Postmastectomy radiation therapy and survival outcome in older patients with T1-2N1 breast cancer

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ABSTRACT

Background: The prognostic impact of postmastectomy radiation therapy (PMRT) on contemporary older patients with T1-2N1 breast cancer is unclear. We aimed to investigate the effect of PMRT in this setting.
Methods: Leveraging the Surveillance, Epidemiology, and End Results (SEER) program data from 2004 to 2015, 7052 patients aged 70 years or older with T1-2N1 breast cancer were identified for this propensity-matched analysis. Fine and Gray competing risks regression was conducted to explore the correlation between PMRT and breast cancer-specific survival, in subgroups defined by tumor size and positive lymph nodes.
Results: The median follow-up was 60.1 months (interquartile range, 28.0 to 87.0). Among propensity-matched patients, multivariate analysis identified an association between PMRT and decreased breast cancer mortality (BCM; HR 0.637; 95 % CI 0.436−0.931; $P = 0.020$) in patient subset with three positive nodes and tumors 2−5 cm in size, and this benefit was limited to patients with three positive nodes and tumors 2−5 cm in size who did not receive chemotherapy. In patient subsets who received chemotherapy, no association between PMRT and BCM was found.
Conclusion: PMRT was not associated with BCM in older patients with T1-2N1 breast cancer who received chemotherapy. The benefit of PMRT was limited to those with three positive nodes and tumors 2−5 cm in size who did not receive chemotherapy.

1. Introduction

Patients aged 70 years or older represent one third of breast cancer diagnoses and this proportion keeps increasing over time [1,2]. Owing to the functional status, comorbidities and life expectancy, the treatment strategies for older patients with breast cancer are complicated and cannot crudely be extrapolated from those administrated in younger patients.

The role of postmastectomy radiation therapy (PMRT) in patients with T1-2N1 breast cancer is still a matter for debate [3,4]. In addition, due to the underrepresentation of older patients in clinical trials [5], there is limited evidence examining the prognostic effect of PMRT in older women with T1-2N1 breast cancer. Based on older patients diagnosed between 1992 and 1999 from the

Surveillance, Epidemiology, and End Results (SEER) program database, a previous study found no overall survival benefit from PMRT for those with T1-2N1 breast cancer [6]. However, as the advances in radiation technology reduced toxicity [7] and contemporary systemic therapy improved the outcome of patients with breast cancer [8], the impact of PMRT on older patients with T1-2N1 breast cancer in modern era needs to be clarified.

In the present study, we analyzed older patients diagnosed with T1-2N1 breast cancer between 2004 and 2015 from the SEER database, to examine the impact of PMRT on breast cancer-specific survival for the entire cohort and subgroups defined by the combination of tumor size and number of positive lymph nodes.

2. Materials and methods

2.1. Patient cohort

The present study was based on the National Cancer Institute's SEER program database released in November 2018. Between 2004

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and 2015, 23562 women aged 70 years or older were diagnosed with pathologically confirmed T1-2N1M0 (AJCC 6th staging edition) breast cancer and received surgery of the primary site. We further excluded patients according to the following criteria: history of prior malignancy (n = 8337); not treated with mastectomy (n = 7666); unknown or borderline estrogen receptor (ER) status (n = 240); unknown or borderline progesterone receptor (PR) status (n = 68); unknown histological grade (n = 199). A total of 7052 patients were included into this study. Due to the potential comorbidities of older patients, breast cancer mortality (BCM) was considered as the suitable primary outcome of this study. Death from other causes was deemed as competing risk event for BCM. The variable accounting for receipt of radiation therapy was "None/ unknown" or "Beam radiation". Moreover, radiation therapy must be administrated after mastectomy. The variable accounting for receipt of chemotherapy was "No/unknown" or "Yes". Institutional review board approval and informed consent was not required for this study.

2.2. Statistical analysis

Cumulative incidence function was performed to estimate the rates of BCM, with Gray's test examining the differences between groups. Leveraging Fine and Gray competing risks proportional hazards regression, univariate and multivariate analysis was conducted to test the correlations between variables and survival outcome. Hazard ratios (HR) in multivariate analysis were adjusted for age, year of diagnosis, tumor size, positive lymph nodes, ER status, PR status, histologic grade, receipt of chemotherapy and receipt of PMRT.

In order to balance the clinical baseline of PMRT group and no-PMRT group, propensity score matching was conducted using nearest neighbor method or exact matching. Matching was based on the following eight covariates: age, year of diagnosis, tumor size, number of positive lymph nodes, ER status, PR status, histologic grade and receipt of chemotherapy. Standardized mean difference was used to examine the balance of baseline covariates between groups. A standardized mean difference whose absolute value not greater than 0.2 was deemed acceptable balance [9]. Patient subgroups were defined by the combination of tumor size (≤ 2 or 2.0−5.0 cm) and positive lymph nodes (1, 2 or 3). In subgroup analysis, adjusted Fine and Gray regression model was performed for estimating the effect of PMRT in different subgroups, with the HR adjusted by age, year of diagnosis, ER status, PR status, histologic grade, receipt of chemotherapy. All data analyses were two sided using R version 3.5.0 (R Foundation for Statistical Computing,

Table 1
Characteristics of older patients from SEER 2004−2015 with T1-2N1 breast cancer before and after matching.

	Pre-matching			Post-matching		
	No-PMRT (%)	PMRT (%)	SMD	No-PMRT (%)	PMRT (%)	SMD
	n = 3805	n = 3247		n = 3247	n = 3247	
Age (mean, SD)	77.75 (5.09)	76.34 (4.71)	0.286	76.99 (4.94)	76.34 (4.71)	0.133
Year of diagnosis			0.158			0.078
2004−2009	1902 (50.0)	1368 (42.1)		1493 (46.0)	1368 (42.1)	
2010−2015	1903 (50.0)	1879 (57.9)		1754 (54.0)	1879 (57.9)	
Laterality			0.002			0.011
Left	1946 (51.1)	1657 (51.0)		1639 (50.5)	1657 (51.0)	
Right	1859 (48.9)	1590 (49.0)		1608 (49.5)	1590 (49.0)	
Tumor size			0.260			0.140
≤ 2 cm	1632 (42.9)	1811 (55.8)		1584 (48.8)	1811 (55.8)	
2−5 cm	2173 (57.1)	1436 (44.2)		1663 (51.2)	1436 (44.2)	
Positive nodes			0.090			0.027
1	2354 (61.9)	2148 (66.2)		2110 (65.0)	2148 (66.2)	
2	905 (23.8)	689 (21.2)		703 (21.7)	689 (21.2)	
3	546 (14.3)	410 (12.6)		434 (13.4)	410 (12.6)	
ER			0.160			0.045
Negative	662 (17.4)	382 (11.8)		430 (13.2)	382 (11.8)	
Positive	3143 (82.6)	2865 (88.2)		2817 (86.8)	2865 (88.2)	
PR			0.171			0.052
Negative	1185 (31.1)	765 (23.6)		838 (25.8)	765 (23.6)	
Positive	2620 (68.9)	2482 (76.4)		2409 (74.2)	2482 (76.4)	
Grade			0.131			0.058
Well differentiated	616 (16.2)	650 (20.0)		588 (18.1)	650 (20.0)	
Moderately differentiated	1848 (48.6)	1624 (50.0)		1618 (49.8)	1624 (50.0)	
Poorly differentiated	1341 (35.2)	973 (30.0)		1041 (32.1)	973 (30.0)	
Histology			0.052			0.046
Ductal	2902 (76.3)	2465 (75.9)		2478 (76.3)	2465 (75.9)	
Lobular	333 (8.8)	328 (10.1)		288 (8.9)	328 (10.1)	
Other	570 (14.9)	454 (14.0)		481 (14.8)	454 (14.0)	
Surgery			0.032			0.026
Simple mastectomy	1319 (34.7)	1176 (36.2)		1135 (35.0)	1176 (36.2)	
MRM	2486 (65.3)	2071 (63.8)		2112 (65.0)	2071 (63.8)	
Chemotherapy			0.160			0.075
No	2836 (74.5)	2185 (67.3)		2298 (70.8)	2185 (67.3)	
Yes	969 (25.5)	1062 (32.7)		949 (29.2)	1062 (32.7)	

Abbreviations: PMRT, postmastectomy radiation therapy; SMD, standardized mean difference; ER, estrogen receptor; PR, progesterone receptor; MRM, modified radical mastectomy.

Vienna, Austria), with a *P* value less than 0.05 being statistically significant.

3. Results

Of 7052 patients identified, the median age at diagnosis was 77 years (interquartile range, 73 to 81). A total of 3247 (46.0 %) patients received PMRT, and 2031 (28.8 %) patients received chemotherapy. Based on the aforementioned matching criteria, we performed 1:1 propensity score matching for patients receiving PMRT and those not receiving PMRT, resulting in 6494 patients retained for subsequent analysis, and the balance of baseline covariates was achieved between two groups. Characteristics of all patients before and after matching are presented in Table 1, stratified by receipt of PMRT.

Among the matched patients, at a median follow-up time of 5.0 years (interquartile range, 2.3 to 7.3), a total of 723 (11.1 %) patients died from breast cancer. In multivariate analysis, PMRT was significantly correlated with longer breast cancer-specific survival (HR 0.768; 95 % CI, 0.661—0.892; *P* < 0.001; Table 2). Other correlates of breast cancer-specific survival included age at diagnosis, year of diagnosis, tumor size, positive nodes, PR status, histologic grade and receipt of chemotherapy (Table 2). Compared with patients receiving PMRT, those not receiving PMRT presented higher BCM (5-year cumulative incidence 11.7 % vs 8.7 %; Fig. 1; HR 0.768; 95 % CI, 0.661-0.892; *P* < 0.001; Table 3).

A total of 2031 patients received chemotherapy in the primary cohort. After exact propensity score matching, 1329 patients were identified for subsequent analysis (Supplementary Table 1). There was no correlation between PMRT and BCM in patients who received chemotherapy (Fig. 1; *P* = 0.500; Table 3). A total of 5021 patients did not receive chemotherapy in the primary cohort. After nearest-neighbor matching, 4370 patients were identified for subsequent analysis (Supplementary Table 2). PMRT was associated with decreased BCM in patients who did not receive chemotherapy (5-year cumulative incidence 10.8 % vs 7.9 %; Fig. 1; HR 0.747; 95 % CI, 0.618—0.902; *P* = 0.002; Table 3).

In subgroup analysis, a forest plot was created to present the heterogeneous survival impact of PMRT in different subgroups. As shown in Fig. 2, PMRT was significantly correlated with longer breast cancer-specific survival for patients with three positive nodes and tumors 2—5 cm in size (5-year cumulative incidence of BCM 8.7 % vs 11.7 %; HR 0.637; 95 % CI, 0.436—0.931; *P* = 0.020), whereas this benefit was limited to patients with three positive nodes and tumors 2—5 cm in size who did not receive chemotherapy (5-year cumulative incidence of BCM 13.9 % vs 24.6 %; HR 0.487; 95 % CI, 0.266—0.892; *P* = 0.020). In patient subsets who received chemotherapy, no association between PMRT and BCM was found.

4. Discussion

The benefit of PMRT on contemporary older patients with T1-2N1 breast cancer remains unclear. The findings of this population-based study suggest a heterogenous impact of PMRT for older patients with T1-2N1 breast cancer. PMRT was associated with an absolute 10.7 % risk reduction of 5-year BCM for older patients with high-risk disease (three positive nodes and tumors 2—5 cm in size) who did not receive chemotherapy, while it was not significantly associated with BCM in patients who received chemotherapy.

The survival effect of PMRT for younger patients with T1-2N1 breast cancer is still controversial, waiting for the results of

SUPREMO trial (NCT00966888) [10,11]. However, none of randomized controlled trials was performed for PMRT in older patients with T1-2N1 breast cancer. In a retrospective study including 2145 older patients with T1-2N1 breast cancer from SEER 1992—1999, PMRT was not found to be significantly correlated with overall survival, while the heterogenous impact of PMRT was not further analyzed in patient subgroups. Moreover, the percent of patients receiving chemotherapy from SEER 1992—1999 was 21.0 % [6], and the percent of patients in our study was 28.8 %. Older patients were more likely to receive guideline-concordant de-intensified treatment. Barriers to guideline-concordant care in older cancer patients might include life expectancy, comorbidities, functional status, biologic aggressiveness of disease, benefits of palliation, availability of alternatives and access to treatments.

As the modern systemic therapy decreased the local recurrence risk of breast cancer patients, the benefit of PMRT might decrease and needs to be interpreted cautiously. Although the EBCTCG meta-analysis demonstrated PMRT benefit in patients with T1-2N1 breast cancer who received systemic therapy [12], these findings may not be suitable to those in modern era, when the rate of locoregional recurrence (LRR) for patients with T1-2N1 breast cancer is relatively low. Increasing evidence found no correlation between PMRT and improved survival outcome in all younger patients with T1-2N1 breast cancer who mostly received chemotherapy [13—16]. Consistently, the present study found no correlation between PMRT and older patients who received chemotherapy. The benefit of PMRT was limited to older patients with three positive nodes and tumors 2—5 cm in size who did not receive chemotherapy.

In the present study, the early separation of BCM curves in the first five years between no-PMRT group and PMRT groups was seen

Table 2
Multivariate analysis for BCM in older patients from SEER 2004—2015 with T1-2N1 breast cancer after matching.

	HR (95 % CI)	*P*
Age (continuous)	1.036 (1.019—1.053)	<0.001
Year of diagnosis		
2004—2009		
2010—2015	0.750 (0.639—0.879)	<0.001
Tumor size		
<2 cm		
2—5 cm	1.853 (1.583—2.169)	<0.001
Positive nodes		
1		
2	1.174 (0.976—1.412)	0.089
3	1.284 (1.166—1.414)	<0.001
ER		
Negative		
Positive	0.795 (0.627—1.007)	0.058
PR		
Negative		
Positive	0.587 (0.480—0.718)	<0.001
Grade		
Well differentiated		
Moderately differentiated	1.916 (1.428—2.57)	<0.001
Poorly differentiated	1.871 (1.607—2.179)	<0.001
Chemotherapy		
No		
Yes	0.741 (0.617—0.890)	0.001
Radiotherapy		
No		
Yes	0.768 (0.661—0.892)	<0.001

Abbreviations: BCM, breast cancer mortality; HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor.

Table 3
Effect of PMRT on BCM according to adjusted Fine-Gray model in different matched subgroups[a].

	PMRT	BCM	
		HR (95%CI)	P
All patients	No (n = 3247)		
	Yes (n = 3247)	0.768 (0.661–0.892)	<0.001
Patients receiving chemotherapy	No (n = 642)		
	Yes (n = 687)	0.884 (0.618–1.265)	0.500
Patients not receiving chemotherapy	No (n = 2185)		
	Yes (n = 2185)	0.747 (0.618–0.902)	0.002

Abbreviations: PMRT, postmastectomy radiation therapy; BCM, breast cancer mortality; HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor.
[a] The Fine-Gray model was adjusted by age, year of diagnosis, tumor size, number of positive lymph nodes, ER status, PR status, histologic grade and receipt of chemotherapy.
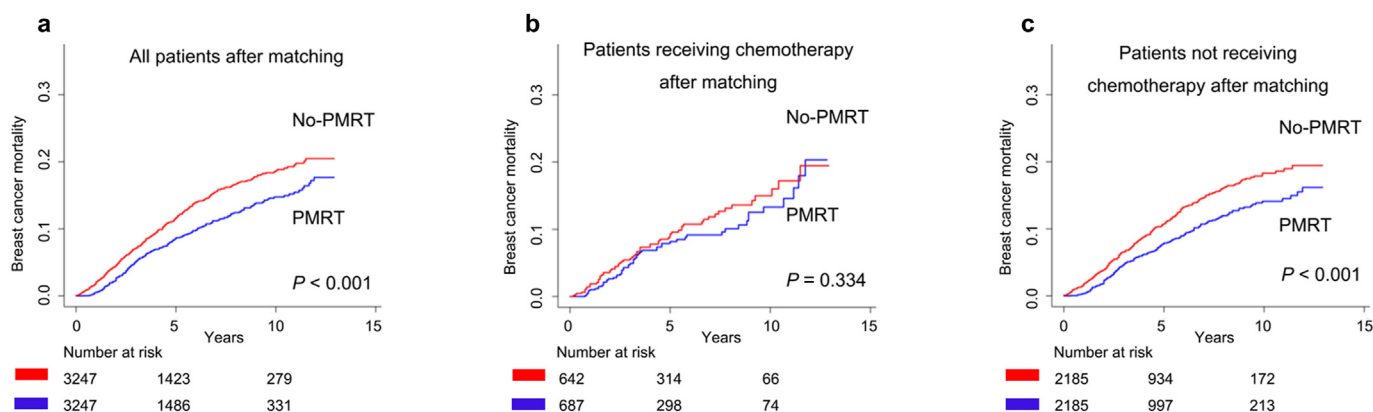

Fig. 1. Cumulative incidence of breast cancer mortality (BCM) in all patients (**a**), patients who received chemotherapy (**b**) or patients who did not receive chemotherapy (**c**), stratified by receipt of postmastectomy radiation therapy (PMRT).

in the plots of all patients or patients who did not receive chemotherapy. In contrast, this early separation was not found in the plot of patients who received chemotherapy, as well as the BCM curves of patients with one to three positive nodes in EBCTCG meta-analysis. Of note, the percent of patients receiving systemic therapy from EBCTCG meta-analysis was 86.2 %. Thus, absence of chemotherapy might account for the early separation of BCM curves, since patients with T1-2N1 breast cancer who received neither chemotherapy nor PMRT might experience disease recurrence earlier than those who received PMRT.

The benefit-harm assessment of PMRT is important for both older and younger patients with T1-2N1 breast cancer. Patients with higher tumor burden might benefit more from PMRT since the residual tumor foci after surgery can be eliminated by radiation therapy. In contrast, the potential risk of adverse effects from PMRT might exceed these benefits in patients with low tumor burden, even though the progress in radiation technology has reduced cardiac toxicities [7]. In the present study, for older patients with higher tumor burden (three positive nodes and tumors 2–5 cm in size) who did not receive chemotherapy, PMRT was associated with decreased BCM. Consistently, PMRT also presented heterogeneous survival effects on younger patients with T1-2N1 breast cancer. Leveraging patient data from the National Cancer Database (NCDB) and SEER between 1998 and 2008, Huo et al. found that PMRT was correlated with improved breast cancer-specific survival and overall survival in higher tumor burden subgroups [16]. Moreover, there is increasing evidence to demonstrate that tumor size [17,18]

and number of positive lymph nodes [19–21] are correlated with benefit from PMRT in younger patients with T1-2N1 breast cancer.

Despite some strengths including the large sample size, propensity score matching and subgroup analysis, the retrospective nature of this study might introduce selection bias. Although propensity score matching and multivariate analysis was performed to minimize the inherit bias, the SEER database had insufficient information for lymphovascular invasion, receipt of endocrine therapy and detail of comorbidities, which were likely associated with receipt of PMRT, receipt of chemotherapy and survival outcome in older patients. In addition, data on human epidermal growth factor receptor 2 (HER2) status before 2010 and HER2-targeted therapy were not available from the SEER database. Despite the potential comorbidities of older patients, we assessed the breast cancer-specific survival other than overall survival using competing risk model to avoid potential confounding effect of comorbidities. Based on the data from NCDB and SEER 18 registry, a retrospective study demonstrated a correlation between PMRT and improved overall survival in patients with T1-2N1 breast cancer and a low 21-gene recurrence score (Oncotype DX) (RS) [22]. However, the SEER database used for our study did not cover the RS of patients. Prospective trials will explore the predictive role of RS for PMRT benefit in patients with positive nodes.

5. Conclusion

In conclusion, PMRT was associated with decreased BCM in

Nodes & Tumor size	No-PMRT	PMRT		Hazard ratio, 95% CI	P
All patients					
1 node & ≤ 2 cm	86/1098	70/1098		0.797(0.579—1.099)	0.170
1 node & 2—5 cm	39/313	22/313		0.901(0.699—1.161)	0.420
2 nodes & ≤ 2 cm	25/173	15/173		0.671(0.393—1.147)	0.150
2 nodes & 2—5 cm	145/1012	105/1012		0.711(0.477—1.060)	0.094
3 nodes & ≤ 2 cm	65/390	41/390		0.785(0.400—1.538)	0.480
3 nodes & 2—5 cm	64/261	46/261		0.637(0.436—0.931)	0.020
Patients receiving chemotherapy					
1 node & ≤ 2 cm	8/163	11/191		1.443(0.564—3.693)	0.440
1 node & 2—5 cm	4/52	5/69		0.784(0.218—2.822)	0.710
2 nodes & ≤ 2 cm	0/19	0/18			
2 nodes & 2—5 cm	32/256	27/253		0.888(0.527—1.494)	0.650
3 nodes & ≤ 2 cm	12/91	7/86		0.595(0.233—1.518)	0.280
3 nodes & 2—5 cm	10/61	7/70		0.607(0.219—1.682)	0.340
Patients not receiving chemotherapy					
1 node & ≤ 2 cm	68/860	51/1044		0.721(0.501—1.038)	0.079
1 node & 2—5 cm	23/207	14/215		0.855(0.434—1.685)	0.650
2 nodes & ≤ 2 cm	13/109	10/88		1.045(0.444—2.458)	0.920
2 nodes & 2—5 cm	102/665	72/525		0.868(0.638—1.180)	0.370
3 nodes & ≤ 2 cm	36/227	24/197		0.793(0.472—1.334)	0.380
3 nodes & 2—5 cm	31/117	18/116		0.487(0.266—0.892)	0.020

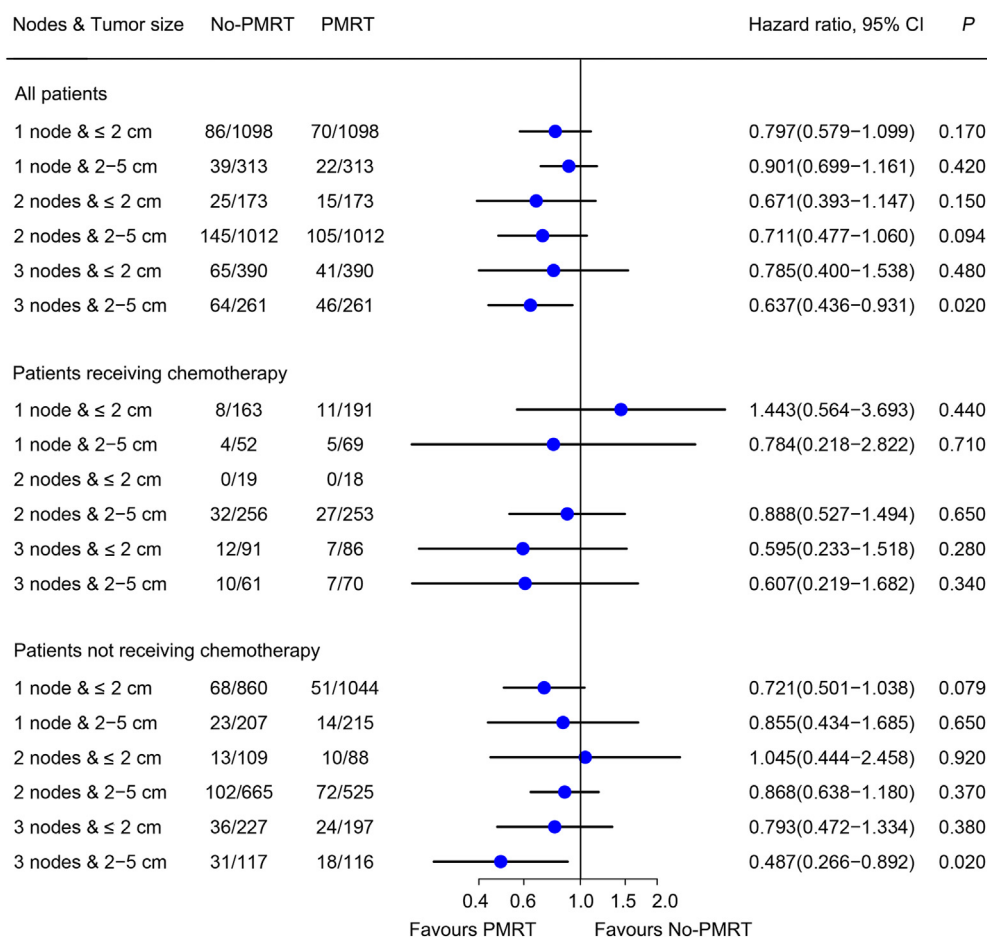0.4 0.6   1.0 1.5 2.0
Favours PMRT   Favours No-PMRT

Fig. 2. The effect of postmastectomy radiation therapy (PMRT) on patient subgroups defined by the combination of tumor size and positive lymph nodes, in terms of breast cancer-specific survival.

older patients with three positive nodes and tumors 2—5 cm in size who did not receive chemotherapy. No correlation between PMRT and BCM was found in patients who received chemotherapy.

Further study is needed to validate the effect of PMRT in older patients with T1-2N1 breast cancer who received chemotherapy.

Funding

Ethics statement

This study was conducted in full compliance with the publication guidelines provided by SEER. The data were obtained from SEER. Institutional review board approval and informed consent was not required for this study.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.08.002.

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