Annals of Surgical Oncology, 2(4):288–294
Published by Raven Press, Ltd.

Therapy for Inflammatory Breast Cancer: Impact of Doxorubicin-Based Therapy

Ronald L. Bauer, MD, Erna Busch, MD, Ellis Levine, MD, and Stephen B. Edge, MD

Background: Inflammatory breast cancer (IBC) carries an ominous prognosis. Before 1988, women with IBC at our institution were treated with neoadjuvant cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) with or without vincristine and prednisone (CMF/VP). After 1988, women with IBC were treated with cyclophosphamide, doxorubicin, and 5-fluorouracil (FAC). This study compares these two regimens with regard to response and survival.

Methods: The records of all women presenting between January 1973 and December 1991 with a stage IIIB (T4d, any N, MO) breast cancer with proven dermal lymphatic invasion by tumor cells were reviewed retrospectively.

Results: The study comprised 38 women; 28 received CMF (22 CMF, 6 CMF/VP), and 10 received FAC. The overall response rate to induction chemotherapy in the CMF/VP group was 57% (40% PR, 17% CR), and 100% (60% PR, 40% CR) in the FAC group. The median overall survival for women receiving CMF/VP was 18 months compared with 30 months for women receiving FAC ($p = 0.02$). The median disease-free survivals for the CMF/VP and FAC groups were 6 and 24 months, respectively ($p < 0.001$). When comparing responders and nonresponders with CMF/VP induction therapy, the responders had a significantly longer overall median survival (24 versus 10 months) ($p < 0.001$) and disease-free median survival (8 versus 2 months) ($p < 0.001$). All of the five patients remaining alive received FAC with 80% (four of five) having a complete response. These four patients subsequently underwent mastectomy and radiation.

Conclusion: This study suggests that a doxorubicin-containing chemotherapy regimen improves overall and disease-free median survivals when compared with the previously used CMF combination in the treatment of IBC. A favorable response to induction chemotherapy also appeared to be associated with an improved survival.

Key Words: Breast—Advanced—Chemotherapy.

Inflammatory carcinoma of the breast is a relatively rare disease (incidence 1–6%), with an ominous prognosis (1). It began to evolve as a unique diagnostic entity more than a century ago when Bell (2) recognized the seriousness of a breast mass presenting with pain and overlying skin discoloration. The inflammatory characteristics of the disease were emphasized in 1869 by Klotz (3) in his use of the term "mastitis carcinomatosa." The fulminant course of this type of breast cancer was later emphasized by the term "acute mammary carcinoma" by Leitch (4) and Learmonth (5). The first collection of cases was that of Schumann (6) in 1911 under the designation "carcinoma mastitoides." However, it remained for reports of case series by Lee and Tannenbaum (7) and Taylor and Meltzer (8) to describe the present version of the clinical picture and to signify with the term "inflammatory carcinoma" the neoplastic process underlying the inflammatory signs.

Historically, when patients with inflammatory

Received April 22, 1994; accepted July 22, 1994.

From the Departments of Surgical Oncology (R.L.B., E.B., S.B.E.) and Medical Oncology (E.L.), Roswell Park Cancer Institute, Buffalo, New York, USA.

Address correspondence to Dr. S. B. Edge, MD, Division of Breast Surgery, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, USA.

Results of this study were presented at the 47th Annual Cancer Symposium of The Society of Surgical Oncology, Houston, Texas, March 17–20, 1994.

carcinoma of the breast were managed by mastectomy alone, their median survival ranged from 2.4 to 25 months, with a 5-year survival rate of 2.4% (8–12). In addition, there was a high incidence of local recurrence. Therefore, the role of surgery in this disease became limited to the biopsy.

Treatment with radiation therapy resulted in relatively better local control through a reduction in the incidence of skin ulceration, but it did not improve the survival rate. The median disease-free survival ranged from 4 to 6 months, with a mean survival rate of ~12 months and a 5-year survival rate of <5% (13–16). The combination of surgery and radiation has also been tried with no major impact on outcome. Such combined treatment gives a median survival of ~18 months, with a 5-year survival rate of 4% (17–20).

Because the disease tends to have an aggressive course, not only locoregionally but also systemically, a more logical strategy is the use of systemic chemotherapy in addition to the local–regional modality. With the introduction of combined modality treatments in the last decade, the prognosis of this lethal condition has changed favorably, with more patients living beyond 5 years without disease recurrence. This article reviews our experience in 38 patients with inflammatory breast cancer. This study was undertaken to compare the types of response and survival rates of our patients treated in the past with a non-doxorubicin-based chemotherapeutic regimen compared with those of our more recently treated patients, who all received a doxorubicin-based combination.

PATIENTS AND METHODS

Charts and tumor registry reports of those patients with breast cancer stage IIIB (T_{4d}, any N, MO) by 1988 American Joint Committee on Cancer criteria presenting to the Roswell Park Cancer Institute between January 1973 and December 1991 were reviewed retrospectively. The diagnosis was established by incisional biopsy of the primary tumor and overlying involved skin. This study is limited to women with clinical inflammatory breast cancer and histologically proven dermal lymphatic invasion. Four patients presenting with clinical findings consistent with inflammatory breast cancer, but without pathologic identification were excluded. The clinical records of these patients were examined for data regarding median age, tumor size, initial histology, stage, clinical signs and symptoms, menopausal status, receptor status, treatment, and follow-up including recurrence and survival.

Between 1973 and 1988, patients with inflammatory carcinoma of the breast at this institution received monthly cyclophosphamide (500–750 mg/m^2), methotrexate (25–40 mg/m^2), and 5-fluorouracil (500 mg/m^2) (CMF) with or without the addition of vincristine (1.4 mg/m^2) and prednisone (CMF/VP). This regimen was continued monthly until a partial or complete clinical response was achieved or there was progression of disease. After 1987, cyclophosphamide (500–750 mg/m^2), doxorubicin (50–75 mg/m^2), and 5-fluorouracil (500 mg/m^2) (FAC) were administered monthly for three cycles followed by evaluation followed by possible surgery or additional chemotherapy based on initial tumor response.

Types of response were based on clinical examinations after induction chemotherapy. A complete response to induction chemotherapy was defined as a clinically complete resolution of skin erythema, as well as the underlying breast mass and palpable nodal disease. A partial response was at least a 50% decrease in tumor and nodal diameter. Nonresponders were women classified as having a <50% decrease in tumor and nodal size.

Survival data were based on the method of Kaplan and Meier (21). Tests of significance with respect to survival distributions were based on the log-rank test (22). Differences were considered significant when $p < 0.05$.

RESULTS

During the 19-year period, 38 women presented with histologically proven inflammatory carcinoma of the breast. Twenty-two of these women treated between 1973 and 1987 received the CMF regimen, whereas six received CMF/VP. Ten patients treated between 1987 and 1991 received three cycles of FAC. Induction chemotherapy was followed by clinical evaluation and local therapy or additional chemotherapy until the maximal response was obtained. As seen in Table 1, the women in each of the treatment groups were of similar age, race, menopausal status, grade and size of tumor, and tumor receptor status. There were no significant differences in the clinical characteristics between the two groups.

Clinical features exhibited by the women included erythema of more than one-third of the

TABLE 1. *Clinical and pathologic characteristics of 38 women with inflammatory breast carcinoma based on type of induction chemotherapy*

Patient/tumor characteristic	CMF/VP (n = 28)	FAC (n = 10)
Mean age (yrs)	49.7	53.9
Median age (yrs)	50.5	51.5
Race (%)		
White	21 (75)	7 (70)
Black	7 (25)	3 (30)
Menopausal status (%)		
Premenopausal	12 (43)	5 (50)
Postmenopausal	16 (57)	5 (50)
Estrogen receptor status (%)		
Positive	5 (18)	3 (30)
Negative	23 (82)	7 (70)
Initial tumor size (cm)	5.0	6.5
Tumor grade		
Well differentiated	1 (4)	0
Moderately differentiated	2 (7)	3 (30)
Poorly differentiated	25 (89)	7 (70)

breast in 100%, a breast mass in 63%, breast enlargement in 42%, breast pain in 39%, and nipple retraction in 21%.

There was a median follow-up of 19.5 months for all 38 women. The women receiving CMF or CMF/VP had a mean follow-up of 21.9 months with a median of 16.5 months. The women in the FAC group had a mean follow-up of 26.9 months with a median of 27 months. All 28 patients who received CMF or CMF/VP have died. Five of the 10 women in the FAC group are alive and disease-free with a follow-up of 12, 17, 29, 34, and 50 months. No patients were lost to follow-up.

The responses to the initial three cycles of chemotherapy were examined for each regimen. The group of 28 women receiving CMF had an overall response rate of 57%, with 40% having a partial response and 17% having a complete response. All of the 10 women receiving FAC had a clinical response to induction chemotherapy, with 60% having a partial response and 40% having a complete response.

After initial chemotherapy, 16 of 38 patients (42%) had local therapy to the affected breast and axilla consisting of surgery and/or radiation. Six of the women received radiation therapy alone, five women had a modified radical mastectomy alone, and five women had a modified radical mastectomy and radiation therapy (Table 2). In the six women who received radiation therapy alone, four had been given CMF (2NR, 2PR) and two received FAC (2PR). In the group of five women who received surgery alone, CMF induction chemotherapy was given to three (1NR, 1PR, 1CR) and two received FAC (2PR). The nonresponder who received CMF was the only patient in this group treated with surgery alone who had axillary nodal metastases based on histologic evaluation. One of the partial responders who received FAC remains alive and disease-free. In the five women who received radiation and surgery, one woman received CMF (1PR) and four received FAC (4CR). All five of these patients had axillary nodal metastases based on histologic examination. All four of the women who were complete responders to FAC and then later underwent radiation and surgery are still alive and disease-free.

Twenty women (71%) treated with CMF/VP received no follow-up local therapy and all experienced disease progression. Of the eight women in the CMF/VP group who received local therapy, all developed a local recurrence with the exception of the woman who underwent modified radical mastectomy and radiation. All women in the CMF/VP group eventually developed distant disease. In the group of women who received FAC, eight (80%) were treated with either surgery and/or radiation therapy at the completion of induction chemotherapy. Three of these women failed locally (2 had surgery alone, 1 had radiation alone) and 5 of the 10 (50%) in the entire FAC group developed distant disease.

The median survival for the 28 women who received CMF/VP was 18 months compared with 30 months for the 10 women receiving the FAC regimen ($p = 0.02$) (Fig. 1). The overall 3-year survivals by the log-rank test for the CMF/VP and the FAC treatment groups were 14 and 41%, respectively. The median disease-free survival in the CMF/VP group was 6 months compared with 24 months for women treated with FAC ($p < 0.001$) (Fig. 2). The estimated 3-year disease-free survival in the FAC treatment group was 46%; none of the women treated with CMF/VP remained disease-free for even 2 years.

TABLE 2. *Patients receiving a systemic chemotherapy regimen with corresponding types of local treatment*

	CMF	FAC
No local therapy	20	2
Radiation alone	4	2
Surgery alone	3	2
Surgery and radiation	1	4
Patients alive	0	5

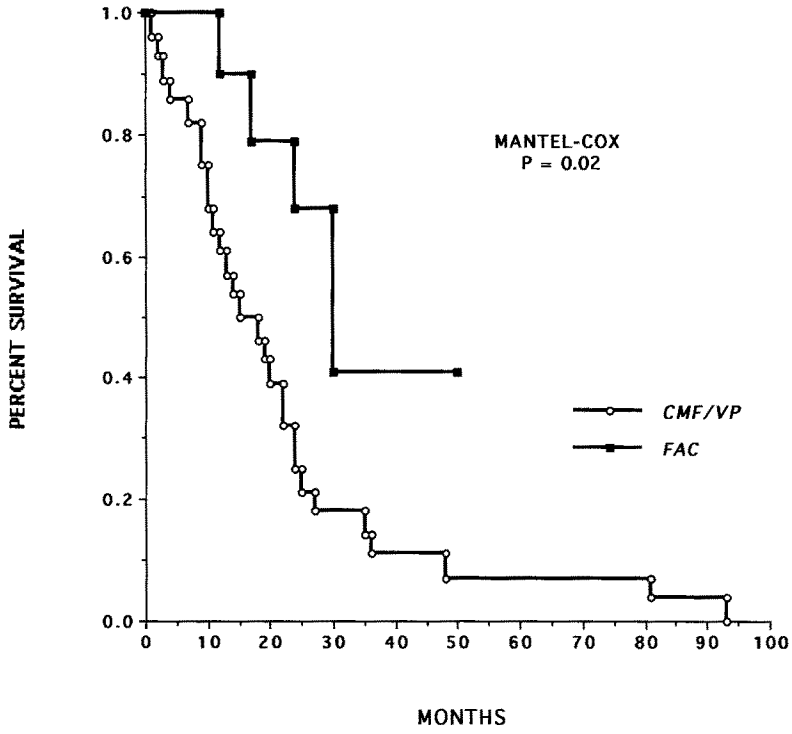

FIG. 1. Overall survival of women with inflammatory breast cancer based on type of induction chemotherapy.

The 12 women who had no response to their initial three cycles of CMF/VP had a median overall survival of only 10 months compared with 24 months for the 16 women having at least a partial response ($p < 0.001$) (Fig. 3). The estimated 3-year survival for the 16 women who responded to the initial three cycles of CMF/VP was 25%; the longest survivor in the nonresponding group lived only 22 months. The median disease-free survival for the responders was 8 months compared with 2 months for the nonresponders ($p < 0.001$) (Fig. 4).

The toxicity related to the chemotherapy was

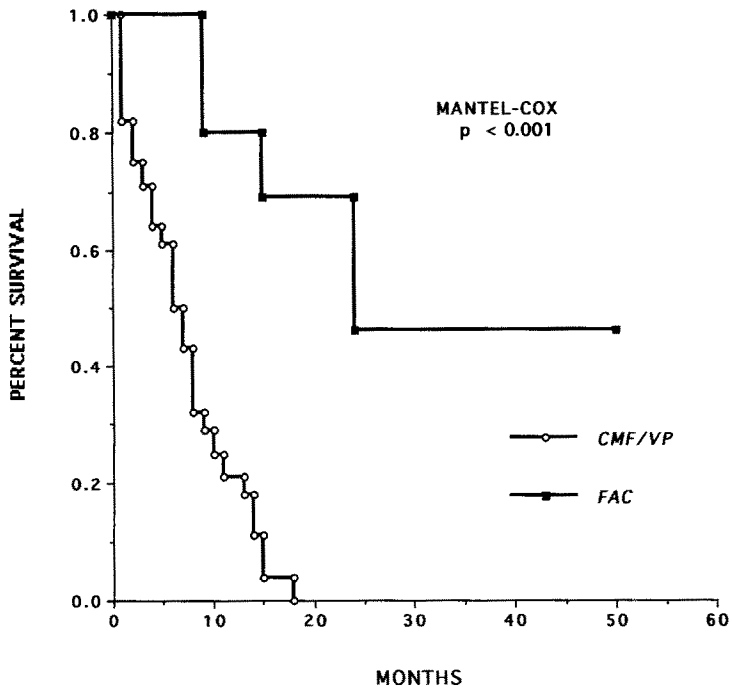

FIG. 2. Disease-free survival of women with inflammatory breast cancer based on type of induction chemotherapy.

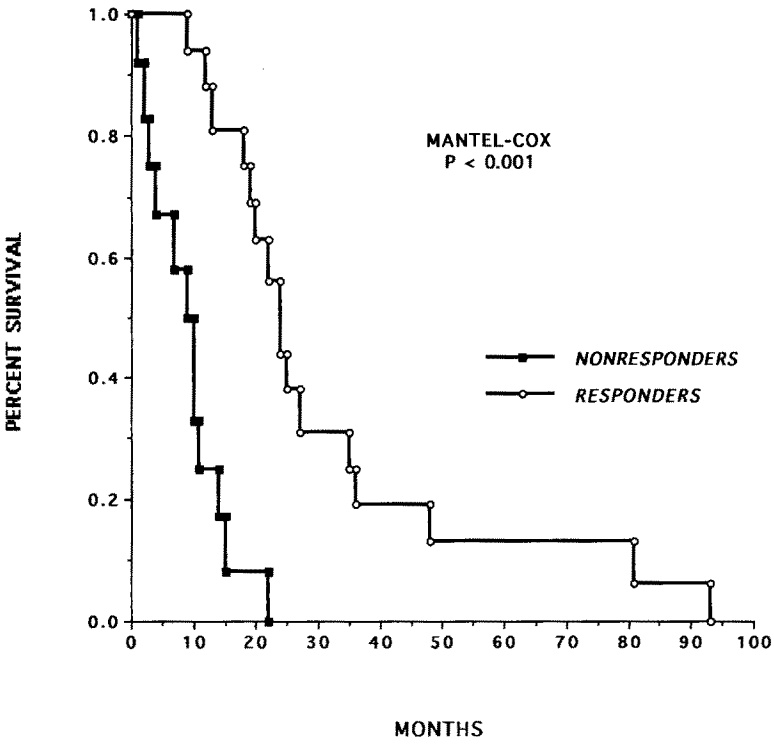

FIG. 3. Overall survival of women with inflammatory breast cancer based on response to induction chemotherapy using CMF/VP.

considerable in each treatment group. The women receiving CMF experienced myelosuppression (96%), nausea (72%), vomiting (38%), diarrhea (23%), stomatitis (11%), and thrombocytopenia (4%). In the group of women receiving FAC, toxicity included myelosuppression (90%), nausea (80%), vomiting (60%), diarrhea (20%), nondisseminated cutaneous zoster (10%), and congestive heart failure (10%).

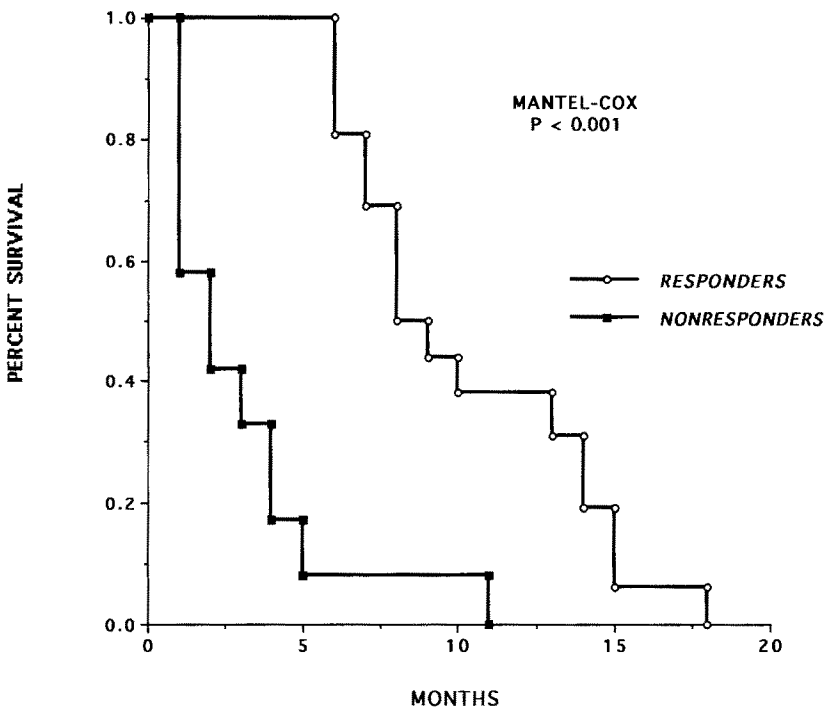

FIG. 4. Disease-free survival of women with inflammatory breast cancer based on response to induction chemotherapy using CMF/VP.

DISCUSSION

Inflammatory breast cancer is a distinct form of breast cancer with respect to clinical and pathologic characteristics, tumor biology, and therapeutic approach. Most patients with inflammatory breast cancer die of distant metastases with or without locoregional failure within months of diagnosis if treated with either radiation therapy, mastectomy, or a combination of these two treatment modalities. These poor results with local therapy alone have led to the use of combined modality treatment, consisting of systemic chemotherapy, followed by evaluation of its efficacy; local therapy in the form of radiation, surgery, or both; and then additional systemic chemotherapy. The advantages of this approach include the administration of chemotherapy before the development of tumor-resistant clones and alteration of the tumor vasculature by radiation therapy and surgery, and an opportunity to evaluate clinically the effectiveness of the chemotherapy. The disadvantages to this approach include inaccurate assessment of stage, potentiation of drug resistance, and delay of local therapy for weeks to months (23).

Inflammatory breast carcinoma should be thought of and treated as a systemic disease. At the time of diagnosis, 46–100% of patients have tumor involvement of the axillary lymph nodes (24). In the present study, 6 of the 10 women (60%) who underwent axillary dissection had metastases and in the entire group, local and distant recurrence rates were 79 and 87%, respectively, suggesting that subclinical distant spread had occurred early.

Several prognostic factors have been shown to be significantly associated with this disease. A poor prognosis has been associated with erythema involving more than one-third of the breast, as well as poor histologic tumor grade (25,26). All 38 women in this study had erythema in greater than one-third of the breast and 84% (32 of 38) had a tumor that was poorly differentiated.

It has also been shown that patients with hormone receptor-positive carcinomas have a better survival initially than those who have receptor-negative tumors (17,27). In this review, 79% (30 of 38) of the women had estrogen-receptor-negative tumors and 95% (36 of 38) had progesterone-receptor-negative tumors. Even the hormone-positive carcinomas in this study usually had low levels of positivity. Such findings suggest that most of the inflammatory breast cancers may contain large numbers of hormone-receptor-negative clones of cells that have a potentially poor prognosis. Veronesi et al. observed no response in any the inflammatory breast cancer patients treated with tamoxifen in their series of locally advanced breast carcinoma (28).

All patients should receive combination chemotherapy as a part of the initial treatment plan, because the initial response rate to chemotherapy is high (often >80%), and the emergence of distant metastases is the primary mode of recurrence (29). Long-term survival has been documented with either cyclophosphamide, doxorubicin, and 5-fluorouracil or cyclophosphamide, methotrexate, and 5-fluorouracil. Because doxorubicin-containing combinations have been reported to produce slightly higher response rates in patients with metastatic cancer (30,31), and inflammatory breast cancer is often a systemic disease at presentation, it may follow that doxorubicin-containing combinations would give better response and survival rates in inflammatory breast disease. In fact, doxorubicin-containing combinations are now the treatment of choice for inflammatory breast cancers.

Although the number of patients is small and the analysis is retrospective, our present study confirms that a doxorubicin-containing regimen gives superior results compared with CMF/VP combination therapy with regard to induction response, local and distant recurrence rates, and overall and disease-free survivals. All of the women who received FAC had at least a partial response to induction therapy, whereas only 57% (16 of 28) of the women in the CMF/VP group responded. The women in the CMF/VP who had at least a partial response to induction chemotherapy had a significantly increased overall and disease-free survival compared with the nonresponders in that group (Figs. 3 and 4).

Of the five women still alive and free of disease in the FAC group, four were complete responders to the induction therapy and one woman was a partial responder. The four complete responders went on to receive a modified radical mastectomy and radiation therapy, whereas the partial responder had surgery alone. Again, all four complete responders had nodal disease. It appears that complete responders to a doxorubicin-based induction regimen who then undergo surgery and radiation therapy, despite nodal metastases, have the best chance at long-term survival.

Further studies are still necessary to determine

the best therapy in this uncommon subset of patients with breast cancer. Although combined-modality therapy has resulted in prolonged survival for increased numbers of these patients, the optimal use of various treatment modalities remains undefined. The optimal duration of chemotherapy, as well as the best doxorubicin-containing regimen, has not been studied. The sequence of radiotherapy and chemotherapy that produces the best tumor control with tolerable side effects is unknown. The toxicity of the two treatment regimens in this study were similar. The role of mastectomy after chemotherapy and radiation is also undefined.

Currently, a slightly improved outlook for patients with inflammatory breast cancer can be attributed to more intensive combination chemotherapy. Despite the small numbers of patients represented in most series and absence of prospective randomized trials, intensive systemic chemotherapy preceding locoregional treatment has become the standard therapy for inflammatory breast cancer. Strategies for improved local therapy might include altered radiation fractionation patterns, radiation hypoxic cell sensitizers, photodynamic therapy, or immunotherapy. Ultimate progress in this disease will, however, depend on improvements in systemic therapy.

Acknowledgment: This study was supported in part by Research Grant CA16056 awarded by the National Cancer Institute.

REFERENCES

1. Levine PH, Steinhorn SC, Ries LG, Aaron JL. Inflammatory breast cancer: the experience of the Surveillance, Epidemiology, and End Results (SEER) Program. *J Natl Cancer Inst* 1985;74:291–7.
2. Bell C. *A System of Operative Surgery*, vol 2. Hartford, Connecticut: Hale and Hosmer, 1814:136.
3. Klotz H. *Ueber mastitis carcinomatosa gravidarum et Lactantium*. Halle, Germany: Lipke, 1869:30.
4. Leitch A. Peau d'orange in acute mammary carcinoma. Its causes and diagnostic value. *Lancet* 1909;1:861–3.
5. Learmonth G. Acute mammary carcinoma (Volkman's mastitis carcinomatosis). *Can Med Assoc J* 1916;6:499–511.
6. Schumann E. Carcinoma mastitoides. *Ann Surg* 1911;54:69–77.
7. Lee BJ, Tannenbaum NE. Inflammatory carcinoma of the breast: a report of twenty-eight cases from the breast clinic of the Memorial Hospital. *Surg Gynecol Obstet* 1924;39:580–95.
8. Taylor G, Meltzer A. Inflammatory carcinoma of the breast 1938;33:33–49.
9. Bozzetti J, Saccozzi R, DeLena M, Salvadori B. Inflammatory cancer of the breast: analysis of 114 cases. *J Surg Oncol* 1981;18:355–61.
10. Chris S. Inflammatory carcinoma of the breast: a report of 20 cases and a review of the literature. *Br J Surg* 1950;38:163–74.
11. Meyer A, Dockerty M, Harrington S. Inflammatory carcinoma of the breast. *Surg Gynecol Obstet* 1948;87:417–24.
12. Stocks L, Patterson F. Inflammatory carcinoma of the breast. *Surg Gynecol Obstet* 1976;143:885–9.
13. Barker J, Montague E, Peters L, et al. Clinical experience with irradiation of inflammatory carcinoma of the breast with and without elective chemotherapy. *Cancer* 1980;45:625–9.
14. Dao T, McCarthy J. Treatment of inflammatory carcinoma of the breast. *Surg Gynecol Obstet* 1957;105:289–94.
15. Richards G, Lewiston E. Inflammatory carcinoma of the breast. *Surg Gynecol Obstet* 1961;113:729–32.
16. Wang C, Griscom N. Inflammatory carcinoma of the breast: Results following orthovoltage and supervoltage radiation therapy. *Clin Radiol* 1964;15:168–74.
17. Rogers C, Fitts W. Inflammatory carcinoma of the breast. A critique of therapy. *Surgery* 1956;39:367–70.
18. Barber K, Dockerty M, Clagett O. Inflammatory carcinoma of the breast. *Surg Gynecol Obstet* 1961;112:406–10.
19. Donegan W. Staging and end results. In: Spratt J Jr, Donegan W, eds. *Cancer of the breast*. Philadelphia: WB Saunders, 1967:117–61.
20. Nussbaum H, Kagan A, Gilbert H, et al. Management of inflammatory breast carcinoma. *Breast* 1977;3:25–9.
21. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–86.
22. Cox D. Regression models and life-tables. *J R Stat Soc B* 1972;34:187–220.
23. Jaiyesimi I, Buzdar A, Hortobagyi G. Inflammatory breast cancer: a review. *J Clin Oncol* 1992;10:1014–24.
24. Haagensen C. *Diseases of the breast*, 2nd ed. Philadelphia: WB Saunders, 1971:576–84.
25. Rouesse J, Friedman S, Sarrazin D, et al. Primary chemotherapy in the treatment of inflammatory breast carcinoma: a study of 230 cases from the Institut Gustave-Roussey. *J Clin Oncol* 1986;4:1765–71.
26. Chevallier B, Asselain B, Kunlin A, Veyret C, et al. Inflammatory breast cancer: determination of prognostic factors by univariate and multivariate analysis. *Cancer* 1987;60:897–902.
27. Kohail H, Elias E, El-Noweim S, Bashirelahi N, et al. A multifactorial analysis of steroid hormone receptor in stage I and II breast cancer. *Ann Surg* 1985;201:61–7.
28. Veronesi A, Frustaci S, Tirelli U, et al. Tamoxifen therapy in postmenopausal advanced breast cancer: efficacy at the primary tumor site in 46 evaluable patients. *Tumori* 1981;67:235–8.
29. Sherry M, Johnson D, Page D, Greco F, et al. Inflammatory carcinoma of the breast: clinical review and summary of the Vanderbilt experience with multi-modality therapy. *Am J Med* 1985;79:355–64.
30. Muss H, White D, Richards F, et al. Adriamycin versus methotrexate in five-drug combination chemotherapy for advanced breast cancer. *Cancer* 1978;42:2141–8.
31. Bull J, Tormey D, Li S, et al. A randomized comparative trial of adriamycin versus methotrexate in combination drug therapy. *Cancer* 1978;41:1649–57.