

Metaplastic Carcinomas of the Breast

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Background and Objectives: Metaplastic carcinomas of the breast are rare neoplasms. The purpose of the present study is to better characterize the clinical course, treatment, and prognostic factors of metaplastic breast carcinomas.

Methods: Data of 14 patients with metaplastic breast carcinoma were retrospectively reviewed. The follow-up period ranged from 2 months to 10 years, 10 months (median 4.3 years).

Results: The patients' ages ranged from 38 to 66 years (median 50.5 years). The tumors were 2.5 to 18 cm (median 4.8 cm) in size. Seven patients had axillary nodal metastases at the time of diagnosis. Estrogen and progesterone receptors were positive in only one tumor. Twelve patients underwent modified radical mastectomy and two patients underwent incisional biopsy. Adjuvant chemotherapy was administered to six patients, and radiotherapy to two patients after mastectomy. Two patients received preoperative chemotherapy. Seven patients were living without evidence of disease at a median of 7.3 years after surgery. A patient died of ovarian carcinoma without recurrence or metastasis of breast cancer. Metastases occurred in five patients at 4 to 16 months (median 8 months) after initial treatment. Duration of symptoms, TNM stage, tumor size, and axillary nodal status were significant prognostic factors of survival.

Conclusions: The patients with metaplastic breast carcinomas may have a favorable prognosis. *J. Surg. Oncol.* 1999;71:220–225. © 1999 Wiley-Liss, Inc.

KEY WORDS: chemotherapy; estrogen receptor; modified radical mastectomy; progesterone receptor; radiotherapy

INTRODUCTION

Metaplastic carcinomas of the breast are rare and interesting, yet confusing neoplasms. It has been reported that these tumors are more likely to occur in women older than 50 years [1–4]. Metaplastic carcinomas of the breast exhibit a variety of histopathologic patterns and appear to be both epithelial and mesenchymal in origin. The major criterion for a diagnosis of metaplastic carcinomas of the breast is the presence of overt carcinomas that are composed largely of squamous and spindle cells, and those with a sarcoma-like growth pattern including heterogeneous elements such as bone and cartilage [1,2,5–9]. Because of the rarity and unusual appearance of metaplastic carcinomas of the breast, a variety of classifications have been proposed, such as matrix-producing carcinoma, spindle cell carcinoma, carcinosarcoma, squamous cell carcinoma of ductal origin, metaplastic carcinoma with

osteoclastic giant cells, and adenosquamous carcinoma [5–10]. Oberman [1] separated metaplastic carcinomas into three groups: spindle cell carcinoma, invasive ductal carcinoma with extensive squamous metaplasia, and invasive carcinoma with pseudosarcomatous metaplasia. However, he suggested that these tumors were variants of a single entity because of the lack of correlation of microscopic pattern with prognosis, as well as the apparent overlapping microscopic findings. Pitts et al. [3] recommended that subclassification of metaplastic carcinomas was of greater pathologic than clinical interest. In contrast, some investigators have reported that different

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TABLE I. Histopathology, TNM Stage, and Laboratory Data of Metaplastic Breast Carcinomas*

Patient	Age	Tumor size	TNM stage	Pathology	Axillary nodes	ER/PR	Flow cytometry		
							DNA ploidy	SPF	DNA index
1	55	4.5 cm	IIA	SpCC	Negative	Negative	N/D	N/D	N/D
2	38	15.0 cm	IV	SpCC	Positive	N/D	N/D	N/D	N/D
3	53	4.0 cm	IIA	SM	Negative	N/D	N/D	N/D	N/D
4	50	4.0 cm	IIA	SM	Negative	Negative	N/D	N/D	N/D
5	51	3.5 cm	IIB	SM	Positive	Negative	Multiploid	—	1.0, 1.32, 1.96
6	47	5.0 cm	IIB	SM	Positive	Negative	Tetraploid	27.5%	1.97
7	66	18.0 cm	IIIB	SM	Positive	Negative	Aneuploid	—	1.30
8	55	2.5 cm	IIB	SCC	Positive	Negative	Aneuploid	6.8%	1.67
9	53	10.0 cm	IIB	SCC	Negative	Negative	N/D	N/D	N/D
10	38	15.0 cm	IIIB	SCC	Positive	N/D	Diploid	6.6%	1.0
11	57	3.0 cm	IIA	PSM	Negative	Positive	N/D	N/D	N/D
12	38	5.0 cm	IIA	PSM	Negative	Negative	N/D	N/D	N/D
13	47	3.0 cm	IIA	PSM	Negative	Negative	N/D	N/D	N/D
14	44	8.0 cm	IIIA	PSM	Positive	Negative	Tetraploid	16.5%	1.91

*ER, estrogen receptor; N/D, not done; PSM, invasive carcinoma with pseudosarcomatous metaplasia; PR, progesterone receptor; SCC, squamous cell carcinoma of ductal origin; SM, invasive carcinoma with prominent squamous metaplasia; SpCC, spindle cell carcinoma; SPF, S-phase fraction.

pathologic patterns may have prognostic significance, and prognosis is particularly poor for those with carcinosarcoma [5–8]. In an attempt to better understand the characteristics of these tumors, data of 14 patients with metaplastic carcinomas of the breast were retrospectively reviewed.

MATERIALS AND METHODS

During a period of 15 years, from 1981 to 1996, 3,725 patients with breast cancer were treated at the Chang Gung Memorial Hospital, Taipei, Taiwan. Among these, 14 (0.38%) were metaplastic carcinomas. Data of these 14 patients, including clinical manifestations, treatment, histopathology, prognostic factors, and outcome, were retrospectively reviewed.

The criterion for the diagnosis of metaplastic carcinomas of the breast has been described [1,2,5–9]. Four subtypes of malignancies were found in the present study. Spindle cell carcinoma had a prominent spindle cell pattern with small foci of squamous epithelium and transition between the squamous epithelium and spindle cells. The second group was the invasive carcinomas with predominant squamous metaplasia. The neoplasm was classified as squamous cell carcinoma of ductal origin if the infiltrating carcinoma was entirely squamous and the lesion did not involve the overlying skin. This group included in situ ductal or lobular carcinoma as long as the infiltrating carcinoma was exclusively squamous. Invasive carcinoma with pseudosarcomatous metaplasia had sarcoma-like appearance that lacked a squamous component or epithelium-lined cysts, but with foci of invasive ductal carcinoma and prominent heterologous elements.

Preoperative evaluation of these patients included

complete blood count, liver function, chest X-ray, and abdominal ultrasonography. Preoperative bone scan, breast ultrasonography, and serum levels of CA15.3 and carcinoembryonic antigen (CEA) were performed in some patients. Follow-up studies for these patients included liver function, serum levels of CA15.3 and CEA, chest X-ray, and mammogram or breast ultrasonography of the contralateral breast. Bone scan was performed in some patients for detection of bony metastases.

Data were presented as mean \pm standard error (SE) and median. Cumulative survival rates of the patients were obtained by use of the Kaplan-Meier method and compared by use of the log-rank test. Statistical significance was defined as a value of $P < 0.05$. The statistical analyses were performed using the StatView version 4.5 program (Abacus Concepts Inc., Berkeley, CA).

RESULTS

All patients were female. Age of the patients ranged from 38 to 66 years, with an average of 49.4 ± 2.2 years and a median of 50.5 years. Six (42.9%) patients were younger than 50 years. Five were premenopausal and nine were postmenopausal. All patients presented with a mass of the breast. Although five tumors were larger than 5 cm, all tumors were not fixed to the chest wall. Nine (64.3%) tumors were located on the right breast and five on the left. The tumor size ranged from 2.5 to 18 cm (average 7.2 ± 1.4 cm; median 4.8 cm; Table I). The duration of symptoms ranged from 10 days to 24 months, with an average of 8.5 ± 2.6 months (median 3 months). Seven (50%) patients had symptoms not longer than 3 months.

The histopathology, TNM staging [11], and laboratory data were shown in Table I. Metastases to axillary lymph

TABLE II. Adjuvant Treatment and Follow-Up of the Patients With Metaplastic Breast Carcinoma

Patient	Chemotherapy ^a	Radiation therapy	Surgery	Follow-up	Outcome ^b
1	Adjuvant, CAF, 6 cycles	No	MRM	8 years, 2 months	Alive, NED
2	No	No	Biopsy	2 months	DOD; metastases to lungs with pleural effusion at diagnosis
3	No	No	MRM	3 years, 2 months	Alive, NED
4	For recurrent tumor, CAF, 10 cycles	For recurrent tumor	MRM	10 years, 10 months	Alive; metastases to sternum 6 months PO, to T9 spine 9 years, 8 months PO, and to liver 10 years, 7 months PO
5	Adjuvant, CEF, 6 cycles	No	MRM	1 year, 11 months	DOD; metastases to ribs and pleural effusion 8 months PO
6	Adjuvant, CAF, 6 cycles	Yes	MRM	5 years, 3 months	NED; died of ovarian cancer
7	Preoperative, FAP	No	MRM	1 year, 5 months	DOD; metastases to lungs 1 year, 4 months PO
8	Adjuvant, CEF, 6 cycles	Yes	MRM	3 years, 3 months	Alive, NED
9	No	No	MRM	9 years, 5 months	Alive, NED
10	Cisplatin, 5-FU, epirubicin, 8 cycles	No	Biopsy	2 years, 3 months	DOD; metastases to contralateral supraclavicular lymph nodes 10 months after diagnosis
11	Adjuvant, CMF, 6 cycles	No	MRM	9 years, 4 months	Alive, NED
12	Adjuvant, CMF, 9 cycles	No	MRM	7 years, 4 months	Alive, NED
13	No	No	MRM	5 years, 5 months	Alive, NED
14	Preoperative, CEF	No	MRM	7 months	DOD; metastases to spine and ribs 4 months PO and pleural effusion 5 months PO

^aChemotherapy: CAF, cyclophosphamide 500 mg/m², Adriamycin 50 mg/m², 5-fluorouracil (5-FU) 500 mg/m²; CEF, cyclophosphamide 500 mg/m², epirubicin 50 mg/m², 5-FU 500 mg/m²; CMF, cyclophosphamide 600 mg/m², methotrexate, 40 mg/m², 5-FU 600 mg/m², FAP, 5-FU 500 mg/m², Adriamycin 60 mg/m², cisplatin 50 mg/m²; preoperative CEF, cyclophosphamide 600 mg/m², epirubicin 60 mg/m², 5-FU 600 mg/m².

^bDOD, died of breast cancer; MRM, modified radical mastectomy; NED, no evidence of disease; PO, after initial surgery.

nodes were found in seven (50.0%) patients at the time of diagnosis. Ten (71.4%) patients had stage II (IIA and IIB) diseases. Estrogen and progesterone receptors were analyzed on 11 neoplasms and yielded negative results in 10 (90.9%). Six cases were studied by flow cytometry. Multiploidy was found in one, diploidy in one, tetraploidy in two, and aneuploidy in two tumors. Serum levels of CEA and CA15.3 were normal in the absence of recurrence or metastasis of breast cancer. Interestingly, serum levels of CEA and CA15.3 in patient 4 and patient 10 were not elevated, even though metastases occurred during the follow-up period. In patient 5, CEA was not elevated during the follow-up period. On the other hand, her CA15.3 was 17.6 U/ml (normal < 25 U/ml) at 13 months after surgery (5 months after metastasis to the ribs) but elevated to 49.6 U/ml 19 months after surgery (11 months after metastasis to the ribs). In patient 14, both CEA and CA15.3 increased when metastases to the spine and ribs occurred.

Biopsy of the tumor and axillary lymph nodes was performed for the stage IV and the stage IIIB patients. Since the stage IIIB patient (patient 10) refused mastectomy, only chemotherapy was administered to her. The remaining 12 patients underwent modified radical mas-

tectomy with levels I and II axillary lymph node dissection. Adjuvant chemotherapy was administered to six patients and radiation therapy to two patients after mastectomy (Table II). Five of these six patients were disease-free at 3 years, 3 months to 9 years, 4 months (median 7 years, 4 months) of follow-up. Preoperative chemotherapy was administered to patient 7 and patient 14. One patient with positive hormone receptors received postoperative adjuvant tamoxifen. Chemotherapy, radiation therapy, and tamoxifen were administered to patient 4 for metastases to the sternum.

Follow-up period ranged from 2 months to 10 years, 10 months (mean 4.9 ± 1.0 years; median 4.3 years). No malignancy developed in the contralateral breast during the follow-up period. Patient 2 presented with lung metastases and pleural effusion at the time of diagnosis of breast cancer. Metastases occurred in another five patients at 4 to 16 months (mean 8.8 ± 2.1 months; median 8.0 months) after modified radical mastectomy. The overall 5-year survival rate was 64.3%. Seven patients were living without recurrence or metastases of malignancy at 3 years, 2 months to 9 years, 5 months (mean 6.6 ± 1.0 years; median 7.3 years) of follow-up. Ovarian carcinoma occurred in patient 6 at 4 years, 2 months after

treatment of breast cancer. She died of ovarian carcinoma without recurrence or metastases of breast cancer. Five patients with distant metastases died at 1 to 17 months (mean 7.6 ± 3.5 months; median 3 months) after the diagnosis of metastases. Patient 4 was alive at 10 years, 4 months after the first metastasis to the sternum. There were no differences in age between survival and mortality groups. The duration of symptoms in the survivors (mean 4.8 ± 3.2 months; median 2 months) was significantly (Mann-Whitney U test, $P = 0.0223$) shorter than that of the nonsurvivors (mean 12.8 ± 3.8 months; median 10.5 months). The size of the tumors in the mortality group (mean 10.8 ± 2.5 cm; 11.5 cm) was significantly (Mann-Whitney U test, $P = 0.0332$) larger than that in the survival groups (mean 4.5 ± 0.8 cm; median 4.0 cm). Age and chemotherapy were not significant prognostic factors in predicting patient survival (Fig. 1A,B). Patients with tumors no larger than 5 cm had better (log-rank test, $P = 0.0129$) survival rates than those with tumors larger than 5 cm (Fig. 1C). Seven patients without nodal metastases were alive after modified radical mastectomy (Table II, Fig. 1D). Of these 7 patients, 6 were alive without evidence of disease and 1 was alive with distant metastases. In contrast, 5 of 7 patients with nodal metastases died of breast cancer with distant metastases, and 1 patient died of ovarian carcinoma. TNM stage of disease was a significant prognostic factor (log-rank test, $P = 0.0002$). As seen in Figure 1e, stage II patients had a better survival rate than did stage III and stage IV patients. In addition, the patients with symptoms for not longer than 3 months had a better (log-rank test, $P = 0.0174$) survival rate than those with symptoms present for longer than 3 months (Fig. 1F).

DISCUSSION

In the present study, the prognosis overall was quite good. Seven of 12 patients who were treated for cure were alive without evidence of disease at 3 years, 2 months to 9 years, 4 months, a median of 7.3 years after their treatment (Table II). A patient was alive without evidence of disease when she died of ovarian cancer at 5 years, 3 months after treatment of breast cancer. Another patient was alive with distant metastases at 10 years, 10 months after modified radical mastectomy. On the other hand, of the patients that died of disease after modified radical mastectomy, median survival was 1 year, 5 months, and the patients died at 7 months, 1 year and 5 months, and 1 year and 11 months. These findings suggest that all deaths occurring in the patients with metaplastic breast carcinoma may occur within 2 years.

The findings in the present study are different from those reported in the literature. The prognosis of the patient with metaplastic carcinoma of the breast has been reported to be poor. Wargotz et al. [5–8] reported a cumulative 5-year survival rate of 68% in 26 patients with

matrix-producing carcinoma, 64% in 100 patients with spindle cell carcinoma, 49% in 70 patients with carcinosarcoma, and 63% in 22 patients with squamous cell carcinoma of ductal origin. Pitts et al. [3] observed an overall survival rate of 47% and a 5-year disease-free survival rate of 43% in 34 patients with metaplastic breast carcinoma. Kaufman et al. [2] reported that the overall survival rate of 26 patients with pseudosarcomatous metaplasia was 44%, with an estimated 5-year survival for TNM stages I, II, and III of 56%, 26%, and 18%, respectively. In our study, four patients had stage III or stage IV disease at the time of diagnosis. These four patients died of breast cancer with metastases within 2 to 27 months (mean 13.3 ± 5.5 months; median 12.0 months). As seen in Figure 1, stage II patients had a better survival rate than did the stage III and stage IV patients. These findings indicate that the prognosis of the patients with metaplastic breast carcinoma depends on the stage of the disease, similar to that seen in invasive carcinomas of the breast [12].

Tumor size is another prognostic factor. In the present study, five (35.7%) patients presented with a tumor larger than 5 cm and four of them died of the breast cancer with metastases. The survivors had a smaller tumor size than did the nonsurvivors (4.5 ± 0.8 cm vs. 10.8 ± 2.5 cm). Patients with a tumor not larger than 5 cm had a better survival rate (Fig. 1C). Similar findings were reported by Oberman [1], Kaufman et al. [2], and Wargotz and Norris [8] that the size of the neoplasm at the time of initial treatment best correlated with prognosis.

It has been reported that the incidence of axillary lymph nodal metastases is low in metaplastic carcinomas. In the studies reported by Bauer et al. [13] and Gersell and Katzenstein [14], none of the patients with spindle cell carcinoma had lymph nodal metastases, and only 30% of the patients were free of the disease during the follow-up period. Kaufman et al. [2] demonstrated that the occurrence rate of axillary nodal metastases in 26 patients with pseudosarcomatous metaplasia of the breast was 25% and the overall 5-year survival rate was 44%. Oberman [1] reported that lymph nodal metastases were found in only 2 (6.9%) of 29 patients, but the disease-free survival rate was less than 50%. Pitts et al. [3] observed that 7 of 29 patients (24.1%) had axillary nodal metastases at the time of diagnosis of metaplastic carcinomas. These findings suggest that, unlike invasive carcinoma of the breast, axillary nodal metastases in the patients with metaplastic carcinoma do not correlate with prognosis. However, the status of the axillary lymph nodes at the time of diagnosis was strongly associated with survival in the present study. Seven (50%) of our patients had nodal metastases at the time of diagnosis, and five of these seven patients died of disease with metastases, suggesting that axillary nodal metastasis is one of the prognostic factors of metaplastic carcinomas of the breast.

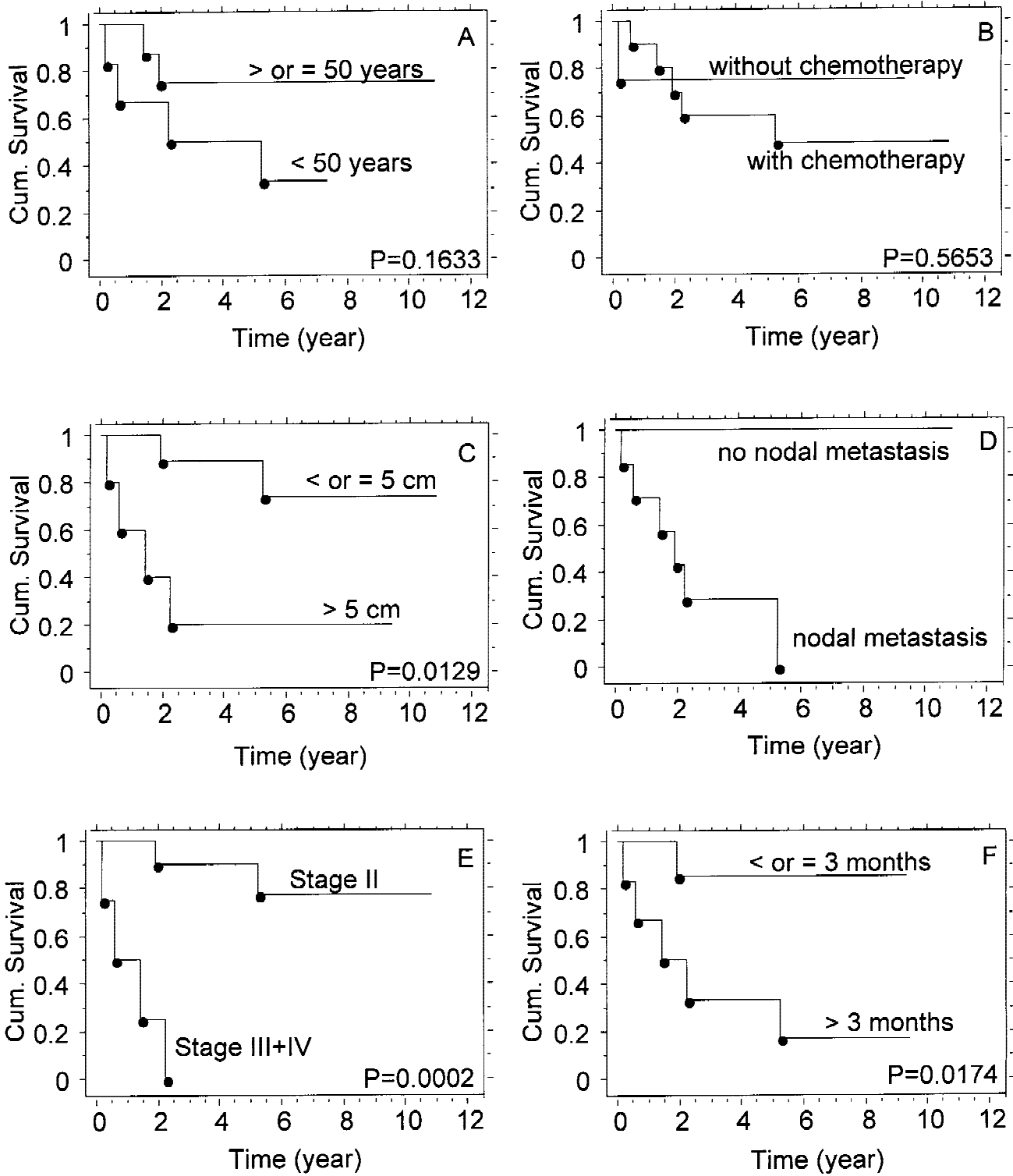


Fig. 1. Cumulative survival rates in the patients with metaplastic carcinomas of the breast. Factors influencing the survival rates are compared: age (A), chemotherapy (B), size of tumor (C), axillary lymph nodes (D), TNM stage (E), duration of symptoms (F). In (D), log-rank test is not computed because the group without axillary nodal metastases contained no mortality. The mortality cases, including patient 6, who died of ovarian cancer, are indicated as filled circles (●).

Estrogen and progesterone receptors were usually negative in the metaplastic carcinomas of the breast. In the present study, estrogen and progesterone receptors were positive in only one carcinoma with pseudosarcomatous metaplasia. Oberman [1] reported that none of the 29 patients with metaplastic carcinoma had positive hormone receptors. Eggers and Chesney [15] found that the hormone receptors were positive only in the neoplasms with mixed patterns of carcinoma and squamous metaplasia, and especially in those with predominance of the former component.

It is unclear what is the best, or is at least better, treatment for metaplastic carcinomas of the breast. Like most investigators [1–3,6], we performed modified radical mastectomy for the resectable tumors. In the present study, 6 (42.9%) patients underwent postoperative adjuvant chemotherapy. Five of these 6 patients were alive without evidence of disease at 3 years, 3 months to 9 years, 4 months (median 7 years, 4 months) after modified radical mastectomy, and only one patient had metastases to ribs with pleural effusion at 8 months after surgery (Table II). Adjuvant chemotherapy was not administered to patient 4, but chemotherapy with radiation therapy and tamoxifen was given to the patient for metastases to the sternum. This patient was still alive at 10 years, 10 months after the initial therapy. In the study of Pitts et al. [3], 7 of 34 patients underwent chemotherapy, and 4 of them were disease-free at 7 months to 70 months of follow-up. It is not clear whether chemotherapy would improve the prognosis since it has not been possible to assemble a sufficiently large series to assess the responsiveness of metaplastic carcinomas to chemotherapy. A proper assessment of prognosis requires sufficient cases to consider tumor size, histologic type, grade, nodal status, and the form of treatment.

In summary, metaplastic carcinomas should be included in the differential diagnosis of breast cancers. The prognosis of the patients with metaplastic breast carcinoma may be quite good. Estrogen and progesterone receptors were negative in the majority of metaplastic car-

cinomas of the breast. The patients with longer duration of symptoms, advanced TNM stage, larger tumor size, and axillary nodal metastases have a less favorable prognosis. Although the type of surgical treatment and the role of chemotherapy and radiation therapy in the treatment of metaplastic carcinomas need further studies, following the guidelines for the treatment of invasive carcinoma is justifiable.

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