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ORIGINAL ARTICLE

Postmastectomy radiotherapy benefit in Chinese breast cancer patients with T1–T2 tumor and 1–3 positive axillary lymph nodes by molecular subtypes: an analysis of 1369 cases

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Abstract The aim of this study was to examine the association between molecular subtype (MST) and prognosis and research the postmastectomy radiotherapy (PMRT) effect in T1–T2 tumors with 1–3 positive axillary lymph nodes (ALNs). This retrospective study studied breast cancer patients with T1–T2 tumors and 1–3 positive ALNs according to MST: Luminal A, Luminal B, human epidermal growth factor receptor-2 (Her-2) positive, and Triple negative. The impact of adjuvant PMRT in T1–T2 tumors with 1–3 positive ALNs was also assessed. This study included 1369 patients: 33.0 % Luminal A, 42.9 % Luminal B, 11.9 % Her-2 positive, and 12.2 % Triple negative. On univariate and multivariate analyses, MST was associated with locoregional relapse (LRR). Kaplan–Meier analysis showed that PMRT significantly decreased LRR risk (p=0.017) and distant metastasis (DM) risk (p<0.0001). In subgroup analysis, PMRT showed significant benefits of improvement in LRR in patients with younger age, positive lymphovascular invasion (LVI), and ratio of positive lymph nodes (LNs) >25 %. Moreover, the nomogram could more accurately predict LRR (c-index 0.75) in T1–2N1 breast cancer patients. MST associated with patient outcomes in breast cancer patients with T1–T2 tumors and 1–3 positive ALN. It makes sense to offer PMRT for patients aged<40 years old, LVI, 2 and 3 positive lymph nodes, and ratio of positive LNs >25 %.

Keywords Breast cancer · Tumor size · Lymph nodes · Molecular subtypes · Postmastectomy radiotherapy · Prognosis

Introduction

Breast cancer is in fact a heterogeneous disease, and gene expression studies have identified distinct molecular subtypes (MSTs) with prognostic implications across multiple treatment settings [1]: These subtypes include Luminal A, Luminal B, human epidermal growth factor receptor-2 (Her-2) positive, and Triple negative which were characterized by distinct clinical and pathological features. Moreover, molecular subtyping has emerged as an important tool in determining prognosis and treatment strategies in breast cancer [2]. However, whether the use of this classification for breast cancer patients with T1–T2 tumor and 1–3 positive lymph nodes might be useful in clinical practice is a hypothesis that has not been tested.

Despite the advent of new tumor markers, axillary lymph node (ALN) status is still the most significant prognostic indicator for patients with breast cancer (BC) [3]. Current treatment guidelines for invasive breast cancer recommend postmastectomy radiotherapy (PMRT) to the chest wall and lymph node drainage pathways for patients with tumors that are locally advanced (>5 cm), with positive lymph nodes (LNs) or extensive ALN involvement (>3 positive LNs)[4–6].

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Moreover, the role of PMRT is not clearly defined in BC patients with tumor ≤5 cm and 1–3 positive ALNs. This controversy is related to difference in the reported locoregional relapse (LRR) risks in the absence of radiotherapy among these patients [7]. In order to identify patients with 1–3 positive ALNs who would benefit from PMRT, prior retrospective studies have identified various clinicopathologic features (such as age, lymphovascular invasion (LVI), and size of axillary nodal metastasis) associated with a higher risk of LRR [8–11]. The Early Breast Cancer Trialists' Collaborative Group [12] have addressed the uncertainty of PMRT in patients with 1–3 positive nodes and concluded that it reduced both recurrence and breast cancer mortality.

The aim of the present study was to evaluate the clinicopathologic features and prognostic significance of BC patients with T1–T2 tumors and 1–3 positive lymph nodes postoperative according to molecular subtype, assess the clinical value of PMRT among the groups, and identify proper patients who could benefit from PMRT.

Materials and methods

Patients

A retrospective consecutive analysis was conducted on 9326 patients diagnosed with and surgically treated for breast cancer at the Cancer Hospital of Tianjin Medical University, China, during January 1, 2003 and June 30, 2009. Of those, 1369 cases met all of the following criteria: (a) patients who had undergone mastectomy (with or without radiotherapy), (b) tumor size 0.1–5 cm, with 1–3 positive lymph nodes, (c) no previous neoadjuvant systemic therapy, (d) ER, PR, Her-2, Ki67, p53 information were all complete, and (e) completed follow-up study period. The major exclusion criteria were as follows: (a) metastatic breast cancer, (b) no sufficient data to allow for the estimation of a hazard ratio (HR) with 95 % confidence intervals (95 % CI), (c) patients who received breast conserving surgery, and (d) male patients.

Routine preoperative workup was done including history and physical examination, bilateral mammography, breast ultrasound, and magnetic resonance imaging of the breasts. Each patient underwent either mastectomy or breast conservation therapy by a dedicated breast surgeon. The extent of ALN dissection and use of sentinel lymph node biopsy were conducted at the discretion of the treating surgeon. The type and dose of chemotherapy were at the discretion of the treating medical oncologist who reviewed the patients on the basis of prognostic factors. The selection of patients to be offered PMRT, radiation dose, and field arrangement was at the discretion of the treating radiation oncologist. When hormonal therapy was used, at least 5 years of treatment were prescribed unless it was not tolerated or declined by the patient.

Immunohistochemical procedure and evaluation

The status of estrogen receptor (ER), progesterone receptor (PR), Her-2, Ki67, and p53 was determined by immunohistochemistry (IHC) and collected from pathology reports. IHC was performed using standard procedures. Formalin fixed, paraffin-embedded samples were obtained from the pathology registry. The paraffin blocks were cut at 4 μm thickness. Briefly, tissue sections were heated in 55–60 °C for 2 h, dewaxed and rehydrated with xylene and a series of grades of alcohol. Antigen retrieval was carried out in 5 mM citrate buffer (pH 6.0) for 2 min and 30 s in an autoclave. After inactivation of endogenous peroxidase with 3 % H_2O_2 for 5 min, the sections were blocked with 10 % normal goat serum for 10 min, and then incubated with either anti-Ki67 antibody or anti-p53 antibody at 4 °C overnight or with either anti-ER antibody or anti-PR antibody or anti-Her-2 antibody at 37 °C for 2 h. Normal mouse serum served as a negative control. After incubation with biotin-conjugated secondary antibody for 20 min at 37 °C and streptavidin–horseradish peroxidase (Zymed) for 20 min at 37 °C according to the manufacturer's protocol, it was continued with 3,3-diaminobenzidine tetra-hydrochloride (DAB) for visualization. In addition, all sections were counterstained with hematoxylin. All steps were preceded by rinsing with phosphate-buffered saline (PBS; pH 7.6).

The immunostaining was scored by two senior pathologists (Y.N and S.L), who were blinded to patients' clinicopathologic characteristics and outcomes. ER and PR were categorized as negative (<1 %) and positive (≥1 %) of tumor cell nuclear staining, in accordance with recent guidelines [13]. Her-2 was scored for the intensity and the completeness of cell membrane staining based on the 2013ASCO/CAP guidelines (−, no staining; +, weak partial membranous staining in more than 10 % tumor cells; ++, moderately complete membrane staining in more than or equal to 10 % tumor cells or strong complete membranous staining in less than or equal to 10 % of tumor cells; +++, strong complete membranous staining in more than 10 % of tumor cells). Her-2 (+++) was defined as positive [14]. FISH assay was performed in selected cases (i.e., those with ++ immunoreactivity). Ki67 status was expressed in terms of percentage of positive cells, with a threshold of 20 % of positive cells [15]. For p53, positive staining of fewer than 10 % of the tumor cells was defined as negative expression and staining of 10 % or more of the tumor cells as positive expression [16].

Based on 2013 St. Gallen Consensus, subtypes of breast cancer (Luminal A, Luminal B, Her-2 positive, and Triple negative) were defined by ER, PR, Ki67, and Her-2 status [15]: Luminal A (ER+ and PR ≥20 %, Her-2-, Ki67 <20 %); Luminal B which include Luminal B-Her-2-negative-like (ER+ and PR-/<20 %, Her-2-, Ki67 ≥20 %), and Luminal

Table 1 Clinicopathologic characteristics among four molecular subtypes

Characteristics	All	Luminal A		Luminal B		Her-2 positive		Triple negative		*p* value
	N	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	
All	1369	452	(100.0)	587	(100.0)	163	(100.0)	167	(100.0)	
Tumor size										
pT1a	11	3	(0.7)	8	(1.4)	0	(0.0)	0	(0.0)	
pT1b	55	27	(6.0)	17	(2.9)	5	(3.1)	6	(3.6)	
pT1c	575	237	(52.4)	253	(43.1)	39	(23.9)	46	(27.5)	
pT2	728	185	(40.9)	309	(52.6)	119	(73.0)	115	(68.9)	0.005*
Age										
<40	129	47	(10.4)	53	(9.0)	8	(4.9)	21	(12.6)	
≥40	1240	405	(89.6)	534	(91.0)	155	(95.1)	146	(87.4)	0.092
Menopausal status										
Pre	608	264	(58.4)	208	(35.4)	57	(35.0)	79	(47.3)	
Post	761	188	(41.6)	379	(64.6)	106	(65.0)	88	(52.7)	<0.001*
Histology										
Ductal	1200	389	(86.1)	528	(89.9)	146	(89.6)	137	(82.0)	
Lobular	68	31	(6.9)	23	(3.9)	5	(3.1)	9	(5.4)	
Ductal+Lobular	44	14	(3.1)	18	(3.1)	3	(1.8)	9	(5.4)	
Other	57	18	(4.0)	18	(3.1)	9	(5.5)	12	(7.2)	0.056
Tumor grade										
G1-G2	738	282	(62.4)	340	(57.9)	56	(34.4)	60	(35.9)	
G3	504	117	(25.9)	198	(33.7)	97	(59.5)	92	(55.1)	
Unknown	127	53	(11.7)	49	(8.3)	10	(6.1)	15	(9.0)	<0.001*
pTNM										
pT1N1M0	452	181	(40.0)	175	(29.8)	44	(27.0)	52	(31.1)	
pT2N1M0	917	271	(60.0)	412	(70.2)	119	(73.0)	115	(68.9)	0.001*
Positive LN (N)										
1	677	217	(48.0)	302	(51.4)	82	(50.3)	76	(45.5)	
2	369	118	(26.1)	153	(26.1)	47	(28.8)	51	(30.5)	
3	323	117	(25.9)	132	(22.5)	34	(20.9)	40	(24.0)	0.629
Nodes removed (N)										
10-15	230	71	(15.7)	119	(20.3)	23	(14.1)	17	(10.2)	
>15	1139	381	(84.3)	468	(79.7)	140	(85.9)	150	(89.8)	0.009*
Ratio of positive LNs (%)										
≤25	1351	443	(98.0)	581	(99.0)	160	(98.2)	167	(100.0)	
>25	18	9	(2.0)	6	(1.0)	3	(1.8)	0	(0.0)	0.208
Soft tissue invasion										
Yes	41	15	(3.3)	18	(3.1)	2	(1.2)	6	(3.6)	
No	1328	437	(96.7)	569	(96.9)	161	(98.8)	161	(96.4)	0.545
LVI										
Yes	624	164	(36.3)	269	(45.8)	96	(58.9)	95	(56.9)	
No	615	236	(52.2)	271	(46.2)	56	(34.4)	52	(31.1)	
Unknown	130	52	(11.5)	47	(8.0)	11	(6.7)	20	(12.0)	<0.001*
Nipple invasion										
Yes	114	29	(6.4)	57	(9.7)	22	(13.5)	6	(3.6)	
No	1255	423	(93.6)	530	(90.3)	141	(86.5)	161	(96.4)	0.003*
P53										
<10 %	825	298	(65.9)	363	(61.8)	72	(44.2)	92	(55.1)	
≥10 %	443	100	(22.1)	201	(34.2)	79	(48.5)	63	(37.7)	

Table 1 (continued)

Characteristics	All	Luminal A		Luminal B		Her-2 positive		Triple negative		*p* value
	N	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	
Unknown	101	54	(11.9)	23	(3.9)	12	(7.4)	12	(7.2)	<0.001*
Ki67										
<20 %	551	313	(69.2)	92	(15.7)	60	(36.8)	86	(51.5)	
≥20 %	818	139	(30.8)	495	(84.3)	103	(63.2)	81	(48.5)	<0.001*
Chemotherapy										
Yes										
Anthracycline	402	154	(34.1)	170	(29.0)	37	(22.7)	41	(24.6)	
Anthracycline+Taxane	429	127	(28.1)	189	(32.2)	57	(35.0)	56	(33.5)	
CMF	340	115	(25.4)	127	(21.6)	49	(30.1)	49	(29.3)	
Other	85	18	(4.0)	39	(6.6)	16	(9.8)	12	(7.2)	
No	113	38	(8.4)	62	(10.6)	4	(2.5)	9	(5.4)	<0.001*
Radiotherapy										
Yes	339	110	(24.3)	135	(23.0)	47	(28.8)	47	(28.1)	
No	1030	342	(75.7)	452	(77.0)	116	(71.2)	120	(71.9)	0.321
Endocrine therapy										
Yes										
TAM±LHRH	565	252	(55.8)	313	(53.3)	0	(0.0)	0	(0.0)	
T→AI	206	97	(21.5)	109	(18.6)	0	(0.0)	0	(0.0)	
AI	219	80	(17.7)	138	(23.5)	1	(0.6)	0	(0.0)	
No	379	23	(5.1)	27	(4.6)	162	(99.4)	167	(100)	<0.001*
Trastuzumad										
Yes	51	0	(0.0)	28	(4.8)	23	(14.1)	0	(0.0)	
No	1318	452	(100.0)	559	(95.2)	140	(85.9)	167	(100.0)	<0.001*

LNs lymph nodes, *LVI* lymphovascular invasion, *CMF* CTX, MTX and 5-Fu, *LHRH* luteinizing hormone releasing hormone, *AI* aromatase inhibitors
*Statistically significant

B-Her-2-positive-like (ER+ and Her-2+, any PR and Ki67); Her-2 positive (nonluminal: Her-2+, ER- and PR-); Triple negative (basal-like: Her-2-, ER- and PR -).

Follow-up study and study endpoints

Follow-up data were obtained via medical records, making telephone calls, and study questionnaire every 3 months for the first 2 years, every 6 months for the third through fifth years, and annually after 5 years. The primary endpoints were the incidence of locoregional relapse, distant metastasis (DM), and death according to the standardized definitions for efficacy end points (STEEP) system [17]. Secondary endpoints were disease-free survival (DFS), including recurrence-free survival (RFS) and metastasis-free survival (MFS) and overall survival (OS). LRR was defined as recurrent breast cancer in the ipsilateral chest wall, skin, axilla, internal mammary, or supraclavicular lymph nodes. DM included all sites of recurrence except LRRs and contralateral breast cancer. OS was determined as the time from surgery until the date of death (from any cause) or was censored at the date of last follow-up. The last follow-up date was defined as the last breast cancer evaluation by a physician or a mammogram.

Statistics

Univariate analysis (the chi-square test or Fisher's exact test) was used to evaluate the relationship between the clinicopathologic variables and the molecular subtypes. Cumulative incidence and survival plots were drawn using the Kaplan–Meier method. The log-rank test was used to assess the difference between strata. Multivariate Cox proportional hazard regression analysis was used to assess the independent prognostic significance of various clinical and histopathological characteristics of the tumor. Odds ratios (OR), 95 % confidence intervals (CI), and *p* values were all calculated. All *p* values were two-sided, and *p* values <0.05 were considered to be statistically significant. All analyses were performed using SPSS version 19.0.

Nomogram development

The Cox proportional hazards regression model was used to construct the nomogram. The model performance was quantified with respect to discrimination and calibration. Discrimination (i.e., whether the relative ranking of individual predictions is in the correct order) was quantified using the concordance index(c-index). The c-index ranges from 0 to 1, with 1 indicating perfect concordance, 0.5 indicating no better concordance than chance, and 0 indicating perfect discordance [18].

Results

We included in the analysis 1369 women with T1–T2 breast cancer and 1–3 positive lymph nodes treated at the Cancer Hospital of Tianjin Medical University, China during 2003–2009. The characteristics of the evaluable patients by MST are given in Table 1. The age of the patients ranged from 24 to 89 years with a mean age and median age of 51.6 years and 50.0 years, respectively. The number of lymph nodes removed ranged from 10 to 65 with a median number of 22. The Luminal A subtype consisted of 452 patients (33.0 %), the Luminal B subtype consisted of 587 patients (42.9 %), the Her-2 positive subtype consisted of 163 patients (11.9 %), and the Triple negative subtype consisted of 167 patients (12.2 %). The Her-2 positive subtype and Triple negative subtype were more likely to have a larger tumor size, higher histologic grade, higher ratio of positive LNs >25 %, nipple invasion, and presence of LVI. A larger number of patients (1256/1369, 91.7 %) had received adjuvant chemotherapy. Among these, 60.7 % had received an anthracycline regimen with or without a taxane, 24.8 % had received a cyclophosphamide, methotrexate, and fluorouracil (CMF) regimen. About 10 % of the patients with Luminal B tumors did not receive adjuvant chemotherapy, and about 95 % of patients with Triple negative tumors received chemotherapy. Adjuvant endocrine therapy was given to 990 (72.3 %) patients with positive ER or PR status. Above all, only 5.1 and 4.6 % of patients with Luminal A and Luminal B tumors, respectively, did not receive any endocrine treatment. Postmastectomy radiation was delivered according to physician discretion. There were no formal institutional guidelines for which patients with 1–3 positive lymph nodes should or should not receive PMRT. Our data showed that 339 (24.8 %) patients had undergone PMRT, while 1030 (75.2 %) patients had not received PMRT. Patients with three positive LNs ($p<0.001$) and LVI ($p<0.001$) were more likely to undergo PMRT (Table 2).

Table 2 Clinicopathologic characteristics among PMRT group and non-PMRT group

Characteristics	PMRT		Non-PMRT		*p* value
	N	(%)	*N*	(%)	
Tumor size					
pT1a	3	(0.9)	8	(0.8)	
pT1b	20	(5.9)	35	(3.4)	
pT1c	129	(38.1)	446	(43.3)	
pT2	187	(55.2)	541	(52.5)	0.111
Age					
<40	40	(11.8)	89	(8.6)	
≥40	299	(88.2)	941	(91.4)	0.084
Tumor grade					
G1-G2	183	(54.0)	555	(53.9)	
G3	123	(36.3)	381	(37.0)	
Unknown	33	(9.7)	94	(9.1)	0.934
pTNM					
pT1N1M0	103	(30.4)	349	(33.9)	
pT2N1M0	236	(69.6)	681	(66.1)	0.235
Positive LN (*N*)					
1	116	(34.2)	561	(54.5)	
2	86	(25.4)	283	(27.5)	
3	137	(40.4)	186	(18.1)	<0.001*
Nodes removed (*N*)					
10–15	50	(14.7)	180	(17.5)	
>15	289	(85.3)	850	(82.5)	0.244
Ratio of positive LNs (%)					
≤25	332	(97.9)	1019	(98.9)	
>25	7	(2.1)	11	(1.1)	0.162
LVI					
Yes	230	(67.8)	394	(38.3)	
No	80	(23.6)	535	(51.9)	
Unknown	29	(8.6)	101	(9.8)	<0.001*
P53					
<10 %	181	(53.4)	644	(62.5)	
≥10 %	105	(31.0)	338	(32.8)	
Unknown	53	(15.6)	48	(4.7)	<0.001*
Ki67					
<20 %	159	(46.9)	392	(38.1)	
≥20 %	180	(53.1)	638	(61.9)	0.004

PMRT postmastectomy radiotherapy, *LNs* lymph nodes, *LVI* lymphovascular invasion

As shown in Table 3, the effect of PMRT on LRR, DM, and OS in different subgroups were examined. For patients aged <40 years, PMRT reduced LRR from 30.3 to 12.5 %, ($p=0.030$). For LVI breast cancer patients, PMRT can reduce LRR from 20.4 to 13.9 %, ($p=0.028$). For BC patients with 2 and 3 positive lymph nodes, PMRT can reduce LRR from 17.0 to 4.7 % ($p=0.004$) and 36.0 to

Table 3 Clinicopathologic features on prognosis in subgroup analysis according to postmastectomy radiotherapy (PMRT)

Characteristic	PMRT	LRR		DM		OS	
		N (%)	*p*	*N* (%)	*p*	*N* (%)	*p*
MST							
Luminal A	Yes	12(10.9)	0.822	15 (13.6)	0.138	90 (81.8)	0. 118
	No	40 (11.7)		30 (8.8)		300(87.7)	
Luminal B	Yes	19 (14.1)	0.734	18 (13.3)	0.058	112 (83.0)	0.091
	No	69(15.3)		36 (7.9)		400 (88.5)	
Her-2 positive	Yes	16 (34.0)	0.039*	10 (21.3)	0.237	35 (74.5)	0.851
	No	22 (19.0)		16 (13.8)		88 (75.9)	
Triple negative	Yes	16(34.0)	0.041*	10 (21.3)	0.664	34 (72.3)	0.482
	No	23(19.2)		22 (18.3)		93 (77.5)	
Age (years)							
<40	Yes	5 (12.5)	0.030*	4 (10.0)	0.385	35 (87.5)	0.879
	No	27 (30.3)		14 (15.7)		77 (86.5)	
≥40	Yes	36 (12.0	0.070	49 (16.4)	0.090	235 (78.6)	0.077
	No	154 (16.4)		118 (12.5)		782 (83.1)	
LVI							
No	Yes	5 (6.3)	0.064	11 (13.8)	0.092	65 (81.3)	0.407
	No	73 (13.6)		43 (8.0)		454 (84.9)	
Yes	Yes	36 (13.9)	0.028*	55 (21.2)	0.312	199 (76.8)	0.104
	No	101 (20.4)		90 (18.2)		405 (81.8)	
Positive LNs (N)							
1	Yes	8(6.9)	0.235	14 (12.1)	0.058	102 (87.9)	0.634
	No	59 (10.5)		42 (7.5)		484 (86.3)	
2	Yes	4 (4.7)	0.004*	13 (15.1)	0.450	73 (84.9)	0.566
	No	48 (17.0)		34 (12.0)		247 (87.3)	
3	Yes	34 (24.8)	0.032*	37 (27.0)	0.080	89(65.0)	0.466
	No	67 (36.0)		35 (18.8)		128 (68.8)	
Ratio of positive LNs (%)							
≤25	Yes	42 (12.7)	0.073	47 (14.2)	0.087	264 (79.5)	0.105
	No	171 (16.8)		109 (10.7)		850 (83.4)	
>25	Yes	1 (14.3)	0.040*	2(28.6)	0.605	5 (71.4)	0.605
	No	7 (63.6)		2(18.2)		9 (81.8)	

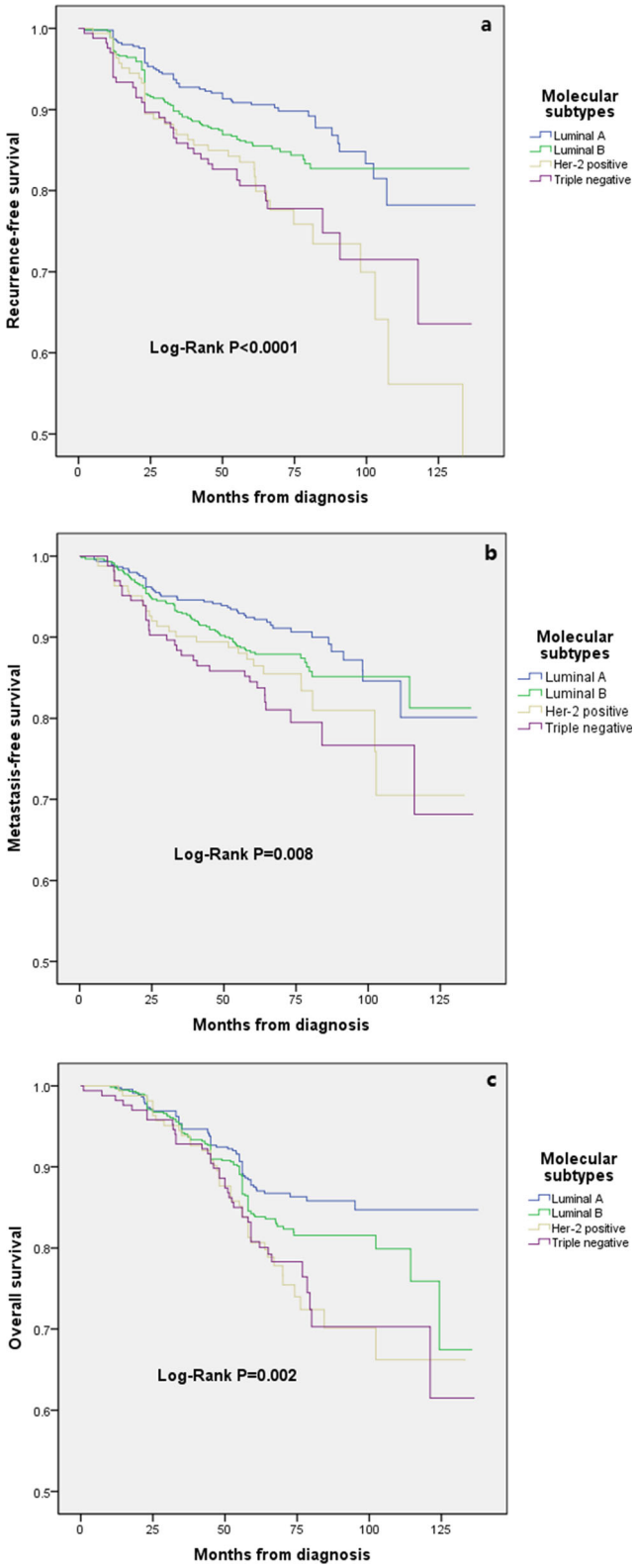
MST molecular subtype, *PMRT* postmastectomy radiotherapy, *LRR* locoregional relapse, *DM* distant metastasis, *OS* overall survival, *LVI* Lymphovascular invasion, *LNs* lymph nodes

*Statistically significant

24.8 % (p=0.032), respectively. PMRT reduced LRR from 63.6 to 14.3 % (p=0.040) significantly in patients with >25 % ratio of positive LNs. However, in the group that received PMRT, the Her-2 positive and Triple negative groups continued to do significantly worse, with an LRR of 34.0 % in the PMRT group compared with 19.0 % in the no-PMRT group (p=0.039) and 34.0 % in the PMRT group compared with 19.2 % in the no-PMRT group (p=0.041), respectively.

In our study, the median follow-up time for all the 1369 patients was 74 months (range 1–138 months). The 5-year LRR and DM rates were 12.9 and 10.5 %, respectively. The 5-year OS rates were 83.9 %. Locoregional relapse happened in 215 (15.7 %) of 1369 T1–2N1 patients. The sites of LRR were the chest wall in 138 patients, axilla in 40 patients, supraclavicular area in 19 patients, axilla and supraclavicular area in 8 patients, and internal mammary area in 10 patients. Distant metastasis occurred in 177 (12.9 %) of all patients, including lung, liver, bone, brain, pleura, uterus, and lymph node metastasis. In all 1369 patients, there were 246 (18.0 %) patient deaths.

Figure 1 shows the incidence of recurrence-free survival and metastasis-free survival and overall survival curves according to MST. Kaplan–Meier analysis



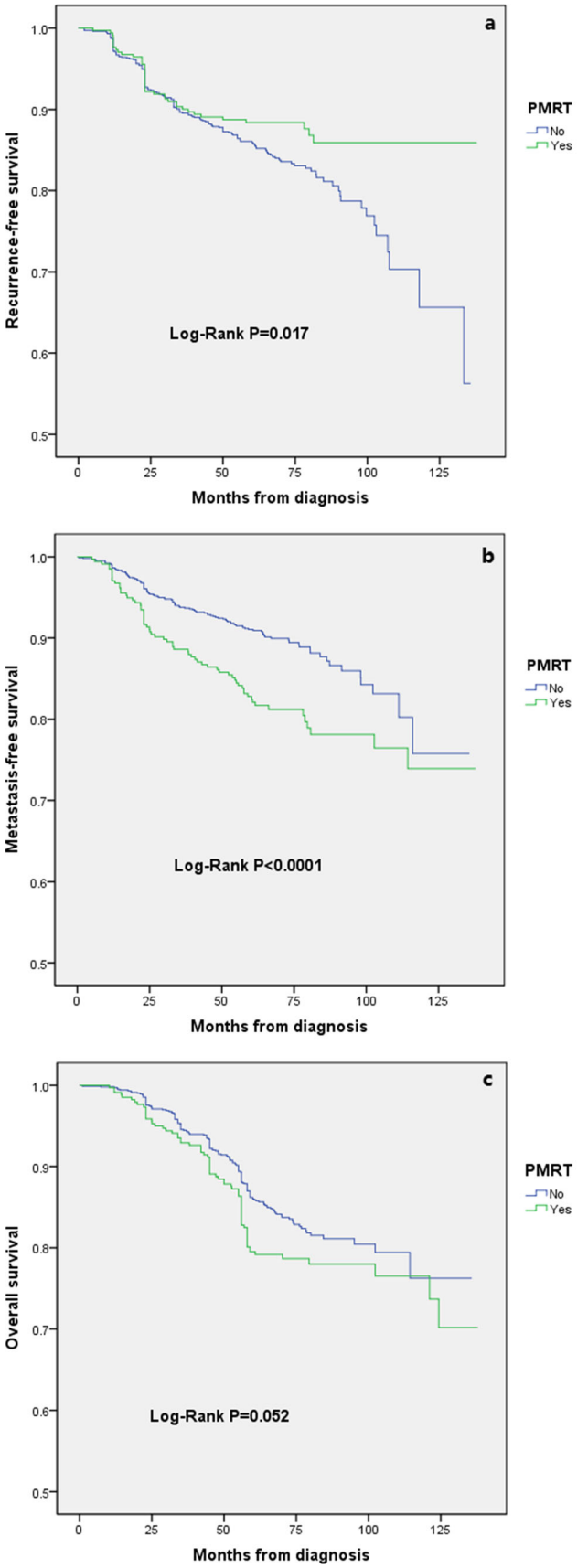


Fig. 1 Kaplan–Meier curves for breast cancer outcome by molecular subtypes. **a** Recurrence-free survival, **b** metastasis-free survival, and **c** overall survival. Log-rank *p* values are shown above

◀ **Fig. 2** Kaplan–Meier curves for impact of postmastectomy radiotherapy on OS, RFS, and MFS. **a** Recurrence-free survival, **b** metastasis-free survival, and **c** overall survival. Log-rank *p* values are shown above

revealed statistical significant difference in the incidence of OS, RFS, and MFS according to the four MSTs. Reduced OS, RFS, and MFS are observed in the Her-2 positive and Triple negative subtypes. There was a higher LRR risk in the Her-2 positive subtype and Triple negative subtype (23.3 and 22.2 %, respectively) compared with the Luminal A and Luminal B subtypes (11.5 and 15.0 %, respectively). Her-2 positive subtype and Triple negative subtype had higher rate of DM (16.0 and 19.2 %, respectively) compared with the Luminal A and Luminal B subtypes (10.6 and 12.6 %, respectively).

PMRT has a significantly improved LRR ($p=0.017$) and DM ($p<0.0001$), while no statistical difference was found on OS ($p=0.052$) among the subtypes (Fig. 2).

We performed a multivariate analysis including significant clinical and biological features at univariate analysis. As shown in Table 4, our data showed that LVI was independent prognostic risk factor of OS and DM. Meanwhile, MST, age, LVI, and PMRT were considered to be independent indicators for LRR.

To predict the survival of patients with T1–T2 breast cancer and 1–3 positive lymph nodes, prognostic nomogram was depicted by Cox regression model analysis using all the significant independent indicators for LRR (Fig. 3). The nomogram can predict the probability of recurrence patients within 3 or 5 years. The c-index of the nomogram for LRR prediction was 0.75.

Discussion

Breast cancer is a complex, heterogeneous disease at the molecular level. Gene expression studies have identified molecularly distinct subtypes with distinct clinical characteristics in different patients even in different ethnic populations [10]. These subtypes include Luminal A, Luminal B, Her-2 positive, and Triple negative, which were initially identified using cDNA microarray analysis. Her-2 positive and Triple negative subtypes are hormone receptor negative and have poor prognosis [19]. Subsequently, an immunohistochemical profile, based on the degree of expression of ER, PR, Her-2, and Ki-67, was used to identify subgroups of breast cancer patients with different outcomes and who will respond to different systemic adjuvant treatments, thus allowing clinicians to apply this concept to patient-care and decision-making[20]. Sanchez-Munoz et al. [21] showed that MST of BC in combination with clinicopathologic features may provide more information for predicting outcome and guiding treatment. Although most of the previous researches [19–21] in many countries concentrated on this issue in the past years, limited information were focused on the relationship between MST and prognosis in patients with 1–3 positive ALNs and tumors ≤5 cm. In this study, we evaluated clinicopathologic features and detected the association between MST and prognosis in patients with T1–T2 tumors and 1–3 positive lymph nodes.

American Society of Clinical Oncology and other guidelines recommend that patients with T3–4 or N2 should receive adjuvant chemotherapy and PMRT definitely if no contraindication [22]. The benefit of PMRT on OS has been demonstrated in women of all ages with positive lymph nodes.

Table 4 Univariate and multivariate analysis of factors associated with OS, LRR and DM

Factors	OS				LRR				DM			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR	*p*	HR(95 % CI)	*p*	HR	*p*	HR(95 % CI)	*p*	HR	*p*	HR(95 % CI)	*p*
MST												
(Luminal B vs. Luminal A)	1.35	0.065	–		1.40	0.056	0.91 (0.46, 1.78)	0.774	1.34	0.118	–	
(Her-2 positive vs. Luminal A)	1.92	0.001*	–		2.24	0.000*	2.28 (1.41, 5.63)	0.003*	1.74	0.039*	–	
(Triple negative vs. Luminal A)	1.84	0.003*	–		2.12	0.000*	1.68 (0.79, 3.59)	0.179	2.09	0.001*	–	
Age (<40 vs. ≥40)	0.71	0.165	–		1.67	0.008*	3.77 (2.16, 6.56)	0.000*	1.07	0.793	–	
Positive LNs												
(2 vs.1)	0.97	0.859	–		1.46	0.044*			1.54	0.029*	–	
(3 vs.1)	2.55	0.000*	–		3.82	0.000*			3.00	0.000*	–	
Ratio of positive LNs (>25 vs. ≤25 %)	1.20	0.721	–		2.72	0.009*			1.72	0.286	–	
LVI (Yes vs. No)	1.34	0.028*	4.71(2.30,9.66)	0.000*	1.57	0.002*	5.96 (2.90, 12.26)	0.000*	4.50	0.000*	9.41 (5.18, 17.08)	0.000*
PMRT (Yes vs. No)	1.31	0.052	–		0.66	0.017*	0.38 (0.20, 0.71)	0.002*	1.78	0.000*	–	

MST molecular subtype, *LRR* locoregional relapse, *DM* distant metastasis, *OS* overall survival, *LNs* lymph nodes, *LVI* Lymphovascular invasion, *HR* hazard ratio, *CI* confidence interval

*Statistically significant

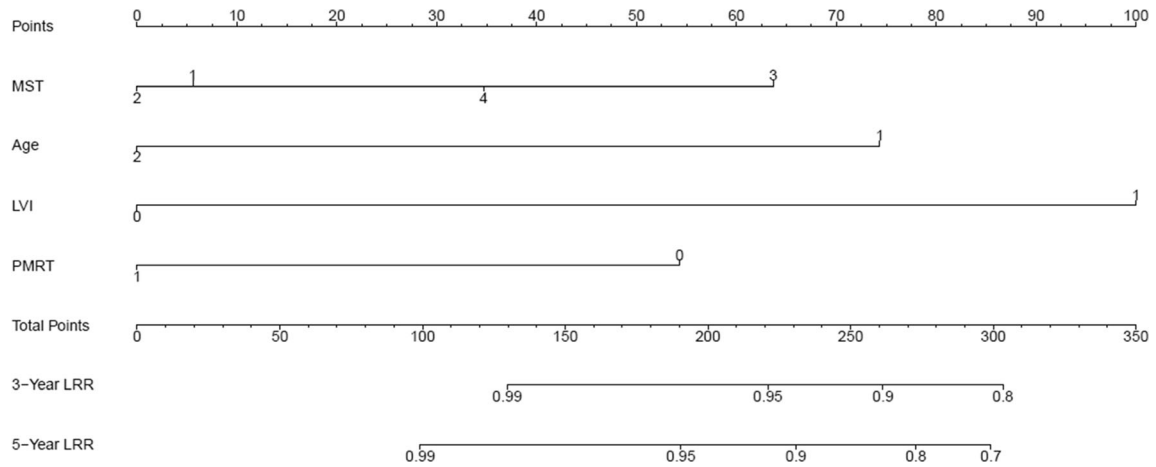


Fig. 3 Postoperative nomogram with significant clinicopathologic characteristics predicted the probability of locoregional relapse (LRR). To use the nomogram, the value attributed to an individual patient is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the total points axis, and a line is then drawn downward to the survival axis to determine the 3-year and 5-year LRR likelihood

However, it remains unclear whether this benefit is simply due to benefit in the ≥4 positive node group, in which there is already no controversy for the effectiveness of radiotherapy. For patients with T1–T2 tumors and 1–3 positive LNs, there are controversies about whether adjuvant PMRT is needed. In addition, PMRT is associated with some risk of morbidity, causing some clinicians to use radiation sparingly after a mastectomy.

This study revealed that molecular subtypes have prognostic significance along with age, PMRT, and LVI. Reduced OS, RFS, and MFS are observed in the Her-2 positive and Triple negative subtypes. Her-2 positive associated with a statistically significant increased risk of LRR compared with Luminal A subtype. These results are in line with a study from New York, USA [2], in which MST was associated with OS and RFS, the Triple negative and Her-2 positive subtypes had significantly lower OS and RFS compared with the luminal subtypes. There was a trend toward an increase in LRR in the Her-2 positive and Triple negative subtypes (4.9 and 6.0 %, respectively) compared with the Luminal A and Luminal B subtypes (2.4 and 2.0 %, respectively). Caudle et al. [23] have shown that distinct molecular subtypes can predict LRR-free survival rates; patients with HR-positive tumors have a low risk of locoregional failure regardless of tumor response to neoadjuvant chemotherapy. However, among the group that received PMRT, the Her-2 positive subtype and Triple negative subtype continued to do significantly worse, with higher risk rates of LRR in the PMRT group compared with the no-PMRT group. This may be due to that we did not take into account the treatment with adjuvant trastuzumab, which has been shown to decrease rates of LRR by 50 % [24]. In our study, there were only 51 patients who received adjuvant trastuzumab therapy. The reason for lack of adjuvant trastuzumab is that during the period of study enrollment (January 2003 to December 2009), the concept of adjuvant trastuzumab had not been built up completely. With the progress of adjuvant therapy, including anthracyclines and taxanes regimen, aromatase inhibitors, the locoregional control was better than in the past. In our study, the 5-year LRR rates were only 4.0 and 2.6 % in patients with and without PMRT (p=0.25), but PMRT decreased 5-year LRR in patients who received none of the above treatments (5.9 vs. 1.4 %, p=0.028). About 95 % of patients with Triple negative tumors received chemotherapy, so the benefit of PMRT in patients may decrease due to the progress of adjuvant therapy. Moo et al. [2] looked at 884 patients between 1995 and 2006 and found that among patients who did receive PMRT, the Her-2 subtype had the poorest 5-year LRR outcomes (17 vs. 7 % in the no-PMRT group). The recent published study by Yang et al. who analyzed 544 T1-2 N1 breast cancer patients with or without PMRT has shown significant reduction of LR and improvement of OS in ER-negative patients [25]. Kyndi et al. had analyzed 1000 of the 3083 patients in the DBCG 82b and c stratified by ER, PgR and Her-2/neu status. In contrast to Yang's result, PMRT did not have a survival benefit in ER-negative cohort, and the Her-2 group did not show a significant improvement in LRR with PMRT (21 vs. 33 %, p=0.2) [26].

Most studies have concluded that locoregional treatment with PMRT improved survival by reducing locoregional failure rate [4, 9, 27]. In this study, we found a statistically significant improvement in the influence of PMRT on RFS and MFS in T1–T2 tumors with 1–3 positive ALNs patients, while it did not show significance in affecting OS. These results are in accordance with the analysis by Cosar et al. [28], in which they conducted a retrospective study of 90 patients with the same endpoints as our study and demonstrated that PMRT in T1–2 and 1–3 axillary lymph node positive patients made a statistically significant improvement in RFS (p=0.034), but

no improvement in OS (p=0.087). Tendulkar et al. [9] reported the results from a retrospective review of 369 breast cancer patients with 1–3 positive lymph nodes, of whom 98 patients who underwent PMRT had a 5-year LRR of 0 % (p=0.004) compared with 8.9 % of 271 patients with no PMRT.

Several factors, such as young age, larger tumor, advanced nodal status, presence of extracapsular extension, positive LVI, high grade, involvement of the skin, nipple or pectoral fascia, and close or positive resection margins had been reported to associate with higher risks of recurrence [29]. In our analysis, age less than 40 years was one of the risk factors of LRR, and for patients aged <40 years, PMRT can reduce LRR rate. Yang et al. [25] showed that for patients with negative ER and vascular invasion, adjuvant PMRT could significantly reduce the LRR rate (40 vs. 12.5 %, p=0.038), and the 5-year OS rate was also elevated from 43.7 to 87.1 % (p<0.001). As shown in our analysis, patients with known risks such as >25 % ratio of positive LNs and LVI present, PMRT certainly reduced LRR rates, which was compatible with previous reports. In the multivariate analysis, Her-2 positive subtype, younger patients, ratio of positive LNs, and LVI were independent prognostic factors of recurrence.

Some nomograms have been developed in various cancers, and nomograms have shown to be more accurate than the conventional staging systems for predicting prognosis in cancers [30]. The present study attempted to establish a predictive nomogram to predict the probability of patients who will recur within 3 and 5 years based on clinicopathological factors. The nomogram performed well in predicting LRR, and the prediction was supported by c-index (0.75). The results supported that the nomograms could better predict prognosis in patients with T1–T2 and 1–3 axillary positive LNs.

In conclusion, our study found that the prognosis of breast cancer patients with 1–3 positive ALNs and tumors less than 5 cm depends on variable features. We show that risk of recurrence and metastasis significantly correlates with tumor subtypes identified by immunohistochemistry. Both Her-2 positive and Triple negative subtypes were significantly associated with patient outcomes in T1–T2 tumors with 1–3 positive ALNs. Thus, biologically more aggressive traits such as Her-2 positive status should be considered when counseling patients about treatment interventions and when developing clinical trials to prospectively evaluate treatment options. It should however be emphasized that the MST identified in the current study still include heterogeneous groups of tumors and that the identification of further MST amenable to targeted treatments represents a research priority. On the other hand, although the benefit of administering PMRT to all patients with 1–3 positive lymph nodes seems to be an overtreatment in modern series, it should still be considered in high-risk patients such as with LVI and young age, which will bring on better locoregional control and longer survival.

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Compliance with ethical standards

Conflicts of interest None

Ethical approval This study was approved by the Tianjin Medical University Cancer Institute and Hospital, China and has been performed in accordance with the ethical standards laid down in the 1964 Helsinki declaration and its later amendments.

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Synopsis

Our study examined the association between MST and prognosis and researched the PMRT effect in T1–T2 tumors with 1–3 positive ALNs. Data showed MST associated with patient outcomes in breast cancer patients with T1–T2 tumors and 1–3 positive ALNs. PMRT significantly decreased LRR and DM risk. Our results suggest that PMRT should be offered to patients aged <40 years old, LVI, 2 and 3 positive lymph nodes, and ratio of positive LNs >25 %. The nomogram could more accurately predict LRR (c-index 0.75) in T1–2N1 breast cancer patients.