PAPER

Impact of Chemotherapy on Postoperative Complications After Mastectomy and Immediate Breast Reconstruction

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Objectives: To determine the impact of chemotherapy and the timing of chemotherapy on postoperative outcomes after mastectomy and immediate breast reconstruction.

Design: Retrospective review.

Setting: University tertiary care institution.

Patients: One hundred sixty-three consecutive patients undergoing mastectomy and immediate breast reconstruction.

Intervention: Systemic chemotherapy for breast cancer.

Main Outcome Measures: Postoperative complications following mastectomy and immediate breast reconstruction.

Results: One hundred sixty-three patients underwent mastectomy and immediate breast reconstruction during the study period, with a mean postoperative follow-up of 19.2 months. Sixty-six percent of the patients had expander/implant reconstruction, while 33% underwent autologous reconstruction. Fifty-seven patients received neoadjuvant chemotherapy and 41 received postoperative chemotherapy. Eighteen patients (44%) in the adjuvant chemotherapy cohort developed postoperative infections, compared with 13 patients (23%) in the neoadjuvant chemotherapy group and 16 patients (25%) who did not receive any chemotherapy ($P=.05$). Overall, 31% of patients had a complication requiring an unplanned return to the operating room; this rate did not differ between groups ($P=.79$). Of patients who underwent expander/implant reconstruction, 8 women (26%) in the neoadjuvant chemotherapy cohort, 7 women (22%) in the adjuvant chemotherapy cohort, and 8 women (18%) without chemotherapy required expander or implant removal ($P=.70$).

Conclusions: Although the highest rate of surgical site infections was in the adjuvant chemotherapy group, there were no differences between groups with respect to unplanned return to the operating room, expander loss, and donor-site complications. Neither the inclusion of chemotherapy nor the timing of its administration significantly affected the complication rates after mastectomy and immediate breast reconstruction in this population.

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Recent studies[1,2] and national registry data have demonstrated that the number of women undergoing mastectomy for breast cancer or as a prophylactic intervention in women with genetic predisposition to breast cancer has been increasing in the past decade.[3] With this rise in the mastectomy rate, there has been a resultant increase in the number of patients who choose to undergo postmastectomy reconstruction.

See Invited Critique at end of article

Historically, women have undergone mastectomy and subsequent chemotherapy and/or radiation therapy, followed by an additional procedure for breast reconstruction once adjuvant treatment is completed. However, many centers, including our own, now offer women the option of immediate breast reconstruction performed at the time of initial mastectomy. Multiple studies have demonstrated the benefits of immediate reconstruction, which include improved psychological and aesthetic outcomes.[4] Immediate reconstruction has been shown to be safe from both the oncologic and surgical perspectives,[5] without any evidence of increased complications when compared with delayed reconstruction.[6] Specific examination of any adverse effects from systemic chemotherapy on immediate breast reconstruction outcomes has not been well evaluated previously. To determine whether the timing of chemotherapy or the inclusion of chemotherapy would affect postoperative complication rates after mastectomy and

Table 1. Patient and Tumor Characteristics

Characteristic	Chemotherapy: None (n=65)	Chemotherapy: Neoadjuvant (n=57)	Chemotherapy: Adjuvant (n=41)	*P* Value
Patient characteristics				
Age at diagnosis, mean (range), y	49.8 (25.1-70.2)	46.4 (28.1-71.8)	48.2 (26.1-72.5)	.18
BMI, mean (range)	25.1 (17.3-43.8)	25.1 (18.6-38.1)	25.4 (18.1-35.9)	.94
History of radiation therapy, No. (%)	8 (12)	4 (7)	10 (24)	.05
History of smoking, No. (%)[a]	14 (22)	18 (32)	11 (27)	.63
Tumor histology, No. (%)[b]				<.001
No cancer	5 (8)	1 (2)	0	
In situ	25 (40)	3 (5)	2 (5)	
Ductal invasive	28 (44)	40 (70)	35 (88)	
Lobular invasive	5 (8)	13 (23)	3 (7)	
Tumor stage, No. (%)[c]	56	54	40	<.001
0	21 (38)	1 (2)	0	
I	27 (48)	8 (15)	13 (33)	
II	6 (11)	20 (37)	14 (35)	
III	2 (3)	25 (46)	13 (33)	
IV	0	0	0	

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] History of smoking was unknown in 11 patients in the no chemotherapy group and 4 patients in the neoadjuvant chemotherapy group; percentages represent the proportion of patients reporting history of smoking excluding patients with unknown smoking status.

[b] Two patients in the no chemotherapy group and 1 in the adjuvant chemotherapy group had rare tumor subtypes, including angiosarcoma, small cell cancer, and phyllodes tumor, which are not included here.

[c] Tumors were not staged in 9 patients in the no chemotherapy group, 3 patients in the neoadjuvant chemotherapy group, and 1 patient in the adjuvant chemotherapy group as they were recurrent tumors or were in patients undergoing prophylactic mastectomy.

immediate breast reconstruction, we performed a prospectively collected outcomes study of women who underwent this procedure at our institution.

METHODS

All women who underwent mastectomy and immediate reconstruction at the Carol Franc Buck Breast Care Center, University of California, San Francisco, between January 1, 2005, and December 31, 2007, were eligible for study inclusion. With the approval of our institutional review board, patient characteristics and treatment details were retrospectively collected from medical treatment records. Additionally, throughout the data collection period, weekly meetings were held with research coordinators and breast and plastic surgeons to ensure that data on postoperative complications had been comprehensively and prospectively captured. An interdisciplinary group of practitioners including breast surgeons, plastic surgeons, and surgical nurse practitioners evaluated patients for complications. A team-based approach was used for determining management of complications, including the decision to start oral or intravenous antibiotic therapy.

Surgical outcomes recorded in our prospectively maintained database included wound complications, unplanned return to the operating room, donor-site complications in patients undergoing autologous reconstruction, and cancer outcomes. Wound complications included skin flap necrosis, flap loss, nipple-areolar complex loss (for patients undergoing nipple-sparing procedures), infections, or tissue expander/implant loss. Skin flap or nipple necrosis was defined as full-thickness skin loss. Infectious complications included both those requiring oral antibiotics and treatment in the outpatient setting as well as those requiring hospital admission for intravenous antibiotic therapy. Reasons for unplanned return to the operating room included hematoma evacuation, irrigation and débridement for wound infections or necrosis, tissue expander or implant removal in cases of severe infection, and repair of incisional hernias or rectus diastasis in patients who had undergone transverse rectus abdominis muscle flap reconstruction. If patients developed more than 1 complication, they were included in the analysis for each of the relevant complications, including return to the operating room. Given the prospective nature of the data collection, all postoperative complications that occurred while the patient was continuing to be followed up by a breast or plastic surgeon were included in the analysis.

Patients were categorized based on whether they had received chemotherapy and on the timing of their chemotherapy. Neoadjuvant chemotherapy was defined as chemotherapy given prior to mastectomy and immediate reconstruction, while adjuvant chemotherapy included all chemotherapy given after mastectomy. Categories were thus based on an intent-to-treat analysis, with all patients who received postoperative chemotherapy placed in the adjuvant group irrespective of the timing of any postoperative complication with initiation of chemotherapy.

All statistical analyses were performed using the Stata version 11.0 software package (StataCorp LP, College Station, Texas). Continuous variables were compared between the 2 groups using a 1-way analysis of variance analysis, while dichotomous variables were analyzed between groups using Fisher exact χ^2 test. For all statistical analyses, significance was determined at the $P \leq .05$ level; all comparisons were 2-tailed.

RESULTS

During the study period, 163 patients underwent mastectomy and immediate breast reconstruction. Fifty-seven patients received neoadjuvant chemotherapy and 41 received postoperative chemotherapy, while the rest (65 patients) did not receive any systemic therapy. Patient and tumor characteristics are described in **Table 1**. Patients ranged in age from 25 to 72 years (mean, 48.2 years) at the time of mastectomy; this did not differ significantly between groups ($P = .18$). Overall, almost 30%

Table 2. Surgical Procedures Performed in the Cohort

Procedure	Chemotherapy: None (n=65)	Chemotherapy: Neoadjuvant (n=57)	Chemotherapy: Adjuvant (n=41)	*P* Value
Type of mastectomy, No. (%)				.78
Skin sparing	44 (68)	34 (60)	25 (61)	
Total skin sparing with nipple-areolar preservation	20 (31)	22 (39)	16 (39)	
Simple	1 (1)	1 (1)	0	
Type of reconstruction, No. (%)				.002
Expander	35 (54)	29 (51)	32 (78)	
Permanent implant	10 (15)	2 (4)	0	
Pedicle transverse rectus abdominis muscle	15 (23)	25 (44)	8 (20)	
Deep inferior epigastric perforator flap	4 (6)	1 (1)	1 (2)	
Other[a]	1 (2)	0	0	
Bilateral mastectomy, No. (%)	24 (37)	24 (42)	20 (49)	.44
Therapeutic	5 (8)	3 (5)	2 (5)	
Prophylactic				
Bilateral	3 (5)	1 (2)	0	
Contralateral	16 (25)	20 (35)	18 (44)	

[a] Includes 1 free transverse rectus abdominis muscle flap reconstruction.

of patients reported a history of tobacco use, although no patient in the cohort reported smoking at the time of surgery. There was no difference in prevalence of smoking history between groups ($P=.63$). The average body mass index was also similar between the 3 groups ($P=.94$). Only 2 patients in the entire cohort, one in the adjuvant chemotherapy group and one who did not receive chemotherapy, had diabetes mellitus. Thirteen percent of patients had a history of radiation therapy prior to mastectomy, with a higher percentage in the adjuvant chemotherapy group. As expected, there were greater numbers of node-positive and locally advanced cancers among the adjuvant and neoadjuvant chemotherapy groups compared with the patients who were not treated with chemotherapy. Although there were proportionally fewer patients with stage I disease in the neoadjuvant chemotherapy group than in the adjuvant chemotherapy group, this difference was not significant ($P=.14$).

All patients routinely received prophylactic intravenous antibiotics prior to skin incision, typically 1 g of cefazolin, unless patients reported a penicillin allergy, in which case 600 mg of clindamycin hydrochloride was given. Most patients in both the neoadjuvant and adjuvant chemotherapy groups received a standard chemotherapeutic regimen consisting of doxorubicin hydrochloride/cyclophosphamide followed by paclitaxel, including 91% of patients in the neoadjuvant chemotherapy group and 67% in the adjuvant chemotherapy group. Twenty-one percent of patients in the neoadjuvant chemotherapy group and 17% of patients in the adjuvant chemotherapy group additionally received subsequent trastuzumab therapy. Adjuvant chemotherapy was initiated 4 to 6 weeks after mastectomy and immediate reconstruction to allow adequate time for wound healing.

Most patients underwent mastectomy for known breast cancer, with a significant percentage undergoing simultaneous prophylactic contralateral mastectomy (**Table 2**). Surgical techniques included total skin-sparing mastectomy with nipple-areolar preservation, skin-sparing mastectomy, and simple mastectomy. Sixty-six percent of patients had immediate reconstruction with tissue expander placement and subsequent implant exchange or initial implant placement, while the rest had autologous reconstruction. Type of mastectomy did not differ between groups ($P=.78$). However, there was significantly greater use of transverse rectus abdominis muscle reconstruction among patients who had neoadjuvant chemotherapy, with comparable rates of transverse rectus abdominis muscle reconstruction between adjuvant and no chemotherapy groups.

The most common postoperative complications included postoperative infections, unplanned return to the operating room, and tissue expander or implant loss (**Table 3**). Almost a third of patients in the cohort (31%) had an unplanned return to the operating room. The most frequent indication for intraoperative intervention was tissue expander/implant removal or unplanned implant exchange, with 21% of patients who underwent expander/implant reconstruction having loss of expander or implant. The rate of implant loss did not differ significantly between groups ($P=.70$). Fifty-nine percent of patients undergoing neoadjuvant chemotherapy had postoperative radiation therapy, compared with 36% of patients treated with adjuvant chemotherapy ($P=.05$). Despite this difference, the neoadjuvant chemotherapy group did not have a significantly greater implant loss rate. Other indications for unplanned surgical intervention included ventral hernia repair in patients who had undergone prior transverse rectus abdominis muscle flap reconstruction (3 patients in the neoadjuvant chemotherapy cohort, 1 in the adjuvant chemotherapy cohort, and 4 in the group who received no chemotherapy), repair of a small-bowel perforation (1 patient), and lipectomy and local tissue rearrangement in 1 patient with flap loss due to venous thromboembolism. Specific analysis of the patients in the adjuvant chemotherapy group who developed major complications revealed that 9 patients developed complications prior to receiving their postoperative chemotherapy, likely delaying the initiation of adjuvant therapy. All 9 of these pa-

Table 3. Postoperative Complications

Complication	Chemotherapy			*P* Value
	None (n=65)	Neoadjuvant (n=57)	Adjuvant (n=41)	
Overall, No. (%)				
Infection	16 (25)	13 (23)	18 (44)	.05
Oral antibiotic regimen	3 (5)	2 (4)	7 (17)	
Intravenous antibiotic regimen	13 (20)	11 (19)	11 (27)	
Unplanned return to operating room	18 (28)	19 (33)	13 (32)	.79
Skin necrosis, minor and major	6 (9)	9 (16)	6 (15)	.55
Hematoma	1 (2)	5 (9)	0	.04
Implant/expander reconstruction–specific, No. (%)	45	31	32	
Implant/expander loss	8 (18)	8 (26)	7 (22)	.70
Autologous reconstruction–specific, No. (%)	20	26	9	
Ventral hernia or laxity requiring repair	4 (20)	3 (12)	1 (11)	.87
Donor-site seroma	2 (10)	0	0	.27
Flap loss	0	1 (4)	0	.57

tients had surgical site infections requiring oral or intravenous antibiotic therapy; 6 of these patients had an unplanned return to the operating room secondary to their infectious complications, 5 of whom had removal of their tissue expanders or permanent implants.

At a mean postoperative follow-up of 19.2 months (range, 8-35 months), 3 patients had locoregional recurrence and 5 had developed distant metastases.

COMMENT

Many of the studies examining complications after mastectomy and immediate reconstruction have focused on the role of radiation therapy, which has been associated with a number of postoperative complications, particularly in patients who have undergone expander/implant reconstruction.[7,8] Much of the discussion regarding strategies for minimizing complications after expander/implant reconstruction has been driven by the impact of radiation therapy and has led to techniques such as delayed-immediate reconstruction[9] or approaches using a combination of autologous and prosthetic reconstruction.[10] However, a similar assessment of the role of chemotherapy on postreconstructive outcomes after immediate breast reconstruction has been limited in the literature.

With the widespread use of modern chemotherapy regimens in patients with breast cancer, particularly dose-dense regimens, the risk of neutropenia is significant. Concern for the development of infections in patients who are receiving adjuvant chemotherapy is heightened in patients who have recently undergone placement of a prosthetic implant as part of their immediate breast reconstruction. Interestingly, infectious complications did not appear to be more common in our analysis in patients receiving neoadjuvant chemotherapy as compared with those who received adjuvant chemotherapy or those who did not require any systemic therapy; in fact, patients in the adjuvant treatment group had the highest rate of infectious complications (44%). Moreover, we found that a number of patients who underwent adjuvant chemotherapy as part of cancer treatment developed postoperative complications prior to the initiation of chemotherapy. For these patients, a postoperative complication was clearly not attributable to chemotherapy but rather to other patient or surgical factors. Nevertheless, the high infection rate among patients for whom the intent was to treat with adjuvant chemotherapy is clinically important and of concern, as systemic chemotherapy was likely delayed by surgical complications in 22% of patients in this group.

Multiple experimental studies performed in animals have shown decreased wound strength after the administration of preoperative or postoperative chemotherapy, particularly when chemotherapy is given in the early postoperative period.[11,12] However, these findings have not been duplicated in clinical trials, with several studies across surgical specialties showing no increased risk of wound-related complications in patients who had received neoadjuvant or adjuvant systemic therapy as compared with patients who had not received chemotherapy, supporting the findings of the current study.[13,14] Studies analyzing the impact of chemotherapy on wound complications specifically in patients who have undergone mastectomy and immediate reconstruction have shown no increased incidence in surgical site complications among patients who received postoperative chemotherapy.[15-17] Similar results have been demonstrated in patients who have undergone neoadjuvant chemotherapy.[18] Postreconstructive wound complications in these series, including infection, skin necrosis, and seroma, ranged from 15% to 30%, although infectious complications did not uniformly include both infections requiring oral antibiotics and those requiring intravenous antibiotics. It is important to note that the complications data in these studies were retrospectively collected as compared with the prospectively collected outcomes database used in our study. This may have led to an underestimation of complications, particularly those occurring later in the postoperative course. We found no associated risk of wound-related complications or increased infections in patients who received neoadjuvant chemotherapy. Importantly, no patients in our cohort were treated with systemic bevacizumab, which has been shown to significantly impair normal wound healing.

Others have reported their experience with reconstruction in the setting of chemotherapy. McCarthy et al[19] found no increased incidence of complications in women who had undergone neoadjuvant or adjuvant chemotherapy compared with those who did not receive chemotherapy. Mitchem et al[20] examined a series of 30 women who had undergone skin-sparing mastectomy and immediate breast reconstruction with tissue expander or permanent implant placement and both neoadjuvant and adjuvant chemotherapy. They reported an overall 38% failure rate after expander/implant reconstruction as a result of infection, expander extrusion, or skin flap necrosis. Woerdeman et al[21,22] found a 14% to 20% explantation rate in their series of patients undergoing skin-sparing mastectomy and immediate expander or permanent implant reconstruction, which is comparable to the 21% rate of expander/implant loss in our cohort.

Given the impact of chemotherapy on wound healing demonstrated in animal models, it could be assumed that the administration of neoadjuvant chemotherapy followed by the placement of a prosthetic tissue expander or the potential pressure on skin flaps from the volume of an autologous reconstruction could increase the incidence of postoperative surgical site complications. Despite these concerns, our results did not reveal any significant difference in noninfectious postoperative complications in patients who received systemic therapy as compared with those who did not. Furthermore, the timing of administration of chemotherapy with regard to mastectomy and immediate breast reconstruction was not found to play a significant role in surgical outcomes.

Based on the results of our study, we conclude that for women who are planning to undergo mastectomy and immediate reconstruction, neoadjuvant chemotherapy is a safe option that does not appear to increase the rate of postoperative complications. Although the number of patients in each of the study groups is relatively small, the data support considering the use of neoadjuvant chemotherapy in patients who require systemic therapy as part of their breast cancer treatment. In fact, the use of neoadjuvant chemotherapy in this setting may prevent delay to systemic chemotherapy in a notable proportion of patients who develop postoperative complications.

Although systemic chemotherapy has been thought to increase wound-related complications, our study demonstrates that risk of noninfectious postoperative complications is not increased after mastectomy and immediate breast reconstruction among women who receive chemotherapy. Additionally, the timing of chemotherapy in relation to mastectomy did not have a significant impact on surgical outcomes. However, the wound infection rate was significantly higher in patients who had received adjuvant chemotherapy and in some cases resulted in delay of chemotherapy. These results suggest a possible benefit for preoperative administration of chemotherapy in those patients who require chemotherapy, even in women who will undergo mastectomy, and they support the use of immediate reconstruction in this patient population.

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INVITED CRITIQUE

Chemotherapy and Breast Reconstruction

This study examines the impact of chemotherapy on complications after 163 consecutive mastectomies with immediate reconstruction. The authors examine the infection rate, reoperative rate, prosthesis loss, skin necrosis, hematoma, donor-site complications, and flap loss. The overall complication rate of more than 30% is high for an elective procedure, and many of these complications are very difficult to determine retrospectively and may be underestimated. Some, however, are not, such as reoperation or prosthesis loss. The authors report a statistically significant increased infection rate among patients who received postoperative adjuvant chemotherapy but not neoadjuvant chemotherapy.

Intuitively, we would expect that chemotherapy given before surgery might increase the infection rate more than or at least as much as postoperative chemotherapy because patients are more likely to be immunosuppressed at the time of operation. Many studies, however, have shown that not to be the case. Postoperative chemotherapy is given about 1 month after operation when incisions are healing well. Why should chemotherapy increase infections at this time when incisions are well along in the healing process? Starting chemotherapy too early postoperatively could be more of a problem. In fact, 9 of the 18 infections occurred prior to the institution of postoperative chemotherapy, suggesting that the drugs were not to blame. Could there be other factors such as ischemia or necrosis of the incision? Chemotherapy should not be started if there are already minor wound problems.

It would be helpful to know whether prosthesis loss and reoperation were due to technical factors such as dehiscence, infection, necrosis with prosthesis extrusion, or even in part to patient dissatisfaction, capsular contraction, or displacement of the prosthesis. Other factors in addition to chemotherapy, such as age, body mass index, smoking, and diabetes, are well known to affect complication rates for reconstructive surgery. These factors are not reported.

While the complication rate seems high in this study, it is very similar to results reported by others. This article is timely and important because it brings to the attention of general surgeons the important reminder that reconstructive surgery after mastectomy for cancer is a complex, ongoing process that involves multiple operations, technical difficulties, and interactions with influences beyond our control: chemotherapy, radiation, aesthetics, patient expectations, and perceptions. All of these are likely to affect the final outcome and complication rate, and all treating surgeons must be aware of these factors. Plastic and general surgeons, however, must do what they can to decrease the rate of serious complications in this physically and emotionally vulnerable group.

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