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The effect of adjuvant chemotherapy in male breast cancer: 134 cases from a retrospective study

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ABSTRACT

Background Male breast cancer (BC) is a kind of rare tumour. There were few researches concerning the effect of chemotherapy for it. The purpose of this study is to estimate the value of chemotherapy on prognosis in male BC.

Patients and methods Complete clinical and pathological information of male BC were collected from January 1990 to January 2008 in Zhejiang Cancer Hospital in China. 134 cases of male BC were included for analysis and separated into two groups based on receiving chemotherapy or not receiving chemotherapy. The disease-free survival (DFS) and overall survival (OS) between chemotherapy group and non-chemotherapy group were compared with Kaplan-Meier survival curve. Stratified analysis was used to evaluate the strength of the association between chemotherapy and each risk factor. Multivariate analysis was conducted by using COX proportional hazard regression model.

Results There were 58.21% (78/134) cases who underwent chemotherapy and 41.79% (56/134) cases without chemotherapy. There were 20 cases (25.64%) with recurrence/metastasis in patients with chemotherapy and six cases (10.71%) in patients without chemotherapy. The mean DFS time of male BC with chemotherapy and non-chemotherapy is 150.87 and 154.13 months, respectively (χ^2=3.825, p=0.050). The mean OS time of male BC with chemotherapy and non-chemotherapy is 155.33 and 154.26 months, respectively (χ^2=2.542, p=0.111). COX proportional hazard regression model showed that the two groups had similar DFS (HR=0.386, p=0.165), while chemotherapy might be a protective fact on OS (HR=0.140, p=0.026).

Conclusion The utility of chemotherapy should be considered in the high risk level of recurrence/metastasis in male BC.

Key questions

What is already known about this subject?

- Male breast cancer (BC) is a kind of rare tumour, the incidence rate is generally below 1 per 100 000 males annually. There were few researches about male BC. The effect of chemotherapy for male BC is still unknown.

What does this study add?

- Compared with male BC patients without chemotherapy in our study, those with chemotherapy harboured more poor prognosis factors, such as more lymph node (LN) metastasis, HER2 expression and lymphovascular invasion. However, the two groups achieved the similar prognosis finally. Thus, the utility of chemotherapy should be considered in the high risk level of recurrence/metastasis in male BC.

How might this impact on clinical practice?

- Although the treatment of male BC is based on the guideline of female BC in clinical practice, there are lots of differences between them. In this study, we want to discuss the effect of chemotherapy in male BC.

INTRODUCTION

Male breast cancer (BC) incidence rate is generally below 1 per 100 000 males annually, in contrast to the much higher rate of female breast cancer (FBC).[1 2] According to the national cancer centre surveillance, epidemiology and end results (SEER) database statistics, male BC proportion is less than 1% of all BC.[1] Studies have reported differences in the biomarkers between male BC and FBC. Over 90% of male BC patients are oestrogen receptor (ER) positive, 80%–96% are progesterone receptor (PR) positive and 87% are androgen receptor (AR) positive.[3–5] It is similar as our previous studies showed that ER/PR positivity was in more than 85% of male BC cases.[6 7] What is more, the differences of genomic landscape between male BC and FBC were reported recently. Compared with ER-positive/HER2-negative FBC, those male BC less frequently had 16q losses, and PIK3CA and TP53 mutations.[8] Obviously, there were many differences in composing subtypes between male and female. However, the treatment of male BC is still based on the guideline of FBC. Some small sample studies in the past have attempted to use endocrine therapy intended for postmenopausal FBC treatment to treat male BC based on high ER/PR positivity similarities.[9] There were also some case reports

about using gonadotropin-releasing hormone analogue combined with aromatase inhibitors (AIs) in the treatment of male BC.[10–12] However, thus far, these treatment attempts have failed to prove that AIs can be more effective in treating male BC than tamoxifen.[13 14] Therefore, tamoxifen remains commonly used to treat male BC patients. The endocrine therapy has been proved effective for male BC, while there were few researches concerning the effect of chemotherapy for male BC. Early in 1980s, there were reports about chemotherapy in metastasis and advanced male BC patients.[14 15] But in those patients, the prognoses were not satisfied due to single-agent regimen or regimen without anthracycline. Recently, there was a small sample study on the efficacy of chemotherapy in metastatic male BC. The disease control rate was 84%, overall response rate was 56%.[16] But there were not enough prognostic evidence-based proofs for adjuvant chemotherapy in male BC. The purpose of this study is to estimate the value of adjuvant chemotherapy on disease-free survival (DFS) and overall survival (OS) in male BC.

Table 1 Standards of recurrence risk score

Risk score	Key points	
	LN status	Others
Low	Negative	Conform to all standards as follows: pathological tumour size ≤2 cm, histological grade I, LVI negative, HR positive, HER2 negative, ≥35 years old
Medium		Conform to at least one standard as follows: pathological tumour size >2 cm, histological grade II–II, LVI positive, HR negative, HER2 positive, <35 years old
High	1–4 positive LNs	HER2 negative and HR positive
		HER2 positive or HR negative
	≥4 positive LNs	–

HER2, human epidermal growth factor 2; HR, hormone receptor; LN, lymph node; LVI, lymphovascular invasion.

PATIENTS AND METHODS

Patients' clinical material

We excluded patients with carcinoma in situ or stage IV when they first diagnosed from January 1990 to January 2008 in Zhejiang Cancer Hospital in China. Finally, 134 cases male BC with complete clinical and pathological information were brought into our study.

Clinical data included patients' age, chemotherapy and endocrine therapy. Pathological data included tumour size, histological grade, lymphovascular invasion (LVI), lymph node (LN) metastasis, ER, PR, Ki67 and human epidermal growth factor receptor-2 (HER2) in immunohistochemistry (IHC). All pathological data were reconfirmed by two specialists in breast pathology. Because of the variation of ER/PR and HER2-positive standards during the past decades, we reconfirmed these by the latest guideline of the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP).[17] If ER >1% or PR >1%, we defined the patient as hormone receptor (HR) positive. HER2 3+ (by IHC) or fluorescence in situ hybridisation (FISH)+ was determined HER2 expression positive, IHC 1+/− or FISH− was determined negative. HER2 2+ (by IHC) would be tested by FISH for determination, and some early data cannot be retested by FISH would be counted as uncertain status of HER2. A cut-off value of 14% was used to identify the Ki67 low or high expression. The recurrence risk score of all patients was based on the diagnosis and treatment guidelines of Chinese Breast Cancer Society version 2015 (table 1).[18] All clinical and publishing data were used with consent of all patients or patient's family member if the patient died.

Follow-up data

All cases were followed up by telephone or face-to-face interview, including recurrence/metastasis events (recurrence/metastasis symptoms, signs or auxiliary examination results) and death events related to BC. The DFS was defined as the time from death events due to all causes or diagnosing to the first time patients had BC-specific recurrence/metastasis events, which were finally confirmed by adjuvant examination or puncture biopsy. The OS was defined as the time from diagnosing to death events due to all causes.

Statistics

All data were analysed by SPSS (v22), Wilcoxon rank-sum test for ordered categorical variables, χ^2 test for unordered categorical variables and t-test (mean±SD) for continuous variables. DFS and OS between chemotherapy and non-chemotherapy were compared with Kaplan-Meier survival curve (log-rank test). Stratified analysis was used to evaluate the strength of the association between chemotherapy and each risk by calculating the HR, 95% CI and associated p-value. Multivariate analysis was conducted using Cox-regression model. Statistically significant results were considered as $p<0.05$.

RESULTS

Clinical materials

One hundred and thirty-four cases of male BC were included for analysis (table 2). The median age at diagnosis was 57 years old (37–73 years old). There were 47.76% cases with histological grade I (improved Bloom Richardson score standard) and 52.23% cases with grade II. LVI was noted in 40.30% cases; 28.36% of all patients were in stage I and 48.53%, 22.06% and 1.47% were in stages II–III, respectively. 85.07% cases had positive HR, 13.43% cases had positive HER2 and 16.42% cases with uncertain HER2 status. The mean Ki67 of all

Table 2 Clinical materials of 134 male BC patients

Clinical parameters		Total (n=134)		Chemotherapy (n=78)		Non-chemotherapy (n=56)		p-Value
Age (years, mean±SD)		56.36±9.00		55.23±8.71		57.93±9.24		0.087
Tumour size (mm, mean±SD)		26.60±10.65		29.69±10.24		22.29±9.73		<0.001
Number of positive LNs (mean±SD)		1.51±2.88		2.54±3.41		0.07±0.38		<0.001
Histological grade (n, %)	I	64	47.76	44	56.41	20	35.71	0.018*
	II	70	52.23	34	43.59	36	64.29	
LVI (n, %)	Positive	54	40.30	40	51.38	14	25.00	0.002†
	Negative	80	59.70	38	84.72	42	75.00	
Stage (n, %)	I	38	28.36	8	10.26	30	53.57	<0.001*
	II	66	49.25	44	56.41	22	39.29	
	III	30	22.39	26	33.33	4	7.14	
HR (n, %)	Positive	114	85.07	60	76.92	54	96.43	0.002*
	Negative	20	14.93	18	23.08	2	3.57	
HER2 (n, %)	Positive	18	13.43	14	17.95	4	7.14	<0.001*
	Negative	94	70.15	42	53.85	52	92.86	
	Uncertain	22	16.42	22	28.20	0	0	
Ki67 (n, %)	High	110	82.09	70	89.74	40	71.43	0.006†
	Low	24	17.91	8	10.26	16	28.57	
Risk (n, %)	High	30	22.39	30	38.46	0	0	<0.001*
	Medium	86	64.18	40	51.28	46	82.14	
	Low	14	10.45	4	5.13	10	17.86	

*Wilcoxon rank-sum test.
†χ^2 test.
HER2, human epidermal growth factor 2; HR, hormone receptor; LN, lymph node; LVI, lymphovascular invasion.

male BC was 24.00%, and there were 82.09% male BC cases with high expression of Ki67.

All patients underwent mastectomy and axillary LN dissection. All of the HR-positive patients took tamoxifen as endocrine therapy for at least 5 years. Because of the lack of trastuzumab in early time of this study during last decade in China, only two patients with HER2 positive got anti-HER2 treatment for 1 year.

Chemotherapy and regimens

There were 78 cases receiving chemotherapy, which counted 58.21% of all male BC patients. It seemed that the patients underwent chemotherapy had later stage, larger tumour size, more positive LNs, more negative HR, more positive HER2, more positive LVI and higher Ki67 (table 2).

All of those parameters might be important factors for considering chemotherapy. The regimens included CMF*6 (cyclophosphamide, methotrexate, 5-fluorouracil), FEC*6 (5-fluorouracil, epirubicin, cyclophosphamide)/EC*4 (epirubicin, cyclophosphamide), FEC*3 T*3 (docetaxel)/EC*4 T*4 and TEC*6 (docetaxel, epirubicin, cyclophosphamide) (table 3).

Follow-up and prognosis

The median follow-up time was 91 months. There were 26 cases with recurrence or metastasis in the follow-up time. Among them, 20 patients received chemotherapy,

Table 3 Regimens and dose of chemotherapy

Regimens	n (%)	Dose and cycle
CMF	30 (38.46)	C 500 mg/m^2 dI, M 50 mg/m^2 dI, F 500 mg/m^2 dI, cycled every 28 days for six cycles
FEC	30 (38.46)	F 500 mg/m^2, E 100 mg/m^2, C 500 mg/m^2, cycled every 21 days for six cycles
EC		E 100 mg/m^2, C 830 mg/m^2, cycled every 21 days for four cycles
FEC-T	14 (17.95)	64.03436575875486F 500 mg/m^2, E 100 mg/m^2, C 500 mg/m^2, cycled every 21 days for three cycles followed by T 100 mg/m^2, cycled every 21 days for three cycles
EC-T		E 100 mg/m^2, C 600 mg/m^2, every 21 days for four cycles followed by T 100 mg/m^2, cycled every 21 days for four cycles
TEC	4 (5.13)	T 75 mg/m^2, E 75 mg/m^2, C 500 mg/m^2, cycled every 21 days for six cycles

C, cyclophosphamide; E, epirubicin; F, 5-fluorouracil; M, methotrexate; T, docetaxel.

Table 4 Status of recurrence and metastasis

Events	n (%)
Local recurrence	2 (7.69)
Multiple lesion-metastasis	5 (19.23)
Liver metastasis	3 (11.54)
Bone metastasis	11 (42.31)
Lung metastasis	3 (11.54)
Brain metastasis	2 (7.69)

whereas other 6 were not. About 19 (73.08%) patients were mono lesion-metastasis, and bone metastasis accounted for almost the half (table 4).

The mean disease-free survival time of male BC with chemotherapy and non-chemotherapy was 150.87±7.75 months versus 154.13±4.95 months, respectively, which could not achieve a significant difference (χ^2=3.825, p=0.050) (figure 1A). The 10-year OS rate of all 134 patients was 82.09%. The mean OS time of male BC with chemotherapy and non-chemotherapy is 155.33±7.30 versus 154.26±4.90 months, respectively, no significant difference as well (χ^2=2.542, p=0.111) (figure 1B).

According to the stratified analysis (figure 2A,B), patients with younger age (≤50 years old), with tumour size ≤2 cm, HER2 over-expression, advanced stage or medium risk experienced better DFS and OS from chemotherapy, though without statistical difference.

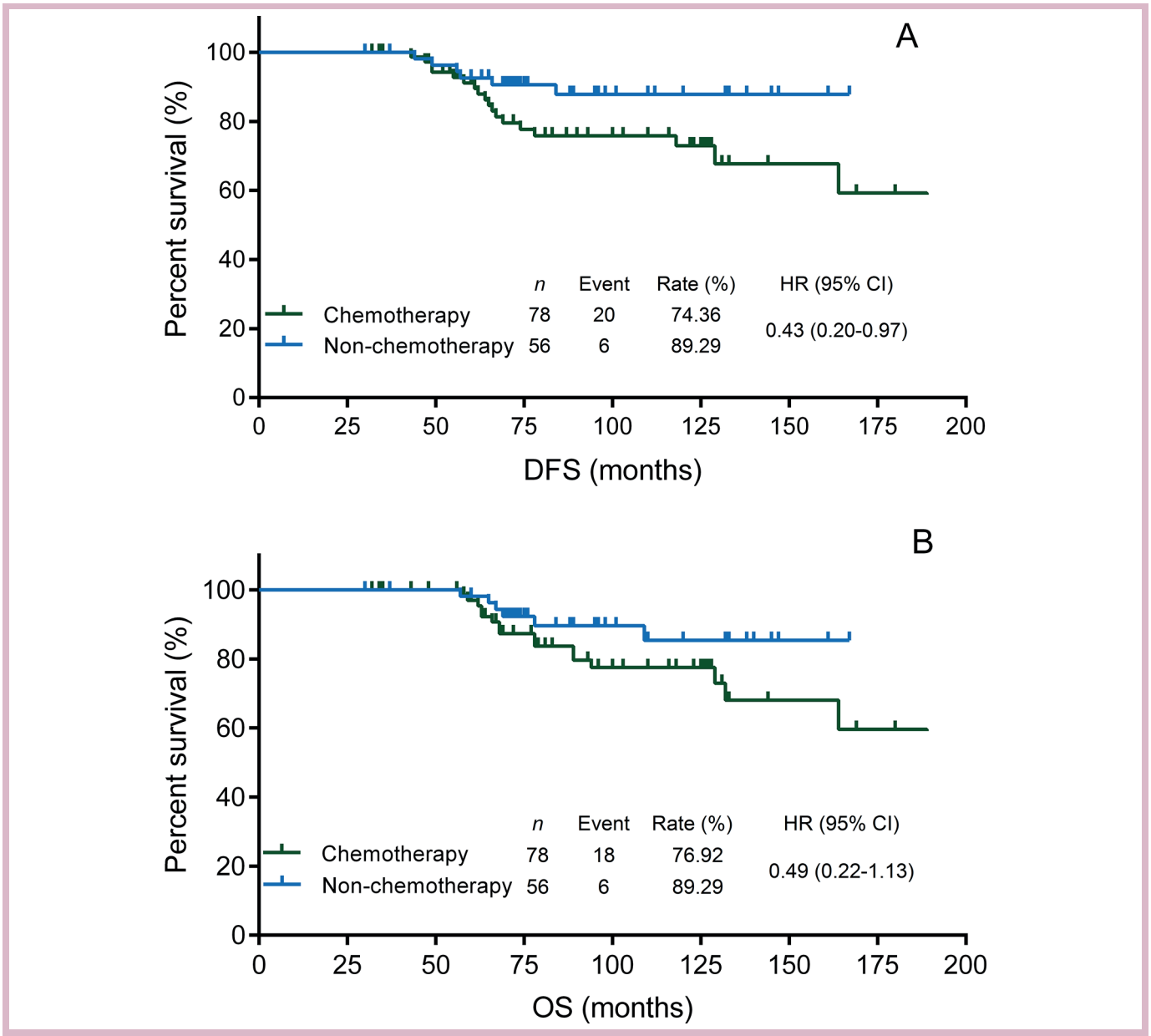

Figure 1 (A) Kaplan-Meier survival curve for disease-free survival. (B) Kaplan-Meier survival curve for overall survival. BC, breast cancer; DFS, disease-free survival; OS, overall survival.

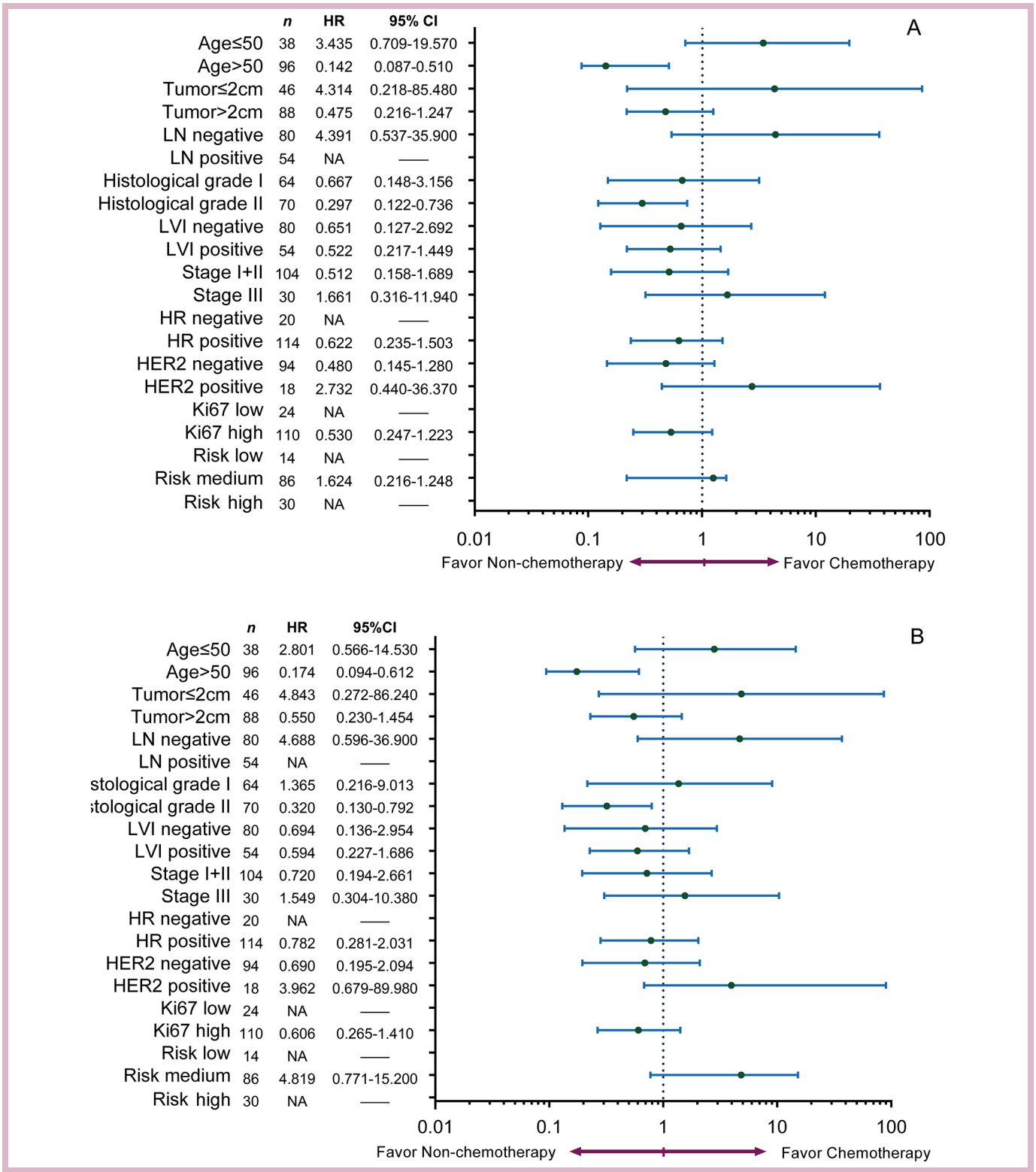

Figure 2 (A) The stratified analysis for DFS because of the uncertain status of HER2, 132 patients could be calculated the recurrence risk score. (B) The stratified analysis for OS because of the uncertain status of HER2, 132 patients could be calculated the recurrence risk score. DFS, disease-free survival; HER2, human epidermal growth factor 2; OS, overall survival.

Five subgroups, LN positive, HR negative, Ki67 low, risk low and risk high, were not considered (NA) because we thought there was much bias in them. There were 54 patients in subgroup LN positive, but only 2 did not receive chemotherapy, and they both had recurrence/metastasis and died finally. It was completely contrary to the phenomenon in subgroup HR negative. Twenty patients totally, but no interested terminal event happened on the

Table 5 COX proportional hazard regression model test (enter method) for DFS

	B	SE	Wald	p-Value	Exp(B)	95% CI for Exp(B) Lower	Upper
Age	0.052	0.027	3.691	0.055	1.053	0.999	1.110
Tumour size	0.042	0.025	2.863	0.091	1.042	0.993	1.094
Number of positive LNs	0.287	0.109	6.876	0.009	1.332	1.075	1.651
Histological grade	−0.736	0.711	1.069	0.301	0.479	0.119	1.932
LVI	1.198	0.724	2.738	0.098	3.313	0.802	13.693
HR	−0.590	0.508	1.344	0.246	0.555	0.205	1.502
HER2	0.702	0.389	3.265	0.071	2.018	0.942	4.323
Ki67	−0.406	2.636	0.024	0.878	0.666	0.004	116.750
Chemotherapy	−0.952	0.686	1.925	0.165	0.386	0.101	1.481

DFS, disease-free survival; HER2, human epidermal growth factor 2; HR, hormone receptor; LN, lymph node; LVI, lymphovascular invasion.

only two non-chemotherapy patients. Simultaneously, all patients with low Ki67 expression harboured well prognosis, no matter chemotherapy or not, the relevant data could not be got. All patients in subgroup risk high and only four patients in subgroup risk low received chemotherapy, we gave NA as well.

COX proportional hazard regression model indicated that chemotherapy did not have significant correlation with DFS (HR=0.386, p=0.165) (table 5), while it might be a protective factor on OS (HR=0.140, p=0.026) (table 6). The inconsistency of chemotherapy effect on DFS and OS can be partly explained by the OS definition (death events to all causes).

DISCUSSION

The incidence of male BC is much lower than female, but its mortality rate is as same as female BC.[13 19–21] Our results suggest that 10-year OS rate of male BC is 82.09%, similar to other researches. There are few reports concerning male BC prognosis correlation with clinical parameters, but some literature have proved that statuses of HR and HER2 can influence the prognosis of male BC a lot.[3 22] Although 80% of male BC are ER positive, male ER-positive tumours do not respond to tamoxifen therapy in the same manner as female ER-positive tumours do. In addition, a recent analysis of the SEER data from 1996 to 2005 suggests that there is a 42% decrease in BC-specific mortality among women compared with only a 28% decrease among men, suggesting that the treatments being used in male BC are not as effective as they are for FBC. Single HR status cannot predict treatment effect very well.[13] In our results, many male BCs with HR positive also have other poor prognostic factors, such as high histological grade, LN involvement, HER2 and high Ki67 expression. All of those should be considered for adjuvant chemotherapy.

Adjuvant chemotherapy has been proved benefit for most FBCs, and it can reduce the risk of recurrence and metastasis by 10%–30%, especially in FBCs with high-risk standard. However, comparing with FBC, male BC has more HR expression, as high as 85.29% in our result. Furthermore, the molecular subtypes are also different between male BC and FBC.[5 6] However, this distinction has not been transferred into a changing of clinical

Table 6 COX proportional hazard regression model test (enter method) for OS

	B	SE	Wald	p-Value	Exp(B)	95% CI for Exp(B) Lower	Upper
Age	0.039	0.032	1.437	0.231	1.040	0.976	1.108
Tumour size	0.103	0.029	12.729	0.000	1.109	1.048	1.173
Number of positive LNs	0.326	0.140	5.431	0.020	1.385	1.053	1.821
Histological grade	0.167	0.885	0.036	0.851	1.181	0.209	6.694
LVI	−0.417	0.862	0.234	0.628	0.659	0.122	3.570
HR	−0.779	0.603	1.670	0.196	0.459	0.141	1.495
HER2	1.504	0.504	8.917	0.003	4.500	1.677	12.079
Ki67	−0.504	3.053	0.027	0.869	0.604	0.002	239.819
Chemotherapy	−1.964	0.882	4.961	0.026	0.140	0.025	0.790

HER2, human epidermal growth factor 2; HR, hormone receptor; LN, lymph node; LVI, lymphovascular invasion; OS, overall survival.

treatment decision. Generally, for chemotherapy, male BCs are treated in the same way, stage for stage, as FBC. There are few articles about the chemotherapy in male BC. Early in 1955–1996, Goss *et al*[23] published a retrospective review of 229 patients with a shorter DFS and OS, although patients were more likely to have chemotherapy if they had node positive (and thus poorer prognosis) disease. Another review from the MD Anderson Cancer Center examined the treatment of 135 men in the adjuvant treatment. An OS benefit was seen for those receiving systemic therapy (32 received chemotherapy and 38 received endocrine therapy) compared with those who did not (HR=0.57).[24] A study included that 50 patients supported the use of adjuvant therapies, with favourable survival benefits.[25] However, several small sample studies show conflict results that male BC could benefit from chemotherapy because there are several parameters impacting the decision of using chemotherapy or not. Our results show that there are more patients with later clinical stage or HER2 positive in chemotherapy group when compared with non-chemotherapy group. It may be a reason explaining why chemotherapy could not have a favourable impact on this research. The HER2 and numbers of positive LNs have important relationship with OS as poor prognostic factors, and chemotherapy could play a well-prognostic factor, which was similar to Goss *et al*[23] As a result, although chemotherapy could not achieve a significant difference in OS by log-rank test, it shows an important influence on OS by COX model test. Male BC is rare, but heightened awareness of the increased risk in certain men by both physicians and patients may results in earlier detection.

We collected 134 cases during a long following-up time, and it is a relatively large-scale retrospective study. In our study, we discovered that male BC who received chemotherapy have much more poor prognostic clinical and pathological factors than those who did not receive chemotherapy. But these two groups reached almost the same DFS. From this point, we can conclude that chemotherapy may have some protective value for those male BC patients with high risk of recurrence/metastasis. The inconsistency of chemotherapy effect on DFS and OS can be partly explained by the OS definition (death events to all causes). From the stratified analysis, we discovered that male BC could have benefited from chemotherapy, especially with more numbers of LN metastasis, and HER2 over-expression. The utility of chemotherapy should be considered in the high-risk level of recurrence/metastasis in male BC, although we did not have prospective research data for this result due to the very low incidence of male BC.

Since our study collected most patients' data early in 1990s, some of the patients' data would be different from now because of changes in diagnosis, examinations and IHC standards. This may cause the bias of chemotherapy strategy in male BC. Simultaneously, we may take gene testing and AR detection into consideration for our future study.

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Contributors XFY, CW and HJY designed this study. XFY was in charge of statistics. CW were in charge of writing the article, BC checked up the pathological data, CLL, DBC and YY were in charge of data collection and following-up work.

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