

A retrospective study of optimal surgical management for occult breast carcinoma

Mastectomy or quadrantectomy?

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Abstract

The diagnosis and treatment for occult breast carcinoma (OBC) remain controversial because of no detectable primary lesions. We aimed to analyze optimal surgical management for OBC.

A total of 26 female patients diagnosed with OBC, which were based on available criteria, were collected at a single clinic center from January 2005 to May 2016. We classified all patients into 4 groups: group A1, mastectomy with axillary lymph node dissection (ALND)+radiotherapy (RT); group A2, mastectomy with ALND; group B1, quadrantectomy with ALND+RT; group B2, quadrantectomy with ALND. Patient characteristics, disease-free survival, and overall survival were compared between groups.

There were 14 cases in group A1, 5 cases in group A2, 4 cases in group B1, and 3 cases in group B2. Baseline characteristics were similar among groups. Compared with OBC patients treated with quadrantectomy, the disease-free survival (DFS) and overall survival (OS) rate of those treated with mastectomy had significantly improved (A1 vs. B1, DFS: hazard ratio [HR] 0.018, 95% confidence interval [CI] 0.001–0.241, $P=.002$; OS: HR 0.002, 95% CI 0.000–0.102, $P=.002$). Patients treated with radiotherapy had higher local recurrence and OS rate compared with patients treated with no radiotherapy on univariate survival analysis (A1 vs. A2, DFS: HR 0.018, 95% CI 0.001–0.240, $P=.002$; OS: HR 0.005, 95% CI 0.000–0.170, $P=.003$).

The diagnosis of OBC will need continuous improvement with advances of diagnostic breast imaging. Modified radical mastectomy+RT is still a safe and effective choice.

Abbreviations: ALND = axillary lymph node dissection, OBC = occult breast cancer, RT = radiotherapy.

Keywords: mastectomy, occult breast cancer, quadrantectomy, radiotherapy

1. Introduction

Occult breast cancer(OBC) is a rare form of breast cancer presenting axillary carcinoma metastases as the only symptom and absence of clinically and radiologically (mainly ultrasound and mammography) identifiable breast lesions (cT0N+).^[1] Fewer than 1% of patients were diagnosed with OBC.^[2] Magnetic resonance imaging (MRI) has great importance in diagnosis of

OBC according to the current National Comprehensive Cancer Network guidelines.^[3] However, the definition of OBC remains controversial. Most of the studies suggested that “occult” can be defined as undetectable primary lesions by mammography and color Doppler ultrasonography regardless of MRI, breast scintigraphy(Tc-99m), and Positron Emission Tomography-Computed Tomography (PET-CT).^[4–7]

With no clear guidelines published for the treatment of OBC, there are 3 methods for ipsilateral breast currently: mastectomy, quadrantectomy (upper outer quadrant) and breast conservation with RT. Owing to lack of large prospective studies or randomized controlled trials, we do not know which strategy is appropriate to patients. It was reported that there was no significant difference between mastectomy and breast conservation with RT in the local control and long-term survival rate.^[8] However, there is a serious controversy about the choice of target area and dose because of unclear primary tumor. So we performed a retrospective, single-center observational study to compare prognosis between mastectomy and quadrantectomy for OBC patients and put forward our own understanding about the definition of OBC.

2. Methods

2.1. Study population

The study population of this retrospective, single-center study was consisted of all patients who were diagnosed with OBC by excisional or cannulated needle biopsy of axillary mass. Female patients underwent the breast surgery at Tongji Hospital between January 2005 and May 2016. Patients who had partial breast or

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Synopsis: We can conclude that modified radical mastectomy is an optimal procedure for occult breast carcinoma (OBC) by comparing with quadrantectomy.

The authors report no conflicts of interest.

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unspecified/unknown breast surgery or a history of malignant tumor were excluded.

Data of the included patients were extracted from the hospital's electronic patient record system. Institutional review board approval was not required for this study, as no protected health information was utilized.

2.2. Study design, primary endpoints

Based on the ipsilateral axillary lymph node dissection (ALND), patients were categorized into 4 groups according to different treatments: group A1, mastectomy with RT; group A2, mastectomy; group B1, quadrantectomy with RT; group B2, quadrantectomy. Immunohistochemical detections from the excisional lymph nodes including estrogen receptor (ER), progesterone receptor (PR), Her-2 receptor, and monoclonal antibody GCDFP-15 were routinely used as diagnostic tools in our hospital.

The primary outcome measure was time from OBC initial diagnosis to progression of disease, which included local recurrence, distant metastases, and death. Date of OBC diagnosis was defined as the moment when axillary mass was first confirmed by pathology. Moreover, we compared patient characteristics before surgery, including age, menstruation status, American Society of Anesthesiologists physical status classification, body mass index (BMI), history, clinical and pathologic N stage, number of lymph nodes examined (<4, >10), types of treatment, tumor characteristics, ER, PR, Her-2 receptor, and GCDFP-15 status (positive vs. negative), use of radiotherapy, chemotherapy, and endocrine therapy (yes vs. no), and survival rate on univariate analysis.

2.3. Statistical analysis

Statistical analyses were performed using SPSS statistical version 22.0 (SPSS for Windows, IBM Corporation, Armonk, NY). Mean \pm standard deviation (SD) expressed continuous variables in descriptive tests. Count (n) and percentage (%) described categorical variables. Patient and treatment characteristics between groups were compared using independent sample *t* test or Mann-Whitney *U* test for continuous variables, and Pearson χ^2 test for differences between variables. *P*-value <0.05 was considered statistically significant. Survival curves were calculated using the Kaplan-Meier method.

3. Results

3.1. Patient characteristics

A total of 32 OBC patients were identified at Tongji Hospital from January 2005 to May 2016. Twenty-six patients met our inclusion criteria. All patients underwent excisional or cannulated needle biopsies of the axillary mass and were confirmed metastasis from breast. No distant metastasis was detected through PET-CT, chest/abdominal CT or bone scan before surgery. Three of 7 patients had negative breast MRI. All patients underwent ultrasound and mammography. Suspicious lesions were found in 4 cases by ultrasound, which were diagnosed as fibroadenosis or fibroadenoma of breast after mammotome. Four of 20 patients had calcifications indicating fibrous tissue or scar after resection through mammography guided wire localization. There were 14 cases in group A1, 5 cases in group A2, 4 cases in group B1, and 3 cases in group B2. Twenty-three patients (88.5%) received adjuvant chemotherapy. Twelve patients with

ER or PR positive received hormonal therapy. 57.1% of patients received HER2-targeted therapy. Patient characteristics and progression of disease for all treatment groups are listed in Tables 1 and 2, respectively.

3.2. Tumor and lymph nodes characteristics

Breast lesions were detected (a size range of 2–8mm) by continuous cutting slides with 5-mm intervals in 7 of 19 cases (36.8%) treated with mastectomy. The minimal size of tumor was 0.1 \times 0.2 \times 0.2cm. Seven patients, who had negative pathology, were treated with quadrantectomy.

ER-positive tumors (57.1%), GCDFP-15-positive tumors (78.6%), and pathological N2 disease (64.3%) were more common. The 5-year survival rate for OBC patients with >10 positive axillary lymph nodes was 37.5% compared with 66.7% for patients with 1 to 3 positive lymph nodes (*P* < .05). (Table 1)

When comparing these groups, significant differences were observed in age and pathologic N stage. Younger patients more likely tended to mastectomy, whereas older patients tended to be treated with quadrantectomy. Younger patients had higher pathologic N stage than older patients.

3.3. Survival analysis

3.3.1. All treatment groups. On the basis of ALND, 7.1% (1/14) of patients who had mastectomy and RT had progression of disease, compared with 75.0% (3/4) of patients who had quadrantectomy and RT. 40.0% (2/5) of patients who had mastectomy without RT died, whereas 66.7% (2/3) of patients who had quadrantectomy without RT died. The mean disease-free survivals (DFSs) for group A1 and group B1 were 71 months and 36 months, respectively. Patients who were treated with mastectomy or radiation had better DFS and overall survival (OS) compared with those with quadrantectomy or no radiation on univariate survival analysis. The 5-year OS rate was 100% in group A1 and 50% in group B1.

3.3.2. Treatment with mastectomy versus quadrantectomy. Patients treated with mastectomy+ALND+RT had a significantly better DFS and OS compared with those with quadrantectomy+ALND+RT on univariate survival analysis (Fig. 1; hazard ratio [HR] 0.018, 95% confidence interval [CI] 0.001–0.241, *P* = .002; Fig. 2; HR 0.002, 95% CI 0.000–0.102, *P* = .002).

3.3.3. Treatment with radiotherapy or not. Compared with radiotherapy and no radiotherapy group, univariate survival analysis showed that local recurrence and OS rates had significant difference (Fig. 3; HR 0.018, 95% CI 0.001–0.240, *P* = .002; Fig. 4 HR 0.005, 95% CI 0.000–0.170, *P* = .003).

4. Discussion

Studies have shown that if the primary tumor is identified, a longer survival is generally facilitated by properly treating the lesion.^[9] For OBC, treatment of ALND is routinely recommended for local control and completing staging information. However, because of lack of primary focus, treatment of ipsilateral breast remains controversial. In this retrospective, single-center study examining treatments and outcomes in patients with OBC, we showed that patients treated with mastectomy had a significant improvement in OS and DFS compared with patients treated with quadrantectomy after adjusting for other covariates. Several reasons may explain this

Table 1
Patient, tumor, and treatment characteristics by group.

Characteristic	Group A1 ^[14]	Group A2 ^[5]	P (A1 vs. A2)	Group B1 ^[4]	Group B2 ^[3]	P (A1 vs. B1)
Patient factors						
Age at surgery, y	44.2±15.6	44.8±14.2	.941	51.4±16.9	51.2±15.7	.045
BMI, kg/m ²	24.3±8.3	23.4±7.5	.732	24.5±9.6	24.9±8.7	.784
ASA classification			.121			.064
I-II	11 (78.6)	4 (80.0)		4 (100.0)	2 (66.7)	
III	3 (21.4)	1 (20.0)		0 (0.0)	1 (33.3)	
History of diabetes			.071			.032
+	2 (14.3)	0 (0.0)		0 (0.0)	1 (33.3)	
-	12 (85.7)	5 (100.0)		4 (100.0)	2 (66.7)	
Menstruation			.086			.050
Premenopausal	2 (14.3)	2 (40.0)		0 (0.0)	0 (0.0)	
Perimenopausal	10 (71.4)	3 (60.0)		3 (75.0)	2 (66.7)	
Menopause	2 (14.3)	0 (0.0)		1 (25.0)	1 (33.3)	
Tumor factors						
Clinical N stage			.063			.124
1	6 (42.9)	3 (60.0)		2 (50.0)	2 (66.7)	
2	8 (57.1)	2 (40.0)		2 (50.0)	1 (33.3)	
Pathologic N stage			.051			.096
1	1 (7.1)	0 (0.0)		1 (25.0)	1 (33.3)	
2	9 (64.3)	4 (80.0)		2 (50.0)	0 (0.0)	
3	4 (28.6)	1 (20.0)		1 (25.0)	2 (66.7)	
Number of lymph nodes examined			.034			.005
<4	4 (28.6)	1 (20.0)		0 (0.0)	1 (33.3)	
>10	10 (71.4)	4 (80.0)		4 (100.0)	2 (66.7)	
Histology			.014			<.001
Ductal carcinoma in situ	1 (7.1)	1 (20.0)		0 (0.0)	0 (0.0)	
Invasive ductal carcinoma	2 (14.3)	2 (40.0)		0 (0.0)	0 (0.0)	
Nonspecific invasive ductal carcinoma	1 (7.1)	0 (0.0)		0 (0.0)	0 (0.0)	
Unknown	10 (71.4)	2 (40.0)		4 (100.0)	3 (100.0)	
ER status			.008			.007
ER+	8 (57.1)	1 (20.0)		1 (25.0)	2 (66.7)	
ER-	6 (42.9)	3 (60.0)		3 (75.0)	1 (33.3)	
Unknown	0 (0.0)	1 (20.0)		0 (0.0)	0 (0.0)	
PR status			.081			.004
PR+	7 (50.0)	2 (40.0)		1 (25.0)	2 (66.7)	
PR-	6 (42.9)	2 (40.0)		3 (75.0)	1 (33.3)	
Unknown	1 (7.1)	1 (20.0)		0 (0.0)	0 (0.0)	
Her-2 receptor			.116			.054
Her-2+	3 (21.4)	1 (20.0)		2 (50.0)	1 (33.3)	
Her-2-	9 (64.3)	3 (60.0)		2 (50.0)	2 (66.7)	
Unknown	2 (14.3)	1 (20.0)		0 (0.0)	0 (0.0)	
GCDFP-15 status			.067			<.001
GCDFP-15+	11 (78.6)	3 (60.0)		1 (25.0)	2 (66.7)	
GCDFP-15-	0 (0.0)	1 (20.0)		1 (25.0)	1 (33.3)	
Unknown	3 (21.4)	1 (20.0)		2 (50.0)	0 (0.0)	
Treatment factors						
Hormonal therapy			.051			.041
Yes	8 (57.1)	2 (40.0)		1 (25.0)	1 (33.3)	
No	4 (28.6)	3 (60.0)		2 (50.0)	2 (66.7)	
Unknown	2 (14.3)	0 (0.0)		1 (25.0)	0 (0.0)	
Chemotherapy			.124			.116
Yes	12 (85.7)	5 (100.0)		3 (75.0)	2 (66.7)	
No	1 (7.1)	0 (0.0)		1 (25.0)	1 (33.3)	
Unknown	1 (7.1)	0 (0.0)		0 (0.0)	0 (0.0)	

ASA=American Society of Anesthesiologists, BMI=body mass index, ER=estrogen receptor, PR=progesterone receptor.

improvement. First, mastectomy has a higher percentage of patients with positive pathology for OBC.^[6,10,11] Because the whole breast tissue would be examined by pathology. Sufficient pathological information will contribute to following comprehensive treatment and evaluating prognosis. However, quad-

rantectomy is just tantamount an extended resection for axillary mass. Primary lesions are not found in OBC patients, which does not mean that there is no lesion in the breast. Most of breast tissues were not examined by pathology, which might lead to the missing of breast lesions. Second, quadrantectomy has poorer

Table 2

The progression of OBC patients among 4 groups.

		Mastectomy (19)				Quadrantectomy (7)			
Radiotherapy (18)	No progression of disease	Local recurrence	Distant metastasis	Death	No progression of disease	Local recurrence	Distant metastasis	Death	
	13	1	0	0	1	0	1	2	
No radiotherapy (8)	No progression of disease	Local recurrence	Distant metastasis	Death	No progression of disease	Local recurrence	Distant metastasis	Death	
	2	0	1	2	1	0	0	2	

OBC=occult breast cancer.

prognosis. Our study showed that more patients treated with quadrantectomy had progression of disease compared with those treated with mastectomy. The missing breast lesion in some patients treated with quadrantectomy might grow into a larger tumor, which belongs to higher T stage. Lastly, there was no systematical research or basis of evidence-based medicine to guide the operative range of quadrantectomy. Surgeons may decide the range according to their personal experience and patients' general conditions, which leads to unstable effects.

Owing to lack of primary tumor, some studies reported that the prognosis of OBC was slightly better than breast cancer with a palpable lesion at the same stage.^[11] So, breast radiotherapy was gradually popular in recent years for OBC. It was reported that there was no significant difference between mastectomy and

breast radiotherapy in the local control and long-term survival rate.^[8] However, there is a controversy about the choice of target area and dose for radiotherapy.^[12] Then, the whole breast radiation therapy could possibly lead to breast deformation, which is contrary to the requirement of cosmetic effect.

In 1907, Halsted^[13] first described a clinical phenomenon known as “cancerous axillary glands with nondemonstrable cancer of the mamma.” In this stage, breast cancer was mainly found by physical examination. OBC was also known as nonpalpable breast cancer. As early as 1950s, x-ray photography was used for the examination of breast diseases.^[14] Subsequently, color Doppler ultrasonography was also popularized. The combination of them greatly improved the detection rate and diagnostic rate of breast lesions. Then OBC was defined as

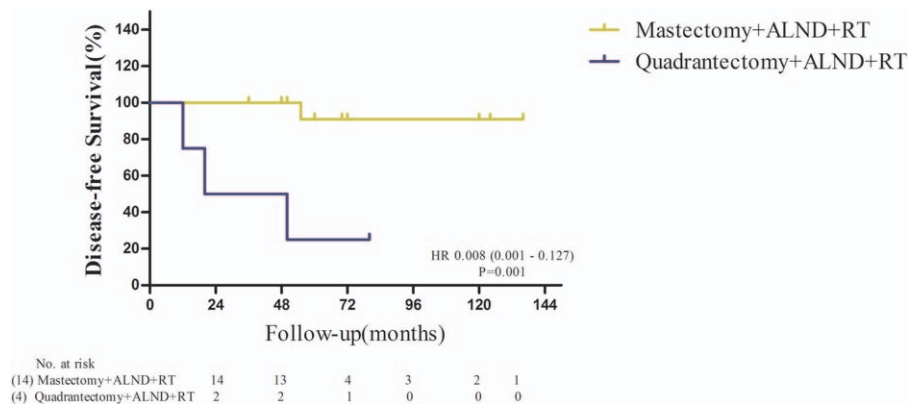


Figure 1. Kaplan–Meier curve illustrating disease-free survival for occult breast cancer patients treated with mastectomy+ALND+RT and quadrantectomy+ALND+RT. ALND= axillary lymph node dissection, HR=hazard ratio, RT=radiation therapy.

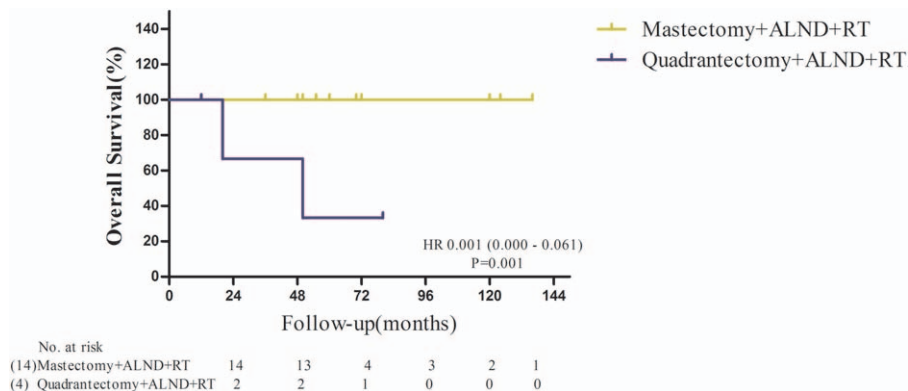


Figure 2. Kaplan–Meier curve illustrating overall survival for occult breast cancer patients treated with mastectomy +ALND+RT and quadrantectomy +ALND+RT. ALND= axillary lymph node dissection, HR=hazard ratio, RT=radiation therapy.

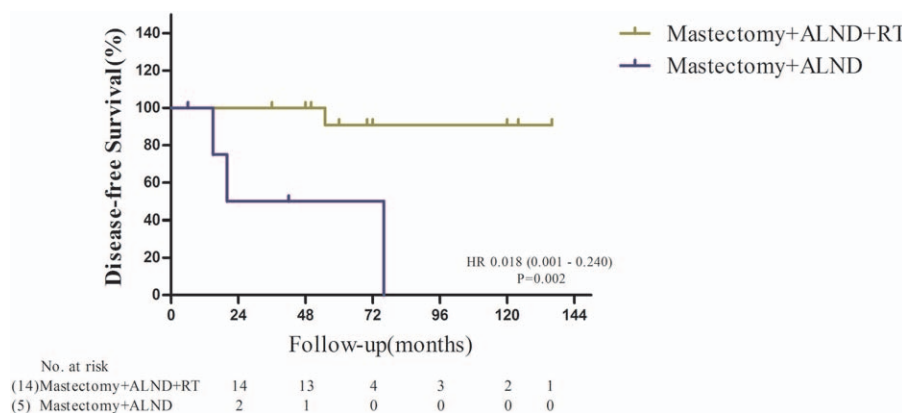


Figure 3. Kaplan–Meier curve illustrating disease-free survival for occult breast cancer patients treated with mastectomy + ALND ± RT. ALND = axillary lymph node dissection, HR = hazard ratio, RT = radiation therapy.

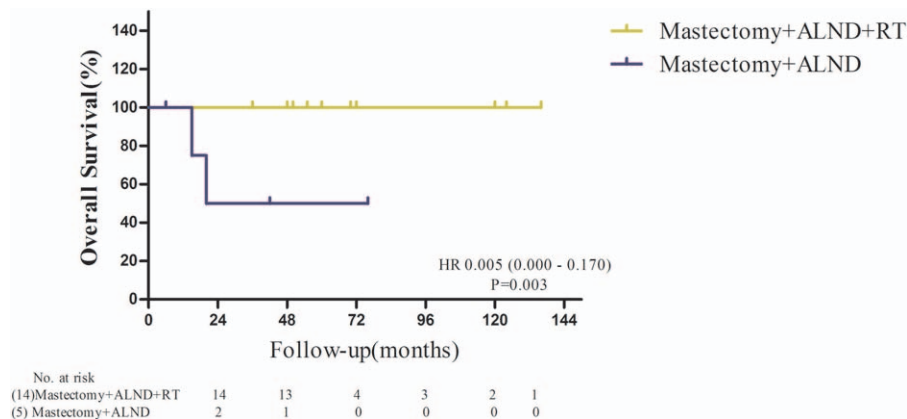


Figure 4. Kaplan–Meier curve illustrating overall survival for occult breast cancer patients treated with mastectomy + ALND ± RT. ALND = axillary lymph node dissection, HR = hazard ratio, RT = radiation therapy.

breast cancer which could not be detected by these 2 conventional breast imaging and this definition has been used ever since. As more imaging technologies were continuously developed, such as MRI, PET-CT, breast scintigraphy (Tc-99m), the diagnosis of OBC entered the advanced breast imaging phase. Breast MRI has significantly improved our ability to identify OBCs that are not detected on mammography.^[15,16] In 2010, American College of Radiology recommended that breast MRI should be the criterion for the existence of primary breast tumors.^[17,18] So we think that the definition of OBC needs to be perfected: except for metastases which is considered to arise from breast, none cancer focus could be detected through any imaging techniques or pathological examination.

This study has certain limitations that need to be addressed. First, our sample size was small and all data came from a single center. It may have some biases in our electronic patient record system. Second, breast MRI was not popular in these cases. Although a negative MRI could not exclude breast primary tumor, it has higher sensitivity compared with conventional imaging technologies.

5. Conclusion

Mastectomy is associated with better survival rates in OBC patients compared with quadrantectomy. So, modified radical mastectomy plus radiotherapy is considered to be an optimal treatment for OBC.

References

- [1] Macedo FI, Eid JJ, Flynn J, et al. Optimal surgical management for occult breast carcinoma: a meta-analysis. *Ann Surg Oncol* 2016;23:1838–44.
- [2] Walker GV, Smith GL, Perkins GH, et al. Population-based analysis of occult primary breast cancer with axillary lymph node metastasis. *Cancer* 2010;116:4000–6.
- [3] National Comprehensive Cancer Network. NCCN Guidelines Version 1.2017 Invasive Breast Cancer. 2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed March 26, 2017.
- [4] Baron PL, Moore MP, Kinne DW, et al. Occult breast cancer presenting with axillary metastases. Updated management. *Arch Surg* 1990; 125:210–4.
- [5] Kemeny MM, Rivera DE, Terz JJ, et al. Occult primary adenocarcinoma with axillary metastases. *Am J Surg* 1986;152:43–7.

- [6] Rosen PP, Kimmel M. Occult breast carcinoma presenting with axillary lymph node metastases: a follow-up study of 48 patients. *Hum Pathol* 1990;21:518–23.
- [7] Patel J, Nemoto T, Rosner D, et al. Axillary lymph node metastasis from an occult breast cancer. *Cancer* 1981;47:2923–7.
- [8] Rueth NM, Black DM, Limmer AR, et al. Breast conservation in the setting of contemporary multimodality treatment provides excellent outcomes for patients with occult primary breast cancer. *Ann Surg Oncol* 2015;22:90–5.
- [9] Abbruzzese JL, Abbruzzese MC, Lenzi R, et al. Analysis of a diagnostic strategy for patients with suspected tumors of unknown origin. *J Clin Oncol* 1995;13:2094–103.
- [10] Shannon C, Walsh G, Sapunar F, et al. Occult primary breast carcinoma presenting as axillary lymphadenopathy. *Breast (Edinburgh, Scotland)* 2002;11:414–8.
- [11] Foroudi F, Tiver KW. Occult breast carcinoma presenting as axillary metastases. *Int J Radiat Oncol Biol Phys* 2000;47:143–7.
- [12] Kim BH, Kwon J, Kim K. Evaluation of the Benefit of Radiotherapy in Patients with Occult Breast Cancer: A Population-based Analysis of the SEER Database[J]. *Cancer research and treatment: official journal of Korean Cancer Association*. 2017. doi: 10.4143/crt.2017.189.
- [13] Halsted WSI. The results of radical operations for the cure of carcinoma of the breast. *Ann Surg* 1907;46:1–9.
- [14] Dalsace J. [Radiography of the breast; a new technic: logetron printing]. *C R Soc Fr Gynecol* 1957;27:360–2.
- [15] de Bresser J, de Vos B, van der Ent F, et al. Breast MRI in clinically and mammographically occult breast cancer presenting with an axillary metastasis: a systematic review. *Eur J Surg Oncol* 2010;36:114–9.
- [16] Buchanan CL, Morris EA, Dorn PL, et al. Utility of breast magnetic resonance imaging in patients with occult primary breast cancer. *Ann Surg Oncol* 2005;12:1045–53.
- [17] Lee CH, Dershaw DD, Kopans D, et al. Breast cancer screening with imaging: recommendations from the Society of Breast Imaging and the ACR on the use of mammography, breast MRI, breast ultrasound, and other technologies for the detection of clinically occult breast cancer. *J Am Coll Radiol* 2010;7:18–27.
- [18] Ahmed I, Dharmarajan K, Tiersten A, et al. A unique presentation of occult primary breast cancer with a review of the literature. *Case Rep Oncol Med* 2015;2015:102963.