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ORIGINAL ARTICLE

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Is adjuvant chemotherapy necessary for patients with microinvasive breast cancer after surgery?

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ABSTRACT

Objective: Survival and treatment of patients with microinvasive breast cancer (MIBC) remain controversial. In this paper, we evaluated whether adjuvant chemotherapy is necessary for patients with MIBC to identify risk factors influencing its prognosis and decide the indication for adjuvant chemotherapy.

Methods: In this retrospective study, 108 patients with MIBC were recruited according to seventh edition of the staging manual of the American Joint Committee on Cancer (AJCC). The subjects were divided into chemotherapy and non-chemotherapy groups. We compared the 5-year disease-free survival (DFS) and overall survival (OS) rates between groups. Furthermore, we analyzed the factors related to prognosis for patients with MIBC using univariate and multivariate analyses. We also evaluated the impact of adjuvant chemotherapy on the prognostic factors by subgroup analysis after median follow-up time of 33 months (13-104 months).

Results: The 5-year DFS and OS rates for the chemotherapy group were 93.7% and 97.5%, whereas those for the non-chemotherapy group were 89.7% and 100%. Results indicate that 5-year DFS was superior, but OS was inferior, in the former group compared with the latter group. However, no statistical significance was observed in the 5-year DFS (P=0.223) or OS (P=0.530) rate of the two groups. Most relevant poor-prognostic factors were Ki-67 overexpression and negative hormonal receptors. Cumulative survival was 98.2% *vs*. 86.5% between low Ki-67 (≤20%) and high Ki-67 (>20%). The hazard ratio of patients with high Ki-67 was 16.585 [95% confidence interval (CI), 1.969-139.724; P=0.010]. Meanwhile, ER(-)/PR(-) patients with MIBC had cumulative survival of 79.3% compared with 97.5% for ER(+) or PR(+) patients with MIBC. The hazard ratio for ER(-)/PR(-) patients with MIBC was 19.149 (95% CI, 3.702-99.057; P<0.001). Subgroup analysis showed that chemotherapy could improve the outcomes of ER(-)/PR(-) patients (P=0.014), but not those who overexpress Ki-67 (P=0.105).

Conclusions: Patients with MIBC who overexpress Ki-67 and with negative hormonal receptors have relatively substantial risk of relapse within the first five years after surgery. However, adjuvant chemotherapy can only improve the outcomes of ER(-)/PR(-) patients, but not those who overexpress Ki-67. Further studies with prolonged follow-up of large cohorts are recommended to assess the prognostic significance and treatment of this lesion.

KEYWORDS Microinvasive breast cancer; adjuvant chemotherapy; survival

Introduction

Microinvasive breast cancer (MIBC) has been paid much attention since the term "microinvasive" in breast pathology was introduced by Lagios in 1982[1]. Microinvasiveness is characterized by invasion of less than 1 mm size. Various definitions have been used to define MIBC[2-4]. In 1997, the fifth edition of the staging manual of the American Joint Committee on Cancer (AJCC) defined MIBC as "the extension of cancer cells beyond the basement membrane into adjacent tissues with no focus more than 0.1 cm in greatest dimension", and AJCC was the first organization to recognize a specific T stage as pT1mic[5]. Although the World Health Organization (WHO) classification of tumors had admitted and supplemented interpretations for the definition by the fifth edition of the AJCC staging manual published in 2003[6], the definition seemed to have been used generally until the seventh edition of the AJCC staging manual[7]. Moreover, MIBC, which is one of the rare breast carcinomas, has incidence rate ranging from 0.24% to 3.3%[8,9] based on various definitions. Consequently, the clinical characteristics, prognosis, and treatments of MIBC are highly controversial.

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Current studies focused on the clinical characteristics of MIBC[10-12]. However, only a few studies have evaluated the survival and treatment, especially adjuvant chemotherapy after surgery, for patients with MIBC.

The aim of this study was to evaluate the necessity of adjuvant chemotherapy for patients with MIBC, identify risk factors influencing the prognosis of MIBC, and decide the indication for adjuvant chemotherapy.

Materials and methods

Patients

Patients with MIBC were recruited as defined by the seventh edition of the AJCC staging manual from January 2006 to June 2013 in Tianjin Medical University Cancer Institute and Hospital. The following patients were excluded: with bilateral primary breast cancers; received neoadjuvant chemotherapy; previously diagnosed with invasive breast cancer; or with first tumor lumpectomies not conducted in our hospital and no information of specimens. All eligible patients underwent physical examination, chest radioscopy, mammography, electrocar diogram (ECG), complete blood counts, routine biochemical tests, and ultrasound (US) (breasts, axillary lymph nodes, supraclavicular and infraclavicular lymph nodes, abdomen, and pelvis) before surgery. Each patient was treated with breast-conserving surgery or mastectomy (most with axillary lymph node dissection) according to the standard guideline. This retrospective study was approved by the institutional ethical board. Written informed consent was obtained before each patient was provided with each treatment.

Pathological and immunohistochemical (IHC) assessment

All surgical specimens were serially sectioned, sequentially submitted in their entirety when approximately <5 mm in greatest dimension, and then reviewed to be MIBC by two breast pathologists at the Tianjin Medical University Cancer Institute and Hospital. The status of ER, PR, HER2, Ki-67, and P53 were determined by IHC staining, which was performed through a standard operating procedure by the Department of Pathology. Cutoff value for ER or PR positivity was at least 10% of tumor cells with positive nuclear staining. HER-2 staining was classified into four groups (0, 1+, 2+, or 3+). Ki-67 and P53 staining were expressed as the percentage of positive cells (at least 1,000) with nuclear staining in each case. The same pathologists evaluated IHC staining of pathological sections from each case and performed section examination separately. After examination, the two pathologists compared their staining outcomes.

Endpoints

Disease-free survival (DFS) and overall survival (OS) were endpoints of this study. DFS was measured from the time of diagnosis until recurrence and metastasis in any site, and OS was defined as the time from diagnosis to death from any cause.

Statistical analysis

Patient characteristics of the two groups (chemotherapy *vs.* non-chemotherapy) were compared by R×C Pearson's χ^2-test (or Fisher's exact test when appropriate). Survival curves were constructed by Kaplan–Meier method and compared by log-rank test. All P values were two-sided, and $P<0.05$ was considered statistically significant. Log-rank test and Cox regression analysis were used to conduct univariate and multivariate analyses to identify the risk factors of survival. We conducted the subgroup analysis to evaluate the impact of adjuvant chemotherapy on the risk factors associated with survival of MIBC. All statistical analyses were performed using SPSS software version 20.0.

Results

We retrospectively collected 19,656 breast cancer patients from January 2006 to June 2013 in Tianjin Medical University Cancer Institute and Hospital. Among the 19,656 patients, 118 women were diagnosed with MIBC according to the definition by the seventh edition of the AJCC staging manual. Ten of the 118 patients diagnosed with MIBC were excluded, because one patient had been previously diagnosed with invasive breast cancer, one patient accepted neoadjuvant chemotherapy before surgery, and eight patients lacked information on follow-up. The rate of loss was appropriately 6.8%. Finally, 108 patients were eligible for analysis.

Among the 108 patients with MIBC, 79 patients were given chemotherapy after surgery, while the remaining 29 did not accept chemotherapy. **Table 1** shows the clinical and pathologic characteristics of the chemotherapy and non-chemotherapy groups. Statistical significance was observed in both menopause and estrogen receptor status.

Median follow-up was 33 months (range 13–104 months). Nine patients had positive axillary lymph nodes, and 8

Table 1 Comparison of patients' characteristics between chemotherapy and non-chemotherapy

	No. of chemotherapy	No. of non-chemotherapy	*P*
All	*n*=29	*n*=79	
Age, years			0.098
<40	8	11	
≥40	21	68	
Abortion			0.218
Yes	21	47	
No	8	32	
Menopause			0.024
Yes	8	41	
No	21	38	
Family history			0.948
Yes	9	24	
No	20	55	
Max diameter			0.378
~2	11	29	
2-5	14	38	
5~	0	6	
Unknown	4	6	
Grade			0.265
G_1	9	38	
G_2-G_3	2	3	
Unknown	18	38	
Necrosis			0.948
Yes	9	24	
No	20	55	
Lymph nodes			0.266
Positive	1	8	
Negative	28	71	
ER			0.018
Positive	16	24	
Negative	13	55	
PR			0.443
Positive	13	29	
Negative	16	50	
ER/PR			0.172
ER(+)/PR(+)	5	69	
ER(-) PR(-)	24	10	
Her2			0.219
-/1+/2+	22	50	
3+	7	29	
Ki-67			0.187
≤20%	11	45	
>20%	17	35	
P53			0.102
Positive	11	44	
Negative	18	35	

patients had breast-related positive events, such as local recurrence, distant metastasis, and death. The rate of positive events was 7.4%. **Table 2** shows the characteristics of the 8 patients with breast-related positive events, 5 of which belonged to the chemotherapy group, and the rest in the non-chemotherapy group. Among the 8 patients, one patient had chest wall relapsed after 43 months from the time of diagnosis, one patient had controlateral breast tumor metastasis 14 months after surgery, one patient manifested metastasis of supraclavicular lymph nodes, and the rest had distant metastasis at 18, 21, 26, 43, or 64 months after the surgical operation. Two patients died from breast-associated causes, such as pulmonary and liver metastasis. **Table 2** shows that 6 patients had negative hormonal receptors, whereas 2 had positive hormonal receptor. In addition, only one patient had Ki-67≤20%, and the rest had Ki-67>20%. In addition, 7 of these patients had positive events related to breast cancer within 5 years after surgical operation.

The 5-year DFS rates for patients in the chemotherapy and non-chemotherapy groups were 93.7% and 89.7%, respectively. The OS rate in the chemotherapy group was 97.5%, compared with 100% in the other group. **Figures 1** and **2** illustrate the curves of 5-year DFS and OS of both groups. No significant difference in 5-year DFS (*P*=0.223) or OS (*P*=0.530) was found between the two groups (**Table 3**).

We assessed the relationship between biological features and breast-associated positive events using the log-rank and Cox proportional regression analysis. Ki-67 and ER/PR were the most significant prognostic factors for MIBC in both univariate (**Table 4**) and multivariate analyses (**Table 5**). Cumulative survival of patients with tumors bearing low Ki-67 was 98.2%, compared to 86.5% for patients with tumors bearing high Ki-67 (**Figure 3**). Hazard ratio (HR) for patients

Table 2 Characteristics of 8 patients who developed breast-related events

No.	Age	Menopause	Lymph nodes	ER	PR	Her2	Ki-67	Chemotherapy	Events	DFS (months)
1	36	No	-	+	+	-	50%	Yes	Local	43
2	58	Yes	-	-	-	-	70%	No	Controlateral	14
3	36	No	-	+	-	-	65%	Yes	Distant	26
4	41	Yes	-	-	-	3+	50%	No	Distant	21
5	51	Yes	+	-	-	3+	40%	Yes	Distant	18
6	50	No	+	-	-	-	40%	No	Local	38
7	69	Yes	-	-	-	-	1%	No	Distant	64
8	49	No	-	-	-	1+	85%	No	Distant	43

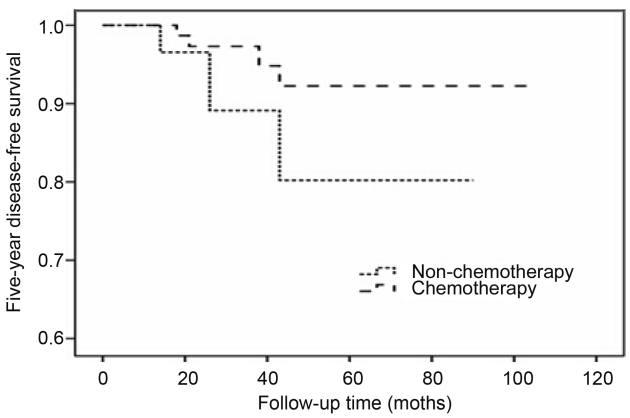

Figure 1 Kaplan-Meier plots of 5-year DFS comparing chemotherapy *vs*. non-chemotherapy for patients with MIBC.

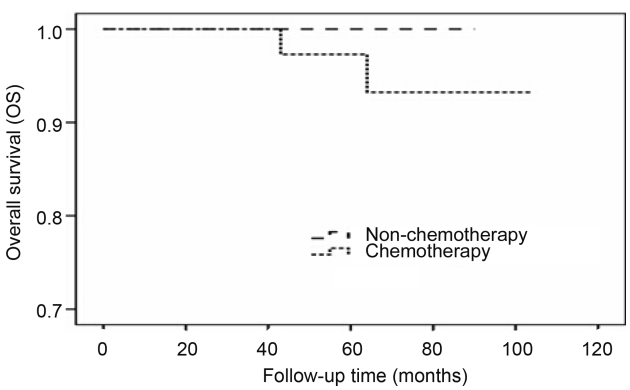

Figure 2 Kaplan-Meier plots of OS comparing chemotherapy *vs*. non-chemotherapy for patients with MIBC.

Table 3 Five-year DFS and OS of patients with MIBC between chemotherapy and non-chemotherapy groups

	All	Chemotherapy	Non-chemotherapy	*P*
5-year DFS	92.6%	93.7%	89.7%	0.223
OS	98.1%	97.5%	100%	0.530

Table 4 Univariate analysis on 108 patients with MIBC (continued)

	No. of positive events	No. of negative events	*P*
All	*n*=8	*n*=100	
Age, years			0.567
~40	2	17	
40~	6	83	
Abortion			0.464
Yes	6	62	
No	2	38	
Menopause			0.642
Yes	3	46	
No	5	54	
Family history			0.215
Yes	4	29	
No	4	71	
Max diameter (cm)			0.133
~2	6	34	
2-5	2	50	
5~	0	6	
Unknown	0	10	

Table 4 (*continued*)

Table 4 (*continued*)

	No. of positive events	No. of negative events	*P*
Grade			0.058
G_1	2	45	
G_2-G_3	3	2	
Unknown	2	53	
Necrosis			0.723
Yes	2	31	
No	6	69	
Lymph nodes			0.076
Positive	2	7	
Negative	6	93	
ER			0.464
Positive	2	38	
Negative	6	62	
PR			0.112
Positive	1	41	
Negative	7	59	
ER/PR			0.001
ER(+)/PR(+)	2	77	
ER(-) PR(-)	6	23	
Her2			0.603
-/1+/2+	6	66	
3+	2	34	
Ki-67			0.021
~20%	1	55	
20%~	7	45	
P53			0.127
Positive	2	53	
Negative	6	47	

Table 5 Multivariate analysis in 108 patients with MIBC

Variables	HR	95% CI	*P*
ER(-) PR(-)	19.149	3.702-99.057	<0.001
Ki-67	16.585	1.969-139.724	0.010

with high Ki-67 was 16.585 [95% confidence interval (CI), 1.969–139.724; *P*=0.010]. Patients with high Ki-67 (>20%) still had a significantly poorer survival, compared with patients with lower Ki-67 (≤20%, *P*=0.021). Meanwhile, patients with ER(-)PR(-) tumors had cumulative survival of 79.3%, whereas those with ER(+)/PR(+) tumors had 97.5% (**Figure 4**). HR for patients with ER(-)/PR(-) tumors was 19.149 (95% CI, 3.702–99.057; *P*<0.001). **Figure 4** shows that patients tested negative for both hormonal receptors had significantly poorer survival (*P*=0.001).

We conducted subgroup analysis to evaluate the impact of chemotherapy on Ki-67 and the status of hormonal receptors. **Table 6** shows that chemotherapy could improve the outcomes of ER(-)/PR(-) patients (*P*=0.014), but not those who overexpress Ki-67 (*P*=0.105).

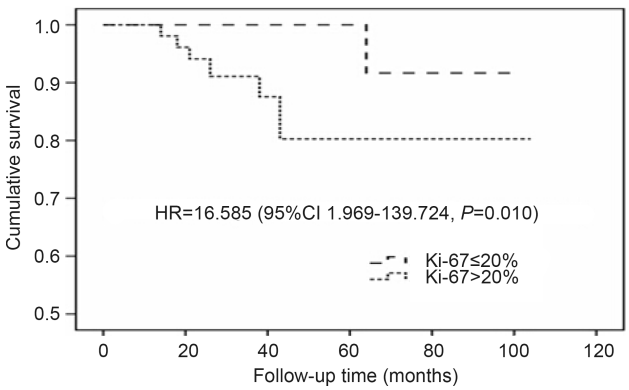

Figure 3 Kaplan-Meier plots of cumulative survival comparing elevated Ki-67 (>20%) *vs*. low Ki-67 (≤20%) for patients with MIBC.

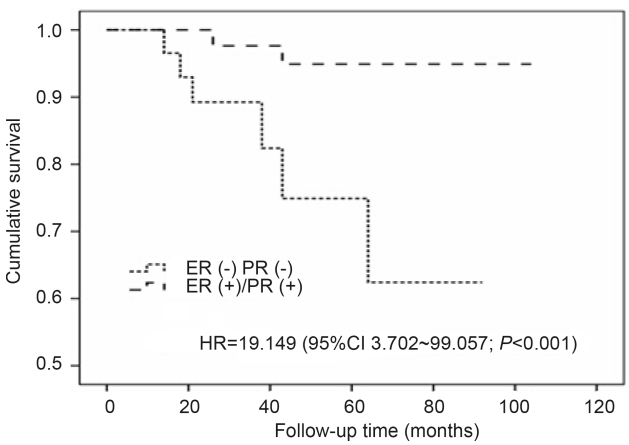

Figure 4 Kaplan-Meier plots of cumulative survival comparing ER(-) PR(-) *vs*. ER(+)/PR(+) for patients with MIBC.

Table 6 Subgroup analysis of Ki-67 and the status of ER and PR

Subgroups	Factor	No. of positive events	No. of negative events	*P*
Ki-67≤20%	Chemotherapy	0	11	
	Non-chemotherapy	1	44	0.674
Ki-67>20%	Chemotherapy	3	13	
	Non-chemotherapy	4	32	0.105
ER(+)/PR(+)	Chemotherapy	2	3	
	Non-chemotherapy	0	69	0.083
ER(-) PR(-)	Chemotherapy	1	23	
	Non-chemotherapy	5	10	0.014

Discussion

MIBC is reported to be a distinct entity from pure ductal carcinoma *in situ* (DCIS) and represents the interim stage in the progression from DCIS to invasive ductal carcinoma (IDC)[12,13]. However, MIBC accounts for less than 1%[12,14] of all newly diagnosed breast cancers according to the criteria of the fifth edition of AJCC staging manual[5]. MIBC accounted for 0.56% of all patients recruited in our study.

Controversy on MIBC is related to the limited information available on the prognosis of this disease[15]. The rate of axillary metastases at diagnosis was 8.3% in our study, which was within the 6%–11% rate of axillary metastases reported in other MIBC studies[9,14,16]. Long-term DFS ranging between 91% and 100% had been reported[3,17]. Factors related to good prognosis were low-grade[12] and ER(+) disease[17]. However, these studies suffered from small sample size. In the current study, we collected 108 patients with MIBC according to the definition of the seventh edition of AJCC. The 5-year DFS was 92.6%, and OS was 98.1%. Elevated expression of Ki-67 was found to be one of the significant predictors of poor outcome. HR for patients with high Ki-67 tumors was 16.585 (95% CI 1.969–139.724, P=0.010) with cumulative survival of only 86.5%. The role of Ki-67 was reported in a study with 425 assessable patients with pT1a and pT1b, where the value of Ki-67 overexpression was significantly correlated with poor outcome[18], similar to this study. These results indicated a possible role of Ki-67 in the identification of high-risk patients. Alternative poor prognostic factor was the characteristic of having both negative hormonal receptors. HR for patients with negative hormonal receptors was 19.149 (95% CI, 3.702–99.057; P<0.001), whose cumulative survival was only 79.3%. The role of status for hormonal receptors was commonly reported. However, previous studies reported that the status of single hormonal receptor (ER or PR) was related to the outcome[19]. We found for the first time that ER(-)/PR (-) patients with MIBC had poorer prognosis compared with patients with MIBC who were either ER (+) or PR (+). This characteristic was primarily due to the fact that patients of MIBC with ER(+) or PR(+) and ER(+)PR(+) were provided with adjuvant endocrinotherapy. By contrast, ER(-)/PR(-) patients with MIBC were not administered endocrine treatment, indicating the function of endocrinotherapy.

Recommending treatment for patients with MIBC who had insufficient information caused by small sample size and varying definitions is quite difficult. Adjuvant chemotherapy plays a very important role in breast cancer treatment, especially for triple-negative breast cancer[20,21]. However, chemotherapy is considered synonymous to cytotoxic treatment. Tumor cells are wiped out, but normal cells are also injured, in chemotherapy which leads to various adverse reactions. Thus, risk–benefit balance of chemotherapy should be considered to avoid widespread use of aggressive treatments for patients with MIBC.

To our knowledge, only a few studies have provided information on adjuvant treatment received by patients with MIBC. Our study is unique since we were the first to select patients with MIBC to review the necessity of adjuvant chemotherapy after surgical operation. We found no statistical significance on the 5-year DFS or OS between chemotherapy and non-chemotherapy groups. However, 5-year DFS was superior, but OS was inferior, in the chemotherapy group compared with the other group. This result indicates that chemotherapy may have short-term benefits for patients with MIBC. However, long-term chemotherapy may produce side effect on patients with MIBC caused by adverse events. Therefore, selecting the best implication of adjuvant chemotherapy for MIBC is important. According to our subgroup analysis, ER(-)/PR(-)patients had the best implication, which is reported for the first time.

In addition, difference was found in the menopause and estrogen receptor status between the chemotherapy and non-chemotherapy groups. This result implies that the proportion of ER(+) and post-menopause was higher in non-chemotherapy than chemotherapy group in our study. On one hand, the diversity may be attributed to empirical therapy of clinicians who tend to provide chemotherapy for

patients with negative hormonal receptors. On the other hand, the majority of postmenopausal patients were old women with some medical diseases. These patients were not advised to accept chemotherapy by oncologists considering the risk of chemotherapy. However, despite the above difference, our conclusions that menopause and estrogen receptor status were neither connected with the outcome of MIBC were rational (**Tables 4** and **5**).

Thus, adjuvant chemotherapy should be cautiously administered to patients with MIBC. Adjuvant chemotherapy can be considered to patients with negative hormonal receptors when costs and benefits of adjuvant chemotherapy are weighed accurately. These patients have substantial risk of relapse within the first 5 years after surgical operation, contrary to that reported by Rosner[2]. The report of Rosner published in *Cancer* indicated that MIBC was an entirely curable disease when treated by mastectomy alone, without the need for adjuvant therapy, regardless of the status of other prognostic factors, such as tumor size, histologic differentiation, age, or steroid receptor status through mean follow-up of 57 months. The difference in results may have been caused by several reasons, such as small sample and short follow-up time. However, the most important reason was different diagnostic criteria. The diagnosis of MIBC in Rosner's study followed the principles elucidated by Schwartz that DCIS had limited microscopic stromal invasion below the basement membrane in one or several ducts, but not invading more than 10% of the surface of the histologic sections examined[4]. In other words, the definition by Schwartz, which is beyond the definition by the seventh edition of the AJCC staging manual, should include part of IDC classified as pT1a or pT1b according to TNM staging in the seventh edition of AJCC Staging Manual published in 2010[22].

However, our study has limitations. We cannot establish firm conclusions because of the small sample size and short follow-up period.

Conclusions

Patients with MIBC have the good prognosis. However, patients who overexpress Ki-67 and with negative hormonal receptors have relatively substantial risk of relapse within the first 5 years after surgical operation. Adjuvant chemotherapy can only improve the outcomes of patients with negative hormonal receptors, but not those who overexpress Ki-67. Further studies with prolonged follow-up of large cohort are warranted to assess the prognostic significance and treatment of this lesion.

Conflict of interest statement

No potential conflicts of interest are disclosed.

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