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Feasibility of Breast Preservation in the Treatment of Occult Primary Carcinoma Presenting With Axillary Metastases

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Background: The objective of the study was to compare the treatment outcomes in patients with occult primary carcinoma with axillary lymph node metastasis who were treated with mastectomy or with intent to preserve the breast.

Methods: From 1951 to 1998, 479 female patients were registered with axillary lymph node metastasis from an unknown primary. After clinical workup, including mammography, 45 patients retained this diagnosis and received treatment for T0 N1–2 M0 carcinoma of the breast. Clinical and pathological data were collected retrospectively, and survival was calculated from the date of initial diagnosis using the Kaplan-Meier method. Median follow-up time was 7 years.

Results: Median age was 54 years (range, 32–79). Clinical nodal status was N1 in 71% and N2 in 29% of the patients. Surgical treatment was mastectomy in 29% and an intent to preserve the breast in 71% of the patients. Locoregional radiotherapy was used in 71% and systemic chemoendocrine therapy was used in 73% of the patients. Of the 13 mastectomy patients, only one had a primary tumor discovered in the specimen. Two patients (4%) were ultimately diagnosed with lung cancer and neuroendocrine tumor. No significant difference was detected between mastectomy and breast preservation in locoregional recurrence (15% versus 13%), distant metastases (31% versus 22%), or 5-year survival (75% vs. 79%). Regardless of surgical therapy, the most important determinant of survival was the number of positive nodes. Five-year overall survival was 87% with 1–3 positive nodes compared with 42% with $\geq$4 positive nodes ($P < .0001$).

Conclusions: Occult primary carcinoma with axillary metastases can be treated with preservation of the breast without a negative impact on local control or survival.

Key Words: Breast neoplasm—Occult primary—Axillary metastasis—Breast preservation.

Despite the use of advanced diagnostic tools such as mammography, ultrasonography, and magnetic resonance imaging, an axillary metastasis without an obvious primary tumor remains a difficult diagnostic and therapeutic challenge. The differential diagnosis includes metastasis from adenocarcinoma of the breast, uterus, ovary, stomach, thyroid, and kidney; lymphoma; melanoma; squamous cell carcinoma of the head and neck, lung, or skin; primary tumors of the sweat glands; and neurogenic tumors. When the diagnostic workup is negative and pathological evaluation suggests an adenocarcinoma, undifferentiated carcinoma, or unclassified carcinoma, the occult primary is most likely to be an ipsilateral breast cancer.[1,2] The incidence of this uncommon presentation ranges from 0.3% to 1% of all patients with breast cancer.[3–6] First described by Halsted in 1907,[7] the first large series of patients with axillary metastasis from an unknown primary (n = 25) was reported in 1954 by Owen and colleagues.[4] To date, <400 cases have been described in the literature.

Because of the limited number of published cases, no optimal therapeutic approaches have been defined for the

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management of this clinical entity. Beginning in 1909, the recommended treatment was a blind radical or modified mastectomy, based on the assumption that the surgical specimen would contain the primary tumor.[8] As the overall role of surgery in breast cancer management has evolved to less invasive procedures, breast preservation has been increasingly proposed as an alternative to blind mastectomy, using radiotherapy to eradicate the occult disease.[9–11]

In 1990, Ellerbroek and colleagues[12] published a clinical study examining outcomes in patients diagnosed with axillary metastasis from an unknown primary. Their results confirmed that patients with axillary metastases histologically consistent with breast carcinoma should be treated identically to patients with similar nodal stages and proven primary tumor in the breast. Our study includes a larger patient base, additional clinical outcomes, and a significantly longer follow-up period to determine the feasibility of breast preservation in this patient population with an unknown primary.

PATIENTS AND METHODS

Patient Selection

From July 1951 to August 1998, 479 patients were registered at The University of Texas M.D. Anderson Cancer Center with a preliminary diagnosis of axillary lymph node metastasis from an unknown primary. The patient population was identified through a search of the database maintained by the Department of Medical Informatics. After initial diagnostic workup, including mammography, 45 nonpregnant women without prior cancer received treatment for T0 N1–2 M0 carcinoma (UICC-AJCC classification)[13] consistent with a breast primary tumor (i.e., adenocarcinoma, undifferentiated or unclassified carcinoma).

Diagnostic Workup

Patients were evaluated by history, careful physical examination, and diagnostic mammography. Additional imaging studies were performed to exclude distant metastatic disease. Basic diagnostic tests included blood tests, tumor markers, chest radiography, bone scintigraphy, and computerized axial tomography. Recently, ultrasound and magnetic resonance imaging of the breast were added to the diagnostic workup. Diagnosis of axillary metastasis was confirmed through cytological or pathological examination by the Department of Pathology at M.D. Anderson. Hormone receptor status (estrogen and progesterone) was assessed, when possible, on the nodal specimen.

Treatment

The surgical options available to the patient were: (a) modified radical mastectomy or (b) breast preservation with either excisional biopsy of clinically involved axillary lymph nodes or standard (i.e., level I and II) axillary lymph node dissection (ALND).

Patients received systemic treatment with a variety of different regimens, reflecting changes in institutional protocols during the study period. Since 1974, most patients have been treated on doxorubicin-containing protocols[14,15] with or without the addition of taxanes.

For patients who received irradiation, the treatment schema was determined by the status of the axilla. If the patient had N1 disease and all gross disease was removed with a lymph node dissection, the intact breast or postmastectomy chest, axilla, and supraclavicular basin were treated with 50 Gy in 5 to 6 weeks. If the patient had N2 disease which was downstaged to N1 with preoperative chemotherapy and underwent subsequent axillary lymph node dissection (ALND), the radiation dose was similar to that used for de novo N1 disease, except that the midaxilla was also treated to at least 40 Gy.

Data Collection and Analysis

Clinical information was obtained from a retrospective review of the patient charts. Information regarding clinical presentation, imaging studies, lymph node status, Black's nuclear grade, and the presence of estrogen and progesterone receptors was collected, if available. Follow-up time was calculated from the date of diagnosis to the date of last follow-up visit.

The SPSS 10.0 software package (SPSS Inc., Chicago, IL) was used for statistical analysis. Descriptive statistics were calculated to assess the frequency distributions in the two groups. Differences in the distribution of characteristics were analyzed by the χ^2 test or Fisher's exact test. Differences between the medians of continuous variables were analyzed with the Mann-Whitney *U*-test. Disease-specific and disease-free interval probabilities were calculated by the product limit method of Kaplan and Meier.[16] Probability values $\leq .05$ were considered to be statistically significant.

RESULTS

Clinical Characteristics

This study included 45 patients, all of whom presented with axillary metastases from an occult primary. Clinical characteristics of the patients are shown in Table 1. There were no significant differences between surgical groups in age, race, or family history. The median age was 54 years (range, 32–79). Most patients in the study

TABLE 1. *Characteristics of patients with breast preservation compared with patients who underwent mastectomy*

Characteristic	Breast preservation (N = 32) (N, %)	Mastectomy (N = 13) (N, %)	*P* value
Age			.515
Median	55	53	
Range	32–79	41–65	
Race			.177
White	22 (69)	11 (85)	
Black	7 (22)	0 (0)	
Hispanic	3 (9)	2 (15)	
Family history			.243
Yes	7 (23)	1 (8)	
No	25 (77)	12 (92)	
Clinical lymph node status			.046
N1	20 (62)	12 (92)	
N2	12 (38)	1 (8)	
Number of positive nodes			.930
1–3	25 (78)	10 (77)	
≥4	7 (22)	3 (23)	
Extranodal disease			.064
Yes	10 (31)	2 (15)	
No	12 (38)	2 (15)	
Unknown	10 (31)	9 (70)	
Radiation therapy			.103
Yes	25 (78)	7 (54)	
No	7 (22)	6 (46)	
Systemic therapy			.030
Chemotherapy	20 (62)	3 (23)	
Hormonal therapy	2 (6)	0 (0)	
Both	5 (16)	3 (23)	
None	5 (16)	7 (54)	

were Caucasian. Hormone receptor status was available for ≤50% of the patients and was not analyzed. There was a significant difference between surgical groups in clinical lymph node status and in the percentage of patients receiving chemotherapy. In the breast preservation group, 62% of the patients were N1 compared with 92% of the patients in the mastectomy group ($P = .046$). The median clinical size of the largest axillary node was 3 cm (range, 0.5–9).

All patients had mammograms, with abnormal findings reported in five patients. Of these, suspicious calcifications were found in two cases, a mass in two cases, and asymmetry in the parenchyma in one case. Excisional biopsies in these cases revealed only benign pathological features.

Thirteen patients (29%) were treated with mastectomy and 32 (71%) with intent to preserve the breast. Of all patients (mastectomy plus breast preservation), 35 (78%) had a standard ALND while 10 had only excisional biopsy of the axilla. The median histological size of the axillary metastases was 2 cm (range, 0.1–4). The median number of lymph nodes removed in patients receiving ALND was 16 (range, 3–34). There was no significant difference between the mastectomy group and the breast preservation group in the percentage of patients who had one or more histologically positive lymph nodes (77% vs. 78%) or in the frequency of patients with ≥4 positive nodes (23% versus 22%). Extranodal disease was assessed in 58% of the patients and was positive in 46% of those assessed. Of the 13 mastectomy patients, examination of the mastectomy specimen revealed one 2-cm adenocarcinoma and one case of Paget's disease.

Locoregional radiotherapy was used in 78% of the breast conservation therapy (BCT) group compared with 54% of the mastectomy group. Systemic therapy was used in 84% of the BCT group and 46% of the mastectomy group. The large percentage of patients in the mastectomy group who received no systemic therapy reflects treatment standards during the 1950s and early 1960s. While most patients received doxorubicin-based regimens, three patients received cyclophosphamide, methotrexate, and fluorouracil, one received bleomycin, and four received taxanes.

Clinical Outcome

At a median follow-up time of 7 years (range, 1–33), there were no significant outcome differences between the mastectomy group and the breast preservation group (Table 2). The rate of locoregional recurrence was very low in both groups (13%–15%). Both mastectomy patients who experienced locoregional recurrence received radiotherapy, compared with two of the four BCT patients with locoregional recurrence. Distant recurrence

TABLE 2. *Outcome in patients with breast preservation compared with patients who underwent mastectomy*

Characteristics	Breast preservation (N = 32) (N, %)	Mastectomy (N = 13) (N, %)	*P* value
Follow-up in years (median, range)	6 (1–19)	7.5 (1.4–33)	.483
Locoregional recurrence			1.000[a]
Yes	4 (13)	2.0 (15)	
No	28 (87)	11.0 (85)	
Distant recurrence			.529
Yes	7 (22)	4.0 (31)	
No	25 (78)	9.0 (69)	
Contralateral cancer			1.000[a]
Yes	1 (3)	0.0 (0)	
No	31 (97)	13.0 (100)	
Disease-free survival			.815
5 year	72%	67%	
10 year	63%	56%	
Overall survival			.868
5 year	79%	75%	
10 year	64%	66%	

[a] Fisher's exact test.

was reported in approximately 24% of the patients. Contralateral breast cancer occurred in one patient. The 5-year and 10-year disease-free and overall survival rates were not significantly different between the two groups (Figs. 1 and 2). In patients receiving breast preservation, there was no difference in overall survival in patients experiencing local recurrence compared with no local recurrence. In patients receiving mastectomy, there was a significant difference in overall survival as a function of local recurrence ($P = .012$).

Regardless of surgical therapy, the most important determinant of survival was the number of positive nodes. Five-year overall survival was 87% with 1–3 positive nodes compared with 42% with 4 or more positive nodes ($P < .0001$) (Fig. 3). For all patients (mastectomy plus breast conservation), the 5-year overall survival rate for patients receiving ALND was 82% compared with 54% in patients receiving excisional biopsy only. This difference was not significant. Considering only patients receiving breast conservation, there was a significant difference in 5-year overall survival in those patients who received radiotherapy (91%) compared with those who did not receive radiotherapy (43%; $P = .001$). There was no significant survival difference in the radiation versus no-radiation subsets of the mastectomy group.

The median time to first relapse was 1.5 years (range, 0.4–17). In the mastectomy group, five patients (38.5%) are currently alive with no evidence of disease, three (23.1%) are dead of disease, and three (23.1%) are dead of other causes. In the breast preservation group, 20 patients (62.5%) are currently alive with no evidence of disease, seven (21.9%) are dead of disease, and three (9.4%) are dead of other causes.

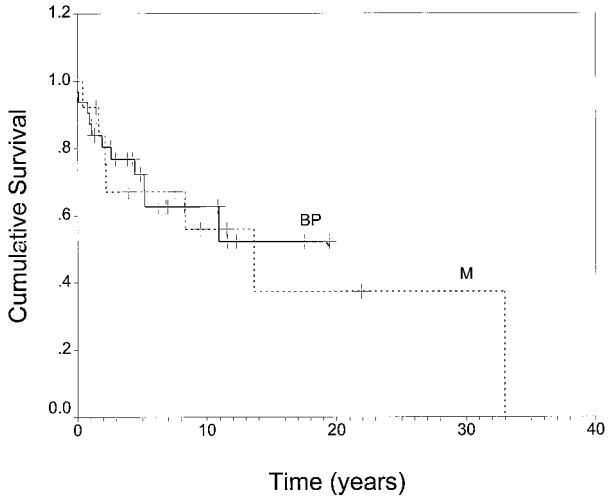

FIG. 1. Disease-free survival in patients with occult primary carcinoma treated with breast preservation (—) vs. patients who underwent mastectomy (- - -).

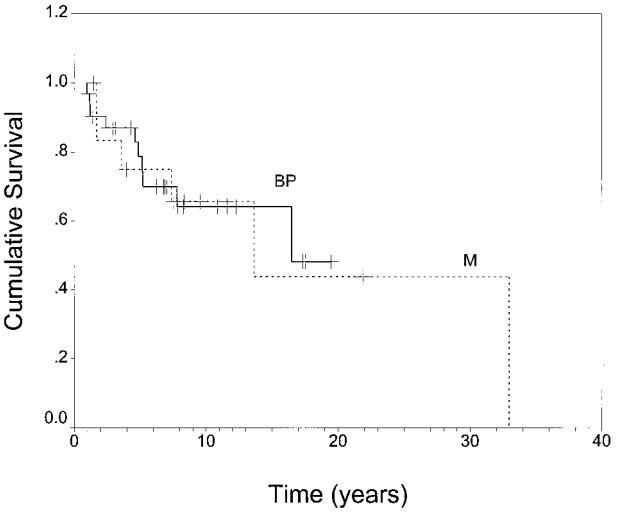

FIG. 2. Overall survival in patients with occult primary carcinoma treated with breast preservation (—) vs. patients who underwent mastectomy (- - -).

Two patients (4%) were ultimately found to have non-breast cancers: one lung cancer and one neuroendocrine cancer. These patients died from the non-breast cancer at 62 and 75 months, respectively, after an initial diagnosis of axillary disease.

DISCUSSION

Management Options for the Breast in Cases of Occult Primary with Axillary Metastases

There are two options for management of the ipsilateral breast in cases of axillary metastasis with unknown primary: mastectomy, or breast preservation consisting of either upper outer quadrantectomy or observation with or without irradiation.

Mastectomy

Since the early 1900s, mastectomy has been a standard recommendation for women with axillary metastases consistent with breast cancer but with no detectable primary tumor. This treatment was based on evidence showing that primary breast cancer was found in 55%–92% of the breast specimens of these women.[17] These data, however, are difficult to interpret. Because of the rarity of this clinical entity, retrospective studies typically draw patients' samples spanning extended periods of time. Thus, some patients in a study may have been screened by physical examination only, some by early-stage mammography, and still others by advanced imaging techniques. It certainly seems likely that the rate of

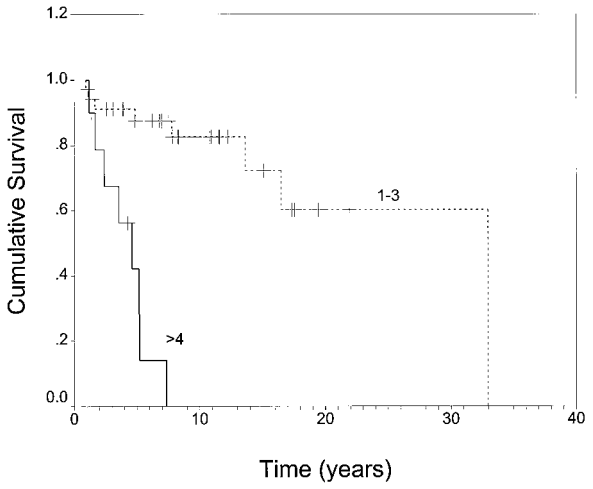

FIG. 3. Overall survival in patients with occult primary carcinoma with 1–3 positive lymph nodes (- - -) vs. ≥4 positive lymph nodes (—).

detection of occult primary cancer within mastectomy specimens should decrease with the use of state of the art mammography and breast ultrasound.

Even in cases where a cancer is found in the mastectomy specimen, the lesion is often either noninvasive or very small. A study by Meterissian and colleagues[18] found that, of 71 primary breast cancers that were undetectable by clinical examination, 35 of 71 (49%) were noninvasive and 27 of 36 (75%) of the invasive tumors were ≤1 cm. With mammographic screening, the probability of finding a significant tumor on mastectomy should be even smaller.

Surgical removal of the breast can have an impact on a woman's quality of life, body image, and sexuality. For occult primaries in mammographically screened patients, where the probability of finding a large invasive tumor is quite small, it is medically appropriate to consider the option of breast preservation. This is especially true because of the small but significant possibility that the primary tumor, if found, may prove to be of non-breast origin. Even in the carefully screened group of cases in this study, for example, two of the 45 patients (4%) were ultimately found to have non-breast tumors (one lung and one neuroendocrine).

Breast Preservation

Breast conservation therapy, consisting of lumpectomy and postoperative radiotherapy, has become the treatment standard for early-stage nonoccult breast cancers. The clinical characteristics of patients with an occult primary associated with axillary metastasis appear to be comparable to patients with stage II breast cancer; reports by several groups suggest that the survival rates of patients with T0 N1 breast cancer may be even higher than those of patients with nonoccult stage II breast tumors.[19,20] Thus, breast preservation in this patient group would be consistent with the treatment standard.

Upper outer quadrantectomy has been suggested for occult primary breast cancer based on the observation that invasive lesions are statistically more likely to occur in this quadrant, due to the denser distribution of glandular tissue.[21] This surgical approach is of limited use, however, as quadrant analysis by Tench[3] suggests that approximately half of all tumors would be missed. Thus, upper outer quadrantectomy would be an improved approach compared with mastectomy only in those cases where the primary tumor was found to be located within the excised tissue, surgical margins were free, and the disease in the breast was not multifocal or associated with a diffuse and extensive in situ component.

A nonsurgical option for occult primary breast cancer is observation with or without radiotherapy. In patients who have undergone axillary biopsy/dissection and observation of the breast, the reported incidence of breast cancer development in subsequent years is 14%–53%.[20,22] This contrasts with women who have undergone axillary dissection but subsequently received breast irradiation. In this group, the incidence of breast cancer development ranges from 12%–33% range.[22–25] This is consistent with the results of the current study. In the group of patients who did not undergo mastectomy, the addition of radiotherapy had a significant impact on survival compared with patients treated with observation only (83% versus 50%, respectively; $P = .001$). Thus, the natural history of these patients favors the use of some treatment method of the breast, either mastectomy or radiation.

We found no significant survival difference between patients who underwent mastectomy versus those who received breast preservation with irradiation (75% versus 91%, respectively) at 5 years posttreatment. This is supported by published studies[22,23] which have shown that survival rates for patients who receive breast-preserving treatment that included irradiation are roughly equivalent to those of patients undergoing mastectomy. Thus, breast preservation with radiation treatment is a reasonable alternative to mastectomy for these patients.

Axillary Lymph Node Dissection

For maximum locoregional control as well as staging and prognostic information, a level I and II ALND is the current treatment standard for all patients with node-positive breast cancer. Our study also found an improvement in survival in patients who received lymph node

dissection compared with those receiving axillary biopsy alone, although the difference was not statistically significant.

In patients with nonoccult breast carcinoma, the prognostic importance of absolute number of involved lymph nodes is supported by a large body of clinical data.[26,27] Not surprisingly, survival in patients with occult breast carcinoma is also associated with the degree of nodal involvement. Campana and colleagues[23] reported a 5-year survival rate of 91% for those with 1–3 involved nodes compared with 65% in those with ≥4 nodes ($P = .03$). The present study of 45 patients at M.D. Anderson Cancer Center had similar findings. We were also able to stratify patients into two groups (1–3 lymph nodes versus ≥4 lymph nodes) and found a statistically significant ($P < .0001$) survival benefit in patients with 1–3 involved nodes.

Adjuvant Therapy in Patients With Occult Breast Carcinoma

Current treatment standards favor the use of multidrug chemotherapy in all but the most favorable patients. Thus, virtually all node-positive patients are now offered chemotherapy, and this should include patients with an unknown primary site and isolated axillary nodal metastases whose histology is consistent with breast carcinoma. The CMF regimen has been widely used, although there is a growing bias in favor of doxorubicin-based regimens, especially in patients who have more than three positive nodes.

More recently, the use of non-cross-resistant drug combinations has been investigated in high risk cancer patients. A collaborative study of the Cancer and Leukemia Group B, the Eastern Cooperative Oncology Group, the North Central Cancer Treatment Group, and the Southwest Oncology Group[28] has been examining the effectiveness of paclitaxel when added sequentially to standard doxorubicin-containing chemotherapy in node-positive breast cancer patients. The group receiving paclitaxel plus doxorubicin has shown a 22% reduction in the risk of recurrence and a 26% reduction in overall risk of death compared with the group receiving doxorubicin-based chemotherapy alone. (It should be noted that, at a median follow-up time of 30 months, this benefit is clearly established only in estrogen receptor-negative patients, although a trend is also apparent in estrogen receptor-positive patients.) Several other studies have verified that taxane therapy initiated after standard chemotherapy combinations results in increased response rates.[29,30]

Although originally recommended only for postmenopausal estrogen-receptor positive patients, tamoxifen is now indicated for a much broader age range of patients. When used for 5 years, adjuvant tamoxifen results in a 10.9% absolute improvement in 10-year survival for node-positive women, regardless of age or menopausal status.[31] There appears to be no additional treatment benefit after 5 years.[32] For postmenopausal women, a further increase in survival may be obtained by the use of chemotherapy in combination with tamoxifen.[33,34]

Adjuvant chemotherapy should be started as soon as possible after healing of the surgical wounds of either the axillary-node dissection or, if the patient prefers, the standard mastectomy. For patients who desire to preserve the breast, deferment of irradiation of the breast until completion of adjuvant chemotherapy does not appear to compromise local control.[35–38]

CONCLUSION

Occult primary carcinoma with axillary metastases can be treated with preservation of the breast, including level I and II ALND and radiotherapy, without a negative impact on local control or survival. Treatment standards approved for stage II breast cancer patients are appropriate for this patient group.

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