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ORIGINAL ARTICLE

Comparison of clinical characteristics between occult and non-occult breast cancer

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Summary

Purpose: *To compare the clinicopathological characteristics of patients with occult (OBC) and non-occult breast cancer (non OBC).*

Methods: *A total of 93 female patients with OBC registered at the First and Second Affiliated Hospitals of Zhejiang Chinese Medical University from January 1980 to December 2005 were included in this retrospective study. Their clinicopathological data were analyzed and compared with those from 1,576 female patients with non OBC, registered during the same time period.*

Results: *The rates of estrogen receptors (ER) and progesterone receptors (PR) in OBC cases were 46.2 and 56.6%, respectively, and 44.1 and 55.6%, respectively ($p<0.05$). The overall 5- and 10-year overall survival rates for OBC were 51 and 43%, respectively; the overall 5-year survival rates for stage 0-I, stage II and stage III OBC patients were 90, 83 and 52%, respectively, while the overall 10-year survival rates of the three stage groups were 83, 76 and 42%, respectively.*

Conclusions: *Compared to non OBC, the ER positive rate of OBC was lower. Furthermore, no significant difference was noticed in 5- and 10-year survival rate between OBC and stage III non OBC patients.*

Key words: *breast cancer, lymph node metastasis, occult breast cancer, survival*

Introduction

Approximately 0.1-0.8% of all breast cancer cases are occult [1-6], meaning, patients present with axillary lymph node metastasis or other metastases that are histologically consistent with a primary breast cancer, but clinical and mammographic evaluation of the breast fails to identify a tumor. The low incidence rates of OBC creates a difficult diagnostic and therapeutic challenge despite the use of advanced diagnostic tools such as mammography, ultrasonography, and magnetic resonance imaging [7,8]. As a result the therapeutic approach of such as continues to be a controversial issue since its initial description by Halsted in 1907 [9]. Until now, the natural history of OBC has remained unclear [10].

This retrospective study conducted at the First and Second Affiliated Hospitals of Zhejiang Chinese Medical University on 93 women diagnosed with OBC between January 1980 and December 2005 aimed to clarify the similarities and differences regarding clinicopathological characteristics in OBC and non OBC.

Methods

Clinical resources

The clinicopathological data of 93 female patients with OBC registered from January 1980 to December 2005, and the clinical data of 1,576 cases with non OBC registered during the same time period were analyzed and compared. All of the 1,576 non OBC cases enrolled

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were one from every 6 cases out of the 10,543 female patients registered during the same period according to their date of admission. In all cases, clinicopathological data were complete with a deadline of follow-up set at December 31, 2012. (Clinical data of patients in two groups are shown in Table 1).

Detection of ER and PR

Before surgery all the 93 OBC cases were identified as metastatic adenocarcinoma after enlarged axillary lymph node biopsies. Immunohistochemistry was performed to examine the ER and the PR status.

Statistics

Chi-square test was used to compare differences between different groups (OBC group vs non OBC group) or within individual groups. Comparison of patient age groups was performed using the independent data sample's t-test within two groups. Survival was calculated using the Kaplan-Meier method with log rank test. The statistically significant level was set at $p<0.05$. All data analyses were carried out using the SPSS 14.0 statistical package (SPSS Inc., Chicago, IL).

Table 1. Comparison of clinical data of occult and non-occult breast cancer

Clinical data	*Occult breast cancer N (%)*	*Non-occult breast cancer N (%)*	x^2	*p-value*
Age, years			1.245	0.537
≤35	7 (7.5)	128 (8. 1)		
36-55	58 (62.4)	1055 (67.0)		
≥56	28 (30.1)	393 (24.9)		
Menopausal status			0. 050	0. 822
Pre	42 (45.2)	693 (44.0)		
Post	51 (54.8)	883 (56.0)		
Type of operation			8.080	0. 018
Radical	48 (51.6)	851 (54.0)		
Modified radical	34 (36.6)	646 (41.0)		
Other	11 (11.8)	79 (5.0)		
Chemotherapy			0.172	0.679
Yes	67 (72.0)	1166 (74.0)		
No	26 (38.0)	410 (26.0)		
Radiotherapy			0.345	0.557
Yes	54 (58.1)	866 (56.2)		
No	39 (41.9)	710 (43.8)		
Clinical stages			48.671	0.000
I	0	206 (13.0)		
II	93 (100)	1024 (65.0)		
III	0	346 (22.0)		

Results

Comparison of age at disease onset

Non OBC patients had a median age of 48 years (range 22-82), while OBC patients had a median age of 54 years (range 31-76). Compared with the non OBC OBC patients had a significantly higher age ($t=1.853$, $p=0.016$).

Histopathology type comparison

After analyzing the postoperative pathology of 1,576 non OBC patients it was found that carcinoma *in situ* (including Paget's disease), special invasive carcinoma (equals invasive ductal carcinoma) and non-special invasive carcinoma (equals invasive carcinomas, except invasive ductal carcinoma which includes invasive lobular, cribriform and medulary carcinomas) accounted for 4.04% (63 patients), 2.0% (31 patients) and 94.0% (1,482 patients) respectively. Eighty three of the OBC patients were operated with either radical mastectomy plus axillary node dissection or modified radical mastectomy plus axillary node dissection (the remaining 10 patients had axillary lymph node dissection only), and in 49 (52.7%) cases primary breast carcinoma was found in pathological sections. Among them, carcinoma *in situ*, early invasive carcinoma, special invasive carcinoma and non-special invasive carcinoma accounted for 10.2, 20.4, 6.1 and 63.36%, respectively. Compared with non OBC, OBC had significantly more cases of carcinoma in situ and early invasive carcinoma ($x^2=24.75$, $p=0.000$).

Comparison of ER and PR between occult and non-occult breast cancer

The rate of positive ER in OBC cases was significantly lower than that of non OBC cases ($p<0.05$). However, when it came to the PR positive rate, there was no statistically significant difference between the two groups ($p>0.05$; Table 2).

Comparison of mortality

The overall 5- and 10-year survival rates of non OBC were 51 and 43% respectively, which re-

Table 2. Comparison of the ER-positive, PR-positive expressions of occult and non-occult breast cancer

Hormone receptor	*Non-occult breast cancer*	*Occult breast cancer*	x^2	*p-value*
ER	56.6% (892/1576)	46.2% (43/93)	0.017	0.895
PR	55.6% (876/1576)	44.1% (41/93)		

sembled the corresponding numbers for stage III breast cancer patients (Table 3, Figure 1).

Discussion

OBC is a rare disease that accounts for about 0.46-1.0% of breast cancer cases in Western countries [2]. An incidence of 0.7% (33 of 4,900) was reported by Tianjin Cancer Hospital, and data from the Shangdong Tumor Preventing and Treating Institute from 1971 to 1986 showed an incidence rate of 0.71% (6 of 851). Our study showed an incidence of 0.88%, which is higher than the average level of 0.71% mentioned above. In addition, age groups did not differ between OBC and non OBC.

Comparison of non OBC (median age at disease onset 48 years) and OBC (median age at disease onset 54 years) showed that patients with OBC were significantly older than patients with non OBC.

The initial symptoms of OBC are not always directly related to clinical or mammographic evidence of disease in the breast, including axillary lymph nodes metastasis, distant metastasis, nipple discharge, nipple dermatitis, papillary dermal edema, eczema and skin retraction [11]. As a result, there is no reliably effective diagnostic method for this disease. MRI and mammography can be used to detect non OBC, but they fail to detect OBC cases. However, considering the efficacy of epidermal growth factor receptor 2 (HER-2/neu) and breast cancer specific glycoprotein monoclonal antibodies (MAB M4G3), diagnostic methods have improved considerably in recent years [12,13].

Although melanoma, renal cell cancer and colorectal cancer all can express ER positivity, yet positive ER and PR stains are still considered to be breast cancer-specific [2]. Kaufmann et al. found that the sensitivity and specificity of ER ex-

Table 3. Comparison of survival rates of occult and non-occult breast cancer in different clinical stages

Groups	*5-year overall survival %*	*10-year overall survival %*
Non OBC		
Stage 0-I	90	83
Stage II	83	76
Stage III	52	42
OBC	51 a, b	43 a, b

a: p<0. 05, compared with stage 0-I in non OBC; b: p>0.05 compared with stage III non OBC

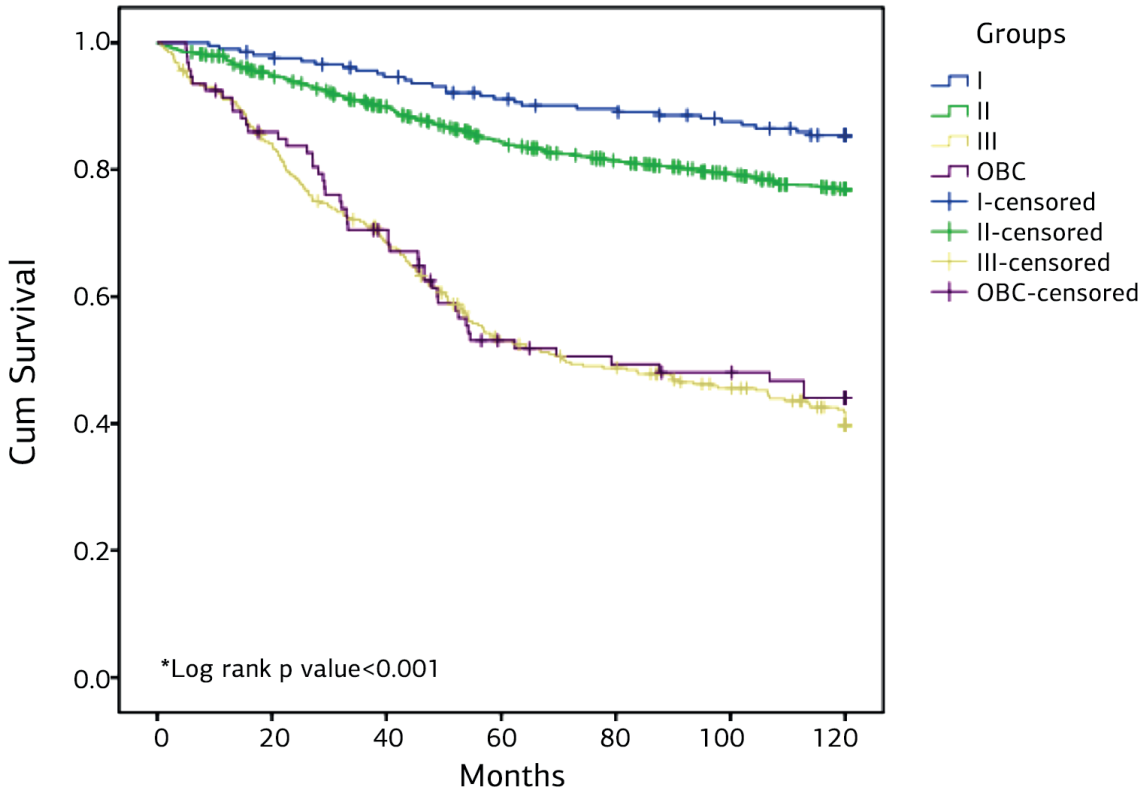

Figure 1. Overall survival of patients of occult and non-occult breast cancer in different clinical stages *.

pression in breast carcinoma compared with other carcinomas were 0.63 and 0.95 respectively and lower values were found in PR determination. All these findings confirm that the assessment of ER and PR are still necessary parts of breast cancer diagnosis and follow-up [13]. In our study, the rates of ER-positive OBC and non OBC cases were 46.2 and 56.6% respectively, and the difference was statistically significant ($p<0.05$), whereas, the rates of PR-positive OBC and non OBC cases were 44.1 and 55.6% respectively, the difference being without statistical significance ($p>0.05$). In a recent study, Walker et al. pointed out that ER-negative OBC patients are impacted by independent factors relating to poor treatment [14], which was partially supported by a study from Montagna et al. [6]. In this study, ER-negative, PR-negative and MAB M4G3-negative OBC patients had higher rates of relapse and mortality. Univariate analysis performed by He et al. [15] in their study with OBC patients showed that ER-negative tumors had a significant influence on the breast cancer specific survival rate as compared to ER-positive tumors. They also found that patients with ≥4 positive lymph nodes were more likely to experience breast cancer-specific death and recurrent/metastatic events compared to patients with <4 positive lymph nodes. In our study, non OBC patients had a lower mortality rate than OBC patients, which confirms that ER-negative status is a crucial factor in predicting prognosis.

Despite the fact that OBC is a rare condition and results on this topic are scarce, previous studies have shown that stage II OBC patients can have a longer survival than those with stage II non OBC [3,6,16,17]. The overall 5-year survival rates for different stages of non OBC (stage 0-I, II and III) were 90, 83 and 52%, respectively, while the overall 10-year survival rates for the three stages were 83, 76 and 42%, respectively. On the other hand, the overall 5- and 10-year survival rates for OBC were 51 and 43% respectively, closely corresponding to the results for stage III non OBC patients. This conclusion is, to some extent, similar to the results found by Matsuoka et al., who demonstrated that stage III non OBC with nodal metastasis had almost the same therapeutic outcome as OBC [18]. Furthermore, some reports have suggested that stage T0N1 patients with OBC could indeed have a higher survival rate than non OBC stage II patients [3,19]. Thus, the standard treatment for stage II non OBC (including radical and modified radical mastectomy, and breast-conserving surgery plus radiotherapy) should be carried out to treat OBC patients.

Which treatment for OBC could be characterized as proper has always been a controversial issue. According to a recent survey conducted by the American Society of Breast Surgeons, mastectomy is the most widely treatment used for OBC (47%), followed by breast radiotherapy (37%) [20]. Although many studies support the idea that breast radiotherapy should be used to treat patients with OBC, most surgeons will still choose mastectomy first [17,20]. In this study, 51.6% (48 out of 93) patients with OBC were subjected to radical mastectomy. This result was consistent with the study conducted by the American Society of Breast Surgeons, confirming that mastectomy is still the first choice for occult breast cancer treatment [20]. However, mastectomy can be the source of serious effects on women's quality of life and body image. Thus, it is widely considered as medically feasible to perform breast-conserving surgery coupled with axillary radiotherapy in OBC patients [5]. Besides, breast-conserving surgery had little effect on survival in this study [5]. Therefore, breast-conserving surgery may be a wise choice in the treatment of OBC, followed by postoperative adjuvant radiotherapy plus chemotherapy.

Some authors have pointed out that patients without axillary lymph node dissection have a 14-53% likelihood of developing later cancer into the breast if they do not accept to have radiotherapy as well [19,21]. On the other hand, when such patients accept to have radiotherapy, this likelihood drops to 12-33%. In another study, Vlastos et al. also reported that the survival rates of patients receiving radiotherapy versus those being only observed were 50 and 83%, respectively [5]. Patients treated with radiotherapy accounted for 58.1% (54/93) in this study. Despite the high percentage of patients receiving radiotherapy in our study, we hope in the future more patients will opt to receive radiotherapy, at the very least as adjuvant treatment.

Conclusions

Despite that OBC has a characteristically low incidence, the lack of typical symptoms and clinical findings in the breast has brought great difficulties to its diagnosis. So, the standardization of its treatment creates considerable controversy around the world. This study has found that the survival of OBC patients resembles that of stage III non OBC patients. Therefore, we recommend standardized treatment of stage III non OBC to be performed to patients with OBC.

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