

## Diagnoses and Therapy of Occult Breast Cancer: A Systematic Review

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### Abstract

Occult breast cancer (OBC) is a unique type of breast cancer that initially presents with metastasis to the axillary lymph nodes or other metastatic carcinoma, while no breast mass is palpable by finger examination and simultaneously undetectable by usual radiography. The morbidity of OBC is quite low, less than 1% among all types of breast cancers. However, OBC has only been described in case reports and retrospective studies with small samples. Hence, there is no consensus on a therapy due to lack of high quality randomized clinical trials. The aim of the present study was to review the literature from China and the PubMed/Medline database published prior to December, 2016. Key findings in the diagnosis and therapy of OBC are discussed and reviewed.

**Keywords:** Occult breast carcinoma; Diagnoses; Therapy

### Clinical Features and Key Points to Consider in Diagnosis

Occult breast cancer (OBC) was first described by Halsted et al. [1]. Who reports three cases presenting with enlarged axillary lymph nodes and no breast mass was detectable until 1-2 years later. Traditionally, OBC is characterized by metastasis to the axillary lymph nodes with no detectable breast mass at the initial presentation [2-4]. All systematic reviews and meta-analyses of the diagnoses and therapy of OBC to date are based on this definition. The morbidity of OBC is approximately 0.3% to 0.8% globally [2,4-7] and about 0.7% in China [8,9]. Obviously, with the development of imaging techniques, the morbidity of OBC will continue to gradually decrease. Ultrasonography and mammography are very popular modalities for imaging of breast cancer. Besides magnetic resonance imaging (MRI), positron emission tomography-computed tomography of the breast is also often applied in clinical practice worldwide. As a result, some OBC cases will be revised once a palpable breast mass is detected by these advanced imaging examinations [10-15].

Notably, most enlarged axillary lymph nodes detected by finger examination and/or mammography are in the preliminary stage. However, the choice of treatment may change once an enlarged axillary lymph node begins to show signs of malignancy. The most frequent cause of metastasis of breast cancer to the axillary lymph nodes is unique to the origin of the breast cancer. Besides, other primary foci, including axillary lymphoma, malignant blood disease, lung cancer, ovarian carcinoma, head and neck squamous cell carcinoma, colon carcinoma, gastric cancer and thyroid cancer etc. can also result in enlargement of the axillary lymph nodes [16-24]. Therefore, based on past-experience, detailed family history and intensive physical examination are becoming more and more crucial to identify the essential cause of enlarged axillary lymph nodes.

Patients with OBC usually have no detectable breast mass, but rather enlarged axillary lymph nodes. For detection of metastatic lymph nodes derived from breast cancer, mammography and ultrasonography of the breast and bilateral axillary lymph nodes, supraclavicular lymph nodes, and internal mammary lymph nodes are highly recommended [25,26].

If these examinations of the breast are still not sufficient to identify the position of the carcinoma, biopsy of enlarged axillary lymph nodes by fine-needle aspiration or blunt needle aspiration will be necessary. Approximately 1.6 million women in the US undergo breast biopsies

annually and nearly one-quarter of the biopsies demonstrate the origin of invasive breast cancer. It is very important that fine-needle biopsy is performed by an experienced pathologist and blunt-needle biopsy requires an adequate tissue sample to accurately determine the histological features of the foci. If a definitive diagnosis cannot be determined by the tissue biopsy, the lymph nodes should be enucleated [27-29]. Once of breast cancer to the lymph nodes is confirmed, conservative examination by mammography is required. MRI of the bilateral breasts is an alternative choice when there are no specific findings by mammography. MRI is extremely useful to locate the primary focus in suspected OBC cases with negative results by mammography and/or B-type ultrasonography. The sensitivity (85% to 100%) and specificity (37% to 77%) of MRI are greater than those of traditional finger examination and other imaging techniques [30-33].

Olson et al. [34] compared the efficacy of MRI to that of traditional imaging methods for diagnosis of OBC in 40 patients and found that MRI accurately located the primary foci in resected specimens after modified radical oncology breast surgery in 21 (95%) of 22 suspected cases. Of 12 cases with negative MRI results, five underwent breast surgery, but no primary lesion was detected in four (80%) of the cases. These findings substantiate the high sensitivity of MRI and its value in clinical application.

Breast-specific  $\gamma$ -imaging (BSGI) is another physiological imaging tool used to detect breast cancer, which uses a radiotracer,  $^{99m}\text{Tc}$ -sestamibi, to identify physiologic differences between malignant and normal breast tissue. Brem et al [35] demonstrates that BSGI detects occult breast cancer in women at increased risk at a rate of 16.5 cancers detected per 1,000 women screened, higher than the rate reported for both MRI and screening ultrasound. Furthermore, BSGI can also enhance the ability to detect breast cancer in women at increased risk compared with mammography alone. Eleven of 14(78.6%)

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mammographically occult cancers were detected in patients with heterogeneous or extremely dense breast tissue (BI-RADS c or d).

Based on this evidence, it is necessary to upgrade conventional examinations for OBC to tissue punctures or MRI-guided direct needle biopsy to improve diagnostic reliability. Kuhl et al. [35] reported that MRI combined with finger examination, B-type ultrasonography, and X-ray imaging was useful for diagnosis of OBC, successfully increasing the detection rate up to 98%, with a sensitivity of up to 96% and a specificity of up to 100%. Moreover, the positive prophylactic value increased to 100%, while the negative prophylactic value increased to 97%.

### Pathological and Differential Diagnoses

Nearly one-half of OBCs occur in the upper outer quadrant of the breast. Pathological sections from the entire breast specimen should be examined at thicknesses of 5 mm to avoid overlooking smaller primary tumors.

First, the pathologists should be able to discern the difference between metastatic lymph nodes and OBC. If the glands around the foci or in the nest's interstitial tissue are normal, the specimen will be considered as positive for breast cancer based solely on morphologic features. However, if lymphocytes or lymph node capsules are found around the focus, secondary metastasis to the lymph nodes should be considered. Tumors occurring separately from breast cancer are quite rare, as about 90% of metastatic axillary lymph nodes are derived from breast cancer [27-29].

A differential diagnosis of adenocarcinoma from squamous cells carcinoma or lymphoma can be made by the pathologist via light microscopy. Adenocarcinoma and malignant melanoma are thought to be the major causes of breast cancer metastasis to the axillary lymph nodes. A diagnosis of breast cancer is highly supported by the finding of sieve pore structure or comedo structure in the cancer nests. Alternatively, if tall columnar cells secreting mucous are visible by microscopy, most should be considered to have gastric or colonic origins. The presence of the typical features of nuclear ground glass-like appearance or psammoma body structure suggests metastatic thyroid carcinoma. In addition, the presence of melanin granules in the cells supports a definite diagnosis of melanoma.

In clinical practice, pathologists can also request additional immunohistochemical staining prior to arriving at a final pathological diagnosis. Therefore, immunohistochemical analysis may be another helpful method for the pathologist to arrive at a diagnosis of melanoma. To be more detailed, HMB-45 and MARI-1 are negative in breast cancer. G-CDFP-positivity highly suggests that the tumor originated in the breast [36]. Lung and thyroid cancer are typically positive for TTF-1, while breast cancer is negative [37-39]. Moreover, calcitonin is positive in medullary thyroid carcinoma and thyroid globin protein is positive in thyroid carcinoma. N-1 expression is positive in non-mucous ovarian tumors, which can be used for differentiation from breast cancer. Colorectal cancer is positive for CEA and CK20, but negative for CKT, while breast cancer is frequently negative for CK20 and positive for CKT. Although ER and PR are positive in 30% of OBC cases and negative in 40%, they appear to have no significant value for diagnosis of OBC. M4G3, an anti-human breast cancer monoclonal antibody, may be a useful immunohistochemical marker with high specificity (positive rate, 93.55%) for breast cancer. Primary micro-foci can be detected in 84.62% of cases with M4G3-positive axillary lymph nodes, while the remaining cases may be severe papillary disease or ductal epithelium hyperplasia. Therefore, M4G3 is valuable for the diagnosis of OBC. It is believed that among the 40% to 80% of cases in

which breast tissue sections are obtained after surgery, 75% are invasive ductal carcinoma and about 5% are carcinoma *in situ* [40-46].

So far, there is no consensus on pathological criteria for a diagnosis of OBC. Therefore, experience and informal learning gained within larger group practices may contribute to reducing diagnostic discordance and enhancing interpretive performance for breast and lymph node biopsy. Currently, the accuracy of pathological diagnoses is directly determined by the intensive extent of tissue selective procedure and the extensive field of histological tissue. The potential causes of OBC without a primary focus may be associated with several of the following factors: A) the primary focus may disappear or diminish after systematic therapy prior to surgery; B) a small primary focus may not be easy to identify because it may be located deeper within the breast specimen; and C) a primary focus may be overlooked because of the interruption of hypoplastic nodes surrounding the actual focus. Obviously, it is necessary to perform an intensive and detailed histological examination. Therefore, "whole breast, whole section" will facilitate identification of a primary focus in OBC [47].

### Management of Comprehensive Therapy

Breast carcinoma therapy consists of treatment directed at the axillary nodes, the involved breast, and the whole body. OBC is a rare entity, thus it is not realistic to engage a high-quality randomized clinical trial and there is currently no consensus on a standard surgical strategy. In practice, retrospective studies with small samples have no value for guidance of treatment due to the lack of effective screening criteria and reliable clinical therapeutic regimens.

### Management of OBC

The choice of an optimal regimen for treatment of OBC remains controversial. An investigation of the preferred therapeutic strategy of 1837 breast surgeons (American Society of Breast Surgeons, 2005) showed that 43% preferred radio chemotherapy, 37% chose whole breast radiology, and the rest choose surveillance [48].

In general, surveillance of the affected breast only is not an appropriate choice. A study by Foroudi and Tiver reported that the average survival period of patients undergoing local therapy without local recurrence was obviously longer than that of the patients undergoing only surveillance (182 vs. 7 months, respectively,  $p=0.003$ ) [49]. Shannon et al reported a higher local recurrence rate among patients who received no radiological therapy as compared to those who did (69% vs. 12.5%, respectively,  $p=0.021$ ) [50]. Ellerbroek et al. also found that detection of a primary focus within 5 years was greater among patients who did not receive radiotherapy than those who did (57% vs. 17%, respectively) [51]. However, some scholars pointed out that time-delayed therapy for patients with an obvious breast mass was feasible. Merson et al. found no significant difference between time-delayed therapy and mastectomy or breast radiotherapy [52]. The biggest advantage of "wait and see" therapy is preservation of the breast, but with regard to the higher local recurrence rate, the patients will suffer from the risk of losing potential benefits from breast radiation. Furthermore, failure to identify the primary focus may cause a long-term psychological burden to the patient. So, this approach is not acceptable by most breast surgeons.

Cameron et al. reported that the typical surgical intervention among 1909 OBC cases included axillary lymph node dissection with same-side mastectomy. To date, surgery remains the most widely applied intervention for OBC in clinical practice. Theoretically, radical breast resection is reasonable with the largest advantage

being the potential to identify the primary focus in 40% to 80% of OBC cases so as to ensure a pathological diagnosis. Blanchard and Farley reported that among 35 patients with OBC, 18 underwent mastectomy and 16 underwent breast-preserving surgery, of which eight simultaneously received either chemotherapy or radiotherapy. The survival period and overall survival rate of mastectomy (72.7%) were higher than that of breast-preserving surgery ( $p=0.047$  and 0.07, respectively), while the recurrence rate was also lower (36% vs. 81%). Therefore, it is necessary to add radiochemotherapy after local therapy for optimal management [53].

Studies have confirmed that standard radical radiotherapy of the whole breast is a suitable alternative to mastectomy. Meterissian evaluated postoperative tissue sections (49% non-invasive breast cancer and 75% invasive breast cancer, <1 cm) and found that breast-preserving surgery was feasible for some OBC patients [54]. A study by Ellerbroek et al. also found no significant difference between whole radiotherapy and mastectomy in the incidence of local recurrence (13% vs. 15%, respectively) or remote metastasis (22% vs. 3%, respectively) [51]. Moreover, nipple-sparing mastectomy, which provides another valuable choice for both patients and surgeons, was recently proposed. Besides the similar survival rates (79% vs. 75%, respectively), whole breast radiotherapy may result in breast fibrosis and distortion of breast shape, which may betray the initial aim of breast-preserving surgery [55].

Reference	local recurrence			surveil- lance	Corelation
	Local therapy				
	No radiotherapy	With radiotherapy	Mastectomy		
Foroudi et al. [49]	182 months			7 months	$p = 0.003$
Shannon et al. [50]	12.5%	69%			$p = 0.021$
Ellerbroek et al. [51]		13%	15%		no significant difference
Blanchard et al. [53]	36%			81%	

### Management of Axillary Lymph Nodes

The most recent study still supports the necessity of axillary lymph node dissection, which not only provides the number of metastatic lymph nodes, accurate tumor stage, and clues predictive of prognosis, but also the expression of various receptors. On the other hand, axillary lymph node dissection improves axillary control and metastatic axillary control in most OBC cases. Usually, there are three to four of metastatic axillary lymph nodes [56,57].

Whole axillary radiotherapy after surgery is essential to reduce the risk of local axillary recurrence, especially to the axillary and supraclavicular lymph nodes [55]. In general, a reduction in the radiotherapy dose will reduce damage to viscera, such as the heart and lungs. Of course, individual therapy is also reasonable [58].

### Systematic Therapy

Comprehensive therapy, including neoadjuvant/adjuvant chemotherapy, endocrine therapy, and targeted therapy, should be based on the expression of C-erb-2, Her-2, ER and PR, among other markers.

### Unique Situations

Cross-metastasis is a unique situation in OBC. In general, OBC

patients have received previous comprehensive therapy. Although metastasis to the axillary lymph nodes of the opposite side may occur during the progression of breast carcinoma, it is thought that metastasis may occur via the subcutaneous tissue or dermal net of lymph nodes [59,60].

To the best of our knowledge, an optimal therapy for OBC with cross-metastasis remains challenging, since it is difficult to determine the natural trajectory of metastasis because of the absence of adequate clinical studies. Secondly, classification of a unique type as stage II or stage IV also remains controversial. Based on these complications, bilateral mastectomy continues to be gradually accepted by women in western countries.

### Prognosis

OBC is classified as  $T_0N_{1-2}M_{0-1}$  according to the AJCC (American Joint Committee on Cancer) criteria, although most scholars consider it as stage II. In general, the prognosis of OBC is equal to or better than that of other breast cancers with metastasis to the axillary lymph nodes. Merson et al. reported that OBC may result from strong host defensive reactions in the tumor micro-environment.

A study of Vlastos found that the number of metastatic lymph nodes is the deciding factor that impacts prognosis. The 5-year survival rate with one to three positive lymph nodes is up to 42%, but only 8.7% for cases with four or more positive lymph nodes ( $p<0.0001$ ). There was no significant difference in the 5-year survival rate between mastectomy and breast preserving surgery [55]. Wang et al indicated that PR expression should be taken into account when evaluating the prognosis of OBC because PR-positive patients achieved better overall survival and were at a lower risk of local recurrence ( $p=0.052$  and 0.067, respectively) [61,62].

### Summary

OBC is a unique type of breast cancer and is quite rare in clinical practice. Therefore, it is very important to perform extensive examinations that include bilateral mammography, B-scan ultrasonography, and MRI to evaluate the status of the axillary lymph nodes and to identify the primary focus in the breast. Current OBC treatment is mastectomy or breast-preserving surgery combined with entire breast radiotherapy. Axillary lymph node therapy is essential and can provide the chance to evaluate the breast carcinoma stage to arrive at a differential diagnoses. Neoadjuvant/adjuvant chemotherapy is also applied to improve control performance. OBC is classified as  $T_0N_{1-2}M_0$  (stage II) and its prognosis is better than that of stage II primary breast cancer.

The number of metastatic lymph nodes is the deciding factor to arrive at a prognosis. In general, prognosis is poorer if four or more lymph nodes are positive. Some scholars postulated that PR-positive patients may achieve better survival and a lower incidence of local recurrence [47,63,64].

In conclusion, the management of OBC remains controversial and varies significantly with geographic location. It is unclear whether mastectomy, radiotherapy, and chemotherapy provide long-term benefits. It is recommended to perform breast MRI for patients with axillary lymphadenopathy but no evidence of an intramammary tumor on clinical examination. It is strongly recommended to establish an online registry of OBC patients for a potential longitudinal study and eventual development of international standards for diagnosis and optimal treatment.

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