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CLINICAL INVESTIGATION

METAPLASTIC CARCINOMA OF THE BREAST: A RETROSPECTIVE REVIEW

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Purpose: Metaplastic carcinoma of the breast represents a rare and heterogeneous group of malignancies that accounts for less than 1% of all breast cancers. The purpose of this study is to better characterize the clinical management of this disease including the role of radiation therapy after surgery. We compared patients that have been treated with either modified radical mastectomy (MRM) or breast-conserving surgery (BCS).

Methods and Materials: We performed a retrospective review of 43 patients with metaplastic breast cancer who were evaluated in our regional radiation oncology department between 1987 and 2002. Twenty-one patients were treated with an MRM and 22 with BCS. Five patients from the MRM group received adjuvant radiation, as did 19 patients from the BCS group. Univariate and multivariate analysis of pathologic and treatment-related factors was performed. Local control, disease-free, and overall survival rates were calculated by the Kaplan-Meier method and compared for the two groups.

Results: Mean follow-up for all patients was 44.2 months. Mean tumor size was 3.4 cm. Four patients (9%) had positive estrogen receptors and 20 (25%) had positive nodes. The overall 5-year projected local recurrence-free (88% vs. 85%, $p = 0.86$), disease-free (55% vs. 84%, $p = 0.13$), and overall survivals (80% vs. 89%, $p = 0.58$) were not significantly different for both groups. The only tumor parameter significantly associated with overall survival was nodal status.

Conclusion: Our study suggests that breast conservation appears to be a reasonable treatment option for women with metaplastic breast cancer, achieving equal survival to mastectomy. The use of adjuvant radiation seems essential for achieving high local control rates after conservation therapy. Further studies will be needed to determine the impact of chemotherapy on survival outcomes. © 2005 Elsevier Inc.

Metaplastic breast cancer, Radiation therapy, Breast-conserving surgery, Modified radical mastectomy.

INTRODUCTION

Metaplastic carcinoma of the breast represents a rare and heterogeneous group of malignancies that accounts for less than 1% of all breast cancers. These tumors include invasive breast cancers in which a portion of the glandular epithelial cells have undergone transformation or metaplasia. The transformation can be into a nonglandular epithelial cell type such as squamous cell or into a mesenchymal cell type such as spindle cell or carcinosarcoma (1).

No uniform classification scheme exists for metaplastic carcinoma. Many have divided these tumors into two main categories: tumors with squamous metaplasia and tumors with heterologous components (1). Heterologous components may include cartilage, bone, muscle, adipose tissue, melanocytes, or vascular elements. Wargotz *et al.* described five categories of metaplastic carcinomas: carcinosarcoma, matrix-producing carcinoma, spindle cell carcinoma, squamous cell carcinoma, and carcinoma with osteoclastic giant cells (2–6).

Some series suggest that metaplastic carcinomas have an inherently aggressive course. The pattern of progression in metaplastic breast carcinoma has been described as local recurrence followed by metastases to other sites including the pleura and lungs. The 5-year survival of metaplastic carcinomas has been reported to be approximately 65% (7).

The optimal treatment for metaplastic breast carcinoma remains controversial. Although breast-conserving surgery (BCS) has been used, most patients in the surgical and pathologic literature have undergone some type of mastectomy (7). The use of systemic adjuvant therapy in these tumors has been described (8). The role of adjuvant radiation therapy is less clearly defined.

The purpose of this study is to better characterize the clinical management of this disease including the role of

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radiation therapy after surgery. To our knowledge, our series is the largest clinical series on patients with this disease entity. It is unique in that we attempt to compare patients that have been treated with either modified radical mastectomy (MRM) or BCS. In addition, we provide details on adjuvant radiotherapy (AR).

METHODS AND MATERIALS

Forty-three patients that were evaluated in the Kaiser Permanente regional radiation oncology department between 1987 and 2002 were identified and retrospectively reviewed. The patients were surgically treated by Kaiser Permanente surgeons. Surgery included either wide excision with or without lymph node sampling or MRM. Twenty-two patients underwent BCS and 21 patients underwent MRM as definitive surgical procedures. Nineteen of the 22 BCS patients underwent pathologic axillary nodal evaluation, 3 of which were positive for metastases. Mean tumor size was 2.9 cm. Seven of the 21 MRM patients had positive lymph nodes at evaluation. Mean tumor size was 3.9 cm (Table 1).

Pathology was centrally reviewed in the majority (34) of patients (Table 2). Patients with pathologic specimens interpreted as metaplastic carcinoma with variants including, but not limited to, spindle cell metaplasia, sarcomatous metaplasia, and squamous carcinoma were eligible. Patients with metastases to the breast, primary squamous cell carcinoma of the skin, and primary sarcoma of the breast were excluded.

All patients who received radiation were treated in our regional radiation oncology department. Radiation therapy was delivered up to 4 months after surgery or chemotherapy using 6-MV or 15-MV photons. All patients undergoing BCS were advised to undergo adjuvant radiation. Of the 3 patients who did not receive radiation, 1 had severe cardiomyopathy, 1 was elderly, and 1 developed a recurrence while receiving adjuvant chemotherapy and was subsequently treated with MRM. This patient who developed a local recurrence during chemotherapy was included in the BCS group analysis, consistent with the intent-to-treat analysis. Five patients who underwent MRM were offered adjuvant radiation. Indications for chest wall radiation included T3 tumor size, positive nodes, or positive margins. Tangential fields were used and additional anteroposterior supraclavicular fields were added when regional nodes were treated. Total radiation doses to the intact breast ranged from 50 to 66 Gy. Total doses to the chest wall ranged from 50 to 51.2 Gy.

Chemotherapy consisted primarily of Cytoxan- and Adriamycin-based regimens. The type of chemotherapy and the dose intensities were determined by the treating medical oncologists (Table 3).

Patients were followed every 3–6 months with physical examination, mammograms, computed tomography scans, and bone scans as deemed necessary. Local and distant failures were defined radiographically or by palpation with or without histopathologic confirmation.

Kaplan-Meier life table analyses were used, with statistical inferences on actuarial curves made using log–rank test models (9). Multivariate analyses for independent prognosticators were performed utilizing the Cox proportional hazards model (10).

Table 1. Patient and tumor characteristics

	BCS	MRM
Number of patients	22	21
Age	26–83	37–72
Average age	54.6	53.1
T size	1.4–7.8	1.5–8.3
Average tumor size	2.89	3.88
p value >0.05		
ER+	3	1
N+	3	7
Treatment		
Lymph node evaluation	19	18
Systemic	16	16
Therapy		
Chemotherapy	13	15
Tamoxifen	3	1
Adjuvant radiation	19	5
Radiation dose	50–66 Gy	50–51.2 Gy
Boost	8–16 Gy	10 Gy

Abbreviations: BCS = breast-conserving surgery; ER = estrogen receptor; MRM = modified radical mastectomy.

Table 2. Centrally reviewed pathologic subtype

Purely epithelial
3 Squamous
11 Adenocarcinoma with spindle cell differentiation
7 Adenosquamous carcinoma
Mixed epithelial and mesenchymal
7 Carcinoma with chondroid metaplasia
6 Carcinosarcoma

RESULTS

Follow-up period ranged from 2 months to 165 months (mean, 44.2 months). The mean age at diagnosis was 53.6 years (range, 26–83 years). Thirty-three patients (77%) presented with a palpable mass, 6 (14%) presented with mammographic abnormalities alone, and in 4 patients this information was unavailable. Tumor size ranged from 1.4 to 8.3 cm (mean 3.4 cm). Four patients (10%) were estrogen receptor positive. Ten patients (25%) had positive nodes. Twenty-eight patients (65%) received systemic chemotherapy. See Table 1 for patient characteristics and Table 3 for treatments.

The 5-year projected local recurrence-free survival for all patients evaluated was 80%. The 5-year projected disease-free survival for all patients studied was 64%, whereas the 5-year projected overall survival was 72% (Fig. 1).

When evaluating for treatment outcomes between those treated with either BCS or MRM, the 5-year projected local recurrence-free survivals were 88% for the BCS-treated patients and 85% for the MRM-treated patients (p = 0.8585, Fig. 2). The 5-year projected disease-free survival for those treated with BCS was 55% and 84% for those treated with MRM (p = 0.1269). The 5-year projected overall survival for those treated with BCS was 70%, whereas those treated with MRM demonstrated a 5-year projected overall survival of 89% (p = 0.5776, Fig. 3).

Prognostic factors were analyzed for all 43 patients that underwent BCS and MRM. These included T stage, nodal status, estrogen receptor status, surgical modality, and use

Table 3. Treatment characteristics

BCS	Adjuvant RT (Gy)	Adjuvant systemic therapy	MRM	Adjuvant RT (Gy)	Adjuvant systemic therapy
1	50 + 16		1		
2	50 + 9.6	CAF × 6	2		CAF × 6
3	50	AC	3		Taxotere
4	50.4	CAF × 6	4	50	CAF
5	50 + 16		5		CAF × 8
6	50 + 9.6	CAF × 6	6		AC, Taxotere
7	50.4	CMF × 3	7		CAF
8	50.4		8		
9	50 + 8	AC × 7	9		
10	50	Tam	10		AC
11		Tam	11		CMF
12		AC × 4	12		CMF
13	50	Tam	13	50.4 + 10	AC × 8, Tam
14	50		14		AC × 4, Taxotere
15	50	AC × 4	15		
16	50 + 9.6	AC × 4	16		AC
17			17	50	Preoperative CAF
18	50.4 + 9.6	FAC × 6	18		Preoperative AC, Taxotere
19	50.4 + 9.6	AC × 4	19	50	CAF × 6
20	50 + 9.6	CAF × 3	20	51.2	
21	50.4 + 9.6	AC × 4, Taxotere	21		
22	50 + 9.6				

Abbreviations: AC = doxorubicin (Adriamycin) and cyclophosphamide; FAC = fluorouracil, doxorubicin (Adriamycin), cyclophosphasmide; C = Cytoxan; A = Adriamycin; F = 5 Fluorouracil; M = Methotrexate; Tam = Tamoxifen; BCS = breast-conserving surgery; RT = radiopherapy; MRM = modified radical mastectomy; CAF = cyclophosphasmide, doxorubicin (Adriamycin), and fluorouracil; CMF = cyclophosphamide, methotrexate, and fluorouracil.

of chemotherapy. On univariate analysis, none of the factors was found to be significant. On multivariate analysis, nodal status was significantly associated with overall survival. Those women with positive nodes were found to have decreased overall survival compared with those with negative nodes ($p = 0.0478$).

Four of the patients with BCS—2 of 3 treated with wide excision alone and 2 of 19 treated with wide excision and adjuvant radiation—developed a breast recurrence and were treated with mastectomy (Table 4). Mean time to recurrence from initial surgery was 15 months. Five of the patients developed distant metastases (Table 5).

Four of the patients with MRM developed chest wall recurrence, 1 of whom was treated with palliative radiation (Table 4). None of these patients who developed chest wall recurrence had previously received AR. Mean time to recurrence from initial surgery was 24 months. One patient developed distant metastases (Table 5).

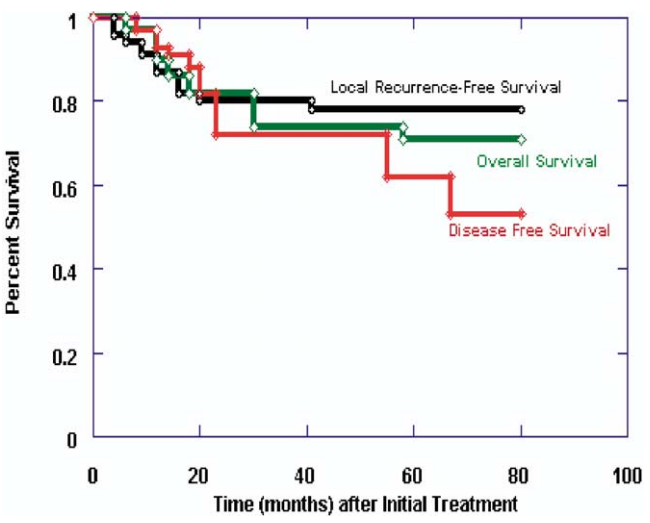

Fig. 1. Local recurrence-free, disease-free, and overall survival for all patients evaluated.

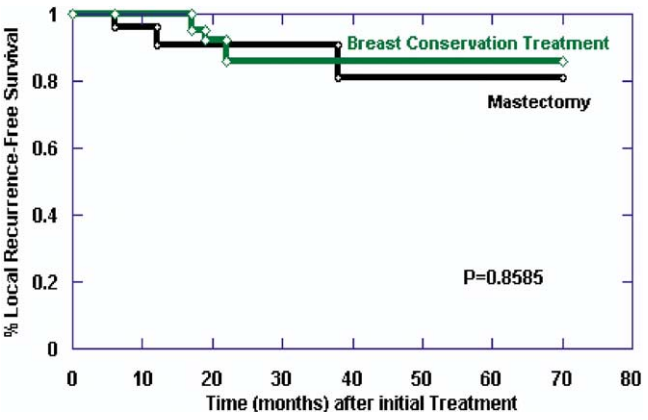

Fig. 2. Impact of treatment modality on local control.

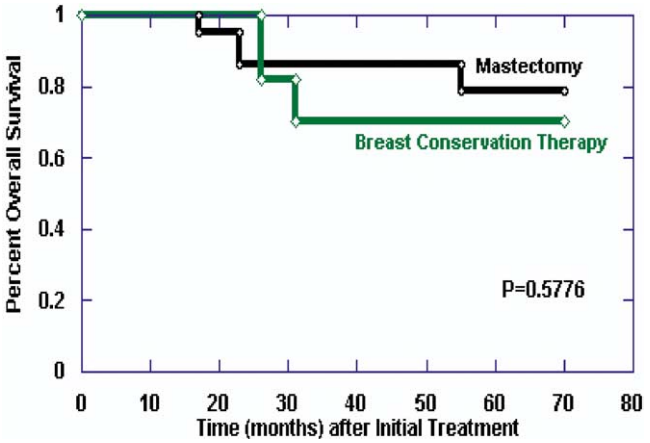

Fig. 3. Impact of treatment modality on overall survival.

DISCUSSION

In the present study, we focused on the clinical characteristics, management, and outcomes of 43 patients with metaplastic carcinoma. We included all patients that were evaluated in our radiation oncology department at initial presentation. Our series differs from other publications in that we provide detailed information on patients that have been treated with adjuvant radiation therapy after BCS or MRM.

The survival outcomes in our study are comparable with previously reported series, with a 5-year projected overall survival of 72%. In the literature, prognosis has been related to some degree with the type of metaplasia present. The 5-year survival for metaplastic carcinoma made up of predominantly epithelial components and sarcomatous components are reported to be approximately 65% and 40%, respectively (7). Our overall survival compares favorably with the 3-year overall survival of 71% reported by Rayson *et al.* and 5-year overall survival of 64% reported by Chao *et al.* (8, 11). The mean time to death from metaplastic breast cancer for the whole group was 28 months. This differs from the findings by Chao *et al.*, who found all deaths occurring within 2 years.

In our series, the majority of patients presented with a palpable mass and a mean tumor size of 3.4 cm. Wargotz *et al.* and Oberman found tumor size to be significantly prognostic for recurrence, whereas the series by Rayson *et al.* did not (2, 3, 8, 12). Chao *et al.* found tumor size to be a significant prognosticator for survival (11). In our analysis, tumor size based on T stage was not significant for local recurrence, disease-free survival, or overall survival.

Table 5. Site of distant metastases or recurrence

BCS + RT	MRM	BCS
Brain	Lung	Brain
L4, hilum		
Right lung, liver		
L5		

Abbreviations as in Table 4.

We found 4 of 43 (9%) patients to have positive estrogen receptors. This is consistent with previous reports of low levels of estrogen receptor expression in metaplastic carcinoma (1). Estrogen receptor status was not a significant prognosticator in our analysis.

Approximately 25% of our patients were found to have pathologically involved lymph nodes. The literature suggests that metaplastic breast cancer has axillary nodal involvement less frequently than invasive ductal carcinoma. Wargotz *et al.* reported incidences of axillary involvement of 6–26%, whereas Rayson *et al.* and Chao *et al.* reported rates of 13% and 50%, respectively (2–4, 8, 11). The findings of Kauffman *et al.* and Oberman suggest that axillary nodal metastases in metaplastic carcinoma do not correlate with prognosis (12, 13). However, Chao *et al.* found that positive axillary nodes at presentation were strongly associated with survival (11). This was confirmed in our study on multivariate analysis.

The majority (65%) of patients received systemic chemotherapy as part of their definitive treatment. There are limited reports on the use of chemotherapy in metaplastic carcinoma. In the Rayson *et al.* series, 9 of 27 (33%) patients received adjuvant chemotherapy and in the Chao *et al.* series, 6 of 14 (43%) underwent postoperative adjuvant chemotherapy. Their data suggest that chemotherapy may not affect outcome (8, 11). Similarly, our analysis did not find the use of chemotherapy to be a significant prognostic factor for outcomes (Fig. 4). It is difficult to draw conclusions about the impact of definitive chemotherapy in the absence of randomized trials.

In our series, a similar number of patients was treated with either BCS (22) or MRM (21). The majority of patients in reported series has been treated with some form of mastectomy. In the Chao *et al.* study, 0 of 14 patients underwent BCS, whereas in the studies by Rayson *et al*. and Bellino *et al.*, 7 of 27 and 6 of 11 patients, respectively, did (8, 11, 14). These series did not report the prognostic significance of surgical modality. Our findings suggest that patients treated with BCS experience similar local control

Table 4. Outcome

	MRM + RT	BCS + RT	MRM alone	BCS alone
Local recurrence	0/5	2/19	4/16	2/3
Distant metastases	0/5	4/19	1/16	1/3

Abbreviations: MRM = modified radical mastectomy; RT = radiotherapy; BCS = breast-conserving surgery.

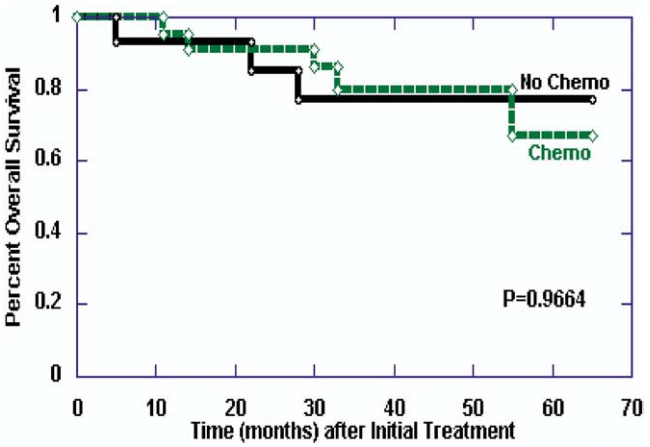

Fig. 4. Impact of chemotherapy on overall survival.

and survival outcomes to those treated with MRM. This suggestion of comparable outcomes is similar to what has been reported in the literature for the more common infiltrating carcinoma.

The majority of the BCS patients received AR, whereas only a small proportion of MRM patients were treated with AR. The BCS and MRM groups had similar rates of local recurrences. In the BCS group, AR was given to 19 patients. Two of these had local relapses. Of the 3 patients that did not receive AR, 2 developed a local recurrence (at 2 and 10 months, respectively, after surgery). This suggests that radiation is an important and effective adjuvant treatment in patients with metaplastic carcinomas that undergo BCS. The doses of radiation used were similar to those typically employed in the treatment of the more common infiltrating carcinomas. The high control rates we noted argue against the idea that these tumors are inherently radioresistant and further support the viability of BCS, even for larger tumors.

In conclusion, our data support previous reports of good overall survival for this group of patients. Breast conservation appears to be a reasonable treatment option with equal survival to mastectomy. The use of AR seems essential for achieving high local control rates after conservation surgery.

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