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ORIGINAL ARTICLE

Breast

Optimizing Breast Reconstruction through Integration of Plastic Surgery and Radiation Oncology

Aska Arnautovic, MD*
Sigurast Olafsson, BS*
Julia S. Wong, MD†
Shailesh Agarwal, MD*
Justin M. Broyles, MD*

Background: Post-mastectomy radiation therapy (PMRT) is an important adjunct to improve oncologic outcomes and survival in select breast cancer patients at increased risk for local recurrence. As recommendations for PMRT broaden, an increasing number of patients will have it included as part of their breast cancer treatment plan.

Methods: This overview of the literature strives to broaden the exposure of the plastic surgeon to PMRT and describe the indications, guidelines, and considerations relevant to reconstructive surgery. The primary targets and dosing considerations will also be reviewed. Finally, the short- and long-term toxicities are outlined with the goal of providing the plastic surgeon insights with which to recognize certain toxicities in the clinic during follow up and to develop the fluency to be able to talk to patients about the potential for certain toxicities.

Results: Generally, PMRT is safe and well tolerated. Considerations in breast reconstruction should be made on a patient-by-patient basis. Plastic surgeon familiarity with PMRT, its indications, and complications will amplify the surgeon's ability to optimize outcomes.

Conclusions: As more women undergo breast reconstruction, an increasing number of patients will have PMRT as part of their breast cancer treatment plan. By understanding the basic principles of PMRT, plastic surgeons can engage patients in conversations of shared decision-making and maximize outcomes. *(Plast Reconstr Surg Glob Open 2021;9:e3577; doi: 10.1097/GOX.0000000000003577; Published online 6 May 2021.)*

INTRODUCTION

Post-mastectomy radiation therapy (PMRT) is an important adjunct to improve oncologic outcomes and survival in select breast cancer patients at increased risk for local recurrence. As recommendations for PMRT broaden, an increasing number of patients will have it included as part of their breast cancer treatment plan. The adverse effects of PMRT on breast reconstruction include increased rates of infection, capsular contracture, and decreased patient-reported satisfaction.[1]

When evaluating a patient with breast cancer for reconstruction, plastic surgeons must consider several key factors such as the potential for PMRT, timeline of reconstruction, type of reconstruction, and patient comorbidities. Currently there is no clear consensus as to what the optimal reconstructive plan is for patients who require PMRT. The limitations of existing evidence result in many plastic surgeons operating based on institutional tradition or anecdotal experience.

To be an effective member of the patient's multidisciplinary cancer treatment team, the plastic surgeon should have a general understanding of how radiation is dosed and administered, where on the chest/axilla the radiation targets will be, and overall indications for therapy. Several aspects surrounding PMRT may be of particular interest to the plastic surgeon and include delayed toxicity, capsular contracture, skin quality changes, and upper extremity lymphedema. Consequently, the way patients perceive their reconstruction may be influenced by the unfavorable effects of radiation. Therefore, it is critical for

*From the *Division of Plastic and Reconstructive Surgery, Brigham and Women's Hospital, Boston, Mass.; and †Department of Radiation Oncology, Dana Farber Cancer Center, Boston, Mass.*

Received for publication January 2, 2021; accepted March 15, 2021.

DOI: 10.1097/GOX.0000000000003577

Disclosure: *Justin Broyles, MD serves as a consultant for AHRQ. All the other authors have no financial interest to declare in relation to the content of this article.*

a plastic surgeon to be familiar with and have the ability to recognize these outcomes as well as possess the knowledge of how these may be mitigated.

This review serves to provide a digestible yet comprehensive overview of PMRT. By understanding the basic principles of PMRT, plastic surgeons can have a stronger foundation of knowledge to help maximize outcomes when managing breast reconstruction patients who are also undergoing radiation therapy. Furthermore, this additional knowledge will better prepare surgeons to further engage with their colleagues in a multidisciplinary oncology setting.

MECHANISM OF ACTION OF PMRT

PMRT involves the use of ionizing radiation, delivered by external beam radiation, to the chest wall and/or surrounding lymph nodes. Its mechanism of action serves to directly disrupt protein and DNA molecules and form free radicals and electrons to cause molecular damage. Although these effects of radiation are directly toxic to malignant cells, healthy tissue included in the radiation field may also be inadvertently damaged. Direct cellular damage with chromosomal alteration, microvascular occlusion with ischemia, and inhibition of fibroblast actions are all implicated as mechanisms in radiation-induced tissue damage which lead to progressive loss of endothelial cells in the walls of vessels and subsequent regional ischemia. Structural changes to the skin include changes in epidermal and dermal keratinocytes and melanocytes, damage to skin appendages, skin thinning, and fibrosis.[1]

CURRENT INDICATIONS FOR POST-MASTECTOMY RADIATION

Patients with breast cancer who experience locoregional disease recurrence will do so in the chest wall or regional lymph node basins (axillary, internal mammary nodes, and supraclavicular nodes). Evidence has shown that radiation therapy helps decrease the risk of post-mastectomy locoregional recurrence and improves overall survival.[2] A large meta-analysis of 22 randomized trials demonstrated a 10.6% decrease in locoregional recurrence after 10 years and 8.1% decrease in 20-year mortality from breast cancer.[3] PMRT has been shown to significantly increase overall survival rates in breast cancer patients with locally advanced disease.[4,5]

Tumor features associated with recurrence include tumor size ≥ 5 cm, ≥4 axillary lymph nodes involved, inflammatory breast cancer, and positive surgical margins. Patients with these characteristics are routinely recommended PMRT to decrease their chance of locoregional recurrence.[6] The evidence to support PMRT in certain patients with T1/T2 disease, such as those also with 1–3 positive axillary lymph nodes, young age, margins < 1 mm, lymphovascular tumor invasion, and low nuclear grade or negative nodal disease is less clear in regard to locoregional recurrence (LRR), overall recurrence, and breast cancer mortality.[7,8] In light of this controversy, the American Society of Clinical Oncology, along with the American Society for Radiation Oncology and the Society of Surgical Oncology recently published a guideline update to address the risks and benefits of PMRT in this patient cohort. As of 2016, they concluded that the available evidence shows PMRT reduces the risk of LRR, OR, and breast cancer mortality in this patient population overall. However, they advised that certain subsets of patients are likely to have a sufficiently lower risk of LRR for which the risks of PMRT might outweigh the benefits. Some of these low risk characteristics include patient age > 40–45 years, limited life expectancy because of older age or comorbidities, pathologic findings associated with a lower tumor burden (T1 tumor, absence of lymphovascular invasion, presence of a single positive node, and/or small size of nodal metastases), and biologic characteristics of the cancer associated with better outcomes and survival and/or greater effectiveness of systemic therapy (eg, low tumor grade or strong hormonal sensitivity).[9] These findings are displayed in Table 1.[9]

TARGETS OF PMRT

It is well established that the chest wall, which tends to have the highest rates of local recurrence, should be the main target of PMRT.[6] However, controversy exists regarding whether certain regional lymph node basins should be included in the radiation field. In the United States, axillary dissections tend to be more extensive, resulting in a low risk of axillary recurrence.[10] The incidence of isolated axillary recurrence after level I and II dissection in the United States is usually between 1% and 3% (9–27 months after surgery). Given this low risk of recurrence, it is accepted that routine PMRT to the axilla is often unnecessary, although specific cases of extensive axillary disease with a high probability of harboring residual disease may warrant axillary PMRT.[10]

Overall, isolated recurrence in the supraclavicular and/or internal mammary nodes is relatively uncommon.[11] Including the supraclavicular nodes in the radiation target zone is generally supported because this area is not

Table 1. Current Indications and Considerations regarding PMRT as Outlined in Guidelines Published by the American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology

Positive indications for PMRT:
• Four or more positive lymph nodes • Axillary nodal involvement that persists after neoadjuvant systemic therapy • T3 tumors and operable stage III tumors
Requires additional considerations regarding PMRT administration:
• T1-2 tumors with 1–2 positive lymph nodes: the following factors should be considered ◦ Patient characteristics: Age: >40–45 Limited life expectancy Coexisting conditions that may increase risk of complications ◦ Pathologic findings: T1 tumor size Absence of lymphovascular invasion Single positive node and/or small size of nodal metastases Substantial response to neoadjuvant systemic therapy ◦ Biologic characteristics of the cancer: Low tumor grade Strong hormonal sensitivity

surgically accessible, and recurrence in this area is associated with decreased survival.[6] Additionally, radiating the supraclavicular region carries a small risk of toxicity to adjacent tissue.[6] In contrast, radiating the internal mammary nodal region can be associated with potentially significant cardiac and pulmonary toxicities given the nodal location in relation to the heart and lungs. As such, routine inclusion of the internal mammary nodes in the PMRT target zone is often debated. Recent data support an oncologic benefit to including IMNs in the radiation field, but these decisions are complex due to the toxicity concerns.[12,13] Current practice guidelines do not advocate for or against routine irradiation of the internal mammary nodes, and this decision is left to the discretion of the radiation oncologist.

ADMINISTRATION AND DOSING OF PMRT

During PMRT, patients are placed in the supine position with their arms raised above the head. The head is turned up slightly (and sometimes away from the treated breast) to protect the chin from the radiation beam. The mastectomy scar is delineated with a radio-opaque marker or wire to make sure the entire scar is included in the radiation plan. Additionally, the medial (or midline, as a reference point), lateral (mid-axillary line), superior (caudal edge of clavicle), and inferior (1–2 cm below the inframammary line) field borders can be delineated to guide initial beam placement (Fig. 1).

For patients with left-sided breast cancer, a deep-inspiratory breath hold technique may be used to minimize cardiac toxicity. By instructing patients to hold their breath for 20–30 seconds during peak inspiration, the distance between the heart and chest wall is increased to lower the cardiac radiation dose[6] (Fig. 2).

Advances in radiation technology have resulted in more targeted PMRT that minimizes radiation toxicity to unnecessary structures. Three-dimensional conformational planning is utilized with a goal of covering the chest wall with tangent beams of high-energy photons. The chest wall is treated with 2 opposing tangential fields, which are placed at an angle to avoid the contralateral breast and minimize toxicity to heart and lungs. Supraclavicular and infraclavicular regions may be treated with anterior photon fields that are carefully positioned to avoid the esophagus, thyroid, and/or spinal cord. There are multiple techniques utilized to treat the internal mammary nodes. One commonly used method is via a wide tangent technique in which the footprint is extended beyond the midline at the level of the first three intercostal spaces. Care is taken to block inferiorly and avoid unnecessary radiation to the heart and lungs[6] (Fig. 3).

Conventional dosing for PMRT is 50–50.4 Gy in 1.8–2.0 Gy per fraction (25–28 total fractions) to the chest wall and 45–50 Gy in 1.8–2.0 Gy per fraction (25 total fractions) to the regional lymph nodes. The typical duration of treatment is 5 days per week for 4–6 weeks.[6] An alternative technique, known as hypofractionation, involves giving a larger daily dose over a shorter period (fewer total fractions) to reduce treatment costs and increase convenience for patients. This approach has been shown in randomized trials to have comparable oncologic outcomes and side effects compared with conventional fractionation in early-stage invasive breast cancer managed with breast conservation.[14,15] A recently completed randomized controlled trial compared segmental mastectomy patients with negative resection margins and negative axillary lymph nodes metastases to either hypofractionation or standard radiation. Their findings showed that the risk

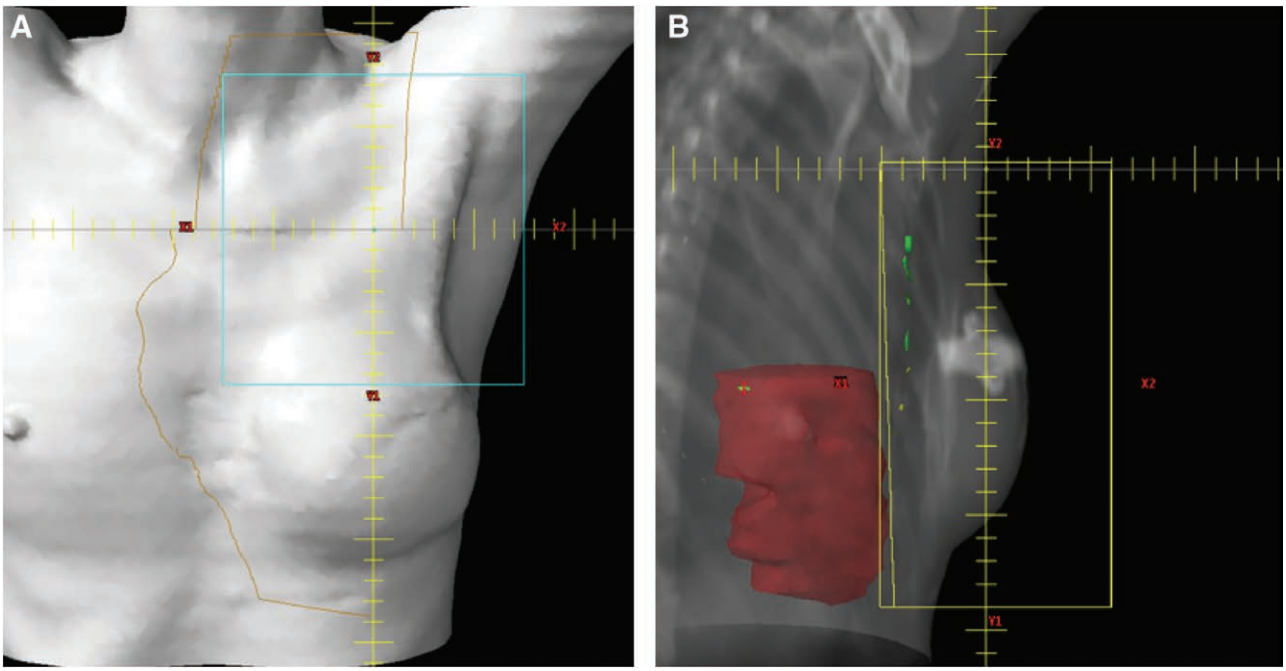


Fig. 1. Radiation field mapping in a patient with an inflated left tissue expander . A, Field mapping for anterior supraclavicular and axillary nodal field. B, Lateral mapping with internal mammary nodes (green) and exclusion of the heart (red).

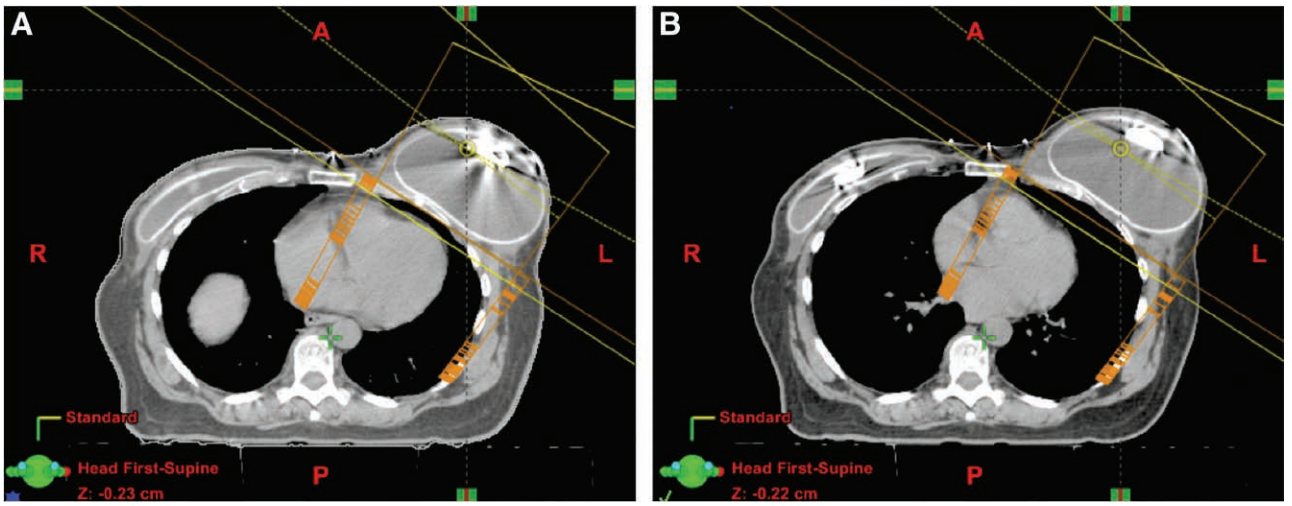
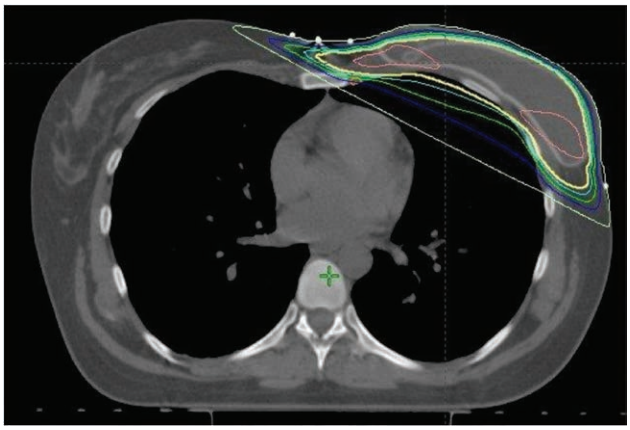


Fig. 2. Radiation field mapping. Cardiac radiation is changed with expiration (A) and inspiration (B). Providing treatment during inspiration improves cardiac avoidance.

of local recurrence at 10 years was 6.7% among the 612 women assigned to standard irradiation when compared with 6.2% among the 622 women assigned to the hypofractionated regimen. At 10 years, 71.3% of women in the control group as compared with 69.8% of women in the hypofractionated-radiation group had an excellent or good cosmetic outcome.[14] There is ongoing debate in this area, particularly regarding patients who are at higher risk of locoregional recurrence. Current ASTRO guidelines recommend hypofractionation in patients who are >50 years old, T1–T2 tumors, negative nodal disease, hormone positive cancer, and low grade disease.[16]

The radiation dose at the skin surface is lower than the dose at the target because photons require tissue interaction to build up the total radiation dose. An additional bolus may be used to increase the chest wall skin dose for patients who have an increased risk of chest wall recurrence (ie, large tumors, positive/close margins, and inflammatory breast cancer). However, a bolus is generally avoided in patients planned for reconstruction if they do not have the aforementioned risk factors for recurrence given the potential for skin desquamation, infection, fibrosis, and hyperpigmentation.[6]



AQ7 **Fig. 3.** Left chest wall with tissue expander placement dosimetry.

RADIATION TOXICITY

Generally, PMRT is safe, well tolerated, and patients often continue their normal routines without feeling ill or experiencing decreased immunity. Acute toxicities of radiation are defined as those occurring within three months of PMRT. The most common adverse effects include fatigue and radiation dermatitis.[6] Radiation dermatitis worsens as the radiation dose increases, often peaking 1 to 2 weeks after radiation administration. Symptoms of radiation dermatitis include skin erythema, hyperpigmentation, dryness, rash, and moist desquamation and can be treated in a similar manner as a burn by using aloe, hydrocortisone, or other topical preparations. Topical steroids can be utilized in treating radiation dermatitis due to their anti-inflammatory properties. Data from several prospective randomized trials have shown a decrease in erythema and pruritus with application of mometasone furoate, a medium potency topical steroid.[17] These skin changes usually heal 2–4 weeks after the cessation of radiation therapy, but some hyperpigmentation or fibrosis may persist indefinitely (Fig. 4).

Chronic toxicity occurs beyond 3 months of PMRT, and most often includes hyperpigmentation and fibrosis of the chest wall.[6] Other potential but less common long-term toxicities of radiation include radiation pneumonitis, rib fractures, radiation-induced heart disease, hypothyroidism (if treating the supraclavicular region), and risk of secondary malignancy.

As chronic or delayed toxicity of PMRT may present to the plastic surgeon, it is important to know how to manage these outcomes. If the patient has ulcerations and chronic wounds, local wound care is typically recommended. Small trials have suggested that fibrosis of the chest wall may be improved with long-term use of pentoxifylline with vitamin E with the goal of altering TGF-β expression to slow or reverse the process of fibroblasts proliferation and

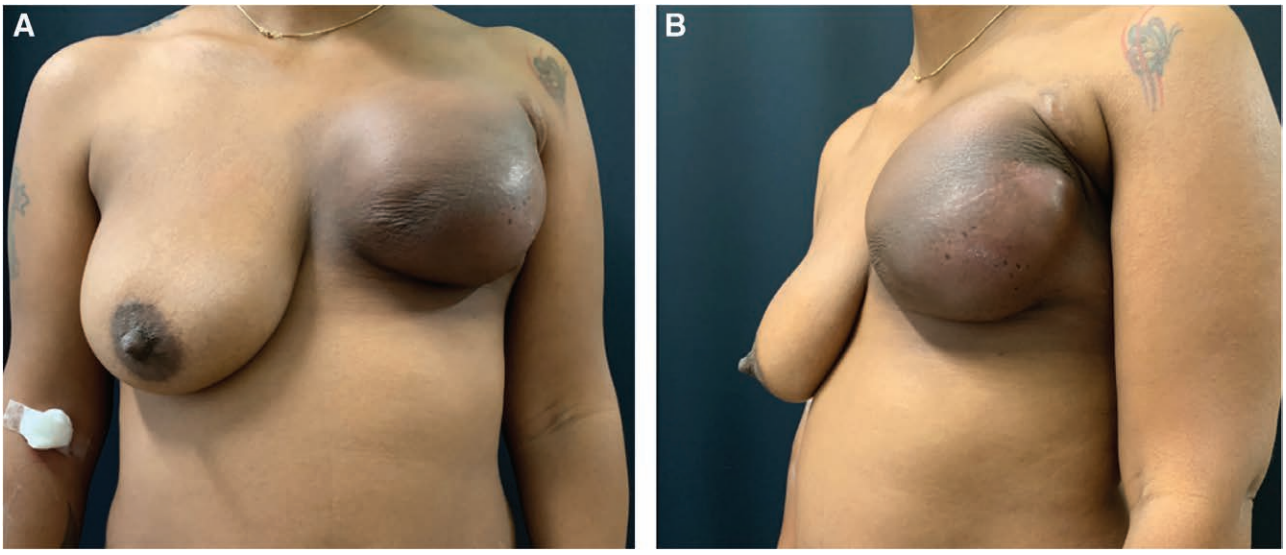


Fig. 4. Example of PMRT changes in a patient 6 months after completing treatment: anterior view (A) and lateral view (B).

differentiation.[18–21] Additional management strategies that have varying levels of evidence regarding their efficacy include superoxide dismutase, interferon gamma, and hyperbaric oxygen therapy.[22]

The risk of lymphedema has been repeatedly shown to be significantly increased following radiation therapy.[23–25] The increased risk is amplified when radiation therapy is coupled with lymph node dissection. It has been found that this risk can increase by almost 5-fold when a patient receives PMRT and almost 10-fold with concurrent axillary node sampling.[26,27] A retrospective analysis of 2579 women undergoing breast conserving treatment for breast cancer revealed results of 16%–31% of women developing lymphedema following radiation therapy depending on the area that was irradiated.[28] The development of lymphedema following radiation was 16% in women receiving radiation to the breast only and increased to 31% when supraclavicular radiation and post-axillary boost were added.

RADIATION TREATMENT AND BREAST RECONSTRUCTION

Since the Women's Health and Cancer Rights Act mandated insurance coverage of breast reconstruction nationally in 1997, an increasing number of women are choosing to undergo reconstruction. In 2019 there were 107,238 breast reconstruction procedures performed by plastic surgeons in the United States.[29] Breast reconstruction has been shown to play an important role in improving quality of life and psychological wellbeing of breast cancer patients after mastectomy.[30]

Additionally, rates of breast conservation therapy for early breast cancer treatment are increasing over time (from 54.3% in 1998 to 60.1% in 2011).[31] As the number of patients undergoing breast conservation therapy grows, the use of adjuvant radiation will also increase accordingly. As a result, more patients and their physicians will have to make complex decisions regarding the integration of radiation therapy with their reconstruction.

The type of reconstruction is multifactorial and is ultimately a joint decision between the patient and reconstructive surgeon. A large survey revealed that 90% of radiation oncologists did not take into account the type of reconstruction when planning a radiotherapy regiment, but rather that tumor biology and dose homogeneity were more important considerations.[32] For patients undergoing delayed-immediate reconstruction with a tissue expander, it is essential that the reconstructive surgeon is aware of certain aspects of adjuvant radiotherapy. For example, should a patient require radiation to the internal mammary nodes, the tissue expander requires deflation to achieve the appropriate dose to the target area.

It is vital for reconstructive surgeons to be familiar with the radiation protocols and timeframes to anticipate potential adverse effects and toxicities in the context of reconstruction. Radiation to both tissue expanders and permanent implants has demonstrated high rates of capsular contracture and need for revision or explantation. A meta-analysis of 2348 patients undergoing irradiation of tissue expanders or permanent implants found high overall rates of reconstructive failure (17.6%) and Baker grade III/IV capsular contracture (37.5%).[33] Additionally, it is important to consider that tissue expanders contain a metallic port. Several models have been developed to investigate the effect of radiation delivery to the breast with an implanted metallic port. It has been found that the metallic port does absorb some radiation, but the amount of attenuated signal is small, and does not diminish the overall effectiveness of the radiation therapy.[34,35]

Two-stage implant-based reconstruction poses an additional question to the surgeon: when to exchange the tissue expander for a permanent implant? A study investigating the impact of time between PMRT conclusion and implant exchange found that increasing time to exchange led to lower rates of reconstructive failure.[36] The patient groups were composed of those undergoing implant exchange earlier (average 3.4 months) or later (average

8.6 months) than 6 months following PMRT conclusion. The group with the shorter time to implant had a significantly higher rate of reconstructive failure (22.4% versus 7.7%; $P = 0.04$).[36] A third cohort of patients underwent implant exchange before PMRT. There was no significant difference between overall complication rate or reconstructive failure across the 3 groups.[37]

Immediate autologous free flap reconstruction necessitates a consideration of risks including radiation-induced flap thrombosis and fat necrosis. However, several cohort studies have demonstrated no significant difference in postoperative complications between radiated and nonradiated immediate deep inferior epigastric perforator flaps with acceptable patient satisfaction of aesthetic outcomes.[38,39] For delayed autologous free flap reconstruction, it is ideal for a patient to undergo definitive reconstruction after the acute radiation toxicities have resolved. In any reconstructive scenario, radiotherapy to skin and soft tissue is damaging. The acute effects as reviewed above can contribute to impaired wound healing of the incisions forming the mastectomy skin envelope and/or the autologous flap skin paddle, which can ultimately influence aesthetic outcomes for a patient.

CONCLUSIONS

PMRT is an important adjunct to improve oncologic outcomes and survival in select breast cancer patients at increased risk for local recurrence. As a growing number of women will undergo PMRT, the interaction between PMRT and breast reconstruction will be an increasingly common and important consideration in breast cancer management. Plastic surgeons should have a strong baseline understanding of PMRT to maximize reconstructive outcomes for their patients. Given that there is currently a lack of definitive evidence for optimal reconstructive algorithms, a mainstay of breast reconstruction is shared decision-making with the patient. Having an understanding of PMRT utilization and its lasting effects will allow the plastic surgeon to better inform patients about realistic postoperative expectations and outcomes. New advances in radiation therapy will continue to develop in tandem with improvements in reconstructive breast surgery. It will be important for the plastic surgeon to be aware of the developments in radiation oncology and utilize a collaborative team approach to maximize patient safety and reconstructive outcomes.

Justin M. Broyles, MD
Brigham and Women's Hospital
Harvard Medical School
Boston, MA
E-mail: jbroyles@bwh.harvard.edu

PANTIENT CONSENT

The patient provided written consent for the use of her image.

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