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Conservation Surgery After Primary Chemotherapy in Large Carcinomas of the Breast

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Objective

The authors evaluated the utility of preoperative chemotherapy in patients with large size breast carcinoma, with a view to rendering a conservative surgical approach possible or easier.

Summary Background Data

Two hundred twenty-six of 227 patients with breast cancer involving a tumor larger than 3 cm at greatest dimension were candidates for mastectomy. They were treated with various primary preoperative chemotherapies and evaluated for surgery.

Methods

After administering various chemotherapeutic regimens, the authors reevaluated the patients' conditions clinically and radiologically to plan definitive surgical treatment. If the tumor diameter was sufficiently reduced, quadrantectomy was planned; otherwise, mastectomy was performed. Complete axillary lymph node dissection was done in all cases.

Results

In 90% of the cases, the size reduction was sufficient to justify breast conservation; in 10%, tumor size did not decrease enough or increased, thus mastectomy was performed. In 11.8% of the cases, the tumor was no longer identifiable at surgical inspection, and in 3.5% no tumor was found on microscopic examination. Axillary lymph nodes were free of metastases in 39% of cases. Twelve local recurrences occurred among the 203 patients treated with breast conservation (5.9%) and five among the 23 patients treated with mastectomy (21.7%).

Conclusions

Primary chemotherapy can expand the indication for breast conservation to large tumors; careful attention, however, must be paid to surgical technique. The position of the tumor should be marked with tattoo points on the skin before chemotherapy. The macroscopic extent of the tumor regression must be evaluated carefully, and multiple frozen section biopsies may be needed. The margins of the resected breast should be evaluated microscopically. All microcalcifications present before treatment must be resected. The skin incision and mammary resection must fulfill criteria of radicality as well as good cosmetic outcome.

Primary (preoperative, neoadjuvant) chemotherapy was introduced nearly 20 years ago in breast cancer treatment to elicit a rapid response before surgery or radiotherapy in locally advanced cases.[1-3]. More recently, the introduction of conservative treatments to substitute for mastectomy among women with small carcinomas has led to a new indication for primary chemotherapy, whose objective is to induce a reduction of the tumor mass to make the conservative surgical approach possible or easier.[4-7] Primary chemotherapy in breast carcinoma, however, presents the surgeon with difficult decisions concerning the type and extent of surgery to be used for each patient, because chemotherapy responses can differ greatly among patients. The main problems for the surgeon are (1) identification of the original tumor site when the tumor is no longer palpable, (2) clinical evaluation of the extent of regression, (3) reliability of the gross evaluation of the residual mass, (4) reliability of the frozen section examination, and (5) significance of the persistence of microcalcifications. A sound evaluation of all these aspects will guide the surgeon in deciding how much normal tissue around the tumor must be removed. Bonadonna et al.[7] recently described the results of treating 165 breast cancer patients with five different regimens of preoperative chemotherapy at the Milan Cancer Institute; all were candidates for mastectomy because of the large diameter of their tumors. The study showed that chemotherapy reduced the tumor mass to less than 3 cm in 81% of patients, thereby allowing for conservative surgery in 89% of the total. The same series plus an additional 61 cases are reconsidered in the current report regarding the surgical aspects of this multidisciplinary treatment.

PATIENTS AND METHODS

Patient Characteristics

The patient population was enrolled in this study from January 1988 to October 1990; criteria for eligibility were the size of the primary carcinoma (≥ 3 cm at greatest diameter at mammography), age younger than 65 years, geographic accessibility, and acceptance of chemotherapy as first treatment. The main characteristics of the women selected and the stages of the primary tumors are shown in Table 1. The only criterion for exclusion was tumor fixation to underlying pectoral fascia and/or muscle or direct tumor extension to chest wall or skin. Patients with central or retroareolar tumors and those presenting with more than one nodule at mammography were included in the study. In all cases, a biopsy was performed before treatment: 163 patients (72.1%) underwent incisional biopsy, 52 (23%) tru-cut, and 11 (4.9%), fine-needle aspiration biopsy. Estrogen and progesterone receptors, ploidy, and cell kinetics data were determined in most cases in addition to histopathologic findings. The complete staging procedure consisted of mammography, chest x-ray, bone scan, and liver ultrasound. One patient was not included in the analysis because she developed liver metastases during chemotherapy and did not undergo surgery. Therefore, the results of 226 patients who underwent surgery were analyzed. The lesion affected the right breast in 101 cases and the left in 125.

Table 1. MAIN PATIENT CHARACTERISTICS (N = 226)

	N (%)
Primary tumor size	
3.0–4.0 cm	141 (62)
4.1–5.0 cm	56 (25)
>5.0 cm	29 (13)
Premenopausal	150 (66)
Postmenopausal	76 (34)
Median age	49 years
Stage (clinical)	
T2N0	48 (21)
T2N1	149 (66)
T3N0	6 (3)
T3N1	23 (10)

Chemotherapy Regimens

Consecutive groups of approximately 33 patients were assigned the following treatment regimens: cyclophosphamide and fluorouracil 600 mg/m^2 of body surface area, and methotrexate 40 mg/m^2 × 3; cyclophosphamide, fluorouracil, and methotrexate × 4; fluorouracil on days 1 and 8 at 500 mg/m^2 and doxorubicin and cyclophosphamide on day 1 at 50 and 500 mg/m^2, respectively, × 3; fluorouracil, doxorubicin, and cyclophosphamide × 4; the previous regimen with epirubicin substituted for doxorubicin at 75 mg/m^2 × 3 (*i.e.*, 3 cycles of therapy); mitoxantrone 10 mg/m^2 and cyclophosphamide and fluorouracil 500 mg/m^2 × 3; and doxorubicin 75 mg/m^2 every 21 days × 3. For 220 patients the treatment was completed as scheduled. If disease progression occurred (6 cases) the patients received immediate mastectomy (4 cases) or were switched to another chemo-

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therapeutic regimen (1 case). In one case, local progression of inflammatory type occurred after the first cycle (fluorouracil, doxorubicin, and cyclophosphamide), but the remaining six cycles of the same combination produced good regression, and the patient was treated with quadrantectomy. Patients with histologically determined axillary involvement or with negative estrogen receptor status received postoperative adjuvant chemotherapy consisting of additional cycles of the same drug combination, to reach a total of six cycles.

Surgical Procedures

Before the start of chemotherapy, the position and size of the tumor mass was marked on the skin surface with a china ink tattoo. If the tumor was sufficiently reduced in size, conservative treatment was planned, consisting of quadrantectomy and axillary dissection followed by radiotherapy.[8] Skin incision was guided by the tattoo marks. During the operatión, the removed tissue was carefully examined for multifocality and to assess residual tumor size and resection margins. If the margins were positive, a re-resection was performed and the new margins evaluated. Axillary dissection was either contiguous with the mammary resection or performed through a separate incision, depending on tumor site. Axillary dissection was always total, and the three levels were marked with metal tags.[9] If total ablation was indicated, a modified radical mastectomy was performed. The minor pectoral muscle with its nervous–vascular tract was preserved in all but one case.

Radiotherapy

Radiotherapy was given to patients undergoing conservative treatment, starting 3 to 6 weeks after the operation. The breast tissue was irradiated with either a linear accelerator or a cobalt-60 unit. The two opposing tangential fields had an extension wide enough to cover the breast and adjacent tissues. The regional axillary, supraclavicular, and internal mammary nodes were not irradiated. The daily dosage, calculated at the breast midplane, was 2 Gy, administered with both opposing fields. With five weekly sessions, the required dose of 50 Gy was reached in 5 weeks. During the 6th week, an overdose was delivered through a field of approximately 12 × 8 cm around the tumor bed with roentgen therapy or with 10-MeV electrons.

Table 2. ASSESSMENT OF LOCAL RESPONSE BY PHYSICAL EXAMINATION AND BY MAMMOGRAPHY

Response	PE (%)	RX (%)
No change	14 (6.2)	29 (12.8)
Regression		
<50%	124 (58.9)	133 (58.9)
>50%	55 (24.3)	28 (12.4)
Complete regression	23 (10.2)	16 (7.1)
Not evaluable	3 (1.3)	12 (5.3)
Progression	7 (3.1)	8 (3.5)

PE = physical examination; RX = mammography.

Table 3. CONSERVATIVE AND ABLATIVE SURGERY ACCORDING TO SIZE OF PRIMARY CARCINOMA AT GROSS SURGICAL EXAMINATION

	≤2.5 cm	>2.5 cm	Total
Quadrantectomy	151 (74.4%)	52 (25.6)	203
Mastectomy	5 (21.8%)	18 (78.2%)	23
Total	156	70	226

Follow-Up

The patients were seen every 4 months. A thorough checkup (bone scan, liver ultrasound and chest x-ray) was performed every year. Mean follow-up was 36 months (range, 13–56 months).

RESULTS

Clinical Evaluation of Response

Table 2 compares the physical and radiologic assessments of the response to chemotherapy. Physical examination indicated 23 cases of total regression, and mammography indicated 16 total regressions. In seven cases, palpation indicated complete regression, but mammography revealed a residual mass, which was confirmed to be malignant by histology. It generally was easier to identify smaller changes in size and mass hardness by palpation, whereas mammography was more sensitive in identifying total regression.

Type of Surgery

Of the 226 patients operated on, 203 (90%) received conservative and 23 (10%) ablative treatment. Of the former, 151 (74.4%) had tumors 2.5 cm or smaller, as determined in the operating room (Table 3). The larger the initial size of the tumor, the less likely the tumor would shrink to a size compatible with conservative treatment

Table 4. SURGICAL TREATMENT ACCORDING TO INITIAL CLINICAL SIZE AND TO CHEMOTHERAPY REGIMEN

	n	Quadrantectomy	Mastectomy
Initial clinical size			
3.0–4.0 cm	141	138	3
4.1–5.0 cm	56	45	11
>5.0 cm	29	20	9
Chemotherapy regimen			
CMF × 3	32	30	2
FAC × 3	30	25	5
CMF × 4	33	30	3
FEC × 3	33	30	3
FNC × 3	33	28	5
FAC × 4	32	28	4
ADM × 3	33	31	2

(Table 4). In most cases where the initial diameter was 5 cm or smaller, conservative treatment proved possible. The proportion of patients who received conservative treatment was the same for all chemotherapy regimens.

Gross Evaluation

At surgical inspection, we could find no lesion in 26 instances: in 8 cases the removed mammary parenchyma showed no gross evidence of cancer (but 2 cases were histologically positive), whereas in 18 cases an ill-defined area was found consisting mainly of fibrous tissue with rare islands of pale pink–grey tissue but no grossly recognizable tumor remnants. Histologic examination revealed the persistence of cancer tissue in all 18 cases.

Histologic Findings

Microscopic examination revealed complete regression in eight cases;, in two of these cases, however, the surgeon had suspected gross remnants. The final histologic examination revealed infiltrating duct carcinomas in 127 cases (56.2%), infiltrating lobular carcinomas in 35 (15.5%), and mixed infiltrating duct carcinomas and infiltrating lobular carcinomas in 17 (7.5%). In 27 cases (12%), the infiltrating duct carcinomas were associated with intraductal carcinoma (ductal carcinoma *in situ*), and in 5 cases (2.2%) only the *in situ* component remained (four ductal carcinomas *in situ* and one lobular carcinoma *in situ*). Other histotypes were diagnosed in seven cases (3.1%): four gelatinous, two metaplastic, and one medullary carcinoma. Of the eight cases (3.5%) with histologically complete regression, six were originally infiltrating duct carcinomas; one, infiltrating lobular carcinoma; and one, medullary carcinoma. Histologic examination revealed multifocality in the primary in 37 patients (16.3%). In 22 (60%) of these cases, mammography showed a carcinoma associated with microcalcifications. Multifocality was observed more frequently in larger tumors, probably because these tumors had not been destroyed uniformly by chemotherapy.

Estrogen Receptors

Of the 126 evaluable patients, 77 had estrogen-receptor positive and 49 estrogen-receptor negative conditions before the start of chemotherapy. Clinical remission (≥ 50%) was observed in 44 (58%) of the estrogen-receptor-positive patients and in 27 (55%) of the estrogen-receptor-negative patients. Limited changes were observed in the prechemotherapy and postchemotherapy percentages of the estrogen-receptor-positive cases: 85% of the cases that were initially estrogen-receptor-positive remained so at final postchemotherapy evaluation, whereas 15% became negative. Among the estrogen-receptor-negative cases, 65% were also negative at postchemotherapy evaluation, whereas 35% became positive.

Nuclear Grading

Nuclear grading was evaluated histologically and cytologically before primary chemotherapy and histologically after chemotherapy. Comparisons between prechemotherapy and postchemotherapy data were impossible in nearly half of the cases either because the material collected through prechemotherapy tru-cut and fine-needle biopsy was inadequate for the grading evaluation or because after chemotherapy the cancer tissue was so damaged that it did not allow for proper analysis. In 107 cases, the comparison was possible: in 79 cases, the grade remained unchanged after the chemotherapeutic treatment. In the remaining 28 cases the grade changed in both directions: in 19 cases there was an upgrading after chemotherapy (mainly from grade 2 to grade 3) and in 9 there was a downgrading.

Axillary Nodes

At histologic examination, axillary node metastases were found in 136 of 226 patients (60%). Although not statistically significant, the percentage of patients with positive nodes varied according to the different chemotherapy regimens. In two subgroups (fluorouracil, doxorubicin, and cyclophosphamide and mitoxantrone, cyclophosphamide, and fluorouracil), axillary metastases were present in fewer than 50% of patients, whereas in the other three subgroups (cyclophosphamide, fluorouracil, and methotrexate; fluorouracil, epirubicin, and

Table 5. LOCAL AND DISTANT RECURRENCES (AS FIRST EVENT) ACCORDING TO LYMPHONODAL STATUS AND TYPE OF CHEMOTHERAPY

Drug Regimen (No. of Cycles)	N	No. With Positive Nodes (%)	Local Recurrences	Distant Metastases	No. With Negative Nodes (%)	Local Recurrences	Distant Metastases
CMF (3)	32	23 (71.9)	3	9	9 (28.1)	2	—
CMF (4)	33	19 (57.6)	2	6	14 (42.4)	—	2
FAC (3)	30	19 (63.3)	1	6	11 (36.7)	1	—
FAC (4)	32	11 (34.3)	1	6	21 (65.6)	1	2
FEC (3)	33	24 (72.7)	1	10	9 (27.3)	—	2
FNC (3)	33	15 (45.5)	—	4	18 (54.5)	—	3
ADM (3)	33	25 (75.8)	4	4	8 (24.2)	1	1
Total	226	136 (60.1)	12	45	90 (39.9)	5	10

cyclophosphamide; and doxorubicin), the proportion was 65% or more.

Local and Distant Recurrences

Local recurrences were more frequent among node-positive (12 of 136 patients) than among node-negative patients (5 of 90 patients) (Table 5). Local recurrences were also more frequent among patients who underwent mastectomy (5/23 [22%]) than among patients treated with quadrantectomy (12/203, [5%]). The 12 cases of recurrence in the quadrantectomy group arose after a mean of 28 months: 7 were subsequently treated with local excision and 3 were treated with total mastectomy. Two patients who had developed a small local recurrence were subsequently found at hospitalization to have an isolated distant metastasis and were then treated with chemotherapy. In the mastectomy group, local recurrences were evident after a mean of 15 months and were treated by surgery and radiotherapy. Metastases occurred in 10 of the 23 mastectomy patients (44%) and in 56 of the 203 quadrantectomy patients (27%). Metastases were three times more common among patients with positive axillary nodes (45/136 [33%]) than among patients with negative axillary nodes (10/90 [11%]). Table 6 shows the site of distant metastases as first event according to preoperative treatment. Patients who underwent mastectomy had, on average, larger tumor size at initial diagnosis (mean, 5.5 cm) than the conservative group (mean, 4.0 cm) and more often had positive axillary nodes (19/23) than patients who were treated with quadrantectomy (117/203).

DISCUSSION

Reasons for the wider use of conservative surgery in breast carcinoma are the effectiveness of local control and the increasing demand for results that are more acceptable cosmetically. An alternative to conservative treatment is breast reconstruction after mastectomy,[10,11] sometimes leading to unsatisfactory results. Data from several clinical trials have shown that careful conservative surgery is associated with a low but not negligible incidence of local recurrence, thus the development of treatment procedures able to reduce local recurrences as well as expand the indication for conservative treatment is a priority.

Over the last few years, there have been a limited number of studies on preoperative chemotherapy in operable breast cancer.[4–6,12,13] All of these studies reported a high rate of response of the primary carcinoma, an increased percentage of conservative procedures, and a satisfyingly low rate of side effects with certain drug regimens, but none of them have devoted much attention to the surgical problems posed by the preoperative chemotherapy. A large randomized clinical trial by the National Surgical Adjuvant Breast and Bowel Project is in progress to determine whether primary chemotherapy prolongs survival more effectively than the same therapy given after surgery. If primary chemotherapy is more effective, then we must confront the surgical problems it brings about.

The results of our study show that preoperative chemotherapy significantly reduces primary tumor size in a high percentage of cases, often permitting conservative surgery with low risk of local recurrence in patients who would otherwise undergo mastectomy. Quadrantectomy was usually possible when the initial diameter did not exceed 5 cm, but this objective was less often achieved when the tumor was larger. The chemotherapeutic regimen chosen did not influence the extent of regression as measured in the operating room.

Accurate estimation of the tumor size after preoperative chemotherapy is crucial for deciding the type and extent of operation to be performed. Measurement by

Table 6. DISTANT METASTASES AS FIRST EVENT ACCORDING TO CHEMOTHERAPY REGIMENS

Group (n)	Mean Follow-up (Mon)	Bone	Lung	Liver	Distant Lymph.	Skin	Brain	Mult. Site	No. Relapses
CMF (65)	45	8	1	—	4	—	3	1	17
FAC (62)	39	4	2	1	2	1	1	3	14
FEC (33)	29	4	1	1	2	1	1	2	12
FNC (33)	33	1	2	3	1	—	—	—	7
ADM (33)	26	—	1	—	2	1	—	1	5
Total (226)		17	7	5	11	3	5	7	55

physical examination is important but may be misleading, because the tumor may become soft to palpation due to destruction of a portion of the tumor mass. In addition, this process may be incomplete and scattered islands of cancer tissue may remain in the original tumor area. For this reason it is essential that the involved area, as determined and defined by the tattoo marks on the skin, be totally removed. To obtain this objective, the surgeon can use a good preoperative mammogram, as compared with a prechemotherapy mammogram, to observe the extent of the regression. This process is superior to physical examination and helps the surgeon decide the extent of the resection.

The presence of microcalcifications may also be useful in the decision process. In our study, microcalcifications were present in 94 cases. When regression after chemotherapy was marked, the microcalcifications did not disappear, but instead tended to shrink and aggregate so that the total area they occupied was reduced. Such changes represent an important index of the regression process and an excellent guide for the operation. Moreover, intraoperative x-ray examination of the specimen may confirm the completeness of tumor mass removal. When microcalcifications were dispersed in various parts of the breast, primary chemotherapy was not proposed.

When the clinical and mammographic evaluation showed that the tumor was reduced to a size compatible with breast conservation, then surgery consisted of an initial probing quadrantectomy. The surgical specimen was then examined carefully, and the residual tumor area was identified and measured, if possible. Frozen-section examinations were often necessary to obtain a clear picture of the extent of the regression. The surrounding tissues were also examined carefully to exclude the presence of residual cancer foci. In this way, only quadrantectomies that conformed to the criteria of oncologic radicality were performed. The tattoo previously marked on the skin was essential for guiding the excision in such cases. Whenever there were strong doubts as to the completeness of tumor tissue removal, a modified radical mastectomy was performed. Of 23 mastectomies performed, 9 involved primaries of less than 3 cm in diameter, but gross surgical examination revealed cancer foci in the surrounding tissue. Conversely, 21 of the 203 (10.3%) conservative treatments were performed on tumors 3 cm or larger; in such cases, the favorable ratio between tumor size and breast volume ensured a good cosmetic result while fulfilling our radicality criteria.

The skin incision and surgical technique were usually the same as are used in traditional quadrantectomy. When the tumor was located in the outer-upper breast quadrant, we preferred a single incision through the breast and axilla rather than the two separate incisions used for tumors in other quadrants. In some cases in which the tumor was near the areolar region, we made a curved incision to spare the areola and nipple. After resection, the breast was painstakingly reconstructed and the cosmetic outcome was usually satisfactory.

A full axillary clearance was always performed and the three node levels identified and marked with metal disks. In 82.6% of mastectomies, lymph node involvement was proved, compared with 57.6% in quadrantectomies.

Will preoperative chemotherapy reduce the risk of local recurrences after breast conservative treatments? Although it is too early to tell, our preliminary data suggest that it will. With a mean follow-up of 36 months, we have observed 12 local recurrences in 203 quadrantectomies (5.9%). Considering that in all of these cases the original tumors were large (3–6 cm in diameter), we believe that this is an acceptable rate of recurrence. Conversely, we observed a high rate of local recurrences in our patients who underwent mastectomy (5/23 [21.7%]). This shows that in this subgroup carcinoma was resistant to chemotherapy and also was very aggressive, making its management problematic. The high risk of local recurrence indicates that additional local treatments (such as chest wall postoperative radiotherapy) should be considered in these chemotherapy-resistant patients. In the

current study, resistance to chemotherapy served as a marker of tumor aggressiveness.

CONCLUSIONS AND RECOMMENDATIONS

Conservative breast surgery followed by radiotherapy is a valid treatment for large tumors if three cycles of preoperative chemotherapy reduce the tumor size to less than 3 cm. We emphasize, however, that the final decision on the type of surgery to perform should be made in the operating room after careful evaluation of tumor regression, examination of the resection margins, assessment of tumor size in relation to breast size, and assessment of microcalcifications.

It is evident, therefore, that the surgeon plays a central role in choosing the type of operation to be performed. On the basis of our experience, we make the following recommendations. First, the extent of tumor regression must be evaluated carefully by frequent physical examination and measurements and strict mammographic monitoring. For very large tumors, it is unlikely that reduction will be sufficient to permit conservative treatment. Second, in deciding the type of operation, the surgeon should consider not only the size of the tumor, but also the volume of the breast and the likely cosmetic outcome. Third, at the operating table, the surgeon must be able to rely on the cooperation of an experienced pathologist for a careful examination of the specimen, with multiple frozen-section biopsies if necessary, to quantify the extent of tumor regression. Fourth, microcalcifications should always be considered carefully, because they are unlikely to disappear after chemotherapy, and the excised specimen must contain all of them. A specimen x-ray taken in the operating room must confirm that all microcalcifications have been removed. Fifth, use of tattoo marks on the skin is mandatory when the tumor is no longer palpable. Sixth, if breast remodeling is performed hastily or without sufficient care, the result will abrogate the raison d'être of the whole approach.

Finally, a word of caution: Although full-dose chemotherapy produced various degrees of tumor regression in 90% of our patients, in the remaining patients the tumor did not regress or even progressed. In the rare cases of total resistance to chemotherapy, the condition must be discovered as early as possible so that an immediate mastectomy can be performed.

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