BREAST-CONSERVING TREATMENT IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER

By

Abdel-Salam Megahed* &. El-Sayed El-Hendawy**

From

Department of Surgery, Department of Radiotherapy***

Mansoura University Hospital

ABSTRACT

Purpose : Breast - Conserving surgery (BCS) has generally been limited to T1 and T2 lesions because it has been thought impossible to achieve good local control with satisfactory cosmesis in patients with more advanced disease . However, many patients with T_3 and T_4 lesions will exhibit dramatic tumor downstaging with neoadjuvant Chemotherapy. It is our hypothesis that for these patients BCS can be performed with good local control and cosmesis.

Material and Methods : Between February 1999 and Jan 2003, 34 patients with T_3/T_4, N0-N2 , M_0 breast cancer completed treatment consisting of 4 Courses of (FAC) 500 mg Cyclophosphamid / m2, 50 mg/ m2 of doxorubicin, 500 mg fluorouracil every 3 weeks, Surgery (a local excision if sufficiently downstaged, or mastectomy if not) Followed by another 3 courses of FAC and post radiation therapy. Patients were evaluated for toxicity, local control, cosmesis, disease - free and overall survival.

Results : Median follow-up is 30 months. 15/34 (44%) patients underwent BCS with only one local - regional failure and actuarial 3- years disease - free and overall survival of 77% and 88%. Cosmetic results were good to excellent in 80% of the patients.

Conclusion : These results suggest that with this regimen a subset of patients with locally advanced breast cancer can preserve their breast with acceptable cosmesis without compromising local control or survival.

INTRODUCTION

Breast - Conversing therapy has generally been limited to T_1 and T_2 Lesions because it has been thought impossible to achieve good local control with satisfactory cosmesis in patients with more advanced disease. With the advent and increasing popularity of neoadjuvant chemotherapy for locally advanced breast cancer, it has become evident that significant down staging of the primary tumor often occurs. It is not Known, however, Whether such patients can be treated successfully with local excision and radiation therapy as if they had originally presented with lower stage disease, It is our hypothesis that for some of these patients breast-conversing surgery and radiation therapy can safely achieve local control with good cosmesis. This paper reports on the results of 34 Patients with advanced breast cancer.

MATERIAL AND METHODS

Patient eligibility:

Patient eligible for the study included those with breast cancer staged T_3 or T_4 but no clinically detectable distant metastatic disease (M_0) The patients had to be between 18 and 65 years old, nonpregnant, and with a Karnofsky performance of 70 or greater. Patients could not have had a concomitant malignancy.

Initial Workup :

Prior to enrollment in the protocol all patients had to have cytologically or histologically confirmed adenocarcinoma of the breast. Early in the study fine needle aspirations (FNAs) were sometimes performed to obtain the definitive diagnosis, However, Because FNA alone cannot establish, invasive disease, a core needle or incisional biopsy was later required. Staging included mammograms, complete blood counts, serum chemistries, liver function tests, chest x- ray, bone scan, ECG.

Patients were then classified as to suitability for breast - conserving surgery, although the final determination for tylectomy versus mastectomy was finalized only after the first 4 cycles of chemotherapy.

Treatment Schema

The treatment scheme consisted of 4 cycles of FAC (Chemotherapy). The Scheme therapy was followed either by mastectomy or tylectomy plus axillary dissection as the circumstances dictated. The surgery was followed by 3 cycles of (FAC) over the next 9

weeks, and radiation to either the intact breast or chest wall and peripheral lymphatic.

Breast - Conserving Surgery

The decision to employ breast-conserving surgery (BCS), either tylectomy or quadrantectomy, took place at the initial workup, at review following completion of doxorubicin chemotherapy and at the time of surgery. Some patients were deemed not eligible for BCS on the initial workup because of diffuse spread of tumor throughout the breast, gross multicentricity, inflammatory carcinoma, or extensive involvement of the nipple by tumor. A patient who did not have these contraindications might still not receive BCS if the tumor did not down staged sufficiently for the surgery to be reasonably cosmetic. Initial tumor size, or even skin invasion was not per se a contraindication for BCS.

Radiation Therapy :

Radiation treatment was scheduled to begins maximally week 24-25/ fields consisted of opposed tangential fields to the breast / chest wall for a minimum dose of 50 Gy using standard fractionation. The supraclavicular fossa was treated in all patients, but the axilla was treated only if the patient was clinically Staged as N_2, if there was gross extracapsular extension of tumor, or if the number of pathologically positive nodes was excessive more than 3 positive LN. The decision to boost the tumor bed was based on pathologic review of the surgical specimen and left to the discretion of the treating radiation oncologist.

Parameters Followed

Data collected on the patients include the patient's age, TNM staging, histologic type, tumor grade, estrogen/progesterone receptor (ER/PR) status, response to FAC, breast cosmesis (in those undergoing BCS), disease - free survival, local regional disease - free survival, and overall survival. Cosmesis was measured by observing the patients at least 6 months after completion of radiation therapy by using the Harris Criteria[1].

Our patients outcomes were then compared to historic controls where no attempt at BCS was made.

RESULTS

Patients characteristics :

We report on the first 34 patients who entered this trail between Febru-

ary 1999 and January 2003. Their mean age was 41 years with a range of 29-62.

Twenty-seven patient had a clinical and mammographic tumor size between 5 and 7 cm, 6 patients had a 8-10 cm tumor, and one patient a 15 cm tumor. Thirteen tumors (38%) were considered hormone receptor positive (table 1).

The average treatment duration for all patients was 31.4 weeks. The average time to local therapy (definitive surgery) for all patients was 11.2 weeks, and the average time from the start of chemotherapy to the start of radiation was 25.6 weeks.

Response to 3 cycles of FAC

Following completion of 3 cycles of FAC and lumpectomy/ mastectomy, 18/26 (69%) of 13 patients, and 4/8 (50%) of 14 patients were significantly downstaged to pT_1 or pT_0. Seven of the 34(21%) patients had no evidence of tumor in the surgical specimen. (table 2a). No patients were upstaged. Fifteen of 34, or 44% of the patients were found to be node-negative at surgery (table 2b).

Fifteen of 34(44%) of the patients were able to have BCS. Mastectomy was done in 19 patients (table 3).

Cosmesis

Of the 15 patients undergoing lumpectomy, 12(80%) had a cosmetic result judged "excellent" or "good" on the Harris scale(1). Three patients were judged "fair" and none judged "poor".

Local control and survival

All patients have had at least 12 months follow-up, with a median follow-up of 30 months. There were no local, and only 1 regional failure. That patient recurred in the supraclavicular fossa. There were a total of 6 patients with a disease recurrence and 3 patients who died (table 4).

Table (1): Correlation between clinical T-stage, N-stage, and tumor grade

Stage	Grade 2	Grade 3	Lobular	Unknown	Total
T_3N_0		2			2
T_3N_1	5	9	2	1	17
T_3N_2	1	4		2	7
T_4N_1	1	4			5
T_4N_2	1	2			3
Total	8	21	2	3	34

Table (2a): Tumor size distribution after doxorubicin

Initial T-stage	pT_0	pT_1	pT_2	pT_3	pT_4
cT_3 (26)	5	13	4	4	0
cT_4 (8)	2	2	1	2	1

Table (2b): Nodal distribution after doxorubicin

Node-negative	1-3 nodes positive	4-9 nodes positive	>10 nodes Positive
15(44%)	7(21%)	8(23%)	4(12%)

Table (3): Reasons for mastectomy

9/34	(26%)	disease did not regress sufficiently for BCS
5/34	(15%)	had diffuse disease on presentation
1/34	(3%)	had inflammatory breast cancer
3/34	(9%)	had gross multicentric disease on presentation
1/34	(3%)	patient refusal

Table (4): Survival data

Local Failure rate	0/34	0%
Regional Failure rate	1/34	3%
Distant Failure	5/34	15%
Actuarial 3 -Years disease - Free survival		77%
Actuarial 3 - years overall Survival		88%

DISCUSSION

Breast-conserving therapy has been traditionally employed only for early stage breast cancer as most of the large randomized prospective trials have compared mastectomy with breast-conserving surgery and radiation therapy for tumors less than 5 cm [2,3,4,5,6].

Larger tumors were excluded due to the belief that radiation therapy in combination with tylectomy in these patients would lead to poor local control and cosmesis.

This trial has tested the hypothesis that breast – conserving therapy can be successfully extended to patients with more locally advanced tumour provided they are adequately downstaged with neoadjuvant chemotherapy.

The preliminary results reported here support this claim. With neoadjuvant chemotherapy regimen using doxorubicin, we were able to produce breast conservation in 44% of patients with no local failure, one regional failure, and excellent early survival results.

A previous study has looked at the feasibility of breast conservation surgery after induction chemotherapy for locally advanced breast cancer, Singletary et al.(7) retrospectively reviewed patients at M.D. Anderson who had received neoadjuvant chemotherapy followed by mastectomy, all patients received 3 cycles of vincristine, doxorubici, cyclophospbamide, and prednisone followed by mastectomy. Of the 143 reviewed patients, only 33(23%) were retrospectively considered potential breast conservation candidates based on clinical and radiographic criteria of complete resolution of skin edema, residual tumor size of less than 5cm, and absence of known tumor multicentricity or extensive intramammary lymphatic invasion. This 23% compares to 44% of our patients who actually received lumpectomy. Of the 33 BCS candidates in the Singletary study only 14, or 10% of the original cohort were down staged to pT0 compared to 7/34 (21%) in our series. The better response to neoadjuvant chemotherapy in our series may be due to our patients had less advanced disease. In addition to downstaging of the primary tumor, nodal downstaging doubtless also occurs. However, because the initial pathologic nodal stage is not known it is impossible to quantify.

However, we can estimate the number of patients with pathologically positive nodes at the time of diagnosis. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial[8] 755 of clinically node-positive and 40% of clinically node-negative patients were actually pathologically node-positive.

As regard cosmesis for locally advanced disease treated with lumpectomy and radiation with which to compare our outcome, that of the first report by Jacquillat et al.[9]. In this study a good to excellent cosmetic result was seen in 73% of patients and fair in 27 % which is consistent with our data. A compilation of cosmetic outcomes in early breast cancer by Fowble et al.[10] suggest a good to excellent cosmetic result rate of 69% - 90% which is also similar to our findings.

There have been a number of studies which have looked at the issue of Breast- conserving therapy for locally advanced breast cancer. One of the first centers to use primary chemotherapy in an effort to avoid mastectomy was the Salpetriere Hospital in Paris. Baillet et al.(11) used external beam radiation and an interstitial Brachtherapy boost following neoadjuvant vinblastine, thiotepa, methotrexate, and 5-fluorouradil (5 FU) with or without doxorubicin. Radiation was started 7-12 weeks after the initiation of induction chemotherapy. Surgical resection was reserved for salvage. One hundred thirty - five patients with tumors greater than 5 cm were treated between 1980-1985. Despite 100% clinical complete response, 21% of these patients developed a local recurrence. Many people would consider this an unacceptable local control rate. These failures were likely related to a lack of surgery as a component of local therapy and, less so, to the chemotherapy. These findings suggest the importance of surgery as part of the multimodality management of these cancers, even in the setting of a complete clinical response. In our study, a complete clinical response to the neoadjuvant FAC did not always correlate with a complete pathologic response at the time of surgery.

Three additional French studies also used neoadjuvant chemotherapy for advanced breast cancer as part of breast - conserving treatment(12,14). However, a significant number of the patients had tumors as small as 3 cm

and therefore are not directly comparable to ours and therefore do not significantly extend the indications for breast - conserving treatment.

Mauriac et al.[13] reported on a prospective single- institution trail from Bordeaux where 272 patients with operable breast cancers > 3 cm were randomized to either modified radical mastectomy plus adjuvant chemotherapy (if node - positive or hormone receptor negative) or breast-conserving therapy. BCS consisted of three cycles of epirubicin, vincristine, and methotrexate and three cycles of Mitomycin- C thiotepa, and vindesine followed by local regional treatment which was based on response to induction chemotherapy. If a clinically complete response was achieved, radiation therapy alone was given; if the residual was less than 2 cm the patients underwent lumpectomy and radiation therapy; and if the residual was greater than 2 cm, mastectomy was done. Twenty-nine of the 134 Patients in the primary chemotherapy had T_3 tumors and the rest had T_2 lesions. With a median follow-up of 34 months, 11 patients (8%) in the primary chemotherapy experienced local regional failure. The local failure rate and breast conservation rate were not mentioned in the subset of patients with T_3 tumors. So although their local regional failure rate is similar to ours, the series are not directly comparable because the majority of these patients had early-stage disease.

The 56 study of Scholl et al.[14] was a prospective trial from Institute Curie Where 414 premenopausal patients with T_2-T_3 NO-N1 MO (no metastatic disease breast cancer were randomized to receive either four cycles of neoadjuvant chemotherapy cyclophosphamide, doxorubicine,5-FU), followed by local-regional treatment (group I) or four cycles of adjuvant chemotherapy after primary irradiation plus surgery (group II). In group I, surgery was limited to those patients with a persisting mass after Irradiation. In spite of the fact that the majority of patients in-group I had T_2 tumors the 5-year actuarial local recurrence was 27%. The local regional failures in T_3 tumors were not broken out, again making a direct comparison with our study Impossible.

Calais et al.[12] reported preliminary results from a prospective trial from Hospital Bretonneau in Tours, France on 80 patients with primary breast cancers greater than 3 cm who

received three cycles of neoadjuvant mitoxantrone, vindesine cyclophosphamide and 5-FU followed by locoregional treatment based on drug response. Breast-conserving therapy was achieved in 42.5% of these patients, comparable to the 44 % rate in our study. With a median follow-up of 38 months local failure rates were 6% for conservatively treated patients and 6% for patients treated with mastectomy. These local control and survival rates are likewise similar to those in our study. Again, the major difference in the trial compared to ours is the number of patients with T_2 tumors (More than half).

Bonadonna et al.[15] reported on 161 patients with tumors greater than 3 cm in a recent study from Milan. All patients received neoadjuvant chemotherapy and local excision if the primary tumor had shrunk to less than 3 cm. Postoperative irradiation was given if a breast-saving procedure was performed. Of the 32 patients with primary tumors of 5 cm or greater, 19(59%) achieved reduction of tumor size to less than 3 cm and had conservative surgery followed by local radiation therapy with a minimum follow-up of 12 months there had been only 1 local failure.

The University of Micihgan[16] reported results of prospective phase II trail which sought to maximize breast conservation rates in 89 patients with locally advanced breast cancer. All patients received nine 21- day cycles of combined neoadjuvant chemohormonal therapy followed by local therapy determined by post-chemotherapy biopsy, those with a pathological complete response received irradiation as local therapy, Whereas those with residual disease received a mastectomy plus radiation. All patients then received an additional eight cycles of chemobormonal therapy. Much like our trial clinical complete response did not correlate well with a pathologica l complete response (61% clinical CR and a 28% pathologic CR). The 5-Year actuarial local-regional control with local-regional failure as a component of first failure was 74 % with the majority of local failures occurring within the first 3 years of follow-up. Interestingly, of the 21 pathologic complete responders who received irradiation as the only mode of local therapy, only 14 % had an isolated. Local failure, which compared well with the group who received mastectomy and radiation. This would suggest that post induction biopsy

may be an accurate means of selecting the subgroup of patients who may not require surgery.

The Michigan trial differed from ours in these important ways: Total treatment time was a minimum of 57 weeks compared to our 27 weeks. Their delay to local therapy was 27 weeks compared to our 10 weeks. This 27 weeks delay to local therapy may contribute to the higher incidence of local failures in their trail for reasons first elucidated by Recht et al.[17].

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الجراحة المتحفظة لحالات أورام الثدى المتتقدمة

د. عبد السلام مجاهد ، د.السيد الهنداوى*

قسم الجراحة العامة- الطب النووى - بمستشفى المنصورة الجامعى*

الجراحة المتحفظة لأورام الثدى كانت محدودة لحالات أورام الثدى الأولية لأنه كان يعتقد أن هذا النوع من الجراحة لايناسب حالات أورام الثدى المتقدمة، ولكن مع إستخدام نظام العلاج الاشعاعى والكيماوى للحالات المتقدمة قبل إجراء الجراحة جعل من الممكن إستخدام الجراحة المتحفظة لعلاج هذه الأورام المتقدمة.

هذه الدراسة تمت فى مستشفى المنصورة الجامعى بالاشتراك بين قسم الجراحة العامة وقسم العلاج بالأشعة والطب النووى وذلك فى الفترة من فبراير ١٩٩٩ الى يناير ٢٠٠٣ على ٣٤ مريضه بأورام ثدى متقدمة.

وكانت فكرة العلاج عبارة عن أربعة مجموعات من العلاج الكيماوى قبل إجراء الجراحة، ثم إجراء الجراحة، ثم اتبعت بثلاث مجموعات من العلاج الكيماوى والعلاج الإشعاعى.

وقد تم إجراء جراحات متحفظة لأورام الثدى فى عدد ١٥ حالة بنسبة ٤٤٪ وكانت نتائج الجراحات مشجعة.

أما بقية الحالات فقد تم إجراء جراحات كاملة لها لعدم ملائمتها للعلاج التحفظى.

ومن هذه الدراسة وجد أنه يمكن المحافظة على الثدى بإجراء جراحات متحفظة لحالات أورام الثدى المتقدمة دون التأثير على إنتشار المرض موضعى أو كلى.