Observational Study

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Effect of postmastectomy radiotherapy on pT1-2N1 breast cancer patients with different molecular subtypes

A real-world study based on the inverse probability of treatment weighting method

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Abstract

To investigate the significance of postmastectomy radiotherapy (PMRT) for different molecular subtypes of female breast cancer T1-2N1M0 based on inverse probability of treatment weighting (IPTW). The data of breast cancer patients diagnosed between 2010 and 2014 from the Surveillance, Epidemiology, and End Results (SEER) database were extracted. According to the status of hormone receptor (HR) and human epidermal growth factor receptor-2 (HER2), the patients were classified into luminal-A (HR+/HER2-), luminal-B (HR+/HER2+), HER2-enriched (HR-/HER2+), and TNBC (HR-/HER2-) subtypes. The association between radiation therapy and breast cancer-specific survival (BCSS) and Overall survival (OS) was retrospectively analyzed. Inverse probability of treatment weighting (IPTW) was applied to balance measurable confounders. Among the 16 894 patients, 6 055 (35.8%) were in the PMRT group and 10 839 (64.2%) were in the nonPMRT group, with a median follow-up of 48 months. There were 1003 deaths from breast cancer and 754 deaths from other causes. After IPTW, the covariates between groups reached complete equilibrium, the multifactorial Cox regression analysis showed that PMRT significantly prolonged OS and BCSS in Luminal-A and TNBC subtype breast cancer patients, yet it brought little significant survival advantage in Luminal-B and HER2-enriched subtype patients. Our study demonstrates a beneficial impact for PMRT on OS and BCSS among Luminal-A and TNBC subtype breast cancer patients with T1-2N1 disease.

Abbreviations: BCSS = breast cancer-specific survival, CI = confidence interval, HER2 = human epidermal growth factor receptor-2, HR = hormone receptor, IPTW = inverse probability of treatment weighting, NA = not available, NCCN = national comprehensive cancer network, OS = Overall survival, PMRT = postmastectomy radiotherapy, SEER = Surveillance Epidemiology and End Results, TNBC = triple-negative breast cancer.

Key words: breast cancer, molecular subtype, prognosis, postmastectomy radiotherapy, SEER database

1. Introduction

Breast cancer is one of the most common cancers and the second leading cause of cancer death among women in the United States.[1] Postmastectomy radiation therapy (PMRT) has been shown in various studies to reduce locoregional recurrence risk and breast cancer mortality in women with node-positive disease.[2] The national comprehensive cancer network (NCCN) guidelines recommend PMRT as a standard therapy for those breast cancer patients with more than 4 positive axillary nodes,[3] but for those with tumor size <5 cm or 1-3 positive axillary nodes, the indication of PMRT is still controversial.[4–7]

As a heterogenous disease, T1-2N1 breast cancer has a broad risks of disease progression[8] and requires accurate treatment, especially in the era of precision medicine guided by molecular subtypes.[9] Breast cancer with different molecular types has completely different molecular characteristics, biological behavior and prognosis. With the development of the treatments, if pT1-2N1 patients do receive hormone therapy, anti-HER2 therapy or chemotherapy, PMRT may be dispensable for them.

Thus, we performed this retrospective analysis of T1-2N1 breast cancer patients according to subtypes trying to identify those patients who would benefit from PMRT.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2. Methods

2.1. Study design and data source

The present study retrospectively collected data for patients between 2010 and 2014 using the SEER program. The SEER program of the National Cancer Institute is a cancer statistics resource that includes data on cancer incidence, demographics, clinicopathological variables, treatment, and vital status derived from 18 cancer registries in the United States. Patients fitting the following criteria were included: 1.female patients, 2.primary breast cancer, 3.diagnosed with invasive breast cancer between 2010 and 2014, 4.tumor size <5 cm, 5.one to 3 lymph nodes invasion, 6.no distant metastasis, 7.one primary carcinoma only, 8.mastectomy performed. The following patient characteristics were included in this study: years of diagnosis, age at diagnosis, race/ethnicity, marital status, tumor size, number of positive lymph nodes, histology, grade, subtypes (HR+/HER2-; HR+/HER2-; HR-/HER2+; HR-/HER2-), receipt/nonreceipt of chemotherapy or radiotherapy. Considering this study was reviewed and approved by the institutional review board at the Shaoxing Second Hospital and determined to not be a human participant research, patient consent was not involved.

2.2. Outcome of interest

The primary endpoint of this study was overall survival (OS) and breast cancer specific survival (BCSS), which was defined as an internal from time of diagnosis to overall death (BC specific death) or date of last contact and considered as censored statuses if patients were alive until date of last contact. SEER defines mortality data based on the International Classification of Diseases Revisions 8 to 10, which categorized the cause of death as BC specific death and other cause death.

2.3. Statistical analysis

We adopt the similar statistical analytic approaches with previous studies[10,11] that examined the benefit of interventions for breast cancer subsets. Baseline patient, tumor and treatment characteristics were compared between nonPMRT and PMRT group using Pearson Chi-square and T test for categorical and ordinal factors, respectively. For inferring missing values of race, marital status, nuclear grade, and subtypes, we applied a multiple imputation procedure with the following variables: age at diagnosis, year of diagnosis, histological type, tumor size, number of positive lymph nodes, and receipt of chemotherapy.

The inverse probability of treatment weighting (IPTW)[12] was used to balance clinicopathological characteristics between nonPMRT and PMRT groups. To calculate propensity scores, baseline characteristics of patient age, year of diagnosis, race, marital status, histological type, nuclear grade, tumor size, number of positive lymph nodes, subtypes and receipt of chemotherapy were applied to a logistic regression model for receipt of PMRT. The hazard ratios for the OS and BCSS of patients in the PMRT group compared with patients in the nonPMRT group were evaluated using propensity score weights for log-rank tests and Cox regression models. Adjusted hazard ratios were reported from multivariable Cox proportional hazards models with age at diagnosis, year of diagnosis, race, marital status, histological type, nuclear grade, tumor size, number of positive lymph nodes, and receipt of chemotherapy. An interaction test was performed to examine whether there was a difference in the survival benefit conferred by surgical treatment according to subtypes.

All P values were calculated from 2-sided tests with threshold of 0.05 to evaluate statistical significance of survival benefit by surgery, and all statistical analyses were performed using R software (version 4.0.2).

3. Results

3.1. Patient characteristics by PMRT

A total of 16,894 female breast cancer patients with T1-2N1M0 stage were included in this study. Of this initial cohort, 10 839 patients (64.2%) were stratified into the nonPMRT group, and 6 055 patients (35.8%) were stratified into the PMRT group. The median follow-up time of our study was 48 months (interquartile range 33–64 months). The proportion of elderly patients, patients diagnosed during earlier years, white people, single patients, patients with small tumor size, patients with less lymph node invasion, patients with low nuclear grade, and patients with luminal-A was larger for the nonPMRT group compared with the PMRT group. Table 1 summarizes the demographic and clinicopathologic cohort parameters before and after IPTW.

3.2. Survival by PRMT among different subtypes

A total of 1003 deaths due to breast cancer (5.9%) and 754 deaths resulting from other cancers (4.5%) were identified in the cohort. Considering the possible interaction among variables, we conducted multivariate Cox regression analysis adjusting for patient age, year of diagnosis, race, nuclear grade, histology, receipt of chemotherapy, breast subtype, marital status,

Table 1

Patient Characteristics Weighted by Propensity Score.

Characteristic	No. of Patients (%)	
	nonPMRT Group (n = 10839)	PMRT Group (n = 6055)
Age (yr)		
≤46	2783 (25.7)	1597 (26.4)
47–55	2770 (25.6)	1394 (23.0)
56–65	2590 (23.9)	1429 (23.6)
≥66	2697 (24.9)	1635 (27.0)
Year of diagnosis		
2010	2195 (20.3)	1201 (19.8)
2011	2183 (20.1)	1292 (21.3)
2012	2194 (20.2)	1219 (20.1)
2013	2203 (20.3)	1137 (18.8)
2014	2063 (19.0)	1206 (19.9)
Race		
White	8443 (77.9)	4713 (77.8)
Black	1219 (11.2)	723 (11.9)
Others	1177 (10.9)	619 (10.2)
Marital status		
Married	6588 (60.8)	3647 (60.2)
Single	4251 (39.2)	2408 (39.8)
Histology		
Ductal	8413 (77.6)	4602 (76.0)
Lobular	893 (8.2)	680 (11.2)
Others	1533 (14.1)	773 (12.8)
Grade		
I	1466 (13.5)	876 (14.5)
II	5066 (46.7)	2824 (46.6)
III-IV	4307 (39.7)	2355 (38.9)
Tumor size (cm)		
≤2	4459 (41.1)	2492 (41.2)
2 to 5	6380 (58.9)	3563 (58.8)
No. of positive lymph nodes		
1	6484 (59.8)	3620 (59.8)
2	2855 (26.3)	1599 (26.4)
3	1500 (13.8)	836 (13.8)
Chemotherapy		
None	3534 (32.6)	2014 (33.3)
Yes	7305 (67.4)	4041 (66.7)
Subtypes		
Luminal-A	7787 (71.8)	4413 (72.9)
Luminal-B	1415 (13.1)	773 (12.8)
HER2-enriched	551 (5.1)	277 (4.6)
TNBC	1087 (10.0)	593 (9.8)

tumor size and number of positive lymph nodes. After adjusting for clinical factors and considering the propensity score, it was found that the OS was significantly better for patients with molecular subtype of luminal-A and TNBC in PMRT group than the nonPMRT group, while it brought no significant OS and BCSS advantage in luminal-B and HER2-enriched subtypes. The weighted 5-year OS of the PMRT and nonPMRT groups were 91.1% and 89.1% in luminal-A patients (absolute difference, 2.0%), 74.5% and 70.0% in TNBC patients (absolute difference, 4.5%), 89.9% and 90.2% in luminal-B patients (absolute difference, –0.3%), and 85.5% and 85.0% in HER2-enriched patients (absolute difference, 0.5%), respectively (Fig. 1). As for BCSS, PMRT was an independent prognostic factor in TNBC patients, yet PMRT brought no survival benefit in the luminal-A, luminal-B and HER2-enriched subtype patients. The weighted 5-year BCSS of the PMRT and nonPMRT groups were 80.7% and 75.1% in TNBC patients (absolute difference, 5.6%), 94.7% and 94.6% in luminal-B patients (absolute difference, 0.1%), 93.8% and 95.1% in luminal-B patients (absolute difference, –1.3%), 89.7% and 89.1% in HER2-enriched patients (absolute difference, 0.6%), respectively (Fig. 2).

4. Discussion

Although PMRT has been recognized as one of the most important treatments for T1-2N1 breast cancer patients, the effect of molecular subtypes on PMRT response in patients with T1-2N1 breast cancer is still controversial.[13–16] This study included a total of 16,894 breast cancer patients, including a large number of patients, which can provide us with sufficient information to reflect the benefits of PMRT for T1-2N1 breast cancer patients according to different molecular subtypes in the real world. To our knowledge, this is the first retrospective population study used propensity score weighting to explore the prognostic effect of PMRT on breast cancer patients and its effect on OS and BCSS according to molecular subtypes.

Propensity score weighting is an effective way of removing overt indication biases for the purpose of investigating treatment effects seen in observational studies.[17–20] Using this method, we attempted to balance the background characteristics of patients between the PMRT and nonPMRT groups (Table 1). Our study observed that Luminal-A and TNBC subtype breast cancer could gain significant OS and BCSS benefit from PMRT, while Luminal-B and HER-2 positive patients did not receive survival benefits (including OS and BCSS). This finding was consistent with the DBCG 82 b & c study which reported that PMRT significantly reduces the risk of LRR in breast cancer patients with luminal-A and TNBC subtypes, but had no effect on LRR in patients with HER2-enriched subtype.[21]

It is generally agreed that PMRT can significantly reduce the risk of LRR in patients with luminal breast cancer and can even improve their OS. In contrast, the effects of PMRT on HER2-enriched or TNBC patients are inconsistent. At the 2019 Saint Gallen Consensus,[22] panelists agreed on recommending irradiation for tumors with 1 to 3 positive axillary nodes and TNBC molecular subtype, while they did not reach consensus on HER2-positive or ER positive tumors. In the present series, Multivariate analysis showed that Luminal-A (HR+/HER-) patients treated with PMRT presented a significantly better OS, while Luminal-B (HR+/HER+) patients had no survival benefits. This might be related to the radiation resistance of HER2 positive tumor cells, which were associated with a loop-like HER2-NF-kB-HER2 pathway[23] and epithelial-to-mesenchymal transition.[24]

Similar to the luminal-B subtype, our study revealed that there is no significant improvement in OS and BCSS after PMRT in HER2-enriched breast cancer patients, which was in consistent with the previous findings[21,25] Basic studies have confirmed that

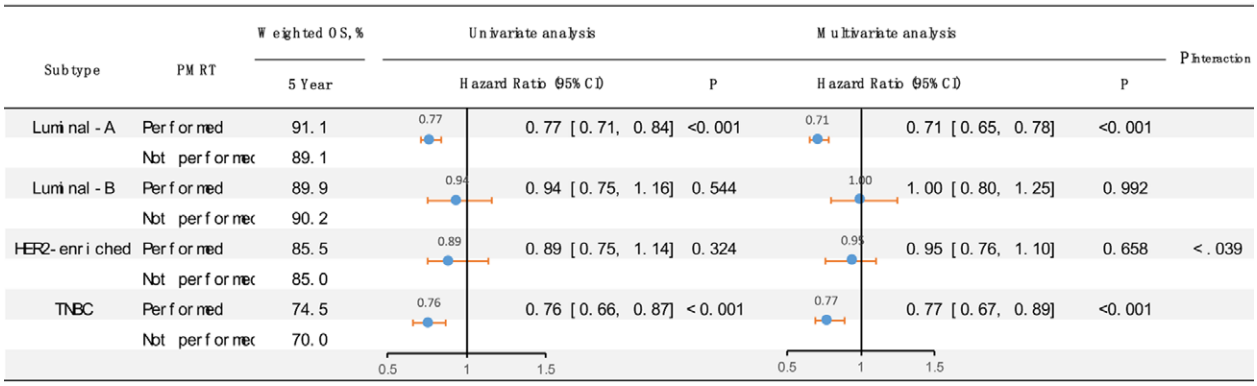

Figure 1. Effect of PMRT on OS in different molecular subtype groups.

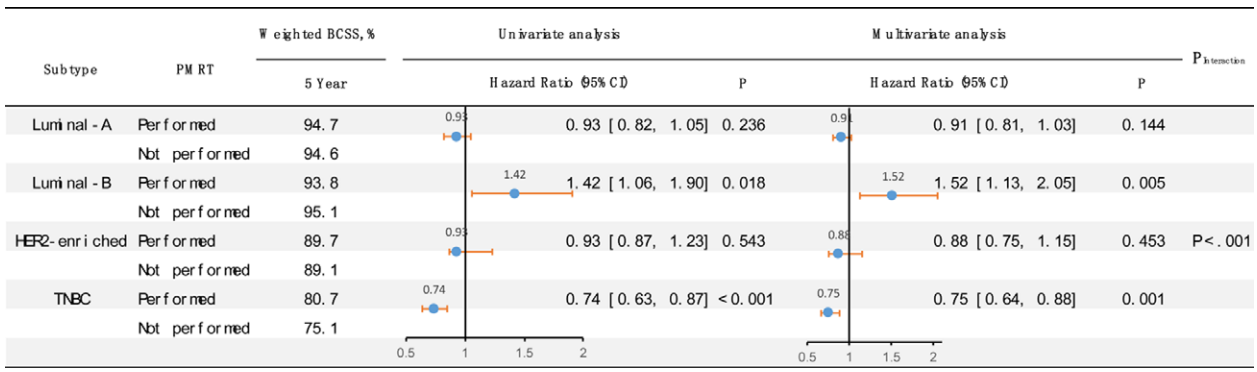

Figure 2. Effect of PMRT on BCSS in different molecular subtype groups.

HER2-positive breast cancer cells are resistant to radiation, and antiHER2-targeted therapy can reverse the radiation resistance of HER2-positive cells. Pietras et al[26] reported that MCF-7 cells transfected with HER2 were more resistant to radiation than parental MCF-7 cells, and antiHER2-targeted therapy could reverse the radiation resistance of HER2-overexpressing cell lines by regulating the repair of radiation induced DNA damage.[27] Indeed, antiHER2 therapy can be administered under RT and has been shown to be safe, although special attention should be given with regard to cardiotoxicity.[28–30]

Previous studies have shown that high-risk tumors have the greatest benefit from RT. Although there is heterogeneity in TNBC, most of the TNBC have a high risk of recurrence.[31] Radiotherapy is a major treatment for patients with tumors of the TNBC subtype, since their triple negativity does not provide an option for hormone or HER2 therapy. Our result is consistent with a report showing that adjuvant radiation is associated with improved OS in TNBC.[32] Xia et al also conducted a retrospective analysis of TNBC patients from a single institution and found that PMRT was associated with lengthened disease-free survival (DFS) in patients with T1-2N1 disease.[33] However, a few studies have shown increased mortality after radiotherapy in TNBC subtype.[21,34] This discrepancy could be due to additional heterogeneity within tumors of the TNBC subtype. At present, it is still challenging to identify patients who benefit from PMRT, and considering the lack of other effective treatment for TNBC, current clinical practice therefore considers PMRT still stands as an indispensable option.

Our study takes an initial step towards more personalized treatment with the ultimate goal of reducing overtreatment with radiotherapy while retaining low breast cancer mortality. There also exist limitations in our study. First of all, since the HER2 status in SEER database has not been available since 2010, the follow-up period is relatively short. Secondly, some important information, including Ki-67 level, lympho-vascular invasion, chemotherapy and endocrine therapy strategies, are not available in the SEER database, which may lead to potential bias. Lastly, the retrospective nature is an unavoidable weakness, future larger perspective studies will need to confirm the results.

5. Conclusions

Our study demonstrates a beneficial impact for PMRT on OS and BCSS among Luminal-A and TNBC subtype breast cancer patients with T1-2N1 disease. The results could help predict PMRT response and improve patient survival by adjusting individual treatment strategies. Further studies are needed to determine the potential mechanism of differences in PMRT sensitivity among molecular subtypes of breast cancer.

Author contributions

Conception or design: Shangyue Ye. Acquisition, analysis, or interpretation of data: Shangyue Ye and Weixian Hu. Drafting of the manuscript: Shangyue Ye and Weixian Hu. Critical revision of the manuscript for important intellectual content: Shangyue Ye and Weixian Hu. Statistical analysis: Shangyue Ye. Supervision: Shangyue Ye. All authors have given final approval of the manuscript for submission and publication.

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