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Retrospective Study

Clinicopathological features, psychological status, and prognosis of 33 patients with occult breast cancer

INTRODUCTION

Occult breast cancer (OBC) is a rare form of BC that usually presents as axillary lymph node metastasis without a clear primary breast lesion[1]. OBC is a rare breast disease. According to the foreign literature, the incidence of BC accounts for approximately 0.3%-1% of all BCs[2], with a peak incidence occurring at approximately 55 years of age.

With atypical clinical manifestations, OBC usually presents with painless axillary masses initially, but a few patients seek medical help for neck masses[3]. For patients with the above symptoms, core needle biopsy or incisional biopsy should be performed first to clarify the pathology, along with immunohistochemistry to determine its possible source[4]. Mammography and breast ultrasound are commonly used tools for diagnosing breast lesions in patients with lymph node metastases of unknown origin, but the detection rate of the primary focus of OBC is low[5]. With the development of advanced diagnostic modalities, the incidence of OBC has been decreasing [6]. The 2022 Breast Cancer Diagnosis and Treatment Guidelines suggest that breast magnetic resonance imaging (MRI) has the advantage of high sensitivity compared with other breast imaging methods; additionally, breast MRI can display multifocal, multicenter or bilateral BC lesions as well as axillary lymph node metastasis at the same time and is therefore recommended for identifying the primary focus of patients with axillary lymph node metastasis[7]. Positron emission tomography-computed tomography (PET-

CT) is also used to diagnose OBC. However, there is only one relevant report in the literature thus far[8], which, coupled with its high price, limits its application in OBC detection.

Although OBC is generally accepted to have similar biological behavior to lymph node-positive non-OBC, the clinicopathological features of this disease are unclear[9,10]. Several previous studies have suggested that estrogen receptor (ER) status, triple-negative status, and at least four positive lymph nodes are individual prognostic factors for occult breast cancer[11,12]. Survival outcomes in patients with OBC are also controversial. Patients with OBC have similar or less unfavorable outcomes than non-OBC patients[13], while others have reached the opposite conclusion[14]. Therefore, this study aimed to better reveal the clinicopathological features and prognostic factors of OBC patients through a retrospective analysis of clinicopathological data.

MATERIALS AND METHODS

General information

A retrospective analysis of the clinical data of 33 OBC patients admitted to the Affiliated Hospital of Xuzhou Medical University and Xuzhou Central Hospital was conducted from November 2015 to November 2022. Approximately 0.48% (33/6,835) of the 33 OBC patients were included in this study, of whom 20 (60%) were from the Affiliated Hospital of Xuzhou Medical University and 13 (40%) were from Xuzhou Central Hospital. The patient cohort consisted of 32 females and 1 male. Pathology revealed invasive breast cancer (intermediate/poorly differentiated).

Data collection

No obvious primary breast lesions were found by physical examination, breast color ultrasound, mammography or breast CT, MRI, PET-CT or other examinations. Any tumors occurring in any part of the body were confirmed to be metastatic carcinoma by pathological examination and indicated to be of breast origin by histological and immunohistochemical methods.

A total of 30 patients were scored on the Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) for anxiety and depression assessments, and their scores were analyzed.

Patients' emotions, stress perception and psychological resilience were evaluated by the Positive and Negative Affect Schedule (PANAS), the Chinese Perceived Stress Scale (CPSS), and the Connor-Davidson Resilience Scale (CD-RISC), respectively.

Prognostic follow-up

Patients were followed up for recurrence, metastasis and death through inpatient or outpatient information or telephone follow-up. Patients were followed up until November 2022 (5 to 226 months), for a median follow-up of 38 months. Disease-free survival (DFS) and overall survival (OS) were used as follow-up indicators, where the former was defined as the time from the start of follow-up to disease recurrence or metastasis.

Statistical analysis

R 4.3.2 and SPSS27.0 statistical software were used for data analysis, with $P < 0.05$ as the threshold of statistical significance. Nonparametric comparisons between parameters were conducted using the Mann−Whitney *U* test. The survival rate was calculated by using the Kaplan−Meier method, and survival curves were drawn. The difference in survival rate between subgroups was tested by the log-rank test, and the factors with statistical significance in the univariate analysis were further tested by multivariate Cox regression analysis.

RESULTS

Clinicopathological features

The age of onset ranged from 28 to 66 years (median age: 53). There were 9 patients (27.0%) aged ≤ 50 years and 24 patients (73.0%) aged > 50 years. There were 1 (3.0%) male and 32 (97.0%) female patients, including 22 (66.7%) menopausal and 10 (30.3%)

non-menopausal women. While 24 patients (72.7%) had a body mass index (BMI) < 24.0 and 9 patients (27.2%) had a BMI ≥ 24.0, patients' BMI, which was associated with occult breast cancer, was not related to survival (Table 1).

Thirty patients (91%) had an axillary mass at the first symptom, and only three (9.1%) patients had a neck mass at the first symptom. There were 22 patients (66.7%) in whom the lesions were located on the left side and 11 (33.3%) on the right side. There were 15 patients (45.5%) whose axillary lymph node stage was the N1, 18 patients (54.5%) whose axillary lymph node stage was N2 or N3, and 6 patients (18.2%) whose axillary lymph node stage was IV (distant metastases) (Table 1).

Immunohistochemical tests were performed on all patients. There were 18 (54.5%) OBC patients who were ER-positive and 17 (51.5%) patients who were progesterone receptor (PR) positive. There were 18 HER-2-positive patients (including 13 HER-2 IHC 3+ patients and 5 IHC 2+ patients with positive amplification according to the FISH test) and 15 HER-2-negative patients. Ki67 was detected in all patients; 8 had Ki67 ≤ 14%, and 25 had Ki67 > 14% (Table 1).

Patients' emotions, stress perception, and psychological resilience

All 30 patients developed anxiety and depression, with low positive affect scores and high negative affect scores, accompanied by a high stress level and poor psychological resilience (Table 2 and Table 3).

There were no differences in the psychological status of patients according to age, BMI, or menopausal status (Figure 1).

Treatment

Twenty-four of the 33 patients underwent surgical treatment, with 18 patients receiving modified radical mastectomy (MRM), 1 patient receiving breast-conserving surgery (BCS) plus axillary lymph node dissection (ALND), and 5 receiving ALND only. Twelve patients received neoadjuvant therapy before surgery, including 4 patients receiving 6 cycles of PC regimen (docetaxel + carboplatin), 4 receiving 4 cycles of TE regimen

(docetaxel + epirubicin), 3 receiving PC regimen for 4 cycles and sequential EC regimen for 4 cycles (docetaxel + carboplatin sequential epirubicin + cyclophosphamide), and 1 receiving TE regimen for 4 cycles (docetaxel + epirubicin). All patients received adjuvant therapy after surgery, and the treatment schemes were selected based on different factors, such as age, tumor stage and molecular subtyping. There were 20 hormone receptor-positive patients in this cohort, all of whom received endocrine therapy.

As of the follow-up date, a total of 30 OBC patients underwent SDS, SAS, PANAS, CPSS, and CD-RISC testing. The results revealed that patients who received radiotherapy had lower CD-RISC scores (P = 0.02) (Figure 2B). Surgery, neoadjuvant chemotherapy, and endocrine therapy had no significant impact on the psychological status of the OBC patients (Figure 2A, C, and D).

Prognostic characteristics

Overall survival (OS) curve of 33 patients with occult breast cancer. 5-year OS rate: 83.3%. Disease-free survival (DFS) curve of 33 patients with occult breast cancer. 5-year DFS rate: 55.7% (Figure 3).

The patients were followed up for 5-226 months (median: 38 months). A total of 12 patients relapsed and metastasized, three of whom died. Among the patients with metastasis, 4 had simple lung metastasis, 3 had lung and brain metastases, 2 had simple brain metastasis, 2 had simple skeletal metastasis, and 1 had lung and skeletal metastases.

However, there were no significant differences in 5-year DFS according to age, BMI, menopausal status, presence of distant metastasis, Ki67 index, or hormone receptor status. OBC patients with an initial tumor site in the axilla had a greater 5-year DFS rate than did those with an initial lesion in the neck (P = 0.021) (Table 1). Five-year DFS was greater in patients with few involved lymph nodes (P = 0.020) (Table 1). Age, BMI, menopausal status, node staging, initial tumor site, M staging, Ki67, ER, PR, HER-2, molecular subtyping, surgery and radiotherapy (with/without) were selected for

univariate analysis using the log-rank test. The results showed that the 5-year DFS rate of OBC patients who received radiotherapy was greater than that of patients who did not receive radiotherapy ($P < 0.001$), while there was no difference in the 5-year DFS of patients who received different surgeries, endocrine therapies, or neoadjuvant chemotherapy (Table 4).

Furthermore, the 5-year DFS rate of the 24 patients who underwent surgical treatment was analyzed by the log-rank test, revealing no significant difference among patients who underwent different surgical treatments or neoadjuvant therapy (with/without) (Table 5).

In our case series, there were 20 receptor-positive patients, all of whom received endocrine therapy. Univariate analysis using the log-rank test also revealed no significant difference in DFS among patients receiving different endocrine therapies (Table 6).

Moreover, statistically significant factors were included in the multivariate survival analysis, and it was found that radiotherapy (with/without; $P = 0.031$) was an independent prognostic factor.

DISCUSSION

In this study, 33 patients were reported in this cohort, accounting for 0.48% (33/6835) of all patients included in this study; these findings are basically consistent with the literature. All 33 OBC patients underwent relevant examinations after admission, and no primary lesions were found by mammography or ultrasound; 6 patients underwent PET-CT, and no suspicious primary lesions were detected; however, breast MRI detected 6 suspicious cancer lesions, which was significantly greater than the number of other imaging tests. A total of 18 patients underwent MRM, and 11 (11/18) patients were found to have primary lesions in ipsilateral breast tissue after surgery, for a percentage of 61.1%, which was similar to the pathological findings of 51 patients with OBC reported by Wang *et al* in 2010[15]. According to the results of the SEER database-based analysis reported by Zhu *et al*[16], ER-positive and PR-positive patients

accounted for 54.1% and 50.8%, respectively, of the total OBC cases[16], which supports our findings. In addition, approximately 54.5% of the patients were Her-2 positive, which was higher than approximately 20% of the general types of BC[17].

Due to the low incidence of OBC and the lack of sufficient evidence, the choice of treatment methods is still controversial. A number of retrospective studies have shown that using MRM and choosing combined chemoradiotherapy or endocrine therapy according to individual differences are the traditional treatments for OBC[18,19]. However, recent research by Sohn *et al*[20] confirmed that there was no significant difference in the prognosis of patients who received ALND only, BCS plus ALND, or MRM. Tsai *et al*[21] argued that the curative effect of MRM is similar to that of radiotherapy alone. Other relevant studies have also demonstrated that less intensive surgery does not negatively affect the prognosis of OBC patients, adjuvant radiotherapy is beneficial for prolonging OS, and ALND combined with radiotherapy may be the most suitable surgical modality for OBC[22,23]. Eighteen of the 33 patients received MRM, and their prognosis was not significantly different from that of patients who underwent other surgical methods. As an independent prognostic factor, radiotherapy ($P = 0.031$) could become a mainstay treatment for OBC.

OBC is a rare disease, and male OBC is even rarer than female OBC and generally has a poor prognosis regardless of sex. At present, most of the related cases reported internationally progress within a few years, which may be related to the difficulty in diagnosis and the lack of standardized treatment[24-26]. This study included one male OBC patient whose DFS and OS were significantly lower than those of the other patients in the group. Recent relevant studies have demonstrated the efficacy of immunotherapy for male OBC, and anti-androgen therapy can achieve effective control of disease progression with minimal toxicity[25], which provides a new idea for future male OBC management.

The psychological condition of OBC patients, a rare disease group, deserves further study. We analyzed the results of psychological questionnaires administered to OBC patients. The results showed that all 30 patients developed anxiety and depression, with

low PA scores and high NA scores, accompanied by a high stress level and poor psychological resilience. It is well known that the diagnosis and treatment of cancer have both negative physical and psychological long-term side effects that affect the quality of life of patients and survivors[27,28]. Breast cancer patients and survivors experience significant changes in their evaluations of their appearance and their attitudes toward their bodies, particularly with regard to femininity[29]. For example, mastectomy or breast retention may threaten overall self-satisfaction and trigger multiple changes in body perception mediated by sensations within the breast and chest[30]. We also found significant differences in Conner-Davidson resilience scores between patients who did and did not receive radiotherapy. In this nuclear age, people have been repeatedly explained and made aware of the dangers of exposure to radiation and the need to avoid it. Therefore, when patients are receiving radiation cancer treatment, stress and anxiety can ensue. In addition, during radiation therapy, patients must lie alone on a table with a large machine above them, which can create fear, isolation, and anxiety[31]. In addition, 60% of patients have significant anxiety before treatment, and 80% have anxiety after treatment[32]. These findings remind us that, although patients receiving radiation therapy often have a better prognosis, the psychological issues associated with radiation therapy should not be overlooked. Therefore, psychological counseling is needed while patients receive antitumor therapy. We hope that patients can be physically and mentally healthy and return to society normally.

CONCLUSION

The incidence of OBC is low, and diagnosis is difficult, limiting its use in clinical practice. Our research showed that the diagnostic sensitivity of breast MRI is high, which is helpful for clinical diagnosis. In addition, a less invasive surgical modality can be selected according to the individual differences of patients, which has no obvious influence on patient disease progression. Moreover, postoperative adjuvant radiotherapy can obviously improve patient outcomes. To improve the quality of life of

patients, appropriate treatment methods should be selected. Moreover, psychological problems need to be considered. The advantage of this study lies in the use of bicenter case data, but the present study still has limitations. Most of the studies were retrospective in design and included cohort selection, the impact of previous exposure to risk variables, treatment approaches, follow-up, reporting, complications, and genetic mutations. Additionally, the overall sample size was still small, and the follow-up time was short, warranting a prospective study with a large sample size to further guide the diagnosis and treatment of OBC.

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Figure Legends

Figure 1 Psychological status of occult breast cancer patients with different age, body mass index, and menopausal status. A: Different age; B: Different body mass index; C: Different menopausal status. SDS: Self-Rating Depression Scale; SAS: Self-Rating Anxiety Scale; PANAS: Positive and Negative Affect Schedule; CPSS: Chinese Perceived Stress Scale; CD-RISC: Connor-Davidson Resilience Scale.

Figure 2 Psychological status of occult breast cancer patients undergoing different treatment pattern. A: Patients undergoing surgery; B: Patients undergoing radiotherapy; C: Patients undergoing neoadjuvant chemotherapy; D: Patients undergoing endocrine therapy. SDS: Self-Rating Depression Scale; SAS: Self-Rating Anxiety Scale; PANAS: Positive and Negative Affect Schedule; CPSS: Chinese Perceived Stress Scale; CD-RISC: Connor-Davidson Resilience Scale.

Figure 3 The survival curves of 5-years overall survival and disease-free survival for the occult breast cancer patients. A: The disease-free survival curve; B: The 5-years overall survival curve.

Table 1 Clinicopathological features and 5-year disease-free survival rate of occult breast cancer patients

Clinical features	*n*	5-year DFS rate (%)	χ^2	*P* value
Whole patient cohorts	33	55.7		
Age (yr)			0.20	0.887
< 50	9	58.9		
≥ 50	24	55.8		
BMI			0.294	0.588
< 23.9	24	51.7		
≥ 23.9	9	87.5		
Menopause			2.923	0.087
Yes	23	46.9		
No	10	80.0		
N staging			5.448	0.020[a]
1	15	92.3		
≥ 2	18	34.3		
Initial tumor site			5.333	0.021[a]
Armpit	30	60.8		
Neck	3	-		
M staging			1.486	0.223
0	24	46.2		
1	9	53.3		
Ki67			0.317	0.573
≤ 14%	8	60.0		
> 14%	25	54.1		
ER			0.003	0.953
Positive	18	55.1		

Negative	15	56.0		
PR			2.355	0.125
Positive	17	67.1		
Negative	16	34.8		
Her-2			0.111	0.739
Positive	18	66.4		
Negative	15	42.2		
Molecular subtyping			1.690	0.639
Luminal A	15	73.4		
Luminal B	12	27.8		
Her-2 enriched	3	50.0		
TNBC	3	-		

[a]$P < 0.05$ between the groups. OBC: Occult breast cancer; BMI: Body mass index; DFS: Disease free survival; ER: Estrogen receptor; PR: Progesterone receptor.

Table 2 Patients' depression and anxiety scores

Categories	Minimum	Maximum	Score
SDS	44	64	56.40 ± 4.29
SAS	48	69	60.77 ± 4.58

SDS: Self-rating depression scale; SAS: Self-rating anxiety scale.

Table 3 Patients' emotions, stress perception and psychological resilience

Categories	Minimum	Maximum	Score
Positive and negative affect schedule			
Positive	10	32	18.23 ± 4.38
Negative	22	39	27.97 ± 4.37

Chinese Perceived Stress Scale	32	48	42.13 ± 3.12
Connor-Davidson Resilience Scale	38	56	47.53 ± 4.03

Table 4 Univariate and multivariate analysis of prognosis

Treatment method	*n*	5-year DFS rate (%)	χ^2	*P* value
Total	33			
Surgery			1.486	0.223
With	24	46.2		
Without	9	53.1		
Radiotherapy			10.450	< 0.001
With	16	88.9		
Without	17	21.4		

DFS: Disease-free survival.

Table 5 Five-year disease-free survival rate of patients

Surgical modalities used for patients	*n*	5-year DFS rate (%)	χ^2	*P* value
Total	24			
Surgical method			0.751	0.687
Modified radical mastectomy	18	35.7		
Axillary lymph node dissection	5	50.0		
Breast-conserving surgery + axillary lymph node dissection	1	-		
Neoadjuvant therapy			0.168	0.682

With	12	0.571
Without	12	0.458

DFS: Disease free survival.

Table 6 Effects of treatment modalities on disease free survival

Endocrine therapy for hormone receptor-positive patients	***n***	**5-year DFS rate (%)**	χ^2	***P* value**
Total	20			
Drugs used for endocrine therapy			1.669	0.434
Tamoxifen	10	0.370		
Goserelin	6	1.000		
Anastrozole/letrozole	4	0.667		

DFS: Disease free survival.

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