



Radiation and breast reconstruction—quantifying, understanding and applying evidenced-based outcomes

Ara A. Salibian, Jordan D. Frey, Nolan S. Karp

Hansjörg Wyss Department of Plastic Surgery, New York University School of Medicine, New York, NY, USA

Correspondence to: Nolan S. Karp, MD. Hansjörg Wyss Department of Plastic Surgery, New York University School of Medicine, 305 East 47th Street, Suite 1A, New York, NY 10017, USA. Email: Nolan.karp@nyumc.org.

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Introduction

Radiation therapy has become an integral part of multimodal breast cancer treatment. Postmastectomy radiation traditionally was indicated for more advanced disease and continues to be utilized for larger T3 and T4 tumors as well as for more extensive nodal involvement (four or more positive axillary nodes) (1). Indications for radiation, however, have expanded (2). Patients with smaller tumors and less nodal involvement may be considered for therapy as studies have also shown decreased locoregional recurrence in these cases (3).

The administration of radiation therapy has evolved significantly since its introduction in 1997, similar to the surgical treatment of breast cancer over the last several decades that witnessed a transition to more refined and focused techniques (4,5). The introduction of three-dimensional confocal radiation therapy was a landmark development that allowed for volumetric targeting of tumors (6). Subsequent advancements have included intensity-modulated radiation that have allowed for greater dose conformity as well as decreased scatter that can damage normal surrounding tissues, respectively (7,8).

Radiation therapy, however, has always been an obstacle for the plastic surgeon in achieving a desirable reconstructive outcome. The deleterious effects of radiation on healthy tissues are well-known, and result from a cascade of a proinflammatory factors, reactive oxygen species production, hypercoagulability and microvascular thrombosis (9). Subsequently, chronic radiation damage is characterized by dermal atrophy, fibrosis, and impaired

wound healing that can be a formidable force in any attempts at reconstruction.

As more patients opt for breast reconstruction after mastectomy (10) and as radiation continues to be an important adjuvant treatment for breast cancer, the rate of patients receiving both radiation and breast reconstruction is increasing (11). Multiple controllable factors in the reconstruction process can influence outcomes in the setting of radiation therapy. These include reconstruction type, timing of primary and secondary procedures, single or two-staged approaches, and patient selection, among many others. Plastic surgeons must work closely with radiation oncologists to balance the optimal reconstructive outcome with the most efficacious cancer treatment.

Implant-based vs. autologous reconstruction

The article by Jagsi *et al.* aims to elucidate differences in objective and patient-reported outcomes among breast reconstruction techniques in patients that have received postmastectomy radiation with the goal of quantifying these results to allow patients to better understand the implications of their reconstructive choices (12). The study analyzes prospectively gathered data from an 11-center cohort study entitled the Mastectomy Reconstruction Outcomes Consortium (MROC) that enrolled patients between 2012 and 2015. Prior results from this database have suggested increased patient satisfaction after autologous reconstruction compared to implant-based reconstruction (13,14). The current study, with a larger

number of irradiated breasts, importantly incorporates radiation therapy as an independent variable when analyzing outcomes.

The authors analyze rates of reconstructive complications including capsular contracture, implant malposition and reconstructive failure as well as patient satisfaction using the BREAST-Q survey (15), while stratifying for autologous *vs.* implant-based reconstructions and irradiated *vs.* non-irradiated breasts. Several other co-variables including mastectomy timing, body mass index, age, laterality and smoking status, among others, were analyzed and controlled for if found to be significantly different between the irradiated and non-irradiated cohorts.

Out of 2,247 patients with greater than 1 year of follow-up, 622 received irradiation after mastectomy and 1,625 did not; 1,778 completed greater than 2 years of postoperative follow-up at which point the rate of reconstructive failure was significantly higher in irradiated implant-based reconstructions (18.7%) compared to irradiated autologous reconstructions (1.0%). This can be somewhat expected as implant-based reconstructive failure, designed as explantation of an implant or tissue-expander with immediate replacement, can be significantly affected by mastectomy flap complications influenced by radiation therapy, whereas autologous reconstruction failure, defined as total flap loss, is unlikely to be affected by postoperative irradiation.

The authors found that radiation therapy impacted both overall complication rates and patient satisfaction in a reconstruction-dependent manner. Radiotherapy was associated with a 2.12- and 2.64-time higher odds of complications in the implant-based group at the 1- and 2-year postoperative marks, respectively, with comparable risks in the autologous group at these same time points. Importantly, after BREAST-Q patient-reported satisfaction scores were adjusted for significant differences in covariables between irradiated and non-irradiated groups, patient satisfaction with breast scores were significantly higher in the irradiated autologous group compared to the irradiated implant group. These findings confirm the often-cited benefits of using autologous tissue for reconstruction in the setting of breast irradiation (16).

Radiation and autologous reconstruction

Autologous tissue has traditionally been the preferred reconstructive technique in the setting of planned previous or planned radiation therapy. The ability to provide well-

vascularized tissue to an area that will undergo ischemic insult logically becomes the superior alternative to placement of a foreign body under compromised tissues. There are still important considerations, however, that must be taken into account when planning autologous reconstruction in the setting of radiation therapy.

Autologous flaps have been shown to compromise subsequent radiation therapy secondary to increased medial tissue density from adiposity, decreasing the ability to target internal mammary nodes effectively while preventing irradiation of normal adjacent tissues (17). On the other hand, radiation therapy can compromise an autologous reconstruction. Studies have reported higher rates of fat necrosis, flap contracture, and fibrosis as well as worse aesthetic outcomes in flaps that were irradiated (18). Despite these issues, however, patient satisfaction has been suggested to be similar between patients with pre-irradiation or post-irradiation autologous tissue transfer (19,20).

An objective analysis of aesthetic results as well as complications secondary to irradiation such as fat necrosis, fibrosis and flap contracture were not included in the study by Jagsi *et al.* This data may have helped elucidate the prevalence of the previously reported complications of immediate autologous reconstructions exposed to radiation therapy. Though there were small differences in patient satisfaction with breast scores in autologous reconstructions between irradiated and non-irradiated cohorts, it is difficult to determine the impact of radiotherapy on cosmetic outcomes. Importantly, these issues did not significantly impact patient satisfaction with surgical outcomes as reported in the study.

Along these lines, timing of irradiation plays a key role in autologous breast reconstruction. The aforementioned complications are often cited as reasons for delaying autologous reconstruction until after radiation therapy. As this withholds the psychological benefits of immediate breast reconstruction after mastectomy, certain authors have advocated for a delayed-immediate approach, particularly when the need for postoperative radiation therapy is still unknown at the time of mastectomy (21). This approach entails placing a tissue-expander at the time of mastectomy which is subsequently deflated and reinflated before and after radiotherapy, respectively, with definite autologous reconstruction occurring after completion of radiation and re-inflation.

Despite the reports of higher complications with irradiated autologous reconstructions, the need to delay reconstruction is still questionable. Recent studies

have demonstrated negligible flap volume loss with hypofractionated radiotherapy (22) and systematic reviews have suggested comparable rates most complications including wound healing problems and fat necrosis (23). Patients' satisfaction with their breasts has also been reported to be comparable in immediate *vs.* delayed reconstruction with postmastectomy radiation therapy though physical well-being scores for the chest may be lower in those with irradiated flaps (24). While flap fibrosis and contracture remain a concern with flap irradiation, the degree of fibrosis and resulting aesthetic deformity will eventually have to be quantified, along with its impact on patient satisfaction in likely an institution-specific manner to determine whether this complication necessitates a delay in reconstruction.

Radiation and implant-based reconstruction

Historically, the combination and breast irradiation and implant-based reconstruction have been synonymous with poorer outcomes. Studies have reported higher overall complications rates, higher revision rates, increased grade III/IV capsular contracture, greater asymmetry and worse aesthetic results in the setting of radiation therapy (25–28). Irradiated implants have also shown a significantly higher rate of long-term implant loss and conversion to autologous reconstruction (29).

Several factors associated with both the radiation therapy and the reconstruction have been shown to influence these outcomes. The timing of radiation with regards to before or after breast reconstruction is critical. In review of patients at our institution with a history of prior radiation, we have found comparable complications rates between implant-based and autologous reconstruction after nipple-sparing mastectomy (30). On the other hand, patients that received postmastectomy radiation after nipple-sparing mastectomy and implant-based breast reconstruction had a significantly higher overall complication rate than those that were not irradiated (31).

Timing of post-mastectomy radiation and the decision to irradiate tissue-expanders *vs.* permanent implants in two-stage reconstructions remains controversial. Certain studies have demonstrated higher complication rates with irradiation of the tissue-expander as opposed to the implant (32), whereas others have not found any correlation between the timing of implant exchange and radiotherapy (33). Long-term implant failure rates have been found to be higher for irradiated tissue-expanders, though avoiding irradiation of

the permanent implant is suggested to have lower rates of capsular contracture and improved aesthetic results (34). In a sense, these issues are analogous the timing of autologous reconstruction as immediate reconstruction in both situations has been associated with poorer aesthetic results due to radiation damage to either the implant or the flap.

Importantly, several factors associated with the delivery of radiation can impact complications and must be considered when evaluating outcomes. For example, increased maximum radiation doses to the skin were associated with complications (31). Prone as opposed to supine positioning has also been shown to decrease irradiation of vital organs in the chest (35,36), though the effect of positioning on breast reconstruction complications is less clear (31).

Certain adjunct materials in implant-based breast reconstruction, such as acellular dermal matrix, may also affect outcomes in the setting of radiation therapy. Acellular dermal matrix has been suggested to limit the chronic inflammation exhibited by irradiated implants (37) and possibly decrease overall rates of failure in irradiated implant-based reconstructions though capsular contracture rates are still variable (38). More recent studies with prepectoral reconstruction, a technique with historically high rates of capsular contracture, have demonstrated favorable outcomes with utilization acellular dermal matrix after postmastectomy radiation (39). This data further suggests a role for implant-based reconstruction in the setting of radiotherapy though further investigation into the nuances of radiation therapy administration and reconstructive techniques is needed.

Decision-making in breast reconstruction

Jagsi *et al.* importantly cite the need for outcomes-based data and patient-centered metrics to improve the process of preoperative shared decision-making. Studies have demonstrated that despite patients' involvement in the decision-making process on breast reconstruction after mastectomy, their knowledge of the procedures needed to make high-quality decisions is often lacking (40). Clarifying patient expectations preoperatively is critical to informed decision-making, and also has an important role in influencing postoperative patient satisfaction (41). High-quality outcomes-based data is the key to facilitating these discussions and counseling patients to make their own, informed and educated decisions.

The study by Jagsi *et al.* provides invaluable information from the rare prospectively-collected and multicenter

database on expected complication rates and patient satisfaction after breast reconstruction with postmastectomy radiation therapy. Results from analysis of over 2,200 patients further confirm the benefits of using autologous tissue in the setting of planned breast irradiation by demonstrating decreased complications and increased patient satisfaction with the former technique when compared to implant-based reconstruction. While not all patients receiving postmastectomy radiation therapy are candidates for autologous reconstruction and outcomes with implant-based reconstruction and radiation will vary significantly based on institutional radiation protocols and reconstruction, the study provides much-needed high level-of-evidence data to further guide both clinical decision-making and directions for future research.

Conclusions

Eventually, the decision to pursue either autologous or implant-based reconstruction in the setting of radiation therapy must be individualized. High level-of-evidence data should be used as a guide to direct choices and educate patients on the risks and expected outcomes of each scenario. In the end, decisions must be made according to the individual institution with regards to radiation and mastectomy protocols, the individual surgeon in terms of comfort and experience with different procedures, and most importantly the individual patient, taking into consideration the patient's desires, expectations and capabilities. A process of shared decision-making with research-based counseling and patient-directed care will allow for true optimization of outcomes of these reconstructive procedures in the setting of radiation therapy.

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