BREAST RECONSTRUCTION FOLLOWING PROPHYLACTIC OR THERAPEUTIC MASTECTOMY FOR BREAST CANCER

Effective Date: February, 2017

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

Local treatment for early breast cancer has shown the equivalence of total mastectomy and breast conservation surgery plus radiation therapy as it relates to overall survival.[1] As a result, current guidelines on the surgical management of breast cancer recommend lumpectomy and whole breast irradiation as an oncologically equivalent option to mastectomy for patients with stage I or stage II invasive breast cancer.[2-5] Prophylactic bilateral mastectomy may also be considered as a risk reduction strategy for patients at high risk of developing breast cancer.[3,6,7,8]

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.[9-14] However, breast reconstruction may alleviate some of the postmastectomy distress experienced by these patients.[15-17] The purpose of this guideline is to provide practitioners 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 should receive breast reconstruction education information?
2. Who is a candidate for postmastectomy breast reconstruction?
3. Which types of breast reconstruction are available?
4. What is the appropriate timing 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 role of acellular dermal matrix in implant-based breast reconstruction?
8. What is the role of autologous fat grafting as an adjunct to breast reconstruction?
9. How can recovery be improved in breast reconstruction patients?
10. What is the appropriate post-breast reconstruction surveillance?
11. How do we measure outcomes in 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 Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit handbook.

Between initial publication of this guideline in 2013 and the update in 2016, there have been four new clinical practice guidelines published that are focused exclusively on breast reconstruction[18-21] and updates to five breast cancer guidelines to include recommendations on breast reconstruction.[3,22-25] These developments have been reviewed and incorporated into this guideline where appropriate.

SEARCH STRATEGY

Peer-reviewed articles were searched on February 29, 2016 and March 14, 2016 using PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), MEDLINE, EMBASE, and the Evidence-Based Medicine (EMB) Database. The following search terms were used: breast cancer, breast neoplasm, breast carcinoma, breast tumour/tumor, ablative surgery, mastectomy, ablation therapy, breast reconstruction, and mammoplasty. Results were limited to human participants >19 years of age, studies published in English, and publications from November, 2012 to March, 2016. Additional exclusion criteria included studies with ≤25 patients, and studies with singular focuses on costs, patient-reported outcome measures, imaging and prognostic factors. In total, 362 articles were identified, of which 54 were reviewed in detail based on a title/abstract screen.

The National Guideline Clearinghouse (NGC, Agency for Healthcare Research and Quality, www.guideline.gov) was searched for clinical practice guidelines related to breast reconstruction. In addition, the webpages of well-recognized cancer guideline developers was hand-searched to ensure no clinical practice guidelines had been missed.

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. **Patient education.** Women with breast cancer or those deemed to be at high risk for developing breast cancer (e.g. BRCA 1 and 2 mutation carriers) should receive standardized information about breast reconstruction early in their decision making process. Patients who are to undergo either therapeutic or prophylactic mastectomy should receive detailed, individually tailored information to assist with decision making, including appropriate breast reconstruction consultation if desired.

2. **Eligibility for postmastectomy breast reconstruction.** Various patient and treatment factors affect the options, risks, and outcomes of breast reconstruction. Consultation with an expert in breast reconstruction can provide a patient with a specialized treatment plan and anticipated outcomes, risks, and benefits so she can determine if breast reconstruction is appropriate for her. Factors that should be weighed when considering candidates for any method of breast reconstruction (immediate or delayed) include:
    - Cancer factors: tumour stage and location, risk of relapse.
    - Treatment factors: prior, concurrent, or anticipated future breast cancer treatment (such as surgery, radiation, and chemotherapy).
    - Patient factors: co-morbidities, body habitus, smoking status, and behavioral/ lifestyle factors.

3. **Types of breast reconstruction.**
   - Several types of breast reconstruction are available, including: implant-based, autologous flap, and combination reconstructions (i.e., autologous with implant).
   - There is insufficient 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 surgeon(s) and the patient after sufficient 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 T1/T2 tumours	Acceptable	Acceptable	Insufficient
Lymph node-positive either on needle biopsy or upfront, standalone SLNB †	Not recommended	Acceptable	Moderate
Treatment factors			
Prior radiation therapy	Acceptable; favors autologous	Acceptable; favors autologous	Good
Prophylactic mastectomy	Acceptable	Acceptable	Good
Prior non-oncologic breast surgery	Acceptable	Acceptable	Moderate
After preoperative systemic therapy	Acceptable	Acceptable	Good
Before adjuvant chemotherapy	Acceptable, if <61 day delay anticipated	N/A	Good
Before adjuvant radiation therapy †	Not recommended	N/A	Moderate
Prior diagnostic / excisional biopsy	Acceptable, but may affect skin and nipple sparing	Acceptable	Insufficient
Patient factors			
Older age	Acceptable, but may affect risks	Acceptable, but may affect risks	Moderate
Obesity	Acceptable, risks increase with BMI >30	Acceptable, risks increase with BMI>30	Moderate
Diabetes	Acceptable, but may affect risks	Acceptable, but may affect risks	Moderate
Smoking	Acceptable, 3-4 week smoking cessation recommended	Acceptable, 3-4 week smoking cessation recommended	Moderate
Planned future pregnancy	Acceptable; favors implants	Acceptable; favors implants	Insufficient

***Level of evidence:**
Good = 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 radiation therapy, as per CancerControl Alberta guideline "Adjuvant Radiation Therapy for Invasive Breast Cancer."[5]

4. **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, or are unlikely to require postmastectomy radiation therapy** 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 postmastectomy radiation therapy is probable or uncertain should be discussed for breast reconstruction appropriateness in a multidisciplinary setting and meet pre-operatively with a radiation oncologist as needed; in general, reconstruction should be delayed until after treatment with radiation therapy has been completed. Concerns include the inability to include important structures in radiation therapy volumes, and an increase in long term fibrotic complications in both implant and autologous tissue based immediate reconstruction.
- On average, patients who are good candidates for reconstruction and receiving other adjuvant 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.
- Patients for whom immediate breast reconstruction is not appropriate may be considered for delayed breast reconstruction as an acceptable alternative after completion of all recommended adjuvant therapies.

5. **Factors that enhance recovery after breast reconstruction.**
   Irrespective of type or timing of reconstruction, recovery can be improved by adherence to Enhanced Recovery After Surgery (ERAS®) protocols, such as limiting pre-operative fasting, carbohydrate loading, multimodal analgesia, post-operative nausea and vomiting prophylaxis, goal directed fluid therapy, early institution of post-operative feeding, early ambulation, and adequate post-discharge outpatient supports.

6. **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 oncologically safe for prophylactic patients, but may not be suitable for every patient based on risk of nipple necrosis.
   - For patients with malignancy, there is no level one evidence for or against the oncologic safety of nipple-sparing mastectomy (NSM). Multidisciplinary input and discussion between the surgeons and the patient about potential additional risks such as perfusion issues and local recurrence risk associated with this approach are required.
   - 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.

7. **Risks and benefits of breast reconstruction.**
   - Patients should be made aware that breast reconstruction is a complex, major, multi-step surgery and that complications occur.
   - Patient expectations should be assessed prior to surgery, in order to optimize care. In addition, patients should be made aware that the final outcome may vary from patient to patient and that the reconstructive surgery will not restore the breast to its original function, appearance, or sensation.
   - Complications can occur with each type of reconstructive procedure. Listed below are the most common complications associated with each procedure:

  - **Autologous reconstructions:** mastectomy skin necrosis, seroma, scarring, hematoma, chronic back pain, abdominal weakness, bulge, hernia, fat necrosis, partial or complete flap 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 necrosis, infection, seroma, hematoma, chronic breast pain, implant rupture, tissue expander puncture, exposure or malposition, capsular contracture, and an extremely rare form of breast implant associated anaplastic large cell lymphoma (BIA-ALCL).
- Careful patient evaluation for risk factors for complications is required to determine if a woman is appropriate for immediate reconstruction. It is critical to minimize the chance of delay to adjuvant chemotherapy for triple negative or HER-2 positive breast cancer, as a delay of >61 days may lead to inferior breast outcomes.

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 mastectomy skin necrosis, postoperative seroma, and infection, and mastectomy skin 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.** Case control data supports the safety of lipofilling. Data from comparative studies and case reports suggest that patient satisfaction is good; however more data is needed.

10. **Post-breast reconstruction surveillance.** Regarding oncologic surveillance, there is no evidence to support routine screening mammography of the reconstructed breast, therefore is not recommended. Fat necrosis is a common and benign mammographic finding in patients with reconstructed breasts. Post-reconstruction patients with suspicious masses or symptoms should be referred to a surgeon for examination and further workup. Regarding implant surveillance, although MRI can detect silent implant shell rupture, there is no evidence that radiologic screening of asymptomatic reconstructed breasts improves women's health.

11. **Measuring outcomes in breast reconstruction.** Clinical and patient reported outcomes can be recorded, with presently available validated instruments, at the pre-, peri- and post-operative stage to help multi-disciplinary teams deliver consistent, high quality care with minimal variability.

TREATMENT ALGORITHM

An algorithm for the use of breast reconstruction in patients undergoing mastectomy is presented in Figure 1. This algorithm was made in an effort to standardize clinical practice across the province. The information is not meant to be prescriptive or to replace the clinical judgment of any medical practitioner. Please refer to related clinical practice guidelines: Adjuvant Radiation Therapy for Invasive Breast Cancer, Adjuvant Radiation Therapy for Ductal Carcinoma In Situ, Systemic Therapy for Early Stage (Lymph Node Negative and Lymph Node Positive) Breast Cancer, and Neo-Adjuvant (Pre-Operative) Therapy for Breast Cancer – General Considerations for established recommendations. Practice variations for therapy may exist within the province.

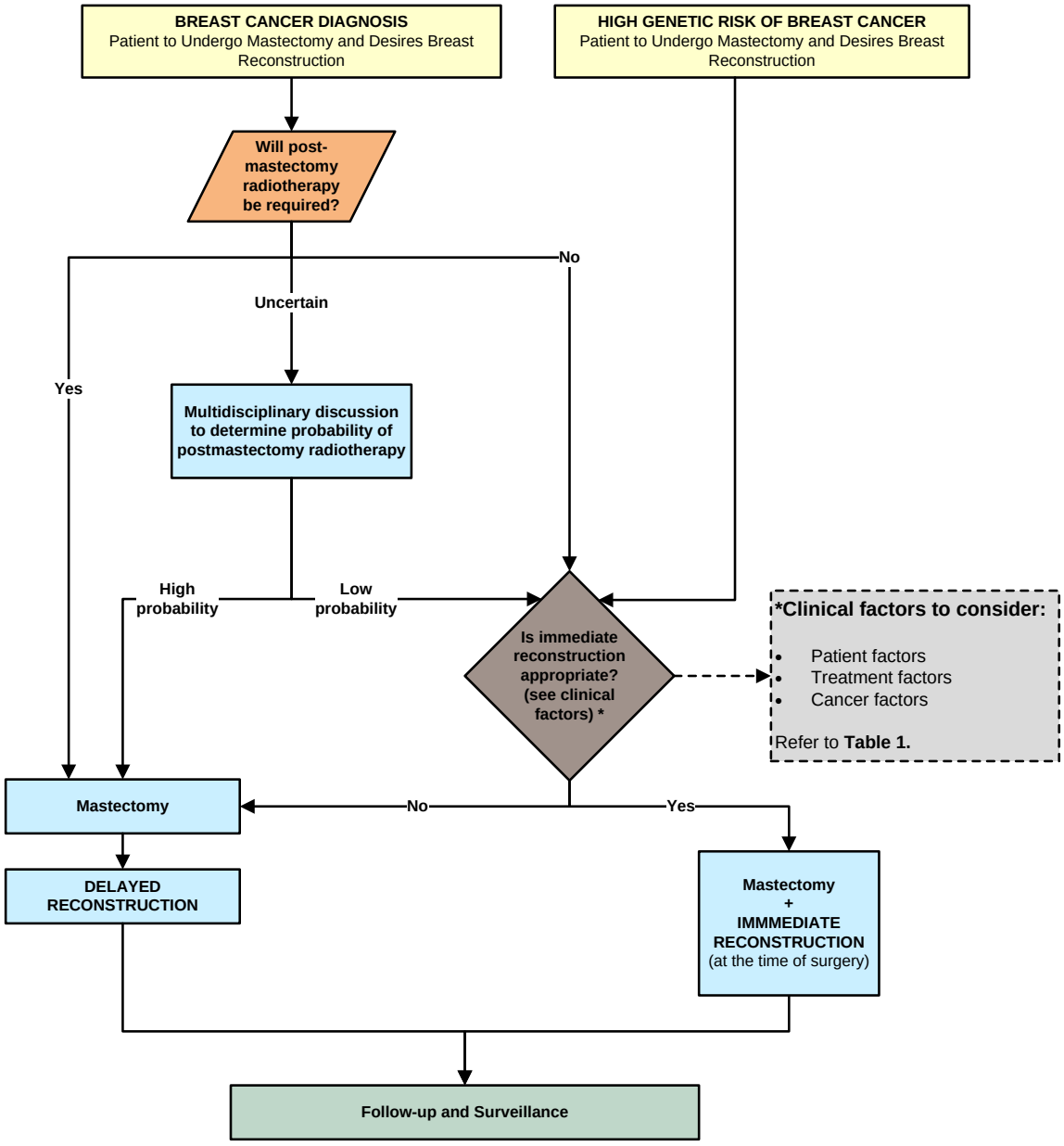

Figure 1. Algorithm for the use of breast reconstruction in patients undergoing mastectomy.

DISCUSSION

Therapeutic reasons for mastectomy often include multicentric tumors, contraindications to radiation therapy, local recurrence following breast conserving surgery, inflammatory breast cancer, failure of down staging or tumour progression following neoadjuvant chemotherapy, and breast cancer during pregnancy if radiation therapy cannot be delayed until the postpartum period.[3] Some women choose to undergo a mastectomy when they are a candidate for breast conservation surgery, despite the known survival equivalence of the two.[3] Prophylactic mastectomy of the contralateral breast is not recommended in patients with a known sporadic ipsilateral breast cancer treated with mastectomy,[3,26] however, women often enquire about this procedure out of efforts to improve symmetry, fear of contralateral breast cancer, anxiety, and inconvenience around ongoing surveillance. Risk reducing surgery with prophylactic mastectomy and reconstruction may be offered to high risk women such as those carrying BRCA1 or BRCA2 gene mutations or those with previous mantle irradiation for lymphoma.[23]

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.[15] 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 breast reconstruction (IBR) 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.[16] 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 with psychosocial morbidity lowest in the wide local excision group, followed by the breast reconstruction group, with the highest morbidity observed in the mastectomy alone group.[17]

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.[27,28] Metcalfe, et al. 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 IBR. However, by 1-year follow-up, there were no significant differences in any of the psychosocial functioning scores between the groups.[11] It should be noted 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.[29] 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).[30-32] Another challenge in interpreting satisfaction data is that prior to 2009, validated patient questionnaires specific to breast reconstruction had not yet been developed.[33,34] Other reasons for not undergoing reconstruction may include the presence of medical comorbidities or patient preference, such as the desire to avoid further surgery.[35] Nevertheless, the option to undergo breast reconstruction should be discussed with patients who are making decisions about mastectomy or breast conserving surgery. The need for patient education has been recognized by the US government; in 2015,

the Breast Cancer Patient Education Act (BCPEA) was passed to raise awareness of the availability and coverage of breast reconstruction procedures, and to ensure that patients are made aware of the option of reconstruction prior to mastectomy.[36]

Despite the evidence for positive outcomes associated with postmastectomy reconstruction, rates of reconstruction are low in Canada and may be influenced by a number of factors, including physician knowledge, attitudes, and practice setting.[37] A population-based retrospective cohort study in Ontario found a patient had twice the odds of receiving IBR when she was treated at a hospital with two or more available plastic surgeons (OR 2.01, 95%CI 1.53-2.65).[38] The reported breast reconstruction rate in Nova Scotia from 1991 to 2001 was 3.8%,[39] and a retrospective cohort study in Ontario revealed that the BR rate among women remained low between 1984 and 1995 (7.9 breast reconstructions per 100 mastectomies in 1984/1985 compared to 7.7 per 100 in 1994/1995).[40] A follow-up study by Platt et al. in 2015 found reconstruction rates in Ontario doubled in the following decade; 23.3% of women had breast reconstruction within 3 years of mastectomy and 13.4% had IBR between 2002 and 2011, however, concerns about underutilization still remain.[41] Several factors may influence breast reconstruction underutilization, including patient proximity to a plastic surgeon, a general surgeon's knowledge of breast reconstruction and patient eligibility, patient preference, or logistical issues and resource constraints limiting access. Platt's geographical analysis showed that a large proportion of the Ontario population has limited access to plastic surgeons who perform breast reconstruction regularly, and this lack of access substantially contributed to the low rates of breast reconstruction and geographic variation in IBR.[41] While rates of delayed breast reconstruction were equally low in this study, there was less geographic variation for this approach in comparison to IBR.

Breast reconstruction can achieve a high level of satisfaction and better psychosocial outcomes for patients.[42-44] There is no evidence to support that reconstruction makes detection of local recurrence more difficult, [23] despite another Canadian guideline recommending that patients should wait 1-3 years after mastectomy before being offered reconstruction[21]. Despite the value of breast reconstruction, there is a lack of uniform, evidence-based consensus 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. Evidence tables are available upon request.

1. Patient Education

Adequate and appropriate patient education around breast reconstruction is recommended. Postmastectomy breast reconstruction decisions are particularly sensitive to patient and practitioner preference and are often made in haste with large knowledge gaps, resulting in women undergoing procedures misaligned with their goals.[45,46] In a systematic review, Preminger et al. identified seven education tools for postmastectomy reconstruction comprising written, audio and visual materials.[47] An educational needs assessment was only present in the development of one of the tools. These tools demonstrated knowledge gains, decreased decisional conflict and a decision 'yes' or 'no' regarding breast reconstruction and type of reconstruction. Two of the seven tools were subjected to RCT testing for efficacy. Causarano et al. showed that a pre-consultation educational group intervention for women pursuing non-time sensitive breast reconstruction (i.e. delayed reconstruction, or reconstruction in the setting of prophylaxis) improved shared-decision making and lessened decision conflict.[45] A full-scale RCT has been designed to test this pilot data.[48]

An interactive decision aid was shown to increase factual knowledge, reduce anxiety and increase postoperative satisfaction.[49] Shared decision-making using a person-centered approach with tailored breast reconstruction information was shown to provide high satisfaction using the BRECON-31© breast reconstruction satisfaction questionnaire across a variety of reconstruction methods.[50] Decision regret was lessened with increased satisfaction with preoperative information, which in turn may be influenced by women possessing higher self-efficacy trait.[51] In a study of 510 women in North America who were mailed the BREAST-Q™ module, satisfaction with information and interaction with their plastic surgeon was highly correlated with patient satisfaction with overall outcome.[52] In another study of 123 patients, decision regret was associated with low satisfaction with preparatory information.[53]

The above information presupposes that women are inquiring about breast reconstruction. It is possible that some women considering breast conservation versus mastectomy may not know that breast reconstruction exists as an option. In a qualitative study of Canadian breast cancer patients and health care providers,[54] themes emerged including difficulty initiating the breast reconstruction conversation with health professionals, absence of a standardized process for initiating a dialogue around breast reconstruction, lack of information on subthemes of timing, modality, quantity and content of resources, and a plea for information to be distributed early in the consultation process. Identical themes surfaced in a similar qualitative study in U.S. patients.[55] In contrast, other qualitative studies[56,57] have indicated that the breast care clinical nurse specialist plays an extremely important role in facilitating the process of receiving information. Additional valuable information sources included the surgeon, photographs of prior patients, contact with other patients, written information, the internet, a recording of the initial reconstruction consultation and standardized information videotapes. Clearly, the type, manner and timing of information delivery are just as important as the information itself.

2. Patient Selection

Several patient factors should be considered when selecting appropriate candidates for breast reconstruction. Existing guidelines list prior cancer therapy (i.e. chemotherapy, radiation therapy; see sections 4 and 5 below), body composition, and smoking status as factors to consider when selecting patients for reconstruction.[3,20,21,58] The National Comprehensive Cancer Network (NCCN) guidelines add medical comorbidities and patients concerns as additional factors to be considered.[3] The American Society of Plastic Surgeons also lists larger preoperative breast size ($\geq$C) as a potential complicating factor (Evidence Recommendation Grade: D).[20] Based on existing evidence and current guidelines it is recommended that the following patient factors be considered when selecting candidates for reconstruction: prior, concurrent, or future cancer treatment, medical co-morbidities (i.e. diabetes, COPD, cardiovascular disease), body habitus (i.e. BMI, breast size, preexisting scars), and smoking history and current smoking status.

Among patients undergoing IBR, a prospective study demonstrated a significantly greater risk of failure on multiple logistic regression analysis, among patients with larger tumours (T3/T4), patients who smoke, and patients with positive lymph nodes.[59] The rate of reconstructive failure in this study (defined as the need for a second intervention consisting of removal 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; which accurately predicted 80% of failures. A risk analysis by Fischer et al. found obesity (BMI $\geq$ 30), active smoking, and a preoperative ASA (American Society of Anesthesiologists) physical status score of $\geq$3 to be independent risk factors associated with surgical morbidity in IBR patients.[60] 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; 48% BMI 25-30; 45% BMI >30 (p=.43). However, reconstruction type did vary by BMI. TRAM (transverse rectus abdominis myocutaneous) flaps were performed in 53% of patients with BMI >30 versus 26% of patients with BMI <25 (p=.01). In patients with BMI 25-30, 48% received TRAM flap reconstruction. Patient satisfaction with surgical decision-making and surgical outcomes was similar across body mass index categories, providing further evidence of the value of matching the appropriate procedure to the appropriate patient.[61] The presence of preexisting abdominal scars from prior surgery may also raise concern for vascularity upon abdominal (TRAM or DIEP) flap transfer, but with careful planning, some scars can be accommodated safely and do not alone preclude the option of autologous tissue transfer,[62] although they have the potential to increase morbidity and complications at the abdominal donor site.[63]

3. Types of Breast Reconstruction

In general, breast reconstruction procedures available to patients vary according to several factors, including timing of the procedure (i.e., immediate versus delayed), laterality (unilateral vs bilateral), the extent of mastectomy (modified radical, total, skin sparing, skin and nipple sparing) and the type of reconstruction used (i.e., prosthetic implant, autologous tissue flap, or combination of the two). The availability of new products and techniques such as acellular dermal matrix and structural fat grafting/lipofilling, add further options for surgeons and patients to consider.

Prosthetic implants (completed in an expander/implant sequence or a direct-to-implant method), autologous tissue, and a combination of implant and autologous tissue are available for breast reconstruction procedures. No randomized controlled trials have been performed to compare these types of reconstructions in terms of cosmesis or complications in patients with breast cancer. The few observational studies available in the literature have used varying, non-standardized measures to assess aesthetic outcomes;[64] factors such as cost,[65] pain,[66] aesthetics,[67-70] compatibility with adjuvant radiation therapy,[71] and complication rates[72-74] have been used as a basis for recommending one reconstructive procedure over another. In general, patient outcomes are favorable regardless of the type of reconstruction used [50] and the decision to use an implant, flap or combined procedure should be left to the discretion of the plastic surgeon and the patient after consideration of the benefits and limitations of all appropriate alternatives. A study evaluating various forms of breast reconstruction with the validated BRECON-31© questionnaire demonstrated similar patient satisfaction across various forms of reconstruction, with the exception that the recovery subscale had lower scores for autologous reconstructions.[50]

Revisions over time: Breast reconstruction may be associated with a need for subsequent procedures or revisions over time. In a retrospective review of 15, 000 breast reconstruction patients across 4 states, secondary breast procedures were high for all reconstruction types, with unplanned revisions highest in the tissue expander patients (tissue expander 59.2%, direct to implant 45.9%, and autologous 34.4%).[75] Fischer's earlier retrospective single-centre reviews of expander/implant patients case-matched to free tissue transfer patients also demonstrated higher rates of unplanned surgical revisions and total system costs in the expander/implant cohort[76,77]; however; the larger database review demonstrated lower complication rates at 90 days after expander/implant (6.5%) or direct-to-implant (6.6%) reconstruction, and higher complication rates at 90 days after autologous reconstruction (13.1%).[75]

Patient satisfaction comparing types of implants: Patient-rated outcome measures, such as the BREAST-Q™[78] and the BRECON©[34], are essential when comparing reconstruction and implant type.[79,80] 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 compare satisfaction among silicone gel (n=75) and saline (n=68) implant recipients (response rate: 58%).[79] Using the BREAST-Q™, silicone gel 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 higher overall physical function, and significantly lower systemic side effects. 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 gel implants were used in 176 women while saline implants were used in 306 women. Patient satisfaction was higher in those with silicone implants (p=0.016); however, postmastectomy radiation therapy had a negative effect on satisfaction (p<0.000) in both silicone and saline recipients, with diminishing satisfaction over time in both groups (p=0.017).[81]

Patient satisfaction comparing implants and flaps*:* 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. In this study, aesthetic satisfaction was nearly three-fold higher in patients who underwent flap reconstruction (OR 2.8, p<0.01), yet there was no difference between these groups in terms of overall general satisfaction.[82] A survey among 33 women who had undergone breast reconstruction sought to compare the 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.[83] Patients who had undergone TRAM flap reconstruction were more satisfied with how their reconstructed breast felt to the touch (p=0.01); however, patients with TRAM flap reconstruction identified greater difficulty functioning at work or school, performing vigorous physical activities, participating in community or religious activities, visiting with relatives, and interacting with male friends (p<0.04). Similarly, in a study using the BRECON-31© questionnaire women who underwent autologous reconstruction demonstrated significantly worse recovery subscale scores than women who underwent implant-based reconstruction.[50] A retrospective study among all patients undergoing IBR (n=186) at a single institution over a five-year period revealed a lower complication rate for patients with expander/implant reconstructions (21.7%), in comparison to those with latissimus-dorsi (LD) flap reconstructions (67.9%) or TRAM flap reconstructions (26.9%).[84] 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 using an ad hoc questionnaire; 42% responded and revealed a higher level of satisfaction (moderate or higher) among the expander/implant reconstruction group (93.8% versus 76.9% for latissimus flap and 83.3% for TRAM flap). A prospective cohort comparing implant-assisted LD with tissue-only autologous LD 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).[85] However, role functioning and pain were significantly worse in the tissue-only autologous group (p=.002 for both). Radiation therapy did not affect quality of life in this study.

A retrospective study among all patients at a single institution over a 7 year time period undergoing postmastectomy breast reconstruction (n=583) compared patients with tissue expander/implant reconstruction with those who underwent LD, TRAM, and DIEP flap reconstructions.[86] When asked about their quality of life, 439 patients (75%) responded, indicating that the highest level of general satisfaction on an ad hoc questionnaire 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).

A systematic review of 1393 patients from 15 studies found with time, expander/implant reconstruction may become less favourable from a satisfaction point of view. However, the author cautioned that the evidence is weak because of methodologic issues within the individual studies and standardized studies with PROMs are required.[87] In 7610 women recruited from the Army of Women, women with breast reconstruction with flaps scored 5.6-14.4 BREAST-Q™ points higher than those with breast conserving surgery (BCS), those with LD flaps the same as BCS patients, those with implant reconstruction 8.6 points lower than BCS patients, and those with mastectomy, 10 points lower than those with BCS.[88]

The challenge with these large and long term retrospective reviews is that they precede the more recent advances of ADM, fat grafting, and cohesive, form-stable gel implants. These advances have improved the outcomes of implant reconstruction, but it will take time to repeat these comparisons to autogenous tissues.

Cost issues: American statistics from 2008 revealed a $2,860 USD difference in cost (including initial hospitalization and complications and revisions up to one year) in favor of a free TRAM flap ($14,080 USD) over an implant ($16,940 USD); however the cost difference disappeared over time.[89] 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).[90] It has been reported elsewhere, however, that the cost of an LD, TRAM, or DIEP flap reconstruction, 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.[91] A 2015 cost analysis found initial healthcare costs at the time of surgery were greatest for autologous patients (autologous=$54,309 USD, direct-to-implant=$46,228 USD, expander/implant=$39,470 USD, p <0.001), but after 3 years, the absolute difference in cost between the groups had decreased (autologous=$66,882 USD, direct-to-implant=$64,145 USD, expander/implant=$63,806 USD, p<0.001). The authors credit this reduced differential to unplanned revisions being lowest among the autologous cohort (autologous=34.4%, direct-to-implant=45.9%, expander/implant=59.2%, p<0.001).[75] As such, no recommendations can be made favoring one type of reconstruction over another from a cost perspective.

4. 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 IBR 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.[92] Similarly, 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.[11] A 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 IBR reduced psychiatric morbidity at three months postoperatively, as compared with

delayed or no reconstruction.[93] Heterogeneity exists between studies in the evaluation of cosmesis and complications between immediate and delayed reconstruction, which needs to be considered when interpreting results.[29,94]

The evolution of adjuvant treatment in breast cancer has resulted in more locoregional radiation therapy and more intense chemotherapy regimens, complicating the integration of reconstruction into a woman's care pathway. There are expanding indications for postmastectomy radiation for single node positive patients, or node negative patients with multiple concerning features (triple negative, high grade, lymphovascular invasion, and young age).[95] Current AHS guidelines for radiation therapy can be accessed here.[5]

Regarding safety, a prospective cohort of patients with T1-T3 tumours (n=677) underwent either mastectomy alone, or mastectomy with IBR; no radiation therapy 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 IBR 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).[96] Furthermore, the meta-analysis by Gieni et al. found no differences in the risk of recurrence between patients who underwent IBR and those who underwent mastectomy alone.[97]

Guidelines on this issue generally indicate that IBR 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 otherwise meet appropriate selection criteria for immediate reconstruction (see Table 1).[58,98-102] Based on the best evidence available, IBR should be considered, whenever possible, for any patient who is a candidate for breast reconstruction, unless she is likely to receive radiation therapy.

Timing of reconstruction in the setting of adjuvant radiation therapy

Immediate versus delayed autologous reconstruction: Most guidelines that address the timing of adjuvant radiation therapy (RT) recommend that breast reconstruction be delayed in patients with breast cancer for whom postmastectomy RT is planned.[21,23,58,98] The 2016 NCCN breast cancer guideline states that when postmastectomy radiation is required and autologous tissue reconstruction is planned, reconstruction is either delayed until after the completion of RT, or it can be initiated at the time of mastectomy with tissue expander placement followed by autologous tissue reconstruction.[3] This "delayed-immediate" approach was described for patients who are likely to receive RT, as it is thought to avoid difficulties associated with radiation delivery after IBR while preserving the opportunity for the aesthetic benefits of skin-sparing mastectomy.[103]

Complications associated with radiation therapy to autologous reconstruction can include fat necrosis, delayed wound healing, fibrosis resulting in contracture, loss of volume and distortion of breast. [104] In patients who underwent TRAM reconstruction (n=680), those who received pre-operative RT were found to have higher rates of fat necrosis (>10% of total reconstruction; 17.6% versus 10.1%, p=.032) than those who did not receive radiation treatment.[105] Obesity and radiation therapy were also both found to be associated with fat necrosis and major infection in logistic regression analyses. Similarly, a systematic review that compared the outcomes of patients in terms of the timing of RT with autologous reconstruction found the overall incidence of complications was increased in patients who received RT in three of four studies. The review provides a case for delayed rather than immediate autologous reconstruction in

patients who are expected to receive post-operative RT.[104] A meta-analysis of postoperative morbidity following immediate or delayed breast reconstruction (n=1,105) found that in IBR patients using prosthesis, those undergoing RT were more likely than those not receiving RT to suffer morbidity (OR 4.2; 95% CI 2.4-7.2). An additional analysis comparing immediate versus delayed autologous reconstruction with combined RT found that delaying breast reconstruction until after RT had no significant effect on morbidity (OR 0.87; 95% CI 0.47-1.62 [delayed BR vs immediate BR]). Autologous reconstruction was associated with less morbidity than implant-based reconstruction (OR 0.21; 95% CI 0.1-0.4).[106]

Despite the reported adverse effects to autologous reconstruction associated with radiation therapy, the question of timing remains controversial. Mirzabeigi et al. reviewed 470 patients who had free flap breast reconstruction with and without postmastectomy radiation. Despite increased volume loss and fat necrosis in the post-operative radiation group, similar rates of revision surgery were observed in the non-radiation group, and the authors concluded deleterious effects of postmastectomy RT do not preclude a discussion of immediate autologous reconstruction.[107] This is in contradistinction to Tran's 2011 retrospective chart review of 102 patients comparing delayed TRAM flap reconstruction following RT versus immediate TRAM flap reconstruction followed by RT (mean RT dose: 50-51 Gy). This study found that the rate of late complications was significantly higher among patients in the IBR 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 IBR group.[108]

Another approach to guide patient selection is to consider an upfront "staging" SLNB as a reliable means of determining the probability of postmastectomy RT in clinically node negative patients. McGuire et al. suggest that SLNB be performed as a separate outpatient procedure several days prior to mastectomy when IBR 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.[109] 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,[110] to avoid the high rate of complications and implant loss among patients undergoing postmastectomy RT after IBR,[111,112] and to identify patients for whom delayed reconstruction is preferred due to a positive SLNB finding.[113] Those against this strategy have provided retrospective data to suggest that the false negative rate when performing SLNB at the time of mastectomy and IBR 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%).[114]. Data on the feasibility of intraoperative SLNB diagnosis suggest that this strategy is practical.[115,116] Further rationale for not performing an upfront SLNB include additional expense, increased delay in initiation of systemic therapy, and the propensity of procedure-related morbidity.[114,117] It is important to note that an upfront SLNB commits the patient to axillary lymph node dissection (ALND) post-chemotherapy should it be positive.[116] An alternative to upfront SLNB is to use high quality axillary ultrasound and FNA, and if positive, to start neoadjuvant chemotherapy, involving the potential to downstage and ultimately minimize axillary surgery.

Immediate versus delayed implant-based reconstruction: Among patients undergoing reconstruction with implants, a retrospective chart review compared those with irradiated implants (average 50 Gy) with those with non-irradiated 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 radiation therapy.[118] Similarly, Eriksson et al.[119] noted a 15% failure in immediate implant-based reconstruction with postoperative radiation versus 6% failure in non-irradiated cases.

If a patient has embarked on an immediate expander-based reconstruction and then needs radiation therapy, radiation therapy can be delivered to the expander, or after exchange to the permanent implant. [3] Cordeiro et al. evaluated 1143 breast reconstruction patients and found greater failure rates in patients with radiation therapy to a tissue expander (32%) compared to patients with radiation therapy to a permanent implant (16.4%; p<0.01). Furthermore, aesthetic results were better and capsular contracture rates lower when radiating the permanent implant. Patient reported outcomes did not differ between groups.[120] Similarly, in a prospective study comparing timing of radiation therapy 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 radiation therapy 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.[121]

Reconstruction in the setting of prior radiation therapy

In previously radiated patients, the use of tissue expanders/implants is relatively contraindicated.[3] Current guidelines recommend autologous or combined autologous/implant reconstruction in women who have received prior irradiation to the breast, as tissue expanders and implants carries higher risk for complications.[3,21]

Timing of reconstruction in the setting of neoadjuvant chemotherapy

Data suggest that IBR can be safely integrated after chemotherapy without a significant impact on complications. A prospective RCT comparing modified radical mastectomy versus initial systemic therapy followed by mastectomy found that there was no significant difference in the risk of complications and that IBR was not an independent predictor of complications.[122] 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 non-significant increase in risk of complications in neo-adjuvant patients undergoing mastectomy with IBR (OR, 1.58; 95% CI, 0.98-2.58).[123] In a case control study of 201 patients, Narui[124] showed no effect of neo-adjuvant chemotherapy in the short or interim outcomes after immediate perforator flap reconstruction. Most prospective and retrospective series have reported similar results,[85,125-132] with only one study reporting greater implant infection rates[132] with chemotherapy and one reporting a higher rate of expander removal with chemotherapy.[129] The American Society of Plastic Surgeons supports that preoperative chemotherapy does not appear to be a significant risk factor for either postoperative complications or implant failure in women undergoing post mastectomy expander/implant breast reconstruction.[20]

Timing of reconstruction in the setting of adjuvant chemotherapy

Data suggest that reconstruction may impact the time to chemotherapy, but not necessarily in a clinically significant manner. The decision whether to perform an IBR should be weighed against this potential delay. Patients who require adjuvant chemotherapy for triple negative or HER-2 positive breast cancer who are delayed due to complications of IBR may have inferior breast cancer outcomes. Consideration of neoadjuvant chemotherapy for this population should be made due to the high response rates for complete pathologic response, as a potential mechanism to downstage the tumour and as a means to facilitate other factors impacting surgery including genetic testing or coordination of IBR. [133]

Several retrospective studies have examined how the time to chemotherapy (TTC) affects outcomes in breast cancer patients. In 24,843 patients with stage I to III breast cancer, there were no adverse oncologic outcomes among patients with a TTC of 31-60 or 60-90 days. Patients who received chemotherapy 91 or more days from surgery had worse overall survival (HR 1.34, 95% CI 1.15-1.57) and worse breast cancer-specific survival (HR 1.27, 95% CI 1.05-1.53), with further subgroup analysis finding the longer delays in TTC particularly detrimental to patients with TNBC.[134] Another retrospective review of 6827 patients found a TTC of $\geq$ 61 days after surgery demonstrated worse outcomes for distance recurrence free survival (DRFS) for stage II, as well as adverse outcomes for OS, recurrence free survival (RFS) and DRFS for stage III breast cancers, in comparison to those treated within 30 days after surgery. Separate multivariable analyses found patients with TNBC as well as HER-2 positive patients treated with chemotherapy and trastuzumab had worse outcomes if TTC was greater than 61 days.[135]

In a 2015 retrospective study of 199 patients, IBR did not delay adjuvant treatment when compared to patients without construction (41 days vs 42 days, p = 0.61). If a patient had a complication, a median 6 day delay in adjuvant therapy was noted.[136] Similarly, Hamahata et al. found adjuvant chemotherapy started at 61 days in an IBR group and at 58 days in a non-IBR group,[137] and Chang et al. found no significant difference in median time to chemotherapy between patients with IBR and patients with a mastectomy alone (32 days vs 34 days, p = 0.2).[138]

Other studies show a delay to chemotherapy after IBR. 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 IBR group.[139] Delays were related to surgical complications. In the only Canadian study examining time to chemotherapy, 391 consecutive women who underwent mastectomy (n=243) or mastectomy and IBR (n=148) showed a statistically significant difference in the median time to chemotherapy (48 days for mastectomy alone vs. 60 days for IBR; p=0.01).[126] In a meta-analysis consisting of 14 trials (n=5270), 7 studies found no significant difference in TTC between IBR and mastectomy only, 4 found delay after IBR with averages of 6.6-16.8 days, one found significantly shorter mean TTC after IBR, and two did not perform statistical analysis for comparison.[140]

In summary, the evidence supports the utility and safety of IBR, particularly if TTC remains within 60 days. For larger tumors (locally advanced, stage III) or more aggressive phenotype (e.g. TNBC or HER-2 positive), it may be ideal to start earlier (<30 days) or treat with neo-adjuvant chemotherapy to plan for more optimal multidisciplinary surgical intervention following adequate or optimal response of neoadjuvant chemotherapy. There does not seem to be an impact of neoadjuvant chemotherapy on type of surgery (IBR vs mastectomy) in terms of post-operative complications. Optimal management can likely be achieved by identifying ideal surgical candidates and through efficient planning by the multidisciplinary surgical team.

5. Extent of Mastectomy

Skin-sparing mastectomy

In a meta-analysis of nine studies including 3,700 patients, skin-sparing mastectomy (SSM) with IBR has been found to be equivalent to conventional mastectomy alone in terms of oncologic safety; the local recurrence rate was 6.2% for SSM 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 SSM and 12.7% for conventional mastectomy (odds ratio, 0.67, 95% CI: 0.48-0.94).[141] In line with these findings, published guidelines recommend SSM as an

acceptable approach.[3,21,58,98] Nevertheless, SSM 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 IBR.[142] Ninety percent felt that SSM did not result in higher rates of local recurrence and 70% felt that cosmesis was superior with IBR after SSM; yet, only 61% reported that they perform SSM in most cases when IBR is planned. SSM can be more technically challenging due to longer skin flaps carrying a risk of skin flap ischemia. In 117 two-stage reconstructions, the inverted-T mastectomy approach had a higher rate of flap necrosis than a horizontal elliptical SSM (25.6% vs 11%), yet 91% of the inverted-T patterns still completed expansion successfully.[143]

Nipple-sparing mastectomy

Oncologic issues:

***Prophylactic*.** Nipple-sparing mastectomy (NSM) with immediate breast reconstruction can be offered to women undergoing a prophylactic mastectomy and women with known DCIS.[21] NSM performed in the setting of immediate reconstruction can achieve excellent cosmetic results[144] and provide psychosocial benefit to the patient.[145] An MRI study of 105 prophylactic NSM patients found that at a retroareolar depth of 5mm, the proportion of total breast fibroglandular tissue in the NAC was 1.3%, suggesting that preserving the NAC in a prophylactic mastectomy creates very little added risk from an oncological perspective.[145] Jakub et al. retrospectively reviewed 551 prophylactic NSMs in a BRCA population; 203 patients underwent bilateral prophylactic NSM and 145 underwent unilateral prophylactic NSM secondary to a previous or current breast cancer in the contralateral breast. After a median follow-up of 34 months, no breast cancers developed on the side of the prophylactic procedure, and none of the patients who underwent bilateral prophylactic NSM developed cancer at any site.[146]

Therapeutic. NSM is a reasonable option for women with early breast cancer who are believed to be lymph-node negative,[21] but there is limited evidence regarding the oncologic safety of NSM in patients with malignancy. Studies include single institutions series and retrospective reviews, often with mixed cohorts of women with and without malignancy. Due to concerns surrounding malignant potential of the tissue remaining in the spared nipple-areolar complex (NAC), NSM is not recommended in women with inflammatory breast cancer, early breast cancer with positive lymph-nodes, locally advanced breast cancer likely to require post-operative RT, or with evidence of NAC involvement such as Paget's disease, nipple retraction, bloody nipple discharge and/or imaging suggesting malignancy.[3,21] A systematic review by Mallon et al. [147] of 29 observational studies reported an occult nipple involvement rate of 11.5% and an overall nipple recurrence rate of 0.9%. Factors that were associated increased incidence of nipple involvement included tumor to nipple distance <2cm, tumour grade, nodal metastases, tumour size >5cm, and HER-2 negative status.[147]

Several recent systematic reviews have found low rates of adverse oncologic outcomes of NSM in carefully selected women with early stage breast cancer.[149,150] An analysis of 12,358 NSM procedures (prophylactic and therapeutic) found an overall pooled locoregional recurrence rate of 2.38% and a 5.9% incidence of partial/total nipple necrosis.[151] Another systematic review of 5,166 patients (48 studies) showed a nipple necrosis rate of 7% and a locoregional reoccurrence rate of 1.8%, concluding that NSM is safe for appropriately selected patients but encouraging future RCTs to determine the best incision and reconstructive methods.[150] In a large, matched cohort series of nipple and skin-sparing mastectomies, there was no significant difference in overall complications,[152] even when patients had previous breast surgery.[153] A propensity score study comparing the local recurrence (LR) rate between nipple-sparing and total mastectomy (TM) in patients with stage 0-III breast cancer found no significant difference in the five-

year LR (7.6% NSM vs 4.9% TM, p=0.398), nor did they find NSM to be a significant risk factor for local recurrence in a multivariate analysis (HR 1.653, 95%CI 0.586-4.663, p=0.343). After propensity score matching, the 5-year LR free survival was similar for the NSM and TM groups (92.3% vs 93.7%, p=0.655), indicating that oncologic safety is comparable between NSM and TM in selected patients.[154]

Despite these promising results with NSM, there is no published data from a randomized controlled trial on the oncologic safety of nipple-sparing as compared to conventional SSM. Retrospective data support NSM as an option for women who are low risk for breast cancer recurrence (e.g. prophylactic mastectomy, DCIS peripherally located in breast [>2cm from the nipple], early stage node-negative)[21]; however, the decision as to whether to pursue NSM requires multidisciplinary input and careful discussion with the patient about the risks and benefits associated with this approach.

Nipple/areola perfusion issues: Even if NSM is considered an oncologically acceptable option following multi-disciplinary assessment, there are still perfusion issues to consider. From a nipple/areola perfusion perspective, a healthy, non-smoking patient with minimal ptosis and a relatively small breast is the optimal candidate for a nipple-sparing procedure.[148] Increasing rates of nipple necrosis are seen with mastopexy (4.8%) radial (8.9%), inframammary (9.1%), periareolar (17.8%), and transareolar incisions (81.8%). Nipple necrosis rates are similar for 2-stage expander and 1-stage direct to implant reconstructions (4.5% and 4.1%, respectively), but higher for autologous reconstructions (17.3%).[150] A literature review including 29 studies showed full and partial nipple necrosis rates of 2.9% and 6.3%.[147] Viability of the nipple-areolar complex may be improved by performing a surgical ischemic preconditioning "delay" procedure 1-2 weeks prior to mastectomy, in conjunction with biopsy of the retroareolar tissue.[155]

The success of immediate breast reconstruction hinges on the consistency and vascularity of the mastectomy flaps. Indocyanine green injection with near-infrared fluorescent imaging is helpful to determine intraoperatively whether the breast skin after mastectomy is sufficiently well perfused to accommodate an immediate reconstruction, or if debridement of poorly vascularized skin and/or delay of the reconstruction is advisable.[156-158] A recent retrospective review comparing complication rates between immediate tissue expander-based reconstruction patients who underwent clinical assessment only (n=53) or ICG angiography (n=61) found the rates of severe flap necrosis to be significantly lower in the ICG patients (4.9% vs 8.9%, p = 0.02).[159] Not only can ICG angiography reduce complications related to mastectomy skin necrosis, but also allow evaluation of ischemic portions of DIEP flaps to reduce partial flap necrosis.[156]

6. Risks and Benefits

Patient expectations should be assessed prior to surgery in order to optimize care. Patients should be made aware that aesthetic results may vary from patient to patient and that reconstructive surgery will not restore the breast to its original appearance, sensation, or function. Systematic measurement and management of patient expectations may improve patient education, shared medical decision-making and patient perception of outcomes.[160]

Autologous reconstructions

As with any major surgery, complications can occur with breast reconstruction and each type of autologous reconstruction may carry site specific risks. The most common complications associated with autologous flap reconstructions are flap necrosis (~5% of patients), infections (~5% of patients), and seroma (~4% of patients). Reoperation is frequently required in patients who develop partial flap necrosis,

and always required in cases of complete necrosis.[161] Less common complications from autologous breast reconstruction include bruising, bleeding, and chronic pain.[162,163] Liu[164] compared 75 flap and 179 expander/implant reconstruction patients and found notable rates of complications in each group (21% flap, 37% expander/implant), and a shorter length of stay (LOS) for expander patients (2.1 vs 4.8 days). Deep inferior epigastric perforators (DIEP) flaps carry a higher risk of fat necrosis and partial flap loss [163] but lower donor-site morbidity (i.e., bulge formation, hernia),[163,165] as compared to muscle-sparing TRAM flaps. A systematic review of 33 articles found the risk of fat necrosis to be greater in DIEP flaps (14.4%, p<0.001) compared to pedicled TRAM flaps (12.3%, p=0.04) and free TRAM flaps (6.9%, p<0.001) [166]. Conversely, a recent study by Macadam et al. looking at 1790 patients found no difference in patient satisfaction, abdominal wall morbidity, or flap necrosis between DIEP flap, muscle-sparing TRAM, and free TRAM patients. Higher partial flap loss, fat necrosis and worse physical wellbeing (abdomen) were seen in pedicled TRAM reconstructions.[167] An NSQIP study of 3296 women with various autologous options revealed that pedicled TRAM flaps and LD flaps remain the most commonly used autologous methods, with free flaps having the highest captured 30 day complication and reoperation rate, and LD flaps the lowest.[168] Although patients frequently request bilateral reconstruction, autologous bilateral free flaps have significantly higher flap loss in comparison to unilateral reconstruction.[169] In addition, a unilateral delayed and contralateral IBR for prophylactic mastectomy carries higher revision rates to achieve symmetry.[169]

Implant-based reconstructions

In patients who undergo implant-based breast reconstruction with human acellular dermal matrix (HADM), the total complication rate is approximately 15%, with the most common complications mastectomy flap necrosis (~7% of patients), infection (~5% of patients), and seroma (~5% of patients).[161] Mastectomy flap necrosis can necessitate removal of the implants and reoperation.[142] As with autologous reconstruction, implant-based reconstruction may be associated with bruising and bleeding,[142] chronic pain,[162,163] implant rupture or malposition,[103,118] and capsular contracture, which more frequently occurs in patients who undergo radiation therapy.[59,170] There is evidence to suggest that the risk of capsular contracture is lower with the use of textured implants, as compared to smooth implants.[171]

In an extremely small number of patients with breast implants, anaplastic large cell lymphoma (ALCL) has been observed. The main presentation of ALCL is late seroma after implant placement. A late seroma detected by ultrasound warrants an ultrasound guided aspiration, sending the aspirate for lymphoma protocol including CD 30 markers, ALK, cytology and culture and sensitivities. Treatment requires a multidisciplinary approach. [172] 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 patients are alive and well.[173] The United States FDA 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.[174] Subsequently, the American Society of Plastic Surgeons and the American Society for Aesthetic Plastic Surgery issued a statement indicating that ALCL is extremely rare, involves a textured device, that the risk of women with implants developing ALCL is extremely low, and that breast implants are safe and effective.[175] Miranda[176] reviewed the literature for 60 published cases of BIA-ALCL, in which 93% of patients with disease confined by fibrous capsule achieved complete remission. Patients presenting with a tumour mass had worse OS and PFS, meriting adjuvant chemotherapy. A recent review[177] emphasizes complete surgical excision (complete capsulectomy and implant removal) to achieve optimal event free

survival. Risk estimates by Brody et al.[178] based on 173 cases known to the author, range between one in 500,000 to 1 in 3 million women with implants.

The Canadian Society of Plastic Surgeons (CSPS) has released a statement acknowledging the low but increased risk of ALCL in women with breast implants. In an effort to improve understanding of the epidemiology and underlying etiology of ALCL, the CSPS is working in partnership with the MD Anderson Cancer Center to develop a reporting questionnaire (PROFILE Questionnaire). Currently, the CSPS encourages that all diagnosed cases be reported to the society.[172] Clemens et al. from the MD Anderson Cancer Center have released a FAQ document for physician use that can be accessed through the CSPS website.[179]

7. Acellular Dermal Matrix (ADM)-Assisted Implant-Based Reconstructions

Human Acellular Dermal Matrices

Over the past decade, human acellular dermal matrices (HADM) have been increasingly utilized to facilitate and enhance the results of standard two-stage expander/implant IBRs, 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.[180] 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[181,182]. 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.

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.[161,183,184] These studies should be interpreted with caution, as they reflect the collective pooling of early results from multiple surgeons' initial experiences with the product. Other studies have demonstrated that with judicious patient selection and precise intraoperative technique[185,186] superior aesthetic results can be achieved with a safety profile that is comparable or superior to reported series of traditional, non-HADM assisted approaches.[187-191] 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.[192].

A retrospective analysis of 417 patients found no significant difference in complication profiles between HADM and non-HADM patients, and after further stratification of patients by exposure to radiation, found a decreased risk of complications related to radiation in HADM breasts. [193] The authors suggest that HADM use may provide a protective influence in patients undergoing postoperative radiation therapy. In a breast that has been previously irradiated, there is evidence which contraindicates the use of HADM; a retrospective study found a tissue expander loss rate of 40.7% in previously irradiated breasts with HADM, a rate that was triple the rate in radiated breasts without HADM (13.5%).[194]

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.[195,196] A retrospective chart review among patients undergoing implant-based IBR, either with

HADM (n=208) or without (n=129), demonstrated significantly better aesthetic outcomes in the HADM group.[197]

Factors to consider for HADM use include matrix product, matrix size, and matrix sterilization. Several HADM products are now offered for use in breast reconstruction. While one analysis found no difference between these products for overall complication rate,[198] other studies have shown differences in major infection[199] and seroma[200]. Cayci et al. compared matrix size and found two-stage IBRs that used a larger matrix (128 or 160cm^2) had a mean 2.8± 1.6 number of fills to reach final expansion volume while the mean number of fills for two-stage IBRs with a small matrix (48 or 96cm^2) was 7.5±2.3, p<0.01. This study suggests using a larger ADM offers a potential to increase the initial expander fill volume-to-breast pathology weight ratio and initial expander fill volume-to-final implant volume ratio, resulting in fewer post-surgery expansions and cost savings.[201]

Aseptic and sterile 'ready-to-use' ADMs were compared in a prospective cohort study of 546 breast reconstructions. Patients with sterile ADM had a lower incidence of infection compared to those with an aseptic ADM (8.5% vs 20%, p = 0.0088).[202] However, a smaller study (n=58) found a higher rate of seroma formation in IBRs using sterile ADM in comparison to those using aseptic ADM.[203]

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,[204] an RCT 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), or rate of expansion (p=0.83) for HADM-assisted techniques.[205] A matched cohort study yielded similar findings.[206]

Data is insufficient to draw definitive conclusions regarding the overall cost-effectiveness of HADM in breast reconstruction. A 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.[196] 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 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.[207]

Alternatives to HADM

Alternative forms of ADM are available. Non-human ADM can be used (porcine or bovine); however, there is relatively little published outcome data for this practice.[191] A retrospective study of 127 patients found that complication rates using porcine ADM in breast reconstruction are comparable to complication rates found in studies using HADM (total major complication rate 7.1%, total minor complication rate 22.9%). [208] These results are similar to an earlier retrospective study of 105 porcine-derived ADMs in implant-based breast reconstructions (total complication rate 8.6%). [209] A systematic review of vicryl mesh shows a 2.6% (95% CI: 0.7-6.6%) infection rate, 3.2% (95% CI: 1.0-7%) reconstruction failure rate, and 1.3% (95% CI: 0.2-4.6%) incidence of seroma.[210] In 231 patients where titanium-coated polypropylene mesh was used in immediate or delayed breast reconstruction, major complications were observed in 13.4%, minor

complications in 15.6%, and implant loss in 8.7% of patients.[211] Prospective studies are needed to further compare various mesh types with ADM. Another alternative to donated dermis is available in women with ptotic breasts requiring a skin-reducing mastectomy who are interested in downsizing their breast size. In these women, a vascularized flap of inferior mastectomy skin can be maintained rather than discarded, de-epithelialized and used in a manner identical to HADM with good results. [212,213]

The majority of evidence surrounding the adjunctive use of ADM in implant based breast reconstruction is retrospective.[214] 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.

8. Autologous Fat Grafting as an Adjunct to Primary Breast Reconstruction (Lipofilling)

There is no data from clinical trials or meta-analyses looking at autologous fat grafting (lipofilling).[215] However, a 2016 study by Kronowitz et al. matched 719 breasts with cancer reconstructed with lipofilling to 670 breasts with cancer reconstructed without lipofilling to determine whether autologous fat grafting in breast reconstruction influenced the rate of locoregional and systemic recurrence in breast cancer patients. Mean follow-up times after mastectomy were 60 months for cases and 44 for controls. The authors found no difference between groups: locoregional recurrence was observed in 1.3% of cases and 2.4% of controls (p=0.455), and systemic tumour recurrence was observed in 2.4% of cases and 3.6% of controls (p=0.514). Multivariate analysis compared recurrence between cases and controls adjusting for chemotherapy, radiation therapy, hormonal therapy and clinical stage. Only the subgroup with hormonal therapy showed a higher risk of recurrence with lipofilling (1.4% vs 0.5%, p=0.038). The authors also followed 305 cancer free breasts reconstructed with lipofilling and found no primary breast cancer over a mean time period of 73 months.[216] This reiterated the safety seen in 321 patients, where comparable cumulative incidence of locoregional recurrence was seen in 321 lipofilled cases compared to 642 matched controls.[217]

In terms of patient satisfaction, an observational study among patients undergoing nipple-sparing, skin-sparing and skin-reducing mastectomies and not requiring adjuvant radiation therapy (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.[218] 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).[219] More importantly from an oncologic safety perspective, after a mean follow-up of 23 months, there were no local recurrences. 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.[220]

Fat graft retention has been reported as being good.[221] 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.[222] Complications appear to be higher with implant-based reconstructions as compared to autologous flap reconstructions. [223] 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.[224]

9. Factors That Enhance Recovery After Breast Reconstruction

Regardless of the type or timing of reconstruction a woman has chosen, it is possible to improve the recovery experience for women. The recovery experience is uniformly the most poorly rated aspect of a woman's satisfaction with reconstruction, irrespective of type of reconstruction. [50] The recovery phase is arduous, and impacts physical and psychosocial domains of quality of life for over 3 months from surgery.[225] A pending publication completed by an international group outlines 18 evidence-based best practices for peri-operative management designed to improve the recovery experience and reduce care time,[226] which is the goal behind the guidelines such as for colorectal surgery[227] previously developed by the ERAS® Society (www.erassociety.com). Some of the key features of the Enhanced Recovery After Surgery (ERAS®) breast protocol include minimizing pre-operative fasting, carbohydrate loading, intra-operative goal-directed fluids, avoiding hypothermia, multimodal analgesics and PONV medications, early refeeding and ambulation, and post-operative discharge support. Mobile apps have been used to aid in post-operative discharge support and minimizing the need for in-person visits. For autologous breast reconstruction, ERAS® protocols reduce opioid requirements and length of stay.[228,229] For implant-based reconstruction, women can be moved safely from in- to out-patient care with higher quality of recovery scores and no increased complications using ERAS® principles, provided adequate outpatient supports are in place.[230] Pedicled TRAM and latissimus dorsi patients have achieved early discharge under 24 hours with enhanced recovery protocols.[231,232] Mobile app follow-up monitoring quality of recovery for patients at home is feasible and acceptable.[233,234]

10. Post-Breast Reconstruction Surveillance

Breast reconstruction following mastectomy is oncologically safe. A meta-analysis found that the risk of breast cancer recurrence among patients who underwent mastectomy and IBR was equivalent to those who underwent mastectomy alone (odds ratio, 0.98; 95% CI 0.62-1.54).[97] A large database study of nearly 50,000 patients showed improved survival in women undergoing IBR in comparison to women than mastectomy alone, controlling for all known confounders for breast cancer survival.[235] In a database study of 6000 women with reconstruction, implants in particular were associated with improved survival [236].

There is no evidence to support routine radiologic screening of the reconstructed breast, in the absence of a palpable recurrence or symptoms of recurrence. Imaging records from 227 patients with a history of postmastectomy 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%.[237] 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. Four recurrences were found in these symptomatic patients.[238] 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.[239] Regarding patients with NSM, it is uncertain whether they require any increased vigilance beyond clinical exam. In properly selected patients, the risk of recurrence should be extremely low.[149,154] Among patients with unilateral mastectomy and either delayed or immediate reconstruction, imaging surveillance of the contralateral, non-reconstructed breast should continue according to local guidelines. [240]

Post-operative surveillance in terms of implant health has been explored by several studies. Pineau et al.[241] looked at 40 ruptured silicone breast implants from reconstruction from 6 centers. Mean time to rupture was 6.97 years and 45% of cases were silent, leading to a proposal of ultrasound surveillance (with or without MRI) at 4, 7, and 10 years after initial surgery.[241] MRI may perform better than ultrasound, but both methods have high concordance for detecting implant rupture[242]. Ultimately there is no conclusive evidence to show the potential benefits of asymptomatic breast implant screening outweigh risks and costs to the patients[243].

11. Measurement

Best practice clinical and patient reported outcomes can be recorded at the pre-, peri- and post-operative stage to help multi-disciplinary teams deliver high quality care with minimal variability. Suggested instruments to use for patient satisfaction measures include the BRECON-31©[34] and BREAST-Q™[78]. Recovery can be assessed by the patient-reported measure 'Quality of Recovery-15' (QoR-15).[244] Complications can be followed by 30 day readmission rates, as well as audit systems from NSQIP and ERAS®. Rates of reconstruction can be tracked by local administrative bases.

In 2012, the British Association of Plastic Reconstructive and Aesthetic Surgeons (BAPRAS) and the Association of Breast Surgery (ABS) released a guideline for oncoplastic breast reconstruction with 25 quality criteria checkpoints and targets.[245] These quality criteria are based on findings from a UK breast reconstruction audit (National Mastectomy and Breast Reconstruction Audit; NMBRA)[246] and are designed to optimize key clinical and patient reported outcomes at every stage of the clinical pathway. The guideline provides examples of key performance indicators and a proposed minimum dataset, however, no core outcome set was established.

Appendix 2 contains examples for quality indicators that have been adapted from the BAPRAS guideline and Cancer Care Ontario Breast Cancer Surgery Quality Indicators. A discussion around clinical outcome metrics for breast reconstruction has been initiated within Alberta Health Services and will continue to be a part of the conversation for provincial practice.

Resource Implications

The recommendations contained in this guideline reflect the best available evidence on postmastectomy 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 postmastectomy radiation therapy.

Summary

Breast reconstruction information should be available early in a woman's decision making process. Breast reconstruction should be made available for patients undergoing mastectomy, for prophylaxis or for the treatment of breast cancer, provided they are eligible from a cancer and patient factors perspective. Factors such as prior, concurrent, or future cancer treatment, especially the intended or actual use of radiation therapy, co-morbidities, body habitus, and smoking history and current smoking status should be considered when selecting candidates for breast reconstruction. IBR should be considered, whenever possible, for any patient who is a candidate for breast reconstruction. The integration of reconstruction and postmastectomy radiation therapy should be addressed in a multidisciplinary setting. In general, breast

reconstruction should be delayed until after radiation therapy is complete. Several types of reconstruction (implant and autologous) are available, including ADM-assisted reconstructions, with the type of procedure left to the discretion of the surgeons and the patient after providing counseling, based on the benefits and limitations of each. Skin-sparing mastectomy for IBR is a safe and appropriate approach. Nipple-sparing can be considered for patients undergoing prophylactic mastectomy. Patients for whom the decision is made to undergo NSM in a therapeutic setting should be made of aware of the lack of evidence from an RCT. Lipofilling does not increase local recurrence and can improve contour irregularities. Post breast reconstruction surveillance for cancer and implant integrity is primarily clinical, with imaging reserved for symptoms. Recovery can be improved by adherence to ERAS® protocols. Measurement of clinical and PROMs at the pre-, peri-, and post-operative stage promote consistent, high quality care.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
ADM	acellular dermal matrix
AHS	Alberta Health Services
ALK	anaplastic lymphoma kinase
ASA	American Society of Anesthesiologists
BCPEA	Breast Cancer Patient Education Act
BCS	breast conserving surgery
BIA-ALCL	breast implant associated anaplastic large cell lymphoma
BMI	body mass index
COPD	chronic obstructive pulmonary disease
CSPS	Canadian Society of Plastic Surgeons
DIEP	deep inferior epigastric perforators
DRFS	distance recurrence free survival
ERAS®	Enhanced Recovery After Surgery
FNA	fine-needle aspiration
HADM	human acellular dermal matrix
HER-2	human epidermal growth factor receptor 2
IBR	immediate breast reconstruction
ICG	indocyanine green
LD	latissimus-dorsi
LOS	length of stay
LR	local recurrence
MRI	magnetic resonance imaging
NAC	nipple-areolar complex
NCCN	National Comprehensive Cancer Network
NSM	nipple-sparing mastectomy
NSQIP	National Surgical Quality Improvement Program
OS	overall survival
PFS	progression free survival
PONV	postoperative nausea and vomiting
QALYs	quality-adjusted life years
QoR	quality of recovery
RCT	randomized control trial

RFS	recurrence free survival
RT	radiation therapy
SEER	Surveillance, Epidemiology, and End Results
SLNB	sentinel lymph node biopsy
SSM	skin-sparing mastectomy
TM	total mastectomy
TNBC	triple negative breast cancer
TRAM	transverse rectus abdominis myocutaneous
TTC	time to chemotherapy
USD	US Dollar

DISSEMINATION

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

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2017. 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. CancerControl Alberta 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 and objective 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 IBR (IBR) in the last two decades.[247] 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[248-250] 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.[247] 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.[141,248,251-253]

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.[254] These borders significantly overestimate the actual extent of the breast gland. Schwartz in "Principles of Surgery," describes the anatomy of the breast gland ore 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.*[255]

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.[256] 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.[257] 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.[258] 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.[259] Here the superficial fascia adheres to the underlying chest wall.[260] Preservation of the inframammary fold is essential to define ptosis and inferior quadrant shape.[260]

APPENDIX B: Suggestions for Quality Indicators for Breast Reconstruction

Indicator	Outcome	Measurement Tool
Preoperative	Breast reconstruction is discussed with patients requiring a mastectomy Full information is available at the time of referral and provided following surgery The role of reconstruction is discussed at multidisciplinary rounds Medical photography is included in medical record Proportion of immediate and delayed breast reconstruction patients that received surgery within the priority target Patients have access to a navigator or equivalent (key worker with expertise in breast reconstruction and psychological assessment and management) Patients receive information in an appropriate format and level of detail for their individual needs Proportion of patients that receive appropriate pre-operative imaging of the breast Patient satisfaction with information received from plastic surgeon	BREAST-Q™, BRECON-31©
Perioperative	Documentation of photographic outcome (pre and post-operative) IV and antibiotics on induction Complication rates (nausea and vomiting, SSI, UTI, pneumonia, DVT, wound dehiscence, flap and skin necrosis, flap failure, etc.) Flap monitoring protocol in place Patients are risk-assessed for thromboembolism and preventative measures adopted Local and systemic recurrence rates Proportion of patients re-operated on (for non-breast ablative procedure) within 30 days after BR Proportion of patients that died within 30 days after a breast surgery Post-operative pain managed Linkages with physiotherapy, nurse navigator as needed Length of stay Implant loss at 3 months Implant returned to OR Unplanned readmission within 30 days Unanticipated radiation in immediate reconstruction patients	ERAS®, NSQIP
Patient rated outcomes	Patient satisfaction with outcome Patient satisfaction with information and involvement in decision making Quality of recovery/patient satisfaction with recovery	BREAST-Q™, BRECON-31© QoR-15

*Includes items from Oncoplastic Breast Reconstruction: Guidelines for Best Practice.[245]

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