

Compliance with multidisciplinary team recommendations and disease outcomes in early breast cancer patients: An analysis of 4501 consecutive patients

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ABSTRACT

Background: Multidisciplinary team (MDT) discussions are widely held to facilitate the diagnosis and treatment of breast cancer, but patient compliance with the MDT recommendations and the impact of compliance on disease outcome are uncertain.

Methods: We conducted a retrospective review of data from a prospective database of breast cancer patients treated at Shanghai Ruijin Hospital between April 2013 and August 2018. MDT discussions were held for all patients before they started adjuvant therapy. The patients were classified into compliant and non-compliant groups according to whether they received the MDT-recommended regimens. We also analyzed which clinicopathological factors were associated with compliance and prognosis.

Results: Of 4501 breast cancer patients, 3681 (81.8%) and 820 (18.2%) were included in the compliant and non-compliant groups, respectively. Age >70 years ($P < 0.001$), invasive ductal carcinoma ($P < 0.001$), and histological grade III ($P = 0.011$) were independently associated with higher risk of non-compliance, whereas Ki-67 labeling index $\geq 14\%$ and history of benign breast disease were independently associated with compliance. Disease-free survival (hazard ratio [HR] 1.813, 95% confidence interval [CI] 1.367–2.405, $P < 0.001$) and overall survival (HR 2.478, 95% CI 1.431–4.291, $P < 0.001$) were worse in the non-compliant group.

Conclusions: Several clinicopathological factors were associated with non-compliance with MDT recommendations for early breast cancer patients. Non-compliance was associated with worse disease outcome.

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1. Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among women [1]. A multidisciplinary team (MDT) strategy is widely used to facilitate the diagnosis and treatment of breast cancer. In the United Kingdom, MDTs are crucial for newly diagnosed breast cancer [2,3] because they

help cancer patients receive the most suitable treatment by providing an opportunity to combine clinical evidence with patient and disease information before any recommendations are made [4]. In an international survey of 152 responding oncologists in 39 countries where MDTs are a mandatory part of breast cancer care, over 90% of the respondents reported that MDTs resulted in more evidence-based treatment decisions that could improve clinical decision making, and provided more coordinated patient care to improve the overall quality of treatment. However, only 9% of the respondents reported that MDT improved disease survival [5]. Other reported benefits of MDT include providing consistent, continuous, and coordinated work for doctors, enhancing supportive care for patients, and improving access to clinical trials [5–7]. However, it remains controversial whether MDT itself and compliance with MDT recommendations improve the prognosis for

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early breast cancer patients [8–11]. Several factors may influence compliance with MDT recommendations among breast cancer patients. Ring et al. reported that compliance with MDT recommendations was lower among older breast cancer patients, especially compliance with adjuvant chemotherapy [12].

The present study was performed to identify which clinicopathological characteristics may influence compliance with MDT recommendations, and to evaluate whether MDT compliance affects the prognosis of early breast cancer.

2. Materials and methods

2.1. Study population

We performed a retrospective review of a prospective database of breast cancer patients treated at Shanghai Ruijin Hospital between April 2013 and August 2018. All patients were discussed at MDT meetings to review adjuvant therapy decision making. The clinical information, surgical procedure, pathological characteristics, MDT recommendations, and actual treatment information for each patient were prospectively collected and recorded in the Shanghai Jiao Tong University Breast Cancer Database (SJTU-BCDB) and an internet-based MDT platform (MDT4BC). All patients were followed every 3 months for the first 2 years after surgery, then every 6 months in years 3–5, and annually thereafter. Patients were classified into compliant or non-compliant groups according to whether they received the MDT-recommended regimen.

All procedures involving human participants were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Review Committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine. Informed consent was exempted due to the retrospective design of this study.

2.2. MDT recommendation procedure and definition of compliance

MDT discussions are routinely held to determine the recommended adjuvant therapy for individual patients with early breast cancer who undergo surgery at Ruijin Hospital. The patient is discussed at an MDT meeting as soon as possible, after completion of the complete pathological report after surgery and before the initiation of further treatment after surgery. The MDT members included breast surgeons, medical oncologists, pathologists, radiation oncologists, and nurses specializing in breast cancer. After the MDT meeting, a complete recommendation, including adjuvant chemotherapy (drugs and cycles), endocrine therapy (selective estrogen receptor modulator or aromatase inhibitor, with or without ovarian function suppression), radiotherapy (yes or no), and targeted therapy with trastuzumab (yes or no) is offered to the patient. The MDT recommendations and the treatments actually received by the patient were prospectively recorded in the database.

Compliance with chemotherapy was defined as the patient receiving the chemotherapy drugs and cycles recommended by the MDT, whereas non-compliance with chemotherapy was defined as the patient refusing to receive the suggested chemotherapy, receiving a different regimen, or receiving an insufficient number of cycles. For example, if the recommended treatment was four cycles of docetaxel and cyclophosphamide, the conditions for non-compliance might include the patient actually receiving doxorubicin and cyclophosphamide, the patient only undergoing three cycles of docetaxel and cyclophosphamide, or the patient rejecting chemotherapy. A similar approach was used to assess compliance with endocrine therapy. For radiotherapy and targeted therapy,

non-compliance was defined as the recommended treatment not being carried out. In other words, the patient was considered non-compliant with the MDT recommendations if any of the patient's treatments did not follow the recommendations.

The actual reasons for non-compliance were collected retrospectively. The recorded reasons were as follows. 'Comorbidity' was recorded if the patient had a comorbidity before starting adjuvant treatment that was considered to affect the outcome of treatment, or a change of the comorbidity condition was likely. 'Adverse event' was recorded if the patient experienced an adverse event that led to a change or termination of the MDT recommended treatment. 'Patient's will' was recorded if the patient decided to stop the recommended treatment at their own will, rather than for objective reasons. 'Flexible recommendation' was recorded if the MDT decision included a flexible recommendation of whether a specific treatment is needed or not. In this case, if the patient chose not to receive the treatment, the patient was recorded as non-compliant due to the flexible recommendation. 'Economic reason' was recorded if the patient was non-compliant because they could not afford the recommended treatment. 'Withdrawal from clinical trials' was recorded if the MDT recommended the patient to participate in a clinical trial, but the patient withdrew from the trial before or during treatment and received another treatment. 'Treated at a local hospital' was recorded if the patient returned to a local hospital for treatment, at which the doctor did not follow the MDT recommendation. 'Menstrual status change' was recorded if the patient's menstrual status at a specific treatment stage differed from that at the time of MDT discussion and resulted in non-compliance with the MDT recommendation.

2.3. Statistical analyses

Disease-free survival (DFS) was defined as the time from the date of breast cancer surgery to the date of any of the following events: local or regional breast cancer recurrence; distant metastasis; a new diagnosis of breast cancer in the contralateral breast; or a second primary malignancy. Overall survival (OS) was defined as the time from the date of breast cancer surgery to the date of death from any cause.

Statistical analyses were performed using SPSS version 25 (SPSS Inc., Chicago, IL, USA) for windows and GraphPad Prism 8 (GraphPad Prism, Inc., San Diego, CA, USA). Categorical variables are reported as the number and percentage. The demographic and pathological characteristics were evaluated using Pearson's χ^2 test. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by multivariable logistic regression analysis. Survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test. Multivariable Cox regression was used to determine associations between clinicopathological factors and survival outcomes in terms of hazard ratios (HR) with 95% CIs. For all analyses, $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patients and clinicopathological characteristics

Complete MDT decisions and follow-up information were available for 4501 patients (Fig. 1). Overall, 342 patients (7.6%) had a family history of breast cancer, and 1017 patients (22.6%) had a history of benign breast disease, including fibroadenoma and intraductal papilloma. Two hundred and one patients (4.5%) were previously diagnosed with a malignant tumor other than breast cancer. The patients' baseline characteristics are shown in Table 1.

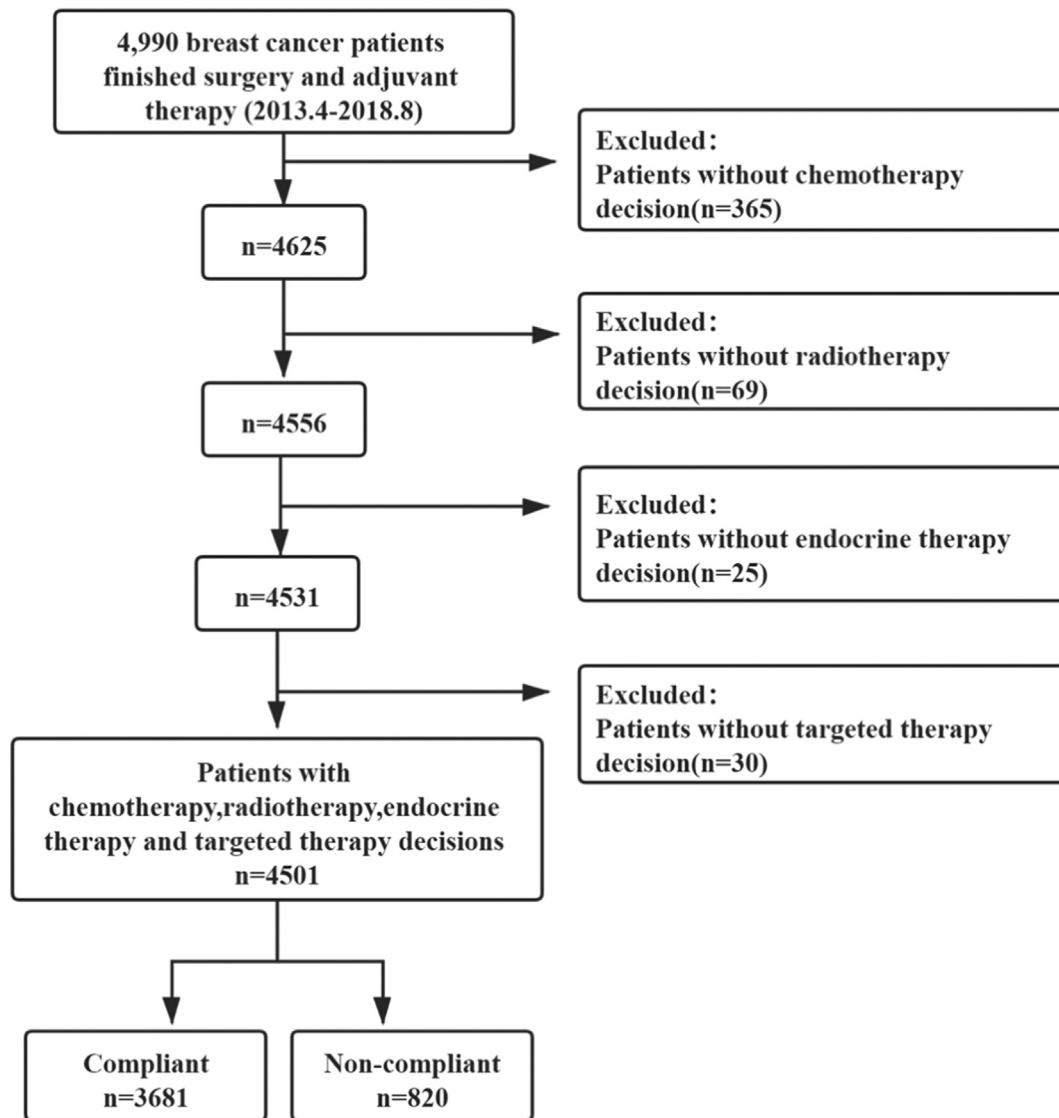


Fig. 1. Flow chart of enrollment.

3.2. Reasons for non-compliance with MDT recommendations

In total, 3681 patients (81.8%) were classified as compliant with MDT recommendations and 820 (18.2%) as non-compliant (Fig. 2).

Among 2809 patients who were recommended to receive chemotherapy, 2389 (85.0%) were compliant and 420 (15.0%) were non-compliant (Fig. 2). Among the non-compliant patients, 154 refused to receive chemotherapy, 195 received a different regimen, and 71 received an insufficient number of treatment cycles (Fig. 3a). The reasons for non-compliance with chemotherapy are shown in Fig. 3a. The most common reasons for refusing chemotherapy was out of concern of a comorbidity (68 patients). Other reasons included the patient's will (42 patients) or flexible recommendation (24 patients). The most common reasons for changing the chemotherapy regimen were onset of an adverse event during treatment (69 patients) and an insufficient number of cycles (44 patients). The chemotherapy was changed in 41 patients and the number of cycles was insufficient in 23 patients due to comorbidities. Thirty-eight patients withdrew from clinical trials and their chemotherapy regimen was changed. Twenty-eight patients were treated at local hospitals with regimens that differed from the MDT

recommendation.

Radiotherapy was recommended in 2410 patients, among whom 2203 (91.4%) were compliant and 207 (8.6%) were non-compliant (Fig. 2). The main reasons for not receiving radiotherapy were comorbidities (64 patients), the patient's will (62 patients), and flexible recommendations (41 patients). Eight patients were treated at local hospitals and did not receive radiotherapy (Fig. 3b).

Endocrine therapy was recommended in 3117 patients, and 2854 (91.6%) were classified as compliant (Fig. 2). Overall, 117 patients who refused endocrine therapy and 146 who received different regimen were classified as non-compliant. The most common reasons for refusing endocrine therapy were the patient's will (43 patients) and comorbidities (39 patients). Other reasons included a flexible recommendation (12 patients) and economic reasons (2 patients). The regimen was changed in 92 patients because of adverse events, in 46 patients because of a menstrual status change, and in four patients because of an economic reason (Fig. 3c).

Targeted therapy was recommended to 970 patients, of whom 860 (88.7%) were compliant (Fig. 2) and 110 were non-compliant

Table 1
Baseline clinicopathological characteristics.

Characteristics	Total (n = 4501)	Non-compliance (n = 820)	Compliance (n = 3681)	p value
Age (y/o)				<0.001
≤50	1739(38.6)	293(35.7)	1446(39.3)	
50-70	2280(50.7)	397(48.4)	1883(51.2)	
>70	482(10.7)	130(15.9)	352(9.6)	
District				0.653
Non-Shanghai	2054(45.6)	380(46.3)	1674(45.5)	
Shanghai	2447(54.4)	440(53.7)	2007(54.5)	
Educational level				0.054
Middle school or lower	1624(36.9)	321(39.8)	1303(36.2)	
High school or higher	2781(63.1)	485(60.2)	2296(63.8)	
Menstrual status				0.043
Pre/Peri-menopausal	1801(40.2)	303(37.1)	1498(40.9)	
Post-menopausal	2677(59.8)	514(62.9)	2163(59.1)	
Family history of breast cancer				0.052
No	4159(92.4)	771(94.0)	3388(92.0)	
Yes	342(7.6)	49(6.0)	293(8.0)	
Benign breast disease history				0.020
No	3484(77.4)	660(80.5)	2824(76.7)	
Yes	1017(22.6)	160(19.5)	857(23.3)	
Malignant tumor history				0.656
No	4300(95.5)	781(95.2)	3519(95.6)	
Yes	201(4.5)	39(4.8)	162(4.4)	
Systemic disease				0.762
No	2749(61.1)	497(60.6)	2252(61.2)	
Yes	1752(38.9)	323(39.4)	1429(38.8)	
Breast surgery				0.027
Breast conserving	1477(32.8)	296(36.1)	1181(32.1)	
Mastectomy	3024(67.2)	524(63.9)	2500(67.9)	
ALN surgery				0.003
SLNB	3009(69.5)	512(65.1)	2497(70.5)	
ALND	1321(30.5)	274(34.9)	1047(29.5)	
Pathological type				<0.001
Non- IDC	1339(29.7)	166(20.2)	1173(31.9)	
IDC	3162(70.3)	654(79.8)	2508(68.1)	
Histological grade				<0.001
I/II	2172(57.6)	361(50.8)	1811(59.1)	
III	1602(42.4)	349(49.2)	1253(40.9)	
TNM stage				0.001
0-II	3754(88.6)	654(85.2)	3100(89.4)	
III	481(11.4)	114(14.8)	367(10.6)	
Tumor size				0.006
≤2.0 cm	2677(59.8)	453(55.6)	2224(60.8)	
>2.0 cm	1798(40.2)	362(44.4)	1436(39.2)	
ALN status				<0.001
Negative	3580(79.5)	609(74.3)	2971(80.7)	
Positive	921(20.5)	211(25.7)	710(19.3)	
LVI				0.075
No	4096(91.0)	773(89.4)	3363(91.4)	
Yes	405(9.0)	87(10.6)	318(8.6)	
ER				0.007
Negative	1171(26.2)	245(30.0)	926(25.4)	
Positive	3294(73.8)	572(70.0)	2722(74.6)	
PR				<0.001
Negative	1675(37.5)	357(43.7)	1318(36.1)	
Positive	2790(62.5)	460(56.3)	2330(63.9)	
HER2				0.431
Negative	3358(75.6)	608(74.5)	2750(75.8)	
Positive	1085(24.4)	208(25.5)	877(24.2)	
Ki-67				<0.001
<14%	1641(36.8)	245(30.0)	1396(38.3)	
≥14%	2824(63.2)	572(70.0)	2252(61.7)	
Molecular subtypes				<0.001
Luminal A	942(21.2)	110(13.5)	832(22.9)	
Luminal B/HER2-	1850(41.6)	339(41.5)	1511(41.7)	
Luminal B/HER2+	513(11.5)	125(15.3)	388(10.7)	
HER2 positive	572(12.9)	83(10.2)	489(13.5)	
TNBC	566(12.7)	159(19.5)	407(11.2)	

Abbreviations: ALN axillary lymph node, ALND axillary lymph node dissection, SLNB sentinel lymph node biopsy, IDC invasive ductal carcinoma, LVI lymph-vascular invasion, ER estrogen receptor, PR progesterone receptor, HER2 human epidermal growth factor receptor 2, TNBC triple negative breast cancer.

(11.3%). The most common reason for not receiving targeted therapy was an economic reason, which occurred in 41 patients. Other

reasons included comorbidities (26 patients), patient's will (17 patients), flexible recommendations (15 patients), and treated at a

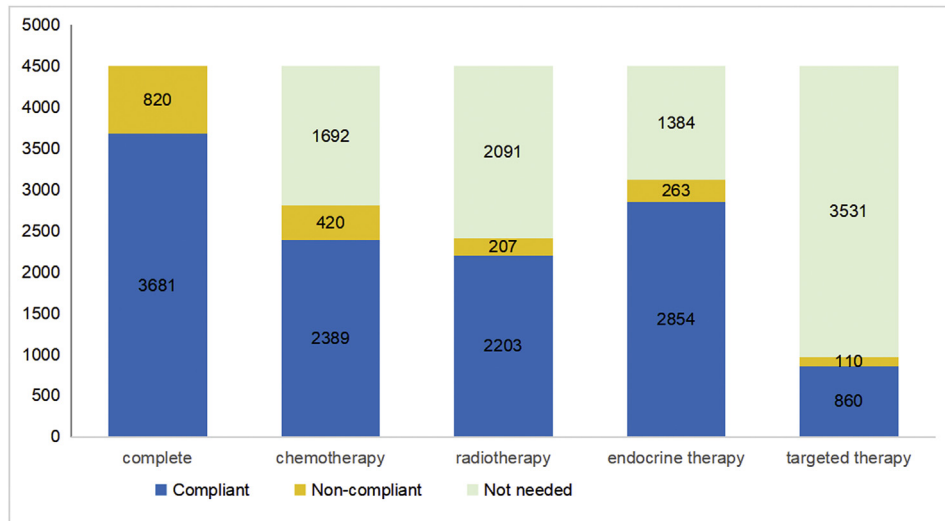


Fig. 2. Distribution of compliance with different MDT treatment recommendations.

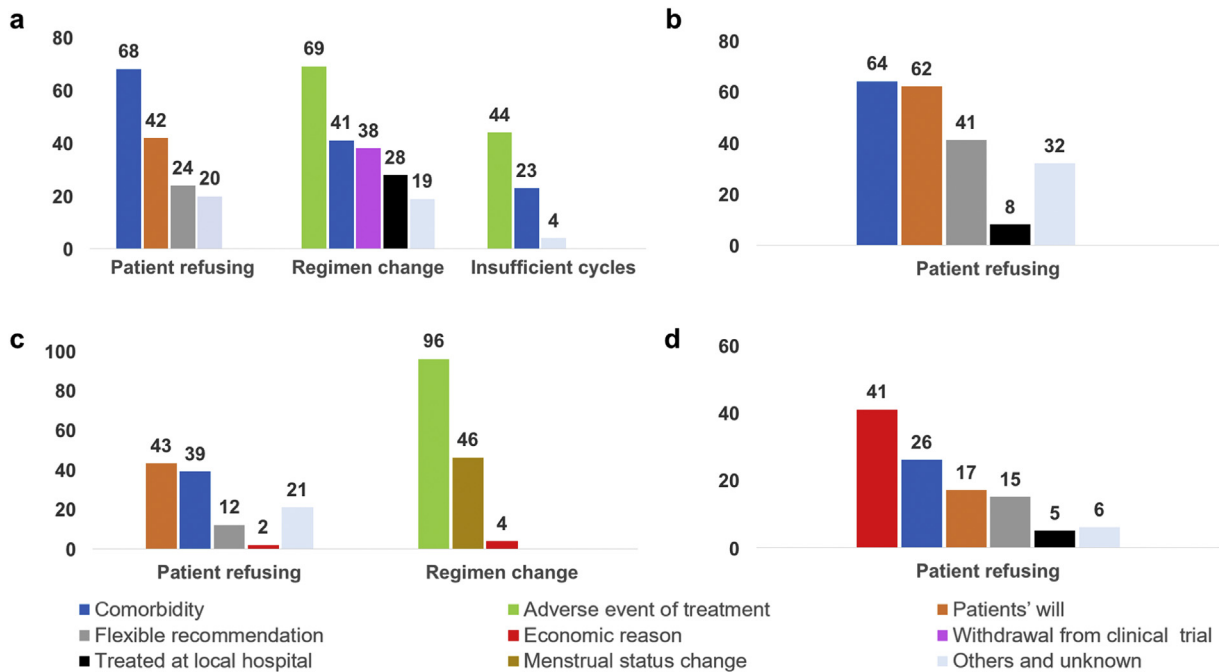


Fig. 3. Reasons for non-compliance with MDT recommendations. a. Reasons for non-compliance with chemotherapy. b. Reasons for non-compliance with radiotherapy. c. Reasons for non-compliance with endocrine therapy. d. Reasons for non-compliance with targeted therapy.

local hospital (5 patients) (Fig. 3d).

3.3. Clinicopathological factors associated with non-compliance with MDT recommendations

Univariate analysis showed that age, menopausal status, history of benign breast disease (BBD), breast surgery, axillary lymph node (ALN) surgery, pathological type, histological grade, tumor-node-metastasis stage, tumor size, ALN status, ER status, progesterone receptor (PR) status, Ki-67 labeling index, and luminal type ($P < 0.05$) were significantly different between the two groups (Table 1). Multivariable analysis revealed that age, invasive ductal carcinoma, histological grade, molecular subtype, history of BBD, and Ki-67 labeling index were independently associated with non-

compliance with MDT recommendations. Age >70 years was associated with greater risk of non-compliance than age <50 years (OR 1.68, 95% CI 1.21–2.17, $P < 0.001$). Invasive ductal carcinoma (OR 2.78, 95% CI 1.96–3.94, $P < 0.001$) or histological grade III tumor (OR 1.31, 95% CI 1.06–1.60, $P = 0.011$) were also associated with higher rate of non-compliance. The luminal B/human epidermal growth factor receptor 2 (HER2)-negative (OR 2.03, 95% CI 1.43–2.89, $P < 0.001$), luminal B/HER2-positive (OR 3.13, 95% CI 2.08–4.71, $P < 0.001$), HER2-positive (OR 1.77, 95% CI 1.15–2.73, $P = 0.009$), and triple-negative (OR 3.76, 95% CI 2.50–5.65, $P < 0.001$) molecular subtypes were also risk factors for non-compliance compared with the luminal A subtype. In contrast, a Ki-67 labeling index of $\geq 14\%$ (OR 0.76, 95% CI 0.70–1.13, $P < 0.001$) and history of BBD (OR 0.79, 95% CI 0.62–0.93, $P = 0.044$) were

independently associated with a higher rate of compliance with MDT recommendations (Table 2).

Clinicopathological factors associated with non-compliance with MDT recommendations for adjuvant therapies.

For recommended adjuvant chemotherapy, the univariate and multivariable analyses demonstrated that age >70 years was a risk factor for non-compliance (OR 3.19, 95% CI 2.20–4.63, $P < 0.001$), whereas ER positivity, ALN positivity, HER2 positivity, and Ki-67 labeling index $\geq 14\%$ were associated with compliance with MDT recommendations (Supplementary Table 1). Where adjuvant radiotherapy was recommended, multivariable analysis demonstrated that age >70 years and mastectomy were associated with non-compliance with radiotherapy, whereas an educational level of high school or above was associated with compliance (OR 0.59, 95% CI 0.43–0.80, $P = 0.001$, Supplementary Table 2).

Adjuvant endocrine therapy was recommended to 3117 patients. Factors associated with non-compliance with endocrine therapy included age >70 years (OR 1.78, 95% CI 1.24–2.55, $P = 0.002$), ER positivity (OR 7.58, 95% CI 1.08–57.22, $P = 0.042$), and HER2 positivity (OR 1.93, 95% CI 1.41–2.63, $P < 0.001$, Supplementary Table 3).

For targeted therapy, an educational level of high school or greater (OR 0.53, 95% CI 0.35–0.80, $P = 0.002$) was associated with compliance, whereas age >70 years (OR 4.38, 95% CI 2.07–9.27, $P < 0.001$) was associated with non-compliance (Supplementary Table 4).

3.4. MDT compliance and disease outcomes

After a mean follow-up time of 32.75 months, there were 182 and 80 DFS events in the compliant and non-compliant groups, respectively. The estimated 3-year DFS was 93.89% in the compliant group, which was greater than that in the non-compliant group of 89.69% ($P < 0.001$, Fig. 4a). A total of 59 OS events were recorded, with 35 in the compliant group and 24 in the non-compliant group. The estimated 3-year OS was 98.98% in the compliant group and 97.19% the non-compliant group ($P < 0.001$, Fig. 4b).

Table 3 shows the factors associated with DFS in univariate analyses. Non-compliance with MDT recommendations, tumor size >2.0 cm, histological grade III, ALN positivity, lymphovascular invasion (LVI) positivity, ER negativity, PR negativity, and Ki-67 labeling index $\geq 14\%$ were associated with worse DFS (all $P < 0.05$). After adjusting for these factors, multivariable analysis demonstrated that non-compliance with MDT recommendations was independently associated with worse DFS (HR 1.81, 95% CI 1.37–2.41, $P < 0.001$).

Table 4 lists the factors associated with OS in the overall population of patients. In univariate analyses, non-compliance with MDT recommendations, tumor size >2.0 cm, histological grade III, ALN positivity, LVI positivity, ER negativity, PR negativity, and Ki-67 labeling index $\geq 14\%$ were associated with worse OS (all $P < 0.05$). After adjusting for these factors, multivariable analysis demonstrated that non-compliance with MDT recommendations was still

Table 2
Multivariable analysis of clinicopathological characteristics associated with non-compliance with multidisciplinary team recommendations.

Characteristics	OR (95% CI)	p value
Age (y/o)		
50–70 vs. ≤ 50	0.943(0.780,1.140)	0.546
>70 vs. ≤ 50	1.681(1.208,2.166)	<0.001
Educational level		
High school or higher vs. Middle school or lower	0.861(0.717,1.033)	0.108
Menstrual status		
Post- vs. Pre/Peri-menopausal	0.989(0.706,1.385)	0.946
Family history of breast cancer		
Yes vs. No	0.823(0.575,1.178)	0.288
Benign breast disease history		
Yes vs. No	0.786(0.621,0.933)	0.040
Breast surgery		
Mastectomy vs. Breast conserving	0.878(0.719,1.073)	0.203
ALN surgery		
ALND vs. TNBC	0.932(0.712,1.219)	0.607
Pathological type		
IDC vs. Non-IDC	2.778(1.959,3.938)	<0.001
Tumor size		
>2.0 cm vs. ≤ 2.0 cm	1.072(0.889,1.292)	0.467
Histological grade		
III vs. I/II	1.306(1.063,1.603)	0.011
ALN status		
Positive vs. Negative	1.188(0.853,1.653)	0.308
ER		
Positive vs. Negative	0.800(0.214,2.989)	0.740
PR		
Positive vs. Negative	0.894(0.676,1.182)	0.431
TNM stage		
III vs. 0-II	1.100(0.789,1.534)	0.574
Ki-67		
$\geq 14\%$ vs. $< 14\%$	0.756(0.696,1.133)	0.045
Molecular subtypes		
Luminal B/HER2- vs. Luminal A	2.030(1.426,2.889)	<0.001
Luminal B/HER2+ vs. Luminal A	3.125(2.075,4.705)	<0.001
HER2 positive vs. Luminal A	1.772(1.152,2.725)	0.009
TNBC vs. Luminal A	3.759(2.503,5.646)	<0.001

Abbreviations: ALN axillary lymph node, ALND axillary lymph node dissection, SLNB sentinel lymph node biopsy, IDC invasive ductal carcinoma, ER estrogen receptor, PR progesterone receptor, HER2 human epidermal growth factor receptor 2, TNBC triple negative breast cancer, OR odds ratio, CI confidence interval.

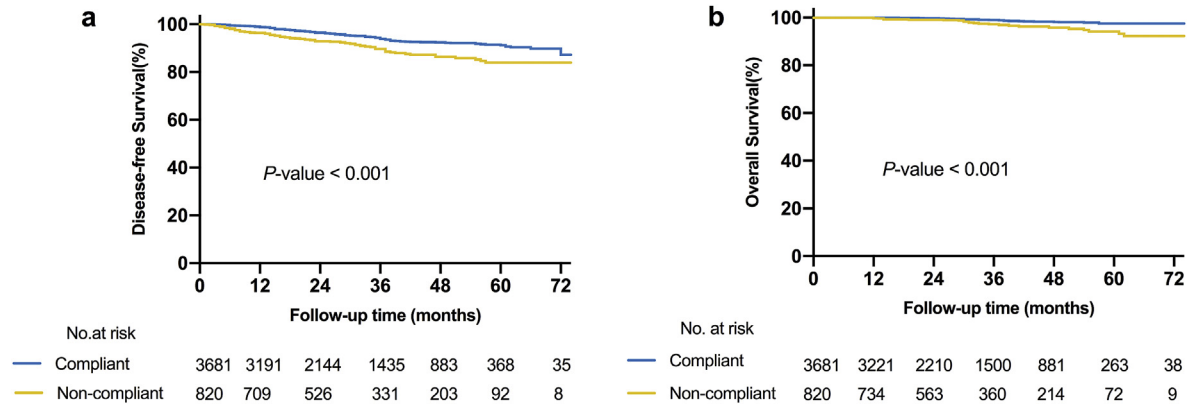


Fig. 4. Prognosis of breast cancer patients compliant or non-compliant with MDT. a. Disease-free survival according to compliance with MDT recommendations. b. Overall survival according to compliance with MDT recommendations.

Table 3
Factors associated with disease-free survival.

Characteristics	Univariable analysis		Multivariable analysis	
	HR (95%CI)	p value	HR (95%CI)	p value
Pathological type IDC vs. Non-IDC	1.164(0.880,1.538)	0.287	–	–
Tumor size >2.0 cm vs. ≤ 2.0 cm	2.150(1.680,2.752)	<0.001	1.411(1.068,1.866)	0.016
Histological grade III vs. I/II	1.849(1.416,2.414)	<0.001	1.088(0.736,1.381)	0.961
ALN status Positive vs. Negative	2.689(2.100,3.443)	<0.001	1.865(1.390,2.502)	<0.001
LVI Yes vs. No	2.394(1.694,3.383)	<0.001	1.653(1.127,2.425)	0.010
ER Positive vs. Negative	0.465(0.364,0.595)	<0.001	0.480(0.364,0.631)	<0.001
PR Positive vs. Negative	0.483(0.378,0.618)	<0.001	0.836(0.543,1.287)	0.416
HER2 Positive vs. Negative	1.287(0.985,1.681)	0.064	–	–
Ki-67 ≥14% vs. < 14%	2.427(1.808,3.259)	<0.001	1.486(1.050,2.103)	0.026
Compliance with MDT Non-compliance vs. Compliance	1.888(1.451,2.456)	<0.001	1.813(1.367,2.405)	<0.001

Abbreviations: IDC invasive ductal carcinoma, ALN axillary lymph node, LVI lymphatic vascular invasion, ER estrogen receptor, PR progesterone receptor, Her-2 human epidermal growth factor receptor-2, HR hazard ratio, CI confidence interval, MDT multidisciplinary team.

an independent risk factor for worse OS (HR 2.48, 95% CI 1.43–4.29, $P = 0.001$).

3.5. Compliance with MDT recommendations according to the type of adjuvant treatment and disease outcomes

Fig. 5 shows the impact of compliance with certain MDT recommendations for adjuvant chemotherapy, endocrine therapy, radiotherapy, and targeted therapy on disease outcomes. For adjuvant chemotherapy, there were 202 DFS events: 165 in the compliant group and 37 in the non-compliant group ($P = 0.131$, Fig. 5a). In multivariable analysis, with adjustment for tumor size, histological grade, ALN status, LVI, ER, PR, and Ki-67 labeling index, non-compliance with the MDT chemotherapy recommendations was associated with a higher rate of recurrence (HR 1.50, 95% CI 1.03–2.18, $P = 0.033$) versus compliance with recommendations (Fig. 5a). There were 40 and 9 deaths in the compliant and non-compliant groups, respectively ($P = 0.425$, Fig. 5b). Multivariable analysis showed that non-compliance with the MDT chemotherapy recommendations was not significantly associated with OS (HR 1.62, 95% CI 0.77–3.39, $P = 0.204$, Fig. 5b).

There were 172 DFS events among patients for whom radiotherapy was recommended: 139 in the compliant group and 33 in the non-compliant group ($P < 0.001$, Fig. 5c), whereas 33 and 13 patients in the compliant and non-compliant groups, respectively, died ($P < 0.001$, Fig. 5d). Multivariable analysis, with adjustment for tumor size, histological grade, ALN status, LVI, ER, PR, and Ki-67 labeling index, showed that non-compliance with the MDT radiotherapy recommendations was associated with shorter DFS (HR 2.31, 95% CI 1.54–3.48, $P < 0.001$) and worse OS (HR 3.62, 95% CI 1.85–7.09, $P < 0.001$, Fig. 5c and d).

A total of 118 DFS events were recorded in the endocrine therapy compliant group. DFS was better in the compliant group than that in the non-compliant group ($P < 0.001$, Fig. 5e). In the multivariable analysis adjusting for tumor size, histological grade, ALN status, LVI, ER, PR, and Ki-67 labeling index, non-compliance with the MDT endocrine therapy recommendation was associated with worse DFS (HR 2.48, 95% CI 1.56–3.95, $P < 0.001$, Fig. 5e). In addition, OS was significantly worse in the non-compliant group (HR 2.69, 95% CI 1.07–6.74, $P = 0.035$, Fig. 5f).

For patients who were recommended to receive targeted therapy, 69 and 15 DFS events were recorded in the compliant and non-

Table 4
Factors associated with overall survival.

Characteristics	Univariable analysis		Multivariable analysis	
	HR (95%CI)	<i>p</i> value	HR (95%CI)	<i>p</i> value
Pathological type				
IDC vs. Non-IDC	1.468(0.779,2.767)	0.235	–	–
Tumor size				
>2.0 cm vs. ≤ 2.0 cm	2.717(1.584,4.658)	<0.001	1.271(0.709,2.279)	0.421
Histological grade				
III vs. I/II	3.192(1.752,5.816)	<0.001	1.157(0.592,2.279)	0.670
ALN status				
Positive vs. Negative	6.520(3.846,11.052)	<0.001	4.369(2.395,7.968)	<0.001
LVI				
Yes vs. No	2.645(1.250,5.596)	0.011	1.107(0.505,2.427)	0.800
ER				
Positive vs. Negative	0.385(0.231,0.641)	<0.001	0.764(0.354,1.649)	0.493
PR				
Positive vs. Negative	0.315(0.183,0.545)	<0.001	0.377(0.205,0.693)	0.002
HER2				
Positive vs. Negative	1.487(0.861,2.567)	0.155	–	–
Ki-67				
≥14% vs. < 14%	6.380(7.740,14.853)	<0.001	4.058(1.430,11.513)	0.008
Compliance with MDT				
Non-compliance vs. Compliance	2.760(1.642,4.641)	<0.001	2.478(1.431,4.291)	0.001

Abbreviations: IDC invasive ductal carcinoma, ALN axillary lymph node, LVI lymphatic vascular invasion, ER estrogen receptor, PR progesterone receptor, Her-2 human epidermal growth factor receptor-2, HR hazard ratio, CI confidence interval, MDT multidisciplinary team.

compliant groups, respectively ($P = 0.095$, Fig. 5g), whereas 16 and 6 patients in the compliant and non-compliant groups died, respectively ($P = 0.054$, Fig. 5h). Multivariable analysis revealed that non-compliance with the targeted therapy recommendation was associated with worse DFS (HR 1.76, 95% CI 1.00–3.11, $P = 0.050$, Fig. 5g) and worse OS (HR 3.15, 95% CI 1.22–8.14, $P = 0.018$, Fig. 5h).

4. Discussion

MDT discussions for breast cancer need to integrate doctors, nurses, medical resources, and essential equipment [12,13], but the association of the strategy with the disease outcomes has been uncertain. In the current study, we studied 4501 breast cancer patients with complete MDT decisions and follow-up information, and found that non-compliance with the MDT recommendations was a risk factor for worse disease outcomes, irrespective of whether the non-compliance was for adjuvant chemotherapy, radiotherapy, endocrine therapy, or targeted therapy. Thus, efforts to increase the rate of compliance with MDT recommendations for breast cancer patients may help to improve their outcomes.

MDT procedures have led to changes in the management of breast cancer patients, but a consistent survival benefit has not been demonstrated and most centers do not track compliance with the MDT recommendations [5,7–9,14]. Thus, there is a clear need to document compliance with MDT decisions and perform comparative analyses to determine whether non-compliance with MDT recommendations is detrimental to prognosis. In our study of breast cancer patients, non-compliance with adjuvant therapy was documented for 18.2% of patients. For specific types of adjuvant therapies, the non-compliance rates were 15.0%, 8.6%, 8.4%, and 11.3% for adjuvant chemotherapy, radiotherapy, endocrine therapy, and targeted therapy, respectively.

The MDT recommendations for chemotherapy may be diverse but there is a high rate of non-compliance with chemotherapy. Many factors are considered in the decision-making process for adjuvant chemotherapy [15] and patients may suffer from chemotherapy side effects, such as fatigue [16,17], which results in a low rate of compliance. A previous study showed that, among selected patients with early breast cancer, 7% of patients did not

complete adjuvant chemotherapy [18]. Questionnaires regarding 803 patients with newly diagnosed breast cancer showed that comorbidities and frailty were the main reasons for not receiving the full course of chemotherapy [12]. We analyzed the association between clinicopathological factors and compliance rates, and found that age >70 years, histological grade III, and invasive ductal carcinoma were associated with lower compliance rates. Patients with the luminal A subtype had a higher rate of compliance than patients with other molecular subtypes, which may be explained by chemotherapy being recommended less frequently for the luminal A subtype. The poor compliance of elderly patients observed here is consistent with previously published studies showing that MDT recommendations were more likely to be changed in elderly women [19]. Among patients aged 70–85 years, only 56.9% patients were reported to receive planned adjuvant chemotherapy after MDT discussions [12], which may be because older women may be frailer and less likely to tolerate conventional chemotherapy [20]. Moreover, clinicians were also unwilling to offer chemotherapy to older patients because of the small survival benefit in these patients [12]. Furthermore, we found that compliance with the MDT recommendations was higher in patients with a history of breast diseases. This might reflect the patient's awareness and experience of previous breast diseases, and may encourage them to accept the recommended therapy. The Ki-67 labeling index is associated with the prognosis and can influence systemic treatment decisions [15,21]. In this study, a high Ki-67 labeling index was associated with a higher rate of compliance with MDT recommendations. We surmise the clinicians were more likely to recommend a relatively strong treatment regimen and that the patients would follow the recommendations because of the otherwise poor prognosis. Prospective studies can be designed to discover the subjective factors and main considerations influencing compliance among patients and attending physicians with the MDT recommendations for early breast cancer.

Longitudinal post-MDT recommendation data provide the most clinically meaningful information to evaluate the benefit of the MDT strategy and to assess whether compliance with the MDT recommendations can confer better patient outcomes. The impact of the MDT approach on real-world disease outcomes offers an opportunity for future research [14]. We have found that the

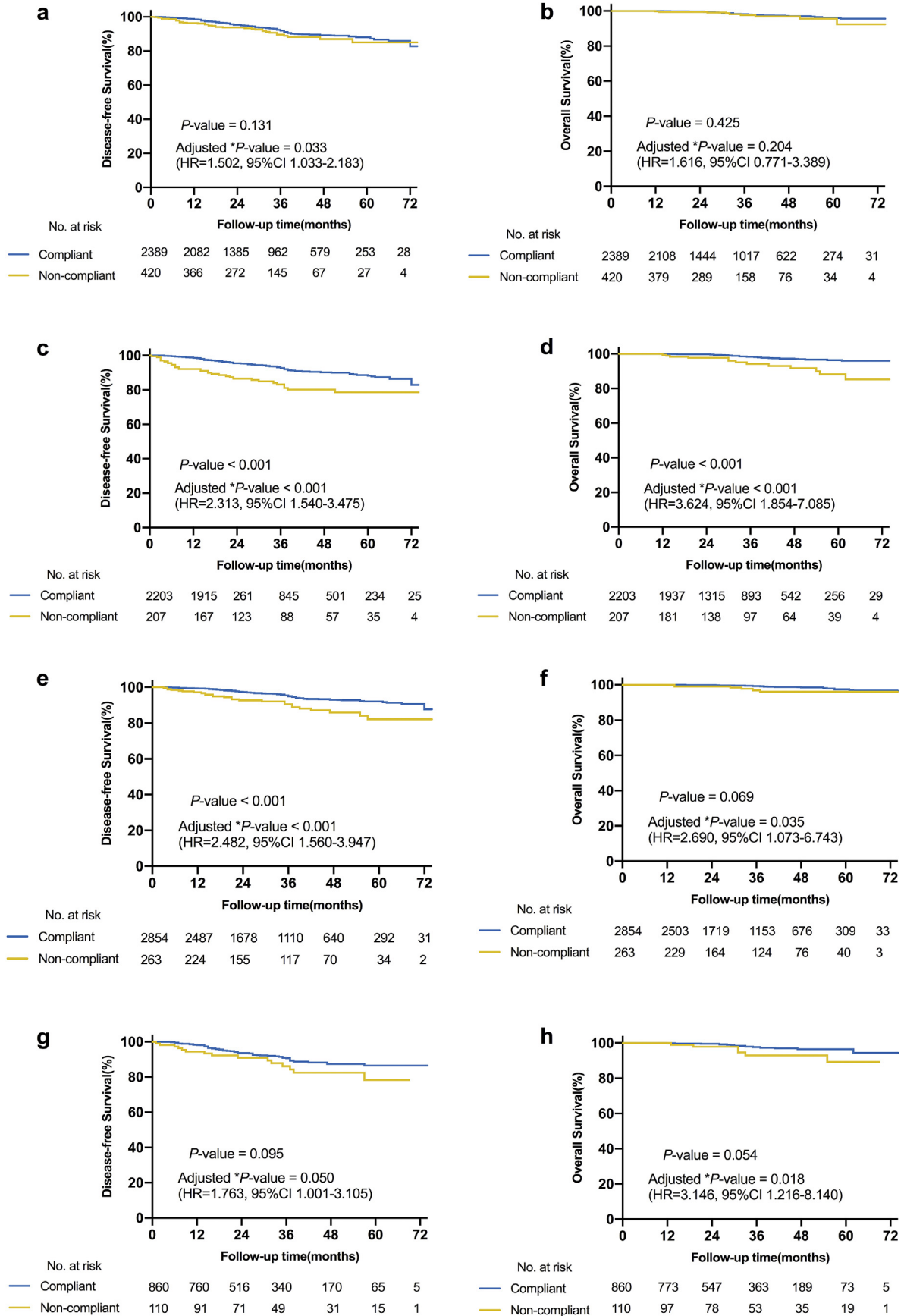


Fig. 5. Disease-free survival and overall survival in breast cancer patients stratified by the recommended adjuvant treatment. a,c,e,g. Differences in disease-free survival according to compliance in patients recommended to receive chemotherapy (a), radiotherapy (c), endocrine therapy (e), and targeted therapy (g). b,d,f,h. Differences in overall survival difference according to compliance in patients recommended to receive chemotherapy (b), radiotherapy (d), endocrine therapy (f), and targeted therapy (h). * P -values were adjusted for pathological variables (tumor size, histological grade, axillary lymph node status, lymphatic vascular invasion, estrogen receptor, progesterone receptor, Ki-67).

prognosis was better in the compliant group than in the non-compliant group. For patients who do not need systemic adjuvant therapy, compliance is better but the risk of recurrence is low, which may result in underestimation of the benefit of compliance with MDT recommendations. Therefore, we performed subgroup analyses to determine the effect of compliance with each treatment modality on prognosis. We found that compliance with chemotherapy was associated with superior disease outcomes, consistent with the effects of adjuvant chemotherapy in the real world [22,23]. We also found that compliance with radiotherapy, endocrine therapy, and targeted therapy was associated with improvements in DFS or OS.

Common reasons for non-compliance with the recommended treatment included concern about comorbidities, the patient's will, adverse events, flexible recommendations made by the MDT, and economic reasons. Regarding comorbidities and adverse events, careful monitoring plans should be implemented for at-risk patients to improve their compliancy rates. Patient education should be strengthened to reduce the rates of non-compliance due to the patient's will. Our findings, which indicate that non-compliance with the MDT recommendations reduces DFS and OS, might help persuade patients to comply with the recommended treatment. A flexible recommendation made by MDT might also result in some non-compliant patients. Thus, the MDT should strive to provide less-flexible recommendations to reduce the rate of non-compliance. The cost (economy) of treatment was another common reason for refusing targeted therapy because it was not covered by China's medical insurance until 2017. Now that trastuzumab and pertuzumab are covered by medical insurance in China, we expect a decrease in the rate of non-compliance with targeted therapy due to economic factors.

Our study included 4501 consecutive breast cancer patients with complete MDT decisions and follow-up information. Moreover, information about the MDT recommendations was prospectively recorded in our database and the patient's actual treatment was recorded, allowing us to evaluate their compliance with breast cancer treatments based on MDT discussions. However, this study has several limitations. First, although the clinicopathological and MDT information was prospectively recorded, the details of compliance were retrospectively collected, which may result in a recall bias. Additionally, the mean follow-up time was 32.75 months, which was too short to calculate long-term disease outcomes, especially for ER-positive breast cancer patients. A longer follow-up time is warranted to validate the association between compliance with MDT recommendations and prognosis.

5. Conclusion

In summary, our study of breast cancer patients revealed that age >70 years, invasive ductal carcinoma, or histological grade III were associated with higher rates of non-compliance with MDT recommendations for adjuvant therapy, and non-compliance was associated with worse disease outcomes. These results warrant further clinical validation.

Declaration of competing interest

The authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2020.05.008>.

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