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Oncologic Outcomes with Neoadjuvant Chemotherapy and Breast Conservation for MRI Occult Breast Cancer

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ABSTRACT

Background: Occult primary breast cancer is a presentation of breast cancer involving lymph nodes without an identified primary tumor within the breast. Mastectomy with axillary node dissection has been the traditional management. However, reported oncologic outcomes with mastectomy have been similar to those with breast conserving therapy (axillary surgery and radiotherapy). With the increased sensitivity of MRI and its routine use in the workup of occult breast cancer, the role of mastectomy for occult breast cancer is now even less clear. We report our institutional experienc of neoadjuvant chemotherapy followed by axillary surgery and radiotherapy for women with occult breast cancer.

Methods: We conducted a retrospective review of women diagnosed with isolated metastatic adenocarcinoma to the axilla histologically consistent with breast adenocarcinoma without evidence of a primary breast tumor. Medical records were analyzed to gather pertinent information regarding diagnostic workup, treatment, recurrence, and survival.

Results: We identified seven patients treated in our institution between 2012 and 2017 who met the criteria for primary occult breast cancer. The median age at diagnosis was 63 years old (range 42-71). Subtypes by immunohistochemistry (IHC) were HER-2 positive (3 pts), triple negative (2 pts), and hormone receptor positive/HER-2 negative (2 pts). All patients received neoadjuvant chemotherapy and axillary surgery without mastectomy followed by adjuvant radiotherapy to the breast and regional nodes. Hormone receptor positive patients received adjuvant endocrine therapy. At a median follow-up of 3.5 years, all patients were alive with no local or regional recurrence of disease while one patient developed distant metastases.

Conclusion: A multimodality approach with neoadjuvant chemotherapy can lead to high rates of breast conservation in women with primary occult breast cancer. This approach appears to be oncologically safe.

Introduction

Occult primary breast cancer (OPBC) is a rare clinical presentation of breast cancer with histologically proven carcinoma in lymph nodes in the absence of a primary cancer in the breast.[1-3] OPBC is estimated to represent 0.1-0.8% of all breast cancer diagnoses.[3-6] Diagnosis of OPBC requires histology and IHC consistent with breast adenocarcinoma in the absence of other suspicious lesions on breast or systemic imaging. Antibodies against tumors of breast origin can facilitate the diagnosis and include ER/PR, mammoglobin, GCDFP-15, and GATA3.[6,7] MRI has

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become the standard of care in the workup of OPBC and can identify a primary breast lesion in up to 70% of women with mammographically occult tumors.[6, 7] As such, the incidence of true OPBC has decreased significantly with improved imaging. Given the rarity of true OPBC, there is limited data to guide optimal management in this setting. Several retrospective case series[4, 8-12] and a population study[13] have evaluated the impact of surgical extent and radiotherapy for OPBC. These have consistently demonstrated equivalent oncologic outcomes between mastectomy compared to breast conservation with radiotherapy. Despite this, the majority of patients diagnosed with OPBC are treated with modified radical mastectomy.[13] Currently, optimal management in several aspects of OPBC remain to be defined. These include surgical management of the breast, extent of axillary surgery, and timing of systemic therapy.

We report our clinical approach and treatment outcomes in management of patients with OPBC treated at a single institution. Based on extrapolation from studies in node positive patients with intact primary tumors, we have adopted a standardized treatment algorithm for OPBC involving increased emphasis on optimal systemic therapy and radiotherapy with omission of mastectomy. Our aim is to demonstrate how a multidisciplinary treatment plan can decrease treatment morbidity without compromising oncologic outcomes in women with OPBC.

Methods

We performed an institutional review board approved, retrospective review of patients diagnosed with OPBC between October 2012 and July 2017 at Banner University Medical Center in Tucson, Arizona. Patients were identified by querying electronic medical records. Inclusion criteria were as follow: diagnosis of adenocarcinoma involving axillary lymph nodes, biopsy pathologically consistent with breast origin, absence of disease within the breast on mammogram and MRI and absence of distant disease on systemic imaging. Patients with a prior history of invasive malignancy or ipsilateral DCIS or invasive ductal carcinoma were excluded. Medical records were analyzed to gather data including: method of diagnosis, imaging workup, tumor characteristics, systemic therapy, radiation, surgery, surveillance imaging and disease status at last date of contact.

Results

Patient Characteristics

Seven patients were identified with primary occult breast cancer treated between 2012 and 2017. Patient characteristics are summarized in Table 1. The median age at diagnosis was 63 years old. (range 42-71). Method of detection was either screening mammogram (57.1%) or self-palpation (42.9%). Six out of seven patients (85.7%) had clinical stage IIA occult breast cancer while one patient had stage IIIA (14.3%). Molecular subtype as approximated by IHC was human epidermal growth factor (HER-2) positive (three patients), triple negative (two patients), and hormone receptor positive / HER-2 negative (two patients). All patients underwent mammography and dedicated breast MRI to evaluate for a breast primary. To evaluate for distant organ involvement, all patients had a metastatic workup with either PET CT (85.7%) or a CT chest/abdomen/pelvis and bone scan (14.3%). Median follow-up time from diagnosis to last contact was 41.1 months.

Table 1. Patient Characteristics

Variables		N(%)
Age	Mean (Range)	58 (42-71)
	Median	63
Method of Detection	Self palpation	3(42.9%)
	Screening mammogram	4(57.1%)
Stage	IIA	6(85.7%)
	IIIA	1(14.3%)
Clinical Stage	cT0N1M0	6(85.7%)
	cT0N2M0	1(14.3%)
Pathologic Stage	ypTxN0M0	4(57.1%)
	ypTxN1M0	2(28.6%)
	ypTxN2M0	1(14.3%)
Tumor Subtype	Luminal B	2(28.6%)
	Triple Negative	2(28.6%)
	HER2+	3 (42.9%)
Investigations	Mammogram, MRI, PET-CT	6(85.7%)
	Mammogram, MRI, CT C/A/P	1(14.3%)

Treatment

Patients were discussed at a multidisciplinary treatment planning conference where workup and treatment strategy was agreed upon before initiation of any therapy. All patients received neoadjuvant chemotherapy, axillary surgery, and radiotherapy to the breast and regional nodes. Four patients received dose-dense doxorubicin and cyclophosphamide (ddAC) followed by weekly paclitaxel. Three of these patients completed 4 cycles of ddAC. One patient stopped ddAC after 2 cycles due to adverse events. All four received 12 cycles of weekly paclitaxel following AC. Two patients with HER-2 positive disease received Taxol and Trastuzumab while the third received Paclitaxel and Trastuzumab followed by ddAC. Both patients with ER positive tumors received adjuvant endocrine therapy with anastrozole. Following neoadjuvant chemotherapy, six out of seven patients received an axillary lymph node dissection (ALND) while one patient (triple negative with clinical complete response to

Table 2. Treatment received for occult breast cancer presenting as axillary lymph node metastases

Variables		N(%)
Neoadjuvant Chemotherapy	PaclitaxelTrastuzumabTrastuzumab	2(28.6%)
	Paclitaxel/ddAC	4(57.1%)
	PaclitaxelTrastuzumabTrastuzumab/ddAC	1(14.3%)
Endocrine Therapy		2(28.6%)
Axillary Surgery	Axillary Lymph Node Dissection	6(85.7%)
	Sentinel Lymph Node Dissection	1(14.3%)
Radiotherapy	Breast, supraclaviular fossa	4(57.1%)
	Breast, supraclavicular fossa, full axilla	2(28.6%)
	Breast, supraclavicular fossa, full axilla, IM chain	1(14.3%)
Disease Status at Last Follow-Up	Local/regional recurrence	0 (0.0%)
	Distant recurrence	1(14.3%)

chemotherapy) underwent negative sentinel node biopsy alone.

All patients received adjuvant radiotherapy to the whole breast (50Gy) and supraclavicular fossa (45Gy) in 25 fractions using a mono-isocentric, three-field technique. Supraclavicular fields included the full level 1-3 axilla in five patients. In two patients (who had axillary dissection with limited residual disease), the dissected axilla was not included in the supraclavicular field.

Outcomes

Four patients (57.1%) had a pathologic compete response within the axilla following neoadjuvant chemotherapy (Hormone receptor positive=1, TNBC=1, HER-2 positive=2). Six of seven patients have continued with annual surveillance breast MRI in addition to annual breast tomosynthesis. At a median follow up of 41.3 months from diagnosis, all patients remain free of local or regional recurrence. One patient with HER-2 positive pleomorphic infiltrating lobular carcinoma developed osseous metastases at 57.4 months from diagnosis.

Table 3. Follow-up time since diagnosis

Follow-Up Time Since Diagnosis	Time (months)
Mean	41.1
Median	41.7

Discussion

Occult breast cancer is a rare but well-defined presentation of breast cancer characterized by lymph node involvement with carcinoma of breast origin but no identifiable primary tumor within the breast. Pathogenesis is unclear, but it is generally felt to represent lymphatic dissemination from either an unidentified, occult cancer within the breast or due to dissemination from a primary tumor within the breast which has subsequently regressed. Mastectomy with axillary node dissection has been the traditional management for OPBC; primarily out of concern for sub-clinical or otherwise undetected disease within the breast. Over the last decade, the sensitivity of breast imaging (with MRI and tomosynthesis) has significantly improved the detection of small-volume breast lesions. Prior studies in OPBC have demonstrated that MRI can detect clinically and mammographically occult lesions with detection rates ranging from 43-86%.[9, 14,15]

The largest reported single institution series evaluating the utility of MRI in OPBC comes from Memorial Sloan Kettering Cancer Center. Olson *et al.* published their initial institutional results in 40 women with clinically and mammographically occult axillary adenocarcinoma. MRI identified a primary breast lesion in 70% of patients. In their series, 47% of patients underwent breast conservation. Five patients with negative MRI underwent axillary dissection and radiotherapy. Among five women with negative MRI who went on to mastectomy, one patient had an invasive tumor identified on final pathology. The authors note that the MRI performed at that time was inadequate by current standards and the region containing the tumor was outside the scan field-of-view.[16] Buchanan *et al.* reported on an updated series from the same institution on 69 patients. MRI was able to identify a breast primary in 49% of patients. Among women with negative MRI who went on to mastectomy, 25% were found to have invasive tumor in the surgical specimen with one patient having a 3cm, non-enhancing IDC. Ten patients with negative breast MRI were treated with breast conservation with ALND and breast radiotherapy and all were free of local disease at a median follow up of 4.5 years.[14]

De Bresser *et al.* conducted a systematic review and identified 8 retrospective studies which evaluated the ability of breast MRI to detect breast tumors in patients with clinically and mammographically OPBC.[17] Breast MRI was found to have 90% sensitivity with the ability to detect a previously unidentified breast cancer in more than two-thirds of patients. Breast MRI had much lower specificity ranging from 22-50%. The

authors concluded that MRI has clear utility in the workup of mammographically occult breast cancer. This study did not specifically report on outcomes of women with negative MRI treated with breast conservation.

The recognition that radiotherapy can eradicate microscopic residual disease within the breast following resection of gross disease provides rationale for applying the same approach in the occult primary setting. Following the publication of multiple large randomized trials demonstrating equivalence between mastectomy and lumpectomy plus radiotherapy, breast conservation became well-established as the standard of care for operable breast cancer. These studies demonstrated that breast conserving therapy provides equivalent disease-free and overall survival compared to mastectomy. In studies that mandated negative surgical margins, adequate axillary staging and tumors smaller than 5cm, lumpectomy plus radiation have also demonstrated equivalent local control to mastectomy.

While there are no prospective studies to guide management of OPBC, numerous retrospective series have demonstrated equivalent oncologic outcomes between mastectomy and breast conserving therapy (axillary dissection and radiation).[3, 9, 18] The results of these studies have consistently shown that patients with occult breast cancer receiving ALND followed by breast radiotherapy have similar outcomes to patients who underwent mastectomy. In contrast, patients treated with axillary surgery alone without radiotherapy have consistently had worse outcomes.

Yang *et al.* published the largest reported single institution study of breast conservation for patients with mammographically occult breast cancer. The authors compared outcomes of 214 mammographically occult breast cancer patients treated with BCT at Yale University between 1973 and 2003 and 2168 mammographically positive breast cancer and found that in breast recurrence rates after breast-conserving therapy and adjuvant radiation therapy were not significantly different between the groups.[19] Likewise, at 10 years, there was no difference in overall survival, cause-specific survival, and distant relapse between patients with occult breast cancer and mammographically positive breast cancer. Receipt of BCT was an independent predictor of nodal relapse–free survival. The authors note that regional nodal irradiation was reserved for patients who had additional risk factors for recurrence such as high nodal burden. This may have been associated with the increased rate of nodal recurrences in the BCT arm. Among patients with in-breast recurrences, patients with initially mammographically occult breast cancers were more likely to have mammographically occult disease at the time of recurrence (32%) compared to patients with initially mammographically positive disease (13%). These findings support the use of MRI for surveillance in women with OPBC treated with BCT.

Walker et. al utilized the Surveillance, Epidemiology, and EndResults (SEER database) to identify 750 patients diagnosed with T0N+ disease between 1983 and 2006 .[13] 202 patients received ALND plus radiotherapy while 268 received mastectomy. Cause specific survival at 10 years was 74.6% and was equivalent for patients treated with axillary dissection plus radiotherapy or mastectomy. Likewise, 10-year overall survival was equivalent between mastectomy and ALND plus radiotherapy at 64.9%. In contrast, 10-year OS following ALND alone without radiotherapy was significantly worse at 58.5% (n=126; log-rank P =.02). While this study lacks locoregional recurrence information (a limitation of the SEER dataset), it does support the long-term oncologic efficacy of breast conservation and radiotherapy for OPBC. Taken together with single institution series, these findings suggest that the same treatment paradigm for known-primary breast cancer yields equivalent oncologic outcomes when applied to OPBC. This is the current approach recommended in NCCN guidelines.[20]

Neoadjuvant systemic therapy has become standard management for patients with node positive breast cancer. As such, there is a strong rationale for neoadjuvant therapy in women presenting with OPBC. Rueth *et al.* reported on outcomes in 36 patients with OPBC treated at MD Anderson Cancer Center. In this series, 27 patients were treated with BCT. 70% of patients received neoadjuvant systemic therapy. At a median follow up of 64 months, the authors reported no local or regional recurrences and one distant recurrence. This series is also notable in that 92% of patients were staged with MRI.[16] Our findings are consistent with those of these authors and demonstrate equivalent outcomes with a similar treatment algorithm.

Optimal axillary management for patients with intact primary breast cancer continues to evolve. Specifically, the necessity for completion axillary dissection in patients with small volume axillary involvement is being questioned. In clinically node negative but sentinel node positive patients, axillary dissection conveys a significantly higher rate of lymphedema compared to axillary radiotherapy without improving oncologic outcomes.[21] Ongoing randomized studies are evaluating the role of completion axillary dissection in patients with clinically positive axillary nodes who convert to clinically negative following neoadjuvant chemotherapy. In our practice, sentinel node biopsy is routinely performed in women who initially presented with clinically positive axillary nodes who have converted to clinically negative following neoadjuvant chemotherapy. Patients who are found to be pathologically node negative at time of sentinel node procedure are then offered axillary radiotherapy in lieu of full axillary dissection.

One patient in our series had a negative sentinel node biopsy after chemotherapy and did not receive

completion axillary dissection. As axillary techniques become further refined, incorporation into the management of OPBC should further reduce the rates of treatment-associated toxicity.

Like any retrospective study, this case series has several limitations. Due to the rarity of occult breast cancer, our study has a small sample size. Likewise, the extended period of time over which patients were treated leads to changes in practice patterns as evidenced by the omission of axillary dissection in patients with pathologic complete response in our current practice. A series such as this can also include medical record errors. Lastly, our follow-up is still relatively short given the long latency period for breast cancer recurrence. Nonetheless, our case series is a valuable addition to the literature in that all patients had occult disease on MRI and all patients were treated with neoadjuvant chemotherapy, regarding the treatment and management of patients with primary occult breast cancer.

Given the increased sensitivity of MRI over mammography, patients diagnosed with OPBC in the current era are less likely to have gross breast involvement than patients diagnosed without MRI. As such, the therapeutic role of mastectomy for OPBC in the modern era is questionable. In our series, all patients underwent diagnostic workup with negative dedicated breast MRI in addition to digital or 3D mammography. Our series highlights the importance of a prospective, multidisciplinary approach for the management of OPBC. All patients were discussed at a multidisciplinary treatment planning conference where workup and treatment strategy were discussed before initiation of any therapy. All patients underwent neoadjuvant chemotherapy followed by axillary surgery and radiotherapy. Patients have continued routine surveillance with MRI and mammogram. At a median follow-up of 41.1 months from diagnosis, all patients remain alive and no patients have had recurrence within the breast or regional nodes. Our results are consistent with other series and support the oncologic validity of this combined-modality approach for OPBC.

Conflict of Interest

The authors have nothing to disclose.

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