Neoadjuvant Chemotherapy for Breast Cancer Treatment and the Evidence-Based Interaction with Immediate Autologous and Implant-Based Breast Reconstruction

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KEYWORDS

• Immediate breast reconstruction • Autologous breast reconstruction
• Breast reconstruction with prosthesis • Adjuvant chemotherapy • Neoadjuvant therapy
• Systematic review

KEY POINTS

- Chemotherapy for the treatment of breast cancer dates to the 1960s. At that time it was used for locally advanced and even inoperable cancer to provide a few more months of life to the patients suffering from it.
- Historically, patients underwent resective surgery (lumpectomy or mastectomy) followed by adjuvant therapy (chemotherapy and/or radiotherapy).
- Later, when the adjuvant treatment was completed and sufficient time had elapsed to be considered disease-free, delayed breast reconstruction proceeded.
- The development of more effective chemotherapy regimens has made it possible to put forth neoadjuvant chemotherapy in the case of breast tumors larger than 2 cm with or without axillary involvement.

INTRODUCTION

Although approximately 30% of oncologists think that breast reconstruction may interfere with the oncological treatment of breast cancer,[1,2] there is currently sufficient scientific evidence to demonstrate that immediate breast reconstruction is a safe procedure from the oncological perspective because it does not modify the patient's overall disease-free survival rate or interfere with subsequent oncological controls.[3,4]

There are multiple benefits for the patient, from the biological to the psychosocial, including a clear improvement in body image acceptance.[5,6]

The authors have nothing to disclose.

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The introduction of neoadjuvant chemotherapy for the treatment of breast cancer before its immediate reconstruction has been a source of controversy. Certain groups have questioned its compatibility with immediate reconstructive surgical treatment. They argue that there is a higher incidence of perioperative complications secondary to the neoadjuvant therapy before the intervention.[7–9] This is also true in certain cases of delays in the implementation of coadjuvant therapy due to the presence of these postoperative complications.

The aim of this review is to examine the effect of neoadjuvant chemotherapy on immediate breast reconstruction by assessing the incidence of postoperative complications and the latency time until the onset of adjuvant therapy, and comparing it with the oncological and surgical results obtained from the combination of immediate breast reconstruction and coadjuvant therapy following surgery.

DISCUSSION

Chemotherapy for the treatment of breast cancer dates to the 1960s. It was used at that time for locally advanced and even inoperable cancer to provide a few more months of life for the patients suffering from it.

With the improved survival rates (currently, around 85% of cases[10]) achieved with the establishment of new chemotherapeutic lines,[11–13] the need has arisen to proceed to breast reconstruction in patients who have suffered the consequences of a partial or total resection of the mammary gland.

Historically, patients underwent resective surgery (lumpectomy or mastectomy) followed by adjuvant therapy (chemotherapy and/or radiotherapy). Later, when the adjuvant treatment was completed and sufficient time had elapsed to be considered disease-free, delayed breast reconstruction proceeded. The development of more effective chemotherapy regimens has made it possible to put forth neoadjuvant chemotherapy in the case of breast tumors larger than 2 cm with or without axillary involvement. This was mainly done to increase the possibility of having conservative surgery.[14–16] Neoadjuvant chemotherapy entails several cycles of chemotherapy before the definitive surgical treatment, which is usually between 4 and 6 weeks after the end of the treatment. The most commonly used programs are based on combinations of anthracyclines and taxanes. Depending on the tumor subtype, specific targeted therapies are combined with chemotherapy, as is the case for antiHER2 therapies in the case of human epidermal growth factor receptor 2 (HER2) positive tumors.[17]

Currently, many studies demonstrate the oncological safety, as well as the aesthetic and psychological benefit, of immediate breast reconstruction after mastectomy, whether it be therapeutic or prophylactic.[18–20] The relationship between breast reconstruction and postoperative adjuvant treatment has been well studied[1,21] and provides data that support the compatibility and even synergy between the 2 procedures.

In contrast, there is no consistent data relative to the interaction that may exist between the introduction of a neoadjuvant therapy before surgery and the results and complications that may result from the surgical procedure performed shortly thereafter.

For this reason, different groups have initiated retrospective clinical studies to assess the incidence of neoadjuvant chemotherapy in the subsequent mammary reconstruction procedure (**Table 1**).

A priori, it might seem that undergoing several cycles of chemotherapy a few weeks before proceeding to a complex and demanding surgery, such as breast reconstruction, would increase the occurrence of perioperative and postoperative complications. It would be the case both locally[22,23] and at the systemic level. Locally, there would be a compromising of immunogenicity and the tissue healing capacity that may predispose to infection or dehiscence. Affectations at the systemic level might include deep vein thrombosis of the lower extremities with potential pulmonary embolization.

The main problem arising from these postoperative complications would be the need to delay the adjuvant chemotherapy treatment,[24–26] which demonstrates increases in the rate of local recurrence of the disease and decreases in the life expectancy of this type of patient.[27–29]

Although it is true that these fears are based on the damage that chemotherapy causes at the local and systemic level, the results obtained from various studies call into question this allegedly harmful relationship between preoperative chemotherapy followed by immediate breast reconstruction.

One of the studies with the largest sample size is that of Mehrara and colleagues.[30] In its analysis of 1195 microsurgical flaps for breast reconstruction, approximately 70 cases had undergone neoadjuvant chemotherapy. Preoperative neoadjuvant therapy was determined to be a predictor of risk for minor complications in the early postoperative phase (with an increase in infections at the donor site) and the late phase (with a greater percentage of patients with flap fat necrosis). There was no delay in any of the cases at the beginning of the postoperative adjuvant therapy.

Table 1
Studies assessing the relationship between chemotherapy and breast reconstruction

Author, Year of Publication	Subjects Receiving NQT per Total in Cohort	Type of Reconstruction			Complications		
		Autologous					
		Free	Pedicled	TE/I	Minor	Major	*P* Value
Mehrara et al,[30] 2006	70/1195 (7.7%)	217 (18.2%)	978 (81.8)	—	Fat necrosis (11%) Infection or wound healing complication (9.2%) Abdominal wall laxity or hernia (3%)	Total flap loss (0.7%) Partial flap necrosis (2.7%) Arterial thrombosis (0.8%) Venous thrombosis (1.3%) Hematoma (1.6%)	Minor complications <.01 (OR 2.1) Major complications <.8 (OR: -)
Deutsch et al,[31] 1999	31/31 (100%)	570 (70%)	9 (30%)	—	Fat necrosis (22%) Infection or wound healing complication (10%) Abdominal hernia (6%)	Total flap loss (0%) Partial flap necrosis (25%)	—
Azzawi et al,[33] 2010	53/171 (31%)	28 (52%)	23 (44%)	2 (4%)	Wound infection, slow healing, wound breakdown, fat necrosis (10%)	Total flap loss (2%) Partial flap necrosis (3%) Hematoma (0%) Infected implant (2%)	Minor complications .380 Major complications 1
Warren Peled et al,[34] 2010	57/163 (35%)	1 (1%)	25 (44%)	31 (55%)	Wound infection (23%) Skin necrosis (16%)	Total flap loss (4%) Implant or expander loss (26%) Hematoma (9%) Abdominal hernia (12%)	Minor complications: Wound infection .05 Skin necrosis .55 Major complications: Total flap loss .57 Implant or expander loss .70 Hematoma .04 Abdominal hernia .87

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Table 1
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Author, Year of Publication	Subjects Receiving NQT per Total in Cohort	Type of Reconstruction			Complications		
		Autologous					
		Free	Pedicled	TE/I	Minor	Major	*P* Value
Forouhi et al,[35] 1995	23/79 (30%)	—	11 (48%)	12 (52%)	Minor seroma (17.5%) Minor infection (10%) Minor necrosis (2.5%)	Major seroma (2.5%) Major infection (10%) Major necrosis (0.5%)	Minor complications .45 Major complications .88
Hu et al,[36] 2011	180/665 (27%)	4.5%	60.3%	35%	Infection (10%) Wound dehiscence Hematoma (3%) Seroma (15%)	Skin necrosis (7%) Flap loss (1%) Tissue expander or implant removal (0%)	Minor complications: Infection .89 Wound dehiscence .41 Hematoma .21 Seroma .36 Major complications: Skin necrosis .44 Flap loss .18 TE/implant removal .39
Abt et al,[37] 2014	820/19,258	157 (20%)		570 (70%) TE/I 90 (direct implant) N = 663 patients	Surgical site complications (superficial and deep incisional surgical site infection, wound dehiscence, graft or prosthesis failure)	Systemic complications (pneumonia, pulmonary embolism, renal failure, cerebrovascular accident, cardiac arrest, sepsis)	Surgical site complications .82 Systemic complications .01

Abbreviations: NQT, neoadjuvant chemotherapy; OR, odds ratio; TE/I, tissue expander/implant.

In the same vein, Deutsch and colleagues[31] found a postoperative complications rate of up to 55% in a group of 31 subjects who had undergone preoperative neoadjuvant therapy, mastectomy, and immediate reconstruction with a transverse rectus abdominis muscle (TRAM) type myocutaneous flap. Of those, 22 were free flaps and 9 were pedicled. There were no statistically significant differences in terms of postoperative complications between the 2 subgroups. This rate of complications was like that found by The Michigan Breast Reconstruction Study group, Alderman and colleagues.[32] It consisted of more than 20 plastic surgeons from 12 centers. They found a complication rate of approximately 45% in subjects who had undergone immediate breast reconstruction before chemotherapy.

Azzawi and colleagues,[33] through a retrospective analysis of a series of cases of a single surgeon, evaluated 170 subjects who had undergone mastectomy with immediate reconstruction. Of those 170 subjects, 53 had undergone neoadjuvant therapy before surgery. The results of that study found a higher clinical incidence of minor surgical complications in the subjects belonging to the group with neoadjuvant therapy, although it was not statistically significant. Therefore, the therapy did not compromise the result of the mammary reconstruction. The start of adjuvant therapy also did not compromise it in the cases that required it.

Peled and colleagues[34] came to a similar conclusion with a retrospective analysis of 163 consecutive cases of subjects who had undergone mastectomy with an immediate autologous or prosthetic reconstruction. Of those 163 subjects, 57 received neoadjuvant therapy. Although there was also a higher incidence of surgical wound infections in this subgroup, there were no statistically significant differences in other items, such as the need for reintervention, complications of the free flap donor-site, or loss of the prosthesis or expander. In fact, they postulate that the use of neoadjuvant therapy in this context can forestall the delay in applying adjuvant chemotherapy in patients who would inexorably develop postoperative complications.

Forouhi and colleagues[35] presented a study of 79 subjects who had undergone mastectomy with immediate reconstruction and randomization of neoadjuvant chemotherapy. They concluded that there was not a higher incidence of postoperative complications in the group that had had preoperative neoadjuvant therapy.

Hu and colleagues,[36] in a study of a cohort of 665 subjects who had undergone mastectomy with subsequent reconstruction, compared the percentage of subjects who underwent immediate reconstruction in the group of subjects treated with neoadjuvant therapy and in the group that had only had adjuvant therapy. Apparently, the subjects who underwent preoperative chemotherapy were less likely to undergo immediate reconstruction (28% of the subjects in this group) than subjects who only had postoperative chemotherapy (44% of the cases). In part, it is attributable to the fatigue generated by the chemotherapy treatment before the surgical intervention. This study specifies that the data lacks statistical validity because the cohorts are not comparable in terms of the number of subjects in each group.

Additionally, the study by Abt and colleagues,[37] which had a larger sample size of 820 subjects who had had immediate reconstruction after neoadjuvant therapy, found that the introduction of chemotherapy before surgery not only did not cause a greater incidence of complications at the local level but also reduced the rate of systemic morbidity during the month after surgery. They argue in support of this finding because preoperative chemotherapy reduced tumor volume, which meant a shorter operative time (known independent risk factor) and, therefore, less of a tendency to develop complications.

SUMMARY

Although it is true that much of the data on local complications may be underestimated, given the retrospective nature of most of the studies, the authors conclude that neoadjuvant therapy is a safe therapeutic option in patients who are going to subsequently undergo an immediate breast reconstruction in its different modalities. This conclusion is based on the overall computation of results. In none of the subgroups treated with autologous tissue or prosthesis is a higher incidence of perioperative and/or postoperative complications statistically significant. It could even have a positive effect on therapeutic compliance, forestalling a potential delay in starting adjuvant therapy after surgery because chemotherapy would anticipate the complications that may result from surgical intervention.

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