EXPERIMENTAL AND THERAPEUTIC MEDICINE 29: 38, 2025

Occult breast cancer in an older woman: A case report

CONG LIU and HUA XING

Department of Breast Surgery, China-Japan Union Hospital of Jilin University, Changchun, Jilin 130033, P.R. China

Received February 16, 2023; Accepted September 20, 2023

DOI: 10.3892/etm.2024.12788

Abstract. Occult breast cancer (OBC) is a relatively rare clinical condition that can complicate differential diagnosis efforts and delay the administration of specific treatments. The individualized therapy of patients with OBC should be performed based on their clinical symptoms, imaging findings and pathological diagnosis. The present case study describes a 51-year-old woman with a painless left axillary tumor. The axillary lymph nodes of the patient were affected by invasive ductal carcinoma, as determined by histological analysis. However, the primary lesion was missed by numerous testing. The patient underwent surgery and testing for positron emission tomography/computed tomography (PET/CT). The present study comprehensively examined this case and offered a systematic analysis of the relevant scholarly works on the diagnosis, treatment and prognosis of OBC. Ultrasonography revealed the presence of three homogenous hypoechoic masses with irregular margins in the left axilla of the patient. PET/CT scanning identified multiple enlarged left axillary hypermetabolic lymph nodes. After that, the patient underwent a nipple-sparing mastectomy and an axillary lymphadenectomy. With the lymph nodes showing metastatic, infiltrating ductal carcinoma from the breast, ductal carcinoma *in situ* of the breast diagnosis was supported by a histological examination. Immunohistochemical staining revealed that resected lymph nodes were positive for both estrogen and progesterone receptors, consistent with the status of the breast as the primary tumor site. Following surgery, the patient underwent adjuvant chemotherapy treatment. At 12 months post-surgery, the patient remained well without evidence of disease. OBC cases lack the typical clinical and imaging findings associated with breast cancer, and a combination of axillary lymph node examination and immunohistochemistry is essential for accurately diagnosing affected patients. Ensuring the best patient outcomes necessitates accurate and prompt diagnosis, achieved by thorough physical examination, cautious utilization of diagnostic tools, personalized surgical interventions and histological investigation.

Correspondence to: Dr Hua Xing, Department of Breast Surgery, China-Japan Union Hospital of Jilin University, 126 Xian Tai Street, Changchun, Jilin 130033, P.R. China
E-mail: xingh@jlu.edu.cn

Key words: occult cancer, breast, axilla, metastasis, diagnostic challenge

Introduction

Occult breast cancer (OBC) is a rare presentation of breast cancer in which axillary lymph node metastasis is the primary or presenting symptom, and both clinical and imaging examinations cannot identify the primary breast lesion. OBC is estimated to comprise 0.3-1.0% of all breast cancer cases (1-3). The most effective method of treating OBC is still controversial because of these low incidence rates and the absence of randomized controlled research that specifically addresses this cancer subtype. Adenocarcinoma of the lymph nodes that has metastatic spread is the primary clinical symptom of patients with OBC and is supported by pathological investigation of the axillary lymph nodes (4-6). The exact diagnostic methodology for OBC is being continuously improved (7). The initial symptoms in individuals finally diagnosed with OBC are typically metastatic tumors in the axillary lymph nodes or other locations (8,9). Standard imaging diagnostic methods may have difficulty detecting initial breast lesions, which lowers the rate of OBC diagnosis and affects the clinical course of treatment and prognosis for patients (7). These difficulties can frequently result in misdiagnosis such that treatment is delayed and patients face a worse prognosis. Thus, the early diagnosis of OBC must be improved to improve patient survival and other prognostic outcomes.

Preoperative primary breast cancer identification can significantly impact the treatment and prognosis assessment of patients with OBC, allowing doctors to choose the most appropriate biopsy and chemotherapy treatment regimens (10). Various clinical methods are currently used to detect and diagnose breast diseases (11). Mammography is among the most common and effective diagnostic technologies, providing high detection rates for early-stage tumors (11,12). By digitizing images and employing different post-processing technologies, mammography can improve diagnostic sensitivity and specificity for OBC instances (13-15). However, using a single imaging modality is often insufficient owing to the influence of a range of factors on imaging findings (16,17). Accordingly, mammography and positron emission tomography/computed tomography (PET/CT) are often combined to diagnose breast diseases reliably (18). Mammography is beneficial for identifying benign and malignant breast lesions and detecting small breast cancer lesions in the deep breast tissue (19,20). PET/CT can help clarify the clinical staging of patients with breast cancer but is insufficient to diagnose breast cancer when used in isolation (21-23). When primary breast lesions cannot be detected through mammography and ultrasonography, magnetic resonance imaging (MRI) can be considered an alternative imaging strategy (24). Enhanced MRI and mammography are routinely used to identify breast cancer, but each has advantages and disadvantages. Thus, increasing evidence indicates that they should be combined for the best diagnostic results (25). Although it might be challenging to identify the primary breast lesions, most patients prefer to have a total mastectomy along with axillary lymph node dissection (26). Several retrospective studies have detected no significant differences in predictive outcomes associated with radiotherapy following breast-preserving surgery or total mastectomy (2,13-15). However, due to a scarcity of large-scale clinical research on OBC, these patients have no clear diagnostic or therapeutic standards. Because initial lesions are not apparent in the breast tissue of individuals with OBC, the most appropriate local treatment techniques are similarly uncertain, and it is unclear whether radiotherapy can provide significant survival benefits to these patients (27-29). The objective of the current investigation was to examine the clinicopathological characteristics, imaging manifestations and therapy alternatives of OBC to establish a basis for developing enhanced personalized treatment approaches for this rare form of breast cancer.

Case report

A 51-year-old female patient initially presented with a recently detected left axillary mass (3.1x1.5 cm) when the patient first attended the China-Japan Union Hospital of Jilin University (Changchun, China). No masses were palpable in either breast, and there was no evidence of nipple discharge. No right axillary lymph node enlargement was detected. Ultrasonography revealed three homogenous hypoechoic left axillary masses with irregular margins, the largest measuring ~3.11x1.61 cm. PET/CT scanning indicated an area of increased glucose metabolism co-registered with the left axillary lymph nodes (SUVmax=9.56; Fig. 1). There was no evidence of aberrant glucose metabolism in the basal/myoepithelial layer of the mammary gland. Mammography and ultrasonography were unable to detect any anomalies in either breast. The patient underwent fine-needle aspiration cytology (FNAC) for imaging-detected indeterminate or suspicious lesions. Pathology results for the analyzed left axillary lymph node were consistent with a diagnosis of invasive ductal carcinoma. Immunohistochemistry results were as follows: Ki-67$^+$ (70%), estrogen receptor (ER$^+$) (90%), progesterone receptor (PR$^+$) (80%), HER-2 (score 2+), E-cadherin$^+$, androgen Receptor (AR$^+$) (90%), CK5/6$^-$, p63$^-$, calponin$^-$, SOX10$^-$, GATA-3$^+$ and gross cystic disease fluid protein 15 (GCDFP-15$^+$). All analyzed tumor markers were within the normal ranges, including serum AFP, CEA, prostate-specific antigen, carbohydrate antigen (CA) 19-9 and CA 15-3 levels. The individual did not disclose any previous personal or familial instances of malignancies. Based on the findings, the patient was diagnosed with OBC and subsequently underwent a left breast nipple-sparing mastectomy with axillary lymph node dissection.

Post-surgical pathology revealed that the dissected axillary lymph nodes exhibited invasive carcinoma and that the left breast tumor was a predominantly intermediate-grade ductal carcinoma *in situ* (DCIS) (Fig. 2A and D). Immunostaining results confirmed tumor positivity for ER$^+$ (60%) (Fig. 2B), Ki-67$^+$ (25%) (Fig. 2C), GATA3$^+$, ER$^+$ (90%) (Fig. 2E), Ki-67$^+$ (40%) (Fig. 2F), PR$^+$ (80%), HER-2 (score 2+) and E-Cadherin. By contrast, tumor tissue was negative for mammaglobin, WT-1 and PAX-8 (Fig. 2). At 1 year after surgery, the patient was discharged and was recurrence-free. The patient was treated with adjuvant chemotherapy (Table I).

The present investigation was approved by the Ethics Committee of China-Japan Union Hospital (grant no. 2023033009), and the patient provided written informed consent for its publication.

Discussion

OBC was first described in 1907 by Halsted (30). Since then, the diagnostic and therapeutic approach has been the subject of debate, and as more effective diagnostic modalities have been created, its prevalence has decreased (17-20). The current definition of OBC refers to a type of primary breast cancer detected histologically by biopsy of the axillary lymph nodes but without any clinically apparent lesions or radiographic evidence (21-23). The development of OBC still remains poorly understood. For the finding of metastatic carcinoma in axillary nodes with only non-invasive carcinoma in the breast, Terada *et al* hypothesized that the origin of OBC is ectopic breast tissue present in axillary lymph nodes (ALNs) (36,37). Recent developments in radiological imaging demonstrate that a primary breast tumor is absent in patients with OBC (37). According to reports, ectopic breasts found in ALNs can cause proliferative breast lesions (37-41). Immunohistochemistry has identified a variety of cellular subtypes in OBC, including ordinary breast cancer. The progression and metastasis of occult breast cancer may indicate that angiogenesis is activated in the axilla instead of the breast, and that this leads to the primary carcinoma metastasis occurring at a sub-clinical level (42). The determination of more general and personalized treatment options is hampered by the lack of comprehensive clinical research in several retrospective researches (43,44). The absence of an in-breast clinical finding is the original definition of OBC; however, it has since been expanded to include negative mammography and ultrasonography results as well. The immunology field and the distinctions in the microenvironments of lymphoid tissue and breast tissue may be explored further.

Occult breast cancer is a medical condition infrequently encountered in clinical practice. The diagnostic process for occult breast cancer is complicated by the challenge of identifying the primary tumor site in affected patients. The diagnosis and treatment of OBC have gained significant research attention since Halsted's initial description of its symptoms, therapy and natural progression (30). Confirming OBC diagnoses requires patients to undergo an axillary mass puncture or mass excision biopsy (31,36). When axillary tumors are pathologically diagnosed as metastatic adenocarcinomas of the lymph nodes, a clinical diagnosis of OBC should be considered (46). Bhatia *et al* revealed that a high proportion of female OBC

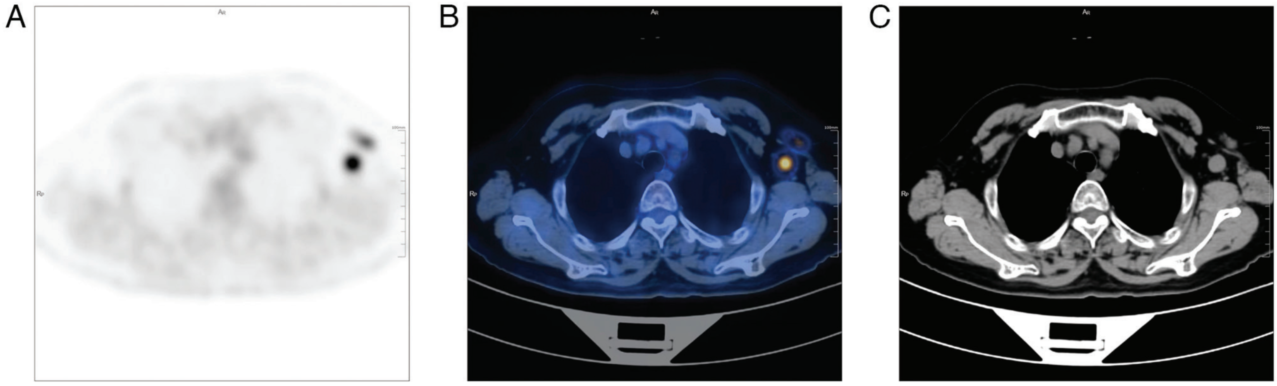

Figure 1. PET/CT images findings. Selected (A) PET, (B) PET/CT and (C) CT images show multiple enlarged hypermetabolic lymph nodes in the left axilla. PET, positron emission tomography; CT, computed tomography.

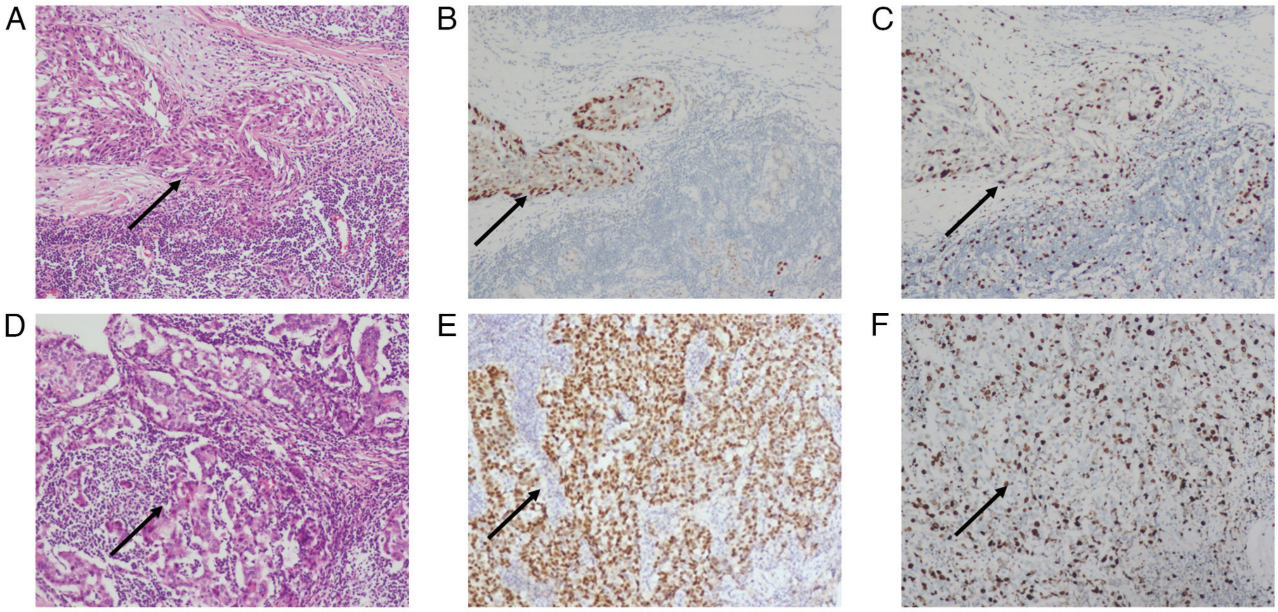

Figure 2. Histopathological analysis and immunohistochemical staining of the primary tumor and lymph nodes metastasis. (A) Breast tumor exhibited a primarily intermediate-grade ductal carcinoma *in situ*. The observed structure exhibited a dense and porous composition, accompanied by nuclear atypia of moderate severity. Hematoxylin and eosin staining shows ductal carcinoma *in situ* (indicated by arrow). (B) Immunohistochemical staining for ER^+, which identifies ductal carcinoma *in situ* (indicated by arrow). (C) Immunohistochemical staining for Ki-67^+ (25%), which identifies ductal carcinoma *in situ* (indicated by arrow). (D) Metastatic infiltrating ductal carcinoma (indicated by arrow). Tumor cells are arranged in strip, tubular and pseudopapillary patterns. (E) Immunohistochemical staining for ER^+, which identifies metastatic infiltrating ductal carcinoma (indicated by arrow). (F) Immunohistochemical staining for Ki-67 (+,40%), which identifies metastatic infiltrating ductal carcinoma (indicated by arrow). Magnification, x100. ER, estrogen receptor.

cases are positive for ER and/or PR (47). Immunohistochemical analyses of PR, ER and HER-2 status following the surgical excision of axillary tumors should be considered as a means of aiding patient diagnosis. The patient in the present case study was ER, PR, and HER-2 positive. However, when lesions are negative for ER and PR, it is impossible to rule out the diagnosis of OBC because certain breast cancer cases are hormone receptor-independent (33,48). Future advancements in diagnostic methods and imaging modalities are anticipated to make it easier to detect intramammary lesions, which have historically been challenging to detect. The diagnosis and management of OBC remains debatable due to these factors.

The percentage of cancer cases with cancer of unknown primary (CUP) ranges from 5-10% (49,50), and 10-40% of these patients have metastatic lesions limited to lymph nodes (51). Only 1% of all cancers have axillary lymph node metastases from an unidentified origin (52). CUP has a higher relative contribution to cancer mortalities because of its high mortality rate (53). The greater success in detecting primary tumors is probably the cause of the declining incidence of CUP (54).

Histologically confirmed metastatic malignant tumors whose primary site cannot be detected after complete clinical and radiological examinations are called CUP (55,56). After completing clinical and pathological diagnostic procedures, the diagnosis of CUP relies on a multidisciplinary consultation to ascertain whether the tumor symptoms align with metastases indicative of CUP or original cancer (57). A subset of CUP, known as OBC, is a metastatic breast cancer confirmed by biopsy that has no recognizable primary breast

Table I. Clinicopathological characteristics.

Characteristic	Value
Age, years	51
Location	Left armpit
Menstrual status	Premenopausal
Axillary staging	N1
Family history	None
Axillary lump size	2.25x0.89-3.11x1.61 cm
Neoadjuvant chemotherapy	No
Molecular classification	Luminal B
Operation method	Nipple-sparing mastectomy with axillary lymph node dissection
Pathological types of primary foci	Ductal carcinoma *in situ*

tumor (56). Metastasis to the axillary and cervical lymph nodes is frequently observed as an initial sign of ovarian breast cancer (56). Imaging and pathological evaluations to rule out a primary breast tumor can be used to diagnose OBC. The incidence of OBC has been declining due to the development of sophisticated diagnostic techniques (58). Due to the scarcity of data, there is currently insufficient information to formulate comprehensive management standards for OBC. The diagnosis and treatment of OBC pose a significant clinical challenge because of the requirement of conducting a thorough physical examination, utilizing specific radio diagnostic testing, and analyzing pathologic and immunohistochemical findings (32,34). The lack of an intelligent and personalized system to rapidly detect patients with OBC in the early stages is among the existing clinical practice issues.

Based on available findings, MRI has demonstrated the capability to generate three-dimensional images, hence aiding oncologists in detecting a primary breast lesion when conventional breast imaging modalities have proven ineffective in identifying the origin of the lesion. This has been observed in ~75% of the cases (59). For the treatment of OBC, mastectomy and breast preservation have been suggested (35), with or without lymphadenectomy, for diagnosis and locoregional control (26,60). Most patients diagnosed with OBC initially seek medical input regarding a mass in the armpit without any palpable breast mass (61,62). Several factors can contribute to the unusual presentation of OBC (62,63). The growth of primary intramammary lesions may have been hindered due to immune-mediated inhibition, leading to relatively modest lesions. Furthermore, fibrous mastitis is responsible for the thickness of the breast tissue, which in turn hampers the identification of minor breast lesions (64). In the current case, the lymph nodes of the patient displayed indications of invasive cancer. A number of metastatic cancer cells exhibited diffuse infiltration at the microscopic scale, destroying the typical lymph node architecture. Consequently, only limited quantities of lymphocytes were observable amidst clusters of cancer cells. Tumor tissue morphology within lymph nodes is typically similar to that in primary lesions, with strip-like, papillary, acinar and clumpy presentations (65-68). In OBC cases where an axillary mass is the first symptom, lymph nodes are generally nodular and diffusely infiltrated by tumor cells, as in the present case, destroying the integrity of normal lymphoid structures. The appearance of tumor nuclei is determined mainly by the degree of differentiation. High-grade nuclei are commonly found in poorly differentiated areas, including large nuclei, vesicular nuclei, uneven chromatin and even tumor giant cells. On the other hand, well-differentiated epithelial papillary areas are predominantly composed of low-grade nuclei equal in size to the nuclei of normal breast cells, with mitotic figures being infrequent (45-49).

There is currently a lack of specific examination procedures for OBC. Nevertheless, it is anticipated that future developments in the field of medical imaging will contribute to the identification of small breast lesions, thereby significantly enhancing the probability of early detection (70,71). Among various techniques, imaging techniques have emerged as practical tools for detecting and monitoring responses to therapy in patients with breast cancer (Table II). Mammography and ultrasonography are the traditional breast cancer screening approaches, but these fail to detect occult lesions in some patients (72,73). Compared to more conventional methods, full-field digital mammography has shown significant gains in image quality and contrast while exposing individuals to less radiation (74). Breast tumors and other high-density lesions can be seen anatomically in the breast tissue using mammography, which measures their size, density, borders and development (19,75,76).

Combining digital breast tomosynthesis with grid positioning technology can accurately diagnose microcalcifications in patients with OBC with negative palpation, further improving tumor detection rates (77-82). MRI can detect undetectable lesions via color Doppler ultrasonography or mammography while allowing for the observation of internal blood flow, thereby providing a high level of detection sensitivity (54-56). As a result, it offers an efficient method of evaluating soft tissue that is especially useful for identifying deep breast lesions. It also enables the evaluation of the quantity, size and extent of these lesions (57-59). Prior MRI results have revealed OBC lesions that present as lump-like regions of irregular circular enhancement or non-lump-like areas of uneven enhancement (84,85). Clinicians can successfully identify breast lesions in numerous cases by using MRI, PET/CT and other systemic diagnostic techniques while ruling

Table II. Imaging techniques employed in identifying patients with breast cancer.

Author, year	Techniques	Functions	(Refs.)
Mariscotti *et al*, 2014; Kim *et al*, 2016; An *et al*, 2014	MRI	MRI can be used on women who have just been diagnosed with BC to determine the extent of the tumor and other lesions with excellent sensitivity, in addition to the first identification of BC. An MRI is routinely utilized before surgery	(91-93)
Van *et al*, 2006	MR mammography	MR mammography is a valuable addition to traditional imaging in preoperative local breast cancer staging	(147)
Zeeshan *et al*, 2018; Li *et al*, 2019	DM	DM is a medical imaging technique that provides superior image quality while minimizing radiation exposure. It can detect breast cancer at its early stages, offering patients a favorable prognosis and potentially increasing their life expectancy	(148,149)
Seeram *et al,* 2019	FFDM	To enhance the perceptibility of fine details and differences in brightness within a picture, hence improving the ability to identify abnormalities in breast tissue, FFDM is employed. This technique involves the use of a digital detector that is coupled to a computer system for the acquisition and processing of radiographic images of the breast	(150)
Jadvar *et al*, 2014; Koolen *et al*, 2014	PET/CT	The use of PET/CT is crucial in breast oncology. It frequently serves as a primary staging and therapy monitoring tool rather than identifying primary BC. The most widely used radiopharmaceutical for imaging BC with PET/CT is ^{18}F-FDG	(151,152)
Singh *et al*, 2016; Ruiz-Ortega *et al*, 2016; Kozegar *et al*, 2017; Mohammed *et al*, 2018; Moon *et al*, 2018; Kim *et al*, 2015	US	US is a widely accepted and commonly employed diagnostic modality for evaluating breast complaints. US is the recommended modality for performing breast biopsies	(100-105, 153-158)
Cai *et al*, 2015; Nakashima *et al*, 2017; Mercier *et al*, 2015; Roganovic *et al*, 2015	DBT	DBT utilizes three-dimensional imaging to provide a range of physical perspectives for breast examination. The addition of DBT to conventional digital mammography has the potential to enhance sensitivity	(159-162)
Das *et al*, 2006	X-ray mammography	X-ray mammography is the primary technique for identifying breast cancer in its early stages. But due to the lack of specificity in X-ray mammography, numerous unnecessary biopsies are performed	(163)
Brem *et al*, 2008; Yoon *et al*, 2015; Tan *et al*, 2016; Yu *et al*, 2016; Cho *et al*, 2016	BSGI	Compared with scintimammography, BSGI is more sensitive and can identify breast tumors <1 cm in size. BSGI is especially useful for imaging BC in dense breasts and multifocal and multicentric diseases	
Simanek *et al*, 2016; Berrington *et al*, 2009	SPECT/CT	SPECT/CT, which combines a gamma camera and non-diagnostic CT, is crucial for detecting BC metastasis. SPECT/CT provides more precise anatomical information compared with planar sentinel lymph node scintigraphy when imaging sentinel lymph nodes	(164-170)

FFDM, full-field digital mammography; US, Ultrasonography; SPECT, single-photon emission computed tomography; PET, positron emission tomography; DM, digital mammography; 3D, three-dimensional; MRI, magnetic resonance imaging; BSGI, breast-specific gamma imaging; DBT, digital breast tomosynthesis; DM, digital mammography.

out the possibility of other malignant tumor sources in the body and spotting any metastases existing within other tissues or organ compartments (86,87). The sensitivity and specificity of PET-CT for axillary lymph node metastasis are 95 and 65%, respectively, and it is commonly used to evaluate patients with OBC with negative mammography results. PET/CT is of particular value for the differential diagnosis of OBC, given its ability to recognize axillary lymph node metastasis and primary lesions of non-breast origin (88). In the present case, the patient received PET/CT imaging, which revealed several enlarged hypermetabolic left axillary lymph nodes. Pathology revealed that these lymph nodes exhibited metastases, and the left breast tumor was primarily intermediate-grade DCIS. When routine examination results are inconclusive or difficult to interpret, PET/CT can provide practical diagnostic assistance, particularly in individuals with locally advanced or metastatic disease. Although a number of investigations have suggested the potential efficacy of PET/CT in detecting OBC, its utility in this specific patient cohort is constrained due to the small size of lesions (89).

Breast-specific γ imaging (BSGI) is a high-resolution imaging approach that can detect occult breast lesions at sub-centimeter resolution with improved sensitivity and specificity compared with MRI. BSGI enables the detection of small tumor foci even in dense breast tissue (90,91). The technique known as radioisotope occult lesion localization involves administering a solution of water-soluble non-ionic iodine contrast agent and radionuclide-labeled albumin gel close to the suspected lesion location, followed by a localization biopsy under the supervision of a γ-ray detector. Implementing this radionuclide localization method reduces the possibility of requiring additional surgical procedures while also considering the post-surgical aesthetic outcomes and their impact on patient appearance (92,93). However, radionuclides are limited by their short duration of activity, such that they can only be injected within one day of the operation (94-96). If primary lesions in the breast tissue are successfully detected in patients with OBC, they can receive a definitive diagnosis.

Nevertheless, there are cases where identifying these initial abnormalities remains elusive, even after undergoing numerous supplementary investigations (13,97). In the case of these individuals, it is imperative to distinguish between OBC and alternative types of malignancies, including auxiliary breast cancer, thyroid carcinoma, lung cancer and melanoma (33,98). The detection of accessory breast cancer relies primarily on pertinent exams and a thorough clinical history. The absence of accessory breast tissue identified during ALND can be considered sufficient evidence to dismiss it as a potential etiological factor for the disease (99). Tumor tissue in these cases with exhibit morphological characteristics similar to those of the primary tumor, and a primary focus may also be found via chest CT, abdominal CT or other examinations (100). The tumor may be poorly differentiated and difficult to detect based on its histological morphology when it is organoid, acinar or lamellar, although further immunohistochemistry analyses can aid in diagnosis (3,69-71). When encountering inexplicable growth of axillary lymph nodes, it is essential to evaluate the possibility of OBC as a potential diagnosis. When breast and accessory breast examinations yield negative results, and the clinical primary tumor site remains uncertain, it is advisable to pursue pathological evaluation. Small amounts of invasive ductal carcinoma tissue and tumor thrombus are observed within the intravascular lymphatic vessels, suggesting a potential case of OBC.

A consensus on the optimal technique for treating OBC has not yet been reached (16), and there is an ongoing debate on the choice between radical mastectomy and breast-conserving surgery for patients. Surgical interventions available for individuals with OBC include mastectomy, breast-conserving surgery or a combination of radiation and ALND. The relative benefits of these three interventional strategies appear similar, with a high local recurrence rate for patients that undergo ALND alone and with patients with OBC facing an overall survival (OS) rate that is relatively poor (72-74). Some small-scale studies have supported the benefits of breast-conserving therapy for patients with OBC (75-77). By contrast, some researchers have cast doubt on the benefits of ALND combined with radiotherapy as an alternative treatment for these patients. When comparing a breast-conserving surgery group to a radical surgery group in a retrospective analysis of clinical data from 750 patients with OBC, Walker *et al* (7) found no significant differences in 10 year OS, with the outcomes in both groups being improved compared with those in the untreated and ALND groups.

He *et al* (28) reported similar levels of therapeutic efficacy in patients with OBC that underwent either mastectomy or a combination of ALND and subsequent radiotherapy. Some authors have posited that treatment can be temporarily discontinued in patients where primary breast lesions cannot be located, following axillary tumor removal and close observation (109). Considering the low rates of OBC incidence and the lack of extensive retrospective investigations of this patient population, breast-conserving surgery or mastectomy should be carried out as necessary when lesions are subsequently discovered (13,69). However, additional research is required to elucidate the comparative advantages of these various therapy alternatives. According to Olson *et al* (44), breast-conserving surgery may be advantageous for patients who do not have a successfully circumscribed primary lesion following MRI scanning. By contrast, De Bresser *et al* (59) suggested that while MRI offers a high degree of specificity to detect primary tumor foci in patients with OBC, its specificity is limited. Additionally, this study recommended that in cases where MRI detects breast lesions, a biopsy should be conducted using ultrasound or MRI guidance. Subsequently, if deemed suitable based on the biopsy results, breast-conserving surgery should be carried out. Kemeny (110) proposed mastectomy as the most appropriate treatment option for female patients exhibiting axillary lymph node metastases without any identified primary breast lesion and negative mammography results. By contrast, Copeland and Mcbride (111) suggest that radical mastectomy cannot be performed in cases where the primary breast lesion cannot be located.

Merson *et al* (26) compared surgical approaches for treating patients with OBC with axillary lymph node metastasis. This study observed no significant differences in 5- or 10-year survival rate when comparing the breast-conserving surgery and radical mastectomy groups. Because the effects of total mastectomy are comparable to those of ALND and radiotherapy, it indicates that patients with negative mammography results do not necessarily need to undergo mastectomy. The therapeutic results for patients with OBC undergoing ALND are the same as those undergoing ALND in conjunction with mastectomy or breast conservation surgery (2).

Studies of local treatment options suggest that patients with OBC that do not undergo mastectomy can benefit from radiotherapy (105,112). According to some reports, systemic treatment is considered the most suitable approach for patients with OBC who do not have a detectable primary breast lesion (107,113,114). This approach involves treating the problem as a systemic disease and enabling breast preservation. This can have the benefit of alleviating the psychological distress often associated with breast surgery. The prognosis results of patients are not improved by local treatment, even in cases where breast abnormalities are discovered (115). In the subset of patients with OBC in whom digestive tract metastases are the first symptom, the disease should be treated as a form of advanced breast cancer and treated through appropriate combinations of chemotherapy, endocrine therapy, targeted therapy and other systemic treatments (116-118). If patients exhibit gastrointestinal bleeding, perforation, obstruction or other difficult-to-treat complications, palliative surgery can be performed to prolong the median survival duration of this patient population (119).

Due to the systemic nature of breast cancer, surgical intervention represents but a single component of the comprehensive therapy approach. Adjuvant therapy options for patients with OBC encompass a range of interventions, such as endocrine therapy, chemotherapy, targeted therapy, targeted regional radiation, and immunotherapy regimens. The selection of these treatment modalities is guided by established treatment guidelines for non-OBC patients and the specific clinical characteristics and needs of the particular patient under consideration. Neoadjuvant chemotherapy (NAC) for OBC can help target axillary lymph nodes and facilitate their surgical removal in these patients while preventing the development of drug-resistant tumor cells, eliminating small metastatic foci, reducing tumor cell activity and restricting metastatic spread (120-123). Some reports have suggested that NAC treatment for patients with OBC can be administered based on the immunohistochemical staining of axillary lymph node biopsy samples, patient age, ultrasound and ^{18}F-FDG PET/CT imaging findings (123-127). In general, managing individuals with OBC should encompass a comprehensive treatment approach comprising surgical intervention, chemotherapy, radiotherapy, endocrine therapy, targeted therapy and other suitable interventions. When determining the appropriate course of action, it is crucial to thoroughly consider patient-specific factors, pathological classification, and staging outcomes.

The identification of pertinent prognostic variables in patients with OBC is ongoing. The prognosis of patients becomes poorer as the number of metastatic axillary lymph nodes increases in breast cancer (83-85). There is also evidence that hormone receptor status, tumor marker expression, primary tumor pathological type, number of axillary lymph nodes, the timing of axillary lymph node diagnosis and the presence or absence of distant supraclavicular metastasis are all related to patient outcomes (86-88). In individuals diagnosed with OBC, nodal status may offer value as an independent predictor of poor outcomes (2,10,26), and those patients harboring distant metastases exhibit a very poor prognosis and a short survival interval. Vlastos *et al* (35) also discovered a connection between outcomes of patients with OBC and the quantity of positive axillary lymph nodes. However, deciding between primary surgery and simple lymph node dissection does not significantly affect patient survival rates.

The 10 year survival rate of patients with atypical axillary metastases is 50-71%, with this rate being slightly improved compared with that associated with stage II disease (35,69,128). Significant prognostic factors include hormone receptor status and the number of involved axillary lymph nodes (35,128). Generally, the 5 year overall survival of patients with 1-3 involved lymph nodes tends to be improved compared with that of patients with 4+ involved nodes (35).

When comparing patients with early breast cancer and OBC, Montagna *et al* (129) found no substantial improvements in 5-year disease-free or overall survival. However, the disease advances more rapidly when patients are determined to have triple-negative breast cancer (TNBC), and patients were at a higher risk of death or recurrence. ER is associated with a poor prognosis in TNBC cases (4,15), and systemic endocrine therapy is an essential element that can influence the survival of individuals diagnosed with hormone receptor-positive breast cancer (130).

The presenting symptom in patients with OBC is typically painless axillary lymph node enlargement, which may coincide with distant tumor metastasis and paraneoplastic neurological syndromes in some cases (131). Patients should undergo prompt breast examination, ultrasonography and mammography when isolated enlarged axillary lymph nodes are detected (132,133). Breast-conserving surgery, mastectomy and ALND should be considered if primary breast lesions are detected through these assessments (134-136). If no primary breast lesion is detected, it is recommended that patients undergo FNAC, core needle biopsy or other forms of puncture biopsy (137-139). If the patient is ultimately diagnosed with metastatic cancer, immunohistochemical staining for ER, PR, HER-2, Ki-67 and GCDFP-15 should be performed together with other tests, including thyroid ultrasound scans and CT scans of the chest, abdomen and pelvis to detect or distinguish between OBC and other forms of metastatic cancer (100,140,141). Each OBC patient's specific conditions should be considered, and neoadjuvant chemotherapy, adjuvant chemotherapy, radiotherapy and targeted therapy should be explored as potential approaches to improving patient survival and prognosis (142). OBC cases are sporadic, and large-scale studies of populations of patients with OBC are thus lacking, with most research instead consisting of analyses of small patient cohorts (143). Accordingly, the basis for diagnosing and treating this cancer type is relatively limited, and additional evidence is needed to establish the most appropriate clinical management of affected patients (142). The further investigation centered on the pathogenesis and attributes of OBC to discern the immunological elements that contribute to the expansion of primary lesions in affected individuals holds promise for enhancing targeted therapeutic interventions, finally improving prognostic outcomes (29,143,144). The present comprehensive discussion of current issues facing the diagnosis of OBC, the importance of sentinel lymph nodes and internal mammary lymph nodes in treating OBC and the standardized treatment of OBC will benefit from rapid advances in artificial intelligence, sequencing and big data technologies in clinical practice (145,146). Formulating robust diagnostic and treatment guidelines will help patients with OBC receive a timely and accurate diagnosis to begin treatment as quickly as possible. An improved prognosis for patients with OBC will also result from the continued use of targeted medications, immunotherapies and other cutting-edge pharmacological drugs.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All data generated and/or analyzed during this study are included in this published article.

Authors' contributions

CL and HX conceived the review and acquired data. CL and HX participated in the process of writing and reviewing the manuscript. CL and HX confirm the authenticity of all the raw data. All authors contributed to the conception and revision of the manuscript and approved its submission. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The China-Japan Union Hospital Medical Ethics Committee approved the present study (approval no. 2023033009). Written informed consent was obtained during the initial data collection for participation.

Patient consent for publication

The patient and control subject consented to the publication of this case report and accompanying images.

Competing interests

The authors declare that they have no competing interests.

References

1. Baron PL, Moore MP, Kinne DW, Candela FC, Osborne MP and Petrek JA: Occult breast cancer presenting with axillary metastases: Updated Management. Arch Surg 125: 210-214, 1990.
2. Sohn G, Son BH, Lee SJ, Kang EY, Jung SH, Cho SH, Baek S, Lee YR, Kim HJ, Ko BS, *et al*: Treatment and survival of patients with occult breast cancer with axillary lymph node metastasis: A nationwide retrospective study. J Surg Oncol 110: 270-274, 2014.
3. Patel J, Nemoto T, Rosner D, Dao TL and Pickren JW: Axillary lymph node metastasis from an occult breast cancer. Cancer 47: 2923-2927, 1981.
4. Huang Y, Wu H and Luo Z: A retrospective study of optimal surgical management for occult breast carcinoma: Mastectomy or quadrantectomy? Medicine (Baltimore) 96: e9490, 2017.
5. Yamaguchi H, Ishikawa M, Hatanaka K, Uekusa T, Ishimaru M and Nagawa H: Occult breast cancer presenting as axillary metastases. Breast 15: 259-262, 2006.
6. Abe S, Abe N, Noda M, Okano M, Tachibana K, Yoshida S, Kiko Y, Hashimoto Y, Hatakeyama Y, Rokkaku Y and Ohtake T: A Case of Occult Breast Cancer. Gan To Kagaku Ryoho 44: 1095-1097, 2017 (In Japanese).
7. Walker GV, Smith GL, Perkins GH, Oh JL, Woodward W, Yu TK, Hunt KK, Hoffman K, Strom EA and Buchholz TA: Population-based analysis of occult primary breast cancer with axillary lymph node metastasis. Cancer 116: 4000-4006, 2010.
8. Frattaroli FM, Carrara A, Conte AM and Pappalardo G: Axillary metastasis as first symptom of occult breast cancer: A case report. Tumori 88: 532-534, 2002.
9. Liu L, Zhang J, Chen M, Ren S, Liu H and Zhang H: Anemia and thrombocytopenia as initial symptoms of occult breast cancer with bone marrow metastasis: A case report. Medicine (Baltimore) 96: e8529, 2017.
10. Woo SM, Son BH, Lee JW, Kim HJ, Yu JH, Ko BS, Sohn G, Lee YR, Kim H, Ahn SH and Baek SH: Survival outcomes of different treatment methods for the ipsilateral breast of occult breast cancer patients with axillary lymph node metastasis: A single center experience. J Breast Cancer 16: 410-416, 2013.
11. Coleman C: Early detection and screening for breast cancer. Semin Oncol Nurs 33: 141-155, 2017.
12. Anderson WF, Jatoi I and Devesa SS: Assessing the impact of screening mammography: Breast cancer incidence and mortality rates in Connecticut (1943-2002). Breast Cancer Res Treat 99: 333-340, 2006.
13. Nguyen QD, Randall JW, Harmon TS, Robinson AS, Cotes C, Lee AE, Mahon BH and Sadruddin S: Detection of a mammographically occult breast cancer with a challenging clinical history. Cureus 10: e3594, 2018.
14. Lee J and Nishikawa RM: Identifying women with mammographically-occult breast cancer leveraging GAN-Simulated Mammograms. IEEE Trans Med Imaging 41: 225-236, 2022.
15. Tartter PI, Weiss S, Ahmed S, Kamath S, Hermann G and Drossman S: Mammographically occult breast cancers. Breast J 5: 22-25, 1999.
16. Prasad SN and Houserkova D: The role of various modalities in breast imaging. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 151: 209-218, 2007.
17. Planche K and Vinnicombe S: Breast imaging in the new era. Cancer Imaging 4: 39-50, 2004.
18. Sánchez LR, Treviño LMT and Sánchez GE: Fusion of Digital Mammography with High-Resolution Breast PET: An Application to Breast Imaging. In: 2nd EAI International Conference on Smart Technology. Torres-Guerrero F, Neira-Tovar L and Bacca-Acosta J (eds). Springer International Publishing, Cham, pp111-125, 2023.
19. Fiorica JV: Breast cancer screening, mammography, and other modalities. Clin Obstet Gynecol 59: 688-709, 2016.
20. Rodriguez-Ruiz A, Lång K, Gubern-Merida A, Broeders M, Gennaro G, Clauser P, Helbich TH, Chevalier M, Tan T, Mertelmeier T, *et al*: Stand-Alone artificial intelligence for breast cancer detection in mammography: Comparison with 101 radiologists. J Natl Cancer Inst 111: 916-922, 2019.
21. Groheux D, Espié M, Giacchetti S and Hindié E: Performance of FDG PET/CT in the clinical management of breast cancer. Radiology 266: 388-405, 2013.
22. Radan L, Ben-Haim S, Bar-Shalom R, Guralnik L and Israel O: The role of FDG-PET/CT in suspected recurrence of breast cancer. Cancer 107: 2545-2551, 2006.
23. Zangheri B, Messa C, Picchio M, Gianolli L, Landoni C and Fazio F: PET/CT and breast cancer. Eur J Nucl Med Mol Imaging 31 (Suppl 1): S135-S142, 2004.
24. Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, Anderson B, Burstein HJ, Chew H, Dang C, *et al*: Breast Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 20: 691-722, 2022.
25. Zhao YF, Chen Z, Zhang Y, Zhou J, Chen JH, Lee KE, Combs FJ, Parajuli R, Mehta RS, Wang M and Su MY: Diagnosis of breast cancer using radiomics models built based on dynamic contrast enhanced MRI combined with mammography. Front Oncol 11: 774248, 2021.
26. Merson M, Andreola S, Galimberti V, Bufalino R, Marchini S and Veronesi U: Breast carcinoma presenting as axillary metastases without evidence of a primary tumor. Cancer 70: 504-508, 1992.
27. Varadarajan R, Edge SB, Yu J, Watroba N and Janarthanan BR: Prognosis of occult breast carcinoma presenting as isolated axillary nodal metastasis. Oncology 71: 456-459, 2006.
28. He M, Tang LC, Yu KD, Cao AY, Shen ZZ, Shao ZM and Di GH: Treatment outcomes and unfavorable prognostic factors in patients with occult breast cancer. Eur J Surg Oncol 38: 1022-1028, 2012.

29. Khandelwal AK and Garguilo GA: Therapeutic options for occult breast cancer: A survey of the American Society of Breast Surgeons and review of the literature. Am J Surg 190: 609-613, 2005.
30. Halsted WS: I. The results of radical operations for the cure of carcinoma of the breast. Ann Surg 46: 1-19, 1907.
31. Lloyd MS and Nash AG: 'Occult' breast cancer. Ann R Coll Surg Engl 83: 420-424, 2001.
32. Ofri A and Moore K: Occult breast cancer: Where are we at? Breast 54: 211-215, 2020.
33. Wong YP, Tan GC, Muhammad R and Rajadurai P: Occult primary breast carcinoma presented as an axillary mass: A diagnostic challenge. Malays J Pathol 42: 151-155, 2020.
34. Xu R, Li J, Zhang Y, Jing H and Zhu Y: Male occult breast cancer with axillary lymph node metastasis as the first manifestation: A case report and literature review. Medicine (Baltimore) 96: e9312, 2017.
35. Vlastos G, Jean ME, Mirza AN, Mirza NQ, Kuerer HM, Ames FC, Hunt KK, Ross MI, Buchholz TA, Buzdar AU and Singletary SE: Feasibility of breast preservation in the treatment of occult primary carcinoma presenting with axillary metastases. Ann Surg Oncol 8: 425-431, 2001.
36. Fayanju OM, Jeffe DB and Margenthaler JA: Occult primary breast cancer at a comprehensive cancer center. J Surg Res 185: 684-689, 2013.
37. Terada M, Adachi Y, Sawaki M, Hattori M, Yoshimura A, Naomi G, Kotani H, Iwase M, Kataoka A, Onishi S, *et al*: Occult breast cancer may originate from ectopic breast tissue present in axillary lymph nodes. Breast Cancer Res Treat 172: 1-7, 2018.
38. Kadowaki M, Nagashima T, Sakata H, Sakakibara M, Sangai T, Nakamura R, Fujimoto H, Arai M, Onai Y, Nagai Y, *et al*: Ectopic breast tissue in axillary lymph node. Breast Cancer 14: 425-428, 2007.
39. Edlow DW and Carter D: Heterotopic epithelium in axillary lymph nodes: Report of a case and review of the literature. Am J Clin Pathol 59: 666-673, 1973.
40. Turner DR and Millis RR: Breast tissue inclusions in axillary lymph nodes. Histopathology 4: 631-636, 1980.
41. Maiorano E, Mazzarol GM, Pruneri G, Mastropasqua MG, Zurrida S, Orvieto E and Viale G: Ectopic breast tissue as a possible cause of false-positive axillary sentinel lymph node biopsies. Am J Surg Pathol 27: 513-518, 2003.
42. Locopo N, Fanelli M and Gasparini G: Clinical significance of angiogenic factors in breast cancer. Breast Cancer Res Treat 52: 159-173, 1998.
43. Blanchard DK, Shetty PB, Hilsenbeck SG and Elledge RM: Association of surgery with improved survival in stage IV breast cancer patients. Ann Surg 247: 732-738, 2008.
44. Olson JA Jr, Morris EA, Van Zee KJ, Linehan DC and Borgen PI: Magnetic resonance imaging facilitates breast conservation for occult breast cancer. Ann Surg Oncol 7: 411-415, 2000.
45. Sanuki JI, Uchida Y, Uematsu T, Yamada Y and Kasami M: Axillary mass suspected to be occult breast carcinoma: A case study of skipped axillary lymph node metastasis from endometrial carcinoma in which core-needle biopsy was useful for diagnosis. Breast Cancer 16: 72-76, 2009.
46. Hulka CA, Smith BL, Sgroi DC, Tan L, Edmister WB, Semple JP, Campbell T, Kopans DB, Brady TJ and Weisskoff RM: Benign and malignant breast lesions: Differentiation with echo-planar MR imaging. Radiology 197: 33-38, 1995.
47. Bhatia SK, Saclarides TJ, Witt TR, Bonomi PD, Anderson KM and Economou SG: Hormone receptor studies in axillary metastases from occult breast cancers. Cancer 59: 1170-1172, 1987.
48. Poulakaki F: Occult Breast Cancer. In: Breast Cancer Essentials. Rezai M, Kocdor MA and Canturk NZ (eds). Springer International Publishing, Cham, pp667-674, 2021.
49. Van de Wouw AJ, Janssen-Heijnen ML, Coebergh JW and Hillen HF: Epidemiology of unknown primary tumours; incidence and population-based survival of 1285 patients in Southeast Netherlands, 1984-1992. Eur J Cancer 38: 409-413, 2002.
50. Randén M, Rutqvist LE and Johansson H: Cancer patients without a known primary: Incidence and survival trends in Sweden 1960-2007. Acta Oncol 48: 915-920, 2009.
51. Hemminki K, Bevier M, Hemminki A and Sundquist J: Survival in cancer of unknown primary site: Population-based analysis by site and histology. Ann Oncol 23: 1854-1863, 2012.
52. Pentheroudakis G, Lazaridis G and Pavlidis N: Axillary nodal metastases from carcinoma of unknown primary (CUPAx): A systematic review of published evidence. Breast Cancer Res Treat 119: 1-11, 2010.
53. Brewster DH, Lang J, Bhatti LA, Thomson CS and Oien KA: Descriptive epidemiology of cancer of unknown primary site in Scotland, 1961-2010. Cancer Epidemiol 38: 227-234, 2014.
54. Binder C, Matthes KL, Korol D, Rohrmann S and Moch H: Cancer of unknown primary-Epidemiological trends and relevance of comprehensive genomic profiling. Cancer Med 7: 4814-4824, 2018.
55. Krämer A, Hübner G, Schneeweiss A, Folprecht G and Neben K: Carcinoma of unknown primary-an orphan disease? Breast Care (Basel) 3: 164-170, 2008.
56. Barbieri E, Anghelone CAP, Gentile D, La Raja C, Bottini A and Tinterri C: Metastases from occult breast cancer: A case report of carcinoma of unknown primary Syndrome. Case Rep Oncol 13: 1158-1163, 2020.
57. Krämer A, Bochtler T, Pauli C, Baciarello G, Delorme S, Hemminki K, Mileshkin L, Moch H, Oien K, Olivier T, *et al*: Cancer of unknown primary: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 34: 228-246, 2023.
58. Urban D, Rao A, Bressel M, Lawrence YR and Mileshkin L: Cancer of unknown primary: A population-based analysis of temporal change and socioeconomic disparities. Br J Cancer 109: 1318-1324, 2013.
59. de Bresser J, de Vos B, van der Ent F and Hulsewé K: Breast MRI in clinically and mammographically occult breast cancer presenting with an axillary metastasis: A systematic review. Eur J Surg Oncol 36: 114-119, 2010.
60. Van Ooijen B, Bontenbal M, Henzen-Logmans SC and Koper PC: Axillary nodal metastases from an occult primary consistent with breast carcinoma. Br J Surg 80: 1299-1300, 1993.
61. Hawes D, Neville AM and Cote RJ: Detection of occult metastasis in patients with breast cancer. Semin Surg Oncol 20: 312-318, 2001.
62. Medina-Franco H and Urist MM: Occult breast carcinoma presenting with axillary lymph node metastases. Rev Invest Clin 54: 204-208, 2002.
63. Owen HW, Dockerty MB and Gray HK: Occult carcinoma of the breast. Surg Gynecol Obstet 98: 302-308, 1954.
64. Chen YC, Chan CH, Lim YB, Yang SF, Yeh LT, Wang YH, Chou MC and Yeh CB: Risk of breast cancer in women with mastitis: A retrospective population-based cohort study. Medicina (Kaunas) 56: 372, 2020.
65. Ping J, Liu W, Chen Z and Li C: Lymph node metastases in breast cancer: Mechanisms and molecular imaging. Clin Imaging 103: 109985, 2023.
66. He M, Liu H and Jiang Y: A case report of male occult breast cancer first manifesting as axillary lymph node metastasis with part of metastatic mucinous carcinoma. Medicine (Baltimore) 94: e1038, 2015.
67. Rosen PP and Kimmel M: Occult breast carcinoma presenting with axillary lymph node metastases: A follow-up study of 48 patients. Hum Pathol 21: 518-523, 1990.
68. Hur SM, Cho DH, Lee SK, Choi MY, Bae SY, Koo MY, Kim S, Nam SJ, Lee JE and Yang JH: Occult breast cancers manifesting as axillary lymph node metastasis in men: A two-case report. J Breast Cancer 15: 359-363, 2012.
69. Matsuoka K, Ohsumi S, Takashima S, Saeki T, Aogi K and Mandai K: Occult breast carcinoma presenting with axillary lymph node metastases: Follow-up of eleven patients. Breast Cancer 10: 330-334, 2003.
70. Zheng H, Gu Y, Qin Y, Huang X, Yang J and Yang GZ: Small Lesion Classification in Dynamic Contrast Enhancement MRI for Breast Cancer Early Detection. In: Medical Image Computing and Computer Assisted Intervention-MICCAI 2018. Vol 11071. Frangi AF, Schnabel JA, Davatzikos C, Alberola-López C and Fichtinger G (eds). Springer International Publishing, Cham, pp876-884, 2018.
71. Lei YM, Yin M, Yu MH, Yu J, Zeng SE, Lv WZ, Li J, Ye HR, Cui XW and Dietrich CF: Artificial intelligence in medical imaging of the breast. Front Oncol 11: 600557, 2021.
72. Uchida K, Yamashita A, Kawase K and Kamiya K: Screening ultrasonography revealed 15% of mammographically occult breast cancers. Breast Cancer 15: 165-168, 2008.
73. Jacob D, Brombart JC, Muller C, Lefèbvre C, Massa F and Depoerck A: Analysis of the results of 137 subclinical breast lesions excisions. Value of ultrasonography in the early diagnosis of breast cancer. J Gynecol Obstet Biol Reprod (Paris) 26: 27-31, 1997 (In French).
74. Asbeutah AM, AlMajran AA, Brindhaban A and Asbeutah SA: Comparison of radiation doses between diagnostic full-field digital mammography (FFDM) and digital breast tomosynthesis (DBT): A clinical study. J Med Radiat Sci 67: 185-192, 2020.

75. Gøtzsche PC and Jørgensen KJ: Screening for breast cancer with mammography. Cochrane Database Syst Rev 2013: CD001877, 2013.
76. Rodríguez-Ruiz A, Krupinski E, Mordang JJ, Schilling K, Heywang-Köbrunner SH, Sechopoulos I and Mann RM: Detection of breast cancer with mammography: Effect of an artificial intelligence support system. Radiology 290: 305-314, 2019.
77. McDonald ES, Hammersley JA, Chou SH, Rahbar H, Scheel JR, Lee CI, Liu CL, Lehman CD and Partridge SC: Performance of DWI as a Rapid unenhanced technique for detecting mammographically occult breast cancer in elevated-risk women with dense breasts. AJR Am J Roentgenol 207: 205-216, 2016.
78. Theunissen CI, Rust EA, Edens MA, Bandel C, Van't Ooster-van den Berg JG, Jager PL, Noorda EM and Francken AB: Radioactive seed localization is the preferred technique in nonpalpable breast cancer compared with wire-guided localization and radioguided occult lesion localization. Nucl Med Commun 38: 396-401, 2017.
79. Morris EA, Liberman L, Ballon DJ, Robson M, Abramson AF, Heerdt A and Dershaw DD: MRI of Occult Breast Carcinoma in a High-Risk Population. AJR Am J Roentgenol 181: 619-626, 2003.
80. Buchanan CL, Morris EA, Dorn PL, Borgen PI and Van Zee KJ: Utility of breast magnetic resonance imaging in patients with occult primary breast cancer. Ann Surg Oncol 12: 1045-1053, 2005.
81. Wecsler JS, Raghavendra A, Mack WJ, Tripathy D, Yamashita M, Sheth P, Hovanessian-Larsen L, Sener SF, Russell CA, McDonald H and Lang JE: Abstract P4-02-05: Predictors of MRI detection of occult lesions in newly diagnosed breast cancer. Cancer Res 76 (Suppl 4): P4-02-05, 2016.
82. Zheng B, Hollingsworth AB, Tan MY, Stough RG and Liu H: Abstract P4-02-06: Improving efficacy of applying breast MRI to detect mammography-occult breast cancer. Cancer Res 76 (Suppl 4): P4-02-06, 2016.
83. Amornsiripanitch N, Rahbar H, Kitsch AE, Lam DL, Weitzel B and Partridge SC: Visibility of mammographically occult breast cancer on diffusion-weighted MRI versus ultrasound. Clin Imaging 49: 37-43, 2018.
84. Gao Y, Bagadiya NR, Jardon ML, Heller SL, Melsaether AN, Toth HB and Moy L: Outcomes of Preoperative MRI-Guided needle localization of nonpalpable mammographically occult breast lesions. AJR Am J Roentgenol 207: 676-684, 2016.
85. Smith LF, Henry-Tillman R, Mancino AT, Johnson A, Price Jones M, Westbrook KC, Harms S and Klimberg VS: Magnetic resonance imaging-guided core needle biopsy and needle localized excision of occult breast lesions. Am J Surg 182: 414-418, 2001.
86. Ryu JK, Rhee SJ, Song JY, Cho SH and Jahng GH: Characteristics of quantitative perfusion parameters on dynamic contrast-enhanced MRI in mammographically occult breast cancer. J Appl Clin Med Phys 17: 377-390, 2016.
87. McCartan DP, Zabor EC, Morrow M, Van Zee KJ and El-Tamer MB: Oncologic outcomes after treatment for MRI occult breast cancer (pT0N+). Ann Surg Oncol 24: 3141-3147, 2017.
88. Ramírez Huaranga MA, Salas Manzanedo V, Huertas MP, Torres Sousa Y and Ramos Rodríguez CC: Lumbar pain as the single manifestation of an occult breast cancer. Usefulness of positron emission tomography. Reumatol Clin 11: 118-120, 2015.
89. Takabatake D, Taira N, Aogi K, Ohsumi S, Takashima S, Inoue T and Nishimura R: Two cases of occult breast cancer in which PET-CT was helpful in identifying primary tumors. Breast Cancer 15: 181-184, 2008.
90. Brem RF, Ruda RC, Yang JL, Coffey CM and Rapelyea JA: Breast-Specific γ-Imaging for the detection of mammographically occult breast cancer in women at increased risk. J Nucl Med 57: 678-684, 2016.
91. Brem RF, Shahan C, Rapleyea JA, Donnelly CA, Rechtman LR, Kidwell AB, Teal CB, McSwain A and Torrente J: Detection of occult foci of breast cancer using breast-specific gamma imaging in women with one mammographic or clinically suspicious breast lesion. Acad Radiol 17: 735-743, 2010.
92. Zand S and Abdolali A: Radioguided Occult Lesion Localisation (ROLL) for Excision of Non-Palpable Breast Lesions, a Personal Experience in a Patient with Multifocal Breast Cancer. Arch Breast Cancer 3: 139-143, 2016.
93. Ong JSL, The J, Saunders C, Bourke AG, Lizama C, Newton J, Phillips M and Taylor DB: Patient satisfaction with Radioguided Occult Lesion Localisation using iodine-125 seeds (‘ROLLIS’) versus conventional hookwire localisation. Eur J Surg Oncol 43: 2261-2269, 2017.
94. Li H, Liu Z, Yuan L, Fan K, Zhang Y, Cai W and Lan X: Radionuclide-Based imaging of breast cancer: State of the art. Cancers (Basel) 13: 5459, 2021.
95. Altıparmak Güleç B and Yurt F: Treatment with radiopharmaceuticals and radionuclides in breast cancer: Current options. Eur J Breast Health 17: 214-219, 2021.
96. Tolmachev V and Vorobyeva A: Radionuclides in diagnostics and therapy of malignant tumors: New development. Cancers (Basel) 14: 297, 2022.
97. Amir E, Bedard PL, Ocaña A and Seruga B: Benefits and harms of detecting clinically occult breast cancer. J Natl Cancer Inst 104: 1542-1547, 2012.
98. Health Commission Of The People's Republic Of China N: National guidelines for diagnosis and treatment of breast cancer 2022 in China (English version). Chin J Cancer Res 34: 151-175, 2022.
99. Zhang S, Yu YH, Qu W, Zhang Y and Li J: Diagnosis and treatment of accessory breast cancer in 11 patients. Oncol Lett 10: 1783-1788, 2015.
100. Pesapane F, Downey K, Rotili A, Cassano E and Koh DM: Imaging diagnosis of metastatic breast cancer. Insights Imaging 11: 79, 2020.
101. Feuerman L, Attie JN and Rosenberg B: Carcinoma in axillary lymph nodes as an indicator of breast cancer. Surg Gynecol Obstet 114: 5-8, 1962.
102. Larsen RR, Sawyer KC, Sawyer RB and Torres RC: Occult carcinoma of the breast. Am J Surg 107: 553-555, 1964.
103. Osteen RT, Kopf G and Wilson RE: In pursuit of the unknown primary. Am J Surg 135: 494-497, 1978.
104. Chen QX, Wang XX, Lin PY, Zhang J, Li JJ, Song CG and Shao ZM: The different outcomes between breast-conserving surgery and mastectomy in triple-negative breast cancer: A population-based study from the SEER 18 database. Oncotarget 8: 4773-4780, 2017.
105. Masinghe SP, Faluyi OO, Kerr GR and Kunkler IH: Breast radiotherapy for occult breast cancer with axillary nodal metastases-does it reduce the local recurrence rate and increase overall survival? Clin Oncol (R Coll Radiol) 23: 95-100, 2011.
106. Macedo FI, Eid JJ, Flynn J, Jacobs MJ and Mittal VK: Optimal surgical management for occult breast carcinoma: A meta-analysis. Ann Surg Oncol 23: 1838-1844, 2016.
107. Foroudi F and Tiver KW: Occult breast carcinoma presenting as axillary metastases. Int J Radiat Oncol Biol Phys 47: 143-147, 2000.
108. Shannon C, Walsh G, Sapunar F, A'Hern R and Smith I: Occult primary breast carcinoma presenting as axillary lymphadenopathy. Breast 11: 414-418, 2002.
109. Buisman FE, van Gelder L, Menke-Pluijmers MB, Bisschops BH, Plaisier PW and Westenend PJ: Non-primary breast malignancies: A single institution's experience of a diagnostic challenge with important therapeutic consequences-a retrospective study. World J Surg Oncol 14: 166, 2016.
110. Kemeny MM: Mastectomy: Is it necessary for occult breast cancer? N Y State J Med 92: 516-517, 1992.
111. Copeland EM and Mcbride CM: Axillary metastases from unknown primary sites: Ann Surg 178: 21-27, 1973.
112. Kim BH, Kwon J and Kim K: Evaluation of the benefit of radiotherapy in patients with occult breast cancer: A population-based analysis of the SEER database. Cancer Res Treat 50: 551-561, 2018.
113. Rubovszky G, Kocsis J, Boér K,Chilingirova N, Dank M, Kahán Z, Kaidarova D, Kövér E, Krakovská BV, Máhr K, *et al*: Systemic treatment of breast cancer. 1st Central-Eastern European professional consensus statement on breast cancer. Pathol Oncol Res 28: 1610383, 2022.
114. Song MW, Ki SY, Lim HS, Lee HJ, Lee JS and Yoon JH: Axillary metastasis from occult breast cancer and synchronous contralateral breast cancer initially suspected to be cancer with contralateral axillary metastasis: A case report. BMC Womens Health 21: 418, 2021.
115. Wu SG, Zhang WW, Sun JY, Li FY, Lin HX, Chen YX and He ZY: Comparable survival between additional radiotherapy and local surgery in occult breast cancer after axillary lymph node dissection: A population-based analysis. J Cancer 8: 3849-3855, 2017.
116. Neal L, Sookhan N and Reynolds C: Occult breast carcinoma presenting as gastrointestinal metastases. Case Rep Med 2009: 564756, 2009.
117. Ciulla A, Castronovo G, Tomasello G, Maiorana AM, Russo L, Daniele E and Genova G: Gastric metastases originating from occult breast lobular carcinoma: Diagnostic and therapeutic problems. World J Surg Oncol 6: 78, 2008.

118. Khan I, Malik R, Khan A, Assad S, Zahid M, Sohail MS, Yasin F and Qavi AH: Breast cancer metastases to the gastrointestinal tract presenting with Anemia and intra-abdominal bleed. Cureus 9: e1429, 2017.
119. Rodrigues MV, Tercioti-Junior V, Lopes LR, Coelho-Neto Jde S and Andreollo NA: Breast cancer metastasis in the stomach: When the gastrectomy is indicated ? Arq Bras Cir Dig 29: 86-89, 2016 (In English, Portuguese).
120. Yang H, Li L, Zhang M, Zhang S, Xu S and Ma X: Application of neoadjuvant chemotherapy in occult breast cancer: Five case reports. Medicine (Baltimore) 96: e8200, 2017.
121. Asaoka M, Gandhi S, Ishikawa T and Takabe K: Neoadjuvant chemotherapy for breast cancer: Past, present, and future. Breast Cancer (Auckl) 14: 1178223420980377, 2020.
122. Hessler LK, Molitoris JK, Rosenblatt PY, Bellavance EC, Nichols EM, Tkaczuk KHR, Feigenberg SJ, Bentzen SM and Kesmodel SB: Factors influencing management and outcome in patients with occult breast cancer with axillary lymph node involvement: Analysis of the National cancer database. Ann Surg Oncol 24: 2907-2914, 2017.
123. Gosset M, Hamy AS, Mallon P, Delomenie M, Mouttet D, Pierga JY, Lae M, Fourquet A, Rouzier R, Reyal F and Feron JG: Prognostic impact of time to ipsilateral breast tumor recurrence after breast conserving surgery. PLoS One 11: e0159888, 2016.
124. Liu YM, Ge JY, Chen YF, Liu T, Chen L, Liu CC, Ma D, Chen YY, Cai YW, Xu YY, *et al*: Combined single-cell and spatial transcriptomics reveal the metabolic evolvement of breast cancer during early dissemination. Adv Sci (Weinh) 10: 2205395, 2023.
125. Chagpar AB, Cicek AF and Harigopal M: Can tumor biology predict occult multifocal disease in breast cancer patients? Am Surg 83: 704-708, 2017.
126. Merkkola-von Schantz PA, Jahkola TA, Krogerus LA and Kauhanen SMC: Reduction mammaplasty in patients with history of breast cancer: The incidence of occult cancer and high-risk lesions. Breast 35: 157-161, 2017.
127. Risk-reducing Salpingo-Oophorectomy in Women at Higher Risk of Ovarian and Breast Cancer: A Single Institution Prospective Series. AR 37, 2017.
128. Abe H, Naitoh H, Umeda T, Shiomi H, Tani T, Kodama M and Okabe H: Occult breast cancer presenting axillary nodal metastasis: A case report. Jpn J Clin Oncol 30: 185-187, 2000.
129. Montagna E, Bagnardi V, Rotmensz N, Viale G, Cancello G, Mazza M, Cardillo A, Ghisini R, Galimberti V, Veronesi P, *et al*: Immunohistochemically defined subtypes and outcome in occult breast carcinoma with axillary presentation. Breast Cancer Res Treat 129: 867-875, 2011.
130. Aydoğan F, Taşçı Y and Sagara Y: Phyllodes Tumors of the Breast. In: Breast Disease. Aydiner A, İgci A and Soran A (eds). Springer International Publishing, Cham, pp421-427, 2016.
131. Li L, Zhang D, Wen T, Wu Y, Lv D, Zhai J and Ma F: Axillary lymph node dissection plus radiotherapy may be an optimal strategy for patients with occult breast cancer. J National Cancer Center 2: 198-204, 2022.
132. Schwab FD, Burger H, Isenschmid M, Kuhn A, Mueller MD and Günthert AR: Suspicious axillary lymph nodes in patients with unremarkable imaging of the breast. Eur J Obstet Gynecol Reprod Biol 150: 88-91, 2010.
133. Shetty MK and Carpenter WS: Sonographic evaluation of isolated abnormal axillary lymph nodes identified on mammograms. J Ultrasound Med 23: 63-71, 2004.
134. Christiansen P, Carstensen SL, Ejlertsen B, Kroman N, Offersen B, Bodilsen A and Jensen MB: Breast conserving surgery versus mastectomy: Overall and relative survival-a population based study by the Danish Breast Cancer Cooperative Group (DBCG). Acta Oncol 57: 19-25, 2018.
135. de Boniface J, Szulkin R and Johansson ALV: Survival after breast conservation vs mastectomy adjusted for comorbidity and socioeconomic status: A Swedish National 6-year follow-up of 48 986 women. JAMA Surg 156: 628-637, 2021.
136. Keelan S, Flanagan M and Hill ADK: Evolving trends in surgical management of breast cancer: An analysis of 30 years of practice changing papers. Front Oncol 11: 622621, 2021.
137. Saha A, Mukhopadhyay M, Das C, Sarkar K, Saha AK and Sarkar DK: FNAC Versus core needle biopsy: A comparative study in evaluation of palpable breast lump. J Clin Diagn Res 10: EC05-EC08, 2016.
138. Lieske B, Ravichandran D and Wright D: Role of fine-needle aspiration cytology and core biopsy in the preoperative diagnosis of screen-detected breast carcinoma. Br J Cancer 95: 62-66, 2006.
139. Willems SM, Van Deurzen CHM and Van Diest PJ: Diagnosis of breast lesions: Fine-needle aspiration cytology or core needle biopsy? A review. J Clin Pathol 65: 287-292, 2012.
140. Calhoun BC and Collins LC: Predictive markers in breast cancer: An update on ER and HER2 testing and reporting. Semin Diagn Pathol 32: 362-369, 2015.
141. Onitilo AA, Engel JM, Greenlee RT and Mukesh BN: Breast cancer subtypes based on ER/PR and Her2 expression: Comparison of clinicopathologic features and survival. Clin Med Res 7: 4-13, 2009.
142. Wang R, Yang HX, Chen J, Huang JJ and Lv Q: Best treatment options for occult breast cancer: A meta-analysis. Front Oncol 13: 1051232, 2023.
143. Tsai C, Zhao B, Chan T and Blair SL: Treatment for occult breast cancer: A propensity score analysis of the National Cancer Database. Am J Surg 220: 153-160, 2020.
144. Mariscotti G, Houssami N, Durando M, Bergamasco L, Campanino PP, Ruggieri C, Regini E, Luparia A, Bussone R, Sapino A, *et al*: Accuracy of mammography, digital breast tomosynthesis, ultrasound and MR imaging in preoperative assessment of breast cancer. Anticancer Res 34: 1219-1225, 2014.
145. Kim WH, Chang JM, Moon HG, Yi A, Koo HR, Gweon HM and Moon WK: Comparison of the diagnostic performance of digital breast tomosynthesis and magnetic resonance imaging added to digital mammography in women with known breast cancers. Eur Radiol 26: 1556-1564, 2016.
146. An YY, Kim SH and Kang BJ: Characteristic features and usefulness of MRI in breast cancer in patients under 40 years old: Correlations with conventional imaging and prognostic factors. Breast Cancer 21: 302-315, 2014.
147. Van Goethem M, Tjalma W, Schelfout K, Verslegers I, Biltjes I and Parizel P: Magnetic resonance imaging in breast cancer. Eur J Surg Oncol 32: 901-910, 2006.
148. Zeeshan M, Salam B, Khalid QSB, Alam S and Sayani R: Diagnostic accuracy of digital mammography in the detection of breast cancer. Cureus 10: e2448, 2018.
149. Li H, Mendel KR, Lan L, Sheth D and Giger ML: Digital mammography in breast cancer: Additive value of radiomics of breast parenchyma. Radiology 291: 15-20, 2019.
150. Seeram E: Full-Field Digital Mammography. In: Digital Radiography. Springer Singapore, Singapore, pp111-123, 2019.
151. Jadvar H and Colletti PM: Competitive advantage of PET/MRI. Eur J Radiol 83: 84-94, 2014.
152. Koolen BB, Vidal-Sicart S, Benlloch Baviera JM and Valdés Olmos RA: Evaluating heterogeneity of primary tumor (18)F-FDG uptake in breast cancer with a dedicated breast PET (MAMMI): A feasibility study based on correlation with PET/CT. Nucl Med Commun 35: 446-452, 2014.
153. Singh BK, Verma K and Thoke AS: Fuzzy cluster based neural network classifier for classifying breast tumors in ultrasound images. Exp Sys Appl 66: 114-123, 2016.
154. Gómez-Flores W and Ruiz-Ortega BA: New fully automated method for segmentation of breast lesions on ultrasound based on texture analysis. Ultrasound Med Biol 42: 1637-1650, 2016.
155. Kozegar E, Soryani M, Behnam H, Salamati M and Tan T: Breast cancer detection in automated 3D breast ultrasound using iso-contours and cascaded RUSBoosts. Ultrasonics 79: 68-80, 2017.
156. Mohammed MA, Al-Khateeb B, Rashid AN, Ibrahim DA, Abd Ghani MK and Mostafa SA: Neural network and multi-fractal dimension features for breast cancer classification from ultrasound images. Comp Elect Eng 70: 871-882, 2018.
157. Moon WK, Chen IL, Yi A, Bae MS, Shin SU and Chang RF: Computer-aided prediction model for axillary lymph node metastasis in breast cancer using tumor morphological and textural features on ultrasound. Comput Methods Programs Biomed 162: 129-137, 2018.
158. Kim SA, Chang JM, Cho N, Yi A and Moon WK: Characterization of breast lesions: Comparison of digital breast tomosynthesis and ultrasonography. Korean J Radiol 16: 229-238, 2015.
159. Cai SQ, Yan JX, Chen QS, Huang ML and Cai DL: Significance and application of digital breast tomosynthesis for the BI-RADS classification of breast cancer. Asian Pac J Cancer Prev 16: 4109-4114, 2015.
160. Nakashima K, Uematsu T, Itoh T, Takahashi K, Nishimura S, Hayashi T and Sugino T: Comparison of visibility of circumscribed masses on Digital Breast Tomosynthesis (DBT) and 2D mammography: Are circumscribed masses better visualized and assured of being benign on DBT? Eur Radiol 27: 570-577, 2017.

161. Mercier J, Kwiatkowski F, Abrial C, Boussion V, Dieu-de Fraissinette V, Marraoui W, Petitcolin-Bidet V and Lemery S: The role of tomosynthesis in breast cancer staging in 75 patients. Diagn Interv Imaging 96: 27-35, 2015.
162. Roganovic D, Djilas D, Vujnovic S, Pavic D and Stojanov D: Breast MRI, digital mammography and breast tomosynthesis: Comparison of three methods for early detection of breast cancer. Bosn J Basic Med Sci 15: 64-68, 2015.
163. Das BK, Biswal BM and Bhavaraju M: Role of scintimammography in the diagnosis of breast cancer. Malays J Med Sci 13: 52-57, 2006.
164. Simanek M and Koranda P: SPECT/CT imaging in breast cancer-current status and challenges. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 160: 474-483, 2016.
165. Berrington de González A, Mahesh M, Kim KP, Bhargavan M, Lewis R, Mettler F and Land C: Projected cancer risks from computed tomographic scans performed in the United States in 2007. Arch Intern Med 169: 2071-2077, 2009.
166. Brem RF, Floerke AC, Rapelyea JA, Teal C, Kelly T and Mathur V: Breast-specific gamma imaging as an adjunct imaging modality for the diagnosis of breast cancer. Radiology 247: 651-657, 2008.
167. Yoon HJ, Kim Y, Chang KT and Kim BS: Prognostic value of semi-quantitative tumor uptake on Tc-99m sestamibi breast-specific gamma imaging in invasive ductal breast cancer. Ann Nucl Med 29: 553-560, 2015.
168. Tan H, Zhang H, Yang W, Fu Y, Gu Y, Du M, Cheng D and Shi H: Breast-specific gamma imaging with Tc-99m-sestamibi in the diagnosis of breast cancer and its semiquantitative index correlation with tumor biologic markers, subtypes, and clinicopathologic characteristics. Nucl Med Commun 37: 792-799, 2016.
169. Yu X, Hu G, Zhang Z, Qiu F, Shao X, Wang X, Zhan H, Chen Y, Deng Y and Huang J: Retrospective and comparative analysis of (99m)Tc-Sestamibi breast specific gamma imaging versus mammography, ultrasound, and magnetic resonance imaging for the detection of breast cancer in Chinese women. BMC Cancer 16: 450, 2016.
170. Cho MJ, Yang JH, Yu YB, Park KS, Chung HW, So Y, Choi N and Kim MY: Validity of breast-specific gamma imaging for Breast Imaging Reporting and Data System 4 lesions on mammography and/or ultrasound. Ann Surg Treat Res 90: 194-200, 2016.