

## Immediate Microvascular Breast Reconstruction After Neoadjuvant Chemotherapy: Complication Rates and Effect on Start of Adjuvant Treatment

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### ABSTRACT

**Background.** The effect of neoadjuvant chemotherapy on immediate microvascular breast reconstruction is of concern because any complication might delay adjuvant treatment. We sought to determine whether the complication rate is increased and whether the interval between surgery and subsequent treatment is delayed compared with patients without neoadjuvant chemotherapy.

**Methods.** Complication rates and interval from surgery until adjuvant treatment of patients with mastectomy for locally advanced breast cancer followed by immediate microvascular breast reconstruction (deep inferior epigastric perforator (DIEP) flap, transverse rectus abdominis musculocutaneous (TRAM) flap, superior gluteal artery perforator (SGAP) flap, transverse musculocutaneous gracilis (TMG) flap, or superficial inferior epigastric artery (SIEA) flap) after neoadjuvant chemotherapy were compared with those of patients who underwent immediate breast reconstruction without neoadjuvant chemotherapy.

**Results.** Forty-seven patients with locally advanced breast cancers who underwent neoadjuvant chemotherapy before mastectomy and immediate microvascular reconstruction and 52 patients without neoadjuvant chemotherapy were identified. 36% of patients with neoadjuvant chemotherapy had one or more complications compared with 29% of patients without previous chemotherapy, but this difference was not statistically significant. The occurrence of complications in patients with neoadjuvant chemotherapy did

not result in a delayed start of adjuvant treatment compared with patients without complications after neoadjuvant chemotherapy (43.6 vs. 44.6 days).

**Conclusions.** Immediate microvascular breast reconstruction after neoadjuvant chemotherapy does not result in an increased complication rate or delay the start of adjuvant treatment even if complications occur and therefore can be performed safely in patients with locally advanced breast cancer.

Breast reconstruction plays a significant role in the management of breast cancer. Immediate reconstruction after mastectomy for patients with early-stage breast cancer is safe and can achieve an acceptable oncologic outcome, as well as a high rate of patient satisfaction.<sup>1</sup>

For patients with locally advanced breast carcinoma at the time of presentation, neoadjuvant chemotherapy has been demonstrated to reduce tumor size, thus allowing preservation of the skin-envelope of the breast, which facilitates immediate reconstruction of the breast mound with autologous tissue.<sup>2,3</sup> Concerns exist about immediate microvascular breast reconstruction after neoadjuvant chemotherapy because this sequence is offered to patients with locally advanced tumors, for whom start of adjuvant treatment without delays is crucial. Delays in initiating chemotherapy or radiotherapy are associated with significant increases in relapse risk and adverse survival outcomes if the delay from definitive surgery exceeds 12 weeks.<sup>4,5</sup> The effect of preoperative chemotherapy on surgical outcome is of particular concern in this patient group because any wound-healing complications might delay postoperative resumption of adjuvant treatment and may have a negative impact on patient prognosis. However, many patients ask for immediate breast reconstruction and regard

it as one of the few consolations in an otherwise devastating life event. Because of the many benefits and excellent results of immediate reconstruction in patients with early disease, it also is offered to patients with locally advanced breast cancer at Guy's and St. Thomas' hospital in London.

In this study, we sought to determine whether immediate microvascular breast reconstruction after neoadjuvant chemotherapy and skin-sparing mastectomy for large operable breast cancer affects the complication rate and if the interval between surgery and adjuvant treatment is delayed whether complications occur.

## METHODS

All patients treated with mastectomy and immediate microvascular breast reconstruction after neoadjuvant chemotherapy for locally advanced breast cancer at Guy's and St. Thomas' Hospital, London, from February 1, 2007 to August 2009 were identified using a prospectively maintained database. The control group consisted of patients who underwent immediate breast reconstruction without neoadjuvant chemotherapy between October 2007 and February 2009 at the same institution. Patients were evaluated for the method of free flap reconstruction (deep inferior epigastric perforator (DIEP) flap, transverse rectus abdominis musculocutaneous (TRAM) flap, superior gluteal artery perforator (SGAP) flap, transverse musculocutaneous gracilis (TMG) flap, or superficial inferior epigastric artery (SIEA) flap), comorbidities, smoking history, preoperative chemotherapeutic regimen, interval from last dose of chemotherapy to surgery and immediate reconstruction, type of complications, and, in the patient group with neoadjuvant chemotherapy, the interval to starting adjuvant therapy after surgery. Untoward events occurring within 30 days of the operation were considered complications that might delay adjuvant therapy. Complications that required operative intervention (total or partial flap loss, hematoma, significant infection, and wound healing problems) were considered

major complications. All other complications (minor infections, small area of wound breakdown, seromas) that did not require a return to surgery were considered minor complications.

Univariate analysis using Fisher's exact test was performed to identify significant differences in complications between patients with and without neoadjuvant chemotherapy. The interval between surgery and start of any adjuvant therapy was compared between patients who experienced complications and those who had an uneventful reconstruction after neoadjuvant chemotherapy using both nonparametric (Mann-Whitney *U*) and parametric (*t* test for unpaired data) statistical tests to omit a type 2 error (i.e., missing a really existing significant difference while applying a statistical test that is too robust).  $P < 0.05$  was considered significant.

## RESULTS

Patient demographics of both groups are summarized in Table 1. Forty-seven patients with locally advanced breast cancers who underwent neoadjuvant chemotherapy before skin-sparing mastectomy and immediate microvascular reconstruction and 52 patients without neoadjuvant chemotherapy who underwent 58 immediate breast reconstructions were identified (control group). The control group corresponded in regards of age, body mass index (BMI), comorbidities, and choice of free flap with the patient group who had undergone primary chemotherapy. Of the patients with neoadjuvant chemotherapy, 45 were operated unilaterally and two patients had bilateral reconstructions. The median age was 47 (range, 31–68) years. Twenty-one patients (45%) were overweight, and eight patients (17%) were obese. Six patients had a smoking history; however, none of them were active smokers at the time of surgery (i.e., smoking stopped more than 3 weeks before surgery). Five patients had noninsulin-dependent diabetes mellitus. All patients finished one of two different neoadjuvant che-

**TABLE 1** Patient demographics

	Neoadjuvant chemotherapy	No neoadjuvant chemotherapy
Total no. of patients	47 (100%)	52 (100%)
Total no. of reconstructions	49	58
Median age, year (range)	47 (31–68)	49 (35–63)
Normal weight (BMI 18–25 kg/m <sup>2</sup> )	18 (38%)	16 (20%)
Overweight (BMI 25.1–30 kg/m <sup>2</sup> )	21 (45%)	21 (40%)
Obese (BMI >30.1 kg/m <sup>2</sup> )	8 (17%)	15 (30%)
<i>Comorbidities</i>		
Coronary artery disease	1 (2%)	3 (6%)
Diabetes mellitus	5 (11%)	1 (2%)
Active smokers	6 (13%)	3 (6%)

BMI body mass index

**TABLE 2** Tumor characteristics

	Neoadjuvant chemotherapy	No neoadjuvant chemotherapy
Total no. of patients	47 (100%)	52 (100%)
<i>Cancer type</i>		
DCIS/LCIS	–	9 (17%)
IDC	37 (79%)	38 (73%)
ILC	7 (15%)	5 (5%)
IBC	3 (6%)	–
<i>Histological grade</i>		
1	–	14 (27%)
2	23 (49%)	38 (73%)
3	25 (50%)	–
<i>Neoadjuvant chemotherapy</i>		
4 × AC → 4 × T	35 (75%)	NA
6 × FEC	12 (25.5%)	NA
<i>Interval between neoadjuvant chemotherapy and surgery</i>		
4–6 weeks (25–42 days)	32 (68%)	NA
6–8 weeks (43–56 days)	15 (32%)	NA

DCIS ductal carcinoma in situ, LCIS lobular carcinoma in situ, IDC invasive ductal carcinoma, ILC invasive lobular carcinoma, IBC inflammatory breast cancer, AC adriamycin/cyclophosphamide, T taxotere (docetaxel), FEC fluorouracil/epirubicin/cyclophosphamide, NA not applicable

**TABLE 3** Methods of microvascular reconstruction

	Neoadjuvant chemotherapy	No neoadjuvant chemotherapy
Total no. of patients	47	52
Total no. of reconstructions	49 (100%)	58 (100%)
Unilateral reconstructions	45 (92%)	48 (83%)
Bilateral reconstructions	2 (8%)	5 (17%)
<i>Type of reconstruction</i>		
DIEP	27 (56%)	34 (58%)
TRAM	11 (22%)	10 (17%)
SGAP	4 (8%)	4 (7%)
TMG	6 (12%)	9 (16%)
SIEA	1 (2%)	1 (2%)
<i>Recipient vessels</i>		
Internal mammary artery/vein	45 (92%)	54 (93%)
Internal mammary perforator artery/vein	3 (6%)	4 (7%)
Thoracodorsal artery/vein	1 (2%)	–

DIEP deep inferior epigastric perforator flap, TRAM transverse rectus abdominis muscle flap, SGAP superior gluteus artery perforator flap, TMG transverse musculocutaneous perforator flap, SIEA superficial inferior epigastric artery

motherapy regimens: four cycles of doxorubicin and cyclophosphamide followed by four cycles of docetaxel (AC → T), or six cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC). Tumor characteristics and type of neoadjuvant treatments are listed in Table 2.

In 32 patients (68%), reconstruction was performed 4–6 weeks (25–42 days) after finishing neoadjuvant chemotherapy; 15 patients (32%) were operated on 6–8 weeks (43–56 days) after completion of neoadjuvant chemotherapy. Type of reconstruction was chosen based on patient preference after consulting the plastic surgeon. Five different free flaps were used (Table 3): 27 breasts (56%) were

reconstructed with a free DIEP flap (deep inferior epigastric perforator), and 11 reconstructions (22%) with a free muscle-sparing TRAM flap (transverse rectus abdominis myocutaneous flap). In four patients (8%), we used an SGAP reconstruction (superior gluteal artery perforator flap), six breasts (12%) were reconstructed with a free TMG (transverse myocutaneous gracilis) flap, and one patient underwent breast reconstruction using a SIEA flap (superficial inferior epigastric). Internal mammary vessels were the recipient vessels of choice in 45 flaps (92%); perforators of the internal mammary vessels were used in three patients. One flap was anastomosed to the thoracodorsal vessels.

Complications are summarized in Table 4. Postoperative wound healing problems, which were treated conservatively, were considered as minor. Wounds that had to return to surgery for debridement, and which necessitated further nonconservative procedures, were labeled as major. Seventeen patients (36%) treated with neoadjuvant chemotherapy and immediate free flap breast reconstruction experienced one or more complications, which accounts for an overall complication rate of 58%, compared with 42% in patients without neoadjuvant chemotherapy. This difference is not statistically significant.

In the patient group with neoadjuvant chemotherapy, two patients (4%) after a DIEP flap experienced complete flap loss and an implant-based reconstruction was performed. Four patients after a DIEP reconstruction and one patient after a muscle-sparing TRAM flap showed a partial flap loss (10%). Seven patients (14%) lost a larger area of skin envelope after skin-sparing mastectomy due to necrosis and needed skin grafting. In seven patients (14%), small wound healing problems were seen on the breast or abdominal donor site. These wounds were all treated conservatively. The difference in complication rates was not statistically significant compared with the patients who did not receive neoadjuvant chemotherapy.

Type of adjuvant treatment after mastectomy and immediate microvascular breast reconstruction for locally advanced breast cancer is shown in Table 5. Nineteen patients (40%) proceeded with radiotherapy only, 10 patients (21%) had adjuvant chemotherapy followed by radiotherapy, 13 patients (28%) underwent radiotherapy followed by tamoxifen, and five patients (11%) received Herceptin and tamoxifen.

The intervals between surgery and the start of adjuvant treatment were determined by the individual patient's notes

**TABLE 5** Type of adjuvant therapy after microvascular breast reconstruction

No. of patients	47 (100%)
Radiotherapy only	19 (40%)
Radiotherapy and tamoxifen	13 (28%)
Chemotherapy and radiotherapy	10 (21%)
Herceptin and tamoxifen	5 (11%)

as the time measured in days elapsing from the day of surgery until the day of receiving the first course of adjuvant treatment. These intervals were compared between the patients without complications after neoadjuvant chemotherapy followed by mastectomy and free flap breast reconstruction ( $n = 30$  (64%)) and patients who had experienced complications ( $n = 17$  (36%); Fig. 1). The group without complications started adjuvant treatment after a mean interval of 43.6 (range, 28–90) days after reconstruction, whereas the group of patients with complications started adjuvant treatment after a mean interval of 44.6 (range, 28–76) days. This difference of 1 day between the two groups was not statistically significant.

## DISCUSSION

Immediate breast reconstruction for patients who undergo mastectomy offers numerous benefits compared with delayed reconstruction and has become the standard of care at Guy's and St. Thomas' Hospital in London. The advantages include greater technical ease, better cosmetic results, and decreased total operative and recovery times.<sup>6</sup>

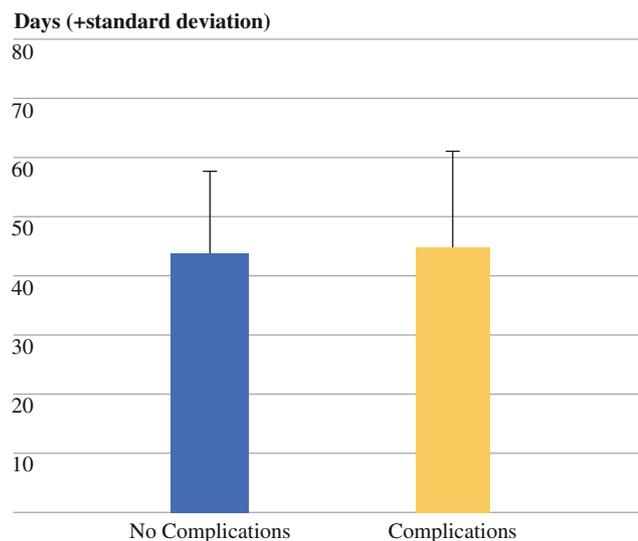
For early breast cancer, it has been shown that immediate breast reconstruction in patients without a history of neoadjuvant chemotherapy does not lead to a delay in the

**TABLE 4** Complications

	Neoadjuvant chemotherapy	No neoadjuvant chemotherapy	Statistical significance ( $p$ )*
Total no. of reconstructions	49 (100%)	58 (100%)	NA
<i>Wound healing problems</i>			
Major	7 (14%)	6 (10%)	0.57
Minor	7 (14%)	4 (7%)	0.34
<i>Flap loss</i>			
Partial	5 (10%)	3 (5%)	0.47
Total	2 (4%)	1 (2%)	0.59
Hematoma	3 (6%)	2 (4%)	0.66
Seroma	2 (4%)	3 (5%)	1
Infection	3 (6%)	5 (9%)	0.72
Total complications	29 (58%)	24 (42%)	0.08
Total no. of patients	47 (100%)	52 (100%)	NA
Patients with $\geq 1$ complication	17 (36%)	15 (29%)	0.4

*s* significant, *ns* not significant, *NA* not applicable

\*  $p < 0.05$  was considered significant



**FIG. 1** Time from microvascular breast reconstruction until adjuvant therapy for patients without complications ( $n = 30$  (64%)) and with complications ( $n = 17$  (36%)). The mean time of the date of reconstruction and the start date of adjuvant therapy was 43.6 (range, 28–90) days in the patient group without complications, and 44.6 (range, 28–76) days in the patient group with complications. The mean difference of 1 day was not statistically significant ( $p = 0.76$  using the nonparametric Mann–Whitney  $U$  test, and  $p = 0.83$  using the parametric  $t$  test for unpaired data)

delivery of adjuvant therapies.<sup>7</sup> For patients with locally advanced tumors who undergo mastectomy and immediate microvascular reconstruction of the breast after neoadjuvant chemotherapy, few data are available in the literature. There are reports on immediate breast reconstruction after neoadjuvant chemotherapy and possible delay in the delivery of adjuvant chemotherapy, but all were reviews of reconstructions with implants and expanders or in combination with pedicled muscle flaps.<sup>8–10</sup> Fears about delaying the initiation of adjuvant treatment because of complications raises the question of whether to subject a patient to this lengthy procedure, especially because undelayed postoperative therapies are crucial for patients with locally advanced breast cancer.

In this study, we have demonstrated that immediate microvascular breast reconstruction with autologous tissue after neoadjuvant chemotherapy does not result in a higher complication rate compared with patients without neoadjuvant chemotherapy and that the start of adjuvant treatment is not delayed in patients experiencing complications compared with patients without complications. To our knowledge, this is the first report to evaluate the effect on the timely start of adjuvant treatment in patients who undergo immediate microvascular breast reconstruction after neoadjuvant chemotherapy in comparison to a control group. These results were achieved in a series of 47 patients with locally advanced breast cancer who all had skin-

sparing mastectomy and immediate breast reconstruction with different free flaps after primary chemotherapy. Initial clinical and follow-up data were prospectively registered in a database and compared with a series of 52 patients who underwent mastectomy and immediate microvascular breast reconstruction without neoadjuvant chemotherapy during the same period of time. The patient groups were shown to be of same age and weight range, presenting with the similar percentage of comorbidities.

Of the patients in the reconstruction group after NC, 17% were obese (29% in the group without primary chemotherapy). Obesity (defined as body mass index  $> 30$  kg/m<sup>2</sup>) is a major independent predictor of postoperative complications, increasing the incidence of adverse events as much as threefold; obese patients have increased rates of partial flap loss and donor-site complications.<sup>11</sup> Chang et al.<sup>12</sup> evaluated the effects of smoking on the rates of complication in 936 free TRAM breast reconstructions and demonstrated that smoking was an independent predictor of mastectomy skin flap necrosis and overall donor-site complications, but no correlation was found with partial flap loss and fat necrosis. Mehrara et al.<sup>11</sup> confirmed these findings in their retrospective review of 1,195 free flaps for breast reconstruction. Overall flap complications were similar among nonsmokers and smokers. In our study, the patient group after neoadjuvant chemotherapy had a higher number of smokers, although all of them had reported to have stopped at least 3 weeks before undergoing surgery. Gouy et al.<sup>13</sup> showed in a group of 48 patients who had mastectomy and immediate reconstruction with implants alone, in combination with a pedicled latissimus dorsi muscle, or a pedicled TRAM after neoadjuvant chemotherapy that it did not delay the start of adjuvant treatment and had no significant effect on local relapse-free or distant disease-free survival.

Mehrara et al.<sup>11</sup> showed that neoadjuvant chemotherapy is a significant predictor of overall complications in free flap breast reconstruction. In our study, we did not observe a significantly increased complication rate.

Reviewing the literature, very few studies were identified that evaluated complication rates of immediate microvascular breast reconstruction after NC and that addressed the question of whether it delays the start of adjuvant treatment. In our study, the intervals between surgery and the start of adjuvant treatment were similar: 43.6 (range, 28–90) days for patients without complications vs. 44.6 (range, 28–76) days for patients with complications after reconstruction. It remains unclear why the longest interval between reconstruction and adjuvant therapy was in a patient with uneventful surgery.

Deutsch et al.<sup>14</sup> evaluated outcomes after TRAM flaps (22 free and 9 pedicled TRAM flaps) for immediate breast reconstruction after neoadjuvant chemotherapy and

reported an overall complication rate of 55%. In our study, the overall complication rate in patients after neoadjuvant chemotherapy was 58% compared with 42% in the group without neoadjuvant chemotherapy, a difference that was not statistically significant. Deutsch and coworkers showed that most complications were minor in nature and did not delay postoperative chemotherapy. The authors did not compare the incidence of complications with those of patients who had not been treated with neoadjuvant chemotherapy, whereas we compared our findings with a control group. Banic et al.<sup>15</sup> evaluated the outcome of free TRAM flap reconstructions; 35 of their patients had received primary chemotherapy. Although they did not see higher complication rates, there were no data given regarding the number of preoperative chemotherapy cycles, or the time from the last cycle until surgery.

Timely start of adjuvant treatment is crucial for the management of locally advanced breast cancer. It has been shown that delays in initiating chemotherapy or radiotherapy are associated with significant increases in relapse risk and adverse survival outcomes if the delay from definitive surgery exceeds 12 weeks.<sup>4,5</sup> The patients in our study started adjuvant therapy well before this time, regardless of whether complications occurred.+

## CONCLUSIONS

Immediate microvascular breast reconstruction after neoadjuvant chemotherapy neither results in an increased complication rate nor does it delay the start of adjuvant treatment, even if complications occur, and therefore can be performed safely in patients with locally advanced breast cancer.

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