Axillary node metastases with occult primary breast cancer

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INTRODUCTION

Cancer of unknown primary site (CUP), defined as the presence of metastatic cancer with an undetectable primary site at the time of presentation, is not a common clinical entity. Although the exact incidence is difficult to ascertain, CUP accounted for 2 percent of all cancer diagnoses in the Surveillance, Epidemiology and End Results (SEER) registries between 1973 and 1987 [1].

Within the category of CUP, tumors from many primary sites with varying biologic behavior are represented. Approximately 70 percent are adenocarcinomas, 15 to 20 percent are poorly differentiated carcinomas, and an additional 10 percent represent poorly differentiated adenocarcinomas. The remainder are squamous cell, neuroendocrine, or poorly differentiated neoplasms. (See "Overview of the classification and management of cancers of unknown primary site".)

The prognosis for most patients with CUP is poor. However, substantial improvements have been made in treating some subsets. The identification of specific subgroups of treatable patients has been made possible by the development of specialized immunohistologic techniques that can aid in tumor characterization (table 1) and by the recognition of several clinical syndromes that are predictive for a durable response to systemic therapy.

One such subgroup consists of women (rarely men) who have adenocarcinoma or poorly differentiated carcinoma in the axillary lymph nodes and who have no evident primary breast

lesion or distant disease spread after completion of the routine staging evaluation. Such patients are potentially curable when managed according to standard guidelines for anatomic stage II breast cancer.

This topic review will focus on the treatment of women with adenocarcinoma or poorly differentiated carcinoma in axillary nodes who do not have an evident primary breast cancer. The identification and management of other subgroups of patients with CUP is discussed in detail elsewhere, as is the general approach to neoplasms of unknown primary site. (See "Adenocarcinoma of unknown primary site" and "Overview of the classification and management of cancers of unknown primary site".)

In this topic, we will use the terms "woman/en" or "patient" to describe genetic females. However, we recognize that not all people with breasts identify as female, and we encourage the reader to consider transgender and gender nonbinary individuals as part of this larger group.

INCIDENCE AND DIFFERENTIAL DIAGNOSIS

Occult primary breast cancer was first recognized by William Halsted, who described three patients presenting with axillary masses that were eventually found to represent breast cancer [2]. In modern series, occult breast cancer accounts for 0.1 to 0.8 percent of all newly diagnosed breast cancers [3-10], and the incidence has not decreased with improvements in breast imaging [5,8].

Differential diagnosis — In general, palpable axillary nodes are more often related to benign rather than malignant disorders [11]. However, when cancer is identified, the most common tumor causing axillary lymphadenopathy is breast cancer. In several series, the incidence of breast cancer in mixed populations of men and women with metastatic axillary adenopathy is 50 percent or higher [12-15]. The vast majority are women; although occult primary breast cancer has been reported in men, it is rare [16].

Other neoplasms that may present with axillary nodal involvement are lymphomas, melanomas, sarcomas, thyroid cancers, skin cancers, lung cancers, and less often, uterine, ovarian, sweat gland, or gastric cancers [13]. In approximately 30 percent of cases, the primary site is never identified [6,13].

INITIAL DIAGNOSTIC WORKUP

Biopsy — The first step in the diagnostic workup of a patient with unexplained axillary adenopathy is a biopsy. Besides standard light microscopic examination of hematoxylin and eosin-stained sections, other techniques such as immunohistochemistry (IHC) and sometimes electron microscopy can help to narrow the differential diagnosis. The remainder of this topic review will focus on patients who are found to have an adenocarcinoma or poorly differentiated carcinoma in the axillary nodes. (See "Poorly differentiated cancer from an unknown primary site", section on 'Electron microscopy'.)

Immunohistochemistry — The pathologic examination of a biopsy specimen for an isolated axillary lymph node metastatic adenocarcinoma or poorly differentiated carcinoma in a woman should include IHC staining for the following markers:

- Carcinoembryonic antigen (CEA)
- Cytokeratins 7 and 20
- Estrogen receptor (ER) and progesterone receptor (PR) [17]
- Gross cystic disease fluid protein-15 (GCDFP, identified by staining with the monoclonal antibody BRST2)
- Mammaglobin
- Thyroid transcription factor (TTF-1)
- Cancer antigen (CA) 125

Men should have routine staining for prostate cancer markers as well.

While none of these markers is sufficiently sensitive or specific to be used alone, certain patterns of expression favor the diagnosis of an occult breast cancer (positive staining for CEA, CK7, ER/PR, mammaglobin, CA 125, and BRST2, and negative staining for CK20 and TTF-1).

CEA is a sensitive marker for adenocarcinomas of the breast, lung, and gastrointestinal tract, but does not help to distinguish among these sites of origin. On the other hand, differential expression of cytokeratins (CKs) can assist in this differentiation. CK20 is a low molecular weight cytokeratin that is normally expressed in the gastrointestinal epithelium, urothelium, and in Merkel cells; CK7 is expressed by tumors of the lung, ovary, endometrium, and breast, and not in the lower gastrointestinal tract. The pattern of CK20 and CK7 may be particularly helpful in suggesting a primary site (table 2). The presence of CK7 and absence of CK20 favors a diagnosis of breast cancer [18].

TTF-1 is rarely positive in breast cancers, while it is positive in 70 to 80 percent of nonsquamous cancers arising in the lung. CA 125 is commonly positive in ovarian carcinomas, but is positive in about 10 percent of breast cancers. As with ER/PR, its presence in an axillary node, particularly

in conjunction with other compatible IHC findings, lends support to a diagnosis of an occult breast primary.

Although positive staining for ER and/or PR supports a possible diagnosis of breast cancer, these markers are nonspecific and they may also be expressed in ovarian, uterine, lung, stomach, thyroid, and hepatobiliary cancers. However, ER/PR staining of an axillary node is compelling evidence of a primary breast cancer.

Other breast cancer-specific IHC stains are BRST2 (for GCDFP) and mammaglobin [18-21]. BRST2 is positive in 65 to 80 percent of cases and is relatively specific for breast cancer; rarely, it is positive in skin adnexal tumors, endometrial cancers, and salivary gland tumors [18,19,22,23]. While mammaglobin is more sensitive, it is less specific for breast cancer (gynecologic, lung, urothelial, thyroid, colon and hepatobiliary tumors may stain positive [18]), and both stains are thus typically used together.

Human epidermal growth factor receptor 2 (HER2) immunostaining is not generally useful for the differential diagnosis of a carcinoma arising in the axillary nodes as it lacks specificity. Furthermore, only 18 to 20 percent of breast cancers overexpress this protein. However, assay for HER2 overexpression by IHC or fluorescent in situ hybridization (FISH) is a routine component of the evaluation of all breast cancers as it permits the identification of those women who are most likely to respond to treatments targeting HER2 (eg, the therapeutic monoclonal antibody trastuzumab). (See "HER2 and predicting response to therapy in breast cancer".)

Breast examination and mammography — In addition to histologic analysis of the biopsy specimen, the diagnostic workup of a patient diagnosed with an adenocarcinoma or a poorly differentiated carcinoma in the axillary lymph nodes is initially targeted toward finding a breast primary carcinoma. A complete physical examination of both breasts is indicated as well as diagnostic mammography [24].

A nonpalpable, clinically occult lesion is identified mammographically in 10 to 20 percent of cases [4,25,26]. However, although mammography may provide useful information, it may also be misleading. Many occult nonpalpable tumors are missed because of their relatively small size (in one series 30 percent of occult breast primaries were 5 mm or less in diameter [26]) and because they are obscured on the mammogram by dense fibroglandular tissue [27]. Furthermore, an abnormal mammogram does not necessarily indicate breast cancer [17,28]. Suspicious findings warrant biopsy to confirm the clinical suspicion, and a negative mammogram in the appropriate clinical setting should prompt further imaging evaluation of

the breast with ultrasound and/or breast magnetic resonance imaging (MRI). (See "Breast imaging for cancer screening: Mammography and ultrasonography".)

Breast MRI — Bilateral breast magnetic resonance imaging (MRI) is now considered the standard approach to evaluation of the breasts in patients with axillary node metastases and occult primary breast cancer, if mammography has been negative [24]. (See "Adenocarcinoma of unknown primary site", section on 'Females with axillary lymph node metastases'.)

Breast MRI is more sensitive than either mammography or breast ultrasound for detection of invasive breast cancers. Data from several small series suggest that breast MRI can detect a primary breast cancer in approximately 75 percent of women who present with axillary adenocarcinoma/poorly differentiated carcinoma and a negative clinical examination and mammogram (table 3) [29-38]. Furthermore, the identification of a primary breast cancer by MRI may facilitate breast-conserving surgery instead of mastectomy.

A systematic literature review on the clinical utility of breast MRI in occult breast cancer included eight retrospective studies, totaling 250 patients [39]. A lesion suspect for primary breast cancer was located by MRI in 72 percent of cases (pooled mean), which in 85 to 100 percent of cases represented a malignant breast tumor. The pooled sensitivity and specificity of MRI for breast cancer detection in the only two studies that reported histopathologic confirmation was 90 and 31 percent, respectively. Breast MRI revealed a lesion that was amenable to lumpectomy in about one-third of cases, although some of the patients who were eligible for lumpectomy elected to undergo mastectomy instead.

The main problem with breast MRI is its high false-positive rates (up to 29 percent of all MRI scans in one study [40]) and difficulty in localizing small contrast-enhancing foci. All suspicious findings on MRI require pathologic confirmation. Some lesions found on MRI can be identified on subsequent, targeted "second-look" ultrasound (US) and may then be biopsied under US guidance. US correlate findings have a high likelihood of malignancy. For the remaining lesions, targeting requires MRI guidance. Breast MRI should be performed with a dedicated breast coil by expert breast imaging radiologists at institutions that have the capability to perform MRI guided needle biopsy and/or wire localization of the findings [29,31,40-43]. (See "Diagnostic evaluation of suspected breast cancer", section on 'Breast MRI' and "MRI of the breast and emerging technologies", section on 'Detection of occult primary breast cancer in women with axillary metastases'.)

MANAGEMENT OF PATIENTS WITH NORMAL IMAGING WORKUP

In the absence of a palpable breast mass and normal imaging workup of both breasts, the mammary origin of a metastatic adenocarcinoma/poorly differentiated carcinoma to the axillary lymph nodes cannot be established with certainty. However, if the histologic and immunohistochemical analysis is compatible, these patients are treated according to established guidelines for anatomic stage II breast cancer (table 4).

Completion of the staging workup — Extensive workup evaluation is not necessary. Recommendations from the National Comprehensive Cancer Network for workup of patients with isolated axillary metastases from adenocarcinoma or a poorly differentiated carcinoma suggest only a chest and abdominal computed tomography scan [24]. As with patients who have an identified breast primary and axillary nodal metastases, radionuclide bone scan is reserved for symptomatic women or those with an elevated serum alkaline phosphatase. The utility of PET scanning is controversial. (See "Clinical features, diagnosis, and staging of newly diagnosed breast cancer".)

Locoregional treatment — All patients should undergo axillary lymph node dissection (ALND). Besides providing prognostic information that will guide further treatment, dissection aids local control. About one-half of patients with occult breast primaries will be found to have four or more positive lymph nodes, an indication for postmastectomy chest wall irradiation [44,45]. (See 'Postmastectomy chest wall RT' below and "Overview of management of the regional lymph nodes in breast cancer".)

The optimal treatment of the ipsilateral breast is controversial. For women who do not have a discrete lesion identified by breast imaging, the options are mastectomy, breast-conserving treatment using whole breast radiation therapy (RT), and observation alone. Patients who undergo mastectomy with ALND may have a more favorable outcome compared with patients undergoing ALND. However, the same study showed that mastectomy and ALND had similar outcomes with whole breast RT and ALND [46].

Mastectomy — Although breast-conserving therapy for occult breast cancer with axillary node involvement has been described [47], the standard approach is to perform a modified radical mastectomy (MRM) at the time of ALND. A breast malignancy will be found upon histologic review of the mastectomy specimen in approximately 65 percent of patients (table 5) [3-5,7,8,15,45,46,48-51]. The primary tumor is usually less than 2 cm in diameter; in occasional patients, only carcinoma in situ is identified. The benefits of local treatment were addressed in a retrospective analysis of 51 cases of occult breast cancer in which women who had mastectomy had a markedly lower rate of local recurrence compared to those who had no local therapy (77 versus 26 percent) [52]. Furthermore, disease-free and overall survival were also superior in the mastectomy group.

Radiation — The role of whole breast RT as a breast-conserving alternative to mastectomy is unclear. There are no randomized trials comparing this approach to mastectomy, and the only available data are from small retrospective case series. In published reports limited to patients with occult breast cancer, local control rates with primary whole-breast RT range from 73 to 100 percent (table 6) [5,9,46,49,51,53-55]. In one of the largest series from the Institut Curie, 32 of 45 patients presenting with an occult breast cancer and axillary metastases underwent whole breast RT, while the remainder had mastectomy [38]. No significant difference was detected between mastectomy and breast preservation in locoregional recurrence (15 versus 13 percent), distant metastasis (31 versus 22 percent) or five-year survival (75 versus 79 percent, respectively). Similar comparative survival rates following mastectomy and whole-breast RT have been reported in smaller series from M D Anderson and Memorial Sloan Kettering [9,49].

In a later report of 53 patients with occult breast cancer, there was a trend toward lower five-year risk of an ipsilateral breast tumor recurrence in patients who received RT compared with those who did not (16 versus 36 percent) [56]. Similarly, the five-year rate of locoregional recurrence was lower in the RT group (28 versus 54 percent) and breast cancer-specific survival was significantly higher (72 versus 58 percent, p=0.0073).

Observation only — Observation of the breast without definitive local therapy is generally **not** recommended at most institutions, given the risks of tumor recurrence and possibly decreased survival.

In some of the more recent case series of patients with an adenocarcinoma of unknown primary in the axillary nodes, an occult primary breast cancer has been identified in fewer mastectomy specimens, perhaps as a result of improvements in imaging modalities (eg, breast magnetic resonance imaging) [7,49,51]. These data, in conjunction with case reports suggesting that survival is similar regardless of whether the breast is treated or not [44,49], have led some to question the necessity of treating the ipsilateral breast [45,49,57].

A compilation of published data on the local recurrence rate in the ipsilateral breast with cases of occult primary breast cancer when the ipsilateral breast is not treated is provided in the table (table 7) [7,44,49,54,57-61]. Overall, approximately one-half of these women will develop an in-breast local recurrence.

Although some reports suggest that observation of the breast does not adversely influence survival, at least three series suggest otherwise [5,10,15]:

- One report consisted of 34 women who presented with axillary metastases and an occult primary breast cancer, all of whom had excisional biopsy of the axillary mass [15]. Eighteen (51 percent) also had a mastectomy, of whom 13 received adjuvant

chemotherapy or RT. Of the 16 women who did not have initial mastectomy, eight had no further treatment while eight underwent either chemotherapy, RT, or both. Following treatment, patients were followed for an average of 72 months.

There was a significant difference in outcomes between the surgery and non-surgery groups. Of the 16 women who did not undergo surgery, 13 (81 percent) recurred, as compared to 6 of the 17 (36 percent) who had mastectomy. Of the women for whom follow-up data were available at five years, a significantly greater number of those who had a mastectomy remained alive (8 of 11 versus 5 of 14 [73 versus 36 percent]). Further analysis of the subgroup of patients who received standard adjuvant therapy revealed that seven of eight patients who did not undergo mastectomy died of their disease, compared to only 3 of 13 patients who did.

- An analysis of the Surveillance, Epidemiology and End Results (SEER) database from 1983-2006 identified 750 cases of occult breast cancer [10]. Of the 470 patients who underwent mastectomy or breast-conserving therapy, the 10-year overall survival was significantly higher than it was for the 126 patients who underwent ALND only (65 versus 59 percent; p=0.02) or the 94 patients undergoing observation only with no surgery (48 percent, p=0.04 for the comparison). Mastectomy did not improve outcomes compared with breast-conserving therapy.

Adjuvant systemic therapy — The benefit of adjuvant systemic therapy has not been systematically studied among women presenting with axillary metastases and an occult primary breast cancer. At least one of the retrospective reports notes a significantly greater survival among the 14 patients who received adjuvant chemotherapy as compared to 28 who did not (93 versus 64 percent five-year survival, respectively) [49].

It seems reasonable to extrapolate from modern treatment principles for clinically apparent breast cancer. The addition of trastuzumab to adjuvant chemotherapy improves outcomes in patients with human epidermal growth factor receptor 2 (HER2)-overexpressing tumors. The addition of pertuzumab to trastuzumab and multiagent chemotherapy in the neoadjuvant setting has been shown to improve pathologic complete response in patients with axillary node-positive breast cancer and can also be used in occult breast cancer. Adjuvant hormone therapy is recommended after the completion of chemotherapy for women with hormone-responsive tumors.

The rationale for adjuvant systemic therapy, specific data supporting the use of adjuvant hormone therapy, chemotherapy, and trastuzumab, and a more thorough discussion of recommendations for such therapy in premenopausal and postmenopausal women with either

hormone responsive or hormone nonresponsive breast cancer are discussed elsewhere. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer" and "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer".)

Postmastectomy chest wall RT — The addition of postmastectomy irradiation (RT) in high-risk women reduces the risk of locoregional recurrence, increases disease-free survival, and reduces a woman's risk of dying from breast cancer. The topic of postmastectomy chest wall RT is discussed elsewhere.

Prognosis — Reported five-year survival rates after treatment of an occult primary breast cancer with axillary metastases range from 59 to 93 percent, averaging about 75 percent (table 8) [3,5,15,25,38,45,48,49,54,62,63]. Some authors have suggested that the prognosis for such women is better than that reported for anatomic stage II clinically apparent breast cancer [3,4,44,45,48,57,64]. However, this is a controversial issue because of the marked heterogeneity in adjuvant treatment (a factor that clearly affects survival) in many of the older large surveys from which the prognostic estimates for node-positive clinically apparent breast cancer were derived, and the limited duration of follow-up in reports of patients treated for occult breast cancer.

In the 2017 cancer statistics report from the American Cancer Society, the five-year survival among patients diagnosed with breast cancer was 90 percent [65]. This result compares favorably to that reported in the series of occult breast cancers specifically. However, survival for women with node-negative breast cancer declines over time, and it may be as low as 30 percent at 20 years [66]. Because of the small size and limited follow-up duration of the available reports of women with axillary metastases and an occult primary breast cancer, it is not possible to conclude that outcomes are similar, worse, or better than expected for women treated for clinically apparent primary tumors.

However, in a database study including 572 occult breast cancer cases and over 117,000 patients with clinically apparent breast cancer between 2004 and 2015, patients with occult breast cancer experienced a better survival than patients with clinically apparent breast cancer, when matched according to nodal stage [67].

METASTATIC DISEASE

Women who present with adenocarcinoma or poorly differentiated carcinoma in the axillary nodes, no evident primary breast tumor, and who have metastatic sites in addition to axillary

lymph nodes should receive a trial of systemic therapy using guidelines for the treatment of metastatic breast cancer.

Patients with estrogen receptor (ER)- and/or progesterone receptor (PR)-positive tumors may derive major palliative benefit from hormone therapy, with or without targeted therapy (eg, inhibitors of cyclin-dependent kinase 4/6). Chemotherapy is indicated for patients who have ER/PR-negative disease as well as those who fail an initial trial of hormone therapy for hormone-responsive disease. Patients whose tumors overexpress human epidermal growth factor receptor 2 (HER2) by immunohistochemistry (ie, 3+) or by fluorescence in situ hybridization (FISH) should be treated with anti-HER2-directed therapy in combination with other cytotoxic agents. (See "Overview of the approach to metastatic breast cancer" and "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer" and "Endocrine therapy resistant, hormone receptor-positive, HER2-negative advanced breast cancer".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Breast cancer".)

SUMMARY AND RECOMMENDATIONS

- **Introduction** – Cancer of unknown primary site (CUP), an uncommon clinical entity, is defined by the presence of metastatic disease with an undetectable primary site at the time of presentation. Although the prognosis for most patients with CUP is poor, specific subgroups of treatable patients have been identified using specialized immunohistologic (IHC) techniques that can aid in tumor characterization (table 1) and by the recognition of several clinical syndromes that predict for a durable response to systemic therapy. (See 'Introduction' above.)

- **Initial diagnostic workup** – Women who present with axillary lymph node metastases who have adenocarcinoma or poorly differentiated carcinoma histology, compatible IHC staining, no other distant metastases and no evidence of a breast cancer primary on clinical examination, mammography, breast ultrasound, and breast magnetic resonance imaging represent a potentially curable subset of individuals with CUP. These women are treated according to guidelines for anatomic stage II breast cancer. (See 'Initial diagnostic workup' above.)

- **Completion of the staging workup** – Extensive staging evaluation is unnecessary. Guidelines for workup of patients with isolated axillary metastases from adenocarcinoma or a poorly differentiated carcinoma from the National Comprehensive Cancer Network suggest only a chest and abdominal computed tomography scan. Radionuclide bone scans are reserved for symptomatic women or those with unexplained elevations in serum alkaline phosphatase. (See 'Completion of the staging workup' above.)

- **Locoregional treatment** – We recommend that all patients undergo axillary lymph node dissection (ALND) (**Grade 1B**). Optimal treatment for the ipsilateral breast is controversial. A standard approach is to perform a modified radical mastectomy (MRM) at the time of ALND. For women who wish to preserve their breast, whole breast radiation therapy is an acceptable option. We suggest not pursuing observation alone for the ipsilateral breast (**Grade 2C**). (See 'Locoregional treatment' above.)

- **Adjuvant systemic therapy** – We recommend that all women with axillary nodal metastases and an occult primary breast cancer undergo systemic adjuvant therapy according to published guidelines for anatomic stage II primary breast cancer (**Grade 1B**). (See 'Adjuvant systemic therapy' above.)

- **Metastatic disease** – Women with axillary lymph node metastases who have adenocarcinoma or poorly differentiated carcinoma histology, compatible IHC staining, and no evidence of a breast cancer primary but who have evidence of other distant metastases should be treated according to guidelines for metastatic breast cancer. (See 'Metastatic disease' above.)

REFERENCES

1. Hainsworth JD, Wright EP, Johnson DH, et al. Poorly differentiated carcinoma of unknown primary site: clinical usefulness of immunoperoxidase staining. J Clin Oncol 1991; 9:1931.
2. Halsted WS. I. The Results of Radical Operations for the Cure of Carcinoma of the Breast. Ann Surg 1907; 46:1.
3. Baron PL, Moore MP, Kinne DW, et al. Occult breast cancer presenting with axillary metastases. Updated management. Arch Surg 1990; 125:210.
4. Fitts WT, Steiner GC, Enterline HT. Prognosis of Occult Carcinoma of the Breast. Am J Surg 1963; 106:460.

5. Foroudi F, Tiver KW. Occult breast carcinoma presenting as axillary metastases. Int J Radiat Oncol Biol Phys 2000; 47:143.
6. Haupt HM, Rosen PP, Kinne DW. Breast carcinoma presenting with axillary lymph node metastases. An analysis of specific histopathologic features. Am J Surg Pathol 1985; 9:165.
7. Kemeny MM, Rivera DE, Terz JJ, Benfield JR. Occult primary adenocarcinoma with axillary metastases. Am J Surg 1986; 152:43.
8. OWEN HW, DOCKERTY MB, GRAY HK. Occult carcinoma of the breast. Surg Gynecol Obstet 1954; 98:302.
9. Vilcoq JR, Calle R, Ferme F, Veith F. Conservative treatment of axillary adenopathy due to probable subclinical breast cancer. Arch Surg 1982; 117:1136.
10. Walker GV, Smith GL, Perkins GH, et al. Population-based analysis of occult primary breast cancer with axillary lymph node metastasis. Cancer 2010; 116:4000.
11. Walsh R, Kornguth PJ, Soo MS, et al. Axillary lymph nodes: mammographic, pathologic, and clinical correlation. AJR Am J Roentgenol 1997; 168:33.
12. de Andrade JM, Marana HR, Sarmento Filho JM, et al. Differential diagnosis of axillary masses. Tumori 1996; 82:596.
13. Copeland EM, McBride CM. Axillary metastases from unknown primary sites. Ann Surg 1973; 178:25.
14. Gupta RK, Naran S, Lallu S, Fauck R. Diagnostic value of needle aspiration cytology in the assessment of palpable axillary lymph nodes. A study of 336 cases. Acta Cytol 2003; 47:550.
15. Blanchard DK, Farley DR. Retrospective study of women presenting with axillary metastases from occult breast carcinoma. World J Surg 2004; 28:535.
16. Namba N, Hiraki A, Tabata M, et al. Axillary metastasis as the first manifestation of occult breast cancer in a man: a case report. Anticancer Res 2002; 22:3611.
17. Bhatia SK, Saclarides TJ, Witt TR, et al. Hormone receptor studies in axillary metastases from occult breast cancers. Cancer 1987; 59:1170.
18. Dabbs DJ. Immunohistology of metastatic carcinoma of unknown primary. In: Diagnostic I mmunohistochemistry, 2nd ed, Dabbs DJ (Ed), Churchill Livingstone/Elsevier, 2006.
19. Han JH, Kang Y, Shin HC, et al. Mammaglobin expression in lymph nodes is an important marker of metastatic breast carcinoma. Arch Pathol Lab Med 2003; 127:1330.
20. Leygue E, Snell L, Dotzlaw H, et al. Mammaglobin, a potential marker of breast cancer nodal metastasis. J Pathol 1999; 189:28.

21. Watson MA, Dintzis S, Darrow CM, et al. Mammaglobin expression in primary, metastatic, and occult breast cancer. Cancer Res 1999; 59:3028.
22. Sasaki E, Tsunoda N, Hatanaka Y, et al. Breast-specific expression of MGB1/mammaglobin: an examination of 480 tumors from various organs and clinicopathological analysis of MGB1-positive breast cancers. Mod Pathol 2007; 20:208.
23. O'Connell FP, Wang HH, Odze RD. Utility of immunohistochemistry in distinguishing primary adenocarcinomas from metastatic breast carcinomas in the gastrointestinal tract. Arch Pathol Lab Med 2005; 129:338.
24. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. B reast cancer. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
25. Kyokane T, Akashi-Tanaka S, Matsui T, Fukutomi Ta. Clinicopathological Characteristics of Non-palpable Breast Cancer Presenting as Axillary Mass. Breast Cancer 1995; 2:105.
26. Leibman AJ, Kossoff MB. Mammography in women with axillary lymphadenopathy and normal breasts on physical examination: value in detecting occult breast carcinoma. AJR Am J Roentgenol 1992; 159:493.
27. Kolb TM, Lichy J, Newhouse JH. Occult cancer in women with dense breasts: detection with screening US--diagnostic yield and tumor characteristics. Radiology 1998; 207:191.
28. Stevens KJ, Smith SL, Denley H, et al. Is mammography of value in women with disseminated cancer of unknown origin? Clin Oncol (R Coll Radiol) 1999; 11:90.
29. Olson JA Jr, Morris EA, Van Zee KJ, et al. Magnetic resonance imaging facilitates breast conservation for occult breast cancer. Ann Surg Oncol 2000; 7:411.
30. Chen C, Orel SG, Harris E, et al. Outcome after treatment of patients with mammographically occult, magnetic resonance imaging-detected breast cancer presenting with axillary lymphadenopathy. Clin Breast Cancer 2004; 5:72.
31. Obdeijn IM, Brouwers-Kuyper EM, Tilanus-Linthorst MM, et al. MR imaging-guided sonography followed by fine-needle aspiration cytology in occult carcinoma of the breast. AJR Am J Roentgenol 2000; 174:1079.
32. Buchanan CL, Morris EA, Dorn PL, et al. Utility of breast magnetic resonance imaging in patients with occult primary breast cancer. Ann Surg Oncol 2005; 12:1045.
33. Schorn C, Fischer U, Luftner-Nagel S, et al. MRI of the breast in patients with metastatic disease of unknown primary. Eur Radiol 1999; 9:470.
34. Henry-Tillman RS, Harms SE, Westbrook KC, et al. Role of breast magnetic resonance imaging in determining breast as a source of unknown metastatic lymphadenopathy. Am J Surg 1999; 178:496.

35. Tilanus-Linthorst MM, Obdeijn AI, Bontenbal M, Oudkerk M. MRI in patients with axillary metastases of occult breast carcinoma. Breast Cancer Res Treat 1997; 44:179.

36. Brenner RJ, Rothman BJ. Detection of primary breast cancer in women with known adenocarcinoma metastatic to the axilla: use of MRI after negative clinical and mammographic examination. J Magn Reson Imaging 1997; 7:1153.

37. Morris EA, Schwartz LH, Dershaw DD, et al. MR imaging of the breast in patients with occult primary breast carcinoma. Radiology 1997; 205:437.

38. Fourquet, A, Meunier, et al. Occult primary cancer with axillary metastases. In: Diseases of t he Breast, 3rd ed, Harris, JR, Lippman, ME, Morrow, M, Osborne, CK (Eds), Lippincott, Willia ms and Wilkins, Philadelphia 2004. p.1047.

39. de Bresser J, de Vos B, van der Ent F, Hulsewé K. Breast MRI in clinically and mammographically occult breast cancer presenting with an axillary metastasis: a systematic review. Eur J Surg Oncol 2010; 36:114.

40. Bedrosian I, Schlencker J, Spitz FR, et al. Magnetic resonance imaging-guided biopsy of mammographically and clinically occult breast lesions. Ann Surg Oncol 2002; 9:457.

41. Floery D, Helbich TH. MRI-Guided percutaneous biopsy of breast lesions: materials, techniques, success rates, and management in patients with suspected radiologic-pathologic mismatch. Magn Reson Imaging Clin N Am 2006; 14:411.

42. Liberman L, Bracero N, Morris E, et al. MRI-guided 9-gauge vacuum-assisted breast biopsy: initial clinical experience. AJR Am J Roentgenol 2005; 185:183.

43. Kuhl CK, Morakkabati N, Leutner CC, et al. MR imaging--guided large-core (14-gauge) needle biopsy of small lesions visible at breast MR imaging alone. Radiology 2001; 220:31.

44. Merson M, Andreola S, Galimberti V, et al. Breast carcinoma presenting as axillary metastases without evidence of a primary tumor. Cancer 1992; 70:504.

45. Rosen PP, Kimmel M. Occult breast carcinoma presenting with axillary lymph node metastases: a follow-up study of 48 patients. Hum Pathol 1990; 21:518.

46. He M, Tang LC, Yu KD, et al. Treatment outcomes and unfavorable prognostic factors in patients with occult breast cancer. Eur J Surg Oncol 2012; 38:1022.

47. Kim H, Park W, Kim SS, et al. Outcome of breast-conserving treatment for axillary lymph node metastasis from occult breast cancer with negative breast MRI. Breast 2020; 49:63.

48. Ashikari R, Rosen PP, Urban JA, Senoo T. Breast cancer presenting as an axillary mass. Ann Surg 1976; 183:415.

49. Ellerbroek N, Holmes F, Singletary E, et al. Treatment of patients with isolated axillary nodal metastases from an occult primary carcinoma consistent with breast origin. Cancer 1990;

66:1461.

50. Patel J, Nemoto T, Rosner D, et al. Axillary lymph node metastasis from an occult breast cancer. Cancer 1981; 47:2923.
51. Vlastos G, Jean ME, Mirza AN, et al. Feasibility of breast preservation in the treatment of occult primary carcinoma presenting with axillary metastases. Ann Surg Oncol 2001; 8:425.
52. Wang X, Zhao Y, Cao X. Clinical benefits of mastectomy on treatment of occult breast carcinoma presenting axillary metastases. Breast J 2010; 16:32.
53. Medina-Franco H, Urist MM. Occult breast carcinoma presenting with axillary lymph node metastases. Rev Invest Clin 2002; 54:204.
54. Campana F, Fourquet A, Ashby MA, et al. Presentation of axillary lymphadenopathy without detectable breast primary (T0 N1b breast cancer): experience at Institut Curie. Radiother Oncol 1989; 15:321.
55. Varadarajan R, Edge SB, Yu J, et al. Prognosis of occult breast carcinoma presenting as isolated axillary nodal metastasis. Oncology 2006; 71:456.
56. Masinghe SP, Faluyi OO, Kerr GR, 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) 2011; 23:95.
57. van Ooijen B, Bontenbal M, Henzen-Logmans SC, Koper PC. Axillary nodal metastases from an occult primary consistent with breast carcinoma. Br J Surg 1993; 80:1299.
58. Feigenberg SJ, Price Mendenhall N, Benda RK, Morris CG. Postmastectomy radiotherapy: patterns of recurrence and long-term disease control using electrons. Int J Radiat Oncol Biol Phys 2003; 56:716.
59. FEUERMAN L, ATTIE JN, ROSENBERG B. Carcinoma in axillary lymph nodes as an indicator of breast cancer. Surg Gynecol Obstet 1962; 114:5.
60. Haagensen CD. The choice of treatment for operable carcinoma of the breast. Surgery 1974; 76:685.
61. Atkins H, Wolff B. The malignant gland in the hospital. Guys Hosp Rep 1960; 1:109.
62. Matsuoka K, Ohsumi S, Takashima S, et al. Occult breast carcinoma presenting with axillary lymph node metastases: follow-up of eleven patients. Breast Cancer 2003; 10:330.
63. Hotta M, Khurana M, Sung M, O'Connor VV. Understanding the Biology of Occult Breast Cancer: Examination of 31 Cases Reveals Aggressive Behavior. Am Surg 2020; 86:e116.
64. Lloyd MS, Nash AG. 'Occult' breast cancer. Ann R Coll Surg Engl 2001; 83:420.
65. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017; 67:7.

66. Weiss RB, Woolf SH, Demakos E, et al. Natural history of more than 20 years of node-positive primary breast carcinoma treated with cyclophosphamide, methotrexate, and fluorouracil-based adjuvant chemotherapy: a study by the Cancer and Leukemia Group B. J Clin Oncol 2003; 21:1825.

67. Huang KY, Zhang J, Fu WF, et al. Different Clinicopathological Characteristics and Prognostic Factors for Occult and Non-occult Breast Cancer: Analysis of the SEER Database. Front Oncol 2020; 10:1420.

Topic 766 Version 29.0

GRAPHICS

Characteristic immunohistochemical staining patterns for undifferentiated neoplasms

Neoplasm	Cytokeratin	EMA	LCA	S-100	Desmin/ vimentin*	OCT 4/ HCG/ AFP/ PLAP*	Chromogranin/ synaptophysin
Carcinoma	+	+	-	S	-	S	S
Melanoma	-, R	-	-	+	+	-	-
Sarcoma	-	S	-	-	+	-	-
Lymphoma	-	-, R	+	-	-	-	-
Neuroendocrine carcinoma	+	+	-	-	-	-	+
Germ cell tumor	-, R	-	-	-	-	+	-

EMA: epithelial membrane antigen; LCA: leukocyte common antigen; S-100: S-100 protein; HCG: human chorionic gonadotrophin; AFP: alpha-fetoprotein; PLAP: placental leukocyte alkaline phosphatase; +: positive; -: negative; S: sometimes positive; R: rare positive cells.

* Positive for one or more of these markers.

Modified from: Dabbs DJ. Immunohistology of metastatic carcinoma of unknown primary. In: Diagnostic Immunohistochemistry, 2nd ed, Dabbs DJ (Ed), Churchill Livingstone, Pittsburgh 2006. p.180.

Graphic 62750 Version 5.0

Differential diagnosis of unknown primary cancers based upon immunostaining for cytokeratin (CK) 7 and 20

CK7+ CK20+	CK7+ CK20-	CK7- CK20+	CK7- CK20-
Urothelial tumors	Non-small cell lung cancer	Colorectal cancer	Hepatocellular cancer
Mucinous ovarian cancer	Small cell lung cancer	Merkel cell cancer	Renal cell cancer
Pancreatic or biliary cancer	Breast cancer		Prostate cancer
	Endometrial cancer		Squamous cell lung cancer
	Nonmucinous ovarian cancer		Head and neck cancer
	Mesothelioma		
	Squamous cancer of cervix		
	Pancreatic or biliary cancer		

CK: cytokeratin; +: positive; -: negative.

Modified from: Dabbs D. Diagnostic Immunohistochemistry, 2nd ed, Churchill Livingstone, Philadelphia, PA 2006.

Graphic 58475 Version 4.0

Utility of breast MRI for mammographically-occult breast cancer in patients presenting with metastatic axillary lymphadenopathy

Author, year	n	MRI-positive, percent	Histologic diagnosis of breast cancer
Morris, E; 1997	12	9 (75)	8
Brenner, R; 1997	4	4 (100)	4
Tilanus-Linthorst, M; 1997	4	4 (100)	4
Schorn, C; 1999	14¶	9 (64)	6/9
Henry-Tillman, R; 1999	10	8 (80)	8
Olson, J; 2000	40	28 (70)	21/22*
Obdeijn, I; 2000	20	8 (40)	8
Fourquet, A; 2004	15	14 (93)	9/11
Buchanan, C; 2005	69	42 (76)	26/42 MRI+
			4/12 MRI–

* Number of patients with confirmed MRI findings at the time of surgery.

¶ Included six axillary nodal metastases, one supraclavicular nodal metastases, three bone metastases, three liver metastases, and one lung metastases with an unknown primary.

Graphic 62800 Version 2.0

Breast carcinoma TNM anatomic stage group AJCC UICC 8th edition

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

- The anatomic stage group table should only be used in global regions where biomarker tests are not routinely available.
- Cancer registries in the US must use the prognostic stage group table for case reporting.

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110848 Version 8.0

Pathologic findings at mastectomy in patients with occult primary breast cancer

Author, year	Years	Mastectomy, n	In situ, n	Invasive, n	Cancer, percent
Owens H; 1954	1907-50	27	0	25	92
Feuerman L; 1962	1949-61	2	0	1	50
Fitts W; 1963	1948-63	11	0	7	70
Haagensen C; 1974	1916-66	13	0	12	92
Ashikari R; 1976	1946-75	34	3	20	67
Patel J; 1981	1952-79	29	0	16	60
Kemeny M; 1986	1973-85	11	2	3	45
Bhatia S; 1987	1977-85	11	2	9	100
Baron P; 1990	1975-78	28	4	16	71
Ellerbroek N; 1990	1944-87	13	0	1	8
Merson M; 1992	1945-87	33	0	27	82
Feigenberg S; 2003	1971-74	4	0	3	80
Blanchard D; 2004	1975-98	18	1	5	33
He M; 2012	1998-2010	64	16	4	31
Total	–	298	28	149	59

Graphic 52940 Version 3.0

Results of whole breast irradiation for node-positive occult primary breast cancer

Author, year	Number of patients	Median follow-up	Breast treatment	Breast-only control, percent	Survival (percent)
Vilcoq J; 1982	11	>5 yr	XRT	73	10/11 (5 year)
Ellerbroek N; 1990	16	133 months	XRT	83	–*
	13		None	43	–*
	13		Mastectomy	N/A	–*
Foroudi F; 2000	12	73 months	XRT	75	11/12 (5 year)
Vlastos G; 2001	25	7 years	XRT	92	79 percent (5 year)
	13		Mastectomy	85	75 percent (5 year)
Medina-Franco H; 2002	6	48 months	XRT	100	100 percent
Varadarajan R; 2006	8	57 months	XRT	100	100 percent
He D; 2012	95	38.2 months	Mastectomy + ALND¶	89	85 (3 year)
			Breast XRT + ALND	92	81
			ALND	72	71

XRT: whole breast radiation therapy; N/A: not available.

* Survival described as "no different" when patients undergoing mastectomy were compared to those who did not undergo mastectomy. Actuarial survival for entire group was 72 percent at five years and 65 percent at 10 years.

¶ ALND: axillary lymph node dissection.

Graphic 65411 Version 4.0

Local recurrence of breast cancer in patients with occult primary breast cancer not undergoing local therapy

Author, year	Breast failures (percent)	Delay in months
Atkins H; 1960	5/9 (56)	9 to 17
Feuerman L; 1962	0/1 (0)	-
Haagensen C; 1974	3/5 (60)	5 to 64
Kemeny M; 1986	0/7 (0)	-
Campana F; 1989	2/2 (100)	9 to 67
Ellerbroek N; 1990	7/13 (54)	11 to 47
Merson M; 1992	9/17 (53)	2 to 34
Van Ooijen B; 1993	3/14 (21)	16 to 56
Fouroudi F; 2000	5/6 (83)	7 (median)
Feigenberg S; 2003	0/4 (0)	-
Blanchard D; 2004	12/16 (75)	-
Total	**46/94 (49)**	**-**

Graphic 67113 Version 4.0

Studies addressing prognosis of occult breast cancer

Study	Place	Year	Number of patients	5 year OS, percent
Ashikari, R; 1976	Memorial Hospital, NYC	1946-75	42	79
Campana, F; 1989	Institute Curie	1960-85	31	76
Baron, P; 1990	MSKCC	1975-88	35	75
Ellerbroek, N; 1990	MD Anderson	1944-87	42	72
Rosen, P; 1990	MSKCC	1966-85	48	60
Kyokane, T; 1995	Japan	NR	97	59
Foroudi, F; 2000	Australia	1979-96	20	93 (mastectomy or XRT)
				41 (no local treatment)
Matsuoka, K; 2003	Japan	1985-98	11	63
Blanchard, D; 2004	Mayo	1975-98	35	73 (mastectomy)
				36 (no mastectomy)

NR: Not reported; OS: Overall survival; MSKCC: Memorial Sloan Kettering Cancer Center; NYC: New York City.

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