Editorial Commentary

Neoadjuvant treatment and premastectomy radiotherapy: oncological and surgical outcomes

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Comment on: Schaverien MV, Singh P, Smith BD, *et al.* Premastectomy Radiotherapy and Immediate Breast Reconstruction: A Randomized Clinical Trial. JAMA Netw Open 2024;7:e245217.

Keywords: Premastectomy radiotherapy; pathologic complete response (pCR); neoadjuvant treatment

Submitted Nov 25, 2024. Accepted for publication Mar 13, 2025. Published online Mar 26, 2025.
doi: 10.21037/gs-2024-514
View this article at: https://dx.doi.org/10.21037/gs-2024-514

This randomized trial on premastectomy radiotherapy comparing conventional versus hypofractionated radiotherapy to the chest wall and lymph node area in case of immediate breast reconstruction, represents a significant advancement (1). It allows for immediate autologous reconstruction without compromising flap integrity due to radiotherapy.

This study complements the findings of the PRADA trial (2) by including more patients receiving lymph node irradiation, thus paving the way for hypofractionated radiotherapy as a less demanding yet equally safe alternative to conventional methods.

However, certain aspects warrant further discussion.

Delay and complications

The incidence of mastectomy skin flap necrosis (MSFN) remains high (17%) compared to the multicenter, prospective M-RIC trial (3), which reported a 6% MSFN rate with a 6–8-week delay from the end of radiotherapy to surgery. This delay, adopted in several retrospective studies (4-6) helps maintain oncological safety by reducing radio-induced inflammation and dermatitis. Bollet *et al.* treated locally advanced tumors by starting concurrent chemo-radiotherapy and doing surgery at least 6 weeks after the last session of radiotherapy. The results showed acceptable pathologic complete response (pCR), overall and disease-free survival (7). Therefore, this delay seems oncologically acceptable and safe, relative to skin flap necrosis, considering none of the aforementioned studies used free flaps for immediate breast reconstruction. The 3±1 weeks delay used by both Schaverien *et al.* and Thiruchelvam *et al.* (1,2) was based on the results of a retrospective study (8) investigating free flaps-based head-and-neck reconstructions and demonstrating that more than 6 weeks, elapsed between radiotherapy and surgery, increased the complication rate. However, in Tall *et al.*'s study (8), the radiation dose was up to 64 Gy, and the complications concerned free flaps, whereas in the prospective multicenter study from Zinzindohoué *et al.*, the delay of 6 to 8 weeks showed a low rate of skin necrosis, and safe oncologic outcomes (3,6).

The PRADA trial (2) reported a 12% MSFN rate with a 2–6-week delay, though only 33% of patients received internal mammary irradiation. Even targeted irradiation can affect the skin envelope's peripheral areas, and this rate of MSFN could be underestimated.

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Table 1 MSFN, delay, and RNI including internal mammary node irradiation, and type of immediate breast reconstruction

Study	Delay	MSFN	RNI	IBR
Zinzindohoué *et al.* (3)	>6 weeks	6%	Not known	Pedicled flap
Paillocher *et al.* (5)	>6 weeks	5.3%	Not known	Pedicled flap
Monrigal *et al.* (4)	>6 weeks	7.6%	Not known	Pedicled flap
PRADA trial (2)	<6 weeks	12%	36%	Free flap
Schaverien *et al.* (1)	<6 weeks	17%	Yes	Free flap

MSFN, mastectomy skin flap necrosis; RNI, regional nodal irradiation including internal mammary area; IBR, immediate breast reconstruction.

Longer delays (≥6 weeks) reduce MSFN but may negatively impact free flap outcomes, while shorter delays (<6 weeks) increase MSFN but reduce free flap complications. However, in the Tall *et al.*'s study, the radiotherapy dose was greater than in breast cancer radiotherapy. Schaverien *et al.*'s study (1) confirms the feasibility and safety of immediate free flap reconstruction, even after internal lymph node irradiation, though MSFN rates remain slightly higher than in other studies (*Table 1*).

Skin-sparing or nipple-sparing mastectomies show a higher necrosis risk with short delays (3). Notably, none of the referenced studies assessed skin flap thickness—an essential, yet challenging to assess objectively, risk factor.

Oncologic outcomes

In a surgery post-radiotherapy approach, the pathologic response reflects both chemotherapy and radiotherapy effects, complicating adjuvant treatment decisions, which are known to improve overall and recurrence-free survival. For example, the KATHERINE trial showed that switching anti-HER2 therapy to TDM-1 in HER2-positive breast cancer patients, who did not achieve pCR after neoadjuvant chemotherapy, led to a 13.7% improvement in recurrence-free survival and a 4.7% increase in overall survival at 7 years (9). Similarly, the CREATE-X trial found that six months of adjuvant capecitabine for patients with residual disease resulted in a 9% increase in 5-year disease-free survival (10). To date, the value of pathologic response to both chemo- and radiotherapy has not been fully investigated, raising the risk that some patients might not benefit from adapted post neoadjuvant systemic treatments, leading to undertreatment. The value of pCR might not have the same meaning after systemic therapy, like chemotherapy, than after a locoregional treatment, like radiotherapy. It might therefore be the biological characteristics, rather than the size of the tumor, that count when it comes to neoadjuvant treatment, since the pCR rate is not correlated with tumor size (11). Some authors proposed a means to circumvent this issue. In the TOPAz protocol (12), a standardized tumor core biopsy was done, in the breast or lymph nodes, at the end of neoadjuvant treatment to objectivate residual disease. However, the use of standardized biopsy in the tumor bed, instead of surgery, to assess the pathologic response, is promising but remains, to date, not standard practice for patients undergoing neoadjuvant systemic therapy (13).

Moreover, in triple-negative breast cancers, the KEYNOTE-522 study showed that the addition of pembrolizumab to neoadjuvant chemotherapy improved recurrence-free survival and overall survival (14). No patients with KEYNOTE-522 regimen were included in the Schaverien *et al.* trial since inclusions started in 2018 and ended in 2022 (1). Immunotherapy may trigger immune-related-adverse events among which small vessel vasculitis (15). Immune-related vasculitis is a rare event but may be underestimated if not proactively searched for, and might compromise any microsurgery anastomosis. In the KEYNOTE-522 trial, skin flap ischemia occurred in 3.6% of patients but only 40% had mastectomy and the rate and type of immediate breast reconstruction are unknown. In a retrospective study (16), the post-operative complications, after chemotherapy and pembrolizumab, was up to 28% for infections, 16% for scar disunion, and 12% for skin necrosis. Immune adverse events are sometimes treated with corticosteroid therapy, which is also a risk factor for post-operative complications. In Woodfin's study, 9% of patients still had corticosteroid therapy at the time of surgery (16). Thus, adding radiotherapy after chemotherapy, when combined with pembrolizumab, might increase complications specifically for microsurgery.

As stated above, both HER2-positive and triple-

negative breast cancers benefit from neoadjuvant systemic treatments, the assessment of pCR selecting patients for the type of adjuvant therapy. For luminal breast cancer, pCR rate is lower than triple negative and HER2 tumors. But HER2, score 1 or 2, tumors have increased pCR rate compared to HER2 score 0 tumors (17). Luminal breast cancers may be considered for neoadjuvant treatment in patients not deemed eligible for breast-conserving surgery. Patients without sufficient clinical response, and therefore still candidates for mastectomy may be a population of choice for neoadjuvant radiotherapy followed by mastectomy and immediate breast reconstruction. The assessment of pathologic response in this group of patients is not as important as in triple negative or HER2-positive tumors since pCR mostly not influence adjuvant treatments and prognosis. However, new approaches involving neoadjuvant hormone therapy followed by response-tailored adjuvant treatment are currently being evaluated (i.e., the RIBOLARIS trial) (18), and could change practices in case of positive results.

Immediate breast reconstruction, radiotherapy and shared decision making

While radiotherapy impacts immediate breast reconstruction (19), it is not a contraindication. Silicone implants risk capsular contracture, affecting aesthetics and comfort, while autologous flaps may suffer volume loss and fibrosis. Depending on the grade, capsular contracture has consequences on body image and pain.

Two options for immediate breast reconstruction have been reported when radiotherapy is required: immediate delayed breast reconstruction or chemotherapy and radiotherapy prior to mastectomy and autologous immediate reconstruction.

The concept of immediate delayed breast reconstruction, developed in 2004 (20), consists of immediate reconstruction with a saline-filled tissue expander to serve as an adjustable scaffold. The expander is expanded, then deflated before radiotherapy to facilitate radiotherapy, and is inflated 2 weeks after completion of radiotherapy. After three months, the expander is replaced by autologous reconstruction. If the capsular contracture is well accepted by the patient, the expander can also be replaced by a silicone implant depending on the patient's choice and preferences.

When chemotherapy and radiotherapy are delivered before surgery, the immediate breast reconstruction is performed with autologous flap, rather than breast implant. Giacalone *et al.* found more complications with breast implant rather than flap (21). However, breast reconstruction with an autologous flap is not reversible, contrary to breast implants. Therefore, when inverted radiotherapy is chosen, the patient will not be able anymore to change her mind, and to decide whether she prefers an irradiated breast implant or autologous reconstruction. Shared decision making is crucial, especially for breast reconstruction, aiming patient's quality of life, and satisfaction (22).

Usually, radiotherapy follows the mastectomy and immediate breast reconstruction. Depending on the contralateral breast morphology, the expectations, the preferences, the choice and the context, some patients could rather keep an irradiated breast implant than a flap. After breast implant immediate reconstruction, it is difficult to anticipate which patients will accept and tolerate the capsular contracture. Even if autologous reconstruction provide excellent outcomes after radiotherapy, the patient's choice remain the most important point.

Acknowledgments

None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Gland Surgery*. The article has undergone external peer review.

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-2024-514/prf

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-2024-514/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Bannier M, Cohen M, Tallet A, de Nonneville A, Houvenaeghel G. Neoadjuvant treatment and premastectomy radiotherapy: oncological and surgical outcomes. Gland Surg 2025;14(3):276-280. doi: 10.21037/gs-2024-514