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ORIGINAL ARTICLE – BREAST ONCOLOGY

Breast Conservation in the Setting of Contemporary Multimodality Treatment Provides Excellent Outcomes for Patients with Occult Primary Breast Cancer

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ABSTRACT

Purpose. To evaluate recurrence and survival for patients with occult (T_0N_+) breast cancer who underwent contemporary treatment, assessing outcomes for breast conservation and mastectomy.

Methods. We performed a single-institution review of women with occult breast cancer presenting with axillary metastasis without identifiable breast tumor or distant metastasis. We excluded patients with tumors in the axillary tail or mastectomy specimen, patients with additional nonbreast cancer diagnoses, and patients with a history of breast cancer. Breast conservation was defined as axillary node dissection with radiation therapy, without breast surgery. We evaluated patient, tumor, treatment, and outcome variables. Patients were assessed for local, regional, and distant recurrences. Overall survival was calculated using the Kaplan–Meier method.

Results. Thirty-six patients met criteria for occult breast cancer. Most of these patients (77.8 %) had N_1 disease. Fifty percent of cancers ($n = 18$) were estrogen receptor–positive; 12 (33.3 %) were triple-negative. All patients were evaluated with mammography. Thirty-five patients had breast ultrasound (97.2 %) and 33 (91.7 %) had an MRI. Thirty-four patients (94.4 %) were treated with chemotherapy and 33 (91.7 %) with radiotherapy. Twenty-seven patients (75.0 %) were treated with breast conservation. The median follow-up was 64 months. There were no local or regional failures. One distant recurrence occurred >5 years after diagnosis, resulting in a 5-years overall survival rate of 100 %. There were no significant survival differences between patients receiving breast conservation versus mastectomy ($p = 0.7$).

Conclusions. Breast conservation—performed with contemporary imaging and multimodality treatment—provides excellent local control and survival for women with T_0N_+ breast cancer and can be safely offered instead of mastectomy.

Occult breast cancer presenting as axillary metastases without an identifiable primary breast tumor (T_0N_+) represents <1 % of breast cancer.[1,2] For women with breast adenocarcinoma limited to axillary lymph nodes, prognosis is favorable,[3,4] and current National Comprehensive Cancer Network (NCCN) guidelines recommend following the treatment pathway of similarly staged women with an identified primary tumor.[5] For these patients, guidelines recommend systemic chemotherapy combined with either breast-conserving surgery (BCS) and axillary lymph node dissection (ALND) or modified radical mastectomy (MRM). Most patients will require radiotherapy, and hormonal therapy and human epidermal growth factor receptor-2 (HER-2)–directed therapy based on individual tumor biology.

These recommendations are based largely on small retrospective studies, many of which were performed prior

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to contemporary breast imaging techniques or the use of taxanes and targeted therapy. It is not surprising, therefore, that practice patterns vary widely, with a large number of women receiving MRM rather than BCS.[4,6–8] In a recent population-based study, less than one-third of women were treated with BCS for T_0N_+ breast cancer, although they had similar survival when compared to those receiving MRM.[8] These results should serve to encourage increased use of BCS for women with T_0N_+ breast cancer; however, one potential disadvantage of database studies is the limited ability to capture the use of imaging studies and multidisciplinary treatment planning and administration. In the current study, we analyzed data from a single cancer center that focuses on multimodality treatment planning, with the aim of determining locoregional recurrence and survival rates among women with T_0N_+ breast cancer who underwent contemporary multimodality imaging and treatment.

PATIENTS AND METHODS

Study Definitions and Patient Cohort

We defined occult (T_0N_+) breast cancer as adenocarcinoma that presented with axillary metastases in the absence of a primary breast tumor identified on physical examination, imaging, or postoperative pathological evaluation (for those having mastectomy). Women were classified as having BCS if they had axillary lymph node dissection with preservation of the breast followed by radiation therapy.

Using those definitions, we performed a retrospective review of patients who were treated at a single institution from January 1, 2000 to December 31, 2011. All women had T_0N_+ breast cancer. We included patients with any American Joint Committee on Cancer (AJCC) nodal stage, including supraclavicular or infraclavicular disease. All patients had biopsy proven invasive adenocarcinoma from axillary specimens (fine needle aspiration [FNA], core needle biopsy [CNB], or excisional biopsy). If the biopsy was thought to arise from the axillary tail of the breast, the patient was excluded. Few pathological reports commented on the presence or absence of lymphoid tissue, so we were unable to use this as an inclusion characteristic. For patients who had part of their treatment at an outside institution, study inclusion was allowed, provided they had sufficient prereferral records.

Adhering to our definition of T_0N_+ breast cancer, we excluded patients with a preoperatively identified breast tumor or patients who underwent mastectomy with subsequent identification of a primary tumor on pathological evaluation. Patients with a history of breast cancer, a current diagnosis of contralateral breast cancer, known ductal carcinoma in situ, those with a subsequent nonbreast cancer diagnosis, and those with distant metastatic disease at the time of diagnosis were also excluded.

Study Variables

Clinical information regarding patient demographics (age, geographic location, family history of breast cancer), tumor characteristics (presenting nodal stage, hormone receptor status, HER-2 expression status, histology, grade), treatment administration (chemotherapy and/or targeted HER-2 therapy, hormone therapy, surgical procedure, radiation therapy dose and fields), and patient outcomes (ipsilateral breast tumor recurrence, regional and distant metastases, overall survival) were collected.

This study was exempt from review under Code of Federal Regulations 45 part 46.101(b) by the local institutional review board Human Subjects Committee.

Data Analysis

We performed a descriptive statistical analysis of the collected variables. Instances of ipsilateral breast tumor recurrences, regional nodal recurrences, and/or distant recurrences were measured from the time of initial diagnosis to the time of recurrence. Survival was measured from the time of diagnosis until the time of death or last follow-up. We used the methods of Kaplan–Meier to estimate unadjusted 5-years overall survival (OS) rates. Differences in OS between patients who underwent BCS treatment versus MRM were compared using the log-rank test.

Data were analyzed using Stata statistical software (SE 12, StataCorp LP, College Station, TX). All p values were two-tailed, with $p \leq 0.05$ considered statistically significant.

RESULTS

During the study period, we identified 4,298 patients who presented with axillary metastases. After incorporating our inclusion and exclusion criteria, 36 patients had T_0N_+ breast cancer (0.8 % incidence) (Table 1). The median age was 55.2 years. Most patients ($n = 28$ [77.8 %]) had AJCC[9] N_1 disease. The average size of the largest radiographically measured node was 30.4 mm (range 12–70 mm). Nineteen patients were diagnosed with CNB, 13 with excisional biopsy, and four with FNA. Although tumor biopsy demonstrated metastatic adenocarcinoma, tumor-specific histology was unavailable or unable to be determined for 77.8 % ($n = 28$). Half of the tumors were estrogen receptor–positive (ER +) ($n = 18$),

TABLE 1 Patient demographics and tumor characteristics

	n	%
Demographics		
Age at presentation (years) mean (range)	55.2	(39–73)
Patient location		
Local	6	16.7
Statewide	21	58.3
National	8	22.2
International	1	2.8
Family history of breast cancer		
Yes	14	38.9
No	22	61.1
Presenting nodal stage		
N1	28	77.8
N2	6	16.7
N3	2	5.6
Location of presenting metastatic lesions		
Axilla	36	100
Size largest nodal tumor (mm) mean (range)	30.4	(12–70)
Infraclavicular/supraclavicular	2	5.6
Lymph node pathology		
Estrogen receptor–positive	18	50.0
Progesterone receptor–positive	10	27.8
HER-2–positive	8	22.2
Triple-negative	12	33.3
Histology		
Ductal	7	19.4
Lobular	1	2.8
Other/unknown	28	77.8
Tumor grade		
Low	0	0.0
Intermediate	3	8.3
High	21	58.3
Other/unknown	12	33.3

TABLE 2 Diagnostic imaging evaluation and oncologic treatment

	n	%
Imaging evaluation		
Mammogram	36	100.0
Ultrasound	35	97.2
MRI	33	91.7
CT	28	77.8
Bone scan	26	72.2
CT/PET	12	33.3
Oncologic treatment		
RT of breast/chest wall		
Yes	33	91.7
No	2	5.5
Unknown	1	2.8
RT of supraclavicular/infraclavicular basins		
Yes	28	77.8
No	6	16.7
Unknown	2	5.5
Systemic chemotherapy		
Neoadjuvant	25	69.4
Adjuvant	8	22.2
Given, but sequence unknown	1	2.8
No chemotherapy	1	2.8
Systemic chemotherapy unknown	1	2.8
Herceptin		
Yes	4	11.1
No	29	80.6
Unknown	3	8.3
Hormonal therapy		
Yes	16	44.5
No	17	47.2
Unknown	3	8.3
Surgery		
No breast surgery (breast conservation)	27	75.0
Bilateral mastectomy	5	13.9
Unilateral mastectomy	4	11.1
Axillary lymph node dissection	33	91.7

CT computed tomography, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *RT* radiation therapy (external beam)

27.8 % were progesterone receptor–positive (PR+) ($n = 10$), and 22.2 % were HER-2-positive ($n = 8$), which are all findings most consistent with breast origin. The incidence of triple-negative (ER, PR, and HER-2) metastatic disease was 33.3 %.

Breast imaging, staging evaluation, and treatment data are listed in Table 2. All patients had a diagnostic mammogram, most patients ($n = 35$ [97.2 %]) had breast ultrasound, and 33 (91.7 %) had breast magnetic resonance images (MRIs). Twenty-six of the breast MRI studies were performed at our institution and dynamic contrast-enhanced images were reviewed by a breast-specific radiologist.

Nearly all women received systemic chemotherapy ($n = 34$ [94.4 %]), most commonly 12 cycles of paclitaxel and four cycles of fluorouracil/doxorubicin (FAC) or epirubicin/cyclophosphamide (FEC). Neoadjuvant chemotherapy was the most common treatment sequence, which was given to 69.4 % of the patients. One patient refused chemotherapy, surgery, and external beam radiotherapy (EBRT), and this patient was alternatively treated with endocrine therapy alone. Another patient received chemotherapy, but with an unknown prereferral regimen.

Our rate of BCS was high, with only nine patients (25 %) undergoing ipsilateral MRM ($n = 4$) or ipsilateral

TABLE 3 Surgical pathology

Surgical pathology[a]	n	%
Number of nodes removed mean (range)	21.8	(0–63)[b]
Additional positive nodes recovered		
Yes	16	48.5
No	17	51.5
Number of additional positive nodes		
Mean (range)	4.0	(1–20)
Extranodal extension		
Yes	4	12.1
No	27	81.8
Unknown	2	6.1
Size largest metastatic deposit (mm) Mean (range)	14.7	(3–32)

[a] Among the 33 patients having ALND; [b] one patient had an axillary dissection, but no lymph nodes on pathological evaluation

MRM with contralateral prophylactic mastectomy ($n = 5$). Among the 27 remaining, non-MRM women, 24 (88.9 %) had an ALND alone with no breast surgery. The other three women had no surgical intervention, either as a personal choice ($n = 2$) or due to medical comorbidities (significant myocardial infarction during neoadjuvant chemotherapy). These women were treated with EBRT to the ipsilateral breast and axilla ($n = 1$), EBRT to the breast only ($n = 1$), or endocrine therapy alone ($n = 1$).

The majority of women received EBRT [$n = 33$ (91.7 %)]. One woman, previously discussed above, had no treatment; one woman had a unilateral mastectomy and no EBRT; and one woman had limited documentation of EBRT received prereferral. The remaining mastectomy patients received postmastectomy EBRT to the chest wall, axillary apex, and supraclavicular or infraclavicular lymph nodes if radiographically indicated. Most EBRT treatment plans included 50 Gy treatment to the axillary apex, and a majority of women ($n = 28$ [77.8 %]) also received 50 Gy EBRT to the supraclavicular and/or infraclavicular regions.

Among the 33 women who had ALND, 17 (51.5 %) had no positive lymph nodes in the specimen (Table 3). Fifteen of those women received neoadjuvant chemotherapy, representing a complete pathological response in 15 of 25 women treated with neoadjuvant chemotherapy (80.0 %). The remaining two women were diagnosed with excisional biopsy of their metastatic lymph node and had no additional evidence of nodal disease on postexcisional imaging, which likely represented clearance of their axillary disease burden with the excisional biopsy alone. For the 16 women who had additional metastatic disease, the mean number of nodes recovered was 21.8, with an average number of four positive nodes in the specimen. The average size of metastatic tumor deposit was 14.7 mm and extranodal extension was rare [$n = 4$ (12.1 %)].

TABLE 4 Patient outcomes

	n	%
Follow-up		
Most recent follow-up		
Within 18 months	30	83.3
>18 months	6	16.7
Length of follow-up (months)		
Median (range)	64	(9–143)
Recurrence		
IBTR	0	0
Regional nodal recurrence	0	0
Distant recurrence	1	2.8
Survival		
Alive	35	97.2
Alive and disease-free	35	97.2
Alive with recurrence	0	0
Breast cancer mortality	1	2.8
Mortality from other cause	0	0

IBTR ipsilateral breast tumor recurrence

Table 4 lists recurrence and survival data. Thirty patients had follow-up within 18 months of this study, representing a low rate lost to follow-up. The median length of follow-up was 64 months. To date, there have been no locoregional recurrences. Only one patient developed distant metastatic disease 70 months after primary diagnosis of T_0N_+ breast cancer (to the bone and subsequently to multiple sites). This patient originally presented with triple-negative ductal adenocarcinoma and was treated with neoadjuvant chemotherapy, BCS with ALND, and EBRT to the breast, axillary apex, and supraclavicular lymph node basins. She died 74 months after original diagnosis; the 5-years survival rate was therefore 100 %, with an overall survival rate of 97.2 % for the entire study period. Given the universal survival of patients in the study, there were no significant survival differences between BCS and MRM ($p = 0.7$).

DISCUSSION

We found that breast conservation—performed in the setting of contemporary breast imaging, chemotherapy, axillary dissection, and radiation therapy—has excellent outcomes for women with T_0N_+ breast cancer. These findings demonstrate that practice patterns can safely use BCS for women with this diagnosis.

NCCN guidelines recommend that women with T_0N_+ breast cancer receive the same treatment as patients with similarly staged cancer and an identified (T_+) primary breast tumor. Despite these recommendations, great variations in clinical practice still remain. A 2005 survey-based

query of members of the American Society of Breast Surgeons [6] found that 43 % of responding breast surgeons would recommend mastectomy for women with T_0N_+ breast cancer, 37 % would recommend BCS with whole breast radiation, and 20 % recommended other forms of treatment ranging from observation to mastectomy plus postmastectomy radiation. These data are similar to a recent Surveillance, Epidemiology, and End Results Program (SEER)-based study of T_0N_+ breast cancer by Walker et al.[8] reported BCS rates of 26.9 %.

In the current study, we had a 75 % rate of BCS. Given low locoregional recurrence and high survival rates, our institution emphasizes BCS for treatment of T_0N_+ breast cancer. Women who present with axillary metastases presumed to be of breast origin undergo radiographic workup, consisting of diagnostic mammogram, breast ultrasound, and breast MRI. Chest radiograph and bone scan evaluate for distant disease, with additional cross-sectional imaging obtained at the treating physician's discretion. In the absence of a primary breast tumor or metastatic disease, women are referred for neoadjuvant chemotherapy, nearly always paclitaxel for 12 cycles, FAC/FEC for four cycles, and trastuzumab when indicated, based on HER-2 overexpression.

Although studies from the 1990s [1,10,11] have not demonstrated a significant survival benefit with the use of cytotoxic chemotherapy for women with T_0N_+ breast cancer, these findings may not translate to contemporary treatment regimens. As such, the present recommendation is to treat T_0N_+ breast cancer patients similarly to stage II/III node-positive breast cancer patients, in whom systemic chemotherapy is recommended.[5] Although there is no demonstrated survival benefit to the use of neoadjuvant chemotherapy versus adjuvant for breast cancer, there are several theoretical advantages. These include the ability to monitor response to specific regimens while tailoring therapy away from ineffective regimens, down stage the tumor, and achieve higher rates of chemotherapy completion.[12] In addition, response to neoadjuvant chemotherapy is an important prognostic indicator, with better long-term survival in patients who have a pathological response to preoperative therapy.[12,13] We found neoadjuvant chemotherapy resulted in an 80 % complete pathological response in the axilla with no distant failures in the first five posttreatment years. Therefore, it is our approach to administer chemotherapy before surgery for women with T_0N_+ breast cancer.

Chemotherapy is followed with surgical dissection of the axillary lymph nodes. Unless patients have a preference or there is a clinical indication for mastectomy, it is our recommendation not to perform primary breast surgery.[14] Postoperatively, women receive EBRT to the ipsilateral breast (50 Gy) and regional lymphatics, including the infraclavicular and internal mammary lymph node basins (50 Gy with a 10 Gy boost to any radiographically prominent nodes). The role of EBRT versus postoperative observation alone for local control of the breast in the setting of BCS for women with a known primary was well established in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial, with a 20-year follow-up demonstrating significantly lower rates of ipsilateral breast tumor recurrences in women who received radiation therapy.[14] In addition, several studies have published that BCS with whole breast EBRT is associated with acceptable rates of locoregional control for women with T_0N_+ breast cancer.[15–18]

There is variability, however, in the use of postoperative EBRT for the axillary, supraclavicular, infraclavicular, and internal mammary lymph nodes after therapeutic ALND. Among women enrolled in the Eastern Cooperative Oncology Group, the number of positive axillary lymph nodes correlated with a risk for locoregional recurrence.[19] Therefore, for women with T_0N_+ breast cancer in whom the risk of having tumor involvement in multiple axillary lymph nodes is increased,[10,20] the role of EBRT to include the axillary apex and undissected draining lymphatics may be even more significant than for women with identified tumors. Our data support this notion; despite our finding that 48.5 % of women had an average of four additional positive nodes recovered with ALND, we found no 5-years locoregional failures using our comprehensive EBRT technique.

For women who present with T_0N_+ breast cancer, guidelines recommend a mammogram and breast MRI and/or ultrasound if the mammogram is nondiagnostic.[5] In patients with clinically occult breast cancer, mammography will detect a primary tumor in 10–20 % of cases.[1,15] Breast MRI, on the other hand, is highly sensitive. Seven studies have evaluated the utility of breast MRI in diagnosing a primary breast tumor for women with axillary lymph node metastases.[21–27] In these studies, breast MRI visualized a lesion suspicious for primary breast tumor between 36–86 % of the time. In 85–100 % of the cases, the visualized abnormality represented a breast primary.

We acknowledge the limitations of this study. As a result of T_0N_+ breast cancer being a rare disease, we had a relative paucity of patients to review. Because of the small numbers, the study is mainly a descriptive analysis of the available variables. It is difficult, therefore, to make specific associations between study variables and patient outcomes. In addition, patients in this study sought treatment at a specialized cancer center with access to a full spectrum of imaging and treatment options. Given the heterogeneity of breast cancer patients throughout the country, we realize that resources available to the patients in this study may not be readily available universally.

Finally, this is a retrospective study. Therefore, we were unable to determine what patient or clinician factors led to individual treatment recommendations unless explicitly documented in the record.

Despite these limitations, we have performed one of the largest contemporary studies of women of T_0N_+ breast cancer including a comprehensive review of the specific treatment administered. We have demonstrated that a multimodality approach with contemporary neoadjuvant chemotherapy followed by BCS with ALND and EBRT is associated with a high rate of complete pathological response, exceptionally low rates of locoregional recurrence, and 5-years survival rates higher than the published rates of 65–75 %.[1,10,20,28] As we become more sophisticated in developing genomic testing and utilizing targeted therapies, and as our systemic treatment options become more effective, recommendations and practice patterns should also evolve. These data demonstrate that multimodality treatment planning with an emphasis on breast preservation is a safe and effective treatment approach.

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