Axillary Primary and Breast Cancer Management

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Abstract

Purpose of Review Axillary primary breast cancer, also known as occult primary breast cancer, is a rare entity representing less than 1% of all breast cancers. The surgical management of the axilla in breast cancer has changed significantly, with implications for the management of axillary primary breast cancer. Much of the data is limited by era, small cohorts, or large retrospective database studies. The purpose of this review is to reinforce the diagnostic work up of occult breast cancer, review updated management strategies of the axilla and breast, and summarize changes and updates in practice management and outcomes.

Recent Findings Pathologic confirmation of breast primary disease and MRI are critical for the diagnostic work up of axillary primary breast cancer. A recent axillary primary specific meta-analyses and several National Cancer Database studies (NCDB) have reinforced that mastectomy versus breast conservation with whole breast radiation has equivalent outcomes. Surgical axillary management is under evolution, with multiple large trials reporting the role of neoadjuvant chemotherapy to downstage the node-positive axilla and decrease the morbidity of axillary lymph node dissection by allowing accurate sentinel node biopsy. Use of neoadjuvant chemotherapy and adjuvant radiation therapy is increasingly used, although no prospective data exists specifically in occult primary breast cancer.

Summary Appropriate diagnostic work up includes MRI to identify possible primary breast lesions in all patients with metastatic axillary disease and negative exam, mammography, and ultrasound. Axillary primary breast cancer should be treated with contemporary management strategies as other anatomic stage II breast cancers. Appropriate management strategies based on recent trial data suggest the use of neoadjuvant chemotherapy to downstage the axilla and allow for less morbid axillary surgery. Outcomes are equivalent with mastectomy or whole breast radiation.

Keywords Occult primary breast cancer · Axillary primary breast cancer · Axillary management · Neoadjuvant chemotherapy · MRI · Cancer of unknown primary

Introduction

Axillary primary breast cancer is a rare clinical entity. Axillary primary breast cancer, also known as occult breast cancer, occurs with identification of metastatic breast cancer to the axilla with no evidence of primary tumor in the breast. Axillary primary breast cancer represents a proportion of cancers that present as isolated axillary metastases, or cancers of

unknown primary. This overview will review work up of isolated axillary metastases to identify the primary cancer, discuss the management of axillary primary breast cancer, and identify contemporary data, strategies, and future directions.

Occult primary breast cancer has been described since the Halsted era of surgery [1]. William Halsted described a case series of 3 patients with axillary metastatic disease and no appreciable primary breast mass, who were ultimately diagnosed as breast cancers. Even in the modern era, data is limited to small case series, and large retrospective database series, many of which predate routine use of modern systemic therapy and MRI. The incidence is low, with modern retrospective database series identifying occult breast cancer in less than 1% of all breast cancers, and the most recent National Cancer Database (NCDB)-based study identified occult breast cancer as less than 0.1% of all breast cancers [2, 3].

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Further, the overall incidence has not decreased with improvements in breast imaging, although MRI has impacted the work up and ability to identify a primary tumor without changing the overall incidence [3–5]. MRI, however, can be incredibly useful in detecting an otherwise occult primary to better facilitate decision making regarding management of the breast [6].

Although primary axillary breast cancer is a rare enough entity that there is limited prospective data regarding management, the available data suggests that patients can be treated with similar algorithms and decision-making as those with axillary metastases and a known primary breast tumor. Axillary management, management of the breast, and decisions about systemic therapy and radiation in this patient population can be driven by contemporary trials and management strategies applicable to all breast cancer patients.

The specific management strategy of axillary primary cancer relies on appropriate diagnostic pathology confirmation, thorough imaging to identify any primary mass, and appropriate selection of neoadjuvant chemotherapy to downstage the axilla and minimize operative morbidity. This review will discuss relevant retrospective data and how contemporary imaging and multidisciplinary management strategies have impacted the best treatment algorithms for primary axillary breast cancer, or occult primary breast cancer.

Differential Diagnosis and Work Up of Axillary Primary Breast Cancer

Axillary primary breast cancer presents as the identification of metastatic cancer to the axilla, without frank evidence of a primary site (also known as cancer of unknown primary). Overall, up to 2% of all new cancer diagnoses are cancers of unknown primary [7]. The most common tumor subtype of cancers of unknown primary are adenocarcinomas (70%), followed by poorly differentiated carcinomas (15–20%). Historically, up to a third of patients had unidentified primary neoplasms; however, improved imaging and pathologic techniques have altered the diagnostic work up [8]. In more modern series of patients (including both men and women) who present with metastatic disease to the axillary lymph nodes, over 50% of these patients are found to have metastatic breast cancer [9, 10]. While breast cancer is rare in men, it should still be considered in patients who present with axillary metastases.
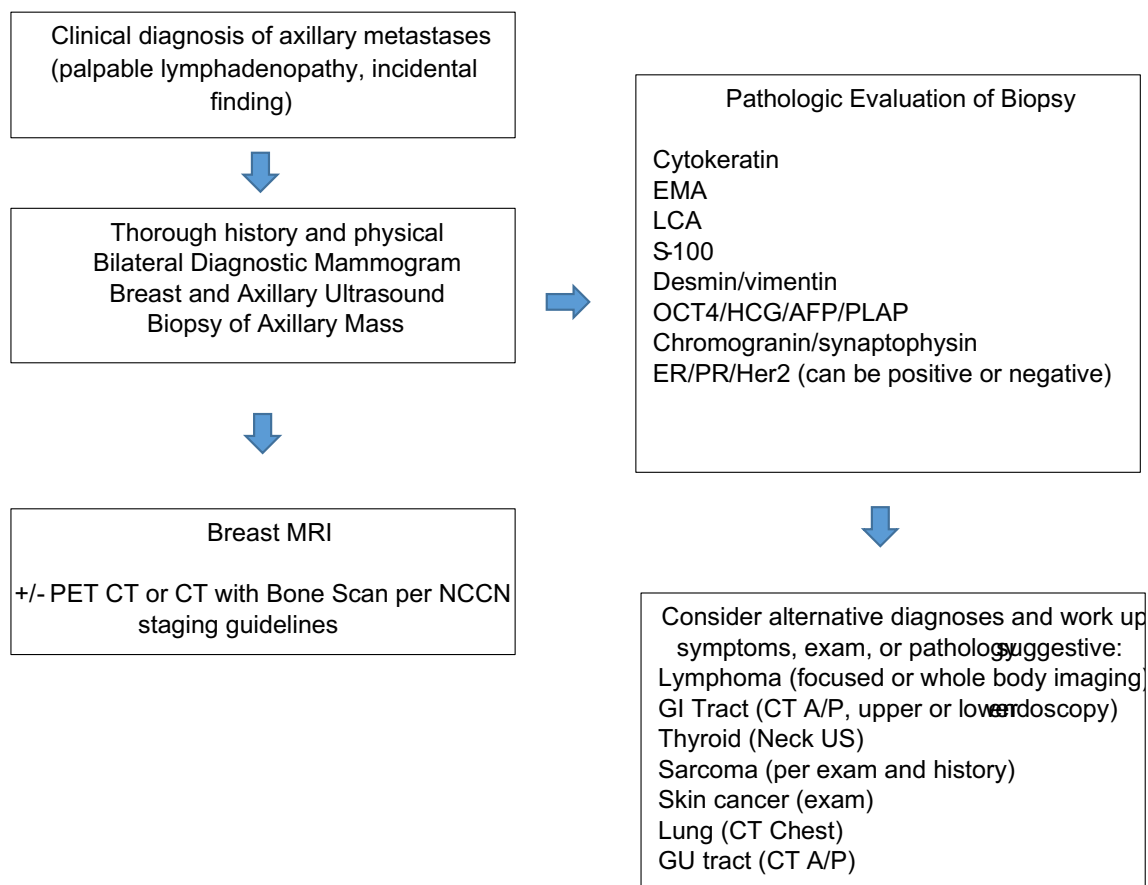
Work up of axillary metastases with unknown primary should include a thorough pathologic evaluation, which includes multiple techniques to characterize the tumor and identify the organ site of origin (Fig. 1). There is no single pathologic marker expression pattern that is diagnostic of breast cancer, although a combination of various markers is highly associated with breast cancer primaries. Patterns consistent with breast carcinomas are characterized by a combination of positive staining for estrogen and progesterone receptors, mammaglobin, CA 125, CEA, CK7, and BRST2 and negative staining for CK20 and TTF-1. Her2 and S-100 staining is nonspecific as diagnostic criteria, but necessary as a part of therapeutic decision-making [11]. As with all breast cancers, staining for the estrogen receptor, progesterone receptor, and Her2 protein should follow nationally established guidelines [12]. Other cancers which may present as axillary nodal metastases include lymphoma, melanoma, non-melanoma skin cancers, thyroid, or rarely lung or gastrointestinal cancers. If pathologic evaluation remains non-diagnostic after thorough immunohistochemical evaluation, consideration of these other pathologies should be considered and pursued with appropriate physical examination and imaging [12].

Once pathologic evaluation has identified the breast as the likely primary site, appropriate imaging work up should be pursued to identify the primary breast cancer. The initial step includes physical exam as well as diagnostic mammography and ultrasound of both breasts and axilla [12]. If no mass or imaging abnormality is identified on exam or routine breast diagnostic imaging, then breast MRI is indicated.

MRI is a highly sensitive imaging modality that is increasingly utilized in the work up of breast cancer, and should be considered standard in the evaluation of occult breast cancer in particular [12]. A review of eight retrospective studies identified a pooled sensitivity and specificity of MRI in occult breast cancer of 90% and 31% respectively [13]. However, this review was limited in that only 2 of the eight studies reported histopathologic confirmation of breast malignancy and the other 6 studies only reported imaging lesions that were suspicious for breast primary without reporting biopsy results or correlation. The pooled detection rate of a breast lesion with MRI was 72%. Non-histopathologically confirmed imaging findings on MRI are associated with a high false-positive rate [14]. All MRI findings should be pursued with a biopsy, typically with a second-look ultrasound and biopsy or MRI-guided biopsy if ultrasound is negative. If MRI identifies the primary tumor confirmed by biopsy, surgical planning is facilitated. Disease extent on MRI will guide whether lumpectomy with radiation is feasible or whether mastectomy is indicated. In the absence of detection of a primary tumor, there is an option of no breast surgery and whole breast radiation [6]. We will review these management strategies in the management portion of this review.

If the above work up identifies a breast primary, appropriate staging based of NCCN guidelines should be pursued [12]. If all imaging, including MRI, is negative for primary breast tumor, whole body staging is appropriate with either PET/CT or CT chest, abdomen, and pelvis in combination with a bone scan if indicated by breast cancer staging criteria.

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│ Clinical diagnosis of axillary  │        │   Pathologic Evaluation of Biopsy   │
│ metastases (palpable            │        │                                     │
│ lymphadenopathy, incidental     │        │ Cytokeratin                         │
│ finding)                        │        │ EMA                                 │
└─────────────────────────────────┘        │ LCA                                 │
              │                             │ S-100                               │
              ▼                             │ Desmin/vimentin                     │
┌─────────────────────────────────┐        │ OCT4/HCG/AFP/PLAP                   │
│ Thorough history and physical   │        │ Chromogranin/synaptophysin          │
│ Bilateral Diagnostic Mammogram  │───▶    │ ER/PR/Her2 (can be positive or      │
│ Breast and Axillary Ultrasound  │        │ negative)                           │
│ Biopsy of Axillary Mass         │        │                                     │
└─────────────────────────────────┘        └─────────────────────────────────────┘
              │                                            │
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│ Breast MRI                      │        │ Consider alternative diagnoses and  │
│                                 │        │ work up symptoms, exam, or          │
│ +/- PET CT or CT with Bone Scan │        │ pathology suggestive:               │
│ per NCCN staging guidelines     │        │ Lymphoma (focused or whole body     │
└─────────────────────────────────┘        │ imaging)                            │
                                            │ GI Tract (CT A/P, upper or lower    │
                                            │ endoscopy)                          │
                                            │ Thyroid (Neck US)                   │
                                            │ Sarcoma (per exam and history)      │
                                            │ Skin cancer (exam)                  │
                                            │ Lung (CT Chest)                     │
                                            │ GU tract (CT A/P)                   │
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Fig. 1 Algorithm for work up of axillary metastases with unknown primary

Management

Treatment of the patient with axillary lymphadenopathy, biopsy-proven axillary metastatic cancer, pathologic evaluation consistent with a breast primary, and negative imaging evaluation (including MRI) of both breasts should be treated following guidelines for the clinically positive axilla in management of breast cancer [12]. In this section, we will review management of the axilla, management of the breast, and regional nodal radiation. Historically, patients with occult primary breast cancer were treated with modified radical mastectomy (MRM); however, this treatment strategy has evolved to both include breast conservation (whole breast radiation) and use of neoadjuvant chemotherapy to allow for sentinel node biopsy over axillary lymph node dissection (ALND).

Axillary Management

The optimal treatment of the axilla in the management of breast cancer is under evolution. Historically, patients who present with a clinically positive axilla all required axillary lymph node dissection. Patients with occult primary breast cancer treated with upfront surgery consisting of axillary lymph node dissection have high rates of additional lymph node positivity. Approximately half of patients who present with axillary primary breast cancer and upfront surgery will have at least 4 positive lymph nodes on final pathology [15, 16].

However, management of the clinically positive axilla has undergone significant changes since these studies. Current management focuses on administration of neoadjuvant chemotherapy in order to downstage the axilla and spare patients the long-term morbidity of axillary lymph node dissection. Axillary lymph node dissection is associated with significant rates of chronic pain and lymphedema, which can require prolonged therapies and interventions to clinically manage [17]. Multiple recent trials have demonstrated that in patients with biopsy-proven axillary metastases, neoadjuvant chemotherapy can convert the patient to a clinically negative axilla, and sentinel node biopsy can reliably determine the presence of remaining disease in the axilla [18, 19•, 20•, 21•]. Here, we will review these studies and the implication to management of the clinically positive axilla, which can be applied to axillary primary breast cancer. The first three are prospective,

Table 1 Axillary management, review of trials of neoadjuvant chemotherapy to downstage axilla

Study	Total patients	T0 iatients	Identification rate	False negative rate	Strategies to lower false negative rate < 10%
SENTINA (Arm C)	592	NR	80.1%	14.2%	Dual tracer technique, > 3 LN
SN FNAC	153	5	87.6%	8.4%	Dual tracer technique, > 3 LN
ACOSOG 1071	649	7	92.9%	12.6%	Dual tracer technique, > 3 LN OR inclusion of clipped node
Caudle	208	1			Targeted axillary dissection

multi-institutional trials, which required a sentinel node biopsy followed by completion axillary lymph node dissection (Table 1).

The first of these, the ACOSOG 1071 trial, enrolled patients who presented with a biopsy-proven lymph node metastasis with breast cancer who received neoadjuvant therapy [20•]. Neoadjuvant therapy was followed by a sentinel node biopsy and completion axillary lymph node dissection to determine the identification rate (ability to perform and identify a sentinel lymph node) and false negative rate (FNR, rate of a negative sentinel node where additional disease was found in non-sentinel lymph nodes in the completion axillary lymph node specimen). In the patients who were able to complete the protocol ($n = 649$), the identification rate of a sentinel node was 92.9%, and the total FNR was 12.6%. In subgroup analysis of this study, a greater number of examined sentinel nodes (9.1%), use of dual tracer technique (10.8%), and patients with clinical N1 (versus N2) disease resulted in a lower FNR. This study did enroll occult primary breast cancer patients, with a total of 7 patients (1% of total cohort).

The second of these prospective trials, the sentinel lymph node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA) study was a four-arm prospective study with 1737 total patients in order to investigate the optimum timing of sentinel node biopsy [18]. Patients with a clinically positive axilla on enrollment received neoadjuvant chemotherapy, and those with a clinically negative axilla after neoadjuvant chemotherapy underwent sentinel node biopsy and completion axillary dissection (arm C). The identification rate of the sentinel node in this cohort was 80.1%, and the FNR was 14.2%. Similar to the ACOSOG 1071 trial, subgroup analysis suggested that a greater number of examined sentinel nodes and dual tracer technique lowered the FNR to 7%. Occult primary breast cancer was not an exclusion criteria for this study, although the exact number of patients who may have had occult primary cancer was not explicitly stated in this paper.

Finally, the Sentinel Node Biopsy After Neoadjuvant Chemotherapy (SN FNAC) study investigated the identification rate and FNR of sentinel node biopsy in 153 patients who presented with biopsy-proved axillary metastases and underwent neoadjuvant chemotherapy who then had a clinical response. Similar to the previous studies, all patients had a sentinel node biopsy followed by a completion axillary lymph node dissection. This study included 5 patients (3% of total cohort) with occult primary breast cancers. The ability to identify a sentinel node was 87.6% in this study, and when identified, the FNR was 8.4% [19•].

An additional prospective single institution trial investigated a different technique in order to further improve the FNR of sentinel node biopsy following neoadjuvant chemotherapy. Caudle, et al. described a prospective study in which the biopsy-proven lymph node (clipped node) was specifically targeted for removal in the setting of traditional sentinel node technique. This procedure was also followed by a completion axillary dissection to identify the false negative rate. Removal of the clipped node alone demonstrated an FNR of 4.2%, while the combination of a sentinel node procedure with clipped node demonstrated an FNR of 1.4%. This study included 1 patient with occult breast cancer [21•]. A subset analysis of the ACOSOG 1071 trial which investigated specifically the identification of the biopsy-proven metastatic lymph node also demonstrated a significantly lower FNR, further confirming this technique as a process to evaluate residual disease in the axilla [22].

Although this final study was a single institutional study, in combination with the three trials discussed above, it emphasizes the feasibility of accurately assessing the presence of residual disease in the axilla. These studies collectively have led to a significant clinical management change for the positive axilla in breast cancer. Modern, directed systemic therapies can lead to high rates of complete pathologic response, so application of these studies can spare significant numbers of patients from the morbidity of a full axillary lymph node dissection. Pathologic complete response rates can approach greater than 40%, and the ability to spare the axilla is associated with improved patient reported outcomes [23]. The axillary management strategies discussed above are applicable in the occult breast cancer population, although as a clinical entity it is too rare for dedicated studies.

There is a single retrospective database study evaluating the use of neoadjuvant chemotherapy and its role in axillary management [24••]. Between 2004 and 2014, 684 patients were identified in the NCDB with occult breast cancer. Only 30% of this cohort underwent neoadjuvant chemotherapy, and only 15.9% of those patients received a sentinel node biopsy.

When adjusting for appropriate locoregional therapy (ALND in the upfront surgical setting and regional RT), performance of sentinel node biopsy was not associated with a difference in overall survival. Although these data reflect an era that preceded the studies described above, it suggests that appropriate selection of patients for neoadjuvant chemotherapy and use of sentinel node biopsy are not associated with worse outcomes.

Additional motivation for the use of neoadjuvant chemotherapy in occult primary breast cancer includes the emerging literature reporting additional adjuvant therapy benefits for patients whose tumors do not achieve a pCR. While neoadjuvant therapy alone is not associated with improved survival compared to adjuvant therapy, several studies have examined patients with residual disease after neoadjuvant chemotherapy and randomized them to a change in adjuvant therapy [25, 26]. Specifically for triple negative and Her2+ breast cancers, these trials demonstrated that a change in their adjuvant therapy significantly improved disease-free and overall survival. Patients with axillary primary breast cancer with residual disease in the breast or axilla after neoadjuvant chemotherapy would benefit from these changes in therapy. This finding makes the decision for neoadjuvant chemotherapy in patients with axillary primary breast cancer even more critical as the patient's pathologic response (or lack thereof) may change their postoperative systemic management in a way that will improve their survival. Patients with ER+/Her2− disease have lower rates of pathologic complete response, but may not benefit from additional cytotoxic therapy [26]. Even in this context of lower rates of axillary response, however, up to 20% of these patients could be spared the morbidity of axillary therapy, and even without changes to their systemic therapy regimen, the neoadjuvant approach may confer benefit in this population [27].

Management of the Breast

Management of the breast in axillary primary breast cancer will depend on whether the primary is identified on MRI. When MRI does not identify the primary site, options include mastectomy or breast conservation with whole breast radiation only. Historically, mastectomy was performed to both identify the primary tumor and confirm its removal; however, mastectomy did not necessarily reveal identification of a tumor in the breast. In fact, up to one-third of patients who underwent mastectomy in this setting did not have an identified primary cancer in the breast in the final pathologic specimen [28]. In the MRI era, the rate of identified primary cancer in the breast on final pathology has decreased significantly, and more modern estimates suggest that less than one-third of patients have a primary tumor identified [29].

In light of the rarity of occult primary breast cancer, there are no randomized controlled trials evaluating mastectomy compared to whole breast radiation in axillary primary breast cancer. A recent meta-analysis identified 7 studies that compared surgery to conservative management, defined as observation or radiation therapy [28]. These studies spanned a significant time period (1951–2011), the majority predating routine use of MRI and contemporary systemic management strategies, and included a range of patients ($n = 10$–95). All of these patients underwent ALND. For those undergoing mastectomy, a primary tumor was identified only 20% of the time on final pathology.

The meta-analysis demonstrated no difference in mortality, locoregional recurrence, or distant metastases in patients undergoing mastectomy versus whole breast radiation. There are limitations to this study, as all included studies in the meta-analysis were non-randomized and retrospective. Meta-analysis is unable to adjust for selection bias or other limitations of these kinds of data. Further, these studies span a time period that limits their applicability in the modern era of biology-driven therapy and MRI. However, with the significant improvements in breast imaging and targeted therapies for breast cancer, it is reasonable to conclude that findings from older studies should apply to current patients as breast cancer mortality continues to decline.

This meta-analysis also explored the role of regional nodal radiation. Patients who underwent ALND and regional radiation therapy had lower locoregional recurrence rates, but similar overall survival and distant metastases [28]. Regional nodal radiation is also a therapy in evolution in the modern treatment of breast cancer. In patients who present with clinically positive disease in the axilla, regional nodal radiation is increasingly recommended to improve locoregional control, and potentially survival [24••]. For occult breast cancer specifically, NCDB data suggests that regional nodal radiation therapy is more likely to be used in patients with more advanced clinical nodal disease (cN2 v. cN1) or those with a high number of pathologically positive lymph nodes [2]. These data are also influenced by the retrospective nature of the NCDB and selection bias.

Outcomes

The historical outcomes of occult breast cancer are difficult to ascertain because of the rarity of the disease. Further, the heterogeneity of treatment strategies also impacts the ability to definitively state whether occult breast cancer survival or locoregional recurrence is favorable or not compared to other breast cancers with clinically positive axillary disease on presentation. The recent meta-analysis included a summary of locoregional recurrence, distant metastasis, and mortality, stratified by treatment approach [28]. However, because of small numbers and limited follow-up, multiple included studies reported no deaths, and a small number of deaths (for example $n = 2$) can imply mortality of over 50%, which is

not representative of the disease process as a whole. These studies also predated most of the modern systemic therapy approaches, including Her2-directed biologic therapy, which limits extrapolation of these data to the modern patient.

Two recent NCDB studies have suggested that use of contemporary management strategies, including neoadjuvant chemotherapy and regional radiation therapy, is associated with improved outcomes. Again, both of these studies cover a time period limited by lower rates of neoadjuvant chemotherapy (partially predating the studies described in the previous section) and are limited by the type of data that is available in the NCDB, which is strongly influenced by selection bias.

The first NCDB study examined 1853 patients with clinically occult breast cancer and only N1 or N2 disease [2]. The authors compared patients who underwent modified radical mastectomy (MRM), with or without regional radiation, to those undergoing axillary lymph node dissection with regional radiation, to those undergoing either axillary dissection alone or observation. Approximately half of patients undergoing MRM received nodal radiation. Patients undergoing axillary lymph node dissection were defined as having at least 10 lymph nodes removed at time of surgery. Patients receiving care at academic institutions were much more likely to undergo axillary dissection with regional nodal radiation compared to MRM +/− radiation therapy. Patients who underwent axillary dissection with regional nodal radiation had statistically improved survival (hazard ratio 0.466, $p = 0.001$) compared to MRM, although they did not compare the group who underwent MRM with radiation therapy specifically. Overall survival rates at 8 years were greater than 70% in patients who underwent either MRM or ALND with radiation, which is similar to American Cancer Society estimates for patients with clinical axillary disease [30].

The second NCDB study specifically looked at the outcomes of occult breast cancer in patients who underwent neoadjuvant chemotherapy [24••]. Only 214 patients with axillary primary breast cancer underwent neoadjuvant chemotherapy from 2004 to 2014 in the NCDB. The majority of these patients underwent full axillary lymph node dissection, although 15.9% of these patients underwent sentinel node biopsy. Since the NCDB does not code specifically for sentinel node biopsy, SLNBx was defined as 4 or fewer lymph nodes retrieved on pathologic specimen. Patients who underwent upfront surgery had improved survival if they underwent ALND compared to SLNBx. However, there was no difference in survival in the neoadjuvant chemotherapy group if they underwent ALND or SLNBx if they received regional radiation therapy. This finding suggests that morbidity of ALND can be spared, but locoregional therapy cannot be omitted and regional nodal radiation therapy remains an important piece of the multidisciplinary approach to this patient population.

Conclusion

Axillary primary breast cancer is a rare clinical entity, representing less than 1% of all new breast cancer cases. Although prospective data is limited, the comprehensive weight of the literature suggests that the behavior of axillary primary breast cancer is similar to that of other anatomic stage II breast cancers. Use of MRI has aided in finding target primary lesions to facilitate diagnosis and management and to select patients who can avoid mastectomy and receive whole breast radiation. Recent management changes in the approach to the axilla can be applied to occult primary breast cancer, which emphasizes a neoadjuvant chemotherapy approach. A recent meta-analysis confirms the equivalence of mastectomy versus whole breast radiation in management of the breast. With appropriate diagnostic work up and staging, even this rare entity should expect similar outcomes to other stage-matched breast cancers.

Compliance with Ethical Standards

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Papers of particular interest, published recently, have been highlighted as:
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