Breast Reconstruction and Adjuvant Therapies

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ABSTRACT

Recent developments in the management of breast cancer have increased the complexity of planning for immediate breast reconstruction. Two recent trials have demonstrated superior locoregional control, disease-free survival, and overall survival in node-positive breast cancer patients with the addition of postmastectomy radiation therapy (XRT) to mastectomy and chemotherapy. On the basis of these results, the use of postmastectomy XRT in patients with early-stage breast cancer is increasing. Unfortunately, it is difficult to predict the presence or extent of axillary lymph node involvement—a major determinant of the need for postmastectomy XRT—before mastectomy. There are two potential problems with performing an immediate breast reconstruction in a patient who will require postmastectomy XRT. First, postmastectomy XRT can adversely affect the aesthetic outcome of an immediate breast reconstruction. Second, an immediate breast reconstruction can interfere with the delivery of postmastectomy XRT. Chemotherapy before or after reconstruction does not significantly increase the occurrence of wound-healing problems and breast reconstruction does not appear to delay the initiation or resumption of chemotherapy. The increasing use of postmastectomy XRT and chemotherapy in patients with early-stage breast cancer necessitates increased communication between the medical oncologist, radiation oncologist, breast surgeon, and plastic surgeon during treatment planning for these patients.

KEYWORDS: Breast reconstruction, radiation therapy, neoadjuvant chemotherapy, adjuvant chemotherapy, sentinel node biopsy

Recent developments in the management of breast cancer, including axillary sentinel lymph node biopsy and the increasing use of both postmastectomy radiation therapy (XRT) and adjuvant and neoadjuvant chemotherapy, have had a significant impact on breast reconstruction. The interplay and sequencing of these diagnostic and treatment modalities in patients with breast cancer has become an important issue.

This article will address the clinical dilemma of predicting which patients will require postmastectomy XRT, current indications for postmastectomy XRT, technical problems associated with the delivery of post-

mastectomy XRT after immediate breast reconstruction, aesthetic outcomes in patients treated with postmastectomy XRT after immediate breast reconstruction, the effects of adjuvant and neoadjuvant chemotherapy on breast reconstruction, and a new approach to breast reconstruction that may optimize outcomes for all patients.

DETERMINING THE STATUS OF THE AXILLARY LYMPH NODES

The status of the axillary lymph nodes is a major determinant of the need for postmastectomy XRT and thus

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can significantly affect the decision of whether to perform immediate or delayed breast reconstruction. Unfortunately, preoperative detection of micrometastases or small-volume metastases in the axillary lymph nodes of breast cancer patients is not always possible.¹ Furthermore, the intraoperative examination of sentinel lymph nodes with frozen-section or imprint cytology techniques or both does not reveal all micrometastases.¹⁻⁴ The reported false-negative rates for intraoperative evaluation of sentinel node micrometastases are as high as 89%.³ In addition, even if a positive sentinel node is identified intraoperatively and a complete level I and II axillary dissection is performed, the final number of positive axillary nodes and the extent of invasive carcinoma within the breast—and thus the need for postmastectomy XRT—will not be known until the final pathology review several days after surgery.

Several recent studies^{5,6} have evaluated clinicopathologic factors that may help identify preoperatively which clinically node-negative patients are at risk for undetectable micrometastatic axillary disease. A recent report from our institution⁵ demonstrated that patients who were 50 years of age or younger, patients who had tumors larger than 2 cm, and patients who had lymphovascular invasion detected in the initial biopsy specimen were at higher risk for harboring axillary metastases. However, although these factors can help identify high-risk patients, the ability to consistently predict and quantify axillary involvement before surgery is limited.

Recently, consideration has been given to performing axillary sentinel node biopsy prior to mastectomy and breast reconstruction. Although premastectomy sentinel node biopsy may be useful to rule out lymph node involvement in high-risk patients, it probably will not benefit all patients with invasive breast cancer. At present, only patients with four or more positive nodes are advised to receive postmastectomy XRT, so if the premastectomy sentinel node biopsy reveals one to three positive nodes, the need for postmastectomy XRT will still not be known until after the final review of the complete level I and II axillary lymph nodes, several days after mastectomy and completion axillary nodal dissection. If a patient with one to three positive nodes on premastectomy sentinel node biopsy undergoes immediate breast reconstruction before the final pathology report is complete and the final report indicates that postmastectomy XRT is needed, the patient may be at risk for a poor aesthetic outcome, and radiation delivery may be compromised. Additional considerations include the increased cost, patient inconvenience, and potential complications associated with sentinel node biopsy. In the future, if the indications for postmastectomy XRT are changed such that XRT is recommended for patients with any axillary disease, the use of premastectomy sentinel node biopsy probably could be further justified.

CURRENT ISSUES RELATED TO RADIATION THERAPY AFTER IMMEDIATE BREAST RECONSTRUCTION

The increasing use of postmastectomy XRT in patients with early-stage breast cancer along with the inability to determine preoperatively which patients will require postmastectomy XRT has increased the complexity of planning for immediate breast reconstruction. There are two potential problems with performing an immediate breast reconstruction in a patient who will require postmastectomy XRT. First, postmastectomy XRT can adversely affect the aesthetic outcome of an immediate breast reconstruction. Second, an immediate breast reconstruction can interfere with the delivery of postmastectomy XRT. Because XRT is one of the most important considerations affecting the timing and technique of breast reconstruction, plastic surgeons and radiation oncologists must work together in planning surgery for patients with breast cancer who desire reconstruction after mastectomy.

Current Indications for Postmastectomy Radiation Therapy

Recently, both the American Society for Therapeutic Radiology and Oncology⁷ and the American Society of Clinical Oncology⁸ published consensus statements regarding postmastectomy XRT. Both groups currently recommend postmastectomy XRT in patients with four or more positive lymph nodes or advanced tumors. However, on the basis of recent prospective, randomized controlled trials (the so-called Danish and Canadian trials^{9,10}) that demonstrated superior locoregional control, disease-free survival, and overall survival in breast cancer patients with T1 or T2 disease and one to three positive lymph nodes with the addition of postmastectomy XRT to mastectomy and chemotherapy, both societies have emphasized the need for additional prospective data concerning the use of postmastectomy XRT in these patients. In the future, depending on the outcome of ongoing trials, postmastectomy XRT may be widely recommended in patients with early-stage breast cancer. Some institutions have already instituted routine XRT in patients with early-stage disease.

Technical Problems with Radiation Delivery after Immediate Breast Reconstruction

An important issue in immediate breast reconstruction is whether the reconstructed breast will impair the delivery of postmastectomy XRT. Immediate breast reconstruction can cause technical problems with the design of the radiation fields for postmastectomy XRT.^{11,12} The previously mentioned randomized trials that reported a survival advantage with postmastectomy XRT^{9,10} included the internal mammary nodes within the radiation

fields. To treat these areas and minimize the dose to the heart and lungs, a separate electron beam on the medial chest wall is often required to match the laterally placed opposed tangent fields.¹¹ Some anatomic configurations make it difficult to successfully deliver XRT using such a separate medial electron-beam field.¹² The sloping contour of a reconstructed breast leads to an imprecise geometric matching of the medial and lateral radiation fields. Alternative radiation fields will result in either exclusion of the internal mammary nodes or increased irradiation of normal tissues.

Aesthetic Outcomes with Radiation Therapy after Immediate Breast Reconstruction

Our experience at The University of Texas M. D. Anderson Cancer Center¹³⁻¹⁵ and many of the other experiences reported in the literature^{13,16-19} indicate that autologous tissue is preferable for breast reconstruction in patients who have received XRT and that breast reconstruction should probably be delayed in patients who are known preoperatively to require postmastectomy XRT. Unfortunately, evaluation of complication rates and aesthetic outcomes is extremely difficult because of significant variation in the sequencing of XRT and reconstruction, the administration of systemic therapy, the duration of follow-up, and the techniques of radiation delivery and breast reconstruction.

In 1997, Williams and colleagues¹⁹ from Emory University compared outcomes of pedicled transverse rectus abdominis myocutaneous (TRAM) flap breast reconstruction in 19 patients who received XRT after reconstruction and 108 patients who received XRT before reconstruction with outcomes in 572 patients who underwent TRAM flap breast reconstruction without XRT. At a mean follow-up time after reconstruction of 47.6 months, 52.6% of the patients who received XRT after TRAM flap reconstruction demonstrated postirradiation changes, and 31.6% required surgical intervention.

Spear and Onyewu¹⁶ published a review in 2000 evaluating the effects of irradiation on outcomes after two-stage breast reconstruction with saline-filled implants. These authors retrospectively compared 40 patients who underwent two-stage, saline-filled implant breast reconstruction followed by irradiation with 40 other patients who underwent the same reconstruction procedure without irradiation. The incidence of complications was significantly higher in the irradiated group than in the control group (52.5 versus 10%; $P < 0.001$). Thirty-two percent of the irradiated patients had symptomatic capsular contractures, whereas no contractures occurred in the control group. Forty-seven percent of the 40 irradiated breasts needed flap procedures, whereas only 10% of the nonirradiated breasts needed flaps.

In 2001, investigators at our institution published a retrospective study¹⁵ comparing immediate and delayed free TRAM flap breast reconstruction in patients receiving postmastectomy XRT. In this study, 32 patients had immediate TRAM flap reconstruction before XRT, and 70 patients had XRT before TRAM flap reconstruction. The mean follow-up times after the end of treatment for the immediate and delayed reconstruction groups were 3 and 5 years, respectively. The incidence of early flap complications (vessel thrombosis and partial or total flap loss) did not differ significantly between the two groups. However, the incidence of late complications (fat necrosis, flap volume loss, and flap contracture) was significantly higher in the immediate reconstruction group than in the delayed reconstruction group (87.5 versus 8.6%; $P < 0.001$). Furthermore, 28% of the patients with immediate reconstruction required an additional flap to correct the distorted contour that resulted from flap shrinkage and severe flap contracture after XRT.

In 2002, Rogers and Allen²⁰ published the results of a study on the effects of XRT on breasts reconstructed with a deep inferior epigastric perforator (DIEP) flap. In this study, a matched-pairs analysis was performed of 30 patients who had breast reconstruction with a DIEP flap and postoperative XRT and 30 patients who underwent DIEP flap reconstruction without XRT. Patients who received postoperative XRT had higher incidences of fat necrosis in the DIEP flap (23.3% versus 0%; $P = 0.006$), fibrosis and shrinkage (56.7 versus 0%; $P < 0.001$), and flap contracture (16.7 versus 0%; $P = 0.023$).

EFFECTS OF ADJUVANT AND NEOADJUVANT CHEMOTHERAPY ON BREAST RECONSTRUCTION

An increasing number of breast cancer patients with stage I disease are being treated with adjuvant (postoperative) chemotherapy. Concerns have been raised that the cytotoxic and myelosuppressive effects of chemotherapy may result in poor wound healing or an increased incidence of postoperative wound infections²¹⁻²³ after breast reconstruction. Concerns have also been raised that complications of immediate breast reconstruction may interfere with the subsequent administration of adjuvant chemotherapy.²⁴⁻²⁷ Most studies of chemotherapy in patients treated with breast reconstruction have found no significant prolonged problems with wound healing,²⁴⁻²⁷ no delays in the initiation or resumption of chemotherapy as a result of wound-healing problems or infections,²⁴⁻²⁷ and no need for premature cessation of chemotherapy as a result of wound-healing problems.²⁵⁻²⁷

A study by Yule and colleagues²⁴ evaluated 46 patients who underwent immediate breast reconstruction with tissue expanders and subsequent permanent

implants. Twenty-three patients received adjuvant chemotherapy, and 23 did not. The authors reported no statistically significant differences in wound healing, wound infection, or capsular contracture between the patients treated with chemotherapy and those who did not receive chemotherapy. Several studies^{25,26} have shown that patients who undergo immediate breast reconstruction are not predisposed to delays in the initiation of adjuvant chemotherapy compared with patients who have mastectomy without reconstruction. Schusterman and coworkers²⁸ compared the free TRAM flap with the pedicled TRAM flap in patients requiring postoperative chemotherapy and found that 29% of patients who underwent reconstruction with a pedicled TRAM flap had a delay in the start of chemotherapy, compared with only 14% of the patients who underwent reconstruction with a free TRAM flap. In another study, by Caffo and colleagues,²⁷ patients who underwent immediate breast reconstruction did not require more frequent adjustments in the dose intensity of their chemotherapy as compared with patients who underwent mastectomy without reconstruction. Caffo and associates also observed that the interval between surgery and the start of expander inflation was not influenced by chemotherapy.

Neoadjuvant (preoperative) chemotherapy is being used with increasing frequency in breast cancer patients with stage II and III disease. The effect of

neoadjuvant chemotherapy on surgical outcome is of particular concern in these patients, as is the potential for wound-healing problems that may delay any subsequent adjuvant therapy. As the interval between chemotherapy and surgery increases, the impact on wound healing diminishes²⁹; the white blood cell count nadir occurs at 10 to 14 days after the last chemotherapy treatment, and recovery occurs by 21 days.³⁰ It is clinically recognized that an absolute neutrophil count less than 500 cells per cubic millimeter is detrimental to wound healing and wound strength.³¹ Wound healing can usually occur normally when the white blood cell count is greater than 3000 cells per cubic millimeter.³¹ Therefore, the timing of mastectomy with immediate breast reconstruction after neoadjuvant chemotherapy is important to avoid wound-healing problems.

Deutsch and colleagues³² evaluated 31 patients who underwent immediate reconstruction with a TRAM flap after neoadjuvant chemotherapy. Seventeen patients had postoperative complications, but only two had a delay in the start of adjuvant chemotherapy. Seven patients were smokers, five of whom had complications. Both delays in chemotherapy occurred in smokers. Neither delay was longer than 6 weeks after the normal 4-week interval. The authors found no correlation between the number of preoperative chemotherapy cycles, interval from chemotherapy to surgery, or stage of disease and surgical outcome. There was no statistically

Figure 1 An algorithm for decision making in clinically node-negative breast cancer patients who desire autologous breast reconstruction and sentinel lymph node biopsy. TRAM, transverse rectus abdominis myocutaneous flap; LD, latissimus dorsi myocutaneous. From Kronowitz SJ, Chang DW, Robb GL, et al. Implications of axillary sentinel lymph node biopsy in immediate autologous breast reconstruction. *Plast Reconstr Surg* 2002;109:1888–1896. Reprinted with permission of © Lippincott Williams & Wilkins.⁵

significant difference in the incidence of complications between pedicled and free TRAM flap reconstructions. The authors concluded that immediate breast reconstruction with the TRAM flap can be performed safely in patients who receive neoadjuvant chemotherapy but that the combination of neoadjuvant chemotherapy and smoking may significantly increase the risk of complications.

CONSIDERATIONS FOR CLINICAL PRACTICE

Surgeons should educate patients about breast reconstruction and increase their awareness of the interplay among the currently evolving diagnostic and treatment modalities. All patients who are candidates for immediate breast reconstruction should be made aware that if it is determined after reconstruction that XRT is required, the presence of the reconstructed breast could decrease

the quality of the aesthetic outcome^{13–20,33–36} and cause technical difficulties with radiation delivery.^{11,12} However, patients should also be made aware that the aesthetic results of delayed breast reconstruction are often less optimal than those of immediate reconstruction.^{33,37} Throughout the patient education process, it is prudent to obtain appropriate patient consent and document it in the medical record.

Careful planning prior to surgery is required to minimize adverse effects of XRT on breast reconstruction, which can result in significant patient dissatisfaction. During planning for immediate breast reconstruction, it is imperative to carefully review the stage of disease and the likelihood that the patient will require adjuvant XRT. If XRT is planned, the use of an implant for breast reconstruction should be strongly discouraged because of the risk of capsular contracture.^{14,17,18,34,38} Capsular contracture can distort the appearance of the reconstructed breast and cause chronic

Figure 2 Clinical decision making in patients with clinical stage II breast cancer who desire reconstruction after mastectomy.

*Increased risk defined as T2 tumor, T2 tumor with one positive lymph node, T2 tumor with positive biopsy margins, T2 tumor but possibly T3 tumor because of extensive calcifications consistent with ductal carcinoma in situ, T2 tumor either before or after neoadjuvant therapy, or T2 tumor with lymphovascular invasion on initial biopsy. †Breast reconstruction was performed with a transverse rectus abdominis myocutaneous flap, a latissimus dorsi flap plus an implant, or initial placement of a tissue expander with subsequent placement of a permanent implant.

chest wall pain and tightness.³⁵ Furthermore, the addition of a latissimus dorsi flap does not protect against the negative effects of radiation on breast implants.¹⁴ Even though autologous tissue alone is preferred in an irradiated patient, autologous reconstructions can also be adversely affected by postmastectomy

XRT.^{13,15,16,19,20,33} Contracture of the breast skin and atrophy of the flap³⁵ can result in anatomic distortion of the reconstructed breast that can progress over time, resulting in displacement of the flap superiorly.³⁵ Improving asymmetry can be extremely difficult,³⁵ and although a local flap may occasionally correct a small contour

Figure 3 Schema for delayed-immediate breast reconstruction. *After the completion of chemotherapy but prior to the initiation of radiation therapy. †Allow several weeks for skin desquamation to resolve. Results regarding expander reinflation are pending. ‡Usually performed 2 weeks after mastectomy and stage 1 of delayed-immediate reconstruction to prevent a delay of chemotherapy. If patient had neoadjuvant chemotherapy, definitive reconstruction may be delayed longer than 2 weeks. Note: Figure shows procedure for patients with unilateral breast cancer not treated with prophylactic contralateral mastectomy and for patients with bilateral breast cancer. In patients with unilateral breast cancer who elect prophylactic contralateral mastectomy, contralateral mastectomy and immediate reconstruction are performed at the time of definitive reconstruction of the breast with cancer. TRAM, transverse rectus abdominis myocutaneous; SGAP, superior gluteal artery perforator; LD, latissimus dorsi myocutaneous.

deformity, often an additional flap is required to restore breast shape and allow adequate healing.

In all cases of decision making about possible postoperative XRT and whether or not to perform immediate breast reconstruction, the situation should be

discussed at a multidisciplinary conference or addressed between the various medical, surgical, and radiation teams, with active participation by the patient. Our institution's multidisciplinary philosophy is to avoid immediate breast reconstruction in patients who will

Figure 4 Outcomes after delayed-immediate breast reconstruction in a 52-year-old woman with bilateral clinical stage II breast cancer. (A) Preoperative view. (B) Postoperative view 11 days after right skin-sparing modified radical mastectomy, left total mastectomy with sentinel lymph node biopsy, and bilateral subpectoral insertion of textured saline tissue expanders with intraoperative fill volumes of 500 mL. (C, D, and E) Postoperative view 5 months after delayed-immediate bilateral breast reconstruction with microvascular transverse rectus abdominis myocutaneous flaps. No revisions have been performed.

Figure 5 “Skin-preserving” delayed free microvascular transverse rectus abdominis myocutaneous flap reconstruction after stage 1 of delayed-immediate reconstruction and postmastectomy XRT in a 39-year-old woman with a clinical stage II (T2N0M0) right breast cancer. (A) Preoperative view. (B) Postoperative view 8 days after right skin-sparing total mastectomy with right axillary sentinel node biopsy and stage 1 of delayed-immediate reconstruction with placement of a subpectoral textured saline tissue expander with an intraoperative saline-fill volume of 750 mL. The permanent pathology after mastectomy upstaged the patient to stage III (T3N1M0). Because the sentinel node biopsy was positive on permanent pathology, the patient required an additional axillary surgery after mastectomy and stage 1 to perform a completion level I and II axillary node dissection. (C) Postoperative view 7 months after mastectomy and stage 1. The patient underwent additional tissue expansion during chemotherapy for a total saline-fill volume of 950 mL. Formation of a mature expander scar capsule prior to deflation allows for reexpansion after postmastectomy radiation therapy. (D) After completion of chemotherapy and prior to postmastectomy radiation therapy, the patient had complete deflation of the expander with removal of 950 mL in our clinic. (E) Complete deflation of the expander during postmastectomy radiation therapy allows for treatment of the internal mammary lymph nodes without excessive injury to the heart and lungs and avoids nonuniform radiation dose distribution.

Figure 5 (continued) (F, G, and H) Several weeks after the completion of postmastectomy radiation therapy, the tissue expander was progressively reinflated to the predeflation volume of 950 mL. (I) Four months after completion of the postmastectomy radiation therapy, the patient underwent a "skin-preserving" delayed breast reconstruction with a microvascular transverse rectus abdominis myocutaneous flap. (J) Postoperative view 17 days after delayed breast reconstruction. No revision or contralateral symmetry procedure was performed.

definitely require or have a high likelihood of requiring postmastectomy XRT. At M. D. Anderson Cancer Center, we have recently implemented a two-stage approach, "delayed-immediate breast reconstruction" (see the next section), for patients who are potential candidates for postmastectomy XRT. In this approach, we delay immediate reconstruction until after review of the final pathology report on the mastectomy specimen and the axillary lymph nodes. With the now routine use of axillary sentinel node biopsy in breast cancer patients, we now commonly use the internal mammary vessels as our first choice in immediate free TRAM breast reconstruction,⁵ which in addition to other benefits has eliminated the potential for vascular injury to the reconstructed breast when the sentinel lymph node is found to be positive on review of permanent sections and additional axillary nodal surgery is required⁵ (Fig. 1). As the indications for postmastectomy XRT and other treatment modalities continue to change, plastic surgeons will have to adapt their approach to breast recon-

struction to maintain an appropriate balance between minimizing the risk of recurrence and providing the best possible aesthetic outcome.

FUTURE DIRECTIONS: DELAYED-IMMEDIATE BREAST RECONSTRUCTION

At our institution, patients with clinical stage II breast cancer are evaluated by a multidisciplinary breast cancer team (Fig. 2), which includes a radiation oncologist. Patients who are deemed to be at increased risk for conditions necessitating postmastectomy XRT and who desire breast reconstruction are considered eligible for a recently implemented two-stage approach, "delayed-immediate breast reconstruction" (Fig. 3). Stage 1 consists of skin-sparing mastectomy with insertion of a completely filled textured saline tissue expander. After review of permanent sections, patients who do not

require postmastectomy XRT undergo delayed-immediate reconstruction (stage 2), and patients who require postmastectomy XRT complete this therapy and then undergo delayed reconstruction. We prefer to perform stage 2 of delayed-immediate reconstruction (definitive reconstruction) within ~2 weeks after mastectomy to avoid delays in the initiation of chemotherapy and to preserve the elasticity of the breast skin.

Delayed-immediate reconstruction (Fig. 4) allows patients to review their final pathology report with a radiation oncologist before committing to delayed-immediate or delayed reconstruction. Placement of the fully inflated expander in stage 1 prevents retraction of the mastectomy skin and loss of breast shape and affords the opportunity to revise the inframammary fold and debride any nonviable mastectomy skin prior to inset of an autologous tissue flap. It can be adapted to any clinical practice and modified to comply with various institutional guidelines for postmastectomy XRT.

Although our experience is limited to a few patients, our early results indicate that in patients who require postmastectomy XRT, delayed-immediate reconstruction may offer the opportunity for a better aesthetic outcome than is achieved with standard delayed reconstruction. Specifically, reexpansion of the mastectomy skin after postmastectomy XRT (Fig. 5) may provide additional usable skin for standard delayed TRAM flap reconstruction or decrease skin requirements for reconstruction with a latissimus dorsi flap plus an implant.

With the delayed-immediate approach, patients who do not require postmastectomy XRT can achieve aesthetic outcomes similar to those of immediate reconstruction, and patients who require postmastectomy XRT can avoid problems associated with postmastectomy XRT after an immediate breast reconstruction. Delayed-immediate reconstruction provides an additional option that broadens patients' treatment choices and allows patients to participate fully in treatment and reconstruction decisions.

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