Editorial Commentary

Navigating the complexities of preoperative radiotherapy in breast reconstruction: a new paradigm?

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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: Mastectomy; radiation therapy; breast reconstruction; premastectomy radiation therapy

Submitted Nov 12, 2024. Accepted for publication Feb 19, 2025. Published online Mar 24, 2025.
doi: 10.21037/gs-2024-494
View this article at: https://dx.doi.org/10.21037/gs-2024-494

Introduction

Postmastectomy radiation therapy (PMRT) has a long tradition as an integral part of the treatment algorithm of patients with breast cancer but poses a clinical conundrum with respect to reconstruction. While breast reconstruction at time of mastectomy [immediate breast reconstruction (IBR)] has numerous advantages compared with delayed (staged) reconstruction, patients who require PMRT can be advised against IBR due to concern for increased risk of reconstruction complications due to radiation. In this editorial, we discuss the recently published study by Schaverien *et al.* (1).

To address the concerns surrounding reconstruction in patients who require PMRT, Schaverien *et al.* (1) studied the feasibility and perioperative safety of premastectomy radiotherapy (PreMRT) followed by mastectomy and IBR. In this phase II study, 48 patients with cT0–T3, N0–N3b breast cancer underwent PreMRT followed by mastectomy and IBR 2–6 weeks after completing PreMRT. Patients were randomized to receive either hypofractionated radiotherapy (HF-RT) (40.05 Gy/15 fractions) or conventionally fractionated radiotherapy (CF-RT) (50 Gy/25 fractions) regional nodal irradiation (RNI) as part of a separate trial [the Shortening Adjuvant Photon Irradiation to Reduce Edema (SAPHIRE) trial; ClinicalTrials.gov identifier: NCT02912312]. The primary outcome was reconstructive failure, defined as complete autologous flap loss. Secondary outcomes included rates of mastectomy skin flap necrosis, locoregional recurrences, and distant metastasis. The study found no complete flap losses, with 17% of patients experiencing skin flap necrosis, and no locoregional recurrences or distant metastases during follow-up. The current study adds to an emerging clinical experience of delivering preoperative radiotherapy in patients undergoing autologous reconstruction.

In 2022, Thiruchelvam *et al.* (2) reported on 33 patients treated with primary HF-RT to the breast and regional lymphatics followed by skin sparing mastectomy and primary radiotherapy and deep inferior epigastric perforator (DIEP) flap reconstruction (PRADA) reconstruction study. The primary endpoint was the rate of open breast wounds >1 cm width requiring a dressing at 4 weeks post-surgery. While the authors hypothesized that this rate would be ≤5%, the 12% (4 of 33 patients) rate found in their study was within the expected confidence interval and deemed safe. There was a similar 12% rate of mastectomy skin flap necrosis at 4 weeks and no patients experienced a DIEP

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flap failure with 12 weeks of follow-up. Combined, these two studies demonstrate the perioperative surgical safety of PreMRT followed by mastectomy and IBR.

Potential benefits of PreMRT

There are many perceived benefits by offering autologous reconstruction at the time of mastectomy. In doing so, this effectively bypasses the placement of a tissue expander at the time of mastectomy, ultimately leading to less surgery. Furthermore, the tissue expansion phase can be time-consuming, onerous to patients, and is associated with complication rates of up to 30% in some series. Finally, assuming the patient has no complications, many centers advocate waiting up to 6 months after the administration of PMRT to performing autologous reconstruction, thereby prolonging the reconstructive phase (3-5).

From an economic standpoint, there are clear benefits to offering immediate reconstruction with autologous tissue as this is one less surgical endeavor required. At a granular level, this leads to less direct costs in the consumption of devices, meshes, and surgical time. Furthermore, by effectively shortening the recovery time, this leads to less time off work for patients and potential mitigation of financial toxicity associated with the tissue expansion phase of care.

Finally, aesthetics can be compromised by PMRT in the setting of tissue expansion (6). The changes of skin discoloration, flap volume loss, and inframammary fold heightening are potential stigmata of PMRT and many times obligate the patient to a "delayed pattern" skin paddle inset. While not explicitly mentioned in this manuscript, immediate DIEP after radiation could conceivably bypass this inset pattern leading to improved aesthetic inset.

Technical considerations

The authors should be congratulated on their thoughtful trial design and willingness to challenge traditional dogma. While the results of the trial focused mainly on oncologic and surgical safety, additional details would be helpful in broadening the applicability. Mastectomy flap necrosis can occur during IBR and is more common in patients with a history of radiation. Many times, real-time laser angiography is utilized during surgery to assess perfusion of the overlying mastectomy skin. We would question whether the authors utilized this technology during the course. Additionally, there is a reference in the trial about patient's mammary vessels being unsuitable for microsurgery which required abandoning of microsurgery in favor for utilization of the thoracodorsal system. This is a very uncommon occurrence in microsurgical practice and additional description of this event as it relates to radiation damage would be helpful.

Finally, as previously mentioned, autologous tissue flaps can be inset in various ways to provide differential skin flap coverage. Traditionally, immediate reconstruction without prior radiation can allow for the patient to utilize the majority of the native mastectomy skin without the need for significant skin resurfacing and inframammary fold lowering providing a superior aesthetic result. Many times, in the setting of radiation, significant amounts of fibrotic mastectomy skin need to be removed and replaced with skin and tissue from the flap to allow for a more natural, durable result without the associated skin contracture, discoloration, and inframammary fold heightening. This provides superior shape at the expense of having a significantly larger autologous skin flap exposed. We would be curious to know which skin pattern (e.g., immediate *vs.* delayed) the authors utilized in these cases. Conceivably, the stigmata of PMRT had not yet been present at the time of mastectomy and if an immediate pattern was selected, we would be curious about the volumetric and aesthetic changes at long-term follow up.

Unexplored aspects of HF-RT *vs.* CF-RT

In the study, patients assigned to the HF-RT group received 40.05 Gy in 15 fractions to the breast and 37.5 Gy in 15 fractions to the undissected axilla. For those assigned to the CF-RT group, 50 Gy in 25 fractions to the breast and 45 Gy in 25 fractions to the undissected axilla were used. The study found that there were similar rates of postoperative complications between HF-RT and CF-RT groups overall and adds to the growing body of literature demonstrating that postoperative HF-RT is as safe and effective as CF-RT in patients with reconstruction or without reconstruction (7-9). However, the incidence of grade 2 dermatitis was higher and long-term patient-reported cosmetic outcome was lower in the CF-RT group. Given the lower cosmetic outcome at 18–24 months, it would be helpful to know if there were differences in the type of postoperative complications between the HF-RT and CF-RT groups.

Future directions

In 2016, 80% of autologous breast reconstructions were performed in a delayed fashion (10). Thus, the authors of the present study postulate that PreMRT has the potential to increase the number of patients undergoing reconstruction after mastectomy. The results of this trial will indeed be practical in allowing for patients to safely access autologous breast reconstruction in a much more expeditious manner. However, we would caution the broad applicability of the trial. Indeed, one must know that a patient will need to receive PMRT, desires autologous reconstruction, is a candidate for autologous reconstruction, and lives in close proximity to a center who has access to microsurgery. All told, this represents a small minority of patients.

While the study findings will need larger scale validation of its results, in light of emerging PMRT clinical trial data, the actualized large-scale impact of changing the sequence of treatment is called to question. Practically speaking, the role of PMRT continues to evolve in the modern era of systemic therapy and understanding tumor biology, which will make identification of ideal candidates for PreMRT even more challenging. First and foremost, in patients receiving neoadjuvant systemic therapy with cN1 axillary nodal disease that converts to ypN0, the recently presented findings of NSABP B51/RTOG 1304 demonstrate that at median follow-up of 59.5 months, there is no significant difference in the breast cancer recurrence-free interval, local-regional recurrence, and/or overall survival in patients who receive PMRT/RNI *vs.* those who do not (11). These findings were particularly striking in the unplanned subgroup analysis by breast cancer subtype where patients with triple-negative disease and human epidermal growth factor receptor 2 (HER2)-positive disease were found to have no benefit of PMRT/RNI. Since the current systemic agents for these types of breast cancer currently help 60–70% of patients achieve pathologic complete response, using only the preoperative cN1 status as the indicator for PreMRT may subject a large number of patients to radiation that may not have been necessary if it was known that the axilla converted to ypN0 disease. In patients with estrogen receptor-positive/HER2-negative breast cancer with Oncotype DX ≤25 with pT1–3pN1 disease after upfront surgery, a recent secondary analysis of the Southwest Oncology Group (SWOG) 1007 RxPonder trial by Jagsi *et al.* (12) demonstrated an exceedingly low risk of local-regional recurrence in patients treated with mastectomy without PMRT, suggesting that PMRT may not be necessary in these favorable-risk patients. Of note, in the SWOG 1007 study, among the 1,724 patients who underwent mastectomy, 54.2% (n=934) received radiotherapy, of whom 81.1% had RNI, and approximately 80% in both no PMRT and PMRT group underwent axillary lymph node dissection. Thus, the oncologic safety of omitting regional RT is currently being studied on the ongoing Canadian Clinical Trials Group (CCTG) MA.39 study (13), where patients that fit RxPonder criteria are randomized to PMRT/RNI *vs.* no PMRT/RNI. Taken together, the results of the NSABP B51/RTOG 1304 trial, the secondary analysis of the SWOG 1007 trial and potentially the results of the CCTG MA39 trial will mean that significantly fewer patients will benefit from PMRT and that identifying who will benefit and is a good candidate for PreMRT is going to become increasingly challenging in the years to come.

However, one of the potential benefits of PreMRT is the potential for radiation to stimulate the immune system, which may lead to improvements in local-regional control but also decrease the risk of distant metastases. The role of preoperative radiation for this indication has been studied prospectively, but the dose, fractionation and field size were limited to ultrahypofractionation (8 Gy ×3) to the gross disease in the breast (14). However, a moderately hypofractionated course of radiation to the entire breast and regional nodal basins may have an immunosuppressive effect as evidenced by the results of the PRADA study where only 27% of patients achieved a pathologic complete response. Still, there remains the opportunity to study this angle of PreMRT, particularly in patients receiving concurrent immunotherapy. In addition, there is further opportunity to study the ideal timing between PreMRT and surgery to determine if PreMRT may help improve pathologic complete response rates.

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-2024-494/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-2024-494/coif). J.M.B. reports compensated service on the US FDA Medical Device Committee and the Abbvie Innovation Committee. The other 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: Broyles JM, Bazan JG, Park KU. Navigating the complexities of preoperative radiotherapy in breast reconstruction: a new paradigm? Gland Surg 2025;14(3):272-275. doi: 10.21037/gs-2024-494