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Action Cancer Ontario

Guideline 17-10

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Breast cancer reconstruction surgery (immediate and delayed) across Ontario: Patient indications and appropriate surgical options

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Report Date: January 5, 2016

WARNING

Increased risk for Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) exists with the use of textured breast implants. See the Health Canada recalls and alerts webpage for more information
https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2019/70045a-eng.php

An assessment conducted in January 2021 indicated that Guideline 17-10 REQUIRES UPDATING. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Note added November 2021

This document is in review and a new document will be forthcoming. Substantial changes will be made based on new literature and current clinical practice. In the interim, the following changes were made in consultation with the Surgical Oncology Program and the Breast Cancer Advisory Committee to reflect current practice and concerns:

Recommendation 3: In patients expected to require radiotherapy, the timing of breast reconstruction should be determined after multidisciplinary discussion including the general surgeon or surgical oncologist, medical oncologist, radiation oncologist, and plastic surgeon and with full consideration of the values and preferences of the patient.

Recommendation 8: Acellular dermal matrix (ADM) is currently widely used in breast reconstruction. The U.S. FDA[1] has issued a safety communication indicating that the complication rate (reoperation, explantation, and infections) may vary depending on the type of ADM, and this is being investigated.

Guideline 17-10 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/31721

Section 1:	**Guideline Recommendations**
Section 2:	**Recommendations and Key Evidence**
Section 3:	**Guideline Methods Overview**
Section 4:	**Systematic Review**
Section 5:	**Internal and External Review**

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[1] **United States Food and Drug Administration. Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates: FDA Safety Communication. Silver Spring (MD): US FDA; 2021 Mar 31 (cited 2021 Oct 8). Available from: https://www.fda.gov/medical-devices/safety-communications/acellular-dermal-matrix-adm-products-used-implant-based-breast-reconstruction-differ-complication.**

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Breast cancer reconstruction surgery (immediate and delayed) across Ontario: Patient indications and appropriate surgical options

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

- To provide clinical guidance with respect to suitability for breast reconstruction, timing of reconstruction, and optimal reconstruction techniques.
- To make recommendations that will inform decisions at the policy and administration level aimed at improving the quality of life of women with breast cancer in Ontario.

TARGET POPULATION

- Women who have been diagnosed with breast cancer who have chosen or been recommended for therapeutic mastectomy.
- Women who are at high risk for breast cancer who have chosen or been recommended for prophylactic mastectomy.

INTENDED USERS

General surgeons practicing breast cancer surgery, plastic surgeons, oncologists, administrators, other referring physicians, and oncology healthcare professionals (e.g., those involved in patient education or psychosocial programs).

RECOMMENDATIONS

Recommendation 1: Patient education and preoperative evaluation
For women who have chosen or been recommended for therapeutic mastectomy: • The discussion of immediate or delayed breast reconstruction should be initiated at the time that mastectomy is offered by the general surgeon. • For women seeking immediate breast reconstruction for ductal carcinoma in situ (DCIS), preoperative evaluation with a general surgeon and a plastic surgeon should be performed. • For women seeking immediate breast reconstruction for early stage breast cancer who will potentially require adjuvant chemotherapy or radiotherapy (RT), a medical oncologist and/or radiation oncologist should be included in preoperative evaluation, either through a formal consultation or by a multidisciplinary cancer conference. • For women seeking immediate reconstruction, there should be adequate preoperative imaging of the breasts, aligning with existing guideline recommendations.

Qualifying Statement
• Please see Cancer Care Ontario guidelines regarding recommendations about the use of mastectomy versus breast-conserving therapy (BCT) in early stage breast cancer (www.cancercare.on.ca).

Recommendation 2: Contraindications for immediate or delayed reconstruction
• Relative medical (non-cancer-related)contraindications for breast reconstruction include: 1. Morbid obesity (body mass index [BMI] ≥40 kg/m^2); 2. Current smoking status. • Advance age is not a contraindication to breast reconstruction. There is no evidence that indicated a specific age cut-off as a contraindication; however, the number of people who received reconstruction after 70 years of age was limited.
Qualifying Statements
• If morbid obesity and smoking status have been resolved, then women may be appropriate candidates for breast reconstruction. • None of the two characteristics listed above are absolute contraindications to reconstruction. • There is insufficient evidence to indicate whether diabetes is a contraindication to reconstruction. • Patients with increased (>BMI 30 kg/m^2) are at higher risk for complications and are encouraged to lose weight if undergoing delayed reconstruction.

Recommendation 3: Timing of immediate breast reconstruction
• Immediate reconstruction is an appropriate option for women who are not expected to require postoperative RT. This includes women with: ○ Prophylactic mastectomy for prevention of breast cancer ○ In situ disease (ductal or lobular) ○ Tumour size to breast volume ratio that may preclude the use of BCT ○ RT not recommended (e.g., previous irradiation of breast or chest [Hodgkin disease], severe collagen vascular disease, or Tp53 mutation) ○ Small invasive cancers with extensive microcalcifications or atypia that would preclude BCT and there is a low likelihood of nodal disease. ○ Positive margins following breast-conserving surgery opting for completion mastectomy ○ Recurrent disease following failed initial BCT and not deemed to be at high risk for metastatic disease

- **Provisional Recommendation October 2021:** In patients expected to require radiotherapy, the timing of breast reconstruction should be determined after multidisciplinary discussion including the general surgeon or surgical oncologist, medical oncologist, radiation oncologist, and plastic surgeon and with full consideration of the values and preferences of the patient. [The 2016 recommendation indicated that the use of immediate breast reconstruction is not recommended for women expected to require postoperative RT]

Qualifying Statement

- **Provisional Qualifying Statement October 2021:** Women who will receive RT and are considering immediate breast reconstruction should be informed of the possibility of increased risk of complications, compromised esthetic outcome, and the potential for increased need for future revisional surgeries. The risk of these may vary depending on type and timing of RT, type of reconstruction, and patient characteristics.

Recommendation 4: Skin-sparing, nipple-sparing, and areola-sparing mastectomy

- Skin-sparing mastectomy (SSM), nipple-sparing mastectomy (NSM) and areola-sparing mastectomy (ASM) are incisions utilized simultaneously with immediate breast reconstruction
- SSM or NSM with immediate breast reconstruction can be offered to women at high risk for breast cancer (>25% lifetime risk) undergoing prophylactic mastectomy and women with known DCIS.
- SSM or NSM with immediate breast reconstruction is a reasonable option for women with early breast cancer who are believed to be likely lymph node negative.
- SSM, NSM, and ASM are **not** recommended for women intending to receive post-operative radiation with:
    - early breast cancer who are lymph node positive, inflammatory breast cancer or locally advanced breast cancer who will require postoperative RT.
    - any clinical skin or nipple-areolar complex (NAC) involvement by invasive tumour
- NSM and ASM are **not** recommended for women with Paget disease of the breast or women with a retroareolar tumour.
- NSM or ASM with immediate reconstruction is reserved for patients with minimal ptosis and do not require skin reducing incisions
- Women with multicentric DCIS or early invasive cancer within 2 cm of the NAC) who are contemplating NSM may consider a sampling taken from the base of the nipple for pathological assessment. Women found to have tumour involvement in the NAC either intraoperatively or postoperatively should have the nipple resected.

Qualifying Statements

- SSM, NSM, and ASM are oncologically safe when the tumour is resected with clear margins.
- Women considering NSM should be made aware that they will experience nipple anesthesia and that there is a risk of nipple necrosis.
- Likelihood of lymph node positivity should be determined by consultation with a breast surgeon with oncology expertise or by a multidisciplinary tumour board discussion. When required, for women with invasive breast cancer and clinically negative nodes, a standalone sentinel lymph node biopsy may evaluate lymph node status prior to definitive mastectomy.

Recommendation 5: Delayed breast reconstruction

- Delayed reconstruction should be offered as an option for any woman undergoing mastectomy who desires reconstruction, has completed any recommended adjuvant chemotherapy and/or RT, and does not have contraindications to breast reconstruction.

Qualifying Statements

- For women who have received RT, it is the opinion of the Expert Panel that reconstruction should not occur sooner than one year after mastectomy.
- For women with advanced disease (T4, or N2 or N3), it is the opinion of the Expert Panel that it may be optimal to wait two or three years before undergoing reconstruction when the risk of recurrence is lowered.

Recommendation 6: Autologous tissue versus implant-based reconstruction

- Women treated by mastectomy should be made aware that autologous tissue reconstruction and implant-based reconstruction are options for immediate or delayed reconstruction.
- Reconstruction methods should be selected based on patient and surgeon factors, because overall patient satisfaction and willingness to recommend reconstruction to others appear to be similar between autologous tissue and tissue-expander implant (TE/I)-based reconstructions. However, if women are candidates for either reconstruction, then they should be informed that TE/I reconstruction may be accompanied by a higher risk of reconstructive failure or soft tissue infection and that there is a trend toward decreased esthetic satisfaction with TE/I reconstruction over time. In patients who have received textured implants, they should be informed of the risk for a rare type of lymphoma called anaplastic large cell lymphoma (ALCL) that is associated with textured implants.

- Latissimus dorsi flap with or without implants is another option to TE/I or abdominal autologous tissue reconstruction.

  Radiation setting:

- For women who have received prior RT to their breast as part of BCT, mastectomy with immediate autologous tissue reconstruction is the recommended option. Current evidence suggests that reconstruction using TE/I alone may be associated with an increased risk of complications.

Qualifying Statement

- Women desiring reconstruction in a previously radiated breast should be informed of the increased risk of complications compared with no radiation.

Recommendation 7: Types of autologous tissue reconstruction

- In patients who will undergo unilateral autologous tissue reconstruction, pedicled transverse rectus abdominis myocutaneous (TRAM), free TRAM, or deep inferior epigastric perforator (DIEP) flaps are all recommended options that are supported by positive patient-reported outcomes.
- In patients who will undergo bilateral autologous tissue reconstruction, DIEP flap is preferred over free or pedicled TRAM flap due to less functional disruption to the abdominal wall following surgery.
- Alternative autologous tissue donor types (e.g., gluteal flaps, thigh flaps) are suitable for selected patients in whom abdominal tissue is not available; however, the evidence on these types of reconstructions is very limited.
- All patients should be told of the risk of fat necrosis that can present as a nodule or mass after autologous tissue reconstruction, a benign condition that can mimic breast cancer recurrence. The risk of fat necrosis is likely to be greater following DIEP flaps compared with TRAM flaps.

Recommendation 8: Acellular dermal matrix

- Original 2016 recommendation: With the shortage of high-quality evidence on the use of acellular dermal matrix (ADM), no recommendation can be made for or against the use of ADM as an adjunct to implant-based breast reconstruction.
- **October 2021 note**: Evidence as to benefit of ADM has been accruing since the 2016 guideline, and ADM is now widely used in breast reconstruction. Several studies have suggested that ADM from different sources or preparation techniques may vary in utility and complications. The U.S. FDA[2] has issued a safety communication indicating that the complication rate (reoperation, explantation, and infections) may vary depending on the type of ADM, and this is being investigated.

Qualifying Statements

[2] **United States Food and Drug Administration. Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates: FDA Safety Communication. Silver Spring (MD): US FDA; 2021 Mar 31 (cited 2021 Oct 8). Available from: https://www.fda.gov/medical-devices/safety-communications/acellular-dermal-matrix-adm-products-used-implant-based-breast-reconstruction-differ-complication.**

- It is the opinion of the Expert Panel that direct-to-implant reconstruction in a *single stage* using ADM may be used as an adjunct to implant-based breast reconstruction to improve esthetic outcomes in selected women who have smaller and non-ptotic breasts.
- Patient selection and surgical technique are critical to good outcomes.
- Other than improved esthetic outcomes, ADM has not been shown to have any other benefit for *two-staged* TE/I reconstruction.
- Esthetic outcomes, especially the inframammary fold, are potentially improved with the use of ADM in implant reconstruction.

Recommendation 9: Autologous fat grafting

- With the shortage of high-quality studies on the use fat grafting, no recommendation can be made for or against the use of autologous fat grafting as an adjunct to improve esthetic outcomes in breast reconstruction.

Qualifying Statement

- Autologous fat grafting is a potential adjunct to improve esthetic outcomes in breast reconstruction following mastectomy; however, more high-quality evidence on the efficacy and safety of this procedure is necessary before its widespread implementation.

Recommendation 10: Routine screening for breast cancer recurrence following postmastectomy breast reconstruction

- There is insufficient evidence to support the use of postmastectomy surveillance mammography in the reconstructed breast.
- Women should be followed with clinical examination of the chest wall and reconstructed breast as per the regular breast cancer follow-up regimen.
- Diagnostic mammography, ultrasound, and magnetic resonance imaging may be helpful in the evaluation of symptomatic women with a reconstructed breast (e.g., lumps, skin changes).

Breast cancer reconstruction surgery (immediate and delayed) across Ontario: Patient indications and appropriate surgical options:

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

- To provide clinical guidance with respect to suitability for breast reconstruction, timing of reconstruction, and optimal reconstruction techniques.
- To make recommendations that will inform decisions at the policy and administration level aimed at improving the quality of life of women with breast cancer in Ontario.

TARGET POPULATION

- Women who have been diagnosed with breast cancer who have chosen or been recommended for therapeutic mastectomy.
- Women who are at high risk for breast cancer who have chosen or been recommended for prophylactic mastectomy.

INTENDED USERS

General surgeons practicing breast cancer surgery, plastic surgeons, oncologists, administrators, other referring physicians, and oncology healthcare professionals (e.g., those involved in patient education or psychosocial programs).

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1: Patient education and preoperative evaluation
For women who have chosen or been recommended for therapeutic mastectomy: • The discussion of immediate or delayed breast reconstruction should be initiated at the time that mastectomy is offered by the general surgeon. • For women seeking immediate breast reconstruction for ductal carcinoma in situ (DCIS), preoperative evaluation with a general surgeon and a plastic surgeon should be performed. • For women seeking immediate breast reconstruction for early stage breast cancer who will potentially require adjuvant chemotherapy or radiotherapy (RT), a medical oncologist and/or radiation oncologist should be included in preoperative evaluation, either through a formal consultation or by a multidisciplinary cancer conference. • For women seeking immediate reconstruction, there should be adequate preoperative imaging of the breasts, aligning with existing guideline recommendations. Imaging results should be available at the time of surgical consult.
Qualifying Statement
• Please see Cancer Care Ontario guidelines regarding recommendations about the use of mastectomy versus breast-conserving therapy (BCT) in early stage breast cancer (www.cancercare.on.ca).
Key Evidence
• Although evidence to support these recommendations was not specifically reviewed for this guideline, the recommendations are in agreement with those from other

groups (Alberta Health Services [AHS]; Massachusetts; American Society of Plastic Surgeons [ASPS]; Association of Breast Surgery [ABS]/British Association of Plastic, Reconstructive and Aesthetic Surgeons [BAPRAS]; National Comprehensive Cancer Network [NCCN]; National Institute for Health and Care Excellence [NICE]; New Zealand Guidelines Group [NZGG]).

Interpretation of Evidence

The primary outcomes considered in the development of these recommendations are quality of life and equitable access to care. The recommendations are based on the expert opinion of the Expert Panel that women should be well informed about care options and that multidisciplinary preoperative evaluation is a quality indicator of multidisciplinary breast cancer care for women with DCIS or early stage disease seeking immediate reconstruction.

Recommendation 2: Contraindications for immediate or delayed reconstruction

- Relative medical (non-cancer related) contraindications for breast reconstruction include:
    1. Morbid obesity (body mass index [BMI] ≥40 kg/m^2);
    2. Current smoking status.
- Advanced age is not a contraindication for breast reconstruction. There is no evidence that indicated a specific age cut-off as a contraindication; however, the number of people who received reconstruction after 70 years of age was limited.

Qualifying Statements

- If morbid obesity and smoking status have been resolved, then women may be appropriate candidates for breast reconstruction. Patients with increased BMI (>30kg/m^2) are at higher risk for complications and are encouraged to lose weight if undergoing delayed reconstruction.
- None of the two characteristics listed above are absolute contraindications to reconstruction.
- There is insufficient evidence to indicate whether diabetes is a contraindication to reconstruction.

Key Evidence

- A study of 15,937 women by the National Surgical Quality Improvement Program (NSQIP) demonstrated that morbidly obese (BMI ≥40 kg/m^2) women had significantly increased major surgical complications, medical complications, wound healing problems, and return to the operating room compared with nonobese and mildly obese (BMI 30 to 39.0 kg/m^2) women (1, 2).
- A prospective single-centre study of 558 women undergoing microsurgical abdominal flap reconstruction by Seidenstuecker et al. reported higher rates of flap and donor site complications in smokers compared with nonsmokers (3). Similar results were reported in an analysis of the NSQIP database by Fischer et al. Evidence regarding the safety of implant-based reconstruction in active smokers is very limited.
- A systematic review by Walton et al. reviewed six observational studies and concluded that breast reconstruction was safe and feasible and provided significant improvements in quality of life for older women (4).

Interpretation of Evidence
The primary factors driving these recommendations are patient safety and informed decision making. The overall certainty of the evidence for morbid obesity, active smoking status, and older age (>50 years) is low to moderate. The decision to undergo breast reconstruction must take into account the balance between the psychosocial benefits of reconstruction and the harmful physical effects from complications. Due to the high risk of complication from breast reconstruction in women with morbid obesity and women who are active smokers, the harms are likely to outweigh the potential quality-of-life benefits of reconstruction in these women. The Expert Panel believes that the potential benefits of breast reconstruction may be greater than the potential harms for older women who desire reconstruction and do not have other contraindications.

Recommendation 3: Timing of immediate breast reconstruction

• When immediate reconstruction is an appropriate option for women who are not expected to require postoperative RT. This includes women with:
  o Prophylactic mastectomy for prevention of breast cancer
  o In situ disease (ductal or lobular)
  o Tumour size to breast volume ratio that may preclude the use of BCT
  o RT not recommended (e.g., previously irradiation breast or chest [Hodgkin disease], severe collagen vascular disease, or TP53 mutation)
  o Small invasive cancers with extensive microcalcifications or atypia that would preclude BCT and there is a low likelihood of nodal disease.
  o Positive margins following breast-conserving surgery opting for completion mastectomy
  o Recurrent disease following failed initial BCT and not deemed at high risk for metastatic disease
• **Provisional Recommendation October 2021:** In patients expected to require radiotherapy, the timing of breast reconstruction should be determined after multidisciplinary discussion including the general surgeon or surgical oncologist, medical oncologist, radiation oncologist, and plastic surgeon and with full consideration of the values and preferences of the patient. [The 2016 recommendation indicated that the use of immediate breast reconstruction is not recommended for women expected to require postoperative RT]

Qualifying Statement
• **Provisional Qualifying Statement October 2021:** Women who will receive RT and are considering immediate breast reconstruction should be informed of the possibility of increased risk of complications, compromised esthetic outcome, and the potential for increased need for future revisional surgeries. The risk of these may vary depending on type and timing of RT, type of reconstruction, and patient characteristics.
Key Evidence
• A small randomized controlled trial (RCT) (5) and a cross-sectional survey study (6) reported that women who underwent immediate reconstruction had less body stigma,

body concerns, and psychological disturbance than women with delayed reconstruction.

- A prospective cohort study (7) and a meta-analysis of observational data (8) reported no significant difference in risk of local recurrence with immediate reconstruction compared with mastectomy alone.
- A 2013 systematic review of observational studies by Schaverien et al. reported a lower reoperation rate with delayed autologous tissue reconstruction compared with immediate autologous tissue reconstruction in the setting of RT (1.4% versus 15.1%; p=0.001) but no significant difference in overall complications or fat necrosis. A comparison of immediate reconstruction with versus without RT demonstrated no significant difference in overall complications or reoperations but significantly increased fat necrosis with the use of RT (23.8% versus 8.5%; p=0.006) (9).
- Two systematic reviews of observational studies assessed the effects of RT on immediate implant-based reconstruction. Lam et al. reported a higher rate of reconstruction failure with RT (18.6% versus 3.1%; p<0.00001) (10) and Barry et al. reported that women with RT had fourfold greater odds of suffering morbidity compared with women not requiring RT (11).

Interpretation of Evidence

The primary outcomes used to inform these recommendations include quality of life, adverse effects, patient satisfaction, and esthetic outcome. It is likely that the relative value of these outcomes will vary among women.

Benefits of immediate reconstruction compared with delayed reconstruction include increased immediate quality of life, improved esthetic outcome, and the convenience of undergoing mastectomy and breast reconstruction in a single procedure. These benefits must be weighed against the potential harms of delayed adjuvant chemotherapy and possible increased complications. Based on expert opinion and the evidence from observational studies reviewed, the Expert Panel believes that the potential benefits outweigh the potential harms for the subgroups of women listed above in Recommendation 3.

For women receiving postoperative RT, the Expert Panel believes that the potential harms of immediate breast reconstruction (complications, poor esthetic outcome of radiating a reconstructed breast mound, delay of adjuvant therapy, and the potential need for future revisional surgeries) outweigh the potential benefits of increased immediate quality of life, and convenience.

Recommendation 4: Skin-sparing, nipple-sparing, and areola-sparing mastectomy

- Skin-sparing mastectomy (SSM), nipple-sparing mastectomy (NSM) and aerola-sparing mastectomy (ASM) are incisions utilized simultaneously with immediate breast reconstruction.
- SSM or NSM with immediate breast reconstruction can be offered to women at high risk for breast cancer (>25% lifetime risk) undergoing prophylactic mastectomy and women with known DCIS.
- SSM or NSM with immediate breast reconstruction is a reasonable option for women with early breast cancer who are believed to be likely lymph node negative.
- SSM, NSM, and ASM are **not** recommended for women intending to receive post-operative radiation with:

- early breast cancer who are lymph node positive, inflammatory breast cancer or locally advanced breast cancer who will require postoperative RT
- any clinical skin or nipple-areolar complex (NAC) involvement by invasive tumour.

- NSM and ASM are **not** recommended for women with Paget disease of the breast or women with a retroareolar tumour.
- NSM and ASM with immediate reconstruction is reserved for patients with minimal ptosis and do not require skin reducing incisions.
- Women with multicentric DCIS or early invasive cancer within 2 cm of the NAC who are contemplating NSM may consider a sampling taken from the base of the nipple for pathological assessment. Women found to have tumour involvement in the NAC either intraoperatively or postoperatively should have the nipple resected.

Qualifying Statements

- SSM, NSM, and ASM are oncologically safe when the tumour is resected with clear margins.
- Women considering NSM should be made aware that they will experience nipple anesthesia and that there is a risk of nipple necrosis.
- Likelihood of lymph node positivity should be determined by consultation with a breast surgeon with oncology expertise or by a multidisciplinary tumour board discussion. When required, for women with invasive breast cancer and clinically negative nodes, a standalone sentinel lymph node biopsy may evaluate lymph node status prior to definitive mastectomy for women.

Key Evidence

- A systematic review and meta-analysis by Lanitis et al. of nine retrospective observational studies reported no significant difference between SSM with immediate reconstruction and non-SSM without reconstruction in local recurrence or postoperative severe complications (12).
- A systematic review by Mallon et al. of 29 observational studies reported an occult nipple involvement rate of 11.5%. Factors associated with increased incidence of nipple involvement were: tumour-to-nipple distance <2 cm, tumour grade, lymph node metastases, estrogen receptor/progesterone receptor-negative, tumour size >5 cm, retroareolar or central location, and multicentric location (13).
- Endara et al. reported a pooled locoregional recurrence rate following NSM of 1.8% across 28 observational studies, although follow-up ranged from 0.2 to 210 months. The pooled nipple necrosis rate across 39 studies was 7.7% (14).

Interpretation of Evidence

The certainty of the evidence for SSM and NSM is low to moderate. The primary outcomes considered in the development of these recommendations are recurrence, adverse effects, and patient satisfaction. There is likely significant variability in the relative value that women would place on each of these outcomes and this variability is expected to lead to different decisions regarding SSM and NSM.

In women who are at low risk for breast cancer recurrence (e.g., prophylactic mastectomy, DCIS, early stage lymph node-negative breast cancer), the potential benefits of SSM or NSM are expected to outweigh the potential harms.

Women who are likely to be lymph node negative (prophylactic, DCIS, or early breast cancer) benefit from immediate breast reconstruction at the time of mastectomy by potentially reducing the need for additional surgery and optimizing cosmesis with a skin-sparing procedure. The potential risk in early breast cancer patients is an unexpected clinical need for adjuvant chest wall RT that may compromise the cosmesis and/or viability of the reconstruction.

Recommendation 5: Delayed breast reconstruction

- Delayed reconstruction should be offered as an option for any woman undergoing mastectomy who desires reconstruction, has completed any recommended adjuvant chemotherapy and/or RT, and does not have contraindications to breast reconstruction.

Qualifying Statements

- For women who have received RT, it is the opinion of the Expert Panel that reconstruction should not occur sooner than one year after mastectomy.
- For women with advanced disease (T4, or N2 or N3), it is the opinion of the Expert Panel that it may be optimal to wait two or three years before undergoing reconstruction when the risk of recurrence is lowered.

Key Evidence

- A 2013 systematic review of observational studies by Schaverien et al. reported a lower reoperation rate with delayed reconstruction compared with immediate reconstruction in the setting of RT (1.4% versus 15.1%; p=0.001) but no significant difference in overall complications or fat necrosis (9).
- Although additional evidence to support this recommendation was not specifically reviewed for this guideline, the recommendations are in agreement with those from other groups (AHS, NCCN, NZGG).

Interpretation of Evidence

The primary outcomes used to inform these recommendations include quality of life, adverse effects (such as delay to adjuvant therapy), patient satisfaction, and esthetic outcome. It is likely that the relative value of these outcomes will vary among women. The overall certainty of the evidence on the safety and efficacy of delayed breast reconstruction is moderate. This recommendation is generalizable to all women who desire breast reconstruction and do not have the contraindications listed in Recommendation 2.

Compared with the alternative of mastectomy alone without reconstruction, the potential benefits of increased quality of life, patient satisfaction, and esthetic outcome are expected to outweigh the potentials harms of complications. The benefits for delayed reconstruction compared with immediate reconstruction include reduced risk of delaying adjuvant therapy and reduced risk of complications. These potential benefits must be weighed against the undesirable effects of delaying reconstruction including not restoring quality of life at the time of mastectomy, reduced final esthetic outcome in most cases, and the inconvenience of undergoing an additional major surgical procedure, when compared with immediate reconstruction.

Recommendation 6: Autologous tissue versus implant-based reconstruction

- Women treated by mastectomy should be made aware that autologous tissue reconstruction and implant-based reconstruction are options for immediate or delayed reconstruction.
- Reconstruction methods should be selected based on patient and surgeon factors, because overall patient satisfaction and willingness to recommend reconstruction to others appear to be similar between autologous tissue and tissue-expander implant (TE/I)-based reconstructions. However, if women are candidates for either reconstruction, then they should be informed that TE/I reconstruction may be accompanied by a higher risk of reconstructive failure or soft tissue infection and that there is a trend toward decreased esthetic satisfaction with TE/I reconstruction over time. In patients who have received textured implants, they should be informed of the risk for a rare type of lymphoma called anaplastic large cell lymphoma (ALCL) that is associated with textured implants.
- Latissimus dorsi (LD) flap with or without implants is another option to TE/I or autologous abdominal tissue (AAT) reconstruction.

Radiation setting:

- For women who have received prior RT to their breast as part of BCT, mastectomy with immediate autologous tissue reconstruction is the recommended option. Current evidence suggests that reconstruction using TE/I alone may be associated with an increased risk of complications.

Qualifying Statement

- Women desiring reconstruction in a previously radiated breast should be informed of the increased risk of complications compared with no radiation.

Key Evidence

- A systematic review by Tsoi et al. compared complications between TE/I and AAT reconstruction (15). This review included 14 studies of low to moderate quality with very small sample sizes. Findings from this review demonstrated a greater risk of reconstructive failure associated with TE/I than AAT reconstruction. Soft tissue infections were significantly higher in TE/I; however, infections requiring re-operation were not significantly different between TE/I and AAT reconstruction. Skin or flap necrosis was significantly higher in the AAT reconstruction group. No significant difference was observed in other complications such as wound dehiscence, deep vein thrombosis/pulmonary embolism, major complications, and reoperation.
- A second systematic review publication by Tsoi et al. compared patient-reported outcomes between TE/I reconstruction and AAT reconstruction (16). This review included 15 studies, the majority of which were low quality. Levels of pain did not differ between types of reconstruction. General satisfaction with method of reconstruction evolved over time but essentially converged, with no significant difference between the two approaches. Esthetic satisfaction remained constant in patients undergoing AAT reconstruction but declined over time following TE/I reconstruction. Overall patient satisfaction and willingness to recommend the surgery to others were similar between reconstruction types.
- The largest retrospective national database study comparing LD flaps (1079) with free flaps (609) and pedicled transverse rectus abdominis myocutaneous (TRAM) flaps (1608) found that overall 30-day complications, flap failure and non-flap

complications were all significantly lower in the LD group compared with the other two techniques (17).

Radiation setting:

- Systematic reviews that compared the reconstructive options in patients who required postmastectomy radiation reported that complications were significantly higher in the implant-based reconstruction group compared with the autologous tissue reconstruction group (15). In addition, a prospective single-centre study that examined 92 patients who underwent immediate reconstruction using autologous tissue (23 patients) compared with TE/I (69 patients) found that major complications, compromised functional status, and poor esthetic outcomes were significantly associated with the use of TE/I (18).

Interpretation of Evidence

- Key outcomes used to inform the recommendations on autologous tissue versus implant-based reconstruction are adverse effects, patient satisfaction, and cosmesis of the final reconstructed result. Certainty of evidence for these outcomes is low, and the systematic reviews are made up of individual studies that are low in quality, small in patient number, and there is a tendency for repeated reporting of studies in the reviews. There is likely significant variability in the relative value that women would place on each of the key outcomes and this variability is expected to lead to different decisions regarding autologous tissue or implant-based reconstruction.
- Although some studies reported that TE/I reconstruction may be accompanied by a higher risk of reconstructive failure or soft tissue infection and that there is a trend toward decreased esthetic satisfaction over time, the Expert Panel believes that this evidence is insufficient at this time to support one option being superior over the other in the absence of radiation.

Recommendation 7: Types of autologous tissue reconstruction

- In patients who will undergo unilateral autologous tissue reconstruction, pedicled TRAM, free TRAM, or deep inferior epigastric perforator (DIEP) flaps are all recommended options that are supported by positive patient-reported outcomes.
- In patients who will undergo bilateral autologous tissue reconstruction, DIEP flap is preferred over free or pedicled TRAM flap due to less functional disruption to the abdominal wall following surgery.
- Alternative autologous tissue donor types (e.g., gluteal flaps, thigh flaps) are suitable for selected patients in whom abdominal tissue is not available; however, the evidence on these types of reconstructions is very limited.
- All patients should be told of the risk of fat necrosis that can present as a nodule or mass after autologous tissue reconstruction, a benign condition that can mimic breast cancer recurrence. The risk of fat necrosis is likely to be greater following DIEP flaps compared with TRAM flaps.

Key Evidence

- One meta-analysis by Man et al. found approximately one-half the risk of abdominal bulge or hernia development following DIEP flaps compared with TRAM flaps (relative risk [RR], 0.49; 95% confidence interval [CI], 0.28 to 0.86) (19). Another meta-analysis

showed a trend toward increased risk of abdominal bulge after TRAM flaps compared with DIEP flaps (RR, 0.80; 95% CI, 0.48 to 1.35; p=0.40) (20).

- Objective measures of abdominal wall function using isometric dynamometry show that bilateral pedicled TRAM flaps suffer the most deficit (up to 40% deficit in trunk flexion and 9% deficit in trunk extension) and a significant decrease in ability to perform sit-up compared with DIEPs. Functional deficits assessed by physiotherapy measures also revealed the greatest deficit in both rectus and oblique muscles after bilateral pedicled TRAM flaps, followed by free TRAM, whereas DIEP flaps returned to their preoperative rectus and oblique muscle functions (21).
- The risk of fat necrosis has been found to be significantly greatest following DIEP flaps (14.4%, p<0.001), followed by pedicled TRAM flaps (12.3%, p=0.04), and free TRAM flaps (6.9%, P<0.001) in a systematic review of 33 articles that analyzed more than 7233 flaps in 6394 patients (22).

Interpretation of Evidence

Key outcomes used to inform the recommendations on the different types of autologous tissue reconstruction are adverse effects, quality of life, and patient satisfaction. The certainty of the evidence for these outcomes is moderate. In terms of adverse effects, the trade-off between the development of compromised abdominal wall function and fat necrosis in the reconstructed breast needs to be presented to the patient in a balanced fashion, and the final choice between DIEP, free or pedicled TRAM flaps will be up to the individual patient. There is moderate evidence that the DIEP flap may be a superior option to pedicled TRAM flaps in the growing subgroup of patients wishing to undergo bilateral autologous reconstruction to better preserve their abdominal muscle function following surgery.

Recommendation 8: Acellular dermal matrix

- Original 2016 recommendation: With the shortage of high-quality evidence on the use of acellular dermal matrix (ADM), no recommendation can be made for or against the use of ADM as an adjunct to implant-based breast reconstruction.
- **October 2021 note**: Evidence as to benefit of ADM has been accruing since the 2016 guideline, and ADM is now widely used in breast reconstruction. Several studies have suggested that ADM from different sources or preparation techniques may vary in utility and complications. The U.S. FDA[3] has issued a safety communication indicating that the complication rate (reoperation, explantation, and infections) may vary depending on the type of ADM, and this is being investigated.

Qualifying Statements

- It is the opinion of the Expert Panel that direct-to-implant reconstruction in a *single stage* using ADM may be used as an adjunct to implant-based breast reconstruction to improve esthetic outcomes in selected women who have smaller and non-ptotic breasts.

[3] United States Food and Drug Administration. Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates: FDA Safety Communication. Silver Spring (MD): US FDA; 2021 Mar 31 (cited 2021 Oct 8). Available from: https://www.fda.gov/medical-devices/safety-communications/acellular-dermal-matrix-adm-products-used-implant-based-breast-reconstruction-differ-complication.

- Patient selection and surgical technique are critical to good outcomes.
- Other than improved esthetic outcomes, ADM has not been shown to have any other benefit for *two-staged* TE/I reconstruction.
- Esthetic outcomes, especially the inframammary fold, are potentially improved with the use of ADM in implant reconstruction.

Key Evidence

- A subgroup analysis in a systematic review by Clemens et al. suggested that there is a higher incidence of complications in women who received ADM in the setting of RT compared with women who did not receive RT (23).
- Two meta-analyses of implant-based reconstruction using ADM suggest that there are increased complications associated with the use of ADM (24, 25).
- A RCT of 69 women comparing reconstruction with ADM versus submuscular placement of implants without ADM reported no significant difference in total complications, pain visual analogue scale, physical well-being, immediate 24-hour postoperative narcotic use, or intraoperative fill volume (26). Outcomes not yet reported include esthetic outcomes, rate of capsular contracture, patient satisfaction, and quality of life.
- Two retrospective studies published since 2010 reported esthetic outcomes. One reported higher esthetic outcome overall and higher inframammary fold esthetic scores in the ADM group (27) and the other reported significantly higher esthetic scores in the ADM group for volume, placement, and inframammary fold but no significant difference for contour or scarring.

Interpretation of Evidence

Key outcomes used to inform this recommendation are cosmesis and adverse effects. The Expert Panel believes that the relative value placed on these outcomes is expected to vary significantly among women. The certainty of the evidence for these outcomes is low. There is currently insufficient evidence to determine whether the potential improvements in cosmesis, quality of life, and patient satisfaction and decrease in number of surgeries outweigh the higher risk of complications and cost. Generalizability of the evidence is highly variable based on patient and treatment factors.

Recommendation 9: Autologous fat grafting

- With the shortage of high-evidence studies on the use fat grafting, no recommendation can be made for or against the use of autologous fat grafting as an adjunct to improve esthetic outcomes in breast reconstruction.

Qualifying Statements

- Autologous fat grafting is a potential adjunct to improve esthetic outcomes in breast reconstruction following mastectomy; however, more high-quality evidence on the efficacy and safety of this procedure is necessary before its widespread implementation.

Key Evidence

- Two systematic reviews addressing the safety and oncological outcomes of autologous fat grafting suggested that fat grafting appeared to be safe but concluded that the

evidence was inconsistent and further studies were required to determine that it is an effective and safe practice (28, 29).

- A low-quality, retrospective, matched cohort study of local recurrence in women with intraepithelial neoplasia by Petit et al. reported a higher rate of five-year local recurrence in women with fat grafting versus women without fat grafting in an exploratory subgroup analysis, although this difference was not statistically significant (18.4% versus 3.6%; p=0.11) (30).

Interpretation of Evidence

Key outcomes used to inform this recommendation are oncologic safety, adverse effects, and cosmesis. The Expert Panel believes that the relative value placed on these outcomes is expected to vary significantly among women. The certainty of the evidence for these outcomes is low. There is currently insufficient evidence to determine whether the potential improvements in cosmesis, quality of life, and patient satisfaction outweigh the potential risk of recurrence and complications. Generalizability of the evidence is highly variable based on patient, tumour, and treatment factors.

Recommendation 10: Routine screening for breast cancer recurrence following postmastectomy breast reconstruction

- There is insufficient evidence to support the use of postmastectomy surveillance mammography in the reconstructed breast.
- Women should be followed with clinical examination of the chest wall and reconstructed breast as per the regular breast cancer follow-up regimen.
- Diagnostic mammography, ultrasound and magnetic resonance imaging may be helpful in the evaluation of symptomatic women with a reconstructed breast (e.g., lumps, skin changes).

Key Evidence

- A 2007 systematic review by Barnsley et al. identified eight small case series and/or case reports investigating the use of surveillance mammography following breast reconstruction (31). Local recurrences were detected by surveillance mammography in only two studies.
- Three additional primary studies reported very low rates of detection of recurrence using surveillance mammography, with the majority of recurrences being detected by clinical examination. One retrospective study reported a recall rate of 4% due to suspicious or indeterminate findings (32).

Interpretation of Evidence

Certainty of the evidence for routine screening for breast cancer recurrence is very low. Critical outcomes informing the recommendations include recurrence, survival, and quality of life (e.g., anxiety and patient concern). The Expert Panel believes that the relative value placed on these outcomes is not expected to vary significantly among women.

The benefits of routine screening are anticipated to be small. It should be noted that there are few data on the effect of routine screening in subgroups by tumour characteristics or type of reconstruction.

IMPLEMENTATION CONSIDERATIONS

Issues related to the implementation of recommendations with respect to feasibility, patient considerations, equity, provider considerations, and system considerations were also considered by the Working Group and Breast Reconstruction Expert Panel. A formal Implementation Considerations statement was prepared by the Working Group and Breast Reconstruction Expert Panel and sent to the leadership of Cancer Care Ontario's Surgical Oncology Program.

RELATED GUIDELINES

Members of the Breast Cancer Disease Site Group. Breast irradiation in women with early stage invasive breast cancer following breast conserving surgery. Dayes I, Rumble RB, reviewers. Toronto (ON): Cancer Care Ontario; 2011 Sep 15 [In Review February 2015]. Program in Evidence-based Care Evidence-Based Series No.: 1-2 Version 2 IN REVIEW 2015.

Shelley W, McCready D, Holloway C, Trudeau M, Sinclair S; Breast Cancer Disease Site Group. Management of ductal carcinoma in situ of the breast. Toronto (ON): Cancer Care Ontario; 2006 Sep 19 [In review 2014 Jan]. Program in Evidence-based Care Evidence-Based Series No.: 1-10 Version 2.2006 IN REVIEW.

Breast cancer reconstruction surgery (immediate and delayed) across Ontario: Patient indications and appropriate surgical options

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (33). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC

JUSTIFICATION FOR GUIDELINE

Guidelines on the appropriate use of postmastectomy breast reconstruction and the role of immediate reconstruction for breast cancer patients are needed for physicians and patients in Ontario to minimize the current disparities in care and provide equitable access to this surgery aimed at improving quality of life.

GUIDELINE DEVELOPERS

Development of the guideline was undertaken by the Breast Reconstruction Guideline Development Group and CCO's PEBC at the request of the Surgical Oncology Program. The group is divided into the Breast Reconstruction Working Group and the Breast Reconstruction Expert Panel and comprises general surgeons, plastic surgeons, radiation oncologists, and a health research methodologist (see Appendix I for membership).

The project was led by a small working committee of the Breast Reconstruction Guideline Development Group (The Breast Reconstruction Working Group) whose members were responsible for creating the evidence base, drafting the first version of the recommendations, and leading the response to the external review. Other members of the Breast Reconstruction Guideline Development Group served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle (33, 34). This process includes a systematic review, interpretation of the evidence by the Working Group and draft

recommendations, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework (35) as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence-base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine if an existing guideline could be adapted or endorsed. To this end, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE) and Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse.
- Guideline developer websites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), and American Society of Clinical Oncology (ASCO).

In addition, the Breast Reconstruction Working Group was aware of a clinical practice guideline being developed by Alberta Health Services (AHS). The AHS guideline was completed and reviewed by the Working Group in September 2013. The following criteria were used to select potentially relevant guidelines: guidelines published in 2000 or later, English language, based on a systematic review of evidence, and addressed one or more of the clinical questions listed in Section 4, Evidence Review. Guidelines that were considered relevant to the objectives and the clinical questions were evaluated for quality using the AGREE II instrument (36).

For this guideline, a search for existing guidelines for adaptation or endorsement did not yield an appropriate source document. A summary of this process can be found in Appendix II. A search of the primary literature was required (see Section 4, Evidence Review).

Using this evidence, recommendations were drafted by the Working Group and approved by the Breast Reconstruction Expert Panel. The Working Group was responsible for the development of the first draft of the Guideline. Once this draft was completed the Breast Reconstruction Expert Panel was convened by CCO's Surgical Oncology Program with the purpose of reviewing and providing feedback on the first draft. The Working Group then amended the initial draft in response to the Expert Panels feedback which culminated into the final draft of the Guideline. The final draft of the Guideline was circulated for internal review to an independent committee of the PEBC and for external review to experts in the field (see Section 5, Internal and External Review). Refinements were made to the document in response to the feedback received and final recommendations approved by the guideline group. To achieve approval of the draft document and final document, a consensus by 75% of the members of the Breast Reconstruction Expert Panel was required, with dissenting opinions noted, where appropriate.

Focus

The primary focus of this guideline is on the clinical evidence. Other features related to the implementation of recommendations such as costs, human resources, unique requirements for special or disadvantaged populations, development and measurement of quality indicators are addressed by other divisions at CCO. The perspectives of the Breast Reconstruction Expert Panel on these issues are described in Section 2.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

ACKNOWLEDGEMENTS

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- Elizabeth Chan for conducting a data audit.
- Sara Miller for copyediting.

A complete list of the members of the Breast Reconstruction Expert Panel and the Working Group, with their affiliations and conflict of interest information, is provided in Appendix I.

Breast cancer reconstruction surgery (immediate and delayed) across Ontario: Patient indications and appropriate surgical options

Section 4: Systematic Review

INTRODUCTION

In 2014, approximately 24,400 Canadian women were diagnosed with breast cancer, and breast cancer continues to be the most commonly diagnosed cancer in Canadian women over the age of 20 (37). Since 39% of Canadians diagnosed with breast cancer undergo mastectomy, and the five-year survival rate for breast cancer is approximately 88%, the long-term deleterious side effects from the treatment of breast cancer are becoming both important and prevalent survivorship issues to consider. While some women with mastectomy have an excellent quality of life (QOL), for other women there are adverse psychosocial consequences including anxiety, depression, and negative effects on body image and sexual function (38-42).

Postmastectomy breast reconstruction (PMBR) has been shown to provide long-term QOL and psychosocial benefits to repair the physical and psychological damage from cancer surgery in many mastectomy patients (43-46). However, PMBR delivery in Canada is currently inequitable and, in some areas, inaccessible; provincial rates of mastectomy with immediate PMBR (at same time as mastectomy) ranged from 7.6% in Ontario between 2004 to 2010 (47) to less than 2% in Nova Scotia for breast cancer patients (48), both markedly lower than the 29% reported by the Surveillance, Epidemiology, and End Results (SEER) database for the same time frame in the United States (49). Additionally, mastectomy patients are often not provided with the full complement of PMBR options, and evidence to guide optimal PMBR practice is often poor (50-53).

The timing and method of PMBR are important considerations when choosing the optimal management strategy for breast cancer patients. There are currently two major surgical approaches to breast reconstruction: implant-based reconstruction and autologous tissue reconstruction. Timing can be immediate (at the same time as mastectomy) or delayed. Further to this, patient selection criteria and the impact of breast reconstruction to adjuvant therapy must be considered. In the past, the use of immediate breast reconstruction (IBR), as compared with delayed breast reconstruction (DBR), was an unpopular concept due to concerns that it may compromise surgical resection or decrease the detection of local recurrence (54, 55). Multiple procedures were required with prolonged hospital stays, and the final esthetic results were inconsistent (56). Today, as the techniques of breast reconstruction have evolved, these concerns are no longer barriers to the use of IBR (5, 45, 57-59). Advancements in autologous tissue techniques, refinements in implant technologies, the development of acellular dermal matrix (ADM), and IBR performed in concert with skin-sparing mastectomy (SSM) or nipple-sparing mastectomy (NSM) have resulted in favourable esthetic outcomes with minimal disruption to the patient's lifestyle (60). In Ontario, the rate of IBR in 2012 was 16% of all mastectomies, a twofold increase from 2002, but still differing significantly from data from the United States whose current rates are reported to be approximately 40% (47, 61). Therefore, guidelines on the appropriate use of PMBR for breast cancer patients are needed for physicians and patients in Ontario to minimize the current disparities in care and provide equitable access to this surgery aimed at improving QOL.

The mandate of the Institute for Health Care Improvement is to "usher in a new era of partnerships between clinicians and individuals where the values, needs, and preferences of the individual are honoured; the best evidence is applied; and the shared goal is optimal functional health and QOL" (62). This process of shared decision making is the optimal model of care for patients considering breast reconstruction – surgery with many different treatment options each with its own advantages and disadvantages. It recognizes the expertise of both participants: the health care professionals as the expert in providing treatment options, benefits, harms, probabilities, and scientific uncertainties; and the patient as the expert in understanding her own personal circumstances and in judging the value or personal importance she attaches to each option.

In the ideal scenario, the decision to choose or decline breast reconstruction should be made by the patient after she has had the opportunity to learn about, discuss, and consider all the possible surgical treatment options for breast cancer. In many jurisdictions, access to breast reconstruction has become a quality indicator of the breast cancer treatment program (63). In the United States, the National Accreditation Program for Breast Centers requires that a breast reconstruction program be a necessary component for any centers seeking or maintaining accreditation (64). Recently, it has been legislated in both the United States as well as France, that options for breast reconstruction be discussed with the breast cancer patients by the physicians prior to committing to a surgical treatment (65). In Canada, Alberta was the first province to publish new guidelines that have highlighted the importance of providing access to PMBR to eligible women as part of their breast cancer treatment (66).

In order to make recommendations as a part of a clinical practice guideline for breast cancer patients in Ontario, the multidisciplinary Working Group of the Breast Reconstruction Guideline Development Group developed this evidentiary base upon which those recommendations are based. Based on the objectives of the guideline, the Working Group derived the clinical questions outlined below.

CLINICAL QUESTIONS

1. Who is a candidate for PMBR? Which patient, cancer, and treatment factors can affect the outcomes of breast reconstruction?
2. a) What is the appropriate timing of breast reconstruction (immediate versus [vs.] delayed) for patients who do not require radiotherapy?
   b) What is the appropriate timing of breast reconstruction for patients who are expected to require radiotherapy?
3. a) What is the outcome of SSM compared with non-SSM?
   b) What is the outcome of NSM compared with non-NSM?
4. What are the risks and benefits associated with implant-based, autologous flap (i.e., deep inferior epigastric perforator [DIEP], transverse rectus abdominis myocutaneous [TRAM], superficial inferior epigastric artery [SIEA]) and combination (i.e., latissimus dorsi [LD] flap with implant) breast reconstruction?
5. What are the benefits and risks of using ADM in implant-based breast reconstruction?
6. What are the benefits and risks of autologous fat grafting as an adjunct to breast reconstruction?
7. Should women who have undergone PMBR receive routine screening for recurrence?

METHODS

This evidentiary base was developed using a planned two-stage method, summarized here and described in more detail below.

1. Search and evaluation of existing systematic reviews and practice guidelines: If one or more existing systematic reviews or evidence-based practice guidelines are identified that address the clinical questions and are of reasonable quality, then those would form the core of the evidentiary base.
2. Systematic review of the primary literature: This review would focus on those areas not covered by existing reviews if any are located and accepted.

The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC and the Surgical Oncology Program is editorially independent from the Ministry.

Search for Systematic Reviews

The MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews (CDSR) databases were searched from 2008 to June 2013 and using OVID to identify existing systematic reviews that addressed one or more of the clinical questions above. The search was later updated on May 13, 2014. Medical Subject Heading (MeSH) terms related to breast reconstruction were combined with relevant text words and a search filter to identify systematic review citations (See Appendix III for the complete search strategy). Systematic reviews published as a component of practice guidelines (not otherwise considered suitable for adaptation or endorsement) were also considered eligible for inclusion. The search was limited to the English language due to unavailability of translation services. If more than one systematic review was identified that addressed the same topic and reported the same outcomes, the most recent review was selected for further assessment. Identified systematic reviews that required further consideration were assessed using the AMSTAR tool, available at www.AMSTAR.ca (67). The results of the AMSTAR assessment were used to determine whether an existing review could be incorporated as part of the evidentiary base.

Any identified reviews that did not meet the criteria above, whose AMSTAR assessments indicated important deficiencies in quality, or that were otherwise not incorporated as part of the evidence base were reported in the reference list, but not further described or discussed.

Search for Primary Literature

If no existing systematic review or evidence-based practice guideline was identified, or if identified reviews were incomplete or out of date, a systematic review of the primary literature was also planned. The criteria described below were written assuming no existing reviews would be incorporated.

Literature Search Strategy

A systematic search was conducted in OVID MEDLINE (2010 through September week 4 2013), OVID MEDLINE In-Process & Other Non-Indexed Citations (2010 through September week 4 2013) and OVID EMBASE (2010 through week 39 2013). The MeSH "exp breast neoplasms" was combined with additional terms and text words for breast cancer, mastectomy, breast reconstruction, surgical flaps, breast implants, acellular dermal matrix, and fat grafting. The results were limited to English language and articles published from 2010 to 2013. See Appendix III for the full search strategies.

Study Selection Criteria and Process

A review of the titles and abstracts that resulted from the search was performed by one reviewer (KS). For those items that warranted full-text review, one reviewer (KS) reviewed each item and consulted the rest of the Working Group whenever there was uncertainty.

Studies were included if they met the following criteria:

- Randomized controlled trials (RCTs), prospective cohort or retrospective case series of the following:
    - Effects of patient, cancer and treatment factors on outcomes of breast reconstruction; immediate vs. delayed reconstruction; reconstruction with vs. without radiation therapy (RT); SSM vs. non-SSM with reconstruction; NSM vs. non-NSM with reconstruction; SSM vs. NSM; mastectomy with vs. without reconstruction; mastectomy plus reconstruction vs. other type of reconstruction; reconstruction with ADM vs. no ADM; reconstruction with autologous fat grafting vs. no fat grafting; post-reconstruction routine screening for recurrence vs. no routine screening.
- ≥30 patients
- English language, due to unavailability of translation services
- Published in 2010 or later

Data Extraction and Assessment of Study Quality and Potential for Bias

Data extraction was conducted by one author (KS) and was reviewed by a second independent individual using a data audit procedure (EC). Disagreements were resolved by consensus. The following items were extracted from each relevant article: author, publication year, study population, follow-up, procedure, number of participants, complications, and other outcomes.

Ratios, including hazard ratios (HRs), were expressed with a ratio <1.0 indicating that the experimental procedure had a better outcome than the control group.

Important quality features were assessed for each study. Quality features of interest included selection of subjects, comparability of groups, outcome assessment, and follow-up. The level of evidence to guide recommendations for PMBR is limited to Level II and III studies and a few smaller RCTs.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, a meta-analysis was planned using the Review Manager software (68) provided by the Cochrane Collaboration. For time-to-event outcomes, HRs, rather than the number of events at a certain time point, would be the preferred statistic for meta-analysis, and would be used as reported. If the HR and/or its standard error were not reported, they would be derived from other information reported in the study, if possible, using the methods described by Parmar et al (69). For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models in Review Manager would be used. Calculation of statistical heterogeneity was planned using the X^2 test for heterogeneity and the I^2 percentage. A probability level for the X^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% would be considered indicative of statistical heterogeneity.

RESULTS

Search for Existing Systematic Reviews

The original search for existing systematic reviews identified 91 citations, of which 38 were retrieved for full-text review. The updated search in May 2014 identified an additional 35 citations, of which 11 were reviewed in full text. Two additional reviews were identified using the PROSPERO registry of systematic review protocols (15, 16). Where multiple systematic reviews were identified that addressed the same outcomes and body of literature, only the most recent reviews are described in detail and assessed for quality. Thirty-five reviews (4, 8-16, 19-25, 28, 29, 31, 70-85) were selected for inclusion and were evaluated for quality using AMSTAR (www.AMSTAR.ca (67)) (Appendix IV). It should be noted that a review by Barnsley et al (31) was published outside of the literature review time constraints. It was identified by Working Group members. As this was the only systematic review that pertained to the use of magnetic resonance imaging in routine surveillance, it was added to the systematic reviews bringing the total number of systematic reviews to 36. There were no systematic reviews attached to Clinical Practice Guidelines identified for inclusion in this review.

Search for Primary Literature

Literature Search Results

Figure 4-1. Literature Search Results.

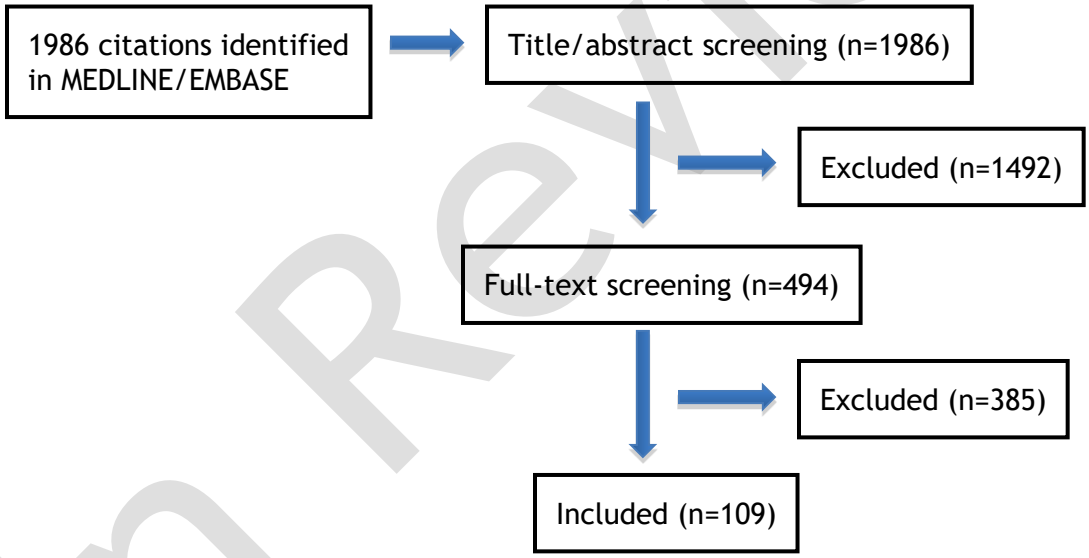

Table 4-1. Studies selected for inclusion.

Question	Number of studies included	Citations
1. Candidates for breast reconstruction	2 systematic reviews 21 observational studies	(4, 70) (1-3, 86-104)
2. Timing of reconstruction	6 systematic reviews 18 observational studies	(9-11, 71-73) (6, 105-117)
3. Skin-sparing and nipple-sparing mastectomy	5 systematic reviews 3 observational studies	(12-14, 74, 75) (118-120)
4. Type of reconstruction	12 systematic reviews	(8, 12, 15, 16, 19-22, 76-79)

Question	Number of studies included	Citations
	47 observational studies	(6, 17, 114, 121, 122, 123 , 124-164)
5. Acellular dermal matrix	8 systematic reviews 1 randomized controlled trial 12 observational studies	(23-25, 80-84) (26) (27, 165-175)
6. Fat grafting	3 systematic reviews 4 observational studies	(28, 29, 85) (30, 176-178)
7. Routine surveillance	1 systematic review 3 observational studies	(31) (32, 179, 180)

Study Design and Quality

Systematic reviews were assessed for quality using the AMSTAR criteria described at www.AMSTAR.ca. Using these criteria, most reviews scored poorly (Appendix IV). Common limitations included lack of duplicate study selection and data extraction, use of only one database, failure to search grey literature, failure to provide a list of excluded studies, lack of quality assessment of included studies, lack of assessment of publication bias, and failure to provide information about conflict of interest for each of the included studies. Despite these limitations, it was believed that the existing systematic reviews provided valuable information to inform the clinical questions addressed in this review.

The majority of primary studies identified in the literature from 2010 to September 2013 were retrospective studies based on chart reviews or database audits, while some were prospective, nonrandomized cohorts, of which many did not include both an experimental and a control group. Common limitations of these studies included small sample size, selection bias, inconsistent measurement and collection of outcome data (information bias), and confounding. These lower level studies were retained because they represent the best available evidence to answer the clinical questions in the absence of high-quality RCTs. They were reviewed to determine whether new evidence confirmed or contradicted the results of the existing systematic reviews. There was no specific weighting of benefits and risks, or selection bias on what results were reported. The tables present all available evidence and outcomes and represent the constraints of the literature.

Outcomes

Clinical Question 1: Candidates for PMBR

Two systematic reviews (4, 70) and 22 prospective or retrospective studies with more than 200 patients published since 2010 were reviewed to inform the guideline recommendations on eligibility for PMBR. Walton et al. published a systematic review in 2011 to examine the available evidence on breast reconstruction in elderly women (4). The authors reported that the evidence was limited in number and quality of studies; however, the available evidence seemed to demonstrate that complications from breast reconstruction in elderly women were comparable to those in younger women. Wolfswinkel et al. conducted a systematic review and meta-analysis of complications following abdominal-based free flap reconstruction in obese women and non-obese women. Results demonstrated a higher risk of infection (relative risk [RR], 1.97), mastectomy flap necrosis (RR, 2.61), partial flap loss (RR, 2.62), total flap loss

(RR, 4.12), and donor site seroma (RR, 4.03) in obese women compared with non-obese women but no difference in overall donor site complications (RR, 1.09).

Primary studies specifically addressing the effect on patients, treatment, or disease factors on outcome of breast reconstruction that were published in 2010 or later were reviewed (Table 4-2). Of the 15 studies reviewed that addressed the effect of obesity on outcome, three were prospective studies (3, 102, 103), one was a cross-sectional survey (95), and the remainder were retrospective reviews of patient charts or databases. Statistical analyses and outcomes measured varied among studies. Most studies reported a significantly increased risk of complications with increasing body mass index (BMI). Types of postoperative complications commonly increased in obese women included flap loss, delayed wound healing, and postoperative complications overall. One study compared outcomes in women with morbid obesity vs. women with intermediate obesity (1) and reported significantly higher rates of major surgical complications, wound complications, and prosthesis or flap failure in women who were morbidly obese. The effect of smoking on complications of breast reconstruction was examined in five studies (3, 86, 87, 91, 104). Three of the five studies did not detect a significant difference in complications between smokers and nonsmokers (86, 87, 91), one reported that smoking was the only factor significantly associated with complications overall in univariate analysis (104), and one study reported that flap complications, donor site complications and delayed wound healing were significantly higher in smokers than in nonsmokers who received abdominal autologous breast reconstruction (3). Psychiatric illness was not assessed as a predictor of breast reconstruction outcome in any of the identified studies. The impact of older age was assessed in five studies (3, 86, 87, 91, 102). Berry et al. reported significantly more overall complications and major complications in women over the age of 50 years with tissue expander/implant (TE/I) reconstruction but no difference in overall or major complications between age groups in women with autologous reconstruction (86). One study reported no significant difference in overall complications, fat necrosis, thrombosis, or hematoma between age groups (87). Khansa et al. reported that age over 50 years was a significant predictor of complications in multivariate analysis but was not a predictor of esthetic or general dissatisfaction (91). Seidenstuecker et al. reported no significant differences in complications between age 65 years and older, and younger than 65 years (3) and Nelson et al. reported no significant difference in abdominal function following autologous abdominal free flap reconstruction between 60 years of age and older, and younger than 60 years (102). The effect of diabetes on outcome of breast reconstruction was assessed in four studies (86, 87, 91, 99). One reported a significant association between diabetes and medical complications (99), two reported no significant difference in overall complications between diabetic and nondiabetic patients (87, 91), and one reported a significantly higher overall complication rate in diabetic patients in univariate but not multivariate analysis (86). Other factors were investigated included hypothyroidism, previous surgery, American Society of Anesthesiologists classification, neoadjuvant chemotherapy, tamoxifen, breast size, hypertension, chronic obstructive pulmonary disease, and tumour size.

Table 4-2. Candidates for breast reconstruction.

Study: Berry 2010 (86)
Type: Retrospective, electronic clinical database
Population: Autologous breast reconstruction, compared with prior single-centre review of TE/I reconstruction
Participants: 1037 (autologous and implant groups)
Outcomes:

Obesity: TE/I reconstruction BMI >30 kg/m^2 vs. BMI <30 kg/m^2: complications 49% vs. 27.5% (OR 1.93, 95% CI 1.48-2.52; p<0.001 logistic regression)
Autologous reconstruction BMI >30 kg/m^2 vs. BMI <30 kg/m^2: complications 48.2% vs. 25.7% (p<0.001 logistic regression). Multivariate analysis of major complications: OR 4.11 (95% CI 2.43-7.04; p<0.001)
Smoking: No significant impact on complications
Older Age: TE/I reconstruction age >50 years vs. age <50 years: complications 37% vs. 28.4% (OR 1.48, 95% CI 1.08-2.05; p=0.016 logistic regression).
Major complications 30.8% vs. 20.6% (p=0.002).
Autologous reconstruction age >50 vs. age <50: no significant impact on complications overall or major complications
Diabetes: Total complications (diabetics vs. non-diabetics): 56.7% vs. 30.8% (p<0.004) in univariate analysis. Not significant risk factor in multivariate analysis.

Study: Chang 2011 (87)
Type: Retrospective, single centre
Population: Microsurgical breast reconstruction
Participants: 650
Outcomes:

***Obesity*:** The only significant predictor of overall complications in multivariate analysis
Smoking: No significant impact on overall complications in a univariate analysis with X^2 test
Older Age: No significant difference in overall complications, fat necrosis, or thrombosis/hematoma between age groups.
Diabetes: No significant impact on overall complications in a univariate analysis with X^2 test
Other: Hypothyroidism and previous surgery were not significantly related to overall complications.
ASA classification correlated with increased risk of overall surgical complications.

Study: Chen 2011 (88)
Type: Retrospective, multi-state database, insurance records
Population: --
Participants: 8000
Outcomes:

***Obesity*:** Presence of any complication (reconstruction subgroup): 29.4% (obese) vs. 1.8% (control), p<0.001

Study: Hu 2011 (89)
Type: Retrospective, single centre
Population: Stage I–III breast cancer, mastectomy, chemotherapy, USA
Participants: 665
Outcomes:

Obesity: BMI >25 kg/m^2: 56.9% vs 41.2%; p<.01 developed surgical complications
Older Age: Aged >50 years: 53.6% vs. 38.4% p<0.01 developed surgical complications
***Other*:** Neoadjuvant chemotherapy: complications after mastectomy and immediate reconstruction: 35.7% with neoadjuvant chemotherapy vs. 37.4% with adjuvant chemotherapy (p=1.00)

Study: Jandali 2011 (90)
Type: Retrospective, single centre
Population: Autologous abdominal breast reconstruction, USA
Participants: 404 (25 BMI ≥40 kg/m^2)
Outcomes:

***Obesity*:** BMI ≥40 kg/m^2 vs. <40 kg/m^2: No significant difference in major intraoperative complications.
Total flap loss 8% vs. 0.5% (p=0.02).
Overall major postoperative complications: 12% vs. 3% (p=0.05).
No major medical complications in morbidly obese group.
Delayed abdominal wound healing 72% vs. 44% (p=0.006).

Study: Khansa 2011 (91)
Type: Retrospective, single centre, online medical records and office charts

Population: Breast reconstruction, USA
Participants: 532 participants for 802 reconstructions
Outcomes:

***Obesity*:** Not a predictor of complications. Obesity decreased general satisfaction (OR 0.29; p<0.001)
Smoking: Not a predictor of complications
Older Age: Age >50 years a significant predictor of complications in multivariate analysis (OR 2.10; p<0.001). Age was not a predictor of esthetic or general dissatisfaction.
Diabetes: Not a predictor of complications
Other: Previous BCT vs. no prior history of BCT: Complications 36.5% vs. 27.1% (p=0.026) but multivariate analysis not significant (OR 1.09; p=0.690). Previous BCT not a significant factor for decreased esthetic or general satisfaction.

Study: Seidenstuecker 2011 (3)
Type: Prospective, single centre
Population: Breast reconstruction, DIEP or free msTRAM, Germany
Participants: 558
Outcomes:

***Obesity*:** BMI ≥30 kg/m^2 had significantly more flap complications, total flap loss, marginal necrosis, donor site complications, and seroma formation
***Smoking*:** Flap complications, donor site complications (p=0.007) and delayed wound healing (p=0.001) were significantly higher in smokers compared with nonsmokers
***Older Age*:** No significant difference in complications between age ≥65 years and age <65 years

Study: Donker 2012 (92)
Type: Retrospective, single centre
Population: Invasive malignancy, skin-sparing mastectomy with immediate reconstruction, subpectoral prosthetic implant, Netherlands
Participants: 213
Outcomes:

***Other*:** Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy: significantly less short-term postoperative complications (15% vs. 29%; p=0.042) and no difference in loss of implant (8% vs. 11%; p=0.566)

Study: Garvey 2012 (93)
Type: Retrospective, single centre
Population: Abdominal-based free flap breast reconstruction, obese (BMI ≥30 kg/m^2)
Participants: 700
Outcomes:

***Obesity*:** Overall complications: 39.5%. Flap vs. implant: 42.3% vs. 35.9% (p=0.04). Significantly more reconstruction loss, infection and hematoma/seroma with implants vs. flaps. More delayed wound healing with flaps. BMI ≥37 kg/m^2 vs. BMI <37 kg/m^2: complications 47.1% vs. 37.4% (p=0.01).

Study: Kelley 2012 (94)
Type: Retrospective, single centre
Population: Delayed microvascular breast reconstruction, USA
Participants: 670
Outcomes:

***Other*:** Tamoxifen vs. no tamoxifen: complications 21.5% vs. 15% (p=0.04). Significantly increased immediate total flap loss and lower rate of flap salvage but no difference in pulmonary embolus.

Study: Kulkarni 2012 (95)
Type: Cross-sectional survey
Population: DCIS or invasive breast cancer, age ≤79 kg/m^2, obese, USA
Participants: 374
Outcomes:

***Obesity*:** Surgical outcome satisfaction similar among normal weight, overweight, and obese patients

Study: Ochoa 2012 (96)
Type: Retrospective, single centre
Population: Consecutive DIEP flap patients, USA
Participants: 418
Outcomes:

***Obesity*:** Delayed wound healing: significantly higher rate in severely obese patients compared with lower BMI. Overall and other flap complications not significantly different between BMI groups.

Study: Duggal 2013 (97)
Type: Retrospective, single centre
Population: Unilateral breast reconstruction, documented mastectomy specimen weight, USA
Participants: 355
Outcomes:

***Other*:** Breast size: Overall complications 44%. Patients with complications had significantly higher mean mastectomy specimen weights than those without complications ($p<0.01$).

Study: Fischer 2013 (1, 2)
Type: Retrospective, national database
Population: Breast reconstruction, USA
Participants: 15,937
Outcomes:

***Obesity*:** Progressive obesity associated with higher rates of wound complications, major surgical complications, graft or flap loss, and reoperation in analysis by WHO obesity class. Morbidly obese vs. intermediate obese: significantly more major surgical complications, wound complications, and prosthesis/flap failure.

Study: Fischer 2013 (98)
Type: Retrospective, free flap database, single centre
Population: Abdominal free-flap breast reconstruction, USA
Participants: 812
Outcomes:

***Obesity*:** Higher incidence of complications with increased BMI. Morbid obesity was associated with significantly higher rates of total flap loss, delayed wound healing, hernia, and abdominal morbidity.

Study: Fischer 2013 (99)
Type: Retrospective, free flap database, single centre
Population: Oncologic breast reconstruction, free flap, USA
Participants: 849
Outcomes:

***Obesity*:** Significant association with major immediate and delayed postoperative complications in univariate analysis. Association with major delayed complications also significant in multivariate analysis. Significant association between BMI and medical complications overall.
***Diabetes*:** Significant association between diabetes and medical complications.
***Other*:** COPD and hypertension associated with delayed major surgical complications in univariate analysis. COPD was also significantly associated with delayed major complications in multivariate analysis. Significant association between COPD and medical complications.

Study: Hanwright 2013 (100)
Type: Retrospective, national database (NSQIP)
Population: Breast reconstruction (autologous or implant), USA
Participants: 12,986
Outcomes:

***Obesity*:** Overall morbidity significantly higher in obese patients. BMI correlated with increased surgical complications for tissue expander, pTRAM and free flaps. Medical complications higher in obese pts with tissue expander and pTRAM but not LD or free flap reconstructions

Study: Kneubil 2013 (101)
Type: Retrospective, single centre, consecutive patients
Population: Total mastectomy, SSM or NSM for primary unilateral invasive breast cancer, immediate reconstruction, no neoadjuvant treatment, Italy
Participants: 1742
Outcomes:

***Obesity*:** BMI significantly associated with risk of locoregional recurrence in univariate and multivariate analysis.
Other: Tumour size significantly associated with risk of locoregional recurrence in univariate and multivariate analysis. Triple negative and luminal B/HER2-positive subtypes were associated with higher risk of locoregional recurrence in multivariate analysis.

Study: Nelson 2013 (102)
Type: Prospective blinded cohort
Population: Autologous abdominal free flap reconstruction, immediate reconstruction, USA
Participants: 145

Outcomes: ***Older Age*:** Age ≥60 years vs. age <60 years: no significant difference in abdominal function
Study: Schaverien 2013 (103) **Type:** Prospective cohort **Population:** Immediate free flap breast reconstruction, SSM, UK **Participants:** 87 **Outcomes:** ***Other*:** Neoadjuvant chemotherapy vs. none: no significant difference in complications overall or reoperations
Study: Yezhelyev 2013 (104) **Type:** Retrospective, single centre **Population:** LD flap reconstruction **Participants:** 277 **Outcomes:** ***Obesity*:** Incidence of overall complications, flap complications and donor site complications not significantly different between obese, overweight and normal weight patients. ***Smoking***: Smoking was only factor on univariate analysis associated with higher incidence of complications (p=0.031)

Abbreviations: ASA: American Society of Anesthesiologists; BCT: breast-conserving therapy; BMI: body mass index; CI: confidence interval; COPD: Chronic obstructive pulmonary disease; DCIS: ductal carcinoma in situ; DIEP: deep inferior epigastric perforator flap; LD: latissimus dorsi; msTRAM: muscle-sparing TRAM; NSM: nipple-sparing mastectomy; NSQIP: National Surgical Quality Improvement Program; OR: odds ratio; pTRAM: pedicled TRAM; TE/I: tissue expander/ implant; TRAM: transverse rectus abdominis myocutaneous; SSM: skin-sparing mastectomy; vs. versus

Clinical Question 2: Timing of breast reconstruction

Immediate vs. delayed reconstruction

Systematic reviews

Five systematic reviews were identified that compared immediate vs. delayed reconstruction or reconstruction before vs. after RT in women undergoing mastectomy for breast cancer: three addressed autologous reconstruction (9, 11, 71) and two reviewed studies of implant-based reconstruction (72, 73). One of the reviews was limited to RCTs only and included women with or without RT (73) while the others included observational studies in which all women received RT (9, 11, 71, 72).

The Cochrane review by D'Souza et al. was limited to RCTs, of which only one was found (73). The RCT was published in 1983 by Dean et al. and included only 64 participants (5). In the IBR group, silicone subpectoral prosthesis was provided for 33 participants. In the DBR group, 31 patients were advised about an implant but only six chose to undergo reconstruction 12 months postmastectomy. At three months, the rate of psychiatric morbidity was lower in patients receiving IBR compared with women in the control group (7% vs. 36%; p=0.05). By 12 months, no difference was detected (4% vs. 10%; p=NS). In addition, by three months, 67% of patients in the IBR group had returned to work vs. 46% in the control group. At three months, 37% of patients reported feeling ugly and mutilated in the IBR group vs. 67% in the DBR group and this did not change by 12 months (p=0.05 for both time points). The RCT was deemed to be at high risk of bias; limitations include its small sample size, absence of information about random sequence generation and allocation concealment, lack of blinding of outcome assessors, incompleteness of outcome data, and possible sampling bias. In addition, Momoh et al. performed a systematic review in 2014 comparing implant reconstruction with RT given pre-reconstruction (often with delayed reconstruction) or following reconstruction (often with immediate reconstruction) (72). Twenty-six observational studies were identified with more than 1500 patients. For the comparison of pre-reconstructive radiation vs. post-reconstructive radiation, similar results between

groups were reported for major complication rates (49% vs. 39%), capsular contracture (25% vs. 32%), and reconstructive failure (19% vs. 20%).

Three systematic reviews examined observational studies comparing immediate vs. delayed autologous breast reconstruction in the context of RT (9, 11, 71). A 2011 review by Barry et al. (11) included three studies comparing immediate and delayed TRAM flap breast reconstruction with RT, all of which were also included in the Schaverien review (9), and is not discussed further. Schaverien et al. (9) published a systematic review in 2013 including 16 studies: 12 studies included both an immediate and delayed reconstruction group and four studies contributed data only for delayed reconstruction. All patients received RT before or after reconstruction. The meta-analysis of data from observational studies demonstrated a lower rate of reoperation in women with delayed reconstruction compared with immediate reconstruction (mean 1.4% vs. 15.1%; odds ratio [OR], 0.15; 95% confidence interval [CI], 0.05 to 0.48; p=0.001) but no significant difference in overall complications (mean 32.5% vs. 32.6%; OR, 1.13; 95% CI, 0.77 to 1.65; p=0.53) or fat necrosis (mean 14.9% vs. 22.2%; OR, 0.63; 95% CI, 0.39 to 1.38; p=0.25). Kelley et al. (71) published a systematic review in 2014 of 20 studies examining autologous reconstruction before or after RT, the majority of which were not included in the Schaverien review (9). Due to heterogeneity among studies, a meta-analysis was not conducted; however, rates and 95% CIs were calculated for each type of complication. The following postoperative complication rates were similar between delayed reconstruction after RT and immediate reconstruction before RT: wound healing (10% vs. 14%), infections (4% vs. 6%), hematoma (2% vs. 1%), seroma (4% vs. 4%), and total flap loss (1% vs. 4%). The systematic reviews included for this outcome are all subject to the limitations with using observational studies as the evidentiary base. The majority of studies involved small patient populations from single centres with retrospective analysis and variable follow-up periods.

Primary studies

Seven studies were identified that compared immediate vs. delayed breast reconstruction. Two were prospective studies (6, 105) and five were retrospective reviews of patient charts or databases (see Table 4-3, below) (106-110). One of the studies compared delayed reconstruction with delayed immediate reconstruction (106). Use of adjuvant RT varied across studies: in two studies, all women received adjuvant RT (105, 106); in two studies, some women received adjuvant RT (107, 109); in two studies no women received adjuvant RT (108, 110); and in one study, the use of adjuvant RT was not reported (6).

Complications of immediate vs. delayed reconstruction were addressed in three studies (105, 108, 109). In a prospective pilot study, Giacalone et al. reported no significant difference in early or late complications except a higher rate of marginal back skin flap necrosis in the immediate reconstruction group (19.3% vs. 5.1%; p=0.04). Baltaci Goktas et al. reported no significant difference in surgical complications or arm lymphedema between groups but significantly higher RT complications with immediate reconstruction in the subgroup of women who received RT (75% vs. 6%; p=0.01); however, it should be noted that only four women in the immediate reconstruction group received RT compared with 17 women in the delayed reconstruction group (109). In the setting of implant-based reconstruction without RT, Hvilsom et al. reported significantly higher rates of hematoma and seroma after immediate two-stage TE/I reconstruction compared with delayed two-stage reconstruction (108). No significant difference was observed in rates of infection, capsular contracture, asymmetry or displacement of the implant, or reoperation. Patel et al. compared delayed autologous

reconstruction with delayed-immediate autologous reconstruction in the setting of adjuvant RT and reported no significant difference in total complications (first-stage reconstruction), vascular complications (second-stage), or non-vascular complications (second-stage); however, reoperations were significantly higher in the delayed immediate group (78.8% vs. 60.8%; p=0.008) (106).

One study reported on the delay to adjuvant chemotherapy with immediate reconstruction (110). Immediate reconstruction was associated with a modest but statistically significant delay in initiating chemotherapy. The authors concluded that this delay was unlikely to have any clinical significance for most women.

A comparison of esthetic outcomes, QOL, or satisfaction between immediate and delayed reconstruction was reported in three studies (6, 105, 109). Giacolone et al. reported that there was no significant difference in esthetic outcome (medical or patient evaluation) for women who were disease free and had no reconstructive failure (105). In the study by Baltaci Goktas et al., the rates of serious sexual problems, loss of feminine feeling, deterioration of body image, and decrease of self-esteem were significantly higher in the delayed reconstruction group compared with the immediate reconstruction group (109). In a Canadian prospective study of 190 women by Metcalfe et al. (6), women undergoing delayed reconstruction had higher levels of body stigma (p=0.01) and body concerns (p=0.002) than women who underwent immediate reconstruction. At one-year follow-up there was no difference between treatment groups, although psychological distress was evident among all women regardless of timing of reconstruction. Psychological functioning including quality of life, sexual functioning, cancer-related distress, and body image was not different at one year post-surgery in the immediate and delayed reconstruction groups.

Four primary studies (all retrospective and single centre studies) were identified that specifically compared RT before vs. after breast reconstruction (111-114). Three studies reported no significant difference in the overall complication rate between groups (111-113). Adesiyun et al. reported that there was no significant difference in early complications between groups but the rate of late complications was significantly higher in women who received RT after reconstruction compared with women who received RT before reconstruction (111). In women who received implant reconstruction, capsular contracture was significantly higher in women who received RT after reconstruction. Lentz et al. compared TE/I exchange before vs. after RT and observed no significant difference in reconstructive failure but significantly more capsular contracture in women who had TE/I exchange before RT (113). Pestana et al. observed a higher rate of failed reconstruction in women who had RT after reconstruction compared with women who had RT before reconstruction (114). Overall general satisfaction and esthetic satisfaction were reported in two studies and neither detected a significant difference between the reconstruction before RT and reconstruction after RT groups (111, 112).

Immediate reconstruction with vs. without postmastectomy RT
Systematic reviews

Schaverien et al. published a systematic review in 2013 comparing immediate autologous breast reconstruction with RT vs. without RT (9). Twenty-five studies were evaluated: 10 were observational studies comparing immediate reconstruction with and without RT and 15 studies contributed data only to the postoperative RT group. Although no difference was observed in overall complications (33.9% vs. 28.6%; OR, 1.10; 95% CI, 0.78 to 1.54; p=0.59; five studies) or reoperations (18.3% vs. 16.1%; OR, 0.65; 95% CI, 0.25 to 1.68; p=0.38; three studies), fat necrosis was increased with the use of RT (23.8%

vs. 8.5%; OR, 2.82; 95% CI, 1.35 to 5.92; p=0.006; six studies). In addition, esthetic outcome was decreased in four of seven studies where patients received RT and volume loss in the flap was observed in two of three studies with rates as high as 77%.

Two systematic reviews with meta-analyses addressed the effects of postmastectomy RT specifically on immediate implant-based reconstruction (10, 11). Lam et al. (10) reviewed 12 observational studies (one prospective and 11 retrospective) of immediate two-stage reconstruction and reported a higher reconstruction failure rate in women who received RT (18.6% vs. 3.1%; p<0.00001; seven studies). This increased failure rate was particularly evident when RT was given after stage 1 placement of the tissue expander (29.7% vs. 5%; p<0.00001; six studies). In the 2011 systematic review by Barry et al. (11), pooled data from four observational studies demonstrated that women undergoing immediate implant-based reconstruction in the presence of postmastectomy RT had fourfold greater odds of suffering morbidity compared with women not requiring RT (OR, 4.2; 95% CI, 2.4 to 7.2).

Primary studies

Four retrospective studies were identified that compared complications for immediate reconstruction with vs. without adjuvant RT (See Table 4-3, below) (112, 115-117). Christante et al. reported a significantly higher overall complication rate and TE/I loss rate in women who received immediate reconstruction plus RT compared with women who did not receive RT (115). Similarly, Lee et al. reported a higher overall complication rate with RT (112). A study of free flap reconstructions by Fosnot et al. reported significantly higher rates of overall vascular complications and intraoperative vascular complications with RT but no difference in delayed vascular complications, fat necrosis, wound infection, skin flap necrosis, hematoma, seroma, delayed wound healing, or flap loss (116). Lin et al. reported more major complications, wound dehiscence and failure to expand in women who received RT in the setting of two-stage implant-based reconstruction (117).

Table 4-3. Timing of reconstruction and radiotherapy

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Immediate vs. delayed reconstruction						
Alderman 2010 (110) Retrospective, multi-centre	Stage I-III unilateral breast cancer for which NCCN guidelines recommended adjuvant chemotherapy; no neoadjuvant RT or chemotherapy, no RT before initiation of adjuvant therapy; USA	NR	Mastectomy with immediate reconstruction Mastectomy with delayed reconstruction	696 with either immediate or delayed reconstruction	NR	Time to chemotherapy from definitive surgery (delayed/immediate)[a]: Age 0-39 years: HR, 2.27 (95% CI, 1.49 to 3.46) Age 40-49 years: HR, 1.38 (95% CI, 0.98 to 1.96) Age 50-59 years: HR, 1.44 (95% CI, 0.88 to 2.34) Age >60 years: HR, 1.50 (95% CI, 0.64 to 3.54)
Giacalone 2010 (105) Prospective pilot study	Non-metastatic invasive breast cancer, mastectomy, neoadjuvant chemotherapy and RT plus immediate reconstruction or adjuvant chemotherapy and RT plus delayed reconstruction	Mean 4.7 yrs (immediate reconstruction) and 4.5 yrs (delayed reconstruction)	Neoadjuvant chemotherapy and RT, IBR Adjuvant chemotherapy and RT, delayed reconstruction	26 78	Early complications: 61% vs. 56% (p=0.645). No difference in breast skin envelope necrosis, marginal LD flap necrosis, implant infection, hematoma, or dorsal seroma. Marginal back skin flap necrosis 19.3% vs. 5.1% (p=0.04) Late complications: 31% vs. 22% (p=0.362). No difference in capsular contracture, back pain, reconstruction failure, implant revision capsule, total implant revision, or symmetrization procedure	Esthetic outcome (for disease-free patients and patients with no reconstructive failure): No significant difference between groups in medical evaluation (77.7% excellent or good vs. 87%) or patient evaluation (89% vs. 94%)

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Losken 2010 (107) Retrospective chart review, single centre	Postmastectomy breast reconstruction using bilateral LD flaps, 17/83 patients had pre- or postoperative RT; USA	Average 2.3 years	Immediate reconstruction Delayed reconstruction Mixed	52 22 8	Insufficient data for analysis of reconstruction timing	Need for additional procedures: no significant association with timing of reconstruction Overall patient satisfaction (n=37): No significant difference for RT vs. no RT or timing of reconstruction
Baltaci Goktas[b] 2011 (109) Retrospective, single centre	Breast cancer, immediate or delayed reconstruction, earlier pathological stage in immediate reconstruction group, 41% had RT; Turkey	10.5 months (immediate) and 12 months (delayed)	Immediate reconstruction Delayed reconstruction	28 (4 had adjuvant RT) 23 (17 had adjuvant RT)	Arm lymphedema: 14% vs. 39% (p=0.05) Surgical complications: 7% vs. 17% (p=0.19) Radiotherapy complications (in patients who received RT): 75% vs. 6% (p=0.01)	Sexual problems: serious 18% vs. 57%, mild 36% vs. 26% (p=0.01) Loss of feminine feeling: 21% vs. 57% (p=0.02) Deterioration of body image: 39% vs. 83% (p=0.04) Decrease of self-esteem: 25% vs. 70% (p=0.03)

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Hvilsom 2011 (108) Retrospective, national database	Immediate implant breast reconstruction (one stage or two stage) or delayed two-stage reconstruction, breast cancer, no RT; Denmark	10.1 yrs (immediate reconstruction)	Immediate one-stage reconstruction Immediate two-stage reconstruction Delayed two-stage reconstruction	40 149 353	Overall complications at 1 year (two-stage reconstructions): 51.7% vs. 44.5% Overall complications at 8 yrs (two-stage): 76.2% vs. 67.2% Higher risk of hematoma and seroma after immediate compared with delayed two-stage reconstruction (p=0.044 and p=0.017) No significant difference in infection, capsular contracture, asymmetry, implant displacement, or reoperation between immediate and delayed two-stage reconstruction.	--
Metcalfe 2012 (6) Prospective longitudinal survey, two centres	Primary invasive breast cancer, RT not reported; Canada	1 year follow-up	Mastectomy with immediate reconstruction Delayed reconstruction Mastectomy alone	24 57 109	--	Psychosocial functioning: At 1 year follow-up, no significant differences in psychosocial functioning scores between groups

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Patel 2013 (106) Retrospective, single centre	Autologous breast reconstruction, adjuvant RT, delayed or delayed immediate reconstruction; USA	Average 3.2 years (delayed) and 2.8 years (delayed immediate)	Delayed reconstruction Delayed immediate reconstruction	118 breasts 74 breasts	Total complications (first stage reconstruction): 8.5% vs. 10.8% (p=0.81) Vascular complications (second stage reconstruction): No significant difference in anastomotic revisions, arterial or venous complications, reoperation/re-exploration, hematoma or total flap failure Nonvascular complications (second stage reconstruction): 5.1% vs. 5.4% (p=0.56). No significant difference in infection, seroma requiring treatment, or skin necrosis	Revision surgery: 60.8% vs. 78.8% (p=0.008), including skin contouring, soft tissue contouring, fat grafting
Reconstruction with vs. without RT						
Christante 2010 (115) Retrospective, single centre, consecutive pts	Primary nonmetastatic unilateral breast cancer, mastectomy; USA	Median 31 months	Immediate reconstruction plus PMRT Immediate reconstruction alone	302	Complication rate (IBR ± PMRT): 42% vs. 16%; OR, 3.3 (95% CI, 1.5 to 7.1; p<0.001) Complication rate (PMRT with IBR vs. delayed reconstruction): 42% vs. 22% (p≤0.001) TE/I loss rate: 31% vs. 6% (p=0.005)	--

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Lee 2010 (112) Retrospective, single centre	Simple or modified radical mastectomy, unilateral or bilateral, no previous RT for failed BCT, autologous or implant; USA	Median 28.3 months, 63.6 months, and 56.8 months for the 3 groups, respectively	PMRT then reconstruction Reconstruction then PMRT Breast reconstruction only	57 59 665	Overall complication rate (any PMRT vs. none): 39.7% vs. 23.2% (p<0.001) Overall complication rate (reconstruction then PMRT vs. reconstruction only): 47.5% vs. 23% (p<0.001) Early complications: 17.5% vs. 15.6% vs. 7.7%	Overall general satisfaction (n=536): 67.5% vs. 68.4% vs. 67.2% Esthetic satisfaction (n=536): 50.0% vs. 63.2% vs. 66.9%
Fosnot 2011 (116) Retrospective chart review	Free flap breast reconstructions, unilateral or bilateral, 22% of flaps in previously irradiated field; USA	NR	No RT RT	799 flaps 226 flaps	Flaps with any vascular complication: 9.6% vs. 17.3% (p=0.001) Flaps with intraoperative vascular complication (arterial or venous thrombosis, technical difficulties): 7.6% vs. 14.2% (p=0.003) Flaps with delayed vascular complication (arterial or venous thrombosis, other delayed issues): 2.4% vs. 4.0% (p=0.19) No significant difference in fat necrosis, wound infection, skin flap necrosis, hematoma, seroma, delayed wound healing, or flap loss	--

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Lin 2012 (117) Retrospective, single centre	Two-stage prosthetic breast reconstruction following modified radical mastectomy, unilateral or bilateral, 18% of breasts had previous RT exposure; USA	Minimum 6 months, mean 26.3 to 28.4 months	Neoadjuvant RT Adjuvant RT No RT	32 17 218	Major complication rates: 43.8% vs. 41.2% vs. 13.8%. Wound dehiscence: 21.9% vs. 23.5% vs. 1.8% Failure to expand: 18.8% vs. 11.8% vs. 0.5%	--
Momoh 2012 (181) Retrospective, operating room records, consecutive patients, single centre	Delayed autologous reconstruction after mastectomy and adjuvant therapy; USA	Mean 33.3 months (RT) and 39.4 months (no RT)	RT No RT	100 99	Total complications: 40% vs. 20.2% (p=0.0023) Wound dehiscence: 11% vs. 3% (p=0.0489) No significant difference in flap loss, vascular thrombosis, fat necrosis, infection, or seroma Overall complications similar in women reconstructed early or late after PMRT	--
RT before vs. after reconstruction						
Lee 2010 (112) Retrospective, single centre	Simple or modified radical mastectomy, unilateral or bilateral, no previous RT for failed BCT, autologous or implant; USA	Median 28.3 months, 63.6 months, and 56.8 months for the 3 groups, respectively	PMRT then reconstruction Reconstruction then PMRT Breast reconstruction only	57 59 665	Overall complication rate (PMRT then reconstruction vs. reconstruction then PMRT): 31.6% vs. 47.5% (p=0.081) Early complications: 17.5% vs. 15.6% vs. 7.7%	Overall general satisfaction (n=536): 67.5% vs. 68.4% vs. 67.2% Esthetic satisfaction (n=536): 50.0% vs. 63.2% vs. 66.9%

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Adesiyun 2011 (111) Retrospective chart review, single centre	Postmastectomy breast reconstruction, PMRT, 87% received chemotherapy, autologous or implant; USA	Median 46.5 months	PMRT then reconstruction Reconstruction then PMRT	57 57	Overall complication rate: 32% vs. 44% (p=0.176) Early complications: 18% vs. 11% (p=0.210) Late complications: 14% vs. 33% (p=0.009) Capsular contracture in patients with implant reconstruction: 2% vs. 19% (p=0.002)	General patient satisfaction (n=77): 68% vs. 68% (p=0.995) Esthetic satisfaction: 50% vs. 62% (p=0.283)
Lentz 2013 (113) Retrospective, single centre	TE/I reconstruction for breast cancer, postmastectomy RT	Mean 46.0 months (exchange before RT) and 27.3 months (exchange after RT)	TE/I exchange before RT TE/I exchange after RT	22 34	Reconstructive failure: 13.6% vs. 20.6% (p=0.72) Overall complications: 54.5% vs. 47.1% (p=0.785) Capsular contracture: 40.9% vs. 11.8% (p<0.05)[c]	--
Pestana 2013 (114) Retrospective, consecutive patients, single centre	Breast cancer, mastectomy and breast reconstruction, autologous or implant, immediate or delayed, RT before or after reconstruction; USA	Mean 6 years	RT before reconstruction RT after reconstruction	94 breasts 63 breasts	Failed reconstruction: 16% vs. 37% (p=0.003)	--
Other comparisons						

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Baumann 2011 (182) Retrospective, single centre	Locally advanced breast cancer, delayed breast reconstruction, free TRAM or DIEP or SIEA, no tissue expander; USA	Median 302 days (delay <12 months) and 211 days (delay >12 months)	Delayed breast reconstruction <12 months after mastectomy Delayed breast reconstruction >12 months after mastectomy	82 107	Total flap loss: 6% vs. 0% (p=0.014) Partial flap loss: 6% vs. 8% (p=0.590) No difference in microvascular thrombosis, wound dehiscence, fat necrosis, or infection	Reoperation <30 days: 14.6% vs. 4.7% (p=0.022)
Peled 2012 (183) Retrospective, surgical outcomes database, consecutive cohorts, single centre	Postmastectomy RT and two-stage expander implant reconstruction, skin-sparing or total skin-sparing, 98% had neoadjuvant or adjuvant chemotherapy; USA	Mean 31 months	Expander-implant exchange <6 months after RT Expander-implant exchange >6 months after RT	49 39	Expander-implant failure: 22.4% vs. 7.7% (p=0.036)	--
Hughes 2012 (184) Retrospective, single centre	Implant-based reconstruction, skin-sparing or conventional mastectomy	N/A	Implant-based reconstruction	132 total	Overall complications and capsular contracture not significantly associated with delayed reconstruction or RT	Reoperation: significantly associated with delayed reconstruction and RT

Abbreviations: BCT: breast conserving therapy; CI: confidence interval; DIEP: deep inferior epigastric perforator flap; HR: hazard ratio; IBR: immediate breast reconstruction; LD: latissimus dorsi; N/S: not available; NCCN: National Comprehensive Cancer Network; NR: not reported; OR: odds ratio; PMRT: postmastectomy radiotherapy; RT: radiotherapy; SIEA: superficial inferior epigastric artery; TE/I: tissue expander/implant; TRAM: transverse rectus abdominis myocutaneous; vs.: versus.

Notes:

[a] HR>1 indicates earlier initiation of chemotherapy in the delayed reconstruction group

[b] Many inconsistencies between table and text data

[c] See paper for additional subgroup analyses

Clinical Question 3: Skin-sparing and nipple-sparing mastectomy

Systematic reviews: SSM

One systematic review with meta-analysis was identified that specifically evaluated the harms and benefits of SSM with immediate reconstruction compared with non-SSM without reconstruction in breast cancer (12). Nine retrospective nonrandomized studies were included, comprising 3739 patients in total, of whom 1104 underwent SSM. No difference between SSM and non-SSM without reconstruction was detected for local recurrence (6.2% vs. 4.0%; OR, 1.22; 95% CI, 0.85 to 1.74) or postoperative severe complications (18.7% vs. 22%; OR, 0.81; 95% CI, 0.57 to 1.16). The SSM group had a significantly lower rate of distant relapse compared with the non-SSM group (10.0% vs. 12.0%; OR, 0.67; 95% CI, 0.48 to 0.94; p=0.02), although the authors stated that they had no explanation for this observation other than the possibility that there were differences in tumour grade and adjuvant therapy between groups. Insufficient data were available to assess time to local or distant recurrence. The authors concluded that long-term follow-up is required to confirm the findings of the meta-analysis.

Systematic reviews: NSM

Four systematic reviews published since 2010 addressed the harms and benefits of NSM (13, 14, 74, 75). While there was some overlap in studies among reviews, inclusion criteria and reporting of results differed substantially among reviews. Studies included in the reviews were prospective or retrospective series based on patient record review, many of which were not comparative in nature.

Occult nipple involvement was assessed in three of the four systematic reviews (13, 74, 75). Mallon et al. (13) reported a mean incidence of 11.5% across 29 observational studies. The following factors were identified that were associated with an increased incidence of occult nipple malignancy: tumour-to-nipple distance less than 2 cm, tumour grade, lymph node metastasis, estrogen and progesterone receptor-negative, tumour size greater than 5 cm, retroareolar or central location and multicentric tumours. Rusby et al. (74) reported an occult nipple involvement incidence rate ranging from 0% to 58% across 18 observational studies; excluding studies with fewer than 100 patients resulted in a range from 5.6% to 31%. Murthy et al. (75) reported similar results across 10 studies. Possible reasons suggested for the wide range across studies included differences in patient selection, definition of nipple involvement, and the pathological technique used to assess involvement.

Local recurrence was addressed in all four systematic reviews of NSM. Endara et al. (14) reported a pooled locoregional recurrence rate of 1.8% with follow-up ranging from 0.2 to 210 months across patients in 28 studies. Nipple recurrence was not reported. Mallon et al. (13) reported a pooled nipple recurrence rate of 0.9% and a skin flap recurrence rate distal to the nipple-areolar complex (NAC) of 4.2% across 20 studies with a median follow-up time of 49.3 months. Murthy et al. (75) identified 10 studies reporting locoregional recurrence in both the prophylactic and therapeutic setting with a mean follow-up between 10.5 and 156 months. Local recurrence, including chest wall and axilla, ranged from 0% to 8.5%. No recurrence in the NAC was reported in nine of the 10 studies, while one study reported a NAC recurrence rate of 1.6%.

Rusby et al. (74) examined the safety of NSM in women undergoing prophylactic mastectomy. Three of four clinical series reported no primary breast cancers originating in the nipple while the fourth series reported that one of 575 women undergoing prophylactic NSM had subsequent breast cancer in the nipple.

The pooled rate of nipple necrosis following NSM was reported to be 7.7% across 39 studies in the systematic review by Endara et al. (14). Necrosis rates varied significantly from study to study (e.g. range from 0% to 48% across studies in the Rusby et al. systematic review (74)) and appeared to be influenced by patient factors, surgical technique, and receipt of radiation. Mallon et al. (13) reported pooled rates of nipple necrosis by level of severity. The pooled rate of full-thickness necrosis was 2.9% while partial-thickness necrosis occurred in 6.3% of patients. Mallon et al. reported additional complications of NSM including hematoma requiring surgical intervention (0.3%) and infection (1.7%).

The 2010 review by Rusby et al. (74) reported data on patient satisfaction, cosmesis, and nipple sensation; however, studies assessing these outcomes were limited in size and design to provide definitive answers.

Primary studies: NSM vs. SSM

Primary studies comparing SSM vs. NSM are described here. Three studies were identified: Kim 2010 (118), Boneti 2011 (119) and Burdge 2013 (120) (see Table 4-4). Kim et al. (118) conducted a retrospective study in Korea comparing NSM or SSM with immediate TRAM flap reconstruction and modified radical mastectomy. Disease-free survival and overall survival were not significantly different between the SSM and NSM groups at five years. Local recurrence was 2.0% in the NSM group, 0.8% in the SSM group and 0.9% in the modified radical mastectomy group. Two nipple areola recurrences were observed in the NSM group (1.3%). A subgroup of 115 NSM patients was followed prospectively and NAC necrosis occurred in 9.6% of these patients (complete necrosis in 11 patients and partial necrosis in 15 patients). Boneti et al. (119) compared nipple-skin sparing mastectomy (removal of the glandular NAC with preservation of the NAC skin) with SSM in a retrospective study of 293 patients. The rate of locoregional recurrence, overall complications, skin flap ischemia, and postoperative infections were not significantly different between the groups. Cosmesis data, available for only 19.1% of patients, indicated a significantly higher score for nipple-skin sparing mastectomy compared with SSM. A small retrospective study by Burdge et al. (120) compared nipple-skin sparing mastectomy with SSM in 60 patients with locally advanced breast cancer. The radiation-induced complication rate was 30.8% in the nipple-skin sparing mastectomy group compared with 38.1%% in the SSM group. Locoregional recurrence rates were 10.3% vs. 14.3% respectively and no recurrences involved the preserved NAC or the nipple-skin sparing mastectomy scar. No statistical comparison between groups was conducted for either of these outcomes. Other outcomes were not reported specifically for the nipple-skin sparing and SSM groups.

Table 4-4. Skin-sparing and nipple-sparing mastectomy primary studies.

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Kim, 2010 (118) Retrospective, single centre. 115 NSM pts followed prospectively for complications	Operable stage 0 to IIIa breast cancer, mastectomy, immediate TRAM reconstruction, Korea	Median 60 months (NSM) and 67 months (SSM)	SSM NSM Modified radical mastectomy	368 152 1900	Reported only for 115 NSM pts followed prospectively. NAC necrosis: 9.6% (11 pts complete necrosis, 15 pts partial necrosis)	5 yr RFS: 87.2% SSM vs. 89% NSM (p=0.695) 5 yr OS: 95.8% SSM vs. 97.1% NSM (p=0.669) Local recurrence: 0.8% SSM vs. 2.0% NSM vs. 0.9% modified radical mastectomy
Boneti, 2011 (119) Retrospective	SSM and TSSM cases, no advanced disease with skin involvement, no inflammatory breast cancer, no collagen vascular disease, and no known smoking in past 6 months, USA	38.2 months SSM (range 4 to 144 months) and 25.3 months TSSM (range 3 to 102 (p<0.001)	SSM NSSM	293 pts total 227 procedures 281 procedures	Overall complications: 6.2% vs. 7.1% (p=0.67) Skin flap ischemia: 3.1% vs. 4.6% (p=0.37) Postoperative infection: 2.6% vs. 1.7% (p=0.79)	Cosmesis (data available for 19.1% of pts): SSM score significantly lower than TSSM Locoregional recurrence: 5.0% vs. 4.6% (p=0.89)
Burdge, 2013 (120) Retrospective, single centre	Locally advanced disease, no inflammatory cancer, SSM or NSSM, USA	38.2 months (SSM) and 25.3 months (NSSM)	SSM NSSM	21 39	Radiation-induced complications: 38.1% SSM vs. 30.8% NSSM	Locoregional recurrence: 14.3% vs. 10.3%

Abbreviations: NAC: nipple-areolar complex; NSM: nipple-sparing mastectomy; NSSM: nipple-skin sparing mastectomy; OS: overall survival; pts: patients; RFS: recurrence-free survival; SSM: skin-sparing mastectomy; TRAM: transverse rectus abdominis myocutaneous; TSSM: total skin-sparing mastectomy; yr: years.

Clinical Question 4: Types of reconstruction

a) Mastectomy with breast reconstruction vs. mastectomy alone or breast-conserving surgery

Systematic reviews

Five systematic reviews were identified that compared mastectomy plus breast reconstruction vs. mastectomy alone or breast-conserving surgery (BCS) (8, 12, 76-78) to evaluate the overall benefits and harms of breast reconstruction. Study inclusion criteria and reported outcomes varied significantly among reviews. Two of the five reviews assessed oncologic outcomes: one compared recurrence rates in patients who underwent immediate reconstruction with patients who had mastectomy alone (8) and one compared recurrence and severe postoperative complications in patients undergoing SSM and immediate reconstruction with patients undergoing mastectomy alone (12). Three reviews evaluated patient-reported outcomes: one included patient outcomes overall (78), one focused on breast sensation (77), and one reported body image outcomes compared with patients undergoing mastectomy alone or BCS (76). All primary studies included in the systematic reviews were observational in design, including prospective or retrospective reviews of patient charts or databases and cross-sectional surveys.

The 2012 meta-analysis by Gieni et al. (8) did not detect a significant difference in local recurrence (OR, 0.98; 95% CI, 0.62 to 1.54; p=0.92) or systemic recurrence (OR, 0.89; 95% CI, 0.63 to 1.26; p=0.51) between mastectomy with IBR and mastectomy alone in eight studies. The 2010 review by Lanitis et al. (12) comparing SSM and immediate reconstruction with non-SSM alone did not detect a significant difference in local recurrence (OR, 1.22; 95% CI, 0.85 to 1.74; seven studies) or severe postoperative complications (OR, 0.81; 95% CI, 0.57 to 1.16; three studies). A significant difference was reported for distant recurrence favouring reconstruction (OR, 0.67; 95% CI, 0.48 to 0.94; five studies); however, the authors could provide no explanation why SSM with immediate reconstruction should decrease the distant recurrence rate.

The 2009 Lee et al. systematic review (78) of studies comparing patient-reported outcomes between mastectomy plus reconstruction and mastectomy alone concluded that, overall, the majority of studies did not find a statistically significant benefit for reconstruction in QOL, body image, or sexuality. However, most of the 28 studies were limited in design by selection bias, low sensitivity of outcome measures, and low statistical power. The 2010 systematic review by Shridharani et al. (77) examining breast sensation following breast reconstruction reported that study results were conflicting. Recovery of adequate sensation appeared to take 18 to 24 months after reconstruction. Recovery was faster for innervated flaps than for noninnervated flaps and was better for DIEP flaps than TRAM flaps, LD flaps, and implant-based reconstruction (77). A meta-analysis published in 2013 by Fang et al. (76) indicated a significantly worse body image in women undergoing mastectomy and breast reconstruction compared with women undergoing BCS; however, there was significant heterogeneity among the results of the 12 studies, indicating that there were clinical differences between studies. The meta-analysis of seven studies comparing body image between mastectomy plus breast reconstruction and mastectomy alone demonstrated better body image scores in women who underwent reconstruction. No statistically significant heterogeneity was detected in this analysis.

Primary studies

Five primary studies were identified and compared outcomes following breast reconstruction vs. BCS: two prospective cohorts, two retrospective studies, and one cross-sectional survey (121-125) (see Table 5). Local or locoregional recurrence was reported in two of the five studies: one reported similar rates for both groups (3.3% in the mastectomy with LD flap group vs. 3.2% in the BCS group) and the other reported that there were no locoregional

recurrences at a mean follow-up of 36 months). Quality of life was reported to be similar between groups in the two retrospective studies (121, 124). The study by Sackey et al. suggested better physical functioning and less limitation due to bodily pain in the mastectomy with reconstruction group compared with the BCS groups but a higher mental health score for the BCS alone group (122). No difference was detected in rates of anxiety or depression between groups. Of the two studies that compared body image between mastectomy with reconstruction and BCS, one reported more body image problems in the mastectomy/reconstruction group (122) and one reported no significant difference between groups (analysis adjusted for severity of surgical side effects) (123). One of the five studies reported reconstruction-related complications (124). The overall morbidity rate for immediate reconstruction was 16.1%, with fat necrosis in 14.1%, wound infection in 11.8%, and capsular contracture in 11.0%. No partial or total flap losses were reported.

Twenty primary studies were identified that compared mastectomy plus breast reconstruction with mastectomy alone: two prospective studies and 18 retrospective studies, four of which utilized data from large registries or national databases (6, 126-144). Eleven of the 20 studies reported data for complications. The overall rate of postoperative complications was not significantly different between groups in one study (138) but was significantly higher in women with immediate reconstruction than women with mastectomy alone in another study (27.0% vs. 15.6%; $p<0.0001$) (139). Major complications were significantly higher in the reconstruction group in this study (15.5% vs. 3.7%; $p<0.0001$) and a small study by Prabhu et al. reported a significantly higher rate of complications requiring unplanned surgical intervention (37.5% vs. 5%; $p<0.001$) (137). Another retrospective matched cohort reported no significant difference in complications within 30 days (7.3% vs. 6.3%) (130). In all three studies reporting lymphedema rates, women undergoing mastectomy with reconstruction had significantly lower rates of lymphedema than women undergoing mastectomy alone (127, 134, 142). Surgical site infection was significantly higher in women undergoing reconstruction in an analysis of a large national database (3.5% vs. 2.5%; RR, 1.4; $p<0.001$) (136) while tissue adhesion was significantly higher at 12 months in women with mastectomy alone in a small prospective cohort study (5.0% vs. 25.0% ($p=0.032$) (140).

Of the six primary studies that compared overall survival between mastectomy plus reconstruction with mastectomy alone (126, 130, 135, 137, 138, 143), four reported no significant difference between groups while two reported a significant survival benefit for reconstruction (126, 130). Breast cancer-specific survival was significantly higher in women who underwent reconstruction in two studies (130, 133) but no significant difference was found between reconstruction and mastectomy alone in another study (137). Disease-free survival was not significantly different in one study (HR, 0.8; $p=0.34$) (143) but a benefit for reconstruction was demonstrated at five years in another (95.2% vs. 92.7%; $p=0.01$) (132). Most of the eight studies evaluating local or locoregional recurrence were not able to detect a significant difference between mastectomy with reconstruction and mastectomy alone (128, 130, 131, 137, 138, 143), although Yi et al. reported a lower recurrence rate in women undergoing reconstruction (5.3% vs. 7.6%; $p=0.04$) (132) and Lee et al. reported a lower regional recurrence rate with reconstruction (1.1% vs. 2.4%; $p=0.0098$) but no difference in local recurrence rate (1.8% vs. 1.2%; $p=0.17$) (135). All three studies examining the effect of reconstruction on time to adjuvant chemotherapy reported additional delay for women undergoing reconstruction (mean additional delay ranged from 1.7 weeks to 2.7 weeks) (129, 139, 144). In the study by Kontos et al. (129), 67% of women undergoing reconstruction received adjuvant chemotherapy greater than six weeks after surgery compared with 28.8% of women undergoing mastectomy alone.

Patient-reported outcomes including QOL, body image, and satisfaction were reported in several small retrospective studies. Overall QOL was not significantly different between

mastectomy with reconstruction and mastectomy alone in one study (128). Psychosocial and sexual functioning and pain scores were better in women who underwent reconstruction in one study (141) while another study reported no significant difference in psychosocial functioning after adjustment for age and stage (6). Body image was significantly higher in women with reconstruction in one study (128) and satisfaction with breasts was higher with reconstruction in two studies (138, 141). A prospective cohort of 104 patients reported significantly better shoulder flexion and abduction at 12 months in the reconstruction group compared with the group undergoing mastectomy alone (140).

Table 4-5. Breast reconstruction vs. mastectomy alone.

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Reconstruction vs. BCS						
Min 2010 (121) Retrospective, single-centre, cross-sectional survey, matched control cohort	Primary breast cancer, Korea	Mean 39.2 months (LD) vs. 42.1 months (BCS)	Mastectomy with LD flap BCS	120 1699	NR	Local recurrence: 3.3% vs. 3.2% QoL: Similar in BCS and mastectomy/LD groups with or without RT
Sackey 2010 (122) Cross-sectional	DCIS, Sweden	NR	Mastectomy and immediate reconstruction BCS alone BCS and RT	42 37 52	NR	HRQoL: Better physical functioning and less limitation due to bodily pain in mastectomy/reconstruction group compared with BCS groups. Higher mental health score for BCS alone group than other groups. Anxiety and depression: No significant differences between groups Body image: More body image problems in mastectomy/reconstruction group
Collins 2011 (123) Prospective cohort	Pathologically confirmed DCIS and stage I and IIA invasive breast cancer, age >39 years, no neoadjuvant chemotherapy, no prior history of breast cancer, USA	2 yr follow-up	Mastectomy with reconstruction Mastectomy alone BCS	127 66 356	NR	Body image at 6 months: Pts with reconstruction had poorer body image than pts with mastectomy alone (p=0.011). No significant difference between BCS and mastectomy with reconstruction (adjusted for severity of surgical side effects)

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Heneghan 2011 (124) Retrospective, single-centre, age- and stage-matched control cohort	Breast cancer, Ireland	Mean 36 months (range 12-70 months)	Mastectomy with immediate reconstruction BCS	179 160	Reconstruction-related morbidity: 16.1%. No partial or total flap loss. Fat necrosis: 14.1% Wound infection: 11.8% Capsular contracture: 11.0%	QoL: No significant difference between groups for functional outcome, symptoms or global health score Locoregional recurrence: none at mean follow-up time of 36 months
Shi 2011 (125) Prospective, 2 centres	Incidental breast cancer, no distant metastasis, no benign tumour, no cognitive impairment, Taiwan	2 yr follow-up	Mastectomy with reconstruction Modified radical mastectomy alone BCS	32 83 57	NR	QoL: Unclear
Reconstruction vs. mastectomy alone						
Agarwal 2010 (126) Retrospective, SEER database	Invasive breast cancer, mastectomy (no partial mastectomy), USA	NR	Immediate or early-delayed reconstruction No reconstruction	8645 43,057	NR	Overall survival: Mean 56.2 vs. 51.9 months; HR, 0.62; 95% CI, 0.57 to 0.68 (p<0.001)
Avraham 2010 (127) Retrospective, single centre	Breast cancer surgery with SLNB or SLNB/ALND, clinically node negative, USA	Median 5 yrs (range 2.7 to 8 yrs)	Tissue expander reconstruction No reconstruction	186 130	Measured lymphedema: 5% vs. 18% (p=0.0004) Severe measured lymphedema: <1% vs. 4% (p=0.09)	--
De Gournay 2010 (128) Retrospective, case-controlled study, single centre	Mastectomy for nonmetastatic breast cancer, alive in July 2008, France	Minimum 6 months after surgery	Immediate or delayed LD flap with or without implant No reconstruction	160 86	NR	Local recurrence: 2.5% vs. 1.2% (p=0.66) QoL: No significant difference in scores between groups Body image: Significantly higher body image questionnaire score for reconstruction group (p=0.0247)

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Kontos 2010 (129) Retrospective, single centre	Mastectomy for breast cancer, adjuvant therapy, UK	NR	Immediate free flap reconstruction (TRAM, DIEP, S-GAP) No reconstruction	27 139	NR	Time between surgery and commencement of adjuvant therapy >6 wks: 67% vs. 28.8% (p=0.0001) Mean time between surgery and commencement of adjuvant treatment: 55 days vs. 40 days (p=0.0025)
Eriksen 2011 (130) Matched retrospective cohort (age, tumour size, nodal status, year of operation), single centre	Invasive breast cancer, mastectomy, no previous ipsilateral breast cancer, Sweden Pts with inflammatory breast cancer, tumours adhering to the pectoral muscle, high BMI and heavy smokers not recommended immediate reconstruction	Median follow-up 11.5 yrs (range 2 to 20)	Immediate implant-based reconstruction Mastectomy alone	300 300	Complications <30 days: 7.3% vs. 6.3% (p=0.622)	Local recurrence: 8.2% vs. 9.0% (p=0.879) Regional recurrence: 8.2% vs. 9.7% (p=0.555) Distant metastases: 20.3% vs. 27.1% (p=0.049) Overall survival: HR, 0.67 (95% CI, 0.48 to 1.0; p=0.038) Breast cancer-specific survival: HR, 0.62 (95% CI, 0.42 to 0.91; p=0.026)
Reddy 2011 (131) Retrospective, single centre	Breast cancer; mastectomy; no bilateral breast cancer, metastatic disease, prophylactic mastectomy, delayed reconstruction; USA	Mean 4.5 yrs	Immediate reconstruction Mastectomy alone	494 427	NR	Locoregional recurrence: 2.2% vs. 4.0% (p=0.1220) 1.9% autologous vs. 2.0% autologous/ implant vs. 3.4% implant alone (p=NS) Overall recurrence: 5.9% vs. 11.5% (p=0.0023)

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Yi 2011 (132) Retrospective	Stage 0 to III primary unilateral breast carcinoma, total mastectomy with or without complete axillary dissection, minimum 2 years follow-up; USA	Median 53 months (range 24-104 months)	SSM (98.1% IBR) Conventional mastectomy (16.9% IBR)	799 1011	NR	Median time to first recurrence: 32.1 months vs. 28.7 months (p=0.06) Recurrence rate: 5.3% vs. 7.6% (p=0.04) 5-yr disease-free survival: 95.2% vs. 92.7% (p=0.01)
Agarwal 2012 (133) Retrospective, SEER database	Breast cancer, mastectomy (no partial mastectomy), USA	NR	Reconstruction Mastectomy alone	8446 43,803	NR	Breast cancer-specific survival: HR 0.73 (0.66-0.81;p<0.0001)
Card 2012 (134) Retrospective, matched cohort (age, post-op RT, SLND) single centre	Therapeutic mastectomy	Minimum 3 yrs follow-up Average follow-up 59 months	Mastectomy and reconstruction Mastectomy alone	541 549	Breast cancer-related lymphedema: 3.7% vs. 9.9%; HR, 0.34 (95% CI, 0.20 to 0.57; p<0.001) Multivariate model of time to development of lymphedema: HR, 0.44 (95% CI, 0.26 to 6.87; p=0.002)	--
Lee 2012 (135) Retrospective, single centre	No stage 4, biannual clinical examination/mammography/chest X-ray, Korea	Median follow-up 57 months (56.4 in TRAM group and 60 in mastectomy alone group)	Immediate pedicled TRAM reconstruction Modified radical mastectomy alone	1000 3183	NR	Local recurrence: 1.8% vs. 1.2% (p=0.1712) Regional recurrence: 1.1% vs. 2.4% (p=0.0098) Distant metastasis: 2.8% vs. 9.5% (p<0.001) Survival: Log-rank p=0.276 (in higher stage pts log-rank p=0.503)

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Metcalfe 2012 (6) Prospective longitudinal survey, 2 centres	First primary invasive breast cancer, age >18 years, able to read and understand English, eligible for breast reconstruction at time of mastectomy, Canada	83.2% completed 1 yr follow-up	Mastectomy plus immediate reconstruction Previous mastectomy plus delayed reconstruction Mastectomy alone	24 57 109	NR	Psychosocial functioning: No significant differences among groups after adjustment for age and stage
Nguyen 2012 (136) Retrospective, national database	Mastectomy as primary or secondary procedure, no nipple-areolar complex reconstruction, USA	NR	Immediate breast reconstruction Mastectomy alone	9315 39,078	Surgical site infection: 3.5% vs. 2.5%; RR, 1.4 (95% CI, 1.3 to 1.7, p<0.001) Flap failure: 1.3% in reconstruction group	--
Prabhu 2012 (137) Retrospective, consecutive pts	Noninflammatory stage III breast cancer, neoadjuvant chemotherapy, postmastectomy RT; USA	Median 30.6 months	SSM with immediate reconstruction Non-SSM (28.3% delayed reconstruction)	40 60	Complication rate requiring unplanned surgical intervention: 37.5% vs. 5% (p<0.001)	2-yr locoregional control: 94.7% vs. 97.4% (p=NS) 2-yr breast cancer-specific survival: 91.5% vs. 86.3% (p=NS) 2-yr overall survival: 87.4% vs. 84.8% (p=NS)

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Shi 2012 (138) Retrospective, randomly selected control group from same time interval	Breast cancer, no distant metastasis, no other life-threatening or chronic diseases	Median 68 months (range 10-104 months)	Subcutaneous NSM and IBR Modified radical mastectomy	35 100	Postoperative complications: no significant difference between groups No severe complications	Local recurrence: no significant difference between groups Distant metastasis: no significant difference between groups Overall survival: no significant difference between groups Satisfaction with esthetic outcome: significantly higher in pts receiving reconstruction
Zhong 2012 (139) Retrospective, 2 centres	Mastectomy, no neoadjuvant chemotherapy, Canada	NR	Mastectomy and immediate breast reconstruction Mastectomy alone	148 243	Major complications: 15.5% vs. 3.7% (p<0.0001) Overall postoperative complications: 27.0% vs. 15.6% (p<0.009)	Time from last definitive breast surgery to start of chemotherapy: 8.5 wks vs. 6.8 wks (p=0.01)
De Oliveira 2013 (140) Prospective cohort	Modified radical mastectomy, Brazil	12 months follow-up	Immediate LD flap reconstruction Mastectomy alone	47 57	Tissue adhesion: 5.0% vs. 25.0% (p=0.032) at 12 months	Shoulder motion: No difference in shoulder flexion at 1 month or 3 months. At 6 and 12 months, reconstruction group had significantly better shoulder flexion. Shoulder abduction significantly better in reconstruction group at 12 months.
Eltahir 2013 (141) Retrospective, cross-sectional survey	Unilateral or bilateral mastectomy for breast cancer or prophylaxis. Excluded age <18 years, severely ill patients, flap or prosthesis loss[a]; Netherlands.	NR	Successful reconstruction Mastectomy alone	92 45	Incidence of mastectomy-associated complications similar between groups. Additional reconstruction-associated complications in the reconstruction group (i.e., partial or total flap necrosis, implant loss).	QoL: Significantly higher satisfaction with breasts, psychosocial and sexual well-being, satisfaction with surgeon and physical functioning and lower pain scores in reconstruction group

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Lee 2013 (142) Retrospective chart review, single centre	Modified radical mastectomy. Excluded stage III and IV disease, prior breast cancer, and pre-existing lymphedema.	Mean follow-up 53 months	Immediate autologous reconstruction Modified radical mastectomy alone	117 595	Lymphedema: 9.4% vs. 18.5% (p=0.017) No significant difference in severity of lymphedema between groups (p=0.556)	--
Sakurai 2013 (143) Retrospective, single centre	Breast cancer (invasive or non-invasive); Japan	Median 87 months	NSM Total mastectomy	788 144	Nipple necrosis: none reported	Local recurrence: 8.2% vs. 7.6% (p=0.81) NAC recurrence rate: 3.7% Disease-free survival: HR, 0.8 (95% CI, 0.7 to 2.2; p=0.34) Overall survival: HR, 0.8 (95% CI, 0.4 to 1.4; p=0.33)
Vandergrift 2013 (144) Retrospective, national database	Stage I to III unilateral breast cancer	Minimum 180 days follow-up	Immediate reconstruction Mastectomy alone	784 1166	NR	Time to adjuvant chemotherapy: Reconstruction associated with additional 2.7 weeks before chemotherapy (p<0.001)

Abbreviations: ALND: axillary lymph node dissection; BCS: breast-conserving surgery; BMI: body mass index; CI: confidence interval; DCIS: ductal carcinoma in situ; DIEP: deep inferior epigastric perforator; HR: hazard ratio; HRQoL: health-related quality of life; IBR: immediate breast reconstruction; LD: latissimus dorsi; NAC: nipple-areolar complex; NR: not reported; NSM: nipple-sparing mastectomy; pts: patients; QoL: quality of life; RT: radiation therapy; S-GAP: superior gluteal artery perforator; SLNB: sentinel lymph node biopsy; SSM: skin-sparing mastectomy; TRAM: transverse rectus abdominis myocutaneous; vs.: versus; yr: year.

Notes:

[a]12 pts excluded due to flap or implant loss

b) Comparisons between types of breast reconstruction
Systematic reviews

Seven systematic reviews articles were identified that compared different types of breast reconstruction: two compared TE/I reconstructions with autologous abdominal reconstruction (15, 16) and five compared flap complications and/or donor site morbidity for various types of autologous abdominal reconstruction (19-22, 79).

Two publications by Tsoi et al represented one systematic review comparing TE/I vs. autologous abdominal tissue (AAT) reconstruction for women with primary breast cancer: one presented patient-reported outcomes (16) and one presented surgical complication outcomes (15). Fourteen observational studies including 3244 reconstructed breasts were included that addressed surgical complications, all of which compared TE/I with one or more variations of TRAM flaps. Only six of the 14 studies involved more than 100 breasts and follow-up ranged from six to 60 months. Compared with patients receiving TE/I, patients undergoing AAT reconstruction were less likely to have reconstructive failure (1% vs. 5%; RR, 0.14; 95% CI, 0.06 to 0.32) and surgical site infections (6% vs. 9%; RR, 0.37; 95% CI, 0.25 to 0.55) but more likely to experience skin or flap necrosis (12% vs. 5%; RR, 2.79; 95% CI, 1.87 to 4.17). No statistically significant difference was demonstrated for infections leading to reoperation (1% vs. 0%; RR, 0.97; 95% CI, 0.22 to 4.16), hematoma or seroma (4% vs. 7%; RR, 0.56; 95% CI, 0.31 to 1.00), skin or flap necrosis requiring reoperation (10% vs. 3%; RR, 2.76; 95% CI, 0.80 to 9.46), wound dehiscence, deep venous thrombosis, pulmonary embolism, major complications, or reoperations, although results suggested a trend toward a lower seroma and hematoma rate in women undergoing AAT reconstruction. Tsoi et al. (15) also reported on complications that were specific to each method of reconstruction. In seven studies, the capsular contracture rate following TE/I reconstruction ranged from 0.0% to 33.3%. Complications specific to women undergoing AAT reconstruction included hernia, abdominal bulge, and impaired trunk function. In a subgroup of patients who received postoperative RT, major complications were less frequently reported in women who received AAT reconstruction compared with TE/I (18% vs. 24%; RR, 0.46; 95% CI, 0.29 to 0.73).

In the Tsoi et al. review (16), 15 articles representing nine studies (1393 patients) were identified that compared patient-reported outcomes between TE/I and AAT reconstruction. All abdominal tissue reconstructions were free or pedicled TRAM flaps and the studies included both immediate and delayed reconstructions. Four smaller studies of less than 100 patients reported similar rates of general and esthetic satisfaction for the two reconstructive approaches while the five larger studies detected a tendency toward better satisfaction in women undergoing autologous tissue reconstruction. One study suggested that patients with AAT reconstruction had stable esthetic satisfaction over time while patients with TE/I experienced declining esthetic satisfaction. The limited data available for psychosocial and functional outcomes suggest that reconstructive approach does not have a great impact on these outcomes.

Five systematic reviews compared flap complications and/or donor site morbidity for different types of AAT reconstruction. The most recent review by Khansa et al. focused specifically on fat necrosis and included observational 70 studies (22). The overall pooled fat necrosis rate was found to be 11.3% across 41 studies (10,764 flaps). Thirty-three articles reported fat necrosis by flap type: DIEP (14.4% fat necrosis), pedicled TRAM (12.3%), SIEA (8.1%), and free TRAM (6.9%). Predictors of necrosis included obesity, RT, active smoking and abdominal scars. An older review by Sailon et al. published in 2009 reported a significant difference between DIEP and free TRAM flaps in overall necrosis rates across eight studies (25.5% vs. 11.3%; $p<0.001$) and total necrosis rates (4.2% vs. 1.6%; $p=0.044$) but no difference in partial necrosis rates (3.5% vs. 11.2%; $p=0.057$) (79). The 2012 meta-analysis by Egeberg et

al. assessed donor site morbidity in five comparative observational studies (20). The risk of bulging and hernia was not significantly different between DIEP and muscle-sparing TRAM flap reconstruction. A 2009 review by Man et al. pooled the results of six studies comparing DIEP with free TRAM flaps; however, they reported significantly lower risk for hernia and bulge in women with DIEP flaps (RR, 0.49; 95% CI, 0.28 to 0.86) (19). Flap-related complications were more frequent with DIEP flaps while donor-site morbidity was more common with free TRAM flaps. Objective measures of abdominal function were reported to be slightly better for DIEP flaps than TRAM flaps in a 2009 systematic review by Atisha et al. (21); however, this did not appear to translate into deficits in performance of activities of daily living.

Primary studies

Twenty-two primary studies were identified that were published between 2010 and 2013 that compared different types of breast reconstruction. Seven compared two or more types of autologous tissue reconstruction (17, 145, 147, 151, 155, 158, 159), four compared different approaches to implant-based reconstruction (146, 156, 157, 161) and 11 included patients with autologous tissue- and implant-based reconstruction (114, 148-150, 152-154, 160, 162-164) (see Table 6).

Of the four studies investigating different approaches to implant-based reconstruction, one compared saline vs. silicone implants (146), two compared one-stage immediate implant reconstruction with the use of tissue expanders (157, 161) and one compared tissue expanders vs. expandable textured implants vs. polyurethane implants (156). Macadam et al. reported no significant difference between saline and silicone implants with respect to satisfaction with outcome, overall quality of life, physical well-being, or sexual well-being in 143 patients. Satisfaction with reconstructed breasts, psychological well-being, and physical well-being were higher in the silicone implant group, however. Based on a retrospective review of insurance claims data, Singh et al. reported no significant difference in complication rates between one-stage immediate implant reconstruction and reconstruction using tissue expanders (157). A larger retrospective analysis of a national database by Davila et al. demonstrated significantly higher rates of 30-day morbidity and prosthesis failure in women undergoing one-stage direct implant compared with tissue expanders but no difference in reconstruction-related complications overall, wound disruption, surgical site infection, reoperation, or major medical complications (161). The study by Pompei et al. comparing tissue expanders, expandable textured implants, and polyurethane implants reported complication rates but did not conduct tests of statistical significance (156). The overall complication rate was highest for tissue expanders (14.7%) and lowest for polyurethane implants (5.0%).

Six retrospective single-centre studies included both a TRAM and a DIEP group: three investigated pedicled TRAM flaps (145, 148, 155) and three investigated free TRAM flaps (147, 151, 159). In one study, there was no significant difference between bilateral pedicled TRAM and DIEP in abdominal hernia or bulge or seroma/hematoma in the donor or recipient site; however, donor site partial skin loss and wound dehiscence and recipient site fat necrosis were more frequent in the DIEP group (145). Another study reported no difference between pedicled TRAM and DIEP for flap loss, major fat necrosis, hematoma/seroma, infection, open wound, mastectomy skin loss, or esthetic satisfaction but better general patient satisfaction in the DIEP group. Yueh et al. reported no significant difference in general or esthetic satisfaction between pedicled TRAM and DIEP in a logistic regression analysis (148). Nelson et al. reported no significant difference between muscle-sparing free TRAM and DIEP flaps for intraoperative complications or postoperative minor or late complications but a higher rate of postoperative major complications in the DIEP group (arterial or venous thrombosis and flap necrosis) (147). Garvey et al. detected no significant difference in fat necrosis, partial flap necrosis, or overall complications between muscle-sparing TRAM and DIEP flaps (151). Chang et al. similarly

reported no difference in early complications between free TRAM, muscle-sparing free TRAM, and DIEP flaps (159).

Nine studies included patients who received LD flap reconstructions: five included a group with LD flap alone (17, 148, 149, 152, 164) and six included LD flaps combined with an implant (150, 152-154, 160, 164). Yueh et al. reported that general and esthetic satisfaction was lower for women receiving LD flap compared with abdominal flaps (148). Christensen et al. compared LD flaps with pedicled TRAM flaps and implants and concluded that LD flaps were associated with significantly higher patient satisfaction than implants (149). None of the 26 women who had LD flap reconstructions had major complications. Gart et al. reported that women with LD flaps had lower rates of overall complications, surgical site infections, and flap failure than free flaps and pedicled TRAM flaps (17). Monrigal et al. included women with LD flap reconstruction and LD flap reconstruction with implant (152). LD reconstructions had less necrosis than TRAM flap reconstructions and required fewer surgical revisions. Winters et al. compared autologous LD flap with LD flap plus implant and reported no statistically significant difference in early complications up to three months after surgery, long-term complications, or health-related QOL (164). Role functioning and pain were significantly better in the group that received LD flaps with implant compared with LD flaps alone. Levine et al. compared delayed LD flaps plus implant with delayed autologous abdominal flap reconstruction in previously irradiated patients (154). No statistically significant differences were found between groups in complications overall, reconstruction failures, or incidence of lymphedema. Costa et al. compared immediate LD flaps plus implant with implants alone and autologous reconstruction. There was no statistically significant difference in incidence of surgical site infections after adjustment for confounding factors (160). Another study by Crosby et al. of women undergoing reconstruction for unilateral breast cancer with a synchronous contralateral prophylactic mastectomy and reconstruction did not statistically compare outcomes between types of reconstruction, but the authors concluded that the risk of postoperative complications was similar for index mastectomy with reconstruction and prophylactic mastectomy with reconstruction (150).

Table 4-6. Breast reconstruction types.

Author, publication year; study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Chun 2010 (145) Retrospective, medical record review, single centre, consecutive patients	Immediate (n=86) or delayed (n=19) TRAM or DIEP; USA	Average 6.2 yrs (TRAM) and 2.3 yrs (DIEP)	Bilateral pTRAM Bilateral DIEP	105 58	Abdominal hernia: 2.9% vs. 0% (p=0.20) Abdominal bulge: 2.9% vs. 6.9% (p=0.22) Donor site partial skin loss/wound dehiscence: 3.8% vs. 10.3% (p=0.04) Abdominal donor site or recipient site seroma or hematoma: no significant difference in incidence Recipient site fat necrosis: 11.4% vs. 19.8% (p=0.04). 1 complete flap loss in DIEP group.	New back pain: 18.5% vs. 22.2% (p=0.77) Patient satisfaction: 79.7% very satisfied vs. 92.6% very satisfied (p=0.13) Physical function: no significant difference between groups
Macadam 2010 (146) Retrospective chart review, cross-sectional survey	Implant-based reconstruction for breast cancer or prophylaxis; USA & Canada	Mean 53.6 months (saline) and 31.4 months (silicone)	Saline implant (62% immediate) Silicone implant (83% immediate)	68 75	NR	Satisfaction with breast: significantly higher in silicone group Satisfaction with outcome: no significant difference between groups Psychological well being: significantly better in silicone group Physical and sexual well being: no significant difference between groups QoL: No significant difference between groups overall. Higher physical functioning score in silicone group.

Author, publication year; study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Nelson 2010 (147) Retrospective cohort study, single centre, single surgeon	DIEP and muscle-sparing free TRAM; USA	12.1 months (only msfTRAM, only DIEP) and 14.0 months (msfTRAM and DIEP)	Only msfTRAM Only DIEP One msfTRAM and one DIEP	91 53 31	Intraoperative complications: 7.1% (msfTRAM) vs. 6.9% (DIEP) (p=0.93) Postoperative major complications (arterial or venous thrombosis, flap necrosis): 0% (msfTRAM) vs. 3.9% (DIEP) (p=0.027) Postoperative minor or late complications: No significant difference	--
Yueh 2010 (148) Retrospective, single centre, cross-sectional survey	Postmastectomy breast reconstruction; USA	NR	Tissue expander/implant LD pTRAM DIEP	87 116 (90 with implants) 119 117	NR	General patient satisfaction: 56.3% vs. 56.9% vs. 70.6% vs. 80.3% Esthetic satisfaction: 48.3% vs. 59.5% vs. 76.5% vs 70.9%
Christensen 2011 (149) Retrospective chart review, single centre	Breast reconstruction for cancer, no known recurrence; Denmark	NR	Implant LD flap pTRAM	206 34 123	Minor complications (chart review): 27% vs. 21% vs. 35% (p=0.30) Major complications (chart review): 13% vs. 0% vs. 13%	Overall satisfaction: 64% vs. 81% vs. 84% (p=0.002) Improved quality of life: 83% vs. 88% vs. 90% (p=0.149) Pleased with breast size compared with opposite breast: 50% vs. 54% vs. 80% (p<0.0001) Pleased with breast shape: 36% vs. 65% vs. 77% (p<0.0001) Pleased with how the breast feels: 41% vs. 77% vs. 94% (p<0.0001)

Author, publication year; study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Crosby 2011 (150) Retrospective, single centre, consecutive patients	Unilateral breast cancer with mastectomy and synchronous contralateral prophylactic mastectomy, bilateral immediate breast reconstruction, no prior or postmastectomy RT; USA	Mean 13.2 months	Implant Abdominal flap LD/implant	334 142 21	At least one complication: 30.5% vs. 30.3% vs. 42.9% Index breast complications: 22.5% vs. 21.1% vs. 33.3% Prophylactic breast reconstructions: 19.2% vs. 19.0% vs. 19.0%	--
Garvey 2011 (151) Retrospective, single centre	Free-flap abdominal autologous reconstruction, flap perfused by either medial-only or lateral-only type II DIEA branch perforators; USA	Average 33.2 months (range 7.6 to 107.0 months)	DIEP msfTRAM	157 71	Fat necrosis: 10.2% vs. 11.3% (p=0.81) Partial flap necrosis: 3.2% vs. 2.8% (p=1.0) Fat necrosis/partial flap necrosis: 13.4% vs. 14.1% (p=0.89) Any complication: 19.7% vs. 19.7% (p=1.0)	--
Monrigal 2011 (152) Retrospective, single centre	Primary operative invasive breast cancer, neoadjuvant chemotherapy and RT; no local recurrence, inflammatory or T4 cancer; France	Mean 96 months	LD/implant free TRAM LD Implant	107 56 25 22	Total early complications (necrosis, seroma, infection, hematoma): 17.8% vs. 33.9% vs. 20.0% vs. 13.6% Early surgical revisions: 7.5% vs. 19.6% vs. 4% vs. 13.6% Total delayed complications (implant complications, abdominal wall hernia, necrosis, lymphedema, functional discomfort, chronic pain, seroma): 24.3% vs. 26.8% vs. 20.0% vs. 40.1% Delayed surgical revisions: 3.7% vs. 7.1% vs. 0% vs. 27.3%	--

Author, publication year; study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Crosby 2012 (153) Retrospective, single centre, consecutive patients	Breast cancer with immediate reconstruction; USA	Mean 56 months	Tissue expander/implant LD/implant pTRAM Free flap	737 breasts 117 breasts 36 breasts 609 breasts	Lymphedema: 3.3% vs. 3.4% vs. 5.5% vs. 3.3%	--
Levine 2012 (154) Retrospective, single centre	Postmastectomy RT, delayed abdominal-based autologous reconstruction or LD flap plus implant; USA	Mean 22.7 months	Abdominal flaps LD/implant	75 56	Reoperation (vascular compromise): 4.0% vs. 0% Flap failure: 2.7% vs. 0% Partial flap loss: 4.0% vs. 2.7% Implant loss: N/A vs. 5.4% Seroma: 13.3% vs. 21.4% Hematoma: 5.3% vs. 1.8% Cellulitis: 2.7% vs. 0% Abdominal bulge: 1.3% vs. N/A	--

Author, publication year; study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Momoh 2012 (155) Retrospective, single centre, cross-sectional survey	pTRAM or DIEP for breast cancer or prophylaxis, immediate or delayed, excluded if different reconstruction on each breast or stage 4; USA	Mean 51.2 months (DIEP) and 74.4 months (pTRAM)	DIEP pTRAM	167 179	Total flap loss: 1.8% vs. 0% (per flap) (p=0.1249) Partial flap loss: 1.4% vs. 1.5% (per flap) (p=1.0000) Major fat necrosis: 15.2% vs. 11.7% (p=0.2940) Hematoma/seroma: 3.6% vs. 3.6% (p=1.0000) Infection: 0.5% vs. 2.5% (p=0.1068) Open wound: 2.8% vs. 3.0% (p=1.0000) Mastectomy skin loss: 10.1% vs. 5.6% (p=0.0875)	General patient satisfaction (based on 234 survey responses): 81.7% vs. 70.2% (p=0.0395) Esthetic satisfaction: 72.5% vs. 77.2% (p=0.4086)
Pompei 2012 (156) Retrospective	Unilateral immediate breast reconstruction with implants; Italy	Median 51 months (range 12 to 90 months)	Tissue expanders Expandable textured implants Polyurethane implants	136 47 119	Infection: 0.7% vs. 2.1% vs. 0% Exposure/extrusion: 5.1% vs. 2.1% vs. 0.8% Total complications: 14.7% vs. 12.8% vs. 5.0%	--

Author, publication year; study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Singh 2012 (157) Retrospective, insurance claims data review	Implant breast reconstruction procedure during same visit as mastectomy, no death during 18-month postmastectomy study period, 17.8% RT; USA	18 months post-reconstruction	1-stage reconstruction Tissue expanders reconstruction	95 1221	No significant differences between groups. Complications of implant/graft/mesh: 28.4% vs. 27.4% (RR=1.03) Complications of tissue/artificial skin graft: 2.1% vs. 0.7% (RR=2.85) Hematoma: 6.3% vs. 2.9% (RR=2.14) Infection: 9.5% vs. 12.4% (RR=0.76) Necrosis: 1.1% vs. 3.3% (RR=0.32) Seroma: 6.3% vs. 4.5% (RR=1.4) Skin/connective tissue: 20.0% vs. 26.4% (RR=0.76)	--
Tong 2012 (158) Retrospective, single centre, consecutive groups	Abdominal breast reconstruction; USA	NR	pTRAM Perforator flaps	69 69	Fat necrosis: 53.6% vs. 15.9% (p=0.0001) Fat necrosis requiring operation: 23.7% vs. 5.9% (p=0.0004) Partial flap necrosis: 20.6% vs. 7.2% (p=0.045) Abdominal bulge: 21.1% vs. 9.7% (p=0.32) Abdominal hernia: 8.8% vs. 1.6% (p=0.21) Hematoma: 1.5% vs. 10% (p=0.06) Full flap necrosis: 0% vs. 1.5% (p=1)	--

Author, publication year; study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Chang 2013 (159) Retrospective, single centre	Unilateral or bilateral microvascular breast reconstruction; 27% prior RT, 28% postoperative RT; 65% immediate reconstruction; USA	Minimum 5 yrs	DIEP msfTRAM free TRAM S-GAP Other (tensor fasciae latae, pedicled TRAM flap, deep circumflex iliac artery flap, T12 perforator flap)	150 flaps 158 flaps 27 flaps 19 flaps 9 flaps	Early complications: no significant difference between flap types except higher breast wound breakdown in S-GAP group (10.5%; p<0.03)	--
Costa 2013 (160) Retrospective, national database	Mastectomy with immediate reconstruction, no NAC reconstruction, no death within 30 days of surgery; USA	NR	Prosthetic Autologous Hybrid	7333 1475 320	Surgical site infection within 30 days of surgery: 3.33% vs. 4.88% vs. 2.19% (p=0.005). Autologous vs. prosthetic unadjusted OR, 1.49 (95% CI, 1.13 to 1.95; p<0.004), adjusted OR, 1.14 (95% CI, 0.83 to 1.58; p=0.42). Hybrid vs. prosthetic unadjusted OR, 0.65 (95% CI, 0.30 to 1.39; p=0.264), adjusted OR, 0.59 (95% CI, 0.27 to 1.27; p=0.18)	--

Author, publication year; study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Davila 2013 (161) Retrospective, national database	Immediate tissue expander or implant reconstruction after mastectomy, no concomitant flap reconstruction, no simultaneous expander and implant; USA	NR	One-stage direct to implant Tissue expander	1528 9033	30-day morbidity: 6.8% vs. 5.4% (p=0.02) Reconstruction-related complications: 5.5% vs. 4.4% (p=0.05) Prosthesis failure: 1.4% vs. 0.8% (p=0.04) Wound disruption: 0.8% vs. 0.4% (p=0.08) No significant difference in surgical site infections, reoperation rates (7.5% vs. 6.9%), or major medical complications	--

Author, publication year; study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Fischer 2013 (162) Retrospective, single centre	Expander/implant or free flap reconstructions, senior surgeon's patients, no postoperative RT, <65 yrs, BMI 25-35 kg/m^2; USA	Minimum 4 yrs	Expander/ implants Free flaps	60 142	Hematoma: 6.7% vs. 2.8% (p=0.24) Seroma: 15.0% vs. 5.6% (p=0.03) Cellulitis: 10% vs. 2.8% (p=0.07) Delayed wound healing: 36.6% vs. 15% (p=0.003) Failure: 7.3% vs. 1.3% (p=0.008) Major complications: 13.3% vs. 7.0% (p=0.15) Minor complications: 43.3% vs. 46.5% (p=0.68) Free flap complications: flap loss (1.3%), fat necrosis (9.9%), hernia/bulge (2.8%) Expander/implant complications: capsular contracture requiring revision (18.3%), implant exposure (6.7%), implant infection (8%)	Rate of revision: 38.3% vs. 49.3% (p=0.17) Contralateral balancing procedure: 33.3% vs. 18.3% (p=0.021)

Author, publication year; study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Gart 2013[a] (17) Retrospective, national database	Autologous tissue-based reconstruction, no mixed reconstruction types; USA	30-day follow-up	Free flap LD flap pTRAM	609 1079 1608	Overall 30-day complications: 19.4% vs. 7.1% vs. 13.4% (p<0.001). Flap complications 12.0% vs. 5.0% vs. 10.0% (p<0.001). Nonflap complications 11.3% vs. 3.2% vs. 5.7% (p<0.001). Wound infection: 5.9% vs. 3.3% vs. 6.7% (p=0.001) Graft/flap failure (30-day): 5.7% vs. 1.3% vs. 3.4% (p<0.001) Wound disruption: 2.0% vs. 0.6% vs. 1.4% (p=0.052) Pulmonary embolism: 0.2% vs. 0.1% vs. 0.9% (p=0.005). DVT 0.3% vs. 0.2% vs. 1.0 (p=0.019) Blood transfusion: 7.7% vs. 1.6% vs. 1.9% (p<0.001)	Reoperation: 15.6% vs. 5.7% vs. 9.9% (p<0.001)
Mioton 2013[b] (163) Retrospective, national database	Autologous tissue-based or prosthetic reconstruction, no mixed reconstruction types, 25.9% delayed reconstruction; USA	30-day follow-up	Prosthetic Autologous	9786 3296	Overall 30-day complications: 5.38% vs. 12.47% (p<0.001) Surgical complications: 4.39% vs. 8.71% (p<0.001) Medical complications: 1.55% vs. 5.92% (p<0.001) Wound infection: 3.45% vs. 5.46% (p<0.001) Prosthesis/flap failure: 0.85% vs. 3.13% (p<0.001) Wound disruption: 0.44% vs. 1.24% (p<0.001)	Reoperation: 6.76% vs. 9.59% (p<0.001)

Author, publication year; study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Pestana 2013 (114) Retrospective	Mastectomy and breast reconstruction for breast cancer, pre- or post-operative RT; USA	Mean 6 yrs	Implant Autologous + implant Autologous	88[c] 38[c] 28[c]	Reconstruction failure (estimated): 33% (implant) vs. 11% (autologous)[d]	--
Winters 2013 (164) Prospective cohort, multi-centre	Stage 0-II breast cancer, immediate reconstruction; UK	NR	LD/implant LD alone	82 100	Early complications (up to 3 months): 66% vs. 51% (p=0.062) Any severe early complication: 46% vs. 29% Infection: 15% vs. 8% Fat necrosis: 13% vs. 16% Skin necrosis: 43% vs. 22% Long-term complications (4 to 12 months): 48% vs. 45% (p=0.845) Any severe long-term complication: 49% vs. 31% Capsular contracture: 15% vs. 0%	Reoperation: 61% vs. 65% (p=0.685)

Abbreviations: BMI: body mass index; CI: confidence interval; DIEA: deep inferior epigastric artery; DIEP: deep inferior epigastric perforator flap; LD: latissimus dorsi; msfTRAM: muscle-sparing free TRAM; N/A: not applicable; NAC: nipple-areolar complex; NR: not reported; OR: odds ratio; pTRAM: pedicled TRAM; QoL: quality of life; RR: relative risk; RT: radiotherapy; S-GAP: superior gluteal artery perforator flap; TRAM: transverse rectus abdominis myocutaneous; vs.: versus; yrs: years

Notes:

[a] Same pts as Mioton 2013

[b] Autologous pts same as Gart 2013

[c] Estimated from reported data

[d] Unclear from article

Clinical Question 5: Acellular dermal matrix

Systematic reviews

Eight systematic reviews of observational studies have assessed the benefits and harms associated with the use of ADM with TE/I-based breast reconstruction (23-25, 80-84). One of the reviews (Clemens et al.) focused exclusively on the use of ADM in the setting of RT (23). Ten clinical studies plus the authors' own experience yielded 276 patients who received radiation and ADM. Although only a minority of patients included in these studies received radiation, subgroup analyses suggest that there is a higher incidence of complications in patients who receive ADM in the setting of radiation compared with patients who do not receive radiation.

A systematic review and meta-analysis by Hoppe et al. published in 2011 assessed complications in seven studies comparing expander/implant reconstruction with vs. without ADM (24). The meta-analysis indicated a higher infection rate in patients who received ADM (OR, 2.33; 95% CI, 1.55 to 3.49; p<0.0001), higher rate of seroma (OR, 3.00; 95% CI, 1.96 to 4.61; p<0.00001) and a higher rate of explantation (OR, 2.41; 95% CI, 1.59 to 3.64; p<0.0001). A second systematic review and meta-analysis published in 2012 by Kim et al. included six of the seven comparative studies included in the Hoppe review and reported similar results (25). The rate of total complications was higher in the ADM group than the submuscular group (RR, 2.05; 95% CI, 1.55 to 2.70), as was the rate of seroma (RR, 2.73; 95% CI, 1.67 to 4.46), infection (RR, 2.47; 95% CI, 1.71 to 3.57) and reconstructive failure (RR, 2.80; 95% CI, 1.76 to 4.45). The risk of hematoma (RR, 2.06; 95% CI, 0.86 to 4.95) and flap necrosis (RR, 1.56; 95% CI, 0.85 to 2.85) was not significantly increased in patients with ADM compared with patients with submuscular reconstruction. Pooled complication rates from 19 studies of human ADM were the following: total complications 15.4%, seroma 4.8%, hematoma 1.0%, infection 5.3%, flap necrosis 6.9%, and reconstructive failure 3.8%. Four additional systematic reviews addressed complications associated with ADM in implant-based reconstruction but are not discussed further (80, 81, 83, 84).

A systematic review by Nguyen et al. published in 2011 evaluated the evidence to support the perceived advantages of ADM (82). The authors reported that the following perceived advantages were based only on anecdotal reports and opinions: reduction in post-operative pain, decreased operative time, precise control of the lateral and inframammary fold, maximal use of mastectomy skin flaps, and improved lower pole expansion. Data were inconsistent for perceived advantages including eliminating the need for expanders, increased initial fill volumes, fewer expansions, faster time to reconstruction completion, decreased rate of revision, and improved esthetic outcome. There was consistent evidence to support decreased incidence of capsular contracture but the studies had limited long-term follow-up.

Primary studies

Thirty additional primary studies addressing ADM in breast reconstruction were identified. Seventeen were retrospective studies of less than 100 patients, noncomparative retrospective studies, or studies that compared ADM vs. a different type of ADM and are not discussed further. The remaining 13 studies are reported in Table 4-7. One was an RCT (26), two were small prospective cohorts (165, 166) and 10 were retrospective studies with more than 100 patients that compared implant-based breast reconstruction with vs. without ADM (27, 167-175).

The multicentre, blinded RCT by McCarthy et al. represents the best attempt to date to examine the benefits and harms of ADM while controlling for confounding factors (26). Sixty-nine patients were randomized intraoperatively to receive ADM or a standard submuscular approach. Accrual to the trial was stopped early after an unplanned interim analysis indicated a low probability of a positive result; however, all patients continued to be followed for the

full 12 months. Outcomes reported to date include patient-reported pain, rate of tissue expansion, and adverse events. Total complications were not significantly different between groups (17% vs. 15%; p=1.00). No significant difference in pain visual analogue score was detected between groups in the immediate postoperative period, in the expansion phase or before the exchange procedure. Similarly, the difference between groups for physical well-being, immediate 24-hour postoperative narcotic use, and intraoperative fill volume was not significant. Outcomes including cosmesis, rate of capsular contracture, patient satisfaction, and quality of life have not yet been reported.

Of the 10 retrospective studies, two reported esthetic outcomes (27, 171). One reported higher esthetic outcome overall and higher inframammary fold esthetics in the ADM group (27) and the other reported significantly higher esthetic scores in the ADM group for volume, placement, and inframammary fold but no significant difference between groups for contour or scarring (171). Results for complications were not consistent between studies, due in part to differences in study populations, methods for measuring complications, and length of follow-up. Of the six studies that reported overall complication rates, one reported that there were significantly more complications in the ADM group (168), one reported more complications in patients without ADM (27), and four reported no significant difference between the ADM and no ADM groups (167, 169, 170, 174). Infections were not significantly different between groups in four studies (27, 167, 169, 174), were higher in the ADM group in two studies (168, 175), and lower in the ADM groups in one study (173). There was a significantly higher rate of seroma in the ADM group in one study (172) and no significant differences between groups in four studies (27, 173-175). Explantation or prosthesis failure was higher in the ADM group in one study (175), lower in another study (173), and no significant difference between groups was detected in three studies (169, 172, 174). The two prospective nonrandomized studies reported low complication rates for patients receiving ADM (165, 166). The prospective series by Wu et al. demonstrated significant ADM stretching at three months compared with baseline (p=0.002) and no significant difference in patient satisfaction or physical and social well-being between ADM and a non-ADM cohort (166).

Table 4-7. Acellular dermal matrix primary studies.

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
McCarthy 2012 (26) Randomized controlled trial, blinded, multicentre	Immediate, postmastectomy two-stage tissue expander/implant reconstruction	Mean/median NR Follow-up continuing	ADM (AlloDerm) No ADM	36 33	Total complications: 17% vs. 15% (p=1.00) Hematoma: 1 vs. 1 Seroma: 1 vs. 3 Infection: 3 vs. 1 Premature removal of device: 1 vs. 0	Pain: No difference in VAS for immediate postoperative pain (p=0.19), average pain in expansion phase (p=0.65), or pain before exchange procedure (p=0.93) Physical well-being (BREAST-Q): No difference in immediate postoperative period (p=0.52), during expansion phase (p=0.77), or before exchange procedure (p=0.82) Immediate 24-hour postoperative narcotic use: No difference (p=0.38) Intraoperative fill volume: No difference (p=0.86) Mean # of percutaneous injections: 6.4 (ADM) vs. 7.3 (no ADM) (p=0.04)
Vardanian, 2011 (27) Retrospective, single centre, consecutive cohorts	Implant-based immediate reconstruction, autologous flap with implant excluded, 90% of reconstructions for breast cancer (10% prophylactic, silicone mastitis, congenital asymmetry), USA	Mean 29 months after implant exchange	ADM (AlloDerm) No ADM	208 129	All complications: 29.3% vs. 40.3% (OR, 0.61; 95% CI, 0.38 to 0.97) Less capsular contracture, problems with inframammary fold, bottoming out, rippling and mechanical shift in ADM group (p<0.05). Seroma/hematoma, infection, overall wound problems, wound dehiscence and skin thinning not significantly different between ADM and no ADM.	Esthetic outcome: Overall higher in ADM group (p<0.05). Inframammary fold esthetics higher in ADM group (p<0.05).

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Brooke, 2012 (167) Retrospective, single centre	Primary cancer-related tissue expander and implant reconstruction, USA	Mean NR. Pts with inadequate data or lost to follow-up were excluded.	ADM (AlloDerm, DermaMatrix or FlexHD) No ADM	131 42	Overall clinically significant complications: 17% vs. 11% (p=0.48) Infections: 10% vs. 2% (p=0.09 after adjusting for RT exposure and smoking)	--
Collis, 2012 (168) Retrospective, single centre	Immediate postmastectomy reconstruction with tissue expanders and permanent implant, USA	NR	ADM (AlloDerm or FlexHD) No ADM	63 42	Total complications (per breast): 18.9% vs. 7.4% (p<0.05) Tissue expander/graft infection requiring removal: 5.7% vs. 4.4% (p<0.05) Epidermolysis: 13.2% vs. 1.5% (p<0.01)	--
Endress, 2012 (170) Retrospective, single centre	Immediate 2-stage reconstruction, USA?	NR	ADM (fetal bovine Surgimend) No ADM	28 91	Overall complications (per breast): 20.8% vs. 13.0% (p=0.241). Data for specific complications also reported	--
Nguyen, 2012 (171) Retrospective, single centre	Expander implant reconstructions, photographically documented postexchange follow-up of at least 90 days, USA	Minimum 90 days after exchange. Mean NR.	ADM No ADM	62 53	Reoperation due to complications: 32.3% vs. 30.2% (p=0.8426)	Significantly higher esthetic scores in ADM group for volume, placement, and inframammary fold. No significant difference between groups for contour or scarring.
Parks, 2012 (172) Retrospective, consecutive cohorts	Breast reconstruction, private practice setting, USA	NR	ADM (AlloDerm) No ADM	232 114	Seroma formation (per pt): 34.0% vs. 20.2% (p<0.001) Skin necrosis (per pt): 13.8% vs. 14.9% (p=0.35) Loss of tissue expander (per pt): 14.7% vs. 9.7% (p=0.88)	--

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Peled, 2012 (173) Prospective review, consecutive cohorts	Total skin-sparing mastectomy, immediate expander/implant, USA	Mean 25.5 months	ADM Selective ADM (based on mastectomy skin flap thickness) No ADM	65 160 63	Infection (per breast): 20% vs.15.8% vs. 27.8% (p=0.04) Unplanned return to OR: 11% vs. 10% vs. 23.3% (p=0.004) Skin flap necrosis: 6% vs. 6.2% vs. 11.1% (p=0.26) Expander/implant loss: 7% vs. 5% vs 17.8% (p=0.001) Seroma: 4% vs. 5.8% vs. 4.4% (p=0.75) Hematoma: 3% vs. 2.7% vs. 3.3% (p=0.95) Nipple necrosis: 1% vs. 1.2% vs. 0% (p=0.82)	--
Seth, 2012 (174) Retrospective, single centre	Mastectomy with immediate tissue expander reconstruction, permanent 2nd stage implant, USA	Mean follow-up 23.2 months (ADM) and 24.4 months (no ADM)	ADM (AlloDerm or FlexHD) No ADM	137 280	Total complications (per breast): 18.1% vs. 14.3% (p=0.19) No significant difference between groups for hematoma, extrusion, infection, seroma, pain/tightness, major flap necrosis, nonoperative or operative complications, or explantation or conversion to flap	--

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Weichman, 2012 (175) Retrospective, single centre	Immediate 2-stage implant-based reconstruction after mastectomy using pectoralis muscle for coverage, USA	NR	ADM (AlloDerm) No ADM	442 189	Mastectomy flap necrosis (per breast): 8.3% vs. 3.2% (p=0.005). Major necrosis: 6.7% vs. 2.7% (p=0.015). Mastectomy flap necrosis with infection: 1.8% vs. 2.1% (p=0.756) Infection: 13.6% vs. 7.5% (p=0.017). Major infection: 8.6% vs. 2.7% (p=0.001). Seroma: 1.8% vs 3.2% (p=0.326) Hematoma: 0.5% vs. 1.1% (p=0.586) Explantation: 7.7% vs. 2.7% (p=0.004)	--
Davila, 2013 (169) Retrospective, national surgical database	Immediate tissue expander reconstruction following mastectomy, USA		ADM No ADM	1717 7442	Total complications: 5.6% vs. 5.3% (p=0.57) No significant difference in operative infection, wound disruption, prosthesis failure, major medical complications, or reoperation within 30 days	--
Venturi 2013 (165) Multicentre prospective cohort, consecutive patients	Immediate expander-based reconstruction, unilateral or bilateral	Mean 12 months (range 9 to 18 months)	ADM (AlloMax, sterile)	39 (65 breast reconstructions)	Early postoperative complications: 3 breasts in 2 patients (1 bilateral mastectomy flap necrosis, 1 unilateral cellulitis)	Average intraoperative fill volume: 50.9% of expander volume

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants	Complications	Other outcomes
Wu 2013 (166) Prospective consecutive case series with comparative cohort from same time period	Postmastectomy prosthetic breast reconstruction	Mean 96 days (ADM group)	ADM (AlloDerm) No ADM	31 45	Postsurgical complications: 10% vs. 13%. 1 late seroma, 1 delayed erythema, 1 urinary tract infection in ADM group. In no-ADM group: 2 cellulitis, 2 expander replacement, 1 delayed wound healing, 1 skin necrosis	ADM stretching at 3 months: mean perimeter increase 11% (p=0.002 vs. baseline) and surface area increase 21% (p=0.002 vs. baseline). Surface area changes range 4% to 35% across patients. Patient satisfaction with breasts, implants, and surgery outcome (BREAST-Q survey): not significantly different between groups Physical and psychosocial well-being (BREAST-Q survey): not significantly different between groups

Abbreviations: ADM: acellular dermal matrix; CI: confidence interval; NR: not reported; OR: odds ratio; OR: operating room; pts: patients; RT: Radiotherapy; VAS: visual analogue scale; vs.: versus.

Clinical Question 6: Autologous fat grafting

Systematic reviews

Three systematic reviews were identified that addressed the safety and oncological outcomes of autologous fat grafting: Krastev 2013 (28), Claro Jr. 2012 (85) and Saint-Cyr 2012 (29). The most recent review by Krastev et al. examined the rate of locoregional and distant recurrence for fat grafting in breast reconstruction after mastectomy or breast-conserving treatment for breast cancer (28). Of the 20 clinical studies identified in the review, only four studies (one retrospective cohort and four case series) were suitable for analysis after excluding studies with overlapping patient populations. Two studies reported a locoregional recurrence rate of 1.35% and 0.72% in women who underwent mastectomy and fat grafting with a mean follow-up of 1.60 and 5.23 years, respectively. The other two case series were smaller and reported no locoregional recurrence during follow-up. Another retrospective cohort study by Petit et al., whose population overlapped significantly with one of the studies above, compared locoregional recurrence in 321 breast cancer patients who underwent fat grafting with 642 matched patients without fat grafting and reported no significant difference in the recurrence rate between groups (1.15% vs. 1.36%). The review authors concluded that the available evidence was inconclusive but promising, with larger prospective studies with longer follow-up being required to determine the oncological safety of fat grafting.

Another systematic review by Saint-Cyr et al. of fat grafting in the reconstructive and esthetic setting reported on clinical outcomes, cosmesis, patient satisfaction, and complications (29). Nineteen studies were included in the review, of which 14 included patients receiving fat grafting as an adjunct to breast reconstruction. Satisfaction of patients and the surgical team with the results of fat grafting varied among studies; however, the majority of studies reported satisfactory or better results. Four studies reported the occurrence of postoperative infections, all of which could be managed with antibiotics. Other complications included a siliconoma, two pneumothoraces, and a sternal fibrous breast tissue. The authors concluded that while autologous fat grafting appeared to be a safe option, further studies were required to confirm that it is an effective and safe practice.

A third systematic review by Claro Jr. et al. included 60 articles, of which 41 addressed fat grafting for partial or total breast reconstruction (85). Complication rates were reported to be low, although results were not reported separately for studies of patients who underwent breast reconstruction.

Primary studies

Ten additional primary studies of fat grafting in the context of breast reconstruction following mastectomy were identified. Six of the 10 studies were noncomparative retrospective studies and are not discussed further. The remaining four studies were prospective cohorts of patients undergoing fat grafting (176) or single-centre retrospective comparisons of fat grafting vs. no fat grafting (30, 177, 178) and are reported in Table 4-8.

Seth et al. compared 69 patients who underwent tissue expander reconstruction with fat grafting vs. 817 patients who underwent tissue expander reconstruction alone (177). In 99 fat grafting procedures in 90 breasts, only one postoperative complication associated with fat grafting was reported (local fat necrosis). Local recurrence (1.5% vs. 0%; p=0.63) and survival (95.5% vs. 100%; p=0.10) were not significantly different between the no fat grafting and fat grafting groups.

A retrospective matched cohort study by Petit et al. (30) investigated local recurrence in patients with intraepithelial neoplasia. In an exploratory subgroup analysis of patients who underwent mastectomy with vs. without fat grafting, five-year local recurrence was 18.4% in patients with fat grafting vs. 3.6% in patients without fat grafting (log-rank p=0.11). Another retrospective study comparing free flap reconstruction with fat grafting to free flap

reconstruction alone reported a postoperative complication of fat grafting in one of 100 breasts: a major infection at the recipient site requiring hospitalization and intravenous antibiotics (178). Choi et al. (176) used three-dimensional imaging to assess volumetric fat graft survival in a prospective cohort of patients receiving autologous fat grafting to the breast. Some women underwent lumpectomy or partial mastectomy and not mastectomy. Results indicated that patients receiving higher volumes of fat grafting had slower volume loss and greater total volume retention. The group with the largest injected volume had 52.3% volume retention at 140 days while the smallest group had 27.1% retention.

Table 4-8. Autologous fat grafting primary studies.

Author, publication year, study design	Study population	Follow-up	Procedure	# of participants (patients without mastectomy excluded)	Complications	Other outcome
Petit, 2012 (185) Retrospective, single centre, matched cohort	No synchronous distant metastases at diagnosis, bilateral or recurrent tumour, previous breast cancer, or neoadjuvant therapy; Italy	Median from primary surgery: 56 months	Mastectomy, reconstruction and fat grafting Mastectomy, reconstruction	196 392	NR	Local or locoregional recurrence: HR, 1.92 (95% CI, 0.68 to 5.43), Gray test p=0.211
Seth, 2012 (177) Retrospective, single centre	Mastectomy, immediate tissue expander reconstruction; USA	Mean from tissue expander insertion: 44 months FG, 42 months control. Mean 25 months from fat grafting in FG group.	Mastectomy, tissue expander reconstruction and fat grafting (Coleman) Mastectomy, tissue expander reconstruction	69 817	1 postoperative complication associated with fat grafting (local fat necrosis at site of injection, managed conservatively)	Local recurrence: 0% vs. 1.5% (p=0.63) Survival: 100% vs. 95.5% (p=0.10)
Petit, 2013 (30) Retrospective, single centre, matched cohort	Intraepithelial neoplasia; no synchronous distant metastases at diagnsosis, bilateral or recurrent tumour, or previous breast cancer; Italy	Median from oncologic surgery: 63 months FG, 66 months control	Mastectomy, reconstruction and fat grafting Mastectomy, reconstruction	47 94	NR	5-year local or locoregional recurrence: 18.4% FG vs. 3.6% control, log-rank p=0.11
Weichman, 2013 (178) Retrospective, single centre	Autologous reconstruction, microvascular free flaps; minimum 1 year follow-up; USA	Mean 18 months, range 12 to 41 months	Mastectomy, free flap reconstruction and fat grafting (modified Colemans) Mastectomy, free flap reconstruction	100 (breasts) 274 (breasts)	1 major infection at the recipient site requiring hospital admission and intravenous antibiotics	-

Abbreviations: CI: confidence interval; FG: fat grafting group; HR: hazard ratio; NR: not reported; vs.: versus.

Clinical Question 7: Routine screening for recurrence

A systematic review of surveillance mammography following breast reconstruction published by Barnsley et al. captured studies published between 1980 and 2004 (31). Eight retrospective reviews, case series, or case reports were included, four of which included fewer than 10 patients. Only one of the eight articles described the mammography regimen, which consisted of semiannual mammography. Significant heterogeneity did not allow for meta-analysis and survival was not addressed. Local recurrences were detected by surveillance mammography or other methods in only two studies. In the largest series of 113 women with TRAM reconstruction, two of three local recurrences were detected by surveillance mammography. The positive predictive value, sensitivity, and specificity were calculated to be 33%, 67%, and 98%, respectively. In another descriptive study of four patients with local recurrence, one case was detected by surveillance mammography. The review authors concluded that there was a lack of evidence to guide clinicians in the use of routine surveillance mammography following treatment of breast cancer with breast reconstruction and further research was required.

Three additional primary studies were identified that addressed detection of recurrence following breast reconstruction; two were identified in the systematic literature search and one from reviewing reference lists (see Table 9). A retrospective database review by Sim et al. compared women who underwent routine surveillance mammography with women who underwent radiological investigation for symptoms in the reconstructed breast and surveillance mammography of the contralateral breast only (32). In the 116 patients who underwent routine surveillance mammograms, one asymptomatic recurrence was identified by surveillance mammography three years after breast reconstruction. One additional patient was diagnosed with a second nonpalpable primary cancer in the contralateral breast. Four patients with symptoms in the reconstructed breast were found to have recurrent cancer. This study demonstrated a 0.86% detection rate of nonpalpable recurrent breast cancer and a 4% recall rate, with the most common diagnosis being fat necrosis. Patterson et al. reported a retrospective study of 390 women with TRAM reconstructions who did not undergo routine surveillance imaging (179). The locoregional recurrence rate was 4.6%; all were detected first by physical examination rather than by imaging. This rate is comparable with rates observed in women who undergo mastectomy without reconstruction. The average time for locoregional recurrence to present after mastectomy and reconstruction was 35.8 months and 22.9 months, respectively, for stage III patients. The 2008 study by Lee et al. retrospectively identified 264 TRAM patients that had completed 554 mammograms in a six-year period (180). Eight recall events occurred, all of which were found to be benign after pathological examination. The recall rate was 1.4% and the detection rate of nonpalpable breast cancer recurrence was 0%.

Table 4-9. Routine screening for recurrence primary studies.

Author, publication year, study design	Study population	Follow-up	Surveillance method	# of participants	Recurrence	Other outcomes
Sim 2012 (32) Retrospective, national database	Reconstructive breast surgery for breast cancer, radiological imaging	Effective follow-up period range 1 to 13 years (median and mode 6)	Mammography of reconstructed breast as routine surveillance Radiological investigation for symptoms in reconstructed breast. Surveillance mammography of contralateral breasts only.	116 111	Surveillance mammography group: 1 asymptomatic recurrent invasive breast carcinoma 3 years after reconstruction (detection rate of nonpalpable cancer 0.86%). Symptomatic reconstructed breast (54 patients): 4 recurrent cancers	Surveillance results: 75% normal, 21% benign findings, 4% indeterminate or suspicious findings
Patterson 2012 (179) Retrospective, 2 centres	Immediate TRAM reconstruction for breast cancer or DCIS, USA	Median follow-up 69.2 months (range 24.1 to 134.4 months)	No routine surveillance imaging	390	18 patients had palpable locoregional recurrence (4.6%). 8 superficial recurrences, 1 deep to the TRAM reconstruction, 5 regional in axilla, 4 in supraclavicular lymph node. No LRR was diagnosed first by imaging.	5-yearr LRR-free rate: 92.4% (95% CI, 87.1 to 95.5). Average time for LRR to present after mastectomy & reconstruction: 35.8 months. Stage III patients: 22.9 months.
Lee 2008 (180) Retrospective, single centre	Mastectomy for primary breast cancer, TRAM reconstruction (immediate or delayed), USA	Median follow-up after mastectomy 4.9 years (range 0.2-22.0 years)	Surveillance mammography	264	No local recurrences. Three patients had distant recurrence.	Rate of detection of nonpalpable recurrent cancer: 0% (95% CI, 0% to 1.4%). 1.4% (8 patients) had false-positive screening mammography results.

Abbreviations: CI: confidence interval; DCIS: ductal carcinoma in situ; LRR: local-regional recurrence; TRAM: transverse rectus abdominis myocutaneous.

DISCUSSION

Candidates for postmastectomy breast reconstruction

a) Patient factors

Older age

Since the incidence of breast cancer increases with advanced age, it is important to re-evaluate the appropriateness of IBR in the older patient population. There has been one systematic review on this topic that summarized six studies. It concluded that breast reconstruction is safe and feasible, and provides significant improvements in the health-related QOL of older patients (4). Contrary to the previously held belief that older patients may not tolerate longer and more complex autologous tissue reconstruction methods, other authors have found that the use of autologous tissue provided more symmetrical results, fewer complications, and less pain compared with implant-based methods in three studies (3, 186, 187).

Obesity

Results from the largest study of this topic that examined 15,937 patients in the National Surgical Quality Improvement Program (NSQIP) from 2005 to 2010 who underwent breast reconstruction in the United States showed that morbidly obese (BMI >40 kg/m^2) patients had significantly increased early postoperative complications in terms of major surgical complications, medical complications, wound healing problems, and an additional return to the operating room compared with both nonobese patients and mildly obese patients (BMI between 30 kg/m^2 and 39.9 kg/m^2) (1). In addition, the same group also found that progressively higher BMI was associated with significantly higher incidence of all complications captured by the NSQIP database, including major surgical complications, medical complications, wounds, return to the operating room, infections, and reconstructive failures (2).

Active smokers

Smoking is seen as a relative contraindication to breast reconstruction as outlined by the National Comprehensive Cancer Network (NCCN) guidelines (Version 3.2014). In a prospective single-centre study (3) that examined 558 patients who underwent microsurgical breast reconstruction techniques using abdominal flaps, the authors found that patients who were active smokers (17%) had significantly higher rates of both flap and donor complications compared with nonsmokers. The NSQIP database also corroborated these findings, and found that minor surgical complications were significantly increased in active smokers who underwent microsurgical flap reconstruction (OR, 1.87; p=0.03) (99).

Evidence on the effect of active smoking on the outcome of implant-based reconstruction is limited to single-centre retrospective studies with small numbers of patients. This is likely due to the provider bias to avoid implant reconstruction in active smokers (86, 93, 188, 189).

b) Cancer factors

Current national and provincial guidelines published by the NCCN in the United States, National Institute for Health and Care Excellent (NICE) in the United Kingdom, Alberta Health Services, and Saskatchewan Cancer Agency *broadly* endorse the use of breast reconstruction as part of the clinical pathway for women with in situ and invasive breast cancer.

The Alberta Health Services Clinical Practice Guidelines endorses the use of IBR for ductal carcinoma in situ (DCIS), T1 and T2 tumours, and multicentric tumours, while it does not endorse the use of IBR for T3 and T4 tumours, inflammatory breast cancer, or where axillary lymph nodes are involved with breast cancer (66). The use of DBR, however, is acceptable in all patients after surgical resection and adjuvant treatments are completed.

A recent systematic review (190) on SSM and IBR listed the following as the generally accepted indications for consideration of SSM and IBR:

1. Multicentric disease
2. In situ disease or diffuse microcalcification
3. Large tumour size to breast volume ratio, which may preclude the use of breast conservation surgery
4. Absence of lymphovascular invasive disease
5. Failed initial conservation surgery necessitating mastectomy
6. Recurrence of breast cancer in a previously conserved breast
7. Radiotherapy is not possible such as in a previously irradiated breast or chest (Hodgkin disease), patient with collagen vascular disease, or with Tp53 mutation.

c) Treatment factors

Chemotherapy

Neoadjuvant chemotherapy: SSM with IBR is safe in the setting of neoadjuvant chemotherapy and does not appear to lead to increased surgical complications as evidenced by several retrospective studies. Hu et al. found comparable overall rates of postoperative complications in a group of 180 patients who received neoadjuvant chemotherapy (30%) compared with 485 patients who did not (31%) following SSM and IBR (p=0.85) (89). In another large single-centre retrospective study of 1037 patients who received IBR, the use of neoadjuvant chemotherapy was not significantly associated with increased postoperative complications (OR, 0.93, p=0.86) (86).

Adjuvant chemotherapy: The concern that the use of IBR in patients with active breast cancer may lead to increased surgical complications and compromise the timely delivery of adjuvant chemotherapy is not supported by the evidence. While a large multicentre cohort study showed a statistically significant delay in median time to chemotherapy following IBR (six weeks) compared with mastectomy alone (five weeks), this was deemed not clinically important (110).

Radiotherapy

Prior radiotherapy: Pre-reconstruction radiotherapy is usually in patients who have undergone previous breast-conserving therapy (BCT) and have developed recurrent disease. A systematic review compared pre and post radiotherapy in implant-based reconstructive patients (72). Investigators identified 26 relevant studies involving over 1500 patients. They were unable to directly compare radiation pre- and post-breast implant reconstruction, because most of the studies were case series and not comparative in nature, there was significant heterogeneity among the studies with respect to patient characteristics, and outcomes of interest were not reported in a consistent fashion. Nevertheless, they did report considerable complications for pre- and postreconstructive radiation: major complications 49% (95% CI, 25% to 72%) and 39% (95% CI, 24% to 55%), respectively; severe contractures 37% (95% CI, 20% to 55%) and 25% (95% CI, 10% to 45%), respectively; and reconstructive failure 19% (95% CI, 10% to 29%) and 20% (95% CI, 15% to 25%), respectively. Other studies suggest that these rates are considerably higher than for patients who undergo implant reconstruction in the absence of any radiotherapy (72). In the largest retrospective series that examined 1037 patients, the authors found that prior radiotherapy significantly increased major complication rates from 21.2% to 45.4% in the TE/I group, while this relationship did not exist for the autologous tissue group (86). In addition, 10.3% of the failed TE/I group went on to receive autologous tissue reconstruction. In another larger retrospective series that examined 532 patients who underwent both implant and autologous tissue reconstruction, prior BCT (in 113 patients) was not significantly associated with higher complications rates (OR, 1.09; p=0.69), or lower

satisfaction on a validated instrument. However, prior radiation was correlated with a significantly higher rate of mastectomy flap necrosis (12.4% vs. 6.8%, p=0.024) (91).

Timing of breast reconstruction

a) Patients not expected to require postoperative radiotherapy

We recommend IBR with SSM as a first-line surgical treatment option to be discussed with all patients diagnosed with breast cancer who will likely not receive postmastectomy radiation. For patients interested in PMBR, IBR appears to be superior to DBR in psychological and QOL outcomes, and equivalent to standard mastectomy (alone) in terms of oncologic outcomes. Based on a randomized trial of immediate vs. delayed reconstruction and a cross-sectional survey study that included 190 breast cancer patients who underwent mastectomy alone, IBR, and DBR, women who had IBR had lower levels of body stigma, body concerns, and psychological disturbance compared with the DBR group (6, 73); however, these results should be interpreted cautiously due to the high risk of bias in these two studies. The RCT was limited in its small sample of women undergoing IBR and lack of psychosocial functioning scores prior to mastectomy in the DBR group.

The oncologic safety of IBR has also been supported by several large-scale studies that employed different study methodologies. A prospective cohort of 677 patients with T1-T3 tumours who underwent either mastectomy alone or mastectomy with IBR without postmastectomy radiation were found at a median of 70 months follow-up to have 5.2% local recurrence rate in the IBR groups compared with 9.4% in the mastectomy alone group (7). There were no differences in regional and distant metastasis rates, disease-free survival, or overall survival rates in the two groups. A recent meta-analysis also confirmed that there was no difference in terms of the risk of local recurrence between patients who had IBR compared with mastectomy alone (8).

b) Patients who are expected to require postoperative radiotherapy

Most guidelines that address the timing of breast reconstruction in the setting of anticipated postmastectomy radiotherapy (PMRT) have recommended that breast reconstruction be delayed for a period of at least several months after the delivery of PMRT has been completed (191-193). The NCCN guidelines have recognized the importance of making separate recommendations about autologous tissue and implant-based reconstructions in the setting of PMRT. The NCCN guidelines (v3.2014) state that when PMRT is anticipated, immediate reconstruction with implants are preferred to avoid tissue expansion of radiated skin flaps (194). The Alberta Health Services clinical practice guidelines stated that there was insufficient evidence to make a recommendation for or against the use of IBR in the setting of anticipated PMRT (195). While most of the existing guidelines on this topic were based on studies that were published prior to 2012, our current review yielded additional systematic reviews that were published between 2012 and 2014 that examined PMRT with implant-based IBR or autologous tissue reconstruction (9, 10, 72, 94, 196). Importantly, our current recommendations were informed by the more current studies that employed the newer and more advanced radiation techniques as well as a greater number of studies than previously available. It should be noted that the studies included in the systematic reviews consisted mainly of observational, retrospective studies which are prone to selection bias. In the autologous IBR setting, the available literature indicates that while reoperation rates are not significantly different with or without PMRT, fat necrosis was significantly different and esthetic outcome was decreased in more than one-half of the studies (9). In an implant-based setting, there was a higher rate of reconstruction failure and risk of morbidity associated with PMRT (10, 86).

The decision-making process between immediate vs. delayed breast reconstruction for the patient requiring adjuvant therapy is highly complex, and must take into consideration both the oncologic and reconstructive outcomes. We now know that from an oncologic perspective, the performance of IBR does not lead to a clinically meaningful delay in adjuvant chemotherapy (110, 139). The literature has also shown that reconstructed breasts do not impair the ability to radiate the chest wall effectively, even when the internal mammary lymph nodes are in the radiated field (159). Thus, the major argument against the use of IBR is no longer only about the oncologic safety of this practice; rather it rests on a detailed examination of the possible detrimental effects of radiation on the reconstructive outcomes. Patients should be made aware of these potential complications so that they can make fully informed decisions.

Skin-sparing and nipple-sparing mastectomy

All studies evaluating the safety and efficacy of SSM in the systematic review were retrospective and therefore subject to selection bias. Median follow-up time was highly variable among studies; therefore, recurrence rates are challenging to interpret. Within the retrospective studies, there is significant heterogeneity among patients; therefore, interpretation and generalizability is limited. Although the evidence is low when comparing SSM with standard mastectomy, recurrence rates for SSM across clinical trials appear to be reasonably low in the prophylactic, DCIS, and early breast cancer patient cohorts (12).

Similarly, all studies included in the systematic review evaluating NSM were retrospective and, therefore, subject to selection bias. Median follow-up time among studies was highly variable; therefore, recurrence rates are challenging to interpret and subject to significant patient and tumour heterogeneity. Although the evidence is low when comparing NSM with standard mastectomy, recurrence rates for NSM across studies appear to be reasonably low in prophylactic, DCIS, and early breast cancer patients (13, 14, 74, 75).

Prospective RCTs will be challenging when patient preference drives the decision to attempt nipple sparing vs. none, or to entertain immediate (skin-sparing) vs. delayed (non-skin sparing) breast reconstruction. Even if patient preference is deferred, patients may be technically ineligible for one or the other, which would further challenge a prospective RCT.

Types of reconstruction

a) Autologous tissue vs. tissue expander/implant reconstruction

There is only a single systematic review examining the rates of complications TE/I reconstructions and AAT (15). Only 14 studies were included and the level of evidence is very low, the studies have small sample sizes, and overlap exists among the patient populations. While reoperation rate and major complications are equivalent between the methods of reconstruction, this review suggests a greater potential for reconstructive failure and soft tissue infection in TE/I reconstructions. More evidence and better quality studies are required to determine the accuracy of this interpretation. Complications associated with implants, including risk of infection and very rare risk of ALCL should be discussed with patients (197).

A single systematic review examining patient related outcomes following different types of breast reconstruction exists (16). This study encompasses 15 studies of very low quality and there is no consistency among measurement method, duration of follow up, or outcomes assessed. This led to the inability to pool data. The trends from this review are for improved social well-being, emotional and mental health associated with reconstruction, regardless of type, similar levels of pain between methods of reconstruction, and similar overall satisfaction or willingness to recommend surgery to others. There is some suggestion that esthetic satisfaction with TE/I reconstruction declines over time, while AAT satisfaction remains level; however, this needs to be validated with better quality studies and larger sample sizes.

Consistency among outcome measures would significantly improve ability to assess patient-related outcomes.

Radiation

Our current recommendation on the type of reconstruction following PMRT have examined autologous tissue separately from implant-based reconstructions, and have focused primarily on short- and long-term complications of PMRT. In all the systematic reviews that compared the reconstructive options in patients who required PMRT, it was found that complications are significantly higher in the implant group compared with the autologous tissue group (196). In addition, a 2008 prospective single-centre study that examined 92 patients who underwent IBR using autologous tissue (23 patients) compared with tissue expander (69 patients) found that major complications, compromised functional status, and poor esthetic outcomes to be significantly associated with the use of tissue expanders (18).

b) Types of autologous tissue reconstruction

Evidence is based on two meta-analyses and three systematic reviews; however, the analyzed studies share some common weaknesses. The reviews are based on individual studies that are made up of very small cohorts, mostly retrospective in design, from single institutions, and lacking uniform definition to define our interested outcomes such as abdominal bulge, hernia, weakness, and fat necrosis. The current literature comparing outcomes among different techniques is also severely limited by the great variability in surgical techniques, the degree to which rectus muscle may be injured or violated by the surgery, and the type of abdominal wall repair that occurs with the reconstruction. Higher level of evidence in the area will require data collected from multicentre, longitudinal studies with clearly defined primary outcomes that are both subjective and objective following pedicled or free TRAM and DIEP flaps.

Acellular dermal matrix

The level of evidence for the use of ADM varies from retrospective single-centre anecdotal reports to meta-analyses of observational studies and RCTs. The largest RCT stopped accrual early and has not reported final outcomes. There was high variability in reporting of complications among studies; however, three meta-analyses suggested an increased rate of complications using ADM. Given the lack of benefit in postoperative pain, time to second operation, and number of tissue expander fills, and the higher rate of complications, ADM is currently not recommended for two-stage expander-implant reconstruction. Given the possibility of avoiding a second surgery, ADM may be considered in appropriate patients for direct-to-implant reconstruction in a single stage. Although cost of using ADM was not examined in this evaluation, it must be considered. A Canadian study evaluating cost suggests that it is not prohibitive (198).

Autologous fat grafting

Overall, the level of evidence for autologous fat grafting is very low. It appears that fat grafting after mastectomy is likely safe in patients with invasive carcinoma. Intraepithelial neoplasia may be a subset that should not receive fat grafting due to higher levels of locoregional recurrence. Complication rates associated with fat grafting are likely minimal; however, complications can occur that would not have occurred without this additional procedure. No standardization exists for fat grafting techniques in terms of timing, number of sessions, volume of fat, or processing of fat.

Routine screening for recurrence

With the increased utilization of reconstructive surgery following mastectomy, questions regarding the application of surveillance mammography in this setting have been raised. Unfortunately, the current literature is lacking in strong evidence to provide conclusive direction. Current breast cancer guidelines for women without breast reconstruction recommend annual ipsilateral mammography for women treated with BCT and contralateral native breast mammography. There is currently no role for routine imaging following mastectomy alone. Postmastectomy surveillance comprises a physical examination of the chest wall as part of a scheduled follow-up program. The locoregional recurrence rate following breast reconstruction appears to be similar to the rate in women who undergo mastectomy without reconstruction (<10%); however, breast reconstruction may interfere with the ability to appropriately evaluate the chest wall for recurrence. The question remains whether mammography should be employed as a surveillance tool for women who have undergone reconstructive surgery.

The available evidence suggests that mammography can identify lesions in the follow-up of women who undergo mastectomy and breast reconstruction but results in high recall rates and the need for further invasive testing. The majority of lesions identified by screening mammography were later determined to be benign on pathological examination. Such results have the potential to cause undue anxiety that may outweigh the benefits of screening for women without symptoms of recurrence.

Important clinical considerations in the determination of optimal follow-up include the type of reconstruction (implant vs. autologous tissue) and the timing and modality of surveillance imaging. The majority of the studies reviewed for the development of these guidelines only included women with autologous breast reconstruction. This is based on the idea that imaging is not required for implant-based reconstruction because the pectoralis major muscle is raised off the chest wall and is adherent to the skin, making clinical evaluation of the chest wall for recurrence technically possible. Conversely, autologous reconstruction is placed over the chest wall, leading to the concern that a chest wall recurrence might be concealed.

There is some suggestion that chest wall recurrences behave differently than skin flap recurrences, with an increased number of women with chest wall recurrence having metastatic disease at the time of diagnosis or identified during early follow-up. It is unclear whether early detection of such recurrences would lead to an improvement of outcomes. A retrospective chart review by Chagpar et al. identified 155 women with chest wall recurrence, of whom 27 had previous breast reconstruction (199). Time from mastectomy to diagnosis of chest wall recurrence, overall survival, and distant metastasis-free survival were not significantly different between women with and without breast reconstruction, although the statistical power to detect clinically meaningful differences in this study is unclear.

If an assumption is made that early detection of chest wall recurrences could improve clinical outcomes, identification of a group of women at higher risk for chest wall recurrence could help to improve the application of post-breast reconstruction mammography. Certain patient and tumour characteristics have been identified that may be indicative of increased local recurrence risk post mastectomy, such as young age, multicentricity, lymphovascular invasion, and positive surgical margins. Utilization of postreconstruction imaging, along with clinical examination, in this population of women may provide improved clinical outcomes. However, these risk factors have also been identified as increased risk for distant metastasis, so the perceived benefit maybe over-estimated. Further studies in this area are required to determine the benefit.

The timing and imaging regimen for surveillance mammography after reconstruction was only described in one of the case reports in the systematic review by Barnsley et al. (semiannual screening) (31). The only imaging modality evaluated in the literature to date for the follow-up of women with breast reconstruction is mammography. There is no clearly defined

strategy for the application of surveillance imaging and evidence on appropriate application is nonexistent.

In the studies reviewed, most recurrences were identified following development of symptoms, such as pain or a palpable mass. A low index of suspicion for evaluation should be considered and symptomatic patients should be evaluated by imaging such as ultrasound and mammography and should be referred to a surgeon.

Based on the current literature there is insufficient evidence to suggest that routine screening mammography following breast reconstruction would improve the clinical outcomes of breast cancer recurrence.

CONFLICT OF INTEREST

Information regarding conflict of interest declarations can be found in Appendix I.

Breast cancer reconstruction surgery (immediate and delayed) across Ontario: Patient indications and appropriate surgical options

Section 5: Internal and External Review

INTERNAL REVIEW

Program in Evidence-Based Care (PEBC) guidelines are reviewed by a panel of content experts—Expert Panel and a methodology panel—Report Approval Panel (RAP). Both panels must approve the document. The Working Group was responsible for incorporating the feedback and required changes of both of these panels. The details of these reviews and actions taken are described below. Appendix I provides a list of members of the Working Group, RAP and Expert Panel and summarizes conflict of interest declarations for all members.

Expert Panel Review and Approval

Of the 11 members of the Expert Panel, eight members cast votes and three abstained, for a total of 72% response in August and September 2015. Of those that cast votes, eight approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. **P4 Recommendation (Rec) 2** 'Qualifying Statement (QS)' mentions 'three characteristics' but only two are listed. Should psychiatric illness be on the list or not?	No, psychiatric illness should not be in this list. We have removed it and modified the text to reflect this.
2. **P5 Rec. 6** QS 'ontologically' should be oncologically.	This has been corrected.
3. **P7 Rec 9** QS should be 'outcomes in select women', 'in' is currently missing.	This has been corrected.
4. **P9 Rec 2** The list numbers are 3 &4; should be 1 & 2	This has been corrected.
5. **P9 Rec2** QS Only 2 characteristics are listed but it states 'three'.	We have corrected this (see comment 1)
6. **P10 top line** "Older age is qualified as <50." Shouldn't this be > 50?	This has been corrected.
7. **P11 Rec4** 'Tp53' should be TP53.	This has been corrected.
8. **P13 Rec 6** QS 'ontologically' should be oncologically	This has been corrected.

9. **P16 'Interpretation of evidence'** The last sentence is confusing and should be rewritten.	We have modified this sentence to help improve clarity.
10. **P20** 'The PEBC is produces evidence-based …' should be 'The PEBC produces evidence-based….'	This has been corrected.
11. **P21** Two thirds of the way down the page, should be 'providing feedback on the first draft', the word 'the' is currently missing.	This has been corrected.
12. **P27** One third of the way down the page reference 35 is cited. Ref 35 is not by Barnsley et al. Please check references.	This has been corrected.
13. **P88** Halfway down text, 'most recurrences where identified' should be 'most recurrences were identified'	This has been corrected.

Report Approval Panel Review and Approval

Three RAP members reviewed this document from April to June of 2015. Two RAP reviewers approved of the Guideline and one RAP reviewer conditionally approved the Guideline on June 24, 2015. The summary of main comments from the RAP and the Working Group's modifications/actions/responses taken in response are showed in Table 5-2.

Table 5-2. Modifications/actions/responses regarding main comments from RAP

Main comments	Modifications, actions, or responses
1. Please add expertises of the Expert Panel and Working Group to the tables in Appendix 1	We have modified Table a.1 and a.2 to include the affiliations and expertises of the Working Group and Expert Panel
2. Consistency with acronyms are needed	We have updated the acronyms in the Guideline to improve consistency.
3. Please clarify the role of the expert panel as it related to the development of the Guideline	We have amended Section 3 to include a more detailed description of the roles and responsibilities of the Working Group and the Breast Reconstruction Expert Panel
4. Please clarify the definitions that are used for "older age" and "advanced disease"	We have modified the recommendation regarding older age to: "There is no age at which breast reconstruction is contraindicated" There is no consistent definition in the evidence as to what age group is "older age". Because the evidence does not find age to be a contraindication to breast reconstruction we have modified the recommendation to reflect this. We have clarified what is meant be advanced disease: advanced disease (T4, or N2 or N3)
5. There is an objective reporting of health-related outcomes. It is not clear what, if any, 'weighting' of benefits or risks was undertaken or if this is deferred to the Expert Viewpoint. In the multiple tables of evidence, there quite a bit of detail regarding the NEGATIVE outcomes (surgical complications, re-operation rates, etc) but the actual positive benefits, such as health-related quality of life (HRQoL, pain), function, esthetic satisfaction are scantily documented --mostly in Table 6.	All evidence, both positive and negative outcomes were reviewed, described and presented when available for transparency. This was done to ensure there was no selection bias on the results that were reported. Negative outcomes were found to be reported more frequently in the evidence that was deemed eligible for inclusion in the Guideline. The Working Group evaluated all outcomes, both positive and negative, when developing the Recommendations; however, no quantitative weighting of benefits and harms was conducted. As a result of this we have added the following statement in the Study Design and Quality section: *There was no specific weighting of benefits and risks or selection bias on what is reported. The tables present the available evidence and outcomes and represent the constraints of the literature*.

Main comments	Modifications, actions, or responses
6. The recommendations are unambiguous but there are some that are too strong for the level of evidence provided. In general, recommendations 1-5 are aligned with the evidence and provide excellent clinical direction. a. *Recommendation 6*, the idea that SSM/NSM **should** be offered is misaligned with the largely retrospective/observational data and possibly selected population providing positive outcomes that cannot be generalized. b. *Recommendations 9 and 10*, the reviewer is left with an impression that these are options that should be considered (but when?? And in what circumstance?), with no definitive positive outcomes and in the case of acellular dermal matrix, many negative consequences. I think the Working Group may wish to consider how it phrases these.	a. In response to this comment the Working Group has modified the statement to read: "SSM/NSM can be offered…" b. The Working Group is aware that the use of ADM and autologous fat grafting is still being evaluated and the literature regarding the optimal timing of these procedures is currently unclear. We agree with the reviewer that based on the current level of evidence, no recommendation can confidently be made for or against the use of ADM or fat grafting and we have modified the recommendations accordingly. As with all PEBC Guidelines, this Guideline will be subject to a yearly review. If any new literature regarding the use of these procedures is uncovered in this updating process, the recommendations will be revised and updated appropriately.
7. This is an excellent document in so many aspects. It provides a timely 'assemblage' of the literature in many domains, most crucially as to the timing of immediate breast reconstruction (IBR) and the pitfalls/complications of many available techniques. There have been seemingly many advances in this area and it is good to find them addressed in one document objectively. Much of the reconstruction literature seems to focus on esthetic outcomes and this document provides a detailed account of the potential complications and adverse outcomes that can serve to inform patients and providers better. There are some areas which are overstated as documented in comments above. The authors need to carefully re-read the document and ensure certain facts are stated correctly, a. eg *"In 2013, approximately 23,800 Canadian women were diagnosed with breast cancer, and breast cancer continues to be the most commonly diagnosed cancer in Canadian women over the age of 20 (38). Since 39% (really??) of Canadians undergo mastectomy for breast cancer, and the five-year survival rate for breast cancer is approximately 88%...."* I know what the author's intent is but the figure is mis-stated	The Working Group agrees that this statement was erroneous in the way that it was written. We have addressed/modified it appropriately to read: "Since 39% of Canadians diagnosed with breast cancer undergo mastectomy, and…"

Main comments	Modifications, actions, or responses
8. What is missing is some statement as to what the actual scope of the problem is. It is not just a mastectomy rate or the fact that IBR rates in Canada 'lag' behind the United States, but somewhere in the document the authors need to convince the reader (and the policy makers) that this issue matters. This could be in the introduction or in the discussion. Is reconstruction the 'norm', a standalone 'quality indicator' or the natural continuum post mastectomy to ensure optimum HRQoL (whether performed for prophylaxis or therapy of breast cancer)?	The Working Group believes this is an excellent point. We have added a statement in the Introduction that outlines the rationale for the development of this Guideline.
9. Statement about women with active psychiatric illness. There are no data and I am not compelled by the rationale provided by the group (see my alternative interpretations and concerns). I think no statements can be made about women in this clinical state. I would be inclined to drop that bit.	The psychiatric illness recommendation is based on personal experience from some members, but the Working Group agrees that there is limited actual evidence to support it. Since this is an evidence-based document, the Working Group agrees with the reviewer that this contraindication for breast reconstruction should be removed.
10. *Recommendation 5*. I think I am more compelled by the evidence than are the panel members. I am not sure you need the caveat about women who want immediate reconstruction. While many outcomes show no difference, there are a series of outcomes that do a show a difference in favour of waiting until after radiation therapy is complete. I think the panel could be a bit more bold and consider dropping the qualifying statement.	This statement was put in because the decision is patient-driven. The Working Group members believe it should be kept in because there is a subgroup of patients who still demand it, and plastics' expert opinion is that it is safe to perform – just the delay to adjuvant therapy and potential poor esthetic outcome.
11. In the summary of the literature results – it might be nice to differentiate between SRs attached to CPGs from SRs not attached to CPGs. I would provide a better logic model for recommendation 1.	Evidence to support these recommendations was based both on a review of evidence is supported by other clinical practice guidelines. There were no systematic reviews included that were attached to clinical practice guidelines. This has been clarified in the results section.

EXTERNAL REVIEW
External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Four targeted peer reviewers from Ontario who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group and expert panel. Two agreed to be the reviewers and both their responses received. Their affiliations and conflict of interest declarations are in Appendix 1. Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	0	0	1	1
2. Rate the guideline presentation.	0	0	1	0	1
3. Rate the guideline recommendations.	0	0	1	0	1
4. Rate the completeness of reporting.	0	0	0	0	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	1	0	1
6. Rate the overall quality of the guideline report.	0	0	1	0	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	1	0	0	1
8. I would recommend this guideline for use in practice.	0	0	1	0	1
9. What are the barriers or enablers to the implementation of this guideline report?	The targeted peer reviewers indicated a possible barrier for those practicing in outside centre would be the difficulty in receiving the inputs of plastic surgeons in a timely manner, especially at Multidisciplinary Cancer Conference or pre-operatively.				

Table 5-4. Responses to comments from targeted peer reviewers.

Comments	**Responses**
1. Excellent format- I like the summary followed by the supporting evidence.	Thank you.
2. The relatively low evidence could be emphasized further. Consider adding more about consensus method.	Members of the Working Group believe that the consensus method was adequately described.
3. The recommendations are very technical re. surgical methods. There could be more specific recommendations about who is a candidate for reconstruction, especially in the high risk/prophylactic category	Members of the Working Group made some modifications to the recommendations to help clarify. The target population is also described in detailed on page 3.

4. The guideline does not really address the significant barriers to reconstruction in Ontario. Given the limited resources, should there be a way to prioritize patients?	Members of the Working Group recognize that there are multiple considerations before such a program can be implemented. The Surgical Oncology Program is addressing ways to overcome them.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. A list of pathologists, radiation and medical oncologists, general and plastic surgeons from Ontario was provided by the Surgical Oncology Program and the PEBC contacted them by email to inform them of the survey. Five hundred sixty-three were included. Forty-one (7.3%) responses were received. The results of the feedback survey from 41 people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0 (0)	0 (0)	6 (14.6)	21 (51.2)	14 (34.2)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0 (0)	0 (0)	10 (24.4)	17 (41.5)	14 (34.1)
3. I would recommend this guideline for use in practice.	0	0	8 (19.5)	16 (39.0)	17 (41.5)
4. What are the barriers or enablers to the implementation of this guideline report?	The barriers listed included lack of plastic or general surgeons with the expertise in some centres, access to care and geographical issues for patients, time constraints in the clinical setting to discuss and coordinate care and help patients understand all the options, challenge to stay within Ministry of Health and Long Term Care wait times, need for administrative support, lack of reconstructive surgeons to participate in multidisciplinary discussions, low quality evidence and the absence of patient input. Enablers listed included a very lucid structure, covers all main aspects immediate and delayed postmastectomy breast reconstruction, comprehensive collection of evidence with reasonable interpretative summaries, addresses key areas and a good summary of evidence, enables individual practice changes by surgeons and team, changing culture, long-needed voice of patients, and psychosocial impact in patient centered OCPF.				

Table 5-6. Modifications/Actions taken/Responses regarding main written comments from professional consultants.

Comments	Modifications, actions, or responses
There were few comments on Recommendation 1 and the qualifying statements. These included: 1. Removing multidisciplinary from second bullet point 2. Excluding the last sentence in the fourth bullet point. "imaging results should be available at the time of surgical consult 3. Missing information on appropriate patient selection on the basis of disease extent and location in the breast	In response to the comments made about Recommendation 1 and the qualifying statements, members of the Working Group: 1. Have removed the multidisciplinary from the second bullet point. 2. Have excluded the last sentence in the fourth bullet point. 3. Have clarified the target population by adding the following "For women who have chosen or been recommended for therapeutic mastectomy" as a precursor to the bullet points.
There were a few comments on Recommendation 2 and the qualifying statements. These included: 1. In delayed reconstruction, women should be told of a higher complication rate with body max index (BMI) > 30 kg/m^2 and strongly encouraged to lose weight 2. There is no age cut off for breast reconstruction, does this mean that we need to discuss with every 75, 80 or 85 year old with multiple co-morbidities who is having a mastectomy? 3. Missing information on appropriate patient selection on the basis of disease extent and location in the breast 4. Psychiatric contraindications are mentioned here for the first time; if this issue is to be included, it should be mentioned elsewhere. 5. The small section on psychological issues out of place and not supported by evidence mentioned. Considered reviewing the evidence or excluding this small section.	In response to the comments made about Recommendation 2 and the qualifying statements, members of the Working Group: 1. have elaborated on the qualifying statement to include information on BMI >30 kg/m^2 2. have clarified the recommendation on advanced age. 3. have clarified the target population by changing the title of the recommendation to "Contraindications for immediate or delay reconstruction" and by changing the first bullet point to include "relative medical (non-cancer-related) contraindications for breast reconstruction". 4. have excluded psychiatric contraindications. 5. agree and have excluded this small section on psychological issues.
Qualifying statement for Recommendation 3, a commenter indicated that while it is of opinion to wait two years, the statement would be stronger with more specifics either in the recommendations or supporting documentation.	Members of the Working Group have clarified the second qualifying statement by adding "optimal to wait two to three years before undergoing reconstruction when the risk of recurrence is lower"

There were a few comments on Recommendation 4 and the qualifying statements. These included: 1. Define low likelihood in bullet point 5 2. Information on appropriate patient selection on the basis of disease extent and location in the breast is not sufficiently stated 3. Recommendation is about timing of reconstruction, but includes some indications for mastectomy which really don't belong here. e.g. tumour size relative to breast size 4. Sentence about positive margins should be revised to read: positive margins but no indication for post mastectomy radiotherapy	In response to the comments made about recommendation 4 and the qualifying statements, members of the Working Group: 1. believe it should stay as written as there was no evidence identified to define low likelihood of nodal disease. 2. believe it is sufficiently stated. Please refer to guidelines on postoperative radiation therapy and guidelines on post-mastectomy radiation. 3. have changed to recommendation title to help clarify. 4. have combined Recommendation 4 and 5 to help clarify. There is now one recommendation along the same theme.
There were a few comments on Recommendation 5 and the qualifying statements. These included: 1. The discussion does not support the strongly worded recommendation to avoid immediate reconstruction if postoperative radiotherapy is possible/probably/planned. Clinical guidance is needed as to whether to agree to immediate reconstruction in the face of post mastectomy radiation if the patient requests it and accepts the risks. 2. Qualifying statement indicates willingness to do something that is not right because the patient wants it. This not evidence based care and ignores societal perspective. Why would we be doing something that we do not believe is the correct course?	There were comments on both sides on the issue, showing the clinical community is divided on this issue. Members of the Working Group have decided to leave the recommendation as is and keeping it neutral and evidence based.
• There were a numerous comments on Recommendation 6 and the qualifying statements. These included: 1. Are skin-sparing mastectomy (SMS) and nipple-sparing mastectomy (NSM) not recommended for node positive women because of issues with radiation post reconstruction?	In response to the comments made about Recommendation 6 and the qualifying statements, members of the Working Group: 1. have clarified by modifying the sub bullets in the recommendation. 2. have clarified by adding a definition on SSM, NPM and ASM to the recommendation.

2. Disagree that SSM or ASM are not appropriate for women with early stage breast cancer and lymph node positive status and agree that NSM is not appropriate. Might be helpful to define what it meant by SSM? Term can mean very different things to different surgeons 3. The rational for the statement of "no NSM if node positive" should be presented. Is it because these patients will receive radiotherapy? There is no mention of any aesthetic considerations in the selection of suitable candidates for NSM (e.g. very ptotic breasts) 4. Disagree with the suggestion that ductal carcinoma in situ or invasive carcinoma "within 2cm of the nipple" should have an intraoperative frozen section from base of nipple; would favour a preoperative nipple biopsy. However, patient selection is stressed in terms of selection or NSM, should this group of patients be excluded from NSM? Should there be uniformity in the definition of "within 2cm of the nipple"? 5. A qualifying statement about who should determine the likelihood of the positivity of the nodes should be included. 6. Should also add the option of a standalone sentinel node biopsy. 7. Surprised there is no discussion of the use of an initial sentinel node biopsy to determine the nodal status prior to making definitive plans for surgery in women with invasive cancer and clinically node negative. 8. Define clear margins FS for breast is almost obsolete, suggest removing that statement, instead of putting patients at risk for false positive results and pathologist for litigation.	3. have added a new qualifying statement on suitable candidates for NSM. 4. have modified and clarified the recommendation. 5. have made no modification. This has been addressed and is the qualifying fourth bullet. 6. Agrees and have added the following to the last qualifying statement "when required, for women with invasive breast cancer and clinically negative nodes, a standalone sentinel lymph node biopsy may evaluate lymph node status prior to definitive mastectomy for women. 7. have address this suggestion with the above changes in comment #6. 8. agree and have removed this qualifying statement. 9. have changed the wording to "may consider"

9. The evidence is low to moderate in quality. How strong this recommendation comes across is inconsistent within the document. Language should be changed to "should be" language in the body of text be weakened.	
• There was a comment on Recommendation 7. A reviewer mentioned the evidence indicates that the complication rate with latissimus dorsi (LD) flaps is lower than either tissue expander or autologous abdominal flaps, yet LD flaps are listed as an alternative form of reconstruction. Some justification for this is required.	In response to the reviewers comment, members of the Working Group have clarified the wording on the recommendation
• Qualifying statement for Recommendation 9: A reviewer questioned if the increased risk of complications seen in acellular dermal matrix (ADM) compared to without ADM, or with radiation compared with no radiation when ADM is used. Please clarify.	There was limited evidence on the use of ADM and the certainty of the evidence is low. Members of the Working Group did not make a recommendation for or against the use of ADM as an adjunct to implant-based breast reconstruction.
• There is no mention on the latest evidence that is coming available slowly on the association of textured breast implants used for reconstruction and ALCL. This is probably slightly outside the scope of the report but should be mentioned as needing to be part of the discussion with the patient when presenting options.	Members of the Working Group believe this is an excellent point. We have added a more information on the emerging evidence on ALCL to the discussion section.
• From limited evidence available, there should be a recommendation against/ caution for fat grafting into wide local excision or lumpectomy defects with or without radiation as this has shown to be associated with local recurrence. This is a separate situation from fat grafting to a mastectomy and reconstruction site	Recommendation is for total mastectomy population. Lumpectomy is not within the target population and is outside the scope of the guideline.
• Family physicians not included in the "intended users". Women who have undergone mastectomies and are under the care of their family physicians may not be aware of their breast reconstruction options.	Members of the Working Group agree and have added "other referring physicians" to the intended users.
• The recommendations favour large centres with lots of resources to do breast construction and biased against small centre surgeons	This guideline is an evidence-based guideline with an extensive literature search that summarizes the best available evidence. It is not meant to favour small or large centres and there is no bias against small centres.
• No discussion regarding barriers to access/resources	Issues related to the implementation of recommendations with respect to feasibility, patient considerations, equity, provider considerations, and system considerations were also considered by

	the Working Group and Breast Reconstruction Expert Panel. A formal implementation Considerations statement was prepared and sent to the leadership of Cancer Care Ontario's Surgical Oncology Program.

Conclusion

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as dragged by the Guideline Development Group (GDG) Working Group and approved by the GDG Expert Panel and the PEBC RAP.

References

1. Fischer JP, Cleveland EC, Nelson JA, Kovach SJ, Serletti JM, Wu LC, et al. Breast reconstruction in the morbidly obese patient: assessment of 30-day complications using the 2005 to 2010 national surgical quality improvement program data sets. Plastic & Reconstructive Surgery. 2013;132(4):750-61.

2. Fischer JP, Nelson JA, Kovach SJ, Serletti JM, Wu LC, Kanchwala S. Impact of Obesity on Outcomes in Breast Reconstruction: Analysis of 15,937 Patients fromtheACS-NSQIP Datasets. Journal of the American College of Surgeons. 2013;217(4):656-64.

3. Seidenstuecker K, Munder B, Mahajan AL, Richrath P, Behrendt P, Andree C. Morbidity of microsurgical breast reconstruction in patients with comorbid conditions. Plastic & Reconstructive Surgery. 2011;127(3):1086-92.

4. Walton L, Ommen K, Audisio RA. Breast reconstruction in elderly women breast cancer: a review. Cancer Treatment Reviews. 2011;37(5):353-7.

5. Dean C, Chetty U, Forrest AP. Effects of immediate breast reconstruction on psychosocial morbidity after mastectomy. Lancet. 1983;1(8322):459-62.

6. Metcalfe KA, Semple J, Quan ML, Vadaparampil ST, Holloway C, Brown M, et al. Changes in psychosocial functioning 1 year after mastectomy alone, delayed breast reconstruction, or immediate breast reconstruction. Annals of Surgical Oncology. 2012;19(1):233-41.

7. Petit JY, Gentilini O, Rotmensz N, Rey P, Rietjens M, Garusi C, et al. Oncological results of immediate breast reconstruction: long term follow-up of a large series at a single institution. Breast Cancer Research & Treatment. 2008;112(3):545-9.

8. Gieni M, Avram R, Dickson L, Farrokhyar F, Lovrics P, Faidi S, et al. Local breast cancer recurrence after mastectomy and immediate breast reconstruction for invasive cancer: a meta-analysis. Breast. 2012;21(3):230-6.

9. Schaverien MV, Macmillan RD, McCulley SJ. Is immediate autologous breast reconstruction with postoperative radiotherapy good practice?: a systematic review of the literature. Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS. 2013;66(12):1637-51.

10. Lam TC, Hsieh F, Boyages J. The effects of postmastectomy adjuvant radiotherapy on immediate two-stage prosthetic breast reconstruction: a systematic review. Plastic & Reconstructive Surgery. 2013;132(3):511-8.

11. Barry M, Kell MR. Radiotherapy and breast reconstruction: a meta-analysis. Breast Cancer Research & Treatment. 2011;127(1):15-22.

12. Lanitis S, Tekkis PP, Sgourakis G, Dimopoulos N, Al Mufti R, Hadjiminas DJ. Comparison of skin-sparing mastectomy versus non-skin-sparing mastectomy for breast cancer: a meta-analysis of observational studies. Annals of Surgery. 2010;251(4):632-9.

13. Mallon P, Feron JG, Couturaud B, Fitoussi A, Lemasurier P, Guihard T, et al. The role of nipple-sparing mastectomy in breast cancer: a comprehensive review of the literature. Plastic & Reconstructive Surgery. 2013;131(5):969-84.

14. Endara M, Chen D, Verma K, Nahabedian MY, Spear SL. Breast reconstruction following nipple-sparing mastectomy: a systematic review of the literature with pooled analysis. Plastic & Reconstructive Surgery. 2013;132(5):1043-54.

15. Tsoi B, Ziolkowski NI, Thoma A, Campbell K, O'Reilly D, Goeree R. Safety of tissue expander/implant versus autologous abdominal tissue breast reconstruction in postmastectomy breast cancer patients: a systematic review and meta-analysis. Plastic & Reconstructive Surgery. 2014;133(2):234-49.

16. Tsoi B, Ziolkowski NI, Thoma A, Campbell K, O'Reilly D, Goeree R. Systematic review on the patient-reported outcomes of tissue-expander/implant vs autologous abdominal tissue breast reconstruction in postmastectomy breast cancer patients. Journal of the American College of Surgeons. 2014;218(5):1038-48.

17. Gart MS, Smetona JT, Hanwright PJ, Fine NA, Bethke KP, Khan SA, et al. Autologous options for postmastectomy breast reconstruction: a comparison of outcomes based on the American College of Surgeons National Surgical Quality Improvement Program. Journal of the American College of Surgeons. 2013;216(2):229-38.

18. Jhaveri JD, Rush SC, Kostroff K, Derisi D, Farber LA, Maurer VE, et al. Clinical outcomes of postmastectomy radiation therapy after immediate breast reconstruction. International Journal of Radiation Oncology, Biology, Physics. 2008;72(3):859-65.

19. Man LX, Selber JC, Serletti JM. Abdominal wall following free TRAM or DIEP flap reconstruction: a meta-analysis and critical review. Plastic & Reconstructive Surgery. 2009;124(3):752-64.

20. Egeberg A, Rasmussen MK, Sorensen JA. Comparing the donor-site morbidity using DIEP, SIEA or MS-TRAM flaps for breast reconstructive surgery: a meta-analysis. Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS. 2012;65(11):1474-80.

21. Atisha D, Alderman AK. A systematic review of abdominal wall function following abdominal flaps for postmastectomy breast reconstruction. Annals of Plastic Surgery. 2009;63(2):222-30.

22. Khansa I, Momoh AO, Patel PP, Nguyen JT, Miller MJ, Lee BT. Fat necrosis in autologous abdomen-based breast reconstruction: a systematic review. Plastic & Reconstructive Surgery. 2013;131(3):443-52.

23. Clemens MW, Kronowitz SJ. Acellular dermal matrix in irradiated tissue expander/implant-based breast reconstruction: evidence-based review. Plastic & Reconstructive Surgery. 2012;130(5 Suppl 2):27S-34S.

24. Hoppe IC, Yueh JH, Wei CH, Ahuja NK, Patel PP, Datiashvili RO. Complications following expander/implant breast reconstruction utilizing acellular dermal matrix: a systematic review and meta-analysis. Eplasty [Electronic Resource]. 2011;11:e40.

25. Kim JY, Davila AA, Persing S, Connor CM, Jovanovic B, Khan SA, et al. A meta-analysis of human acellular dermis and submuscular tissue expander breast reconstruction. Plastic & Reconstructive Surgery. 2012;129(1):28-41.

26. McCarthy CM, Lee CN, Halvorson EG, Riedel E, Pusic AL, Mehrara BJ, et al. The use of acellular dermal matrices in two-stage expander/implant reconstruction: a multicenter, blinded, randomized controlled trial. Plastic & Reconstructive Surgery. 2012;130(5 Suppl 2):57S-66S.

27. Vardanian AJ, Clayton JL, Roostaeian J, Shirvanian V, Da Lio A, Lipa JE, et al. Comparison of implant-based immediate breast reconstruction with and without acellular dermal matrix. Plastic & Reconstructive Surgery. 2011;128(5):403e-10e.

28. Krastev TK, Jonasse Y, Kon M. Oncological safety of autologous lipoaspirate grafting in breast cancer patients: a systematic review. Annals of Surgical Oncology. 2013;20(1):111-9.

29. Saint-Cyr M, Rojas K, Colohan S, Brown S. The role of fat grafting in reconstructive and cosmetic breast surgery: a review of the literature. Journal of Reconstructive Microsurgery. 2012;28(2):99-110.

30. Petit JY, Rietjens M, Botteri E, Rotmensz N, Bertolini F, Curigliano G, et al. Evaluation of fat grafting safety in patients with intra epithelial neoplasia: a matched-cohort study. Annals of Oncology. 2013;24(6):1479-84.

31. Barnsley GP, Grunfeld E, Coyle D, Paszat L. Surveillance mammography following the treatment of primary breast cancer with breast reconstruction: a systematic review. Plastic & Reconstructive Surgery. 2007;120(5):1125-32.

32. Sim YT, Litherland JC. The use of imaging in patients post breast reconstruction. Clinical Radiology. 2012;67(2):128-33.

33. Browman GP, Levine MN, Mohide EA, Hayward RS, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. Journal of Clinical Oncology. 1995;13(2):502-12.

34. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the Practice Guidelines Development Cycle: the role of practitioner feedback. Journal of Clinical Oncology. 1998;16(3):1226-31.

35. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010;182(18):E839-42.

36. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: Advancing guideline development, reporting and evaluation in health care. Journal of Clinical Epidemiology. 2010;63(12):1308-11.

37. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2013. Toronto, ON: Canadian Cancer Society; 2013.

38. Schain WS, Wellisch DK, Pasnau RO, Landsverk J. The sooner the better: a study of psychological factors in women undergoing immediate versus delayed breast reconstruction. American Journal of Psychiatry. 1985;142(1):40-6.

39. Schain WS, Jacobs E, Wellisch DK. Psychosocial issues in breast reconstruction. Intrapsychic, interpersonal, and practical concerns. Clinics in Plastic Surgery. 1984;11(2):237-51.

40. Rowland JH, Meyerowitz BE, Crespi CM, Leedham B, Desmond K, Belin TR, et al. Addressing intimacy and partner communication after breast cancer: a randomized controlled group intervention. Breast Cancer Research & Treatment. 2009;118(1):99-111.

41. Parker PA, Youssef A, Walker S, Basen-Engquist K, Cohen L, Gritz ER, et al. Short-term and long-term psychosocial adjustment and quality of life in women undergoing different surgical procedures for breast cancer. Annals of Surgical Oncology. 2007;14(11):3078-89.

42. Harcourt DM, Rumsey NJ, Ambler NR, Cawthorn SJ, Reid CD, Maddox PR, et al. The psychological effect of mastectomy with or without breast reconstruction: a prospective, multicenter study. Plastic & Reconstructive Surgery. 2003;111(3):1060-8.

43. Elder EE, Brandberg Y, Bjorklund T, Rylander R, Lagergren J, Jurell G, et al. Quality of life and patient satisfaction in breast cancer patients after immediate breast reconstruction: a prospective study. Breast. 2005;14(3):201-8.

44. The Picker Institute. Advancing the principles of patient-centered care. The institute for patient- and family-centered care.

45. Wilkins EG, Cederna PS, Lowery JC, Davis JA, Kim HM, Roth RS, et al. Prospective analysis of psychosocial outcomes in breast reconstruction: one-year postoperative results from the Michigan Breast Reconstruction Outcome Study. Plastic & Reconstructive Surgery. 2000;106(5):1014-25; discussion 26-7.

46. Zhong T, McCarthy C, Min S, Zhang J, Beber B, Pusic AL, et al. Patient satisfaction and health-related quality of life after autologous tissue breast reconstruction: a prospective analysis of early postoperative outcomes. Cancer. 2012;118(6):1701-9.

47. Zhong T, Fernandes KA, Saskin R, Sutradhar R, Platt J, Beber BA, et al. Barriers to immediate breast reconstruction in the Canadian universal health care system. Journal of Clinical Oncology. 2014;32(20):2133-41.

48. Barnsley GP, Sigurdson L, Kirkland S. Barriers to breast reconstruction after mastectomy in Nova Scotia. Can J Surg. 2008;51(6):447-52.

49. National Cancer Institute. Surveillance, Epidemiology, and End Results Program.

50. Graham ID, Logan J, Harrison MB, Straus SE, Tetroe J, Caswell W, et al. Lost in knowledge translation: time for a map? J Contin Educ Health Prof. 2006;26(1):13-24.

51. Hack TF, Degner LF, Watson P, Sinha L. Do patients benefit from participating in medical decision making? Longitudinal follow-up of women with breast cancer. Psychooncology. 2006;15(1):9-19.

52. Lantz PM, Janz NK, Fagerlin A, Schwartz K, Liu L, Lakhani I, et al. Satisfaction with surgery outcomes and the decision process in a population-based sample of women with breast cancer. Health Serv Res. 2005;40(3):745-67.

53. Partridge N, Scadding J. The James Lind Alliance: patients and clinicians should jointly identify their priorities for clinical trials. Lancet. 2004;364(9449):1923-4.

54. Miller SH, Graham WP, 3rd. Breast reconstruction after radical mastectomy. American Family Physician. 1975;11(5):97-101.

55. Lester LJ. A critical viewpoint by a general surgeon toward reconstructive surgery after mastectomy. Clinics in Plastic Surgery. 1979;6(1):15-7.

56. Fine NA, Mustoe TA, Fenner G. Breast reconstruction. In: Harris JS, Lippmann ME, Morrow M, Kent Osborne C, editors. Diseases of the breast. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2000. [Note: there is a 5th ed published in 2014 Babak J. Mehra and Alice Y. Ho. Chapter 36: Breast Reconstruction. see https://www.google.ca/books/edition/Diseases_of_the_Breast/m5qSAwAAQBAJ?hl=en&gbpv=1&printsec=frontcover for excerpt].

57. Morrow M, Scott SK, Menck HR, Mustoe TA, Winchester DP. Factors influencing the use of breast reconstruction postmastectomy: a National Cancer Database study. Journal of the American College of Surgeons. 2001;192(1):1-8.

58. Atisha D, Alderman AK, Lowery JC, Kuhn LE, Davis J, Wilkins EG. Prospective analysis of long-term psychosocial outcomes in breast reconstruction: two-year postoperative results from the Michigan Breast Reconstruction Outcomes Study. Annals of Surgery. 2008;247(6):1019-28.

59. Alderman AK, McMahon L, Jr., Wilkins EG. The national utilization of immediate and early delayed breast reconstruction and the effect of sociodemographic factors. Plastic & Reconstructive Surgery. 2003;111(2):695-703; discussion 4-5.

60. Patani N, Devalia H, Anderson A, Mokbel K. Oncological safety and patient satisfaction with skin-sparing mastectomy and immediate breast reconstruction. Surgical Oncology. 2008;17(2):97-105.

61. Sisco M, Du H, Warner JP, Howard MA, Winchester DP, Yao K. Have we expanded the equitable delivery of postmastectomy breast reconstruction in the new millennium? Evidence from the national cancer data base. Journal of the American College of Surgeons. 2012;215(5):658-66; discussion 66.

62. Institute for Healthcare Improvement. Institute for Healthcare Improvement: Person- and Family-Centered Care. 2014 [cited 2014 July 1]. Available from: http://www.ihi.org/Topics/PFCC/Pages/default.aspx.

63. Health Information and Quality Authority (Ireland). National quality assurance standards for symptomatic breast disease services: Developing quality care for breast services in Ireland [Internet]. 2007. Available from: http://www.hiqa.ie/category/publication-category/healthcare-quality-and-safety/symptomatic-breast-disease-services.

64. American College of Surgeons. NAPBC 2013 Breast center standards manual. [Internet]. 2013. Available from: http://napbc-breast.org/standards/2013standardsmanual.pdf.

65. United States Senate. S.931 - 113th Congress (2013-2014): Breast Cancer Patient Education Act of 2013. [cited 2014 1 July]. Available from: https://beta.congress.gov/bill/113th-congress/senate-bill/931.

66. Alberta Health Services. Breast reconstruction following prophylactic or therapeutic mastectomy for breast cancer: Clinical practice guideline Br-016 version 1. [Internet]. 2013. Available from: http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-br016-breast-reconstruction.pdf.

67. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology. 2007;7(10).

68. The Cochrane Collaboration. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

69. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints.[Erratum appears in Stat Med. 2004 Jun 15;23(11):1817]. Statistics in Medicine. 1998;17(24):2815-34.

70. Wolfswinkel EM, Weathers WM, Bhadkamkar MA, Bullocks J, Izaddoost S, Hollier Jr LH, et al. Complications of abdominal-based free flaps for breast reconstruction in obese patients: A meta-analysis and case series. European Journal of Plastic Surgery. 2013;36(12):765-76.

71. Kelley BP, Ahmed R, Kidwell KM, Kozlow JH, Chung KC, Momoh AO. A systematic review of morbidity associated with autologous breast reconstruction before and after exposure to radiotherapy: are current practices ideal? Annals of Surgical Oncology. 2014;21(5):1732-8.

72. Momoh AO, Ahmed R, Kelley BP, Aliu O, Kidwell KM, Kozlow JH, et al. A systematic review of complications of implant-based breast reconstruction with prereconstruction and postreconstruction radiotherapy. Annals of Surgical Oncology. 2014;21(1):118-24.

73. D'Souza N, Darmanin G, Fedorowicz Z. Immediate versus delayed reconstruction following surgery for breast cancer. Cochrane Database of Systematic Reviews. 2011(7):CD008674.

74. Rusby JE, Smith BL, Gui GP. Nipple-sparing mastectomy. British Journal of Surgery. 2010;97(3):305-16.

75. Murthy V, Chamberlain RS. Defining a place for nipple sparing mastectomy in modern breast care: an evidence based review. Breast Journal. 2013;19(6):571-81.

76. Fang SY, Shu BC, Chang YJ. The effect of breast reconstruction surgery on body image among women after mastectomy: a meta-analysis. Breast Cancer Research & Treatment. 2013;137(1):13-21.

77. Shridharani SM, Magarakis M, Stapleton SM, Basdag B, Seal SM, Rosson GD. Breast sensation after breast reconstruction: a systematic review. Journal of Reconstructive Microsurgery. 2010;26(5):303-10.

78. Lee C, Sunu C, Pignone M. Patient-reported outcomes of breast reconstruction after mastectomy: a systematic review. Journal of the American College of Surgeons. 2009;209(1):123-33.

79. Sailon AM, Schachar JS, Levine JP. Free transverse rectus abdominis myocutaneous and deep inferior epigastric perforator flaps for breast reconstruction: a systematic review of flap complication rates and donor-site morbidity. Annals of Plastic Surgery. 2009;62(5):560-3.

80. Ho G, Nguyen TJ, Shahabi A, Hwang BH, Chan LS, Wong AK. A systematic review and meta-analysis of complications associated with acellular dermal matrix-assisted breast reconstruction. Annals of Plastic Surgery. 2012;68(4):346-56.

81. Jansen LA, Macadam SA. The use of AlloDerm in postmastectomy alloplastic breast reconstruction: part I. A systematic review. Plastic & Reconstructive Surgery. 2011;127(6):2232-44.

82. JoAnna Nguyen T, Carey JN, Wong AK. Use of human acellular dermal matrix in implant-based breast reconstruction: evaluating the evidence. Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS. 2011;64(12):1553-61.

83. Newman MI, Swartz KA, Samson MC, Mahoney CB, Diab K. The true incidence of near-term postoperative complications in prosthetic breast reconstruction utilizing human acellular dermal matrices: a meta-analysis. Aesthetic Plastic Surgery. 2011;35(1):100-6.

84. Sbitany H, Serletti JM. Acellular dermis-assisted prosthetic breast reconstruction: a systematic and critical review of efficacy and associated morbidity. Plastic & Reconstructive Surgery. 2011;128(6):1162-9.

85. Claro F, Jr., Figueiredo JC, Zampar AG, Pinto-Neto AM. Applicability and safety of autologous fat for reconstruction of the breast. British Journal of Surgery. 2012;99(6):768-80.

86. Berry T, Brooks S, Sydow N, Djohan R, Nutter B, Lyons J, et al. Complication rates of radiation on tissue expander and autologous tissue breast reconstruction. Annals of Surgical Oncology. 2010;17 Suppl 3:202-10.

87. Chang EI, Vaca L, DaLio AL, Festekjian JH, Crisera CA. Assessment of advanced age as a risk factor in microvascular breast reconstruction. Annals of Plastic Surgery. 2011;67(3):255-9.

88. Chen CL, Shore AD, Johns R, Clark JM, Manahan M, Makary MA. The impact of obesity on breast surgery complications. Plastic & Reconstructive Surgery. 2011;128(5):395e-402e.

89. Hu YY, Weeks CM, In H, Dodgion CM, Golshan M, Chun YS, et al. Impact of neoadjuvant chemotherapy on breast reconstruction. Cancer. 2011;117(13):2833-41.

90. Jandali S, Nelson JA, Sonnad SS, Low DW, Kovach SJ, Wu LC, et al. Breast reconstruction with free tissue transfer from the abdomen in the morbidly obese. Plastic & Reconstructive Surgery. 2011;127(6):2206-13.

91. Khansa I, Colakoglu S, Curtis MS, Yueh JH, Ogunleye A, Tobias AM, et al. Postmastectomy breast reconstruction after previous lumpectomy and radiation therapy: analysis of complications and satisfaction. Annals of Plastic Surgery. 2011;66(5):444-51.

92. Donker M, Hage JJ, Woerdeman LA, Rutgers EJ, Sonke GS, Vrancken Peeters MJ. Surgical complications of skin sparing mastectomy and immediate prosthetic reconstruction after neoadjuvant chemotherapy for invasive breast cancer. European Journal of Surgical Oncology. 2012;38(1):25-30.

93. Garvey PB, Villa MT, Rozanski AT, Liu J, Robb GL, Beahm EK. The advantages of free abdominal-based flaps over implants for breast reconstruction in obese patients. Plastic & Reconstructive Surgery. 2012;130(5):991-1000.

94. Kelley BP, Valero V, Yi M, Kronowitz SJ. Tamoxifen increases the risk of microvascular flap complications in patients undergoing microvascular breast reconstruction. Plastic & Reconstructive Surgery. 2012;129(2):305-14.

95. Kulkarni AR, Katz S, Hamilton AS, Graff JJ, Alderman AK. Patterns of use and patient satisfaction with breast reconstruction among obese patients: results from a population-based study. Plastic & Reconstructive Surgery. 2012;130(2):263-70.

96. Ochoa O, Chrysopoulo M, Nastala C, Ledoux P, Pisano S. Abdominal wall stability and flap complications after deep inferior epigastric perforator flap breast reconstruction: does body mass index make a difference? Analysis of 418 patients and 639 flaps. Plastic & Reconstructive Surgery. 2012;130(1):21e-33e.

97. Duggal CS, Grudziak J, Metcalfe DB, Carlson GW, Losken A. The effects of breast size in unilateral postmastectomy breast reconstruction. Annals of Plastic Surgery. 2013;70(5):506-12.

98. Fischer JP, Nelson JA, Sieber B, Cleveland E, Kovach SJ, Wu LC, et al. Free tissue transfer in the obese patient: an outcome and cost analysis in 1258 consecutive abdominally based reconstructions. Plastic & Reconstructive Surgery. 2013;131(5):681e-92e.

99. Fischer JP, Sieber B, Nelson JA, Cleveland E, Kovach SJ, Wu LC, et al. Comprehensive outcome and cost analysis of free tissue transfer for breast reconstruction: an experience with 1303 flaps. Plastic & Reconstructive Surgery. 2013;131(2):195-203.

100. Hanwright PJ, Davila AA, Hirsch EM, Khan SA, Fine NA, Bilimoria KY, et al. The differential effect of BMI on prosthetic versus autogenous breast reconstruction: A multivariate analysis of 12,986 patients. Breast. 2013;22(5):938-45.

101. Kneubil MC, Brollo J, Botteri E, Curigliano G, Rotmensz N, Goldhirsch A, et al. Breast cancer subtype approximations and loco-regional recurrence after immediate breast reconstruction. European Journal of Surgical Oncology. 2013;39(3):260-5.

102. Nelson JA, Fosnot J, Selber JC, Wu LC, Serletti JM. Age and abdominal wall strength: assessing the aging abdominal wall after autologous breast reconstruction. Microsurgery. 2013;33(1):14-23.

103. Schaverien MV, Munnoch DA. Effect of neoadjuvant chemotherapy on outcomes of immediate free autologous breast reconstruction. European Journal of Surgical Oncology. 2013;39(5):430-6.

104. Yezhelyev M, Duggal CS, Carlson GW, Losken A. Complications of latissimus dorsi flap breast reconstruction in overweight and obese patients. Annals of Plastic Surgery. 2013;70(5):557-62.

105. Giacalone PL, Rathat G, Daures JP, Benos P, Azria D, Rouleau C. New concept for immediate breast reconstruction for invasive cancers: feasibility, oncological safety and esthetic outcome of post-neoadjuvant therapy immediate breast reconstruction versus delayed breast reconstruction: a prospective pilot study. Breast Cancer Research & Treatment. 2010;122(2):439-51.

106. Patel KM, Albino F, Fan KL, Liao E, Nahabedian MY. Microvascular autologous breast reconstruction in the context of radiation therapy: comparing two reconstructive algorithms. Plastic & Reconstructive Surgery. 2013;132(2):251-7.

107. Losken A, Nicholas CS, Pinell XA, Carlson GW. Outcomes evaluation following bilateral breast reconstruction using latissimus dorsi myocutaneous flaps. Annals of Plastic Surgery. 2010;65(1):17-22.

108. Hvilsom GB, Friis S, Frederiksen K, Steding-Jessen M, Henriksen TF, Lipworth L, et al. The clinical course of immediate breast implant reconstruction after breast cancer. Acta Oncologica. 2011;50(7):1045-52.

109. Baltaci Goktas S, Gulluoglu BM, Selimen D. Immediate or delayed breast reconstruction after radical mastectomy in breast cancer patients: Does it make a difference in the quality of life

Meme kanseri hastalannda radikal mastektomi sonrasi{dotless}nda hemen veya gec yapi{dotless}lan meme rekonstruksiyonu: hayat kalitesinde bir fark yarati{dotless}r mi{dotless}? Turkiye Klinikleri Journal of Medical Sciences. 2011;31(3):664-73.

110. Alderman AK, Collins ED, Schott A, Hughes ME, Ottesen RA, Theriault RL, et al. The impact of breast reconstruction on the delivery of chemotherapy. Cancer. 2010;116(7):1791-800.

111. Adesiyun TA, Lee BT, Yueh JH, Chen C, Colakoglu S, Anderson KE, et al. Impact of sequencing of postmastectomy radiotherapy and breast reconstruction on timing and rate of complications and patient satisfaction. International Journal of Radiation Oncology, Biology, Physics. 2011;80(2):392-7.

112. Lee BT, T AA, Colakoglu S, Curtis MS, Yueh JH, K EA, et al. Postmastectomy radiation therapy and breast reconstruction: an analysis of complications and patient satisfaction. Annals of Plastic Surgery. 2010;64(5):679-83.

113. Lentz R, Ng R, Higgins SA, Fusi S, Matthew M, Kwei SL. Radiation therapy and expander-implant breast reconstruction: an analysis of timing and comparison of complications. Annals of Plastic Surgery. 2013;71(3):269-73.

114. Pestana IA, Campbell DC, Bharti G, Thompson JT. Factors affecting complications in radiated breast reconstruction. Annals of Plastic Surgery. 2013;70(5):542-5.

115. Christante D, Pommier SJ, Diggs BS, Samuelson BT, Truong A, Marquez C, et al. Using complications associated with postmastectomy radiation and immediate breast reconstruction to improve surgical decision making. Archives of Surgery. 2010;145(9):873-8.

116. Fosnot J, Fischer JP, Smartt JM, Jr., Low DW, Kovach SJ, 3rd, Wu LC, et al. Does previous chest wall irradiation increase vascular complications in free autologous breast reconstruction? Plastic & Reconstructive Surgery. 2011;127(2):496-504.

117. Lin KY, Blechman AB, Brenin DR. Implant-based, two-stage breast reconstruction in the setting of radiation injury: an outcome study. Plastic & Reconstructive Surgery. 2012;129(4):817-23.

118. Kim HJ, Park EH, Lim WS, Seo JY, Koh BS, Lee TJ, et al. Nipple areola skin-sparing mastectomy with immediate transverse rectus abdominis musculocutaneous flap reconstruction is an oncologically safe procedure: a single center study. Annals of Surgery. 2010;251(3):493-8.

119. Boneti C, Yuen J, Santiago C, Diaz Z, Robertson Y, Korourian S, et al. Oncologic safety of nipple skin-sparing or total skin-sparing mastectomies with immediate reconstruction. Journal of the American College of Surgeons. 2011;212(4):686-93; discussion 93-5.

120. Burdge EC, Yuen J, Hardee M, Gadgil PV, Das C, Henry-Tillman R, et al. Nipple Skin-Sparing Mastectomy is Feasible for Advanced Disease. Annals of Surgical Oncology. 2013;20(10):3294-302.

121. Min SY, Kim HY, Jung SY, Kwon Y, Shin KH, Lee S, et al. Oncological safety and quality of life associated with mastectomy and immediate breast reconstruction with a latissimus dorsi myocutaneous flap. Breast Journal. 2010;16(4):356-61.

122. Sackey H, Sandelin K, Frisell J, Wickman M, Brandberg Y. Ductal carcinoma in situ of the breast. Long-term follow-up of health-related quality of life, emotional reactions and body image. European Journal of Surgical Oncology. 2010;36(8):756-62.

123. Collins KK, Liu Y, Schootman M, Aft R, Yan Y, Dean G, et al. Effects of breast cancer surgery and surgical side effects on body image over time. Breast Cancer Research & Treatment. 2011;126(1):167-76.

124. Heneghan HM, Prichard RS, Lyons R, Regan PJ, Kelly JL, Malone C, et al. Quality of life after immediate breast reconstruction and skin-sparing mastectomy - a comparison with patients undergoing breast conserving surgery. European Journal of Surgical Oncology. 2011;37(11):937-43.

125. Shi HY, Uen YH, Yen LC, Culbertson R, Juan CH, Hou MF. Two-year quality of life after breast cancer surgery: a comparison of three surgical procedures. European Journal of Surgical Oncology. 2011;37(8):695-702.

126. Agarwal S, Liu JH, Crisera CA, Buys S, Agarwal JP. Survival in breast cancer patients undergoing immediate breast reconstruction. Breast Journal. 2010;16(5):503-9.

127. Avraham T, Daluvoy SV, Riedel ER, Cordeiro PG, Van Zee KJ, Mehrara BJ. Tissue expander breast reconstruction is not associated with an increased risk of lymphedema. Annals of Surgical Oncology. 2010;17(11):2926-32.

128. De Gournay E, Bonnetain F, Tixier H, Loustalot C, Dabakuyo S, Cuisenier J. Evaluation of quality of life after breast reconstruction using an autologous latissimus dorsi myocutaneous flap. European Journal of Surgical Oncology. 2010;36(6):520-7.

129. Kontos M, Lewis RS, Luchtenborg M, Holmberg L, Hamed H. Does immediate breast reconstruction using free flaps lead to delay in the administration of adjuvant chemotherapy for breast cancer? European Journal of Surgical Oncology. 2010;36(8):745-9.

130. Eriksen C, Frisell J, Wickman M, Lidbrink E, Krawiec K, Sandelin K. Immediate reconstruction with implants in women with invasive breast cancer does not affect oncological safety in a matched cohort study. Breast Cancer Research & Treatment. 2011;127(2):439-46.

131. Reddy S, Colakoglu S, Curtis MS, Yueh JH, Ogunleye A, Tobias AM, et al. Breast cancer recurrence following postmastectomy reconstruction compared to mastectomy with no reconstruction. Annals of Plastic Surgery. 2011;66(5):466-71.

132. Yi M, Kronowitz SJ, Meric-Bernstam F, Feig BW, Symmans WF, Lucci A, et al. Local, regional, and systemic recurrence rates in patients undergoing skin-sparing mastectomy compared with conventional mastectomy. Cancer. 2011;117(5):916-24.

133. Agarwal J, Agarwal S, Pappas L, Neumayer L. A population-based study of breast cancer-specific survival following mastectomy and immediate or early-delayed breast reconstruction. Breast Journal. 2012;18(3):226-32.

134. Card A, Crosby MA, Liu J, Lindstrom WA, Lucci A, Chang DW. Reduced incidence of breast cancer-related lymphedema following mastectomy and breast reconstruction versus mastectomy alone. Plastic & Reconstructive Surgery. 2012;130(6):1169-78.

135. Lee TJ, Hur WJ, Kim EK, Ahn SH. Outcome of management of local recurrence after immediate transverse rectus abdominis myocutaneous flap breast reconstruction. Archives of Plastic Surgery. 2012;39(4):376-83.

136. Nguyen TJ, Costa MA, Vidar EN, Shahabi A, Peric M, Hernandez AM, et al. Effect of immediate reconstruction on postmastectomy surgical site infection. Annals of Surgery. 2012;256(2):326-33.

137. Prabhu R, Godette K, Carlson G, Losken A, Gabram S, Fasola C, et al. The impact of skin-sparing mastectomy with immediate reconstruction in patients with Stage III breast cancer treated with neoadjuvant chemotherapy and postmastectomy radiation. International Journal of Radiation Oncology, Biology, Physics. 2012;82(4):e587-93.

138. Shi A, Wu D, Li X, Zhang S, Li S, Xu H, et al. Subcutaneous nipple-sparing mastectomy and immediate breast reconstruction. Breast Care. 2012;7(2):131-6.

139. Zhong T, Hofer SO, McCready DR, Jacks LM, Cook FE, Baxter N. A comparison of surgical complications between immediate breast reconstruction and mastectomy: the impact on delivery of chemotherapy--an analysis of 391 procedures. Annals of Surgical Oncology. 2012;19(2):560-6.

140. de Oliveira RR, do Nascimento SL, Derchain SF, Sarian LO. Immediate breast reconstruction with a Latissimus dorsi flap has no detrimental effects on shoulder motion or postsurgical complications up to 1 year after surgery. Plastic & Reconstructive Surgery. 2013;131(5):673e-80e.

141. Eltahir Y, Werners LL, Dreise MM, van Emmichoven IA, Jansen L, Werker PM, et al. Quality-of-life outcomes between mastectomy alone and breast reconstruction: comparison of patient-reported BREAST-Q and other health-related quality-of-life measures. Plastic & Reconstructive Surgery. 2013;132(2):201e-9e.

142. Lee KT, Mun GH, Lim SY, Pyon JK, Oh KS, Bang SI. The impact of immediate breast reconstruction on post-mastectomy lymphedema in patients undergoing modified radical mastectomy. Breast. 2013;22(1):53-7.

143. Sakurai T, Zhang N, Suzuma T, Umemura T, Yoshimura G, Sakurai T, et al. Long-term follow-up of nipple-sparing mastectomy without radiotherapy: a single center study at a Japanese institution. Medical Oncology. 2013;30(1):481.

144. Vandergrift JL, Niland JC, Theriault RL, Edge SB, Wong YN, Loftus LS, et al. Time to adjuvant chemotherapy for breast cancer in National Comprehensive Cancer Network institutions. Journal of the National Cancer Institute. 2013;105(2):104-12.

145. Chun YS, Sinha I, Turko A, Yueh JH, Lipsitz S, Pribaz JJ, et al. Comparison of morbidity, functional outcome, and satisfaction following bilateral TRAM versus bilateral DIEP flap breast reconstruction. Plastic & Reconstructive Surgery. 2010;126(4):1133-41.

146. Macadam SA, Ho AL, Cook EF, Jr., Lennox PA, Pusic AL. Patient satisfaction and health-related quality of life following breast reconstruction: patient-reported outcomes among saline and silicone implant recipients. Plastic & Reconstructive Surgery. 2010;125(3):761-71.

147. Nelson JA, Guo Y, Sonnad SS, Low DW, Kovach SJ, 3rd, Wu LC, et al. A Comparison between DIEP and muscle-sparing free TRAM flaps in breast reconstruction: a single surgeon's recent experience. Plastic & Reconstructive Surgery. 2010;126(5):1428-35.

148. Yueh JH, Slavin SA, Adesiyun T, Nyame TT, Gautam S, Morris DJ, et al. Patient satisfaction in postmastectomy breast reconstruction: a comparative evaluation of DIEP, TRAM, latissimus flap, and implant techniques. Plastic & Reconstructive Surgery. 2010;125(6):1585-95.

149. Christensen BO, Overgaard J, Kettner LO, Damsgaard TE. Long-term evaluation of postmastectomy breast reconstruction. Acta Oncologica. 2011;50(7):1053-61.

150. Crosby MA, Garvey PB, Selber JC, Adelman DM, Sacks JM, Villa MT, et al. Reconstructive outcomes in patients undergoing contralateral prophylactic mastectomy. Plastic & Reconstructive Surgery. 2011;128(5):1025-33.

151. Garvey PB, Salavati S, Feng L, Butler CE. Perfusion-related complications are similar for DIEP and muscle-sparing free TRAM flaps harvested on medial or lateral deep inferior epigastric Artery branch perforators for breast reconstruction.[Erratum appears in Plast Reconstr Surg. 2012 Jan;129(1):291]. Plastic & Reconstructive Surgery. 2011;128(6):581e-9e.

152. Monrigal E, Dauplat J, Gimbergues P, Le Bouedec G, Peyronie M, Achard JL, et al. Mastectomy with immediate breast reconstruction after neoadjuvant chemotherapy and radiation therapy. A new option for patients with operable invasive breast cancer. Results of a 20 years single institution study. European Journal of Surgical Oncology. 2011;37(10):864-70.

153. Crosby MA, Card A, Liu J, Lindstrom WA, Chang DW. Immediate breast reconstruction and lymphedema incidence. Plastic & Reconstructive Surgery. 2012;129(5):789e-95e.

154. Levine SM, Patel N, Disa JJ. Outcomes of delayed abdominal-based autologous reconstruction versus latissimus dorsi flap plus implant reconstruction in previously irradiated patients. Annals of Plastic Surgery. 2012;69(4):380-2.

155. Momoh AO, Colakoglu S, Westvik TS, Curtis MS, Yueh JH, de Blacam C, et al. Analysis of complications and patient satisfaction in pedicled transverse rectus abdominis

myocutaneous and deep inferior epigastric perforator flap breast reconstruction. Annals of Plastic Surgery. 2012;69(1):19-23.

156. Pompei S, Arelli F, Labardi L, Marcasciano F, Caravelli G, Cesarini C, et al. Breast reconstruction with polyurethane implants: Preliminary report. European Journal of Plastic Surgery. 2012;35(6):441-7.

157. Singh N, Reaven NL, Funk SE. Immediate 1-stage vs. tissue expander postmastectomy implant breast reconstructions: a retrospective real-world comparison over 18 months. Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS. 2012;65(7):917-23.

158. Tong WM, Bazakas A, Hultman CS, Halvorson EG. The transition from pedicle transverse rectus abdominis myocutaneous to perforator flap: what is the cost of opportunity? Annals of Plastic Surgery. 2012;68(5):489-94.

159. Chang EI, Liu TS, Festekjian JH, Da Lio AL, Crisera CA. Effects of radiation therapy for breast cancer based on type of free flap reconstruction. Plastic & Reconstructive Surgery. 2013;131(1):1e-8e.

160. Costa MA, Rommer E, Peric M, Nguyen TJ, Shahabi A, Davis GB, et al. Incidence of surgical-site infection is not affected by method of immediate breast reconstruction. Plastic & Reconstructive Surgery. 2013;132(1):20e-9e.

161. Davila AA, Mioton LM, Chow G, Wang E, Merkow RP, Bilimoria KY, et al. Immediate two-stage tissue expander breast reconstruction compared with one-stage permanent implant breast reconstruction: A multi-institutional comparison of short-term complications. Journal of Plastic Surgery and Hand Surgery. 2013;47(5):344-9.

162. Fischer JP, Nelson JA, Cleveland E, Sieber B, Rohrbach JI, Serletti JM, et al. Breast reconstruction modality outcome study: a comparison of expander/implants and free flaps in select patients. Plastic & Reconstructive Surgery. 2013;131(5):928-34.

163. Mioton LM, Smetona JT, Hanwright PJ, Seth AK, Wang E, Bilimoria KY, et al. Comparing thirty-day outcomes in prosthetic and autologous breast reconstruction: a multivariate analysis of 13,082 patients? Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS. 2013;66(7):917-25.

164. Winters ZE, Haviland J, Balta V, Benson J, Reece-Smith A, Betambeau N, et al. Integration of patient-reported outcome measures with key clinical outcomes after immediate latissimus dorsi breast reconstruction and adjuvant treatment. British Journal of Surgery. 2013;100(2):240-51.

165. Venturi ML, Mesbahi AN, Boehmler JHt, Marrogi AJ. Evaluating sterile human acellular dermal matrix in immediate expander-based breast reconstruction: a multicenter, prospective, cohort study. Plastic & Reconstructive Surgery. 2013;131(1):9e-18e.

166. Wu C, Cipriano J, Osgood G, Jr., Tepper D, Siddiqui A. Human acellular dermal matrix (AlloDerm()) dimensional changes and stretching in tissue expander/implant breast reconstruction. Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS. 2013;66(10):1376-81.

167. Brooke S, Mesa J, Uluer M, Michelotti B, Moyer K, Neves RI, et al. Complications in tissue expander breast reconstruction: a comparison of AlloDerm, DermaMatrix, and FlexHD acellular inferior pole dermal slings. Annals of Plastic Surgery. 2012;69(4):347-9.

168. Collis GN, TerKonda SP, Waldorf JC, Perdikis G. Acellular dermal matrix slings in tissue expander breast reconstruction: are there substantial benefits? Annals of Plastic Surgery. 2012;68(5):425-8.

169. Davila AA, Seth AK, Wang E, Hanwright P, Bilimoria K, Fine N, et al. Human Acellular Dermis versus Submuscular Tissue Expander Breast Reconstruction: A Multivariate Analysis of Short-Term Complications. Archives of Plastic Surgery. 2013;40(1):19-27.

170. Endress R, Choi MS, Lee GK. Use of fetal bovine acellular dermal xenograft with tissue expansion for staged breast reconstruction. Annals of Plastic Surgery. 2012;68(4):338-41.

171. Nguyen KT, Mioton LM, Smetona JT, Seth AK, Kim JY. Esthetic Outcomes of ADM-Assisted Expander-Implant Breast Reconstruction. Eplasty [Electronic Resource]. 2012;12:e58.

172. Parks JW, Hammond SE, Walsh WA, Adams RL, Chandler RG, Luce EA. Human acellular dermis versus no acellular dermis in tissue expansion breast reconstruction. Plastic & Reconstructive Surgery. 2012;130(4):739-46.

173. Peled AW, Foster RD, Garwood ER, Moore DH, Ewing CA, Alvarado M, et al. The effects of acellular dermal matrix in expander-implant breast reconstruction after total skin-sparing mastectomy: results of a prospective practice improvement study. Plastic & Reconstructive Surgery. 2012;129(6):901e-8e.

174. Seth AK, Hirsch EM, Fine NA, Kim JY. Utility of acellular dermis-assisted breast reconstruction in the setting of radiation: a comparative analysis. Plastic & Reconstructive Surgery. 2012;130(4):750-8.

175. Weichman KE, Wilson SC, Weinstein AL, Hazen A, Levine JP, Choi M, et al. The use of acellular dermal matrix in immediate two-stage tissue expander breast reconstruction. Plastic & Reconstructive Surgery. 2012;129(5):1049-58.

176. Choi M, Small K, Levovitz C, Lee C, Fadl A, Karp NS. The volumetric analysis of fat graft survival in breast reconstruction. Plastic & Reconstructive Surgery. 2013;131(2):185-91.

177. Seth AK, Hirsch EM, Kim JY, Fine NA. Long-term outcomes following fat grafting in prosthetic breast reconstruction: a comparative analysis. Plastic & Reconstructive Surgery. 2012;130(5):984-90.

178. Weichman KE, Broer PN, Tanna N, Wilson SC, Allan A, Levine JP, et al. The role of autologous fat grafting in secondary microsurgical breast reconstruction. Annals of Plastic Surgery. 2013;71(1):24-30.

179. Patterson SG, Teller P, Iyengar R, Carlson GW, Gabram-Mendola SG, Losken A, et al. Locoregional recurrence after mastectomy with immediate transverse rectus abdominis myocutaneous (TRAM) flap reconstruction. Annals of Surgical Oncology. 2012;19(8):2679-84.

180. Lee JM, Georgian-Smith D, Gazelle GS, Halpern EF, Rafferty EA, Moore RH, et al. Detecting nonpalpable recurrent breast cancer: the role of routine mammographic screening of transverse rectus abdominis myocutaneous flap reconstructions. Radiology. 2008;248(2):398-405.

181. Momoh AO, Colakoglu S, de Blacam C, Gautam S, Tobias AM, Lee BT. Delayed autologous breast reconstruction after postmastectomy radiation therapy: is there an optimal time? Annals of Plastic Surgery. 2012;69(1):14-8.

182. Baumann DP, Crosby MA, Selber JC, Garvey PB, Sacks JM, Adelman DM, et al. Optimal timing of delayed free lower abdominal flap breast reconstruction after postmastectomy radiation therapy. Plastic & Reconstructive Surgery. 2011;127(3):1100-6.

183. Peled AW, Foster RD, Esserman LJ, Park CC, Hwang ES, Fowble B. Increasing the time to expander-implant exchange after postmastectomy radiation therapy reduces expander-implant failure. Plastic & Reconstructive Surgery. 2012;130(3):503-9.

184. Hughes K, Brown C, Perez V, Ting JW, Rozen WM, Whitaker IS, et al. The effect of radiotherapy on implant-based breast reconstruction in the setting of skin-sparing mastectomy: clinical series and review of complications. Anticancer Research. 2012;32(2):553-7.

185. Petit JY, Botteri E, Lohsiriwat V, Rietjens M, De Lorenzi F, Garusi C, et al. Locoregional recurrence risk after lipofilling in breast cancer patients. Annals of Oncology. 2012;23(3):582-8.

186. August DA, Wilkins E, Rea T. Breast reconstruction in older women. Surgery. 1994;115(6):663-8.

187. Girotto JA, Schreiber J, Nahabedian MY. Breast reconstruction in the elderly: preserving excellent quality of life. Annals of Plastic Surgery. 2003;50(6):572-8.

188. Hirsch EM, Seth AK, Dumanian GA, Kim JY, Mustoe TA, Galiano RD, et al. Outcomes of tissue expander/implant breast reconstruction in the setting of prereconstruction radiation. Plastic & Reconstructive Surgery. 2012;129(2):354-61.

189. Leyngold MM, Stutman RL, Khiabani KT, Shah H, Fong E, Ho CH, et al. Contributing variables to post mastectomy tissue expander infection. Breast Journal. 2012;18(4):351-6.

190. Agrawal A, Sibbering DM, Courtney CA. Skin sparing mastectomy and immediate breast reconstruction: a review. European Journal of Surgical Oncology. 2013;39(4):320-8.

191. Lee BT, Duggan MM, Keenan MT, Kamatkar S, Quinlan RM, Hergrueter CA, et al. Commonwealth of Massachusetts Board of Registration in Medicine Expert Panel on

immediate implant-based breast reconstruction following mastectomy for cancer: executive summary, June 2011. Journal of the American College of Surgeons. 2011;213(6):800-5.

192. Kaufmann M, Morrow M, von Minckwitz G, Harris JR, Biedenkopf Expert Panel M. Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer. 2010;116(5):1184-91.

193. Aebi S, Davidson T, Gruber G, Castiglione M. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2010;21(SUPPL. 5):v9-v14.

194. National Comprehensive Cancer Network. Breast cancer (version 3.2014).

195. Shea-Budgell M, Quan ML, Mehling B, Temple-Oberle C. Breast reconstruction following prophylactic or therapeutic mastectomy for breast cancer: Recommendations from an evidence-based provincial guideline. Canadian Journal of Plastic Surgery. 2014;22(2):103-11.

196. Shah C, Kundu N, Arthur D, Vicini F. Radiation therapy following postmastectomy reconstruction: a systematic review. Annals of Surgical Oncology. 2013;20(4):1313-22.

197. Hart AM, Lechowicz MJ, Peters KK, Holden J, Carlson GW. Breast implant-associated anaplastic large cell lymphoma: Report of 2 cases and review of the literature. Aesthetic Surgery Journal. 2014;34(6):884-94.

198. Macadam SA, Lennox PA. Acellular dermal matrices: economic considerations in reconstructive and aesthetic breast surgery. Clinics in Plastic Surgery. 2012;39(2):187-216.

199. Chagpar A, Langstein HN, Kronowitz SJ, Singletary SE, Ross MI, Buchholz TA, et al. Treatment and outcome of patients with chest wall recurrence after mastectomy and breast reconstruction. American Journal of Surgery. 2004;187(2):164-9.

Appendix I. Members of the Working Group, the Breast Reconstruction Expert Panel, Report Approval Panel, external reviewers and their conflict of interest declarations.

Table a.1: Working Group.

Name	Affiliation	Declarations of interest
Toni Zhong Plastic and Reconstructive Surgeon	University Health Network Toronto, Ontario	*Professional interest:* Principal investigator for a clinical trial involving the objects of study (multi-centred Canadian acellular dermal matrix randomized controlled trial published a clear opinion regarding the objects of study (MCCAI trial)
Kirsty Boyd Plastic Surgeon	The Ottawa Hospital Ottawa, Ontario	*Financial interest*: serves as a consultant for LifeCell. *Financial interest from professional income:* as a breast reconstruction surgeon, income may either increase or decrease depending on guidelines but not related to industry. *Professional interest:* received an educational grant from Allergen (co-chair) to run chief resident review course.
Renee Hanrahan Surgical Oncologist	Royal Victoria Regional Health Centre Barrie, Ontario	None
Muriel Brackstone Surgeon	Victoria Hospital London, Ontario	None
Tim Whelan Radiation Oncologist	Juravinski Cancer Centre Hamilton, Ontario	None
Karen Spithoff Health Research Methodologist	McMaster University, Department of Oncology, Program in Evidence-Based Care Hamilton, Ontario	None

Table a.2: Members of Cancer Care Ontario (CCO) Staff

Name	Affiliation	Declarations of Interest
Amber Hunter Manager	CCO, Surgical Oncology Program Toronto, Ontario	None
Robin McLeod Surgeon VP, Clinical Programs and Quality Initiatives	Mount Sinai Hospital Toronto, Ontario and CCO, Toronto, Ontario	None
Jonathan Irish Surgeon CCO-Provincial Head Clinical Programs	University Health Network Toronto, Ontario	None

Table a.3: Breast Reconstruction Expert Panel

Name	Affiliation	Declarations of interest
Alice Wei Surgical Oncologist CCO-Clinical Lead Surgical Oncology	Toronto General Hospital Toronto, Ontario	None
Susan Done Pathologist	Princess Margaret Hospital Toronto, Ontario	None
Deepa Kumar Surgical Oncologist	Credit Valley Hospital Mississauga, Ontario	None
Dr. Nancy Down Surgeon	North York General Hospital Toronto, Ontario	None
Orit Freedman Medical Oncologist	Durham Regional Cancer Centre Oshawa, Ontario	None
Sandip SenGupta Pathologist	Kingston General Hospital Kingston, Ontario	None
Sundeep Shahi Radiation Oncologist	Grand River Regional Cancer Center Kitchener, Ontario	None
Arianna Dal Cin Plastic Surgeon	McMaster University, Hamilton Health Sciences Hamilton, Ontario	*Publication:* Strang B, Murphy K, Seal S, Dal Cin A. Does the presence of an implant including expander with internal port alter radiation dose? An ex vivo model. Can J Plast Surg. Spring 2013 Vol21:1, 37-40 *Presentation:* Tissue expansion followed by radiation in a porcine model: a pilot study" at the Canadian Association of Laboratory Animal Science Meeting in 2010. *Financial Interest:* Application for more than $5000 for a single year from the Breast Reconstruction Fellowship Fund sponsored by Allergan and Mentor; however, as of the Conflict of Interest declaration (December 3, 2014) no response has been received.
Robert Shenker Plastic Surgeon	The Cosmetic Surgery Clinic Waterloo, Ontario	*Financial Interest:* travel support from a business entity to attend a symposium, but no financial information about the trip was available. *Financial interest from professional income:* as an owner of a cosmetic surgery center, income may either increase or decrease depending

		on guidelines but not related to industry. Other: Frequently speaks publically about breast reconstruction
Julia Jones Surgical Oncologist	Taunton Surgical Centre Oshawa, Ontario	*Financial interest from professional income:* as a general surgeon, income may either increase or decrease depending on guidelines but not related to industry.
Doug McKay Plastic and reconstructive surgeon	Kingston General Hospital Kingston, Ontario	*Financial Interest:* attended a Breast Bioskins Lab on October 17-18, 2014 sponsored by LifeCell.

Table a.4 External Review Targeted Peer Reviewers

Andrea Eisen	Sunnybrook Health Sciences Centre Toronto, Ontario	None
Kristen Gyetvai	Windsor Regional Hospital Windsor, Ontario	None

Conflict of Interest

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Breast Reconstruction Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest. Two authors declared that they had conflicts of interest (TZ, KUB). The PEBC director waived the requirement that the lead author have no professional interest as per the PEBC COI Policy. The conflicts declared did not disqualify any individuals from performing their designated role in the development of this guideline. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi.mcmaster.ca.

For the Expert Panel, eight members declared they had no conflicts of interest (JI, SD, DK, NK-D, OF, SS, AW, SS), and four (AD, RS, JJ, DM) declared conflicts. AD has reported publishing a research study (Strang B, Murphy K, Seal S, Dal Cin A. Does the presence of an implant including expander with internal port alter radiation dose? An ex vivo model. Can J Plast Surg. Spring 2013 Vol 21:1, 37-40), as well as a presentation entitled "Tissue expansion followed by radiation in a porcine model: a pilot study" at the Canadian Association of Laboratory Animal Science Meeting in 2010. AD also reported applying for more than $5000 for a single year from the Breast Reconstruction Fellowship Fund sponsored by Allergan and Mentor; however, as of the Conflict of Interest declaration (December 3, 2014) no response has been received. RS reported receiving travel support from a business entity to attend a symposium, but no financial information about the trip was available. RS is also the owner of a cosmetic surgery center and performs breast reconstructions. He is unsure how this guideline will affect his professional income. RS also frequently speaks publicly about breast reconstruction. JJ indicated that she is a general surgeon who performs mastectomies and is unaware how this guideline will affect her professional income. DM declared that he attended a Breast Bioskins Lab on October 17-18, 2014 sponsored by LifeCell.

Appendix II. Search for existing evidence-based guidelines.

In March 2013, a search was conducted to identify existing evidence-based guidelines that were suitable for adaptation in the Ontario context. Guidelines that were published in the English language between 2008 and March 2013, were based on a systematic review of evidence, and addressed one or more topics of interest were considered. A search was conducted in the Standards and Guidelines Evidence (SAGE) directory of cancer guidelines (www.cancerview.ca/sage). This search was supplemented with a Google search using the terms "breast reconstruction" and "recommendations" or "guideline" and a search of the Medline and EMBASE databases. In addition, the Working Group was aware of a guideline on breast reconstruction being developed by Alberta Health Services.

In total, 28 guidelines were identified that addressed one or more topics of interest related to breast reconstruction. These guidelines were reviewed for relevancy, currency, quality and suitability for adaptation. Fifteen of the 28 guidelines were excluded because they did not include a systematic review of the evidence. Others were excluded due to incomplete coverage of the topics of interest or because their literature searches were out of date.

The Alberta Health Services guideline (66) was published online in September 2013 and was considered for adaptation. The Working Group reviewed the content of the guideline and assessed its quality using the AGREE II instrument (36). Following thorough review, the Working Group decided not to adapt the Alberta Health Services guideline and instead decided to conduct its own literature search and develop its own recommendations for breast reconstruction in the Ontario context. The clinical questions from the Alberta Health Services guideline were used as the basis for the CCO PEBC guideline.

Appendix III. Literature Search Strategies.

MEDLINE (OVID)

1. exp breast neoplasms/
2. (breast adj6 (cancer: or neoplasm: or carcinoma: or tumour: or tumor:)).mp.
3. (mastectom: or (breast and reconstruct:)).mp.
4. or/1-3
5. exp mammaplasty/
6. (mammaplast: or mammoplast:).mp.
7. breast implants/
8. "prostheses and implants"/
9. Reconstructive Surgical Procedures/
10. exp Surgical Flaps/
11. (breast adj6 reconstruct:).mp.
12. (("deep inferior epigastric" or DIEP) adj6 flap:).mp.
13. (("transverse rectus abdominus" or TRAM) adj6 flap:).mp.
14. (("superficial inferior epigastric" or SIEA) adj6 flap:).mp.
15. (("latissimus dorsi" or LD) adj6 flap:).mp.
16. breast implant:.mp.
17. (("skin sparing" or "skin-sparing" or "nipple sparing" or "nipple-sparing") adj6 mastectomy).mp.
18. acellular derm:.mp.
19. ("fat grafting" or lipomodelling or "fat transfer" or fat injection: or lipofilling).mp.
20. or/5-19
21. 4 and 20
22. (case reports or letter or comment or editorial or news).pt.
23. 21 not 22
24. exp animals/ not humans/
25. 23 not 24
26. limit 25 to english language
27. limit 26 to yr="2010 -Current"

MEDLINE In-Process & Other Non-Indexed Citations (OVID)

1. (breast adj6 (cancer: or neoplasm: or carcinoma: or tumour: or tumor:)).mp.
2. (mastectomy: or (breast or reconstruct:)).mp.
3. 1 or 2
4. (mammaplast: or mammoplasty:).mp.
5. (breast adj6 reconstruct:).mp.
6. ((“deep inferior epigastric” or DIEP) adj6 flap:).mp.
7. ((“transverse rectus abdominus” or TRAM) adj6 flap:).mp.
8. ((“superficial inferior epigastric” or SIEA) adj6 flap:).mp.
9. ((“latissimus dorsi” or LD) adj6 flap:).mp.
10. breast implant:.mp.
11. ((“skin sparing” or “skin-sparing” or “nipple sparing” or “nipple-sparing”) adj6 mastectomy).mp.
12. acellular derm:.mp.
13. (“fat grafting” or lipomodelling or “fat transfer” or fat injection: or lipofilling).mp.
14. or/4-13
15. 3 and 14
16. limit 15 to English language
17. limit 16 to yr=”2010 –Current”

EMBASE (OVID)

1. exp breast cancer/
2. breast tumor/
3. (breast adj6 (cancer: or neoplasm: or carcinoma: or tumour: or tumor:)).mp.
4. (mastectom: or (breast and reconstruct:)).mp.

5. or/1-4
6. exp breast reconstruction/
7. (mammaplast: or mammoplast:).mp.
8. exp breast implant/
9. exp "prostheses and orthoses"/
10. plastic surgery/
11. Surgical Flaps/
12. (breast adj6 reconstruct:).mp.
13. (("deep inferior epigastric" or DIEP) adj6 flap:).mp.
14. (("transverse rectus abdominus" or TRAM) adj6 flap:).mp.
15. (("superficial inferior epigastric" or SIEA) adj6 flap:).mp.
16. (("latissimus dorsi" or LD) adj6 flap:).mp.
17. breast implant:.mp.
18. (("skin sparing" or "skin-sparing" or "nipple sparing" or "nipple-sparing") adj6 mastectomy).mp.
19. acellular derm:.mp.
20. ("fat grafting" or lipomodelling or "fat transfer" or fat injection: or lipofilling).mp.
21. or/6-20
22. 5 and 21
23. (editorial or letter or note or journal editorial or journal letter or journal note or conference abstract).pt.
24. 22 not 23
25. limit 24 to english language
26. limit 25 to yr="2010 -Current"
27. limit 26 to exclude medline journals
28. animal/ not human/
29. 27 not 28

Appendix IV. Quality assessment of included systematic reviews (AMSTAR).

Systematic review	'A priori' design	Duplicate study selection and data extraction	Comprehensive literature search	Status of publication as inclusion criterion	List of included and excluded studies	Characteristics of included studies provided	Scientific quality of included studies assessed	Scientific quality of included studies used appropriately in formulating conclusions	Methods used to combine findings of studies appropriate	Likelihood of publication bias assessed	Conflict of interest included
Walton 2011	N	N	Y	N	N	Y	N	N	N/A	N	N
Wolfswinkel 2013	N	N	N	N	N	N	N	N	N	Y	N
Barry 2011	N	N	N	N	N	N	N	N	N	N	N
Schaverien 2013	N	N	Y	N	N	Y	Y	Y	Y	N	N
Kelley 2014	Y	N	N	N	N	Y	N	N	Y	N	N
Momoh 2014	Y	Y	N	N	N	Y	N	N	Y	N	N
D'Souza 2011	Y	Y	Y	N	Y	Y	Y	Y	N/A	Y	N
Lam 2013	N	N	Y	N	N	Y	N	N	Y	N	N
Lanitis 2010	N	Y	Y	N	N	Y	Y	Y	Y	Y	N
Mallon 2013	N	NR	N	NR	N	Y	N	N	N	N	N
Rusby 2010	N	NR	N	N	N	Y	N	N	N/A	N	N
Endara 2013	Y	N	Y	N	N	Y	N	N	N	N	N
Murthy 2013	N	N	Y	N	N	Y	N	N	N	N	N
Fang 2013	N	N	Y	Y	Y	Y	N	N	Y	Y	N
Gieni 2012	Y	N	Y	N	N	Y	N	N	Y	Y	N
Shridharani 2010	N	N	Y	N	N	Y	N	N	N/A	N	N
Lee 2009	N	Y	Y	N	Y	Y	N	N	N/A	N	N
Tsoi 2014	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N
Tsoi 2014	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N
Atisha 2009	N	N	Y	N	N	Y	N	N	N/A	N	N
Egeberg 2012	N	N	Y	Y	N	Y	N	N	Y	Y	N
Khansa 2013	N	N	N	N	N	N	N	N	N	N	N
Man 2009	N	N	Y	N	N	Y	N	N	Y	Y	N
Sailon 2009	N	N	N	N	N	Y	N	N	N	N	N
Clemens 2012	N	NR	Y	N	N	Y	N	N	N/A	N	N

Systematic review	'A priori' design	Duplicate study selection and data extraction	Comprehensive literature search	Status of publication as inclusion criterion	List of included and excluded studies	Characteristics of included studies provided	Scientific quality of included studies assessed	Scientific quality of included studies used appropriately in formulating conclusions	Methods used to combine findings of studies appropriate	Likelihood of publication bias assessed	Conflict of interest included
Ho 2012	N	N	Y	N	Y	Y	Y	Y	Y	Y	N
Hoppe 2011	N	N	Y	N	N	Y	N	N	Y	N	N
Jansen 2011	N	Y	Y	Y	N	Y	N	N	N/A	N	N
Nguyen 2011	N	N	N	N	N	N	N	N	N/A	N	N
Kim 2012	Unclear	Y	N	N	N	Y	N	N	Y	Y	N
Newman 2011	N	N	N	N	N	N	N	N	N/A	N	N
Sbitany 2011	N	N	Y	N	Y	Y	N	N	N	Y	N
Krastev 2013	N	NR	Y	N	N	Y	Y	Y	NR	N	N
Claro Jr. 2012	N	Y	Y	Y	Y	Y	Y	Y	N/A	N	N
Saint-Cyr 2012	N	NR	Y	N	N	Y	N	N	Y	N	N
Barnsley 2007	N	N	Y	N	N	Y	N	N	Y	N	N

Abbreviations: N: no; N/A: not applicable; Y: yes

Appendix V: Guideline Document History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original Jan 5, 2016	2010 through Sep 2013	Full Report	PEBC Website	
Nov 26, 2019	None	Warning added to cover page and Recommendation 6	PEBC Website	Warning on Increased risk for Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)
March 3, 2021	None	Assessed as needing update	PEBC Website	Cover page indicates guideline is to be updated due to assessment in January 2021
November 2021	None	Interim change to Recommendations 3 and 8.	PEBC Website	In the interim, the following changes were made in consultation with the Surgical Oncology Program and the Breast Cancer Advisory Committee to reflect current practice and concerns: Recommendation 3: In patients expected to require radiotherapy, the timing of breast reconstruction should be determined after multidisciplinary discussion including the general surgeon or surgical oncologist, medical oncologist, radiation oncologist, and plastic surgeon and with full consideration of the values and preferences of the patient. Recommendation 8: Acellular dermal matrix (ADM) is currently widely used in breast reconstruction. The US FDA has issued a safety communication indicating that the complication rate (reoperation, explantation, and infections) may vary depending on the type of ADM, and this is being investigated.