Principles for Breast Reconstruction: Indications and Limits

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7.1 Introduction

Breast cancer occurs in one of eight American women. Although many patients are candidates for breast-conservation therapy, the rates of mastectomy and of contralateral risk-reducing mastectomy have risen in recent years in the USA [1]. The vast majority of patients undergoing mastectomy are candidates for breast reconstruction. Accordingly, the number of breast reconstruction operations has also increased [2].

Extensive literature clearly supports the advantages and oncologic safety of reconstruction after mastectomy. Reconstruction after mastectomy has been shown to be effective in restoring body image, improving quality of life, and reducing the psychological distress of mastectomy [3, 4]. At the same time, immediate reconstruction has been found to be oncologically safe after mastectomy, even in cases of advanced breast cancer [5–7]. This has been conclusively demonstrated in multiple studies, including a meta-analysis by Gieni et al. [8], which confirmed no increased risk of local recurrence with immediate breast reconstruction after mastectomy. However, despite its advantages and oncologic safety, fewer than 25 % of American patients undergo immediate or delayed reconstruction after mastectomy [9].

Options for reconstruction include reconstruction with autologous tissue, or with a tissue expander and implant. For unilateral reconstruction, symmetry is more easily obtained with a tissue flap than with an implant [2]. Autologous flap options include latissimus dorsi myocutaneous flaps, transverse rectus abdominus myocutaneous (TRAM) flaps, deep inferior epigastric perforator flaps, and gluteal artery perforator flaps [3]. Implants contain either saline or silicone. An immediate one-stage reconstruction with an implant may be feasible; however, most patients undergo a staged procedure with a tissue expander to allow for interval expansion, followed by an exchange to a permanent implant.

Autologous reconstruction may be difficult or complicated in patients who have undergone prior surgery at potential donor sites, or who have medical comorbidities such as hypertension, diabetes, and chronic obstructive pulmonary disease, who are smokers, or who are at the extremes of body mass index [3].

7.2 Immediate Versus Delayed Reconstruction

Most patients undergoing mastectomy are candidates for immediate reconstruction. Immediate reconstruction offers multiple advantages, including one-stage surgery, better cosmetic outcome, and improved psychological state. In the only randomized controlled trial to date comparing immediate and delayed breast reconstruction, Dean et al. [10] reported increased psychological well-being with immediate reconstruction [3]. Immediate reconstruction often achieves a better aesthetic result than delayed reconstruction, owing to preservation of the skin envelope and inframammary fold [11]. For patients who undergo delayed reconstruction, use of an autologous flap is preferable to use of an implant, as the process of tissue expansion required for an implant is difficult owing to skin stiffness, resulting in a suboptimal cosmetic result [2]. A combination of a tissue expander and an implant with a latissimus dorsi flap is another option for breast reconstruction.

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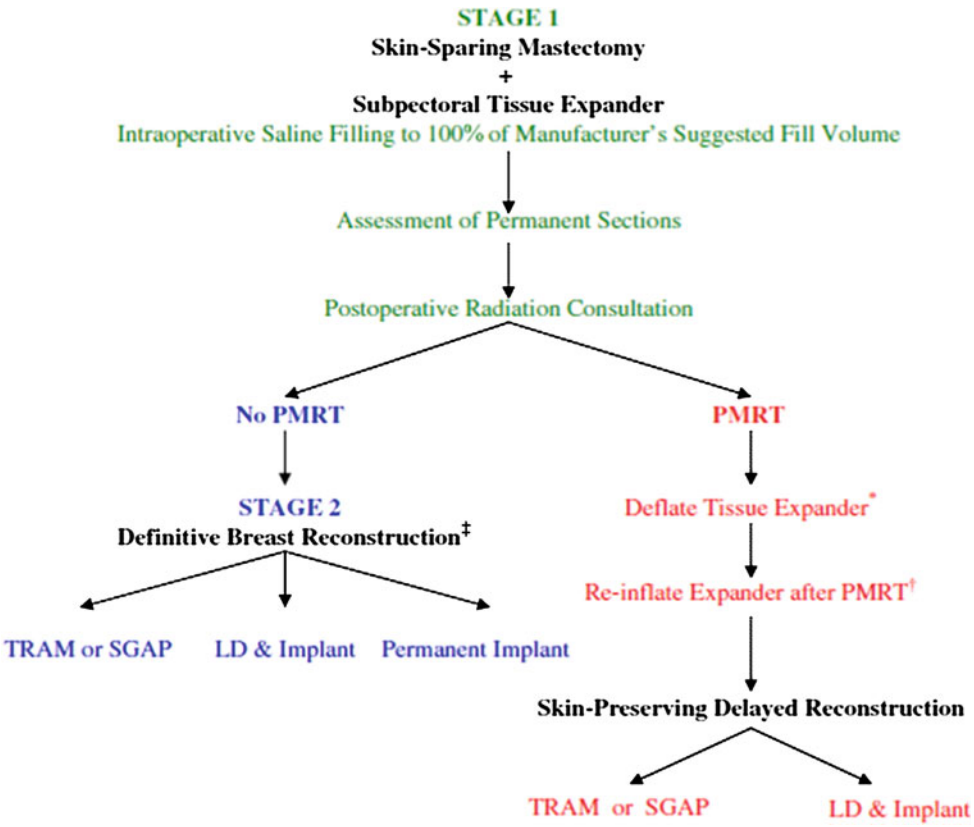

Fig. 7.1 MD Anderson Cancer Center delayed–immediate breast reconstruction protocol. *LD* latissimus dorsi flap, *PMRT* postmastectomy radiation therapy, *SGAP* superior gluteal artery perforator flap, *TRAM* transverse rectus abdominus myocutaneous flap. (Reprinted with permission from Kronowitz et al. [62])

7.2.1 Breast Reconstruction Considerations with Anticipated Postmastectomy Radiotherapy

Immediate reconstruction in patients who will undergo anticipated postmastectomy radiotherapy (PMRT) is controversial. The two main issues that raise concern are compromised delivery of radiotherapy in the face of a reconstructed breast, and the impact of radiotherapy on the long-term cosmetic result of the reconstruction [12].

7.2.2 Oncologic Safety of Reconstruction Prior to PMRT

Historically, delayed reconstruction has been recommended when PMRT is planned. Some still advocate this approach, owing to concerns of compromised delivery of radiotherapy in the presence of a reconstructed breast, whether a tissue flap or an implant [12–16]. Concerns include compromised delivery to the internal mammary lymph nodes, nonuniform radiotherapy delivery, underdosing of the chest wall, and increased radiotherapy dose to normal tissues with a breast reconstruction in place [12]. The evidence is conflicting. On the one hand, Motwani et al. [15] reported compromised delivery of radiotherapy in 52 % of patients who had undergone immediate reconstruction, compared with 7 % of controls. However, Koutcher et al. [17] found no compromised delivery of radiotherapy to the chest wall in most patients, with an excellent 30-month actuarial locoregional control rate of 97 %.

Owing to concerns of compromised radiotherapy delivery attributable to the reconstructed breast, a "delayed–immediate" reconstruction algorithm is advocated at the MD Anderson Cancer Center for patients who will receive PMRT [2]. With this approach, a tissue expander is placed at the time of mastectomy, and is deflated during adjuvant radiotherapy (protocol outlined in Fig. 7.1). Tissue expansion is performed after the completion of radiotherapy, and reconstruction with an autologous flap is performed 4–6 months thereafter [18]. In this series, the approach resulted in low complication rates, with tissue expander loss in 14 % of patients. The recurrence rate at 32 months of follow-up was low, at 3 % [18]. The complication rate with a "delayed–immediate" approach with subsequent flap reconstruction may be lower than that for a standard delayed flap reconstruction (26 % vs. 38 %, $p = 0.40$) [18].

Despite the concerns about radiation delivery that prompted development of the "delayed–immediate approach," many authors have reported acceptable recurrence rates and cosmetic outcomes with immediate reconstruction followed by PMRT [17]. In one retrospective

review of 191 patients requiring PMRT who underwent TRAM flap reconstruction in either an immediate or a delayed fashion, the risk of locoregional recurrence was not significantly increased in the group undergoing immediate reconstruction (3.7 % vs. 1.8 %, $p = 0.65$) at 40 months of follow-up [19]. Similarly, Wright et al. [20] retrospectively reviewed 104 patients who underwent exchange for a permanent implant prior to PMRT. Local control rates were excellent, 0 % at 5 years, and immediate reconstruction was not associated with an elevated risk of distant metastases or death.

In contrast to these data, others have reported higher rates of locoregional recurrence among patients undergoing immediate reconstruction. Nahabedian et al. [21] retrospectively analyzed 146 patients who underwent immediate or delayed reconstruction after PMRT. Locoregional recurrence rates were higher in patients who underwent immediate versus delayed reconstruction (27 % vs. 15 %, $p = 0.04$). These data should be interpreted with caution because of the higher than expected rates of recurrence [21, 22]. As a result of these conflicting data, the safety of immediate reconstruction prior to PMRT remains controversial.

7.2.3 Effects of Radiotherapy on the Cosmetic Outcome of the Reconstructed Breast

In addition to conflicting data about oncologic safety, there is also debate about the impact of reconstruction prior to PMRT on cosmetic outcomes. The main complications caused by radiation on the reconstructed breast include fat necrosis, impaired wound healing, contracture, fibrosis, volume loss, and architectural distortion [23]. There are data to support superior cosmetic results with delayed reconstruction compared with immediate reconstruction. Javaid et al. [23] in a systematic review of ten published reports of patients undergoing immediate and delayed reconstruction and PMRT found a higher incidence of breast fibrosis and contracture with immediate reconstruction. Similarly, Kronowitz et al. [16], in a systematic review of 49 articles, reported high rates of contracture and implant loss among patients undergoing immediate reconstruction prior to PMRT.

Other groups have also reported lower rates of complications after delayed reconstruction. Adesiyun et al. [24], in a review of 113 patients who underwent immediate or delayed breast reconstruction with PMRT, reported a lower rate of complications in the delayed-reconstruction group (32 % vs. 44 %, $p = 0.18$), although this difference was not statistically significant. The patients' general satisfaction with their cosmetic outcome was similar in the two groups (68 %) [24]. Another group found no significant difference in complication rates with immediate or delayed reconstruction with TRAM flaps in patients who received PMRT, but the authors ultimately recommended delayed reconstruction because of possible low power of the study [25].

Compared with the aforementioned studies, other groups have reported acceptable cosmetic results and complication rates with immediate reconstruction. A meta-analysis of 11 studies by Barry et al. [26] concluded that postoperative outcomes did not differ depending on whether reconstruction was performed before or after PMRT. Autologous flaps appeared to have superior outcomes. Postoperative complications such as fibrosis, contracture, infection, fat necrosis, and reoperation were lower with autologous flap reconstruction than with implant reconstruction [26]. Thus, if immediate reconstruction is pursued, many authors advocate reconstruction with an autologous flap over a tissue expander/implant to enhance cosmetic results [6].

Although many authors have reported superior outcomes with flap reconstruction compared with implant reconstruction prior to PMRT, this does not necessarily imply that successful outcomes cannot be achieved with implant reconstruction. For example, Cordeiro et al. [27, 28] reported satisfactory aesthetic results with immediate tissue expander placement, followed by exchange for a permanent implant prior to radiotherapy. Aesthetic results were categorized as "good to excellent" in 80 % of patients, with an implant loss rate of 11 % [27].

7.2.4 Inflammatory Breast Cancer

In patients with inflammatory breast carcinoma, delayed reconstruction is recommended because of extensive skin involvement and a high risk of local recurrence [29]. The required resection of skin precludes a skin-sparing mastectomy. Furthermore, timely administration of radiotherapy is imperative, making the delay for healing after reconstruction undesirable. Therefore, reconstruction should be delayed in patients undergoing mastectomy for inflammatory breast cancer. This recommendation is reflected in the 2012 National Cancer Comprehensive Network guidelines [30].

There are two small series that have reported success with immediate reconstruction. Chin et al. [31] performed a retrospective analysis of 23 patients with inflammatory breast cancer who underwent immediate or delayed reconstruction. They reported similar rates of locoregional recurrence (29 % vs. 33 %, p not significant), suggesting no compromised oncologic outcome with immediate reconstruction. Another small series found no overall survival difference in patients who underwent immediate reconstruction, although six of ten patients did develop local recurrence [32]. Importantly, these small studies do not

offer sufficient statistical power to conclusively demonstrate the safety of immediate breast reconstruction for patients with inflammatory breast cancer.

In conclusion, for patients who will likely require PMRT, immediate reconstruction remains controversial, owing to concerns of compromised radiotherapy delivery and impaired cosmetic outcome of the reconstructed breast. However, many authors have reported acceptable cosmetic outcomes and comparable rates of locoregional recurrence with immediate reconstruction. Immediate reconstruction is not recommended in patients with inflammatory breast cancer.

7.2.4.1 Nipple-Sparing Mastectomy

After a traditional skin-sparing mastectomy, patients may subsequently undergo nipple reconstruction. This requires an additional surgical procedure and tattooing, and ultimately, many patients may never pursue this. Furthermore, results may be disappointing. Jabor et al. [33] reported a 14 % rate of patient dissatisfaction after nipple–areola complex (NAC) reconstruction owing to loss of nipple projection and the overall appearance and texture of the reconstructed NAC. Therefore, preservation of the NAC with a nipple-sparing mastectomy (NSM) may be desirable in some patients.

Subcutaneous mastectomy with NAC preservation and breast reconstruction was first described by Freeman [34] in 1962. Preservation of the NAC may enhance cosmetic outcome and offer psychological benefit, as the NAC plays an important role in the identification of a woman's body image [35]. Indeed, Boneti et al. [36] reported higher patient cosmetic satisfaction in patients who had undergone NSM as compared with skin-sparing mastectomy. There is theoretical concern about the oncologic safety of this procedure owing to an inability to resect all of the retroareolar ductal tissue.

7.2.5 Candidates for NSM

When selecting a candidate for NSM, one must consider the risk of cancer involvement of the NAC, and the size and degree of ptosis of the breast [37]. Candidates for NSM include patients undergoing risk-reducing mastectomy. Patients may pursue risk-reducing mastectomy because of high-risk factors such as a strong family history, the presence or history of a contralateral breast tumor, lobular carcinoma in situ, or previous radiation for Hodgkin lymphoma [38]. Selected patients with ductal carcinoma in situ (DCIS) or invasive breast cancer may also be candidates for NSM [38]. In appropriately selected patients, only 12 % will have tumor involvement at the NAC, precluding preservation [39, 40].

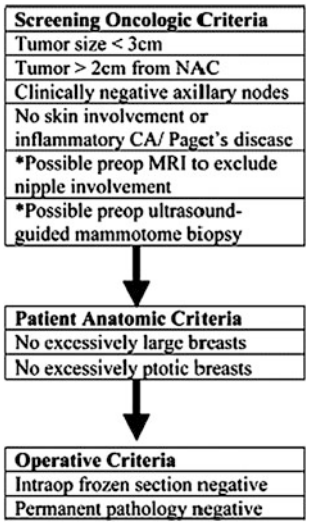

Fig. 7.2 Patient selection criteria for nipple-sparing mastectomy. *CA* cancer, *NAC* nipple–areola complex. (Reproduced with permission from Spear et al. [50])

The factors associated with nipple involvement include tumors larger than 2–4 cm, a tumor–nipple distance of less than 2 cm, breast tumors overlapping more than one quadrant, grade 3 or undifferentiated cancers, stage III disease, human epidermal growth factor receptor 2 (HER2)/neu positivity, and an extensive intraductal component of greater than 25 % [41–43].

For patients with invasive cancer, small tumors located in the periphery of the breast have the lowest risk of NAC involvement. The lowest risk of NAC involvement occurs in tumors smaller than 2 cm, located at least 2.5 cm from the NAC [44]. Tumors located within 2 cm of the NAC, or larger than 4 cm, were found in one report to have occult tumor present at the nipple in 50 % of cases [44]. A pathologic analysis of 140 mastectomy specimens reported a 16 % rate of NAC involvement with cancer. In all cases, the primary tumor was located within 2.5 cm of the NAC [45].

Many series of carefully selected patients have reported low rates of NAC involvement, ranging from 6 to 10 % [37, 38, 46–49]. In one series of patients with peripheral tumors and clinically node-negative disease, a low rate (less than 2 %) of NAC involvement was reported [48]. Therefore, the risk of NAC involvement is lower in patients with low-grade, unicentric, small, peripheral tumors, with clinically uninvolved axillary lymph nodes, who have not undergone neoadjuvant chemotherapy [39, 48, 50, 51]. Patients who will likely undergo radiotherapy are not ideal candidates, as they have advanced disease that portends a higher probability of NAC involvement. Furthermore, radiotherapy may result in distortion and asymmetric displacement of the NAC. A proposed algorithm for patient selection is illustrated in Fig. 7.2.

7.2.6 Intraoperative Assessment of NAC Tumor Involvement

Identification of NAC tumor involvement precludes NAC preservation. Intraoperative pathologic assessment with frozen section of the retroareolar ducts can be useful to identify the presence of NAC tumor involvement at the initial surgery [39, 42, 52]. Dissection of the retroaerolar ducts should be done sharply, as cautery can cause thermal damage to the NAC [52]. Coring of the nipple ducts may be facilitated by everting the nipple [52].

Frozen-section analysis is 91 % sensitive and 99 % specific for assessing tumor involvement of the NAC [53]. Reported rates of positive frozen section range from 2.5 to 12 % in well-selected patients [36, 39, 54, 55]. With careful patient selection and the use of preoperative MRI, Wijayanayagam et al. [56] reported a low rate of NAC involvement of 3 %. NAC tumor involvement may not be identified until final surgical pathologic analysis, necessitating NAC resection at a second surgery. When the NAC is involved with tumor, the histologic finding is usually DCIS, although atypical ductal hyperplasia and invasive breast carcinoma may also be identified [39, 43, 54, 57].

7.2.7 Rates of Recurrence After NSM

Multiple series with less than 3 years of follow-up have reported recurrence rates of 5 % or less after NSM, comparable to rates of recurrence after skin-sparing mastectomy [36, 40, 55, 58]. Voltura et al. [55] reported a 5 % recurrence rate at 24 months in patients with aggressive triple-negative tumors. Sacchini et al. [58] reported recurrences in only two of 123 patients undergoing NSM, with a median follow-up of 25 months. Recurrences did not occur at the NAC [58]. Breast cancer occurred in two patients who underwent risk-reducing mastectomies, located in peripheral locations [58]. In another series of 96 patients who underwent NSM with a median follow-up of 34 months, only one patient developed a locoregional recurrence, and two patients developed distant metastases [40].

The reported recurrence rates of longer-term studies, with follow-up of at least 3 years, range from 5 to 28 % [39, 42, 59, 60]. In a review of 112 patients who underwent NSM and had tumors located at least 2 cm from the nipple, 5 % of patients has recurrence at a mean follow-up of 59 months [42]. Recurrences occurred in the chest wall, upper breast, and inframammary fold, with only one recurrence in the NAC [42]. The location of these recurrences highlights the importance of considering the potential for elevated risk at the periphery of the breast after NSM, as access to the peripheral breast may be more difficult if a small periareolar incision is used.

Studies with long-term follow-up of patients who undergo NSM are limited, and have not definitively demonstrated the long-term oncologic safety of NSM. In a series with a follow-up of 5.5 years, Caruso et al. [59] reported a recurrence rate of 12 % in 50 patients. Recurrences occurred at the NAC in one patient, and distant metastases developed in four patients. In a prospective trial with a median follow-up of 13 years, Benediktsson and Perbeck [53] reported a high overall locoregional recurrence rate of 28 %. This may suggest that NSM is not oncologically safe in the long term, but this high rate may have been due to patient selection. Patients at high risk of recurrence were included, with tumors larger than 3 cm or multicentric disease [53]. Patients in this study who received PMRT had a local recurrence rate of 8.5 %, similar to reported rates after skin-sparing mastectomy [53].

Petit et al. [60] recently published an update of their experience with 934 patients who underwent NSM with a median follow-up of 50 months. These investigators routinely treat the NAC intraoperatively with electron intraoperative treatment if the frozen section is negative, and preserve the NAC even if final pathologic investigation reveals tumor involvement [60]. For patients with invasive ductal cancer, 3.6 % had recurrence in the breast at 5 years, and 0.8 % had recurrence at the NAC [60]. Of the patients who had recurrence at the NAC, most had an extensive intraductal component and had HER2/neu positivity [60]. For patients with DCIS, the rate of locoregional recurrence at 5 years was high: 8 % [60]. The rate of recurrence was 4.9 % in the breast and 2.9 % at the NAC [60]. These high recurrence rates may cause one to pause before offering this procedure to patients with DCIS. Predictors of breast recurrence among patients with DCIS included age under 40 years, positive retroareolar margins, estrogen receptor negativity, progesterone receptor negativity, high-grade histologic findings, HER2/neu positivity, and Ki-67 index greater than 20 % [60].

In conclusion, several studies support the short-term oncologic safety of NSM, with locoregional recurrence rates similar to those of skin-sparing mastectomy, and rare recurrences occurring at the NAC. However, the long-term oncologic safety of this procedure has not been determined, and the recent data of Petit et al. [60] may be a reason for caution in patients with DCIS. More studies with longer-term follow-up are needed, as the literature to date is not yet definitive on the oncologic safety of NSM in the long term.

7.2.8 NSM in BRCA Mutation Carriers

The oncologic safety of NSM in BRCA mutation carriers is controversial, as breast tissue connects with the nipple and cannot be completely resected with NAC preservation [61].

One pathologic analysis of mastectomy specimens of BRCA patients revealed that terminal ductal lobular units were present in 24 % of the NACs and 8 % of nipples [61]. The long-term potential of this retained tissue developing a cancer is unknown [61]. In this study, occult NAC tumor involvement was 0 % in risk-reducing specimens, and 10 % in therapeutic specimens. These rates are similar to those for non-BRCA mutation carriers [61]. Long-term studies are needed before we can say with absolute certainty that NSM is an oncologically sound procedure in BRCA patients.

7.2.8.1 Postoperative Outcomes of the NAC

Patients should be counseled that the NAC preservation in NSM is mainly of cosmetic, not functional benefit. Most patients will not experience sustained preservation of nipple sensation or erectile ability [39]. There is a risk of approximately 12 % of occult tumor involvement at the NAC, requiring resection [39, 40]. Furthermore, there is a risk of partial or complete necrosis of the NAC in approximately 4–11 % of patients [38, 39, 42, 54, 58]. Preservation of the blood supply to the NAC may be maximized by use of a lateral incision, without a circumareolar extension. Also, the NAC may ultimately settle in a displaced or asymmetric position, with lateral displacement occurring in 67 % of cases in one series [54].

Numerous studies have demonstrated the short-term oncologic safety of NSM in risk reduction, and in patients with early-stage breast cancer. Larger studies with longer follow-up are needed to definitely demonstrate that NSM has locoregional recurrence rates comparable to those of skin-sparing mastectomy. Ideal candidates for NSM should have small tumors (less than 3 cm), located at least 2 cm from the nipple, with clinically uninvolved axillary lymph nodes, and without skin involvement [50]. Patients with extensive DCIS are not good candidates for NSM because of reported high rates of locoregional recurrence [60]. Use of intraoperative frozen section can identify most patients with occult NAC involvement. Preservation of the NAC may enhance cosmetic outcome and overall patient satisfaction.

7.3 Conclusions

Most patients are candidates for immediate breast reconstruction after mastectomy. For patients who will require PMRT, immediate reconstruction is controversial, but many authors have reported acceptable cosmetic results and locoregional recurrence rates with immediate reconstruction. NSM may be an attractive option for women for risk reduction, or in selected patients with early-stage breast cancer.

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