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Surgical Aspects of Inflammatory Breast Cancer

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Abstract. Mastectomy alone as a treatment for inflammatory breast cancer results in local recurrence in 20% of cases and a median survival of only 2 years. Current management of inflammatory cancer employs initial chemotherapy with surgery reserved for patients who have complete resolution of inflammatory changes. The combination of chemotherapy, mastectomy, and radiotherapy results in local control in 80% of patients. Breast conserving surgery and sentinel node biopsy are contraindicated in inflammatory cancer.

INTRODUCTION

Inflammatory breast carcinoma (IBC) remains a challenging clinical entity. This cancer is characterized by extremely poor survival and those affected are younger than patients with non-inflammatory breast cancer (NIBC) [1,2]. The overall survival of IBC patients has been improved by the use of combined treatment modalities, though patients with IBC still have survival rates much lower than patients with NIBC [3].

The largest series to examine survival for IBC used data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, the only population-based sample of IBC cases available [4]. In this data set the incidence of IBC appears to have doubled between 1975 to 1977 and 1990 to 1999, increasing from 0.3 to 0.7 per 100,000 for white Americans and 0.6 to 1.1 per 100,000 in African American women. In addition to this, women with IBC rarely survived 10 years although 50% of women with NIBC were alive at 10 years. The most recent update of this data, examining the time periods 1988 to 1990 and 1997 to 1999 demonstrates that the incidence of IBC increased from 2.0 to 2.5 (per 100,000 woman years). A poor survival for those with IBC was again noted: women with IBC had a mean survival of 2.9 years as compared to those with locally advanced breast cancer who survived a mean of 6.4 years [5].

Historically the survival of patients with IBC has been dismal, ranging from only 2.4 months to 26 months from time of diagnosis to death [6,7]. When the outcome of surgery alone has been examined in the management of IBC, patients have inevitably developed systemic disease. Assessment of the role of surgery in the modern management of IBC is complicated by the lack of a standard definition of IBC and the absence of specific histologic features to confirm the diagnosis. This article will examine some of the historical outcomes of surgery in the management IBC and will also focus on the current role of surgery in the multimodal management of IBC.

PRIMARY MASTECTOMY

The goals of surgery in IBC are to maintain local control and to improve survival. The failure of mastectomy as a primary treatment to meet these goals has been recognized for many years and is highlighted by a historic report from 1924 in which Lee and Tannenbaum observed "Our attention was called to this phase of mammary disease when we encountered an early and almost immediate recurrence following a radical oper-

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Table 1
Outcome after mastectomy alone in inflammatory breast cancer

Study Author	Number of Patients	5 year survival (%)	Mean Survival (Months)
Lee and Tannenbaum (1924) [6]	4	0 (0)	15
Taylor and Meltzer (1938) [12]	6	0 (0)	21
Chris (1950) [13]	5	0 (0)	9
Treves (1959) [14]	114	4 (3.5)	na
Rogers and Fitts (1956) [15]	10	1 (10)	na
Dao and McCarthy (1957) [16]	3	0 (0)	4
Byrd and Stephenson (1960) [17]	12	0 (0)	16
Barber et al. (1961) [9]	50	5 (10)	25
Richards and Lewison (1961) [18]	2	0 (0)	na
Wang and Griscom (1964) [7]	23	0 (0)	21
Donegan (1976) [19]	12	0 (0)	18.5
Haagensen (1971) [8]	30	1 (3)	19
Robbins et al. (1974) [20]	4	0 (0)	12
Stocks and Patterson (1976) [21]	10	1 (10)	32
Bozzetti et al. (1981) [10]	8	0 (10)	12
Total	293	12 (4)	19.8 mean

ation. Since that time frequent repetitions of this experience in cases operated elsewhere have made us more certain as to the inefficiency of surgery in the treatment of this disease." [6]. In Lee and Tannenbaum's cohort of 18 IBC patients only 4 were deemed suitable for surgery, 3 of whom underwent radical mastectomy and all 3 died of recurrent disease [6].

In the 1950s Hagensen reported 29 patients with IBC treated with radical mastectomy. The mean survival after surgery was only 19 months and no patients were alive at 5 years [8]. Barber et al. reported their experience with IBC and radical mastectomy in 1961; in 50 patients treated they observed a mean survival of only 25 months with 5 patients alive at 5 years [9]. Bozzetti and colleagues published results from their experience with IBC in the 1980s. In a group of 114 patients 8 were treated with radical mastectomy alone, with only 1 alive at 48 months follow up [10]. In addition to the dismal survival offered by mastectomy as primary management of IBC, this single modality also offers poor local control. Surgery alone results in local recurrence rates of approximately 50% in spite of mean survivals less than 2 years in the majority of cases [6–11].

Survival data for treatment of IBC with surgery alone is summarized in Table 1 [6,7,10–21]. The poor outcome of surgery was recognized in the 1920's and observed again in the 1950's, resulting in radiotherapy becoming the primary therapeutic treatment modality for the management of IBC until the 1970's [6,13].

SURGERY AS PART OF MULTIMODAL THERAPY

The demonstration in the 1970's that adjuvant systemic chemotherapy improved disease free and overall survival for women with node positive breast cancer led to a number of studies examining the role of initial chemotherapy in the management of IBC. Early studies of this approach suggested a prolongation of disease free and overall survival compared to historic controls [22–24]. However, local recurrence occurred in 25% to 39% of cases in spite of the combination of chemotherapy, surgery, and radiotherapy, and persistent tumor was observed in the majority of surgical specimens [23,24].

The results of more recent studies of multimodality therapy are summarized in Table 2 [25–34]. Ueno et al. reviewed the outcome of 178 IBC patients treated on a variety of protocols at the MD Anderson Cancer Center over the past 20 years [30]. Major responses to chemotherapy were seen in 74%, with 23% of patients having less than a partial response or stable disease. With the use of preoperative chemotherapy, 95% of patients were able to undergo surgery, but locoregional failure occurred in 20% [30]. Chevallier et al also reported resolution of inflammatory changes and conversion to operability in 91% of 45 patients receiving preoperative chemotherapy [26]. In another study from the M. D. Anderson Cancer Center the operability rate was 86% of 42 patients after preoperative chemotherapy [35]. Although a measurable response to chemotherapy was seen in 63% of 1202 cases reviewed in Table 2, complete clinical response occurred in only 149 of 930 patients (16%) for whom this information was reported.

As illustrated in Table 2, a wide range of clinical complete response rates to induction chemotherapy have been reported. Less information is available on the incidence of pathological complete response, in part

Table 2
Response to induction chemotherapy in inflammatory breast cancer

Study Author	Number of Patients	Clinical response Rate	Clinical complete response	No Response
Moore et al. (1991) [25]	38	30	na	8
Chevallier (1993) [26]	192	140	23	42
Attia-Sobol et al. (1993) [27]	103	12	na	91
Mourali et al.(1993) [28]	63	12	na	51
Thomas et al. (1995) [29]	125	94	11	31
Ueno et al. (1997) [30]	178	127	21	51
Arthur et al. (1999) [31]	38	27	15	11
De Boer et al. (2000) [32]	34	29	12	5
Baldini et al. (2004) [33]	68	50	na	18
Evans et al. (2005) [34]	363	239	67	124
Total	1202	760 (63.2%)	149 (19.3%)	442 (36.8%)

Table 3
Locoregional recurrence after combined modality therapy

Author	Number of Patients	Treatment regime	% Locoregional recurrence
Fastenberg et al. [41]	63	FAC+/−RT+S	20
Fields et al. [42]	37	CAF+RT+S	19
Elias et al. [43]	28	FAC+S+RT	21
Pisansky et al. [44]	36	CFPr+RT+S	19
Fein et al. [45]	33	CM/AF+S+RT	21
Colozza et al. [46]	14	CAP+S+CMF+RT	16
Perez et al. [47]	86	CAF+S+RT	21
Harris et al. [39]	54	CM/AF+RT+S	19
Total	351		19.5

F, 5 flurouracil, A, doxorubicin, C, cycophosphomide, RT, radiotherapy, S, Surgery, P, cisplatin, M, methotrexate, Pr, prednisone.

because in some studies patients thought to be clinical responders did not undergo mastectomy. Swain et al reported a 33% pathological complete response rate after neoadjuvant chemo hormonal therapy in a group of 46 IBC patients [36]. In this study, a complete pathological response was defined as the absence of tumour cells on fine needle aspiration and in multiple incisional biopsies and patients deemed to be complete responders did not undergo mastectomy. After a median follow up of 16.8 years, 6 of 15 complete responders had locoregional failure alone or in combination with distant metastasis [37]. This local recurrence rate is somewhat higher than might be anticipated based on the high clinical complete response rate, suggesting that the inability to examine the breast in its entirety may have led to an overestimation of the rate of complete pathological response. Other studies report pathological complete response rates of 14% to 30% after preoperative chemotherapy alone or in combination with radiotherapy [35,38,39]. In the study of Harris et al the overall locoregional failure rate was 19%. No locoregional recurrences were observed in the 15 patients who were pathological complete responders, although 7 ultimately developed distant metastasis [39]. Thoms et al also observed a decreased rate of local recurrence in patients who had a complete pathological response to induction therapy, with a 5 year actuarial local control rate of 89%, for complete responders, 68% for partial responders, and 33% for nonresponders [40]. Local failure rates in studies of combined modality treatment are summarized in Table 3 [39,41–47]. It is apparent from these studies that with anthracycline based chemotherapy, regardless of the sequencing of surgery and radiotherapy, locoregional recurrence occurs in approximately 20% of cases.

Other studies have examined outcomes in IBC after treatment with induction chemotherapy followed by radiotherapy and reported good results, leading to some debate about whether any surgery is necessary in the initial treatment of IBC. Ueno et al reported an 18% incidence of initial locoregional failure in 40 patients treated with 3 cycles of fluorouracil, doxorubicin, and cyclophosphamide (FAC) followed by radiotherapy and additional postoperative chemotherapy compared to 26% in 23 patients treated with initial FAC, mastectomy, postoperative chemotherapy and adjuvant radiotherapy [30]. A local failure rate of 14% was observed in 43 patients receiving induction FAC plus vincristine and prednisone (FACVP) followed by mastectomy, 6 additional cycles of chemotherapy and ad-

juvant irradiation [30]. De Boer et al reviewed 64 patients with inflammatory breast cancer treated between 1986 and 1998 [48]. Of these, 35 had radiation as the only local treatment modality and 19 had both radiation and surgery. In a multivariate analysis to adjust for differences in prognostic factors between the groups no survival differences were observed and there were no differences in the rate of local relapse.

Although these results suggest that local control can be maintained without surgery, the added contribution of mastectomy to local control or survival cannot be assessed outside of a prospective randomized trial. Other retrospective studies suggest that there may be a benefit for surgery. A retrospective study examined survival of 454 consecutive patients with advanced breast cancer. Patients underwent either radiotherapy alone or followed by mastectomy. The median survival for the whole series was 2.5 years. Patients treated with radiotherapy followed by surgery had a median survival of 3.9 years compared to 2.1 years for those given only irradiation. Though this group did not utilize additional adjuvant therapy, there appeared to be survival benefit to those patients undergoing mastectomy [49]. Similar results have also been reported by the M. D. Anderson group. They observed the best outcome in patients treated with multimodal therapy which included surgery. The overall survival and locoregional failure rates were 48% and 41% at 5 years respectively, following mastectomy as definitive locoregional therapy, compared to 37% and 35% when radiation was utilized as a single modality following adjuvant chemotherapy [50]. These data suggest that mastectomy may offer some survival advantage, and enhance local control.

Selection bias, in which patients with complete clinical responses were treated with radiotherapy, while those with lesser degrees of response to initial chemotherapy were subject to mastectomy, or vice versa, could account for the variation in results discussed here. In the absence of definitive data, there are several potential advantages of mastectomy to consider. Histologic examination of the mastectomy specimen allows a more accurate evaluation of response than clinical or imaging evaluation. In studies of locally advanced breast cancer not limited to inflammatory cancer, only one half to two thirds of patients thought to have a clinical complete response have this finding confirmed at pathology [51]. The degree of pathologic response is an important indicator of prognosis after neoadjuvant therapy. Harris et al reported that 5 year overall survival for inflammatory cancer patients with a pathologic complete response after induction chemotherapy was 65% compared to 52% for those with lesser responses. At 10 years these figures were 46% and 31% respectively [39]. In a review of 178 IBC patients treated with doxorubicin based chemotherapy initially, the amount of residual tumor in the mastectomy specimen was highly correlated with the risk of local failure, and the mortality rate after local recurrence was 98% [52]. These studies suggest that findings from the mastectomy specimen may influence decisions about the need for additional systemic therapy. In addition, mastectomy has the potential to remove foci of chemoresistant disease, potentially improving local control.

SELECTION

The use of surgery for IBC has increased over the past 2 decades. An analysis of 485 patients treated for IBC between 1980 and 2000 demonstrated an increase in the rate of mastectomy from 10.9% to 69% between the years 1980 to1985 and 1996 to 2000 [53]. During this time there has been a concurrent drop in the rate of surgery used as the initial therapy from 21.7% to 9.9% of cases. The percentage of patients having no surgery also fell during this time from 67.4% to 21.8%. Clearly there is a trend toward incorporating mastectomy in the treatment of IBC, although the timing of surgery has changed from initial cancer management to a post chemotherapy intervention.

Patients who present with clinical evidence of IBC should be considered inoperable at presentation. Core needle biopsy is the optimal method of obtaining a histologic diagnosis. It allows tumour markers to be obtained and avoids the delay in initiating chemotherapy which is necessary when a surgical incisional biopsy is employed. Histologic confirmation of infiltration of the dermal lymphatics is not necessary to make a diagnosis of IBC when the clinical signs and symptoms of IBC are present.

Patients are considered candidates for modified radical mastectomy when all evidence of skin inflammation has resolved in response to chemotherapy; surgery in patients who do not respond to chemotherapy is associated with both poor survival and poor local control. Thoms et al reported the outcomes of mastectomy in 56 patients receiving preoperative chemotherapy [40]. In the 24 patients who did not respond to the three courses of doxorubicin based chemotherapy the 5 year actuarial rate of local control was 33% compared to 68% for partial responders and 89% for those with a

clinical complete response. All patients in the no response group had failed by 34 months. In the anecdotal experience of one of the authors (MM), chest wall recurrence has been observed in the second postoperative week when surgery is performed without resolution of inflammatory skin changes. Chemotherapy should be followed by radiotherapy when skin inflammation persists. The benefit of mastectomy after radiotherapy in patients with chemoresistant disease is uncertain and must be considered on a case-by-case basis. Standard criteria of inoperability also apply in IBC: supraclavicular adenopathy, fixed axillary lymphadenopathy, and edema of the ipsilateral arm; all of these are an indication for radiotherapy for local control.

The role of immediate breast reconstruction in locally advanced disease is controversial [3,54,55]. Concerns include delays in the administration of postoperative therapies if problems with wound healing occur, the negative effect of radiotherapy on the cosmetic outcome of the reconstruction and the high risks of local recurrence. Very limited information on the use of immediate reconstruction in patients with IBC is available. Slavin et al reported that 6 out of 10 IBC patients developed local recurrence after myocutaneous flap reconstruction, although the detection of recurrence in the flap did not appear to be delayed [56]. Chin and co-authors reported a series of 14 IBC patients undergoing immediate reconstruction and 9 who had delayed reconstruction [57]. The median survival after reconstruction was 22 months. Four patients had positive mastectomy margins and all of these patients recurred. In IBC patients undergoing immediate reconstruction, skin-sparing mastectomy should be avoided due to the inability to ensure the eradication of all malignant cells in the skin with preoperative chemotherapy. Since postoperative irradiation is routine and the skin cannot be saved, many of the advantages of immediate reconstruction are lost and we prefer to delay reconstruction until the completion of oncological therapy in the patient with IBC.

SENTINEL NODE BIOPSY

Sentinel lymph node (SNL) biopsy has evolved as the standard method of evaluation of the clinically negative axilla in breast cancer [58,59]. The axillary lymph node status remains the most significant prognostic indicator for patients with invasive breast cancer, and SLN biopsy accurately predicts nodal status in patients with early-stage breast cancer. Historically there have been concerns that SLN biopsy after neoadjuvant therapy might not reliably predict axillary nodal status. Increasing clinical experience suggests that neoadjuvant therapy is not a contraindication to SLN biopsy.

Many small studies have examined the efficacy of lymphatic mapping and the accuracy of SLN biopsy after neoadjuvant chemotherapy with widely varying results. A recent overview of these studies reports a sentinel node detection rate of 89% with a false-negative rate of 11% [60]. The largest single report comes from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B 27 study, which examined the effect of neoadjuvant chemotherapy on outcome in patients undergoing breast cancer surgery [61]. Although SLN biopsy was not part of the protocol design, 428 patients had SLN biopsy attempted after initial chemotherapy with determination of nodal status by axillary dissection. At least one sentinel node was identified and removed in 363 patients (success rate, 84.8%). The sentinel node accurately predicted axillary nodal status in 95.6% of cases, with a sensitivity of 89.3% and a negative predictive value of 93.1%. These results are not significantly different from those obtained in multi-institutional studies of primary sentinel node biopsy during the same period [61].

Inflammatory breast cancer has been regarded as a contraindication to sentinel node biopsy, due to concerns that lymphatics blocked with tumour cells will be unable to carry either blue dye or radiocolloid resulting in failure to identify a sentinel node or a decreased predictive value of the procedure. A recent study examining SLN biopsy in patients undergoing neoadjuvant therapy included eight patients with inflammatory breast cancer. Of those, three had positive nodes on both SLN biopsy and axillary dissection, and one had negative nodes on both SLN biopsy and axillary dissection. In two patients a sentinel node was not identified, and in two additional patients the SLN biopsy produced a false negative result. Although this is a very small cohort, it confirms the impression that SLNB is not a viable option in IBC [62].

SUMMARY

Modified radical mastectomy after chemotherapy is the surgical treatment of choice for patients with IBC. Surgery should be reserved for patients who have a complete resolution of inflammatory skin changes in response to chemotherapy. In spite of the high response rate to chemotherapy locoregional recurrence occurs in approximately 20% of patients after combinations of chemotherapy, mastectomy and radiotherapy.

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