included 77587 cases of breast cancer patients with 1–3 positive lymph nodes. This large cohort can provide more comprehensive results for the real-world situation. Furthermore, all these patients were treated between 2010 and 2015, which reflected the results of state-of-the-art treatment algorithm. Additionally, this study contained some important prognostic factors such as ER, PR and HER2, and can exclude the relevant confounders compared with the studies described above. In the multivariate Cox proportional hazard regression model, the PMRT group demonstrated significantly improved BCSS and OS for patients with 1–3 positive axillary lymph nodes irrespective of T stage.

Since T3, T4 patients have high risk of LRR and can benefit from radiation therapy, thus patients with 1–3 positive axillary lymph nodes are able to benefit from radiation therapy may be because it includes patients with T3-4 tumors. Patients with 1–3 positive axillary lymph nodes and T1-2 were defined as “intermediate risk”, which demonstrated LRR rates of 6–13% after mastectomy and chemotherapy [17–19]. Whether radiotherapy can reduce the LRR of such patients is still controversial [18, 20–24]. Some studies suggested that PMRT can reduce the LRR of such patients [18, 22], while other studies suggested the opposite [20, 23]. McBride A et al. reported that PMRT can reduce LRR for patients in the early era, whereas PMRT does not reduce LRR for patients in the later era [21]. This may be due to advances in other adjuvant treatment techniques leading to a decrease in LRR, as for patients who had not received radiation, patients of the later era had lower LRR than early era. Yang PS et al reported that PMRT did not reduce LRR for such patients, but for patients with high recurrence factors. For example, for patients with ER negative status and positive lymphovascular invasion, PMRT would reduce LRR(from 40–12.5%) and at the same time improve 5-year OS(from 43.7–87.1%) [24]. Smith BD et al. suggested that PMRT conferred a 15–20% relative reduction in mortality for patients with seven or more positive axillary lymph nodes and T1-2 tumors, and not for patients with less than seven positive axillary lymph nodes and T1-2 tumors [20]. In the present study, the PMRT group demonstrated both improved BCSS and OS in the patients with 1–3 positive axillary lymph nodes and T1-2 tumors. Additionally, in the subgroup analysis stratified according to T stage, the PMRT group demonstrated significantly improved BCSS and OS for patients with all T stages except T1 stage. Similarly, Fodor J et al demonstrated that for patients with 1–3 positive axillary lymph nodes, PMRT can significantly reduce LRR(8% vs. 24%, $p = 0.01$) in the T2 subgroup, while the PMRT group and no PMRT group demonstrated similar rate of LRR(8% vs. 8%, $p = 0.9$) in the T1 subgroup [16]. Some other studies identified T2 as an indicator of higher LRR for patients

with 1–3 positive lymph nodes without PMRT [16, 25–27]. These patients with high risk of LRR may benefit from PMRT. Given the data above, PMRT may be applied to T2 subgroup but not to T1 subgroup with 1–3 positive axillary lymph nodes.

Breast cancer is heterogeneous rather than one disease. Based on the intrinsic molecular portraits, breast cancer can be divided into four intrinsic biologic subtypes (luminal A, luminal B, HER2-enriched and triple-negative). Each subtype presents with different biologic behavior, response to treatment and prognosis [28, 29]. Some studies demonstrated that the risk of LRR was different in four intrinsic biologic subtypes. Abdulkarim et al. reported that the LRR in patients with T1-2N0 triple-negative breast cancer treated with modified radical mastectomy and without PMRT was 10% at a median follow-up of 7.2 years [30]. Voduc et al. analyzed the risk of local-regional recurrence of each breast cancer molecular subtypes [31]. The 10-year local relapse-free survival and regional relapse-free survival for Luminal A subtype were 92% and 96%, respectively. The corresponding rates were 86% and 88% in Luminal B subtype, 83% and 88% for HER2 enriched, and 81% and 80% for basal subtype. Dominici et al. examined the risk of LRR for 819 patients after mastectomy and without PMRT [32]. The five-year risk of LRR was 2.5% for the entire cohort, 1% for HR+/HER2- subtype, 6.5% for HR+/HER2+, 2% for HR-/HER2+ and 10.9% for HR-/HER2- ($P < 0.01$). Billar et al. retrospectively reviewed the recurrence rate of 1061 patients, of which 35% received mastectomy. The triple-negative patients demonstrated significantly higher local or regional recurrence (5.7% for triple-negative subtype, 2.9% for HER2+ subtype and 1.0% for ER+ patients, $p = 0.001$) [33]. These data suggested that triple-negative subtype is more aggressive and demonstrated the highest rate of LRR.

The response to PMRT of different subtypes may be heterogeneous. Patients with a high risk of local recurrence may not benefit from PMRT. Kyndi et al. analyzed 1000 of the 3083 high-risk breast cancer patients randomized to systemic therapy alone or systemic therapy and PMRT in the DBCG 82b and c trials [34]. All patients were categorized into four subtypes: ER+/HER2-, ER+/HER2+, ER-/HER2- and ER-/HER2+. The PMRT decreased LRR significantly in all subtypes except the ER-/HER2+ subtype, however, PMRT only improved OS significantly in the ER+/HER2- subtype. However, some studies have found inconsistent conclusions that early triple-negative breast cancer can benefit from PMRT. Wang et al. conducted a randomized trial in China, 681 consecutive patients with triple-negative stage I–II breast cancer received mastectomy were randomized to systemic chemotherapy alone or PMRT after systemic chemotherapy [35]. All patients were T1 or T2 stage, and over 80% were node negative. PMRT significantly improved both five-year recurrence-free survival (HR, 0.77; 95% CI, 0.72–0.98; $p = 0.02$) and five-year OS (HR, 0.79; 95% CI, 0.74–0.97; $p = 0.03$). The inconsistent results may be due to the disparity of patient selection criteria, treatment algorithm and follow-up period. Additionally, in Kyndi's study, the patient numbers in some subtypes were limited in their power to detect differences [34]. However, the study providing data on whether patients with 1–3 positive axillary lymph nodes and T1-2 tumors in different molecular subtypes can benefit from PMRT is scarce. In the present study, we selected 13969 patients with 1–3 positive axillary lymph nodes and T1-2 tumors and conducted a subgroup analysis stratified according to molecular subtypes. The results showed that only in the HER2-/HR+ subgroup, PMRT could produce survival benefits, which was consistent with the findings of Kyndi et al. [34]. This

conclusion is contrary to the traditional view that sub-invasive subtypes are more likely to benefit from PMRT. This may be because the benefit of radiotherapy for patients is mainly local control, and the death of patients is mainly related to distant metastasis, while the remaining three subtypes, rather than the HER2-/HR + subtype, have greater distant metastatic potential.

The advantage of this study is the large sample size, with enough samples in each subgroup to produce sufficient statistical power. Our study has some limitations. First, as declared by the Data Use Agreement for SEER Radiation Therapy and Chemotherapy Information: overall sensitivity was 80% for all SEER radiation therapy data and the specificity was high, radiotherapy data are classified by the type of RT received or “no/unknown”. However, underreporting of PMRT use makes it more difficult to obtain positive results in this study, thus the positive results obtained in this study are more reliable. Second, some treatment information such as endocrine therapy and targeted therapy is not available in the SEER 18 registries custom database. Last, some clinicopathological factors such as lymphovascular invasion and Ki-67 were not available. These limitations may confer some bias to this study.

In conclusion, even in the era of modern therapy, PMRT can confer a survival benefit to breast cancer patients with 1–3 positive axillary lymph nodes. Furthermore, for patients with 1–3 positive axillary lymph nodes and T1-2 tumors, PMRT can provide survival benefits. Additional randomized controlled clinical trials are needed to further support this conclusion.

Abbreviations

BCSS
breast cancer specific survival; CI:confident interval; ER:estrogen receptor; ERM:extended radical mastectomy; HER2:human epidermal growth factor receptor 2; HR:hazard ratio; LN:lymph node; LRR:local-regional recurrence; MRM:modified radical mastectomy; OS:overall survival; PMRT:postmastectomy radiotherapy; PR:progesterone receptor; SM:Subcutaneous mastectomy; TM:total mastectomy.

Declarations

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Consent for publication

Not applicable.

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Not applicable.

Availability of supporting data

The data that support the findings of this study are available from the SEER custom database, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of SEER custom database.

Authors' contributions

HC and QY conceived and designed the study. XZ, JY and YY performed the data analysis. JY and XZ wrote the paper. All authors read and approved the manuscript.

Ethics approval and consent to participate

The information of patients with breast cancer was retrieved from the SEER database. The informed consent was not required because this was a population-based retrospective study and personal information was not involved.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1Patient characteristics

	PMRT N=15126	(%)	no PMRT N=42667	(%)	P
Race					P<0.001
White	11254	74.4	32986	77.3	
Black	2238	14.8	4368	10.2	
Other	1634	10.8	5313	12.5	
Laterality					
Left	7616	50.4	21629	50.7	P=0.475
Right	7510	49.6	21038	49.3	
Grade					P<0.001
I	1097	7.3	7300	17.1	
II	5651	37.4	17866	41.9	
III	8325	55.0	17369	40.7	
IV	53	0.4	132	0.3	
Tumor size					P<0.001
T1	3562	23.5	24376	57.1	
T2	7124	47.1	15611	36.6	
T3	2958	19.6	1862	4.4	
T4	1482	9.8	818	1.9	
Lymph nodes					P<0.001
0	3234	21.4	30221	70.8	
1-3	6779	44.8	9748	22.8	
>=4	5113	33.8	2698	6.3	
Diagnosis year					P<0.001
2010-2011	5193	34.3	13722	32.2	
2012-2013	5043	33.3	14782	34.6	
2014-2015	4890	32.3	14163	33.2	
Age at diagnosis					P<0.001
15-34	977	6.5	1485	3.5	

35-39	1323	8.7	2137	5.0
40-49	4062	26.9	9613	22.5
50-59	3993	26.4	10870	25.5
60-69	2943	19.5	9575	22.4
70-79	1331	8.8	5998	14.1
80-100	497	3.3	2989	7.0
ER				P<0.001
Positive	11161	73.8	33443	78.4
Negative	3965	26.2	9224	21.6
PR				P<0.001
Positive	9465	62.6	28982	67.9
Negative	5661	37.4	13685	32.1
HER2				P<0.001
Positive	3606	23.8	8728	20.5
Negative	11520	76.2	33939	79.5
Surgery				P<0.001
SM	402	2.7	1746	4.1
TM	5436	35.9	27763	65.1
MRM	9117	60.3	12909	30.3
RM	158	1.0	238	0.6
ERM	13	0.0	11	0.0
Chemotherapy				P<0.001
Yes	13195	87.2	18943	44.4
No/Unknown	1931	12.8	23724	55.6

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; SM, Subcutaneous mastectomy; TM, total mastectomy; MRM, modified radical mastectomy; RM, radical mastectomy; ERM, extended radical mastectomy.

Table II: Univariate and multivariate Cox proportional hazard model of breast cancer-specific survival (BCSS)

Variables	Univariate analysis				Multivariate analysis			
	HR	(95% CI)		P-value	HR	(95% CI)		P-value
Radiation								
no PMRT	ref				ref			
PMRT	1.975	1.835	2.126	0.000	0.739	0.679	0.805	0.000
Race								
White	ref				ref			
Black	1.754	1.597	1.926	0.000	1.249	1.136	1.373	0.000
Other	0.587	0.506	0.682	0.000	0.660	0.569	0.767	0.000
Grade								
I and II	ref				ref			
III and IV	4.229	3.879	4.611	0.000	2.163	1.965	2.38	0.000
Tumor Size								
T1	ref				ref			
T2	3.787	3.406	4.210	0.000	2.131	1.907	2.381	0.000
T3	8.825	7.822	9.957	0.000	3.982	3.495	4.535	0.000
T4	14.747	12.967	16.772	0.000	5.377	4.672	6.189	0.000
Lymph nodes								
0	ref				ref			
1~3	2.652	2.406	2.924	0.000	2.327	2.096	2.585	0.000
>=4	7.807	7.121	8.559	0.000	5.384	4.821	6.012	0.000
Diagnosis year								
2010-2011	ref				ref			
2012-2013	0.918	0.845	0.998	0.045	0.999	0.919	1.086	0.985
2014-2015	0.889	0.759	1.041	0.145	1.016	0.867	1.190	0.848
Age group								
15-34	ref				ref			
35-39	0.936	0.749	1.168	0.557	1.010	0.808	1.261	0.933
40-49	0.687	0.570	0.828	0.000	0.862	0.714	1.040	0.120

50-59	0.792	0.659	0.951	0.013	0.932	0.775	1.121	0.457
60-69	0.769	0.638	0.927	0.006	1.008	0.835	1.217	0.934
70-79	1.090	0.900	1.320	0.376	1.380	1.135	1.679	0.001
80-99	2.429	2.004	2.943	0.000	2.416	1.966	2.969	0.000
ER								
Positive	ref				ref			
Negative	3.545	3.296	3.812	0.000	1.588	1.434	1.758	0.000
PR								
Positive	ref				ref			
Negative	3.755	3.480	4.052	0.000	2.171	1.952	2.414	0.000
HER2								
Positive	ref				ref			
Negative	1.162	1.059	1.276	0.002	1.815	1.651	1.995	0.000
Surgery								
SM and TM	ref				ref			
MRM, ,RM and ERM	2.862	2.649	3.092	0.000	1.148	1.052	1.253	0.002
Chemotherapy								
No/Unknown	ref				ref			
Yes	1.733	1.601	1.875	0.000	0.819	0.741	0.906	0.000

Abbreviations: HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; SM, Subcutaneous mastectomy; TM, total mastectomy; MRM, modified radical mastectomy; RM, radical mastectomy; ERM, extended radical mastectomy. Multivariate analysis include radiation, race, grade, tumor size, lymph nodes, diagnosis year, age at diagnosis, ER status, PR status, HER2 status, surgery and chemotherapy.

Table III: Univariate and multivariate Cox proportional hazard model of overall survival

Variables	Univariate analysis				Multivariate analysis			
	HR	(95% CI)		P-value	HR	(95% CI)		P-value
Radiation								
no PMRT	ref				ref			
PMRT	1.378	1.293	1.468	0.000	0.721	0.670	0.777	0.000
Race								
White	ref				ref			
Black	1.541	1.422	1.669	0.000	1.265	1.166	1.372	0.000
Other	0.553	0.488	0.626	0.000	0.636	0.562	0.720	0.000
Grade								
I and II	ref				ref			
III and IV	2.593	2.432	2.763	2.593	1.664	1.547	1.789	0.000
Tumor Size								
T1	ref				ref			
T2	2.594	2.403	2.800	0.000	1.789	1.649	1.941	0.000
T3	4.915	4.469	5.406	0.000	3.026	2.726	3.360	0.000
T4	8.334	7.518	9.239	0.000	3.936	3.510	4.414	0.000
Lymph nodes								
0	ref				ref			
1~3	1.895	1.759	2.041	0.000	1.770	1.632	1.919	0.000
>=4	4.634	4.311	4.982	0.000	3.560	3.256	3.893	0.000
Diagnosis year								
2010-2011	ref				ref			
2012-2013	0.954	0.890	1.022	0.179	1.023	0.955	1.097	0.515
2014-2015	0.878	0.773	0.997	0.045	1.004	0.884	1.141	0.946
Age group								
15-34	ref				ref			
35-39	0.911	0.734	1.130	0.394	0.969	0.781	1.202	0.772
40-49	0.718	0.600	0.860	0.000	0.852	0.712	1.021	0.083

50-59	0.889	0.746	1.059	0.187	0.992	0.832	1.183	0.927
60-69	1.078	0.904	1.284	0.403	1.272	1.066	1.518	0.008
70-79	1.859	1.560	2.215	0.000	2.042	1.707	2.443	0.000
80-99	5.118	4.304	6.085	0.000	4.276	3.560	5.135	0.000
ER								
Positive	ref				ref			
Negative	2.584	2.432	2.746	0.000	1.533	1.405	1.673	0.000
PR								
Positive	ref				ref			
Negative	2.608	2.456	2.771	0.000	1.734	1.590	1.890	0.000
HER2								
Positive	ref				ref			
Negative	1.227	1.135	1.326	0.000	1.632	1.506	1.767	0.000
Surgery								
SM and TM	ref				ref			
MRM, RM and ERM	2.393	2.249	2.546	0.000	1.211	1.129	1.299	0.000
Chemotherapy								
No/Unknown	ref				ref			
Yes	0.958	0.902	1.017	0.162	0.691	0.639	0.748	0.000

Abbreviations: HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; SM, Subcutaneous mastectomy; TM, total mastectomy; MRM, modified radical mastectomy; RM, radical mastectomy; ERM, extended radical mastectomy. Multivariate analysis include radiation, race, grade, tumor size, lymph nodes, diagnosis year, age at diagnosis, ER status, PR status, HER2 status, surgery and chemotherapy.

Table IV: Univariate and multivariate Cox proportional hazard model of breast cancer-specific survival (BCSS) in the LN 1-3 and T1, 2 subgroup

Variables	Univariate analysis				Multivariate analysis			
	HR	(95% CI)		P-value	HR	(95% CI)		P-value
Radiation								
no PMRT	ref				ref			
PMRT	0.822	0.693	0.975	0.025	0.826	0.688	0.992	0.040
Race								
White	ref				ref			
Black	1.363	1.096	1.694	0.005	1.117	0.896	1.391	0.325
Other	0.528	0.375	0.745	0.000	0.557	0.395	0.785	0.001
Grade								
I and II	ref				ref			
III and IV	3.182	2.663	3.802	0.000	2.243	1.833	2.745	0.000
Diagnosis year								
2010-2011	ref				ref			
2012-2013	0.918	0.762	1.106	0.367	0.977	0.810	1.178	0.806
2014-2015	0.936	0.644	1.360	0.729	1.004	0.691	1.460	0.982
Age group								
15-34	ref				ref			
35-39	0.900	0.557	1.452	0.665	0.841	0.521	1.357	0.478
40-49	0.667	0.444	1.001	0.050	0.749	0.499	1.124	0.163
50-59	0.844	0.568	1.253	0.400	0.868	0.583	1.291	0.485
60-69	0.905	0.605	1.353	0.625	1.012	0.674	1.518	0.955
70-79	1.223	0.805	1.858	0.345	1.247	0.813	1.914	0.312
80-99	3.146	2.092	4.731	0.000	3.246	2.087	5.049	0.000
ER								
Positive	ref				ref			
Negative	3.928	3.349	4.608	0.000	1.775	1.418	2.223	0.000
PR								
Positive	ref				ref			
Negative	0.500	0.250	1.000	0.000	0.500	0.250	1.000	0.000

Negative	3.856	3.274	4.542	0.000	2.202	1.746	2.778	0.000
HER2								
Positive	ref				ref			
Negative	1.356	1.093	1.682	0.006	1.996	1.603	2.486	0.000
Surgery								
SM and TM	ref				ref			
MRM ,RM and ERM	1.384	1.171	1.637	0.000	1.213	1.023	1.437	0.026
Chemotherapy								
No/Unknown	ref				ref			
Yes	0.789	0.667	0.934	0.006	0.879	0.709	1.090	0.240

Abbreviations: HR, hazard ratio; CI, confidence interval; PMRT, postmastectomy radiation therapy; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; SM, Subcutaneous mastectomy; TM, total mastectomy; MRM, modified radical mastectomy; RM, radical mastectomy; ERM, extended radical mastectomy. Multivariate analysis include radiation, race, grade, diagnosis year, age at diagnosis, ER status, PR status, HER2 status, surgery and chemotherapy.

Table V: Univariate and multivariate Cox proportional hazard model of overall survival (OS) in the LN 1-3 and T1,2 subgroup

Variables	Univariate analysis				Multivariate analysis			
	HR	(95% CI)		P-value	HR	(95% CI)		P-value
Radiation								
no PMRT	ref				ref			
PMRT	0.604	0.521	0.699	0.000	0.751	0.643	0.878	0.000
Race								
White	ref				ref			
Black	1.307	1.095	1.560	0.003	1.194	0.999	1.428	0.052
Other	0.529	0.402	0.696	0.000	0.593	0.450	0.780	0.000
Grade								
I and II	ref				ref			
III and IV	1.918	1.683	2.187	0.000	1.651	1.421	1.919	0.000
Diagnosis year								
2010-2011	ref				ref			
2012-2013	0.948	0.817	1.100	0.479	1.004	0.865	1.165	0.959
2014-2015	0.847	0.635	1.129	0.258	0.911	0.683	1.215	0.526
Age group								
15-34	ref				ref			
35-39	0.870	0.541	1.397	0.564	0.827	0.514	1.329	0.432
40-49	0.737	0.497	1.094	0.130	0.779	0.525	1.157	0.216
50-59	1.038	0.708	1.522	0.847	1.002	0.682	1.470	0.994
60-69	1.465	1.003	2.142	0.048	1.452	0.990	2.129	0.056
70-79	2.304	1.569	3.385	0.000	2.009	1.357	2.975	0.000
80-99	6.876	4.724	10.008	0.000	5.496	3.692	8.181	0.000
ER								
Positive	ref				ref			
Negative	2.677	2.346	3.055	0.000	1.671	1.382	2.019	0.000
PR								
Positive	ref				ref			
Negative	1.307	0.999	1.714	0.052	1.194	0.999	1.428	0.052

Negative	2.539	2.235	2.886	0.000	1.773	1.474	2.133	0.000
HER2								
Positive	ref				ref			
Negative	1.396	1.172	1.662	0.000	1.756	1.468	2.102	0.000
Surgery								
SM and TM	ref				ref			
MRM, RM and ERM	1.365	1.193	1.560	0.000	1.226	1.070	1.404	0.003
Chemotherapy								
No/Unknown	ref				ref			
Yes	0.473	0.416	0.538	0.000	0.739	0.626	0.873	0.000

Abbreviations: HR, hazard ratio; CI, confidence interval; PMRT, postmastectomy radiation therapy; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; SM, Subcutaneous mastectomy; TM, total mastectomy; MRM, modified radical mastectomy; RM, radical mastectomy; ERM, extended radical mastectomy. Multivariate analysis include radiation, race, grade, diagnosis year, age at diagnosis, ER status, PR status, HER2 status, surgery and chemotherapy.

Figures

Figure 1

Patient inclusion flow chart.

Figure 2

Kaplan-Meier curves of breast cancer-specific survival (BCSS) and overall survival (OS) based on radiation for all patients, PMRT vs. no PMRT.

Hazard Ratio

Figure 3

Forest plot of BCSS based on lymph nodes. The hazard ratio (HR) was calculated by multivariate Cox proportional hazard model adjusted for radiation, race, tumor size, diagnosis year, age group, ER status,

PR status, HER2 status, surgery and chemotherapy. Abbreviation: LN, lymph node. The data source was the whole patients.

Figure 4

Forest plot of OS based on lymph nodes. The hazard ratio (HR) was calculated by multivariate Cox proportional hazard model adjusted for radiation, race, tumor size, diagnosis year, age group, ER status, PR status, HER2 status, surgery and chemotherapy. Abbreviation: LN, lymph node. The data source was the whole patients.

Figure 5

Forest plot of BCSS based on T stage. The hazard ratio (HR) was calculated by multivariate Cox proportional hazard model adjusted for radiation, race, diagnosis year, age group, ER status, PR status, HER2 status, surgery and chemotherapy. Abbreviation: LN, lymph node. The data source was the LN1-3 subgroup.

Figure 6

Forest plot of OS based on T stage. The hazard ratio (HR) was calculated by multivariate Cox proportional hazard model adjusted for radiation, race, diagnosis year, age group, ER status, PR status, HER2 status, surgery and chemotherapy. Abbreviation: LN, lymph node. The data source was the LN1-3 subgroup.

Figure 7

Forest plot of BCSS based on molecular subtypes. The hazard ratio (HR) was calculated by multivariate Cox proportional hazard model adjusted for radiation, race, diagnosis year, age group, surgery and chemotherapy. Abbreviation: LN, lymph node. The data source was the LN1-3 and T1, 2 subgroup.

Figure 8

Forest plot of OS based on molecular subtypes. The hazard ratio (HR) was calculated by multivariate Cox proportional hazard model adjusted for radiation, race, diagnosis year, age group, surgery and chemotherapy. Abbreviation: LN, lymph node. The data source was the LN1-3 and T1, 2 subgroup.