BREAST RECONSTRUCTION FOLLOWING PROPHYLACTIC OR THERAPEUTIC MASTECTOMY FOR BREAST CANCER

Effective Date: September 2013

The recommendations contained in this guideline are a consensus of the Alberta Provincial Breast Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Treatment for breast cancer largely favors breast conservation, whenever possible. Current guidelines on the surgical management of breast cancer recommend lumpectomy and whole breast irradiation as an equivalent option to mastectomy, for patients with stage I or stage II invasive breast cancer. [1,2] In addition, as outlined in the Alberta Health Services, Cancer Care guideline, *Risk Reduction and Surveillance Strategies for Individuals at High Genetic Risk for Breast and Ovarian Cancer*, [3] and other guidelines, [4-6] prophylactic bilateral mastectomy may also be considered as a risk reduction strategy for patients at high genetic risk of developing breast cancer.

For women who do undergo mastectomy, whether for therapeutic or for prophylactic reasons, the side effects of mastectomy can be significant. Anxiety and depression, poor body image, sexual issues, and phantom breast syndrome have been well-documented among patients who have undergone mastectomy. [7-13] However, breast reconstruction may alleviate some of the post-mastectomy distress experienced by these patients. [14-16] The purpose of this guideline is to provide physicians in Alberta with recommendations on the selection of candidates for breast reconstruction, the decision on how much tissue to remove during mastectomy, the timing of reconstruction procedures, the selection of an appropriate reconstruction, and the impact of breast reconstruction on adjuvant therapy.

GUIDELINE QUESTIONS

The questions below are consensus-based and were derived from a discussion among the members of the guideline working group.

1. Who is a candidate for post-mastectomy breast reconstruction?
2. Which types of breast reconstruction are available?
3. What is the appropriate timing of breast reconstruction?
4. Which factors can affect the outcomes of breast reconstruction?
5. What is appropriate extent of mastectomy (i.e., skin-sparing, nipple-sparing)?
6. What are the risks and benefits associated with breast reconstruction?
7. What is the appropriate post-breast reconstruction surveillance?
8. What is the role of acellular dermal matrix in implant-based breast reconstruction?
9. What is the role of autologous fat grafting as an adjunct to breast reconstruction?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Breast Tumour Team. Members of the Alberta Provincial Breast Tumour Team include medical oncologists, radiation oncologists, surgeons, nurses, pathologists, psychologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Breast Tumour Team, a province-wide working group of plastic surgeons, and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit handbook.

SEARCH STRATEGY

The PubMED and EMBASE databases were searched from 1980 to 2012 May 30 for literature on breast reconstruction following prophylactic or therapeutic mastectomy. The search terms *breast reconstruction* and *cancer* or *neoplasm* were used and results were limited to randomized controlled trials, prospective and retrospective cohort studies, meta-analyses, guidelines, and reviews, published in English. The search returned 223 citations, of which 74 were relevant. Prior to publication, the search was extended to 2013 April 20, resulting in an additional eight relevant studies. In addition, reference lists of publications identified by the search were hand-searched for additional publications, resulting in 97 additional citations.

Based on post-hoc discussions among the working group, two subsequent searches of literature were conducted. PubMED was searched for literature on the integration of reconstruction with sentinel lymph node biopsy and of the impact of chemotherapy on breast reconstruction. Both searches were limited to English language publications but were not limited by study design. A total 11 citations on sentinel lymph node biopsy and 12 citations on chemotherapy were deemed relevant.

The National Guidelines Clearinghouse and SAGE Directory of Cancer Guidelines were also searched from 2006 to June 15, 2012 for guidelines on breast reconstruction. The search returned 17 guidelines, of which seven were relevant. The guidelines, plus an additional guideline from PubMED, were included in the literature review. None of these published guidelines focused specifically and solely on breast reconstruction.

TARGET POPULATION

The recommendations contained in this guideline apply to women over the age of 18 years, who are candidates for mastectomy, either for the treatment of breast cancer or for the prophylaxis of breast cancer in patients at high genetic risk.

RECOMMENDATIONS

1. **Eligibility for post-mastectomy breast reconstruction.** Patients who are to undergo either prophylactic or therapeutic mastectomy should have access to breast reconstruction consultation.

   Various patient and treatment factors affect options, risks, and outcomes of a woman's breast reconstruction. Consultation with a specialist in breast reconstruction can provide a patient with a specialized treatment plan and anticipated outcomes so she can determine if breast reconstruction is appropriate for her. Table 1 presents factors which may limit options and outcomes of breast reconstruction.

2. **Types of breast reconstruction.**
   - Several types of breast reconstruction are available, including: implant-based, autologous flap (i.e., DIEP, TRAM, SIEA), and combination reconstructions (i.e., LD with implant).
   - There is no evidence to suggest that one type of procedure can be recommended over another. The decision as to which type of reconstruction to use should be left to the discretion of the surgeons and the patient after providing counseling on the benefits and limitations of each procedure. Table 1 presents factors which may influence the type of reconstruction to be performed.

Table 1. Clinical factors to consider when deciding on the timing and method of reconstruction.

Clinical factor	Guidance by Reconstruction Type		Evidence *
	Immediate	Delayed	
Cancer factors			
Ductal carcinoma in situ	Acceptable	Acceptable	Moderate
T1 or T2 tumours	Acceptable	Acceptable	Moderate
T3 or T4 †	Not recommended	Acceptable	Moderate
Inflammatory breast cancer †	Not recommended	Acceptable	Insufficient
Multicentric tumours	Acceptable	Acceptable	Insufficient
Suspicious, palpable axillary nodes †	Not recommended	Acceptable	Insufficient
Positive pre-mastectomy SLNB †	Not recommended	Acceptable	Moderate
Treatment factors			
Prior radiotherapy	Acceptable; favors autologous	Acceptable; favors autologous	Good
Prophylactic mastectomy	Acceptable	Acceptable	Good
Additional delay to surgery >3 weeks	Not recommended	Acceptable	Insufficient
Prior non-oncologic breast surgery	Acceptable	Acceptable	Moderate
After preoperative systemic therapy	Acceptable	Acceptable	Good
Before adjuvant chemotherapy	Acceptable	Acceptable	Good
Before adjuvant radiotherapy †	Not recommended	Acceptable	Good
Prior diagnostic / excisional biopsy	Acceptable, but may affect skin sparing	Acceptable	Insufficient
Patient factors			
Older age	Acceptable, but may affect risks	Acceptable, but may affect risks	Moderate
Obesity	Acceptable, but may affect risks	Acceptable, but may affect risks	Moderate
Diabetes	Acceptable, but may affect risks	Acceptable, but may affect risks	Moderate
Smoking	Acceptable, but may affect risks	Acceptable, but may affect risks	Moderate
Patient preference	Acceptable	Acceptable	Moderate
Planned future pregnancy	Acceptable; favors implants	Acceptable; favors implants	Insufficient

* Good evidence: at least one well-designed randomized controlled trial or several comparative studies available.
Moderate evidence: non-comparative observational studies (i.e., prospective and/or retrospective cohorts) available only.
Insufficient evidence: only case reports or anecdotal evidence available; when the evidence was insufficient, recommendations were developed based on the working group's consensus or from guideline recommendations elsewhere.

† Recommendation is based on the high likelihood that patients will receive radiotherapy, as per Alberta CancerControl guideline BR-005 "Adjuvant Radiation Therapy for Invasive Breast Cancer" (2013).

3. **Timing of breast reconstruction (immediate versus delayed).**
   - Patients undergoing prophylactic mastectomy should be considered for immediate breast reconstruction (i.e., at the time of surgery).
   - Patients undergoing therapeutic mastectomy who **do not require postmastectomy radiotherapy** should be considered for immediate breast reconstruction. There is sufficient evidence to support the oncologic safety of immediate reconstruction in these patients.

- Patients for whom radiotherapy is planned or highly likely should be discussed for breast reconstruction appropriateness in a multidisciplinary setting; in general, reconstruction should be delayed until after treatment with radiotherapy has been completed.
    - In patients where the likelihood of radiotherapy after mastectomy is uncertain (e.g., clinically staged node negative T1 or T2 tumors), an "upfront" staging sentinel lymph node biopsy (SLNB) could be considered as a separate, outpatient procedure to assist in determining the probability of post-mastectomy radiotherapy prior to proceeding with mastectomy and immediate reconstruction.
    - Data on the benefits and limitations of an "upfront" SLNB is limited to retrospective case series only. Until randomized data is available to compare "upfront" staging with intraoperative staging using frozen section analysis, one strategy cannot be recommended over another.
- Patients receiving other therapies, including chemotherapy, can be safely offered breast reconstruction with no evidence of adverse effects on the outcome of reconstruction and no clinically relevant delay in chemotherapy or adverse effect on the efficacy of chemotherapy.
- Patients for whom immediate breast reconstruction is not appropriate may be considered for delayed breast reconstruction as an acceptable alternative.

4. **Factors that can affect the outcomes of breast reconstruction (Table 1).** Factors that should be weighed when considering candidates for any breast reconstruction (immediate or delayed) include:
    - treatment factors: prior, concurrent, or known future breast cancer treatment;
    - patient factors: co-morbidities, body habitus, smoking status, behavioral/ lifestyle factors; and
    - cancer factors: tumour stage and location, risk of relapse.

5. **Extent of mastectomy (i.e., skin-sparing, nipple-sparing).**
    - Skin-sparing mastectomy is acceptable for any patient undergoing immediate breast reconstruction.
    - Nipple-sparing mastectomy is generally not recommended for patients with malignancy. The decision as to whether to pursue a nipple-sparing procedure requires multidisciplinary input and discussion between the surgeons and the patient about potential additional risks associated with this approach.
    - There is limited evidence around what surgical factors to consider when performing mastectomy; however, based on consensus of the guideline working group, a list of technical considerations is included in Appendix A.

6. **Risks and benefits of breast reconstruction.**
    - Patients should be made aware that breast reconstruction is a complex, major, multi-step surgery and that complications can occur with any reconstruction.
    - Patient expectations should be assessed prior to surgery, in order to optimize care. In addition, patients should be made aware that cosmetic results may vary from patient to patient and that the reconstructive surgery will not restore the breast to its original appearance.

- Complications can occur with each type of reconstructive procedure. Listed below are the most common complications associated with each procedure:
  - Autologous reconstructions: seroma, scarring, hematoma, chronic back pain, flap failure, abdominal weakness, bulge, or hernia, and necrosis. There is evidence to suggest that DIEP flaps carry a higher risk of fat necrosis and flap loss, as compared to muscle-sparing TRAM flaps. There is also evidence to suggest that donor-site morbidity (i.e., bulge formation, hernia) is lower with DIEP flaps, as compared to muscle-sparing TRAM flaps.
  - Implant-based reconstructions: mastectomy skin flap necrosis, infection, seroma, hematoma, chronic breast pain, implant rupture or malposition, and capsular contracture. There is evidence to suggest that the risk of capsular contracture is lower with the use of textured implants, as compared to smooth implants.

7. **Post-breast reconstruction surveillance.** There is no evidence to support routine screening mammography of the reconstructed breast, in the absence of a palpable recurrence or symptoms of recurrence. Fat necrosis is a common and benign mammographic finding in patients with reconstructed breasts. Patients with suspicious masses or symptoms should be referred to a surgeon for examination and further workup.

8. **Implant-based acellular dermal matrix reconstructions.**
   - The use of Human Acellular Dermal Matrix (HADM) in immediate prosthetic breast reconstruction confers the potential benefits of improved aesthetic results, reduced rates of capsular contracture and implant malposition, and the possibility of a single-stage “direct to implant” procedure for carefully selected patients.
   - These benefits should be weighed against the potentially higher risks of postoperative seroma, infection, and mastectomy skin flap necrosis in HADM-assisted prosthetic reconstruction, when compared to traditional, non HADM-assisted techniques.
   - Based on consensus, the use of HADM in breast reconstruction should be at the discretion of the reconstructive surgeon, in consultation with the patient and oncologic team. Indications to use HADM include two-stage expander implant reconstruction or direct to implant single-stage reconstruction, to gain increased control over infra-and lateral mammary fold position and ptosis.

9. **Adjunctive autologous fat grafting (lipofilling) for contour regularities after breast reconstruction.** There is currently limited data on the long-term oncologic safety and long-term contour benefits of lipofilling. Data from comparative studies and case reports suggest that patient satisfaction is good; however more data is needed.

TREATMENT ALGORITHM

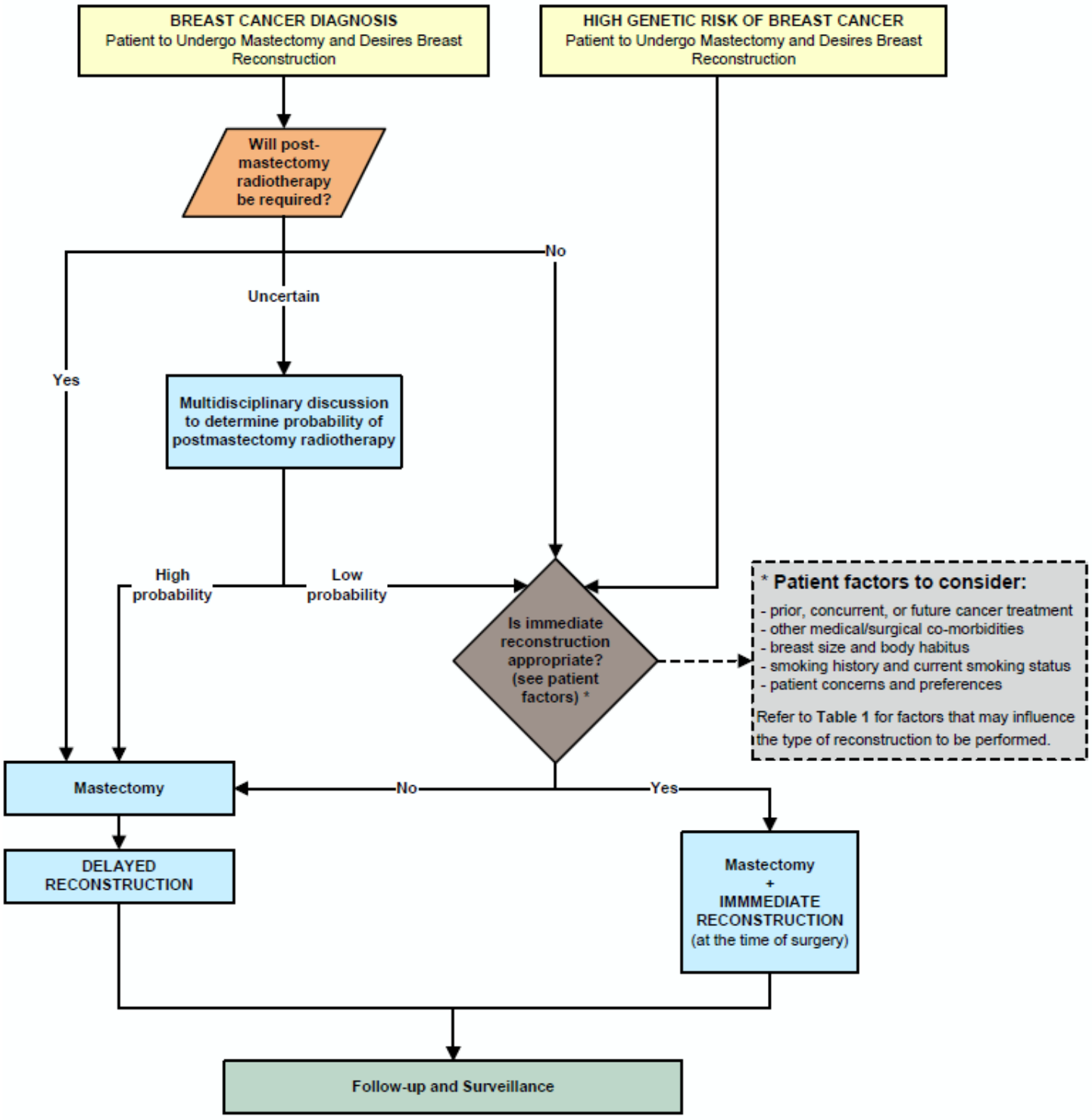

Figure 1. Algorithm for the use of breast reconstruction in patients undergoing mastectomy.

DISCUSSION

Rationale for Breast Reconstruction

Therapeutic reasons for mastectomy often include lack of response or tumour progression following chemotherapy, multicentric tumors, contraindications to radiotherapy, local recurrence following breast conserving surgery, inflammatory breast cancer, and breast cancer during pregnancy if radiation therapy cannot be delayed until the postpartum period. [1] Despite equivalence, some women choose mastectomy out of fear of cancer. Although prophylactic mastectomy to the contralateral breast is not typically encouraged in patients with a known sporadic ipsilateral breast cancer treated with mastectomy, women often opt for this procedure out of fear of cancer. [1]

In patients undergoing reconstructive breast surgery, an evaluation of psychological morbidity showed that recalled distress about mastectomy was lower among those who had reconstruction immediately (i.e., at the time of mastectomy) or early (i.e., within one year), whereas those who had delayed reconstruction (i.e., more than one year later) had significantly more recalled distress about mastectomy. [14] Similarly, a comparison between immediate (n=25) and delayed (n=38) breast reconstruction, using a standardized symptom inventory (BSI) and a self-report questionnaire, revealed that only 25% of the women who underwent immediate reconstruction reported "high distress" about mastectomy, versus 60% of the delayed reconstruction group (p=0.02). Ninety-six percent of the immediate group and 89% of the delayed group reported satisfaction with results. [15] A comparison of psychological outcome and satisfaction among patients who underwent wide local excision with radiation (n=254), mastectomy alone (n=202), or mastectomy with breast reconstruction (n=121) revealed significant differences between the three groups, in terms of satisfaction and psychosocial morbidity (i.e., anxiety, depression, body image, sexuality and self-esteem). Psychosocial morbidity was lowest in the wide local excision group, followed by the breast reconstruction group, with the highest morbidity observed in the mastectomy alone group. [16]

Beyond the first year after diagnosis, a woman's quality of life is more likely influenced by her age or exposure to adjuvant therapy than by her breast surgery. [17,18] Metcalfe, et al. recently reported data on 190 women, which showed that women undergoing delayed breast reconstruction (i.e., already had a mastectomy) had higher levels of body stigma (p=0.01), body concerns (p=0.002), and transparency (p=0.002) than women undergoing mastectomy alone or mastectomy with immediate reconstruction. However, by 1-year follow-up, there were no significant differences in any of the psychosocial functioning scores between the groups. [9] It should be noted, however, that there are inconsistencies in the methods used among studies, the types and definitions of complications reported among studies, and the populations who self-select to undergo each procedure due to aesthetic goals or age. [19] Moreover, the characteristics of patients who undergo reconstruction may be different than those who do not; several analyses of the Surveillance, Epidemiology, and End Results (SEER) database describe factors that are significantly associated with a lower rate of reconstruction among breast cancer patients, including African American race or other minority races (versus Caucasian), nonmetropolitan dwelling (versus metropolitan), receipt of radiation therapy, older age, married (versus never married or widowed), and unilateral mastectomy (versus prophylactic mastectomy of contralateral breast). [20-23] Another challenge in interpreting satisfaction data is that validated specific questionnaires for breast reconstruction have not yet been developed. [24] Other reasons for not undergoing reconstruction many include the presence of comorbidities or patient preference. [25] Patient preference may also influence whether a patient undergoes immediate or delayed breast reconstruction. [26] Nevertheless, the option to undergo breast reconstruction should be discussed with patients who are candidates for mastectomy.

Despite the evidence for positive outcomes associated with reconstruction, the rate of its use may be low. Not all women choose to undergo reconstruction; choosing not to undergo breast reconstruction alleviates the risks associated with breast reconstruction. [9,17,26] Uptake of breast reconstruction may also be due to access issues. The most recent Canadian population-based data, taken from the 1980s and 1990s suggested a rate of approximately 4 to 8%, while in the US the rate ranged from approximately 8 to 17% for that same time period. [27] There were, however, local rate variations at that time; the Calgary rate was reported to be approximately 15%, [28] while the rates in Toronto and urban Nova Scotia were 10% and 4.8%, respectively. [27] More recent US population-based data has shown a rate of 25 to 30%. [27]

The need for radiotherapy complicates breast reconstruction following mastectomy, due to increased risk of capsular contracture, flap fibrosis, need for additional surgery, risk of infection, etc.). As such, there continues to be much debate regarding the timing of mastectomy in patients requiring radiotherapy. Adjuvant radiotherapy is recommended for patients who undergo mastectomy for the management of T1/T2 node positive breast cancer, T3/T4 breast cancer. Radiation may be offered to women with neo-adjuvant chemotherapy in clinical stage II and is recommended in clinical stage III. [29,30] Besides the cancer-related factors described above, physician knowledge and attitudes, as well as practice setting, also influence the rate of reconstruction. [27]

The types of breast reconstruction procedures that are currently available for patients vary by several factors, including timing of the procedure (i.e., immediate versus delayed reconstruction), the amount of skin preserved at the time of mastectomy and type of reconstruction used (i.e., prosthetic implant versus autologous tissue implant). The role of new products, such as acellular dermal matrix, further complicates surgical decision making.

Breast reconstruction following mastectomy is oncologically safe. A recent meta-analysis found that the risk of breast cancer recurrence among patients with breast cancer who underwent mastectomy and immediate breast reconstruction was equivalent to those who underwent mastectomy alone (odds ratio, 0.98; 95% CI 0.62-1.54). [31] Furthermore, breast reconstruction can achieve a high level of satisfaction and better psychosocial outcomes for patients. [32-34] Despite the value of breast reconstruction, there is some uncertainty around aspects of the procedure, such as timing of reconstruction relative to adjuvant therapy, extent of mastectomy, type of reconstruction, and patient selection criteria. This guideline was developed to provide recommendations on these topics, for use by general and plastic surgeons in Alberta. To complement the following discussion, a complete summary of the evidence is provided in table form in Appendix B.

Methods of Reconstruction

Prosthetic implants and autologous tissue are available for breast reconstruction procedures. No randomized controlled trials have been performed to compare these two types of reconstructions in terms of cosmesis, complications, and oncologic safety in patients with breast cancer. Furthermore, the few observational studies available in the literature have used varying, non-standardized measures to assess aesthetic outcomes; [35,36] factors such as cost, [37] pain, [38] aesthetics, [39-41] feasibility with radiotherapy, [42,43] and complication rates [24,44-46] have been used to rank one reconstructive procedure over another. Recently developed patient-rated outcome measures, such as the BREAST-Q [47] and the BRECON [35] will significantly clarify these issues in future comparative studies.

Patient Satisfaction

Recently, patients who had completed alloplastic reconstruction at least one year prior were surveyed using two questionnaires (i.e., the BREAST-Q and the EORTC QLQC30 [Br23]) to compared satisfaction among silicone (n=75) and saline (n=68) implant recipients (response rate: 58%). Using the BREAST-Q, silicone implant recipients had significantly higher scores on overall satisfaction (p=0.008), psychological well-being (p=0.032), sexual well-being (p=0.05), and satisfaction with surgeon (p=0.019). Using the EORTC QLQC30 (Br23), silicone implant recipients had significantly higher overall physical function, and significantly lower systemic side effects. [48] The Michigan Breast Reconstruction Outcomes Study, a prospective cohort study, looked at patient satisfaction at two years following reconstruction with either flaps (pedicle and free TRAM) or with expanders / implants; aesthetic satisfaction was nearly three-fold higher among patients who underwent flap reconstruction (OR 2.8, p<.01), but there was no difference between these groups in terms of general satisfaction. [49] A survey among women (n=33) who had undergone postmastectomy breast reconstruction sought to compare the transverse rectus abdominis musculocutaneous (TRAM) flap with implant reconstruction. Among those who agreed to participate, 23 completed a self-assessment questionnaire on quality of life, psychological symptoms, functional status, body image, and global satisfaction. Patients who had undergone TRAM flap reconstruction were significantly more satisfied with how their recon-structed breast felt to the touch (p=.01); however, patients with TRAM flap reconstruction identified more difficulties, as far as functioning at work or school, performing vigorous physical activities, participating in community or religious activities, visiting with relatives, and interacting with male friends (p<.04). [50] A cross-sectional study among 482 women who underwent mastectomy followed by implant-based reconstruction were surveyed using the Breast-Q tool to assess satisfaction with their procedure; silicone was used in 176 women while saline was used in 306 women. Patient satisfaction was significantly higher in those with silicone implants (p=.016); however, postmastectomy radiotherapy had a significant negative effect on satisfaction (p<.000) in both silicone and saline recipients and in both groups, satisfaction diminished over time (p=.017). [51]

A retrospective study among all patients undergoing immediate breast reconstruction (n=186) at a single institution, over a five-year period revealed a lower complication rate for patients with expander/implant reconstructions (21.7%), than those with latissimus flap reconstructions (67.9%) or TRAM flap recon-structions (26.9%). However, patients who underwent TRAM flap reconstruction had the lowest reoperation rates (5.8% versus 11.3% for expander/implant and 10.7% for latissimus flap) and highest aesthetic scores. Patients were asked to rate their satisfaction with the procedure; 42% responded and revealed a higher level of satisfaction (moderate or higher) among patients who underwent expander/ implant reconstruction (93.8% versus 76.9% for latissimus flap and 83.3% for TRAM flap). [52] A prospective cohort comparing implant-assisted latissimus dorsi with tissue-only autologous latissimus dorsi flap reconstruction (N=182) among primary early-stage breast cancer patients demonstrated equivalent short-term (0 to 3 months) and long-term (4 to 12 months) complication rates (respectively: 66% for implant vs. 51% for autologous; p=.062 and 48% for implant vs. 45% for autologous; p=.845). However, role functioning and pain were significantly worse in the tissue-only autologous group (p=.002 for both). Radiotherapy did not affect quality of life in this study. [53]

Other data, however, suggests higher patient satisfaction with autologous reconstruction. A retrospective study among all patients undergoing postmastectomy breast reconstruction (n=583), at a single institution, compared patients with tissue expander/implant reconstruction with those who underwent latissimus dorsi, TRAM, and deep inferior epigastric perforator (DIEP) flap reconstructions. When asked questions about their quality of life, 439 patients (75%) responded, indicating that the highest level of general satisfaction was among patients who underwent the DIEP procedure (80%; p<.001), while those who underwent

pedicle TRAM had the highest level of aesthetic satisfaction (77%; p<.001). After controlling for health-related quality of life and length of time since surgery, autologous reconstruction had significantly higher general and aesthetic satisfaction than implant-based reconstruction (p=.017 and p<.001, respectively). Abdominal-based flaps were associated with significantly higher general and aesthetic satisfaction than latissimus flaps (p=.011 and p=.016, respectively). [54] A study looking at various forms of breast reconstruction, using the validated BRECON questionnaire showed similar satisfaction across various forms of reconstruction, with the exception that the recovery subscale had lower scores for autologous reconstructions. [55]

Acellular Dermal Matrix (HADM)-Assisted Implant-Based Reconstructions

Over the past decade, human acellular dermal matrices (HADM) have been increasingly utilized to facilitate standard two-stage expander/implant immediate breast reconstructions, as well as emerging, single stage "direct-to-implant" techniques. In a 2010 survey of US Plastic Surgeons, over half reported frequent use of HADMs as an adjunct to implant-based breast reconstruction. [56] HADMs are immunologically inert, processed dermal matrices derived from human cadaveric skin. The product is attached to the inferior border of the released pectoralis major muscle superiorly, and the inframammary fold inferiorly and laterally, thereby forming a "hammock" which covers and supports the expander or implant beneath. [57,58] Over time, the HADM is revascularized and repopulated by the patient's own cellular elements, forming a soft, elastic, living interface between prosthesis and patient.

Aesthetic advantages of HADM-assisted techniques include better definition and control of the implant pocket, better infra- and lateral mammary fold definition, more natural ptosis, and reduced rates of capsular contracture. [59,60] A retrospective chart review among patients undergoing implant-based immediate breast reconstruction, either with ADM (n=208) or without (n=129), demonstrated significantly better aesthetic outcomes in the ADM group. In multivariate logistic regression, ADM use was associated with less capsular contracture (OR = 0.18; 95% CI 0.08-0.43) and mechanical shift (OR = 0.23; 95% CI 0.06-0.78). [61]

Data from meta-analyses has demonstrated slightly higher rates of seroma, infection, and flap necrosis for HADM-assisted reconstructions, compared to traditional, non-HADM-assisted techniques. [62-64] These studies should be interpreted with caution, as they reflect the collective pooling of early results from multiple surgeons' initial experiences with the product. [65] More recent studies have demonstrated that with judicious patient selection and precise intraoperative technique [66,67] superior aesthetic results can be achieved with a safety profile that is comparable or superior [68] to reported series of traditional, non-HADM assisted approaches. [69-71]

Certain questions surrounding HADM-assisted reconstruction have not yet been definitively answered, in particular whether or not the use of HADM results in reduced postoperative pain, shorter hospital stays, and reduced expander fill times, in comparison to traditional techniques. Although retrospective reviews and studies utilizing pooled results have suggested reduced postoperative pain and time to expansion, a randomized controlled trial of 70 patients failed to demonstrate significant differences in postoperative pain (p=0.19), pain during expansion (p=0.65), postoperative narcotic use (p=0.38), nor rate of expansion (p=0.83) for HADM-assisted techniques. [72] A matched cohort study yielded similar findings. [73] A multi-center prospective cohort evaluating HADM-assisted immediate expander-based breast reconstruction reported an overall complication rate of 4.6% (3 of 65 breasts), consisting of one case of cellulitis and two cases of partial mastectomy flap necrosis that required debridement, with no seromas or explantations. [74]

Current data is also insufficient to draw definitive conclusions regarding the overall cost-effectiveness of HADM in breast reconstruction. A recent Canadian cost analysis study demonstrated that although these products are expensive, their use can result in an overall cost savings to the health care system as a result of fewer revisionary and second stage procedures. [75] The authors emphasize the need for further randomized controlled trials to evaluate both the clinical outcomes and costs of ADM-assisted breast reconstruction. One such multicentre Canadian trial (NCT00956384) comparing HADM-assisted single stage, "direct-to-implant" reconstruction to conventional two-stage expander implant reconstruction, is currently underway. Outcomes measures include aesthetic outcomes, short and long term complications, and overall patient satisfaction. This trial should clarify the role of HADM in "direct-to-implant" reconstructions, and will also examine the cost-effectiveness of the procedure. [76]

Currently, the majority of evidence surrounding the adjunctive use of HADM in implant based breast reconstruction is retrospective. [77] Until higher level prospective evidence is available to provide more specific guidelines to clinical practice, the consensus of the guideline working group is that while sufficient evidence exists to support the use of acellular dermal matrices in breast reconstruction, the specific applications for its use are most appropriately left to the discretion of the surgeon, in consultation with the patient and oncologic team. Attempting any immediate device-based reconstruction (i.e., single stage or two stage) is much more likely to achieve an aesthetically acceptable, satisfactory result with ADM, as compared to using a traditional two stage expander implant sequence. [78]

Autologous Fat Grafting (Lipofilling)

As an adjunct to primary breast reconstruction, adipose tissue can be harvested and refined and then injected in small aliquots into the reconstructed breast, theoretically providing better structure and contour than could be achieved with breast implants alone. There is currently no data from clinical trials or meta-analyses looking at autologous fat grafting (lipofilling). There is only limited data on the long-term oncologic safety and prosthetic durability of lipofilling. [79] In terms of patient satisfaction, an observational study among patients undergoing nipple-sparing, skin-sparing and skin-reducing mastectomies and not requiring adjuvant radiotherapy (n=20) employed the use of autologous fat injection secondary to breast reconstruction and found that both patient-reported and surgeon-reported esthetic satisfaction was high, and well-correlated. [80] Data from a prospective series of 68 breast cancer patients, who had had mastectomy and irradiation and then underwent one or more (mean 2.3, range 1-6) fat grafting sessions prior to breast implant reconstruction indicated that cosmesis was good (mean score 4.5 of 5). However, more importantly from an oncologic safety perspective, after a mean follow-up of 23 months, there were no local recurrences. [81] Likewise, a retrospective review, comparing the use of breast reconstruction with fat grafting versus reconstruction without fat grafting, among patients undergoing mastectomy with immediate tissue expander (n=886), showed that after a mean follow-up of 44 and 42 months respectively, showed that fat grafting did not affect local tumor recurrence or survival. [82]

Fat graft retention has been reported as being good. [83] The most common complications with autologous fat grafting include fat necrosis (3.6%), oil cysts (1.8%), and infection (0.9%), according to a retrospective review of patients (n=49) who underwent fat grafting to reconstructed breasts. [84,85] Complications appear to be higher with implant-based reconstructions as compared to autologous flap reconstructions. [86] While data from comparative studies and case reports suggest that complications are minimal and show good patient satisfaction, more data (specifically from randomized controlled trials) is needed.

Cost Effectiveness

Overall, patient outcomes are good, regardless of the type of reconstruction used. [87] In terms of cost, statistics from the U.S. from 2008 revealed a $2,860 difference mean lifetime cost (including initial hospitalization and complications and revisions up to one year) in favor of a free TRAM flap ($14,080) over an implant ($16,940); however the cost difference disappeared over time. [88] A Canadian study comparing DIEP and TRAM flap reconstructions, using a cost-effectiveness analysis incorporating medical costs (inpatient costs only) from the Ontario Ministry of Health (2002) showed that the DIEP flap was slightly more costly than the free TRAM flap ($7,026.47 versus $6,508.29) while providing similar quality-adjusted life years (QALYs) to the free TRAM flap (28.88 years versus 28.53 years). Furthermore, the baseline incremental cost-utility ratio was $1464.30 per QALY, favoring adoption of the DIEP flap. Sensitivity analyses accounting for the incidence of hernia, abdominal bulging, total flap loss, operating room time, and hospital stay were identical between the DIEP and free TRAM procedures. However, increasing the probability of abdominal bulge from 0.041 to 0.103 for the DIEP flap changed the ratio to $2731.78 per QALY; increasing the probability of total flap failure from 0.014 to 0.016 changed the ratio to $1384.01 per QALY; assuming the time in the operating room to be the same for both flaps changed the ratio to $4026.57 per QALY; and finally, assuming the hospital stay to be the same for both flaps, changed the ratio to $1944.30 per QALY. [89] It has been reported elsewhere, however, that the cost of a latissimus dorsi, TRAM, or DIEP flap reconstructions, including both primary surgery and any revisions, are similar, and that any small financial benefits gained from the implant reconstruction at initial surgery will be lost over time, as patients require additional revisions. [90] As such, no recommendations can be made, favoring one type of reconstruction over another from a cost perspective. The decision to use an implant or an autologous flap, or to use a latissimus dorsi or TRAM or DIEP flap should be left to the discretion of the plastic surgeon and the patient after counseling the patient on the benefits and limitations of each type of available reconstruction.

Timing of Reconstruction

Immediate breast reconstruction (i.e., at the time of mastectomy) has been a topic of increased discussion in recent years; however, the use of this combined surgical approach has been around for quite some time. In 1983, Dean, et al. conducted a randomized controlled trial in which patients underwent either immediate breast reconstruction or were offered reconstruction twelve months later. Immediate reconstruction reduced the psychiatric morbidity assessed three months after operation; women who underwent reconstruction were found to have more “freedom of dress” and were less likely to be “repulsed by their own naked appearance” than women who did not undergo reconstruction. [91]

Since then, further evidence on the psychosocial benefits of immediate reconstruction has surfaced. A cross-sectional study, comparing immediate and delayed reconstruction with mastectomy alone, among patients with breast cancer (n=190) found significantly higher levels of body stigma and body concerns among patients in the delayed reconstruction group. [9] A recent Cochrane review showed support for the benefits of immediate versus delayed reconstruction, although there was only one randomized controlled trial with some flaws in terms of bias and outcome reporting, that immediate reconstruction reduced psychiatric morbidity at three months postoperatively, as compared with delayed or no reconstruction. [92] Heterogeneity exists between studies in the evaluation of cosmesis and complications between immediate and delayed reconstruction, which needs to be considered when interpreting results. [19,93]

Regarding safety, a prospective cohort of patients with T1-T3 tumours (n=677) underwent either mastectomy alone, or mastectomy with immediate breast reconstruction; no radiotherapy was given to

any patients. After a median follow up of 70 months (range 13-114 months), the local recurrence rate was 5.2% for immediate reconstruction group and 9.4% for mastectomy only group. The regional and distant metastases rates did not differ either (1.4% versus 1.3% and 13.9% versus 16.4%, respectively). There was also no difference between the groups in terms of overall survival (hazard ratio, 1.03) or disease-free survival (hazard ratio, 0.99). [94] Furthermore, the meta-analysis by Gieni, et al. found no differences, in terms of the risk of recurrence between patients who underwent immediate reconstruction and those who underwent mastectomy alone. [28]

Guidelines on this issue generally indicate that immediate reconstruction is equally as safe, oncologically, as delayed reconstruction and offers patients an improved psychological profile; as such, there is no psychological or oncologic basis for waiting to perform reconstruction, in patients who meet the selection criteria for reconstruction. [95-101] Based on the evidence available, immediate breast reconstruction should be considered, whenever possible, for any patient who is a candidate for breast reconstruction.

Timing of Reconstruction in the Setting of Adjuvant Radiotherapy

Most guidelines that address the timing of adjuvant radiotherapy recommend that breast reconstruction be delayed or at least discussed in a multidisciplinary setting, in patients with breast cancer for whom radiotherapy is planned. [95,96,102] The NCCN breast cancer guideline (v.1.2012) states that radiotherapy should be completed first, when an autologous reconstruction is planned; furthermore, an expander/implant reconstruction can be done immediately, but carries a significantly increased risk of implant capsular contracture. Furthermore, in patients who have previously received radiotherapy, expander/implant reconstruction carries higher risk. [103] A retrospective chart review comparing radiotherapy before delayed TRAM flap reconstruction with immediate TRAM flap reconstruction followed by radiotherapy (mean radiotherapy dose: 50-51 Gy) among 102 patients with breast cancer found that the rate of late complications was significantly higher among patients in the immediate reconstruction group (87.5% vs. 8.6%; p=0.000); furthermore, the need for an additional flap to correct the distorted contour from flap contraction was observed among nine patients (28%) in the immediate reconstruction group. [104]

In patients who underwent TRAM reconstruction (n=680), those who received pre-operative radiotherapy were found to have higher rates of fat necrosis (>10% of total reconstruction; 17.6% versus 10.1%, p=.032). Obesity and radiotherapy were also both found to be associated with fat necrosis and major infection in logistic regression analyses. [105] Similarly, a systematic review, including four studies, that compared the outcomes of patients in terms of the timing of radiotherapy with autologous reconstruction, found that the overall incidence of complications was increased in patients who received radiotherapy in three of four studies. [106] A more recent meta-analysis of postoperative morbidity following immediate or delayed breast reconstruction (n=1,105) found that patients undergoing radiotherapy were more likely than patients not receiving radiotherapy to suffer morbidity (odds ratio, 4.2; 95% CI 2.4-7.2) but that autologous reconstruction was associated with less morbidity than implant-based reconstruction (odds ratio, 0.21; 95% CI 0.1-0.4). Overall, this study found that delaying reconstruction until after radiotherapy had no significant effect on outcome (odds ratio, 0.87; 95% CI 0.47-1.62). [107]

Among patients undergoing reconstruction with implants, a retrospective chart review compared those with irradiated implants (average 50 Gy) with those with nonirradiated implants, all placed submuscularly or beneath a flap (n=297), and found that complications (i.e., capsular contracture, pain, exposure, and implant removal) were significantly more frequent in patients with implants who received radiotherapy. [108] In patients who are likely to receive radiotherapy, a delayed-immediate reconstruction (i.e., expanders are placed at mastectomy) may be preferred, as it is thought to avoid difficulties associated with radiotherapy delivery after immediate reconstruction and preserves the opportunity for the aesthetic benefits of skin-

sparing mastectomy. [109] However, in a prospective study comparing timing of radiotherapy on permanent implants versus on the tissue expanders (all two-stage immediate with subpectoral temporary expanders and permanent implants), the rate of failure (i.e., removal of the implant, leaving the chest wall flat, or change to a flap-based technique) was significantly higher when radiotherapy was delivered at the tissue expander stage rather than at the permanent implant stage(40% versus 6.4%; p<.0001). The capsular contracture rate was similar for both groups. [110]

Where feasible, another approach may be to consider an upfront "staging" sentinel lymph node biopsy, as a reliable means of determining the probability of post-mastectomy radiotherapy in clinically node negative patients. McGuire, et. al. suggest that SLNB be performed as a separate outpatient procedure several days prior to mastectomy when immediate reconstruction is planned. The authors acknowledge the drawbacks of a separate procedure, but argue that this strategy can allow SLNB to be performed with minimal morbidity with monitored anesthesia care and local anesthesia, and can eliminate the need for frozen section diagnosis. [111] Several retrospective reviews have presented data to support this strategy, citing the following reasons for performing an upfront SLNB: to avoid the unreliability of frozen section diagnosis as compared to permanent results, [112] to avoid the high rate of complications and implant loss among patients undergoing post-mastectomy radiotherapy, [113,114] and to identify patients for whom delayed reconstruction is preferred due to a positive SLNB finding. [115] Those against this strategy have provided retrospective data to suggest that that the false negative rate when performing SLNB at the time of mastectomy and immediate reconstruction is low (7.8%) and that the touch preparation analysis from the SLNB changes the plan in only a small number of patients (2.1%). [116] Rationale for not performing an upfront SLNB include additional expense, increased delay in initiation of systemic therapy, and the propensity of procedure-related morbidity. [116,117] Data on the feasibility of intraoperative SLNB diagnosis suggests that this strategy is practical. [118,119] Nevertheless, no randomized controlled trials have been conducted to compare upfront staging with intraoperative staging in the setting of immediate reconstruction. Therefore, a recommendation cannot be made for or against either strategy.

Impact of Chemotherapy on Reconstruction

Data suggest that immediate reconstruction can be safely integrated with chemotherapy, without a significant impact on complications. A prospective randomized trial comparing immediate modified radical mastectomy against initial systemic therapy followed by mastectomy found that there was no significant difference in the risk of complications and that immediate breast reconstruction was not an independent predictor of complications. [120] A retrospective series of patients receiving neo-adjuvant chemotherapy for breast cancer, followed by surgery (N=2,004; American College of Surgeons National Surgical Quality Improvement Program database), looked at factors affecting post-operative complications. Wound complications occurred in 3.1% of patients. There was a trend towards increased complications in neo-adjuvant patients undergoing mastectomy with immediate reconstruction (OR, 1.58; 95% CI, 0.98-2.58). [121] Most prospective and retrospective series have reported similar results. [122-130] One study reported greater implant infection rates [130] with chemotherapy and one reported a higher rate of expander removal with chemotherapy. [127] Understandably, some practitioners prefer a delayed breast reconstruction approach in patients deemed to have a high risk of local recurrence clinically (in the short term setting) or if radiotherapy is required; the need for chemotherapy, however, should not preclude an immediate reconstruction in this patient population.

Data suggest that reconstruction may impact the time to chemotherapy, but not necessarily in a clinically significant manner. A retrospective comparative study analyzed data from patients undergoing mastectomy with and without free flap IBR, followed by adjuvant treatment (N=166) and found that the

mean time period between surgery and commencement of adjuvant treatment was 15 days longer in the immediate reconstruction group. Delays were related to surgical complications. [131] A prospective series of 391 consecutive women who underwent mastectomy (n=243) or mastectomy and immediate reconstruction (n=148) showed a statistically significant, difference in the median time to chemotherapy (6.8 weeks for mastectomy alone vs. 8.5 weeks for immediate reconstruction; p=0.01). [124] A delay of approximately one to two weeks to chemotherapy is not likely to impact clinical outcomes, provided thwe patient is ready to start chemotherapy within 12 weeks; however, the decision whether to perform an immediate reconstruction should be weighed against this potential delay.

Extent of Mastectomy

In a meta-analysis of nine studies with data for over 3,700 patients, skin-sparing mastectomy with immediate reconstruction has been found to be equivalent to conventional mastectomy without reconstruction in terms of oncologic safety; the local recurrence rate was 6.2% for skin-sparing mastectomy and 4.0% for conventional mastectomy (odds ratio, 1.25; 95% CI 0.81-1.94), while the distant relapse rate was 10.0% for skin-sparing mastectomy and 12.7% for conventional mastectomy (odds ratio, 0.67, 95% CI: 0.48-0.94). [132] A prospectively maintained database of patients (n=428) undergoing nipple-sparing mastectomy with immediate breast reconstruction for in situ cancer (16.9%), invasive cancer (45.8%), or prophylactic risk-reduction (37.3%) revealed a locoregional recurrence rate of 2% overall (median follow-up 28 months) and 2.4% among those with at least 3 years' follow-up (median follow-up 45 months). Nipple tissue contained in situ cancer in 11 breasts (1.7%) and invasive cancer in 9 breasts (1.4%) and these were managed with repeat excision (7 cases), NAC removal (9 cases), or radiotherapy without further excision (4 cases); there were no recurrences in the nipple-areolar complex. [133] In line with these findings, current published guidelines recommend skin-sparing mastectomy as an acceptable approach. [95,96,103] Nevertheless, skin-sparing mastectomy may be underutilized. A postal survey administered to general surgeons who perform breast cancer surgery found that most (89%; 331 of 370) perform mastectomy for cancer with planned immediate reconstruction. Ninety percent felt that skin-sparing mastectomy did not result in higher rates of local recurrence and 70% felt that cosmesis was superior with immediate reconstruction after skin-sparing mastectomy; yet, only 61% reported that they perform skin-sparing mastectomy in most cases when immediate reconstruction is planned. [134]

Nipple-sparing mastectomy is performed in the setting of immediate reconstruction and can achieve good cosmetic results. [135] A prospective study was conducted among patients with no disease within 2 cm of the nipple (n=43), for the purpose of either prophylaxis (n=29) or therapy (n=35: 24 invasive and 11 ductal carcinoma in situ). Patients underwent total skin-sparing mastectomy with preservation of the nipple-areola complex, followed by immediate expander/implant-based reconstruction; survival of the nipple-areola complex was complete in 80% (n=51) and partial in 16% (n=10) of patients and was highest (97%) with radial incision (n=34). Complications included implant loss, total skin flap necrosis, and infection, but there were no recurrences. [136] Viability of the nipple-areolar complex may be improved by performing a surgical “delay” procedure 1-2 weeks prior to mastectomy, in conjunction with biopsy of the retroareolar tissue. [137] A retrospective chart review of nipple-sparing mastectomy (45 prophylactic and 53 therapeutic), among patients with tumours≤3 cm in size and ≥2 cm from the nipple, no clinical invasion of the nipple - areola, no multicentric disease, negative intra-operative retroareolar frozen section, and no nodal disease, reported no local or regional recurrences in any patients, with a median follow-up of 22.5 months. [138] Despite these and other studies [139,140] reporting promising results with nipple-sparing mastectomy, there is currently no published data from a randomized controlled trial, on the oncologic safety of nipple-sparing, as compared to conventional skin-sparing mastectomy. Therefore, nipple-sparing mastectomy is generally not recommended for patients with malignancy [95,96,103] but could be considered for carefully selected

patients, and in patients undergoing prophylactic mastectomy, when done in conjunction with a separate biopsy of the ductal tissue directly underlying the nipple-areola complex. The decision as to whether to pursue a nipple-sparing procedure requires multidisciplinary input and careful discussion with the patient about potential additional risks associated with this approach.

Patient Selection

Several patient factors should be considered when selecting appropriate candidates for breast reconstruction. A recent systematic review on mastectomy complications found that previous breast biopsy or operation and preoperative chemoradiation were significant factors associated with surgical site infection, whereas immediate reconstruction, axillary lymph node dissection, and preoperative chemotherapy were not. [141] Among patients undergoing immediate breast reconstruction, a prospective study demonstrated a significantly greater risk of failure, as revealed by multiple logistic regression analysis, among patients with larger tumours (T3/T4), patients who smoke, and patients with positive nodes. The rate of failure (i.e., the need for a second intervention consisting of ablation or replacement of the prosthesis) was 7% for patients with none of these factors, 15.7% for patients with one of these factors, 48.3% for patients with two of these factors, and 100% for patients with all three of these factors, accurately predicting 80% of failures. [103] A follow-up survey of mastectomy-treated breast cancer patients (N=374; SEER database) five years after treatment suggested that the receipt of reconstruction did not vary by body mass index (BMI): 53% BMI <25 kg/m; 48% BMI 25-30 kg/m; 45% BMI >30 kg/m; p=.43). However, reconstruction type did vary by BMI: TRAM flaps were performed in 53% of patients with BMI >30 kg/m versus 26% of patients with B<I <25 kg/m (p=.01). Patient satisfaction with surgical decision-making and surgical outcomes was similar across body mass index categories. [142]

Guidelines published by both the National Comprehensive Cancer Network (NCCN) [103] and the Massachusetts Board of Registration in Medicine Expert Panel (MBRMEP) [95] list prior cancer therapy (i.e., chemotherapy, radiotherapy), body composition, and smoking status as factors to consider when selecting patients for reconstruction. The NCCN also adds comorbidities and patient concerns as factors to be considered. Other guidelines included in the literature review for this guideline did not specifically identify patient selection criteria. [97-102] Based on existing evidence and current guidance, it is recommended that the following patient factors be considered when selecting candidates for reconstruction: prior, concurrent, or future cancer treatment, co-morbidities, body habitus, and smoking history and current smoking status.

Risks and Benefits

Patient expectations should be assessed prior to surgery, in order to optimize care. In addition, patients should be made aware that cosmetic results may vary from patient to patient and that the reconstructive surgery may not entirely restore the breast to its original appearance. Systematic measurement and management of patient expectations may improve patient education, shared medical decision-making and patient perception of outcomes. [143]

As with any major surgery, complications can occur with breast reconstruction. The most common complications associated with autologous flap reconstructions are flap necrosis (~5% of patients), infections (~5% of patients), and seroma (~4% of patients). [136] Reoperation is often required in patients who develop flap necrosis. [144] Less common complications from autologous breast reconstruction include bruising and bleeding and chronic pain. [144,145] Deep inferior epigastric perforators (DIEP) flaps have been shown to carry a higher risk of fat necrosis, flap loss, [145] but lower donor-site morbidity (i.e., bulge

formation, hernia), [146,147] as compared to muscle-sparing transverse rectus abdominis myocutaneous (TRAM) flaps.

In patients who undergo implant-based breast reconstruction with human acellular dermal matrix (HADM), the total complication rate is about 15% and the most common complications are mastectomy flap necrosis (~7% of patients), infection (~5% of patients), and seroma (~5% of patients). [145] Mastectomy flap necrosis can necessitate removal of the implants and reoperation. [133] As with autologous reconstruction, implant-based reconstruction may be associated with bruising and bleeding, [133] chronic pain, [144,145] implant rupture or malposition, [108,109] and capsular contracture, which more frequently occurs in patients who undergo radiation therapy. [141,143,148,149] There is evidence to suggest that the risk of capsular contracture is lower with the use of textured implants, as compared to smooth implants. [150] In a very small group of patients with implants, anaplastic large cell lymphoma (ALCL) has been observed. By 2007, only six cases of ALCL in the setting of breast implant surgery had been reported. [110,151-154] By 2010, a total of 34 unique cases had been identified among an estimated 10 million women with breast implants and the majority of these 34 patients are still alive and well. [155] The United States FDA then conducted an investigation and concluded that: (1) there is a possible association between ALCL and breast implants, adding that although the incidence is low, the occurrence of ALCL in patients with implants may not be a coincidence; (2) it is not possible to identify a specific type of implant that is associated with a higher or lower risk of ALCL; and (3) the true cause of ALCL in patients with implants is unknown. [156] Subsequently, the American Society of Plastic Surgeons and the American Society for Aesthetic Plastic Surgery issued a statement indicating that ALCL is extremely rare, that the risk of women with implants developing ALCL is extremely low, and that breast implants are safe and effective. [146,149,155,157]

Post-Breast Reconstruction Surveillance

There is no evidence to support routine screening mammography of the reconstructed breast, in the absence of a palpable recurrence or symptoms of recurrence. Imaging records from 227 patients with a history of post-mastectomy breast reconstruction due to cancer showed that among 116 patients (51%) who underwent surveillance mammography of the reconstructed breast, only one recurrent cancer was detected in an autologous tissue flap reconstruction (0.86% detection rate of non-palpable recurrent cancer), with a recall rate of 4%. Among 54 patients (24%) who presented with symptoms relating to the breast reconstructions (most commonly lump or swelling), half were subsequently found to have no significant abnormality and a third (29%) were found to have fat necrosis. Only four recurrences were found. [158] Presently, assessment with ultrasound and mammography can only be supported in symptomatic patients, with surgical referral the most efficient means of obtaining a diagnosis while minimizing unnecessary tests or biopsies. [159] While in theory patients at high risk of recurrence may also benefit from routine mammography of the reconstructed breast, [160] data is needed to support the selection of these patients.

Resource Implications

The recommendations contained in this guideline reflect the best available evidence on post-mastectomy breast reconstruction. In order to make this guideline operational, at minimum, resources are required to coordinate operation room time between the general surgeon and the plastic surgeon. In addition, infrastructure is needed to facilitate multidisciplinary case discussions for patients needing post-mastectomy radiotherapy.

Summary

Breast reconstruction should be made available for patients undergoing mastectomy, for prophylaxis or for the treatment of breast cancer. Patient factors, such as prior, concurrent, or future cancer treatment, co-morbidities, body habitus, and smoking history and current smoking status should be considered when selecting candidates for breast reconstruction. Immediate breast reconstruction should be considered, whenever possible, for any patient who is a candidate for breast reconstruction. Delayed breast reconstruction is an acceptable alternative when immediate breast reconstruction is not available or inappropriate. The integration of reconstruction and post-mastectomy radiotherapy should be addressed in a multidisciplinary setting. In general, breast reconstruction should be delayed until after treatment with radiotherapy has been completed. The decision as to which type of procedure to use should be left to the discretion of the surgeons and the patient after providing counseling and based on the benefits and limitations of each procedure. Skin-sparing mastectomy for immediate breast reconstruction is a safe and appropriate approach. Nipple-sparing is generally not recommended for patients with malignancy, but could be considered for carefully selected patients, and in patients undergoing prophylactic mastectomy, when done in conjunction with a separate biopsy of the ductal tissue directly underlying the nipple-areola complex.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
AHS	Alberta Health Services
ALCL	anaplastic large cell lymphoma
DIEP	deep inferior epigastric perforator
HADM	human acellular dermal matrix
LD	latissimus dorsi
SEER	Surveillance, Epidemiology, and End Results
SIEA	superficial inferior epigastric artery
SLNB	sentinel lymph node biopsy
TRAM	transverse rectus abdominis musculocutaneous

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of AHS, Cancer Care.
- Publish the guideline in a peer-reviewed journal.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Breast Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health

Services – Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Breast Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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APPENDIX A: The Mastectomy – Technical Issues Relevant to Reconstruction

Skin-Sparing Mastectomy. A significant learning curve is required in order to produce viable flaps for breast reconstruction. This procedure should be done by should only be performed by experienced practitioners with appropriate training in skin sparing techniques, as it is technically more challenging than a standard total mastectomy. The skin-sparing mastectomy has been one of the greatest advancements in immediate breast reconstruction (IBR) in the last two decades. [161] It is technically more challenging than the traditional modified radical or total mastectomy, requires close coordination between the oncologic and reconstructive surgeons and depends on proper patient selection and meticulous technique.

Mastectomy Flap Necrosis. The success of IBR largely hinges on the health of the mastectomy flaps. Unfortunately, skin flap necrosis is reported in up to 20% of IBR cases [162-164] and remains the single most common complication of skin sparing mastectomy. Even minor flap edge necrosis can lead to infection, exposure, and loss of an implant-based reconstruction; any necrosis can significantly compromise the final shape of autogenous tissue-based reconstructions. Other technical issues that can make the environment unfavorable for proceeding with IBR include insufficient or inconsistent skin flap thickness, resection of muscle fascia, and disruption of anatomic breast landmarks.

Oncologic Safety. Although oncologic safety trumps reconstructive issues whenever the two are incompatible, both should be equally achievable in properly selected patients referred for IBR; otherwise, if healthy, consistent skin flaps cannot be assured in a given patient due to oncologic issues, the patient should be referred for delayed breast reconstruction instead. All forms of mastectomy leave some degree of residual breast tissue behind. [161] The various mastectomy techniques differ in terms of the amount of microscopic breast tissue left behind in the skin. These small differences have not been shown to impact the local recurrence of breast cancer [162,165-168]

Breast Boundaries. Ideally, the mastectomy removes the breast gland only. The historical boundaries of mastectomy (i.e., the clavicle, the rectus sheath, the midline of the sternum, and the anterior latissimus border) were derived from a contrast injection study in 1940. [169] These borders significantly overestimate the actual extent of the breast gland. Schwartz [170] in "Principles of Surgery," describes the anatomy of the breast gland more conservatively: *The mature breast of the female extends inferiorly from the second or third rib, to the inframmamary fold at approximately the sixth or seventh rib. Transversely, it extends from the lateral border of the sternum to the anterior or mid axillary line.*

Each woman has unique breast anatomy; like the reconstruction, the mastectomy should be customized according to a careful preoperative evaluation in the seated or standing position to identify breast boundaries. Dissecting to the clavicle is rarely necessary, leads to superior hollowing, and creates a difficult to hide, telltale sign of mastectomy that will persist even with reconstruction. Dissecting to or beyond the midaxillary line overly lateralizes the reconstruction, thus leading to dissatisfaction regarding lateral breast fullness that interferes with arm movement. Dissecting beyond the medial breast border at the lateral sternum can be particularly problematic for the reconstructive surgeon, as the thin skin in this region precludes most attempts at reestablishing this critical anatomic boundary.

Mastectomy Flap Thickness. Because the breast gland develops as an ectodermally-derived structure that invaginates inward, it is bounded by the superficial and deep layers of the superficial fascia of the abdominal wall. The superficial layer of this fascia, often referred to as the "breast capsule" is subtle, but definitely present. As such, there exists a relatively avascular anatomic plane separating the non-breast

tissue bearing fatty layer of the skin from the underlying breast parenchyma. [171] Mastectomy skin flaps should be raised just superficial to this enveloping fascia of the breast, preserving the subcutaneous fat and its associated vascular plexus in order to ensure skin flap viability. Several studies have confirmed this anatomic plane to be adequate from an oncologic perspective; flaps thinner than this (i.e., dermal) have a much higher risk of ischemic necrosis. Cooper's ligaments attaching the breast parenchyma to dermis require division to remove the gland from the skin flap. [172] End hits and thermal burns to the undersurface of the breast skin should be avoided. A low-blend coagulation setting, in conjunction with meticulous surgical technique and atraumatic retraction of the skin flaps can be helpful to ensure viable skin flaps of appropriate thickness. Other surgeons favor sharp dissection preceded by epinephrine injection, as an alternative means of avoiding thermal injury to the undersurface of mastectomy flaps.

Pectoralis Fascia. For total submuscular implant reconstruction, the fascia of the pectoralis major, serratus anterior, external oblique, and rectus abdominis muscles should be preserved. [173] The gland can be removed whilst protecting the fascia of these muscles as the posterior surface of the breast parenchyma is enveloped by the deep layer of the superficial abdominal fascia, a layer which is distinct from the muscle fasciae. When using acellular dermal matrices, preservation of the fascia is not essential.

Inframammary Fold. The inframammary fold is a distinct embryological and anatomical landmark that marks the end of the breast inferiorly. The breast boundary is at the point where the superficial and deep layers of the superficial fascia of the abdominal wall come together. [174] Here the superficial fascia adheres to the underlying chest wall. [175] Preservation of the inframammary fold is essential to define ptosis and inferior quadrant shape. [175]

APPENDIX B: EVIDENCE TABLES

Table 1: Existing guidance on breast reconstruction in patients undergoing mastectomy for treatment or prophylaxis of breast cancer.

Organization Year	*Immediate Reconstruction Recommendations*	*Patient Factors to Consider*	*Acceptable Types of Reconstruction*	*Skin or Nipple-Sparing Recommendations*	*Optimal Timing for Radiotherapy*
National Comprehensive Cancer Network. 2012 [103]	Supports immediate. *Breast reconstruction for mastectomy can be performed at the same time as mastectomy ("immediate") or at some time following the completion of cancer treatment ("delayed")*	(1) Prior cancer treatment (2) Patient body habitus (3) Smoking history: (smoking is a relative contraindication) (4) Co-morbidities (5) Patient preference	(1) Breast implants (2) Autologous tissue ("flaps") (3) Latissimus dorsi / implant composite reconstruction *Women who are not satisfied with cosmetic outcome following completion of breast cancer treatment should be offered plastic surgery consult*	Skin sparing – supported Nipple sparing – not recommended unless clinical trial *skin sparing mastectomy is probably equivalent to standard mastectomy re: recurrence* *data are inadequate to support the use of nipple-areolar complex sparing procedures*	Autologous – delay until after completion of RT Implant – immediate supported but there is a higher rate of capsular contracture *Surgery to exchange the tissue expanders with implants can be done prior to or after RT* *In previously radiated patients expanders/implants are relatively contraindicated* *Post-mastectomy RT should be applied if skin sparing performed*
European Society for Medical Oncology 2010 [102]	Supports immediate. *Immediate can make prospect of losing a breast easier to accept, but not all pts suitable for immediate* *no basis for waiting 2 yrs after mastectomy*	Not specified.	(1) Silicone gel implants (2) Myocutaneous tissue flaps using latissimus dorsi muscle (back or TRAM) (3) free DIEP flap from the lower abdomen	Not specified.	Not specified. *When postmastectomy RT is anticipated, some women will be advised against immediate reconstruction*
New Zealand Guidelines Group. 2009 [97]	Supports immediate. *Reconstruction may be immediate or delayed. If immediate, discuss the risk of a complication delaying adjuvant chemo or RT*	Not specified.	Not specified.	Not specified.	Not specified. *If post-mastectomy RT is likely women should be aware that this may impact cosmetic out-come of breast reconstruction*
International Expert Panel. 2010 [96]	Not specified.	Not specified.	Not specified.	Skin sparing – supported unless inflammatory *Neither reconstruction nor use skin-sparing increases local recurrence*	Not specified. *The integration of reconstruction and post-mastectomy RT should be addressed in a multidisciplinary setting*

Organization Year	*Immediate Reconstruction Recommendations*	*Patient Factors to Consider*	*Acceptable Types of Reconstruction*	*Skin or Nipple-Sparing Recommendations*	*Optimal Timing for Radiotherapy*
National Institute for Health and Clinical Excellence. 2009 [98]	Supports immediate. *Discuss immediate breast reconstruction with all patients who are advised to have mastectomy, and offer it except where sig comorbidity or (need for) adjuvant therapy may preclude this option*	Not specified.	Not specified.	Not specified.	Not specified.
National Health Service (UK). 2009 [101]	Supports immediate. *Patients should have access to breast reconstruction surgery. All patients having mastectomy (by choice or on advice) should have the opportunity to discuss options and have immediate reconstruction if appropriate*	Not specified.	Not specified.	Not specified.	Not specified.
International Expert Panel on Inflam. Breast Cancer 2010 [100]	*Immediate not recommended for inflammatory breast cancer.* *Breast reconstruction is an option for women with IBC who have undergone a modified radical mastectomy. Immed. not recommended.*	Not specified.	Not specified.	Not specified.	Not specified.
MA Board of Registration in Med. Expert Panel Lee BT. 2011 [95]	Supports immediate if RT is not indicated. *If RT indicated, delay recon.* *Immediate considered for any patient interested in reconstruction who presents for prophylactic mastectomy or early stage (T1-2, N0)*	(1) Smoking status (2) Obesity (3) RT before, during or after reconstruction (4) ischemic or necrotic flaps after reconstruction (5) neo-adjuvant chemo	(1) Prosthetic implants (2) Autologous implants (3) Combination of prosthetic & autologous *- candidates for each are discussed in guideline*	Skin sparing – supported Nipple sparing – not supported *Skin sparing preserves skin envelope and results in superior aesthetic compared to delayed*	*Delay reconstruction until after RT has been completed.*

Table 2a: Evidence on the effect of the timing of reconstruction on oncologic safety, organized by level of evidence.

Author, year	*Design*	*Treatment(s)*	*Patients (N)*	*Oncologic Safety*
Gieni M. 2012 [28]	systematic review	1. mastectomy + immediate reconstruction 2. mastectomy only	3710	local recurrence: OR = 0.98 (95% CI: 0.62-1.54) for mastectomy + IBR vs. mastectomy only
Zhong T. 2012 [124]	prospective comparative study	1. mastectomy + immediate reconstruction 2. mastectomy only	391	median time to chemotherapy: 6.8 (0.71-15) weeks for mastectomy only 8.5 (6.3-11) weeks for immediate (p=.01)
Petit JY. 2008 [94]	prospective comparative study	1. mastectomy only (23.5% of cohort) 2. mastectomy + immediate reconstruction (IBR; 76.5% of cohort) *No RT given* med follow up: 70 mos (13-114 mos)	677 (T1-T3)	local recurrence: 5.2% for IBR vs. 9.4% for mastectomy regional mets: 1.4% for IBR vs. 1.3% for mastectomy distant mets: 13.9% for IBR vs. 16.4% for mastectomy contralateral breast cancer: 1.5% for IBR vs. 1.3% for mastectomy death rate: 10.4% for IBR vs. 16.4% for mastectomy survival: OS HR=1.03; DFS HR=0.99
Kroll SS. 1994 [177]	prospective cohort	bilateral therapeutic or prophylactic mastectomy & reconstruction (implants + TRAM)	100	new dx of invasive breast cancer: 3.4% (3 pts) new dx of DCIS: 5.7% (5 pts) new dx of cellular atypia: 20% (18 pts)
Rinker BD. 2007 [178]	retrospect-tive cohort	immediate reconstruction with a TRAM flap: 57 free and 35 pedicle mean follow-up: 6.7 yrs (4-14 yrs)	103	local recurrence or metastases: 19% (20 pts)

Table 2b: Evidence on the effect of the timing of reconstruction on complications, organized by level of evidence.

Author, year	*Design*	*Treatment(s)*	*Patients (N)*	*Complications/cosmesis*
Xue DQ. 2012 [33]	systematic review	risk factors for breast surgical site infections (SSIs) among patients undergoing treatment for breast cancer	681 (+ 2064 controls)	immediate reconstruction was NOT a significant factor related to SSI
D'Souza N. 2011 [92] Cochrane Review	systematic review	1. immediate 2. delayed following mastectomy	64 (1 RCT)	some, albeit unreliable, evidence that immediate as compared with delayed or no reconstruction, reduced psychiatric morbidity reported 3 months post-op (study at high risk of bias; post-op morbidity & mortality not assessed)
Zhong T. 2012 [124]	prospective comparative study	1. mastectomy + immediate reconstruction 2. mastectomy only	391	<u>complication rate:</u> IBR group 27.0% vs. mastectomy alone 15.6% (p=.009) predictors: none on multivatiate analysis
Donker M. 2012 [122]	prospective comparative study	1. neoadj chemo + skin sparing mastectomy + immediate reconstruction 2. skin sparing + immediate only	213	<u>short-term post-op complications:</u> 15% for neo-adjuvant pts vs. 29% for no chemo (p=.042) loss of prostheses: 8% for neo-adjuvant vs. 11% (p=.566)
Metcalfe KA. 2011 [9]	prospective comparative study	1. mastectomy (M) alone 2. M + immediate reconstruction 3. M + delayed reconstruction	190	<u>psychosocial fxn over 1 yr:</u> no pre-surgical differences b/t groups in quality of life, anxiety, depression, etc. *post-surgical (vs. M or immediate):* body stigma higher in delayed (p=.01) concerns higher in delayed (p=.002) transparency higher in delayed (p=.002)
de Oliveira RR. 2010 [179]	prospective comparative study	1. mastectomy + immediate reconstruction latissimus dorsi flap (LDF) 2. mastectomy without immediate breast reconstruction	87	<u>range of motion (ROM in shoulder):</u> LDF not associated w/ decrease in ROM (p=.84) at 4-week assessment, women in both groups still had an average reduction of 30 degrees in ROM vs. baseline sig factors: ALND, smoking, painful axillary cords
Cheng M. 2006 [180]	prospective comparative study	1. immediate reconstruction (n=21) * 2. delayed reconstruction (n=21) * *unilateral DIEP (n=30) or SIEA (n=12)	42	<u>resource costs:</u> no diff in immediate and delayed <u>success:</u> no diff in immediate and delayed <u>complication rates:</u> no diff in immediate and delayed
Caffo O. 2000 [125]	case-control study	1. immediate reconstruction (IBR) by expander + adj chemo (IBR/CT) 2. mastectomy + IBR only (IBR) 3. mastectomy + adj chemo only (CT)	166	<u>complications:</u> seroma 8 pts; infection 1 pt; skin necrosis 1 pt; expander rupture 2 pts; erythema 3 pts (no stat sig diff in distribution of complications b/t IBR/CT & IBR) timing of inflation not influenced by chemotherapy

Author, year	*Design*	*Treatment(s)*	*Patients (N)*	*Complications/cosmesis*
Kroll SS. 1994 [177]	prospective cohort	bilateral therapeutic or prophylactic mastectomy & reconstruction (implants + TRAM)	100	failure: 5% (2 of the 5 failures were successfully reconstructed w/ alternative techniques) bilateral TRAM flap (n=63) failure: 2% (1 pt) on first try TRAM flap recon. more successful than implants (p=.05)
Lagergren J. 2010 [181]	prospective cohort	mastectomy + immediate reconstruction with permanent adjustable prostheses outcome: cutaneous somatosensory status in breasts	24 invasive or DCIS	somatosensory function: sig impaired; most affected was area above the areola effect of RT: pts given post-op RT (n=9) did not differ from pts without RT (n=15) regarding any modalities patient-reported sensation: reduced sensation in reconstructed breast as compared to pre-op in 24 pts
Seth AK. 2011 [182]	retrospective comparative study	1. tumescent mastectomy and immediate implant reconstruction 2. non-tumescent mastectomy and immediate implant reconstruction mean follow-up was 36.5 months	897	complications (tumescent vs. non-tumescent): overall complications: OR=1.36 (1.02-1.81); p=.04 non-operative complications: OR=1.53 (1.04-2.26); p=.04 operative complications: OR=1.58 (1.11-2.23); p=.01 major flap necrosis: OR=1.57 (1.05-2.35); p=.03 tumescent had additive effect on complication rates in patients with other sig risk factors
Yule GJ. 1996 [183]	retrospective comparative study	1. immediate reconstruction (tissue expanders & implant) + adj chemo 2. immediate breast reconstruction	46	no significant differences within parameters of study (avoidance of expansion or surgery during the period of chemotherapy), there appeared to be no disadvantage posed by adjuvant chemo to the immediate reconstruction patient
Rinker BD. 2007 [178]	retrospective cohort	immediate reconstruction with a TRAM flap: 57 free and 35 pedicle mean follow-up: 6.7 yrs (4-14 yrs)	103	transfusion of non-autologous blood: 48% (49 pts)

Table 3a: Evidence on the effect of skin or nipple sparing on oncologic safety, organized by level of evidence.

Author, year	*Design*	*Mastectomy Type*	*Treatment(s)*	*Patients (N)*	*Oncologic Safety*
Lanitis S. 2010 [132]	systematic review	skin sparing	1. conventional without reconstruction (NSSM) 2. skin-sparing (SSM) with immediate reconstruction no sig heterogeneity between studies	3,739 (9 studies)	invasive breast cancer: 73.9% vs. 83.8% SSM local recurrence: 6.2% SSM vs. 4.0% distant relapses: 10.0% SSM vs. 12.7%
Shen J. 2008 [134]	physician survey	skin sparing	n/a: attitudes towards skin sparing mastectomy (postal questionnaire)	370	331 perform mastectomy for BCa with planned immediate reconstruction 90% did not feel that SSM resulted in higher rates of local recurrence
Benediktsson KP. 2008 [184]	prospective cohort	nipple sparing	nipple-sparing mastectomy and immediate reconstruction with implants (NSM) lymph node mets in 40.3%; 47 pts received post-op RT med f/u 13 years	216	locoregional recurrence: 52 pts (8.5% RT vs. 28.4% non-RT pts; p=.025) distant mets: 44 pts survival: DFS: 51.3%; OS: 76.4%
Sacchini V. 2006 [140]	retrospective cohort	nipple sparing	nipple-sparing mastectomy (NSM) with reconstruction purpose of NSM: prophylaxis (n=55), therapy (n=41), or both (n=27) med f/u 24.6 months	123	local recurrence: 2 pts (1 DCIS; 1 invasive); none in nipple distant mets: 1 patient (death at 50 mo after procedure)
Maxwell GP. 2011 [138]	retrospective cohort	nipple sparing	nipple-sparing mastectomy (NSM) purpose: risk-reducing (45 pts), therapeutic (53 pts; DCIS to stage 1B)	98	DFS (9 mos-3 yrs): no local or regional recurrence in any patient
Voltura AM. 2008 [139]	retrospective cohort	nipple sparing	nipple-sparing mastectomy (NSM) base of the NAC evaluated for occult tumor by permanent histo sections purpose of NSM (51 cases): invasive (24), DCIS (10), prophylaxis (17)	36	malignant NAC involve-ment: 5.9% (2/34) NSM for cancer, prompting removal local recurrence: 5.9% (2 pts)

Table 3b: Evidence on the effect of skin or nipple sparing on complications, organized by level of evidence.

Author, year	*Design*	*Mastectomy Type*	*Treatment(s)*	*Patients (N)*	*Complications/cosmesis*
Meretoja TJ. 2008 [185]	randomized trial	skin sparing	1. conventional diathermy 2. radiosurgery	60	SSM flap complication rate: 23.4% (no diff b/t groups) increased SSM flap complication rate associations: smoking & type of skin incision (tennis-racquet-type) used
Nava MB. 2006 [186]	prospective cohort	skin sparing	combined flap (skin sparing): infero-medial fibers of pectoralis major dissected and sutured to superior border of inferior dermal flap; implant inserted into pouch (1-stage)	28 (ptotic)	overall complication rate: 20% (4 cases were severe with extensive necrosis of the skin flaps requiring implant removal)
Shen J. 2008 [134]	physician survey	skin sparing	attitudes towards skin sparing mastectomy (postal questionnaire)	370	70% felt that cosmesis w/ immediate reconstruction after SSM was better than that of standard mastectomy; only 61% perform SSM in most cases when immediate is planned
Wijayanayagam A. 2008 [136]	prospective cohort	skin sparing	total skin-sparing with preservation of nipple-areola + immediate recon: implant or expander or muscle flaps purpose: prophylaxis (n=29), invasive (n=24), DCIS (n=11)	43 no disease within 2 cm of nipple	nipple-areola skin survival: 80% complete (n=51); 16% partial (n=10); highest (97%) w/ radial incision (n=34) occult DCIS in nipple-areola: 3% (2 pts) & was removed other complications: implant loss, total skin flap necrosis, and infection (no recurrences)
Petit JY. 2003 [135]	prospective cohort	nipple sparing	nipple-sparing (5 mm behind nipple areola was spared) + immediate reconstruction w/ prosthesis or flap characteristics: 19 invasive, 8 DCIS	25	superficial areola slough: 2 pts (spontaneous healing) areola necrosis: 1 pt (extensive retroareolar dissection) color of areola: well preserved in early follow-up; all pts except one expressed satisfaction of having kept areola
Sacchini V. 2006 [140]	retrospective cohort	nipple sparing	nipple-sparing mastectomy (NSM) with reconstruction purpose of NSM: prophylaxis (n=55), therapy (n=41), or both (n=27)	123	necrosis of nipple: 11% (22/192), judged to be <1/3 total skin of nipple in 59% (13/22) overall cosmesis: good to excellent in the majority of patients (patient & surgeon rating); level of satisfaction similar between prophylactic and treatment patients

Table 4: Evidence on the timing of adjuvant radiotherapy (RT) organized by level of evidence.

Author, year	*Design*	*Treatment(s)*	*Patients (N)*	*Complications/cosmesis*
Barry M. 2011 [107]	meta-analysis	1. immediate reconstruction 2. delayed reconstruction with combined RT	1,105	morbidity: higher w/ PMRT (OR=4.2; 95% CI 2.4-7.2) vs. no PMRT less w/ autologous reconstruction (OR=0.21; 95% CI 0.1-0.4) vs. implant-based not better w/ delaying BR until after PMRT (OR = 0.87; 95% CI 0.47-1.62) vs. immediate
Kronowitz SJ. 2009 [109]	systematic review	radiation therapy and breast reconstruction (mean follow-up of more than 1 year)	49 articles	complication rate for implant-based reconstruction with PMRT: >40% modified two-stage reconstruction (expander exchanged for implant before postmast. RT) = higher contracture rate; not generally feasible after neo-adjuvant chemo immediate implant-based or autologous reconstruction = limits ability to treat tissues without excessive exposure of heart/lungs delayed-immediate reconstruction (expanders placed at mastectomy) in pts for whom postmastectomy RT appears likely = less difficulties assoc. w/ RT after immediate recon. & preserves opportunity for aesthetic benefits of skin-sparing
Javaid M. 2006 [106]	systematic review	RT and autologous breast reconstruction	10 studies (no RCTs)	overall incidence of complications increased in patients with RT only four studies directly compared the outcomes of pts who received RT before with pts who received RT after autologous reconstruction; two reported worse outcomes w/ PMRT
Nava MB. 2011 [110]	prospective comparative study	1. postmastectomy RT + implants 2. postmastectomy RT + expanders 3. nonirradiated control group (n=98) * all pts: 2-stage immediate with subpectoral expanders/implants	257	totally failed reconstruction: 40% tissue expander v. 6.4% implant v. 2.3% control (p<.0001) capsular contracture: sig higher for RT groups vs. control shape/ symmetry & patients' opinions: higher rate of good results in implant vs. expander group (best scores in control)
Winters ZE. 2013 [53]	prospective cohort	implant-assisted latissimus dorsi (LDI; 82) or tissue-only autologous latissimus dorsi (ALD; 100) flap reconstruction and adjuvant treatments patients: primary early-stage breast cancer (82 LDI and 100 ALD) QoL: EORTC QLQ-C30 and QLQ-BR23, FACT-B, Body Image Scale, Hospital Anxiety & Depression Scale at 3, 6 and 12 months post-op RT: 30% LDI vs. 53% ALD (p=·004)	182	early complications 3 mos post-op: 66% LDI vs. 51% ALD (p=.062) long-term complications (4-12 mos): 48% LDI vs. 45% ALD (p=.845) role functioning and pain: (p=.002 for both) adversely affected in ALD group vs. LDI predictive factors: RT = not significant on HRQoL; chemotherapy = adversely affected HRQoL, which improved 3-12 mos post-op (p<.010)

Author, year	*Design*	*Treatment(s)*	*Patients (N)*	*Complications/cosmesis*
Cowen D. 2010 [141]	prospective cohort	mastectomy + immediate 2-stage reconstruction with a tissue expander & implant, plus RT (46-50 Gy in 23-25 fractions)	141	capsular contracture: grade 0-2 67.5%; grade 3-4 32.5% associated factors (multivariate): surgeon (p=.009) failures requiring surgery: 32 associated factors (multivariate): T3/T4 tumors (p=.0005), smoking (p=.001), pN+ axillary status (p=.004); pts with 0, 1, 2, or all 3 factors have probability of failure = 7%, 15.7%, 48.3%, 100%, respectively (p=.0000036)
Thomson HJ. 2008 [187]	prospective cohort	immediate LD recon +/- RT (43% of patients) photographic assess. & clinical eval retraction (BRA) at 3, 6 & 12 mo post-op and at 1 yr 53 implant-assisted LD and 20 autologous reconstructions	73	cosmesis: RT adversely affected cosmesis (panel assessment; p=.0002) (BRA assessment; p=.033) (both sig worse w/ implants; p=.020) patient assessment = cosmesis did not differ following RT or between LD groups
Tran NV. 2001 [104]	retrospective cohort	1. RT before delayed TRAM flap reconstruction 2. immediate TRAM reconstruction before RT mean f/u: 3 yr immediate; 5 yr delayed mean RT: 50-51 Gy	102	flap necrosis: one complete flap loss in the delayed group vs. none in the immediate reconstruction group early complications: no sig difference between groups late complications: significantly higher in the immediate group (87.5%) than in the delayed group (8.6%); p=.000) need for additional flap: 9 pts (28%) in the immediate group (to correct the distorted contour from flap shrinkage and contraction)
Williams JK. 1995 [105]	retrospective comparative study	1. RT then TRAM reconstruction (n=108) 2. TRAM reconstruction alone (n=572)	680	fat necrosis (> 10% of reconstr.): 17.6% RT vs. 10.1%, p=.032) subgroup unipedicled vs. bipedicled flaps controlled for RT: 17.7% vs. 17.4% associated factors: obesity and RT
Evans GR. 1995 [108]	retrospective comparative study	1. irradiated implants; mean 50 Gy (n=39) 2. nonirradiated implants (n=338) tissue expanders and f/u time <6 mos excluded patients from the study all implants placed submuscularly or beneath autogenous flap	297	pain, exposure, implant removal: 6/14 implants that received RT vs. 33/266 non-RT implants (p=.001) complications: 10/25 implants placed under auto-genous reconstructions with RT vs. 6/72 in implants placed under auto-genous non-RT reconstr. (p=.000)

Table 5: Select evidence on various types of implants (autologous, prosthetic, etc.).

Author, year	*Implant Type*	*Design*	*Treatment(s)*	*Patients (N)*	*Results*
Petit JY. 2011 [176]	autologous fat/ lipoflling	retrospective cohort	fat grafting (lipoharvest) for reconstruction surgery: 370 mastectomy and 143 BCS disease: 78.9% (n=405) invasive and 21.1% (n=108) DCIS second procedure elected (at 6 mos follow-up) in 24 pts mean f/u after lipofilling: 19.2 mos	513	interval b/t oncologic surgery and lipofilling: mean 39.7 mos complication rate: 2.8% (liponecrosis 2.0%) overall oncologic event rate: 5.6% (3.6%/ yr); locoregional event rate was 2.4% (1.5%/ yr)
Sajid MS. 2011 [188]	LD flap	systematic review	1. quilting of latissimus dorsi (LD) flap 2. no-quilting of LD flap donor site	440	donor-site seroma formation and volume: quilting superior for all measures post-op complications: combined quilting and fibrin glue effective in reducing the average volume of seroma and total drained volume, but did not influence the incidence of seroma
Shridharani SM. 2010 [189]	innervated DIEP, TRAM, LD flaps	systematic review	1. reconstruction using innervated flaps 2. reconstruction using noninnervated flaps	638 20 studies	recovery of sensation: innervated flaps have a greater magnitude of recovery, which occurs at an earlier stage compared to noninner-vated flaps DIEP flaps may recover better sensation than TRAM, followed by LD and finally implants
Atisha D. 2009 [190]	TRAM flaps	systematic review	1. perforator flap (free) reconstruction 2. traditional pedicle TRAM abdominal wall function assessed using isometric dynamometry	20 studies	deficit in trunk flexion: up to 23% deficit for pedicle TRAM vs. 18% deficit in free patients deficit in trunk extension: up to 14% deficit for pedicle TRAM vs. minimal-no deficits for free TRAM abdominal wall function: no sig differences flexion ability: sig higher in DIEP vs. TRAM
Temple CL. 2009 [191]	TRAM flap	randomized controlled trial (QoL study)	1. TRAM reconstruction in innervated flap (T10 intercostal nerve harvested with TRAM flap & neurotized toT4 sensory nerve at the recipient site) 2. TRAM breast reconstruction in non-innervated flaps follow-up: mean 48 months after free TRAM flap reconstruction	18 (response rate 66%)	patient outcomes: statistically significant improvement doe innervated TRAM in all three measures (*Medical Outcomes Study 36-Item Short Form Health Survey, Body Image after Breast Cancer Questionnaire, Functional Assessment Cancer Therapy-Breast*)

Author, year	*Implant Type*	*Design*	*Treatment(s)*	*Patients (N)*	*Results*
Daltrey I. 2006 [192]	LD flap	randomized controlled trial	1. reconstruction: quilting of LD flap 2. reconstruction control group	108	seroma: 83% (43/52) for quilting vs. 96% (46/48) for non (p=.036), including 38 pts who had extended LD flap (+/- implants) seroma volume: sig reduced (p=.004) back pain or shoulder mobility: no effect with quilting
Brandberg Y. 2000 [193] Brandberg Y. 1999 [194] SVEA RCT	Flaps	randomized controlled trial	(1) lateral thoracodorsal flap (n=16) (2) latissimus dorsi flap (n=30) (3) TRAM pedicled transverse abdominis muscle flap (n=29)	75	QoL: most women reported improvements in terms of "social functioning" and "mental health" LD flap and TRAM flap scored sig higher than lateral thoracodorsal flap for similarity with the contralateral breast and reduced problems in social situations
Lee SJ. 2004 [195]	DIEP flap	case-control study	intramuscular dissection of DIEP after harvesting of the flap	25 total	resting muscle thickness: increased in cases at 1-mo post-op resolving by 1-yr follow-up; attributed to post-op edema that resolves with time muscle denervation: none (all muscles in case and control groups retained contractility)
Bondeel PN. 1998 [196]	DIEP and TRAM flaps	prospective comparative study	(1) non-operated breasts (2) DIEP flaps w/ sensory nerve repair (3) DIEP flaps without nerve repair (4) TRAM flaps without nerve repair	104	pressure thresholds: stat sig lower for DIEP flaps with nerve repair temp & vibratory stimuli: more segments of the DIEP flaps with nerve repair reacted to cold, warm and vibratory stimuli vs. flaps without nerve repair sensory evoked potential responses: no response in 46% of TRAM flaps vs. 23% and 0% for DIEP flaps without and with nerve repair, respectively
Gerber B. 1999 [197]	LD flaps	prospective comparative study	breast surgery & immediate reconstruction using latissimus dorsi flap: 1. cutting (n = 29) tendinous muscle insertion on the humerus 2. leaving intact (n = 31) tendinous muscle insertion on the humerus	60	cosmesis: patient = good in 29/31 cases with tendon left intact and in 26/29 cases with tendon cut (p=.59) surgeon = good in 21/31 cases with tendon left intact and in 25/29 cases with tendon cut (p=.09)

Author, year	*Implant Type*	*Design*	*Treatment(s)*	*Patients (N)*	*Results*
Alderman A. 2007 [86] Michigan Br Recon Outcomes Study	TRAM flaps	prospective comparative study	1. autogenous tissue (pedicle and free TRAM flaps) 2. expander/ implant	398	patient satisfaction (2 yrs post operative): higher with TRAM flaps (both free & pedicle) vs. expanders/implants (OR 2.8, p<.01); no diff b/t free & pedicle TRAM general satisfaction: no stat sig diff b/t expander/implant and TRAM (pedicle, free)
Khouri RK. 1998 [198]	Flaps	prospective cohort	microvascular free-flap patient characteristics, surgical technique, pharmacologic treatment, and postoperative outcome	493 free flaps (not all cancer pts)	overall flap failure: 4.1% (20 of 493); RT (OR 4.2; p=.01) and use of a skin-grafted muscle flap (OR 11.1; p=.03) were the only sig predictors of flap failure.
Alderman AK. 2005	TRAM flaps	prospective cohort	post-mastectomy TRAM musculocutaneous reconstructions and abdominal function	183	range of motion (2 yrs post-op): procedure type, timing, and laterality did not sig affect range of motion for trunk flexion / extension peak torque for trunk flexion (2 yrs post-op): sig decreased in pts with TRAM vs. expander/ implant reconstructions (p<.05; 6-19% decrease)
Banic A. 1995 [200]	TRAM flaps	prospective cohort	free TRAM flaps (all 4 zones included in flap & end-to-end anastomoses to thoracodorsal, circumflex scapular, or internal mammary arteries) no preoperative selection of patients mean follow-up: 19 mos	111 123 flaps	fat & flap necroses: 19.5% (24 pts: 6 minor & 4 major fat necroses; 2 minor flap necroses and 6 major flap necroses) abdominal wall complications: 20% (22 pts) preoperative risk factors did not play a major role in the development of complications
Gesson-Paute A. 2008 [201]	Flap	prospective cohort	external oblique myocutaneous flap	20	local recurrence: 68% adjuvant therapy: EBRT 50%; chemotherapy 50% EBRT + chemo: 25%
Dell DD. 2008 [145]	TRAM flap	prospective cohort	TRAM flap breast reconstruction (pain and activity limits)	16	pain / activity limitation: elevated 4 wks post-op returned to near baseline at 8 wks abdominal pain: sig higher for women with free vs. pedicled TRAM flap surgery; women with previous back pain reported more lower back pain after surgery

Author, year	*Implant Type*	*Design*	*Treatment(s)*	*Patients (N)*	*Results*
Gart MS. 2013 [202]	Flaps	retrospective cohort	autologous breast reconstruction 4 cohorts: free flaps, pedicled TRAM, latissimus, and all flaps in aggregate	3296	predictors of complications: BMI >30 kg/m2, delayed reconstruction, recent surgery, prolonged operative times complications, flap failure, and reoperation: highest in the free tissue transfer group (p<.001) lowest in the LD flaps (p<.001) VTE and infections: highest in the pedicled TRAM group
Rinker BD. 2007 [178]	TRAM flap (free and pedicle)	retrospective cohort	mastectomy and immediate reconstruction with a TRAM flap	103	transfusion of non-autologous blood: 48% (49 pts) local recurrence / mets: 19% (20 pts); follow-up ranged 6.7 yrs mean (4-14 years)
Khouri RK. 1997 [199]	TRAM flap	retrospective cohort	simultaneous bilateral TRAM free flap follow-up (mean): 37.2 mos (14-62)	120	thrombosis: 2.5% (6/240 flaps; 4 arterial and 2 venous) minor complications: 15% (18 pts; hematoma, partial wound necrosis, infection, or prolonged postoperative ileus) abdominal wall weakness or hernia: 11.6% (14 pts)
Kim JY. 2012 [63]	HADM	systematic review/meta-analysis	1. two-stage 2. one-stage complication rates of human ADM with submuscular tissue expander for reconstruction	14,884	total complications: 15.4% for AD patients vs. 14.0% (RR 2.05 with AD; 95% CI 1.55-2.70) seroma: 4.8% AD pts vs. 3.5% (RR 2.73 with AD ; 95% CI 1.67-4.46) infection: 5.3% AD pts vs. 4.7% (RR 2.47 with AD ; 95% CI 1.71-3.57) flap necrosis: 6.9% AD pts vs. 4.9% (RR 2.80 with AD; 95% CI 1.76-4.45)
Newman MI. 2011 [203]	HADM	meta-analysis	complication rates of human ADM for coverage of expanders/implants mean follow-up: 13.7 mos	789	total complication rate: 12.0% most common: flap necrosis (3.3%), seroma (3.3%), infection (5.6%)

Author, year	*Implant Type*	*Design*	*Treatment(s)*	*Patients (N)*	*Results*
Jansen LA. 2011 [58,59]	HADM	systematic review	alloplastic breast reconstruction with AlloDerm (complication rates and costs for direct-to-implant reconstruction with AlloDerm vs. two-stage non-AlloDerm reconstruction)	14 studies (university Database)	complication rates: infection 0-11% hematoma 0-6.7%; seroma 0-9%; partial necrosis 0-25%; implant exposure with removal 0-14%; implant exposure with salvage 0-4%; caps. contracture 0-8%; rippling 0-6%
McCarthy CM. 2012 [71]	HADM	multicenter blinded RCT	1. mastectomy + HADM in tissue expander/implant reconstruction 2. mastectomy + submuscular tissue expander/implant placement	70	immediate post-op pain: no differences (p=.19) pain during expansion: no differences (p=.65) post-op narcotic use: no difference (p=.38) post-op expansion: no difference (p=0.83)
Basu CB. 2010 [204]	HADM	phase II study	1. AlloDerm tissue expander 2. native subpectoral capsule (control)	20	complications: granulation tissue, vessel proliferation, chronic inflammatory changes, capsule fibrosis, fibroblast cellularity, foreign body giant cell inflammatory reaction levels were diminished for acellular cada-veric dermis (AlloDerm) vs. native capsules (p<.001)
Venturi ML. 2013 [73]	HADM	prospective cohort	sterile human acellular dermal matrix in immediate expander reconstruction	65	complications: 3 breasts (4.6%); 1 cellulitis (1.5%) and 2 partial flap necrosis (3%) no seromas or explan-tations; grafts incorpo-rated in all cases
Glasberg SB. 2012 [205]	HADM	retrospective comparative study	HADM in tissue expander/implant breast reconstruction human AlloDerm (96) vs. animal Strattice (144)	186	total complications: higher with AlloDerm (21.4%) vs. Strattice (6.3%); p=.0003 seroma rate: 12.7% Alloderm vs. 1.4% (p=.0003) capsular contracture rate grade 1 or 2 = 2.4% AlloDerm vs. 2.8% Strattice

Author, year	*Implant Type*	*Design*	*Treatment(s)*	*Patients (N)*	*Results*
Becker S. 2009. [206]	HADM	retrospective comparative study	1. Alloderm 2. DermaMatrix mean follow-up: 6.7 months	30	complication profile: both dermal substitutes were well incorporated, with evidence of neovascularization
Dietrich M. 2012 [207]	titanium-coated polypropylene mesh (TCPM)	retrospective cohort	TCPM-assisted immediate or delayed implant-based breast reconstruction	42	mild hematoma, seroma or infection: 2 patients skin necrosis or capsular contraction: 1 patient mesh explantation: needed in 3 cases
Eriksen C. 2012 [52]	implant	prospective comparative study	1. one-stage reconstruction with a round permanent expander implant (Becker 25) 2. two-stage reconstruction with a crescent-shaped expander (LV 133) later replaced by anatomical implant	40	median follow-up: 3.5 years (1.5 to 5) revision surgery: 70% in one-stage group (mostly because of upper pole fullness and poor ptosis) quality of life: similar in the two groups
Gahm J. 2010 [208]	implant	prospective comparative study	1. anatomically shaped permanent expander implant McGhan Style 150 2. round permanent expander implant Siltex Becker 25 *bilateral prophylactic mastectomy and immediate reconstruction* mean follow-up: 30 mos (24-49 months)	36	complications: no statistical difference between implant groups breast symmetry: no statistical difference between implant groups outcome scores: no statistical difference between implant groups (expert panel and patient assessment)
Scuderi N. 2011 [149]	implant	retrospective cohort study	breast reconstruction with an anatomical Becker-type implant in the sub-muscular position reconstructions: 248 in 204 pts (143 immediate, 70%); unilateral 78.5% vs. bilateral 21.5%	204	complications: 34.2% (85 pts) in both immediate & delayed groups; related to wound healing, bleeding, and seroma Iatrogenic implant rupture: one case (0.4%) implant malposition: most troublesome compli-cation (34 pts; 13.7%) capsular contracture (Baker grade III/IV): 6 cases (2.4%) at follow-up approx. 1 yr post-op
McCarthy CM. 2010 [49]	implant	cross-sectional study	postmastectomy, implant-based reconstruction silicone used in 176 women and saline used in 306 women	n=482 (response rate 72%)	patients' satisfaction: sig higher in those with silicone implants (p=.016) postmastectomy RT had a sig negative effect on satisfaction (p<.000) in both silicone & saline; satisfaction diminished over time (p=.017)