RESEARCH ARTICLE

Clinicopathological and Prognostic Characteristics of Triple-Negative Breast Cancer (TNBC) in Chinese Patients: A Retrospective Study

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Abstract

Aims: To determine the clinical, pathological and prognostic features associated with triple-negative breast cancer (TNBC). Methods: Clinical and histologic data of 21,749 breast cancer patients who were treated at Tianjin Medical University Cancer Institute and Hospital between July 2002 and December 2011 were collected. Patients were divided into two groups: those with TNBC and those with other types of breast cancer. Patients and tumor characteristics were compared between the two groups using the Chi-square test. The prognostic results of 9,823 patients in the study population were also analyzed to determine long-term survival rates in the two groups of breast cancer patients. Results: Among the breast cancer patients treated in our hospital between 2003 and 2011, 10.4%-13.5% of them had triple-negative breast cancers. Data analyses revealed significant differences in disease onset age, family history of breast cancer, tumor size, tumor histologic grade, lymph note positivity and metastatic status between TNBC and non-TNBC patients. There were also significant differences in 5-year, 7-year and 9-year disease-free and 7-year and 9-year overall survival probability between the groups. Conclusions:TNBC are associated with younger disease onset age, larger tumor size, higher rate of axillary lymph node positivity, and higher tumor histologic grade. TNBC is also related to family history of breast cancer, increased metastatic risk and poor prognosis.

Keywords: Breast cancer - triple negative - prognosis - grade - age at onset - lymph node metastasis

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Introduction

Breast cancer is the most common type of cancer in women worldwide. It accounts for 7-10% of all types of human cancers. In females worldwide, breast cancer accounts for 23% of the total new cancer cases and 14% of total cancer deaths in 2008 (DeSantis et al., 2011; Jemal et al., 2011). The incidence of breast cancer has been increasing rapidly, particularly in young women. Breast cancer has become the leading cause of cancer deaths among women in urban China (Zhao et al., 2010).

Breast cancer is a heterogeneous disease with distinct pathological and histological features, and can be classified into several subtypes based on the expression of 3 receptors: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu). The breast tumors that lack the expression of all these receptors are termed triple-negative breast cancers (TNBC) (Oakman et al., 2011). TNBC is often classified as a basal-like tumor associated with high malignancy, high recurrence rate and poor prognosis (Bertucci et al., 2012). Unlike other types of breast cancer, TNBC is not responsive to conventional hormonal and targeted therapies due to the lack of the expression of receptors. Therefore, no effective therapeutic strategy is currently available for the treatment of TNBC. The adjuvant treatment for TNBC patients is non-targeted therapy. Its successful rate is not comparable to that of targeted therapies for ER/PR positive or HER2 positive patients (Piccart-Gebhart et al., 2005; Romond et al., 2005; Clarke et al., 2008). Despite recent advance in the study of TNBC, the molecular biology and pathology of TNBC are not well understood. More information is needed to assist clinicians for the better management of TNBC.

TNBC displays a significant racial disparity in the incidence and outcomes. For example, African American women have a higher incidence risk for TNBC and have a worse 5-year survival rate than Caucasian women with TNBC (Menashe et al., 2009; Blows et al., 2010; Ray et al., 2010). Few reports have focused on the TNBC incidence

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and survival in Chinese TNBC patients. In this study, we sought to evaluate the differences in clinical features and outcomes of patients with TNBC and with other types of breast cancer. The result may further provide information for the development of better TNBC treatment strategies.

Materials and Methods

Study population and data collection

The clinical records of breast cancer patients who were diagnosed and treated at Tianjin Medical University Cancer Institute and Hospital between July 2002 and December 2011 were reviewed. Patients with sufficient clinical information (21749 cases) were included in the study. Within this study population, 9823 of them had sufficient follow-up information for the evaluation of their long-term efficacies of the treatment.

Determination of breast cancer subtypes

ER and PR positive were defined as positive immunohistochemical staining in more than 10% of tumor cells. HER-2 status was determined according to the guideline recommended by College of American Pathologists (Wolff et al., 2007). Immunohistochemistry assay with anti-HER2 antibodies was used to identify HER negative (0 and 1+) or positive (2+ and 3+). HER2 gene amplification was determined by fluorescent in situ hybridization (FISH). Tumors with a positive FISH result were considered as HER2 positive. Tumors negative for ER, PR and HER2 were considered as triple-negative.

Determination of survival rate

Disease-free survival period was defined as the period from the date of the disease diagnosed to the date when local or distant recurrence occurred. The overall survival period was defined as the time span from the date of diagnosis to the date of death or loss of the follow-up. All follow-ups ended on December 31, 2011.

Statistical methods

SPSS version 16.0 software (Chicago, Ill) was used for data analysis. Disease-free survival and overall survival durations were analyzed with the Kaplan-Meier method. The survival distribution was compared between the groups using Log-Rank test. Comparisons among clinical variables were performed with Person Chi-square test. All tests were 2-tailed and the statistical significance was set as $P<0.05$.

Results

Breast cancer incidence and prevalence of TNBC

During the last 9 years (2003-2011), the annual number of diagnosed breast cancer cases increased significantly, from 966 cases in 2003 to 3049 cases in 2011 (Figure 1A). The percentages of TNBC in those breast cancer cases were 10.39%, 11.97%, 11.42%, 11.02%, 12.01%, 13.08%, 13.16%, 13.46% and 13.13% in year 2003, 2004, 2005, 2006,2007, 2008, 2009, 2010 and 2011 respectively (Figure 1B). Overall, TNBC represented 12.18% of all breast cancer cases diagnosed at our hospital within this

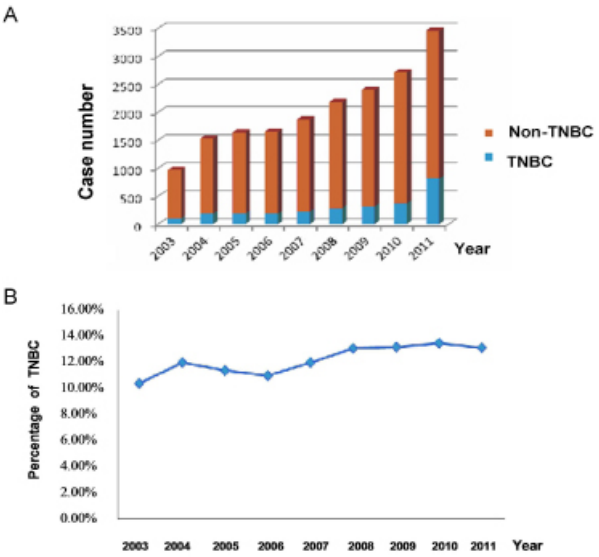

Figure 1. Breast Cancer Incidence and TNBC Prevalence. A. Annual case number of triple-negative breast cancer (TNBC) and other types of breast cancer (non-TNBC) treated in the hospital; B. Percentage of TNBC cases in the annually diagnosed breast cancer cases

9-year period. This result indicted that the rate of TNBC did not increase significantly despite a dramatic increase of total breast cancer incidence.

Comparison of clinical features of TNBC and non-TNBC

There were total of 25507 breast cancer patients received surgeries at Tianjin Medical University Cancer Institute and Hospital between July 2002 and December 2011. Among those cases, 2882 of them did not have sufficient follow-up data and 876 of them did not have sufficient clinical records. Therefore, 21749 cases were included in this study. These cases were divided into two groups: TNBC and other types of breast cancer (non-TNBC). The clinical and pathological characteristics of TNBC and non-TNBC are shown in Table 1. The patient age range at the time of diagnosis was 18 to 89, with a median age of 51. In the TNBC group, the youngest patient was 21 years old and the oldest was 89 years old. The median age of TNBC patients was 50. In the non-TNBC group, the youngest patient was 18 years old and the oldest was 87 years old. The median age of this group was 54. The Chi-square test revealed a statistically significant difference in the mean age of disease onset between TNBC and non-TNBC groups. The mean age of TNBC patients was 49 and the mean age of non-TNBC patients was 54 ($P=0.003$) (Table 1).

In TNBC patients, the termination of menstrual periods was caused by ovariectomy or hysterectomy in 214 patients and by natural menopause in 989 patients. The mean menopausal age of TNBC patients was 53 years old. Pre-menopausal women accounted for 54.59% (1446) of all TNBC patients. In non-TNBC patients, 8759 of them were post-menopausal women and 1182 of them received ovariectomy or hysterectomy. The mean age of menopause in this group of patient was 53 years old. Pre-menopausal women accounted for 54.14% (10341) of all non-TNBC patients. No statistical difference was found in the menstrual status between TNBC and non-TNBC

Table 1. Clinical and Pathologic Characteristics of Patients with TNBC and Non-TNBC

Characteristic	Case (%)		χ^2 value	*P* value
	TNBC (n=2649)	Non-TNBC (n=19100)		
Age (years)			85.60	0.000
≤35	105 (3.96%)	1780 (9.32%)		
35-55	1578 (59.57%)	11097 (58.10%)		
≥55	966 (36.47%)	6223 (32.58%)		
Menopausal status			0.174	0.677
Premenopausal	1446 (54.59%)	10341 (54.14%)		
Postmenopausal	1203 (45.41%)	8759 (45.86%)		
Family history			3.871	0.000
No	923 (34.84%)	12822 (67.13%)		
Yes	1726 (65.16%)	6278 (32.87%)		
Tumor size in diameter			4.631	0.000
≤2cm	554 (20.91%)	1876 (9.82%)		
2cm-5cm	687 (25.94%)	8994 (47.09%)		
≥5cm	1408 (53.15%)	8230 (43.09%)		
Clinical stage			0.929	0.920
0	373(14.08%)	2659(13.92%)		
I	505(19.06%)	3612(18.91%)		
II	668(25.22%)	4712(24.67%)		
III	562(21.22%)	4177(21.87%)		
IV	541(20.42%)	3940(20.63%)		
Pathological stage			0.03	0.985
invasive ductal carcinoma	2172(81.99%)	15664(82.01%)		
invasive lobular carcinoma	344(12.99 %)	2484(13.00%)		
other	133(5.02%)	952(4.98%)		
Histologic grade			4.739	0.000
1	618(23.33%)	4154(21.75%)		
2	1118(42.20%)	8721(45.66%)		
3	913(34.47%)	6225(32.59%)		
Lymph node invasion			8.282	0.000
No	758 (28.61%)	12075 (63.22%)		
Yes	1891 (71.39%)	7025 (36.78%)		
Metastasis			4.946	0.000
No	2116(79.88%)	17929(93.87%)		
Yes	533(20.12%)	1171(6.13%)		
Local recurrence			1.274	0.259
No	2388(90.15%)	17337(90.77%)		
Yes	261(9.85%)	1763(9.23%)		

patients (*p*=0.677) (Table 1).

We also examined the family history of breast cancer in those patients. Among TNBC patients, 1726 (65.17%) of them had a family history of breast cancer. Further analysis revealed that 882 patients had first-degree relatives with breast cancer, 552 patients had second-degree relatives with beast cancer and 292 patients had third-degree relatives with breast cancer. Among those TNBC patients with a family history of breast cancer, 991 of them had one breast cancer family member, 357 of them had two breast cancer family members, and 378 of them had three or more breast cancer family members. In the group of non-TNBC patients, 6278 (32.87%) of them had a family history of breast cancer. Among those, 3208 patients had first-degree relatives with breast cancer, 2008 patients had second-degree relatives with beast cancer and 1062 patients had third-degree relatives with breast cancer. In non-TNBC patients with a family history of breast cancer, 4227 of them had one breast cancer family member, 1607 of them had two breast cancer family members, and 444 of them had three or more breast cancer family members. The Chi-square test showed a significantly higher prevalence of breast cancer in the family members of TNBC patients compared to non-TNBC patients (*P*=0.000). However, the distribution of breast cancer family members, among first, second and third degree relatives, in TNBC and non-TNBC patients did not differ significantly (*P*=1.00) (Table 1).

The original tumor size (in diameter) was also compared between TNBC and non-TNBC patients. In TNBC patients, 554 (20.91%) of them had tumors smaller than 2 cm, 687 (25.94%) patients had tumors with size between 2 to 5 cm, and 1408 (53.15%) patients had tumors larger than 5 cm. In non-TNBC patients, 1876 (9.82%) of them had tumors smaller 2 cm, 8994 (47.09%) patients had tumors with size between 2 to 5 cm, and 8230 (43.09%) patients had tumors larger than 5 cm. The Chi-square test showed a statistical difference in the tumor size between TNBC and non-TNBC patients (*p*=0.00). Overall, TNBC patients had bigger tumors than non-TNBC patients (X^2=87.583, *p*=0.000) (Table 1).

The clinical stage of a breast cancer was determined according to the results of physical examine, biopsy and imaging tests. In TNBC patients, 373 (14.08%) patients were diagnosed with the disease at Stage 0, 505 (19.06%) patients at Stage I, 668 (25.22%) patients at Stage II, 562 (21.22%) patients at Stage III and 541 (20.42%) patients at Stage IV. In non-TNBC patients, 2659 (13.92%) patients were diagnosed with the disease at Stage 0, 3612 (18.91%) patients at Stage I, 4712 (24.67%) patients at Stage II, 4177 (21.87%) patients at Stage III and 3940 (20.63 %) patients at Stage IV. No difference in the distribution of the clinical stage of tumor between TNBC and non-TNBC patients was found based on the Chi-square test (*P*=0.920) (Table 1).

The pathological stage of those breast cancers was also evaluated. In TNBC cases, there were 2172 (81.99%) cases of invasive ductal carcinoma and 344 (12.99%) cases of invasive lobular carcinoma. In non-TNBC cases, there were 15664 (82.01%) cases of invasive ductal carcinoma and 2484 (13%) cases of invasive lobular carcinoma. Again, no difference in the distribution of the pathological stage of tumor was found between these two groups based on the Chi-square test (P=0.985) (Table 1).

The histologic grade of TNBC and non-TNBC was also compared. In TNBC cases, there were 618 (23.33%) Grade 1 tumors, 1118 (42.20%) Grade 2 tumors and 913 (34.47%) Grade 3 tumors. In non-TNBC cases, there were 4154 (21,75%) Grade 1 tumors, 8721 (45.66%) Grade 2 tumors and 6225 (32.59%) Grade 3 tumors. The Chi-square test showed a significant difference in the distribution of histologic grade of the diagnosed TNBC and non-TNBC (*P*=0.00) (Table 1).

Comparison of the lymph node positivity in TNBC and non-TNBC patients revealed that there were 758 (28.61%) TNBC patients and 12075 (63.22%) non-TNBC patients with negative lymph nodes. On the other hand, 1891 (71.37%) TNBC patients and 7025 (36.78%) non-TNBC patients had positive lymph nodes. The Chi-square test showed a significant difference in the lymph node positivity between TNBC and non-TNBC patients. The rate of positive lymph node was much higher in TNBC patients (Table 1).

In TNBC patients, 2116 of them had a nonmetastatic

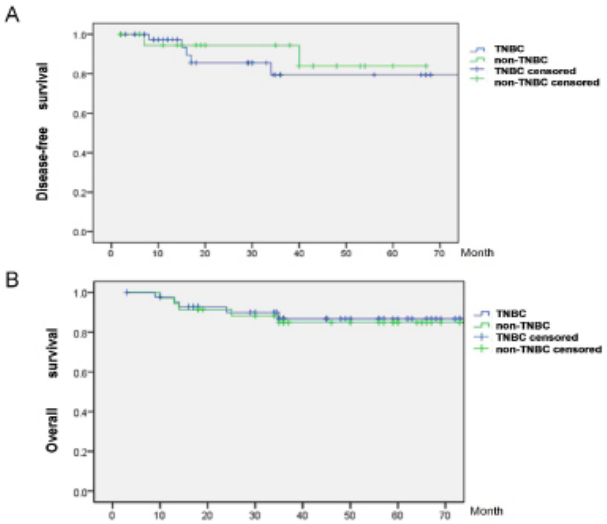

Figure 2. Kaplan-Meier Plot of 5-year Disease-free Survival (A) and 5-years Overall Survival (B) for Patients with TNBC and Non-TNBC

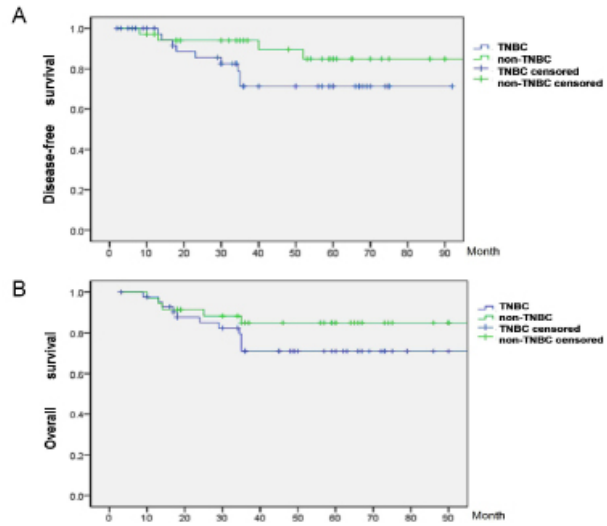

Figure 3. Kaplan-Meier Plot of 7-year Disease-free Survival (A) and 7-year Overall Survival (B) for Patients with TNBC and Non-TNBC

cancer and 533 (20.12%) of them had a metastatic cancer. The metastatic rate in patients with the tumor smaller than 2 cm was 19.45%, while the metastatic rates in patients with the tumor between 2-5 cm and larger than 5cm were 28.45% and 32.18% respectively. This result indicated that the larger tumor size the higher risk of metastasis (p<0.005). Among those TNBC patients with a metastatic cancer, the cancer was metastasized to the lungs in 223 patients (8.42% of total TNBC cases), to the liver in 228 patients (8.62%), to the brain in 48 (1.81%) patients, and to the bones in 34 (1.28%) patients. Overall, metastatic TNBC had a higher rate of metastasis to the lungs and liver than to the brain and bones.

In non-TNBC patients, 17929 had a nonmetastatic cancer and 1171 (6.13%) had a metastatic cancer. In patients with the tumor smaller than 2 cm, the metastatic rate was 15.45%. In patients with the tumor between 2-5 cm and larger than 5cm, the metastatic rates were 17.24% and 19.83 % respectively. Unlike in TNBC patients, the tumor size did not make a difference in the metastatic risk in non-TNBC patients (P>0.005). Among those

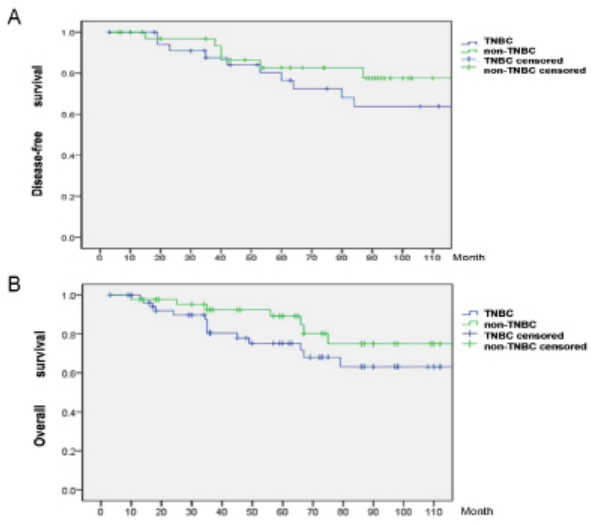

Figure 4. Kaplan-Meier Plot of 9-year Disease-free Survival (A) and 9-year Overall Survival (B) for Patients with TNBC and Non-TNBC

with a metastatic cancer, the cancer was metastasized to the lungs in 319 patients (1.67% of total non-TNBC cases), to the liver in 306 patients (1.6%), to the brain in 327 (1.71%) patients, and to the bones in 193 (1.01%) patients. Statistical analysis of metastatic risk in TNBC and non-TNBC patients showed a higher risk of metastasis in TNBC patients than in non-TNBC patients (P=0.000), particularly the risk of metastasis to the lungs and liver (Table 1).

The risk of local recurrence after the surgery was also evaluated. Among patients with TNBC, 2388 did not have a local recurrence, while 261 (9.85%) had a local recurrence during the follow-up period. The local recurrence in 163 (6.18% of total TNBC) patients occurred within 4 years after the surgery, while in 98 (3.7% of total TNBC) patients occurred more than 4 years after the surgery.

As for non-TNBC patients, the local recurrence occurred in 1763 (9.23%) patients but not in 17337 patients. Among those with a local recurrence, 913 (4.78% of total non-TNBC) occurred within 4 years after the surgery, and 850 (4.45% of total non-TNBC) occurred more than 4 years after the surgery. The overall local recurrence rate did not show a significant difference between TNBC and non-TNBC patients (P=0.259). However, for patients who had a local recurrence, TNBC patients were more likely to have a local recurrence within 4 years after the surgery compared to non-TNBC patients (X^2=11.557, P=0.001).

Survival probability of TNBC patients and non-TNBC patients

The 5-year disease-free survival rates for TNBC patients and non-TNBC patients were 77.78% and 88.34% respectively. This difference was statistically significant (P=0.002) (Figure 2A). The 5-year overall survival rates for TNBC patients and non-TNBC patients were 79.92% and 88.91% respectively, which, however, did not show a statistically significant difference (P=0.072) (Figure 2B). The 7-year disease-free survival rates for TNBC patients and non-TNBC patients were 70.82% and 84.95%

respectively. This difference was statistically significant (P=0.012) (Figure 3A). The 7-year overall survival rates for TNBC patients and non-TNBC patients were 71.64% and 86.48% respectively. This difference was also significant (P=0.023) (Figure 3B). The 9-year disease-free survival rates for TNBC patients and non-TNBC patients were 61.64% and 82.51% respectively. This difference was significant (P=0.021) (Figure 4A). The 9-year overall survival rates for TNBC patients and non-TNBC patients were 62.93% and 82.93% respectively, and showed a statistically significant difference (P=0.001) (Figure 4B).

Discussion

Triple-negative breast cancer (TNBC) is a subtype of breast cancer with characteristic biological and pathological features. Epidemiological studies have shown that TNBC tends to occur in pre-menopausal women, particularly in young African-American women (Carey et al., 2006). TNBC accounts for 39% of breast cancer cases in African-American women under 50 years old, but only 16% in Caucasian women with a breast cancer in the same age group. In post-menopausal African-American women with breast cancers, the rate of TNBC is 14% (Furberg et al., 2001; Ghafoor et al., 2003; Trivers et al., 2009). In this study, we reviewed the clinical records of Chinese breast cancer patients treated at Tianjin Medical University Cancer Institute and Hospital between July 2002 and December 2011, and have found that the prevalence of TNBC is between 10.39% and 13.46% of total breast cancer cases. The mean age of TNBC patients at the time of diagnosis is 49 years old. These results are consistent with those reported by the others (Hudis et al., 2011). However, unlike other studies showing that the disease onset age of TNBC is younger than that of other types of breast cancer, our study does not find an age difference between TNBC and non-TNBC patients. The discrepancy may be due to the difference in the genetic background and environmental factors. The epidemiological approaches may have also contributed to this discrepancy.

TNBC has distinct clinicopathological characteristics compared with other types of breast cancer. This study has shown significant differences in 4 aspects between TNBC and non-TNBC. TNBC is associated with large tumor size, high positive rate of axillary lymph node, high histologic grade and strong family history. However, in terms of clinical stage and pathological stage, no difference was found between TNBC and non-TNBC. Kandel et al have shown that the median tumor size of TNBC is 2 cm (Kandel et al., 2006), while we have found that 79.09% of TNBC tumors are bigger than 2 cm, with the median size of 3.5 cm. The discrepancy might be due to the difference in the diagnostic methods as well as other factors. As for the association between TNBC and axillary lymph node metastasis, some studies have shown that TNBC has a higher rate of axillary lymph node metastasis, while others have not found such association (Albergaria et al., 2011). Some studies have even found that TNBC has a lower rate of lymph node metastasis (Tischkowitz et al., 2007), while we have found that TNBC patients have a much higher rate of lymph node positivity. Therefore, further investigations are needed in this aspect.

We have found a strong association between TNBC and the family history of breast cancer. One possible reason is the mutant BRCA1 gene. It is known that mutations in BRCA1 gene run in the family, and cause a predisposition to breast cancer. Mutant BRCA1 gene is often found in TNBC (Stoppa-Lyonnet et al., 2000). The poor prognosis of the breast cancer with a mutant BRCA1 suggests that the poor prognosis of TNBC might be due to the mutant BRCA1 gene (Stoppa-Lyonnet et al., 2000; Kennedy et al., 2004).

The high invasive nature of TNBC suggests higher risks of metastasis and local recurrence of TNBC. The result of our study and those of others all have shown that the risk of metastasis after tumor resection is much higher in TNBC patients than in non-TNBC patients (Peddi et al., 2012). However, we did not found an increased risk of local recurrence in TNBC patients. A higher risk of metastasis would suggest a relatively lower disease-free survival and overall survival of TNBC patients. In deed, Yuan et al have reported in their study of 305 TNBC cases that TNBC patients have a lower survival rate due to an increased risk of metastasis (Yuan et al., 2008). Our study shows that the increased metastatic risk in TNBC patients is mainly caused by the increased metastasis to the liver and lungs because no difference in metastatic risk to the bones and brain was found between TNBC and non-TNBC. This result further supports the indication of the tissue preference of TNBC metastasis (Sorlie et al., 2001). It is known that cancers are more likely to metastasize to certain tissues (Minn et al., 2005). The tissue preference of metastasis is related to the gene expression profile of the cancer cells as well as the gene expression pattern in the targeted tissue (Minn et al., 2005).

Radiotherapy is currently the most commonly used approach to treat TNBC patients after the tumor resection because TNBC does not respond to immune therapies such as those targeting HER-2 receptors. It seems that TNBC is more sensitive to the radiotherapy than other types of breast cancer (Rouzier et al., 2005; Carey et al., 2007). Nevertheless, no standard approach for the treatment of TNBC is available. Although the specific adjuvant regimens may be effective for TNBC, adjuvant anthracycline-based chemotherapies do not improve the prognosis of TNBC (Piccart-Gebhart et al., 2005; Romond et al., 2005).

In our study, we have found a significant difference in the 5-year disease-free survival, but not in the 5-year overall survival, between TNBC patients and non-TNBC patients. This result is consistent with those of others (Gluz et al., 2009). We have also compared the 7-year and 9-year disease-free and overall survival rates between TNBC patients and non-TNBC patients. A significant difference exists not only in the disease-free survival rates but also in the overall survival rates. This result seems contradictory to the result of a similar study, in which it shows that the adverse effect of TNBC decreases over a 10-year follow-up period (Dent et al., 2007). It is unclear which factors cause the discrepancy. Further studies are needed to clarify this issue.

In summary, the worse prognosis of TNBC might

be related to its unique histologic features such as large tumor size, tumor necrosis, pushing margin of invasion and elevated mitotic rate (Livasy et al., 2006). TNBC often has mutant P53 and BRCA1, and histologically diagnosed as invasive ductal carcinoma or metaplastic carcinoma with low level of differentiation, high histologic grade and high mitotic index (Haffty et al., 2006; Rakha et al., 2007; Siziopikou et al., 2007; Yuli et al., 2007). Results of this study further support the indication that TNBC patients have a worse prognosis. Furthermore, the long-term adverse effect does not diminish for TNBC patients. Therefore, further investigations are needed to identify biomarkers that can be used to monitor the therapeutic efficacy as well as to develop novel targeted and personalized treatments of TNBC.

Acknowledgements

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