Breast Cancer

4

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Introduction

Breast cancer is the most common cancer among Canadian women with the exception of non-melanoma skin cancer. An estimated 26, 300 new cases occurred in Canada in 2017. Breast cancer is responsible for 26% of all new cancers in women and 13% of all cancer-related deaths in women. One in every 8 women is expected to develop breast cancer during her lifetime, and 1 in 31 women will die of breast cancer [1].

Presentation	Prognosis 5-Year overall survival (OS)
Early breast cancer[a] (75–80%)	90–100%
Locally advanced breast cancer[a] (10–20%)	36–67%
Distant metastasis (5%)	22%

[a]See definitions in this chapter

The recommended staging system is the eighth edition of American Joint Committee on Cancer (AJCC) [2].

The surgical management of breast cancer requires an understanding of the complete spectrum of breast pathology, both malignant and premalignant. As a result, an overview of this continuum is presented: from high-risk pathologies, through preinvasive disease, to invasive disease and the management of some of its various subtypes.

Benign, but Worrisome

There exist pathological entities affecting the breast which bridge the divide between benign and malignant. They can present difficulty to the clinician, in terms of their appropriate management and—like many aspects of breast treatment—they are under constant review. Below we have summarized the clinical and pathological features as well as management of several of the more commonly encountered entities:

Entity	Definition and diagnosis	Treatment [3, 4]	Comments
Atypical ductal hyperplasia (ADH) [3]	A proliferation of uniform epithelial cells with monomorphic round nuclei filling part, but not all, of the involved duct Same cytology and architecture as low-grade DCIS but extent is <2 mm or less than 2 involved ducts Diagnosis: asymptomatic, incidental, often calcifications on mammography	If found on CNB, the area should be removed to ensure that no adjacent carcinoma is present If found at the margins of an excised lesion, re-excision is not generally considered necessary unless bordering on the diagnosis of DCIS, or concern that target lesion was not completely excised	Upgrade rate to DCIS or invasive carcinoma often 10–20% [3] Atypical hyperplasia confers a substantial increase in the risk of subsequent breast cancer (RR 3.7–5.3) [5] Follow with clinical exam every 6–12 months and annual screening mammogram (not before age 30); NCCN recommends consideration of tomosynthesis and annual MRI [6], but Cancer Care Ontario currently does not endorse annual MRI [7]
Atypical lobular hyperplasia (ALH) [3]	Often an incidental finding on breast biopsies done for other reasons Proliferation of monomorphic, evenly spaced, dyscohesive cells filling part, but not all, of the involved lobule ALH can also involve ducts (DIAL: duct involvement by atypical lobular cells) Same cytology and architecture of LCIS but quantitatively lesser in extent Diagnosis: asymptomatic, incidental, loss of E-cadherin [8]	If found on CNB, the area should be removed if there is imaging-pathologic discordance If found at the margins of an excised lesion, re-excision is not generally considered necessary	Upgrade rate to DCIS or invasive cancer after diagnosis of incidental ALH on CNB is <3% (usually very small, low-grade invasive carcinomas) Routine excision is not advocated if there is radiologic-pathologic concordance and no other lesions requiring excision are present [4] Similar risk of subsequent breast cancer as ADH (RR 3.7–5.3) [3] ALH is associated with an increased risk of both ipsilateral and contralateral breast cancer, with the Nurses' Health Study demonstrating that only 56% of cancers developing in women with ALH occurred in the ipsilateral breast. The cumulative incidence of breast cancer over 30 years in patients with ALH approached 35% [9] Follow with clinical exam every 6–12 months and annual screening mammogram (not before age 30); NCCN recommends consideration of tomosynthesis and annual MRI [6], but Cancer Care Ontario currently does not endorse annual MRI [7]

(continued)

Entity	Definition and diagnosis	Treatment [3, 4]	Comments
Lobular carcinoma in situ (LCIS) [3]	Abnormal cell growth in the lobules of the breast that represents an increased risk of cancer rather than being a premalignant condition per se Distinguish between classical (cLCIS) and pleomorphic (pLCIS) to plan treatment Diagnosis: asymptomatic, incidental, lacks clinical and mammographic signs, loss of E-cadherin [8]	If found on CNB, the area should be removed if there is imaging-pathologic discordance Excise any nonclassical LCIS (e.g., pleomorphic LCIS, LCIS with necrosis) If found at the margins of an excised lesion (including invasive cancer), re-excision is not generally considered necessary (unless nonclassical LCIS is found at the margin) Multifocal/extensive LCIS involving >4 terminal ductal lobular units on CNB may be associated with an increased risk of invasive cancer on excision [6]	Relative risk of developing invasive cancer is 7–11-fold; absolute risk is 1%/year and is lifelong [3] If there is radiologic-pathologic concordance and no other lesions with risk of concomitant malignancy (i.e., ADH, papilloma, radial scar) are present, upgrade rate is <5% [4] and can observe with close clinical and imaging follow-up [3] or excision [6] Follow-up with clinical exam every 6–12 months and annual screening mammogram (not before age 30); NCCN recommends consideration of tomosynthesis and annual MRI [6], but Cancer Care Ontario currently does not endorse annual MRI [7] Pleomorphic LCIS is an aggressive variant of LCIS often sharing pathologic features with DCIS (central necrosis and calcifications), and is often treated with excision to clear margins, similar to DCIS [10]
Papillary lesions, including intraductal papilloma [11]	Intraluminal epithelial fronds that may exhibit a variety of alterations from atypia or DCIS to carcinoma Diagnosis: breast lump, nipple discharge (often bloody), or nodule on ultrasound or by ductoscopy	Generally, the advice is for excision given the risk of malignancy, especially if palpable or atypia present. If the absence of atypia can be proven, however, there might be a role for observation, but the literature on papillary lesions without atypia is mixed with little consensus	Without atypia, the chance of malignancy is very small (<10%), but with atypia, some authors have reported the associated rate of coexistent cancer to be as high as 67% [12]. One of the largest multicenter series (n = 238) reported an upgrade rate of 14.4%, with only 3.7% upgraded to invasive cancer. Older age and presence of atypia on core biopsy were associated with risk of malignancy [13] Incidental, benign papillary lesions can be followed [3]
Sclerosing adenosis [11]	A benign lobular lesion with increased fibrous tissue and interspersed glandular cells Diagnosis: occasional lump/nodules or pain, and occasional microcalcifications. Perform CNB	No treatment is needed [11] After CNB, excision is only recommended in the following situations: Limited sampling Presence of atypia Radiological discordance	Risk of subsequent cancer is small [11]

Microglandular adenosis	A rare type of adenosis, resembling tubular carcinoma, where irregular clusters of small tubules are present in adipose or fibrous tissues Diagnosis: may present as mass Perform CNB	Given risk of carcinoma, perform excision	Microglandular adenosis is poorly studied, but is associated with a carcinoma rate of approximately 23% [14, 15]
Radial scars and complex sclerosing lesions [11]	Benign, spiculated masses characterized by a sclerotic-appearing (scar-like) center with peripheral entrapped normal breast ducts and lobules Diagnosis: asymptomatic. Perform imaging and CNB	The standard management is to excise if detected as a mammographic lesion However, if the radial scar is an incidental finding on a CNB performed to investigate a suspected different lesion and atypia is not identified, there may be a role for observation	Risk of subsequent breast cancer is twofold [16]
Pseudoangiomatous stromal hyperplasia (PASH) [11]	Benign, stromal (myofibroblast) proliferation that simulates a vascular lesion More common in premenopausal women, possible hormonal etiology Presents as painless mass or imaging abnormality Most common appearance on mammogram/US is a solid, well-defined, noncalcified mass	If diagnosed conclusively on CNB, PASH can be managed expectantly Excise if discordance with imaging or increase in size of lesion	Although PASH is benign, recurrence after excision is reported in 15–22% of cases Excise if suspicious imaging findings, interval growth, and symptomatic lesions No increased risk of subsequent breast cancer

(continued)

Entity	Definition and diagnosis	Treatment [3, 4]	Comments
Columnar cell lesions (CCLs) without or with atypia (CCL-A, the latter also being known as flat epithelial atypia, FEA) [3] Fibroepithelial lesions, including fibroadenoma and phyllodes tumors [3, 11] Mucocele-like lesions (MLLs) [4]	Often seen on CNB performed for mammographic calcifications Enlarged terminal ductal lobular units with replacement of native epithelial cells by 1 or more layers of columnar epithelial cells with or without atypia Diagnosis: asymptomatic. Perform imaging and CNB Present as mass on physical examination or nodule on mammogram or ultrasound [11] Simple fibroadenomas are benign tumors containing glandular and fibrous tissue Complex fibroadenomas contain other proliferative changes (i.e., duct epithelial hyperplasia, sclerosing adenosis, calcification, apocrine change) Phyllodes tumors on histology show leaf-like architecture with elongated cleft-like spaces containing papillary projections of epithelial-lined stroma with degrees of hyperplasia and atypia Rare lesion of dilated ducts filled with mucin; epithelial lining of the duct can have a range of abnormal pathology (atypia, DCIS, or cancer) May or may not be a precursor lesion to mucinous DCIS or mucinous carcinoma	CCLs with associated ADH should be excised FEA without associated ADH has historically been excised but it can now be reasonably observed if there are no other indications for excision or concerning residual microcalcifications If found at the margins of an excised lesion, re-excision is not generally considered necessary [3] Fibroadenomas do not require excision unless rapid growth, symptomatic, or patient preference. Excise giant fibroadenomas (>10 cm in size) Management of complex fibroadenomas is controversial, with some advocating for excision and others recommending expectant management [11] Excise phyllodes tumors with negative margins (aim for >1 cm margin during surgery); SLNB is not necessary [11] Excise fibroepithelial lesions “not further defined” for diagnosis (including “cellular fibroadenoma,” “cellular fibroepithelial lesion,” or “fibroepithelial lesion with cellular stroma”) Excise all MLLs with associated atypia Consider excision of benign MLLs if a finding of atypia would change patient management, but there may be a role for close observation [4]	Similar risk of subsequent breast cancer as proliferative disease without atypia (RR 1.47) [3] Systematic review of 24 studies showed that the upgrade rate to DCIS on excision was 1.5% for pure CCLs, 9% for CCL-A (FEA), and 20% for CCLs with ADH [4] Women with pure FEA on excisional biopsy can be followed with routine surveillance (no need for high-risk screening) [3] CNB findings associated with phyllodes tumor on excision include increased stromal cellularity, stromal mitoses, stromal overgrowth, fragmentation, nuclear pleomorphism, and infiltration of adipose tissue, but this is not consistent [4] There may be a role for close imaging follow-up for indeterminate fibroepithelial lesions [4] Phyllodes tumors are further classified as benign, borderline, or malignant, based on pathologic features (e.g., degree of stromal cellular atypia, mitoses, infiltrative vs. circumscribed margins, and presence of stromal overgrowth) [11] Core biopsy has a 25–30% false-negative rate when used to diagnose phyllodes tumors so excise solid masses that grow rapidly or become symptomatic after an initial benign CNB Consider adjuvant radiotherapy for borderline or malignant, but not benign, phyllodes tumors. Chemotherapy is reserved for large, high-risk (>10 cm) or recurrent malignant phyllodes tumors Pathologic margins >1 mm is acceptable for borderline/malignant phyllodes, while a negative margin is acceptable for benign phyllodes [17] Rate of upgrade from benign MLL on CNB to malignancy on excision is low (<5%), with the upgrade usually to just atypia [4]

ALND axillary lymph node dissection, *CLL* columnar cell-like lesion, *CLL-A* columnar cell-like lesion with atypia, *CNB* core needle biopsy, *DCIS* ductal carcinoma in situ, *FEA* flat epithelial atypia, *MLL* mucocele-like lesion, *MRI* magnetic resonance imaging, *RR* relative risk, *US* ultrasound

Ductal Carcinoma In Situ

Ductal carcinoma in situ (DCIS) is a preinvasive epithelial breast cancer that does not penetrate the basement membrane. With the advent of organized screening, the incidence of DCIS markedly increased from 5.8 per 100,000 women in the 1970s to 32.5 per 100,000 women in 2004 and then reached a plateau [18]. Approximately 90% are asymptomatic and not palpable, with the remainder presenting as a lump, discharge, or Paget's disease of the nipple. When DCIS is observed in the breast lobule, the process is referred to as "cancerization of the lobule."

Although evidence suggests that a significant proportion of DCIS lesions do not progress to invasive cancer, it is currently not possible to accurately distinguish which will progress and which will not. Furthermore, DCIS frequently coexists with invasive disease, and up to 15% of surgical specimens excised for a preoperative diagnosis of DCIS on core biopsy will be upgraded to invasive breast cancer [18]. These factors have led to an aggressive approach to all DCIS [19, 20].

The indications for breast-conserving surgery (e.g., lumpectomy) versus mastectomy are similar in DCIS as with invasive disease, with mastectomy indicated where:

1. Area of DCIS is large, relative to breast size.
2. Disease is multicentric.
3. Radiotherapy is contraindicated.
4. Clear margins cannot be obtained with breast conservation.

The lack of true randomized data regarding breast-conserving surgery (BCS) and mastectomy for DCIS should be noted. The first indication that BCS—in conjunction with adjuvant radiotherapy—was acceptable treatment for DCIS came from a subset analysis of 78 patients in the NSABP B-06 study [21]. Originally enrolled because of presumed invasive breast cancer, these women were downgraded to DCIS on pathologic reanalysis. The local recurrence rate was 9% in those that underwent radiotherapy versus 43% in those that did not. Retrospective studies have since confirmed that BCS provides survival rates similar to mastectomy; however, local recurrence is higher, even with radiotherapy [22, 23]. The recommended surgical margin of 2 mm for DCIS is discussed further below. In patients with DCIS and microinvasion (no invasive focus >1 mm), the DCIS margin guideline should be used, as systemic treatment decisions in these patients are driven by their DCIS. This is in contrast to patients with invasive breast cancer with a DCIS component, where the margin for invasive breast cancer (no ink on tumor) should be used [24].

As mentioned, similar to invasive disease, there is good evidence for radiotherapy following a breast-conserving approach:

Study	Methods	Results
NSABP-B17 Fisher et al. [25]	*N* = 818 RCT Patients assigned to lumpectomy alone vs. lumpectomy and RT	At 7.5 years, RT reduced the incidence of ipsilateral invasive disease (13.4% to 3.9%) as well as ipsilateral DCIS (13.4% to 8.2%) A subset analysis from this study also demonstrated that comedonecrosis was a risk factor for recurrence At 17.25 years, RT reduced ipsilateral breast tumor recurrence by 52% (HR 0.48) [26]
EORTC 10853 Julien et al. [27]	*N* = 1010 RCT Patients with DCIS and BCS randomized to receive no further treatment or RT	RT reduced overall noninvasive recurrence at 10.5 years by 48% and invasive recurrence by 42% At 15.8 years, RT reduced the risk of any local recurrence by 48% (HR 0.52) [28]
UK/ANZ DCIS Cuzick et al. [29] SweDCIS Wärnberg et al. [30]	*N* = 1701 RCT Patients with excised DCIS randomized to receive RT, tamoxifen, both or none *N* = 1046 RCT Patients randomized to RT or not after BCS for DCIS	RT reduced ipsilateral invasive recurrence at 12.7 years by 68% and DCIS by 62%, but with no effect on contralateral breast cancer Relative risk reduction of 37.5% of ipsilateral breast event after 20 years of follow-up

BCS breast-conserving surgery, *HR* hazard ratio, *NSABP* National Surgical Adjuvant Breast and Bowel Project, *RT* radiotherapy, *RCT* randomized controlled trial

These studies, such as NSABP B-17 [25] and EORTC 10853 [27], are marked by limitations relating to the pathological assessment of tumors (such as tumor size measurement and free margin definition), and lack of routine specimen imaging and postoperative mammography [31], thereby questioning the completeness of excision in both studies. As a result, many believe that these data strengthen the argument for complete surgical resection rather than an approach that relies on radiotherapy as a means of dealing with residual disease.

There is some evidence, however, that radiotherapy may be safely omitted in some cases of DCIS. The University of Southern California/Van Nuys prognostic index for DCIS uses four prognostic factors (tumor size, margin width, patient age, and pathologic classification as determined by both nuclear grade and presence or absence of comedonecrosis) to stratify patients by their risk of recurrence at 12 years of follow-up. Patients with low scores (4, 5, or 6) had a combination of being over the age of 60 with tumors less than 1.5 cm in size that were non-high grade (nuclear grade 1 or 2) and without necrosis, and a margin size greater than 10 mm. These patients with low scores, and patients who score 7 but have margins ≥3 mm, were found to gain no additional benefit from adjuvant radiotherapy following BCS in their 12-year local recurrence-free survival [32].

More recently, a prospective study of 670 patients [33] demonstrated a 5-year recurrence of 15% for high-grade DCIS, but only 6% for low- or intermediate-grade DCIS, when excised with a minimum of 3 mm margins. However, the authors note an increase in recurrences beyond 5 years for all grades of DCIS and urge caution

in applying these results to clinical practice. Another prospective trial of wide excision alone (over 1 cm margin) for low-to-intermediate grade DCIS found an unacceptably high local recurrence rate of 12% at 5 years and 15.6% at 10 years [34]. A recent prospective trial found that the local recurrence rate continues to rise after 12 years of follow-up, even in patients with favorable DCIS features [35]. While some studies using contemporary cohorts report that postoperative radiation after BCS for DCIS is associated with a reduced risk for ipsilateral recurrence with no survival benefit compared to observation alone [33], others report that the benefit in survival offered by radiation after BCS is dependent on patient factors and tumor biology [36, 37].

Given the difficulty in determining which patients with DCIS may be safely treated with wide excision alone [38], it remains the standard of practice at the University of Toronto to offer radiation to all patients having undergone breast-conserving surgery (BCS) for DCIS. Whole-breast radiation following lumpectomy decreases DCIS recurrence rates by 50% [39]. The standard dose of adjuvant radiotherapy following BCS for completely excised DCIS is 4000 cGy in 15 fractions or 4250 cGy in 16 fractions, with consideration for a boost of 1000 cGy (in 4 or 5 additional fractions) to the tumor bed for any of the following criteria: age ≤ 50 years, high grade, or close (<2 mm) or positive margins [40].

The Oncotype DX® DCIS score is a multigene assay that provides additional molecular information from the tumor that may help guide treatment recommendations for adjuvant radiotherapy [41]. The DUCHESS (Evaluation of the DCIS Score for Decisions on Radiotherapy in Patients with Low/Intermediate Risk DCIS) trial is a Canadian multicenter prospective cohort study currently recruiting women with low- to moderate-risk DCIS to evaluate the utility of the Oncotype DX® DCIS score in guiding radiation treatment decisions following BCS, the results of which are eagerly awaited [42]. Recently, the updated NCCN guidelines have added that select patients may be considered for accelerated partial breast irradiation if they meet the definition of low-risk DCIS as defined by the RTOG 9804 trial: screen-detected DCIS, low to intermediate grade, tumor size $\leq$2.5 cm, and surgical excision with margins over 3 mm [39].

Adjuvant radiotherapy is generally not recommended for patients with DCIS who are adequately treated with mastectomy. Close or positive DCIS margins following mastectomy may lead to the consideration of postmastectomy radiation. However, the rates of chest wall recurrence following mastectomy for DCIS are low, even with positive or close margins [43, 44].

The NSABP B-24 study demonstrated that adjuvant tamoxifen following BCS and radiation for DCIS reduces a second breast event [45, 46], and subsequent randomized trials showed no difference between tamoxifen and aromatase inhibitors in their efficacy [47]. The benefit gained from endocrine therapy has to be weighed against their known adverse effects (i.e., menopausal symptoms, mood and sleep disturbances, arthralgias, cataracts/deep vein thrombosis/pulmonary embolism/uterine cancer for tamoxifen, and decreased bone mineral density for aromatase inhibitors). Adjuvant endocrine therapy is not routinely offered at the University of Toronto because the additional benefit gained from endocrine therapy for DCIS is

felt to be small following both surgical excision with clear margins and radiotherapy relative to the risks of adverse events. Patients with DCIS may be considered for adjuvant endocrine therapy on a case-by-case basis in discussion with a medical oncologist, in patients with a strong personal preference for avoiding radiation following BCS, or who decline additional surgery in the setting of a positive margin, but this is not standard of care [39, 48–49].

DCIS Recurrence

Approximately 50% of recurrences are invasive disease [39, 50]. Factors associated with an increased risk of recurrence include palpable mass, larger size, higher grade, close or involved margins, presence of comedonecrosis, and age at diagnosis <50 years [39].

Margin status is an important predictor of DCIS local recurrence [22]. The NSABP-B17 [25], NSABP-B24 [45], and EORTC clinical trials [27] have all revealed that clear margins significantly decrease recurrence. No trials, however, have rigorously examined the optimum excision width. An analysis of pooled data from both randomized and nonrandomized studies in 2005 concluded that a margin of 2 mm when excising DCIS was as safe as a larger margin when followed by radiotherapy [51]. In 2016, the Society of Surgical Oncology, American Society of Clinical Oncology, and American Society for Radiation Oncology jointly released a consensus statement recommending a 2 mm margin for BCS with whole-breast radiation for treatment of DCIS [50, 52–53]. In their meta-analysis of studies examining varying margin widths (>0–1 mm, 2 mm, 3 mm, and 10 mm), there was no difference in recurrence when comparing 2 mm to 10 mm margins, while narrower margins (>0 or 1 mm) had a statistically significant increase in recurrence compared to 2 mm margins [54]. The consensus panel did recommend clinical judgment when deciding upon the need for re-excision when DCIS margins are less than 2 mm [50, 52–53], as there is no difference in locoregional recurrence for patients with margins <2 mm or ≥ 2 mm if adjuvant radiotherapy is given [24, 55–56]. Patients with DCIS that do require additional excision following BCS include those with margins <2 mm and do not plan to receive radiotherapy have multiple very close margins or evidence of residual malignant-appearing calcifications on mammography [24].

Although a high-grade lesion was originally thought to be a risk factor for recurrence [27], a 2006 review of the EORTC data [57] with a 10-year follow-up suggested that this might not be the case. That study did confirm that comedonecrosis is an independent risk factor for recurrence, with 3 of 10 patients recurring by 10 years [57]. A 2013 study found that larger DCIS size, margins <1 mm, and presence of lobular neoplasia, but not grade, were associated with increased risk of local DCIS recurrence [58]. Several studies with longer follow-up have since corroborated that high nuclear grade is not associated with DCIS recurrence [59, 60]. High nuclear grade, however, may be associated with invasive recurrence [61]. It may be that nuclear grade becomes less of a risk factor for recurrence in the modern era

when DCIS is appropriately treated with surgical excision (with clear margins) and adjuvant radiotherapy (with or without endocrine therapy).

Age is also a significant factor in DCIS recurrence. The EORTC trial demonstrated a higher recurrence rate in young women under 40, quoting a hazard ratio (HR) of 2.54 [27]. Similarly, the NSABP B-24 trial found that the rate of ipsilateral (invasive and in situ) disease in women under 49 years old was 33/1000 women per year as opposed to 13/1000 for those over 49 years of age [45, 62]. A 2014 study of 5752 DCIS cases in Ontario from 1994 to 2003 found that young age < 45 was significantly associated with both DCIS (HR 2.6) and invasive (HR 3.0) recurrence [63]. Interestingly, one study found that women <40 years of age with DCIS were at higher risk for invasive recurrence than DCIS recurrence (15.8% vs. 11.5% 10-year recurrence risk), although mortality remained low, while the risks appeared equivalent in women ≥40 years of age [64].

The management of recurrence is largely dependent on the type of recurrence, the surgical treatment of prior DCIS, and whether radiotherapy has been administered. For DCIS recurrence, if radiotherapy has not been previously received, then a local resection may be possible followed by adjuvant radiotherapy; otherwise, a mastectomy should be offered [65]. There is increasing interest in the consideration of repeat resection and irradiation for local recurrence, with studies showing that this approach is safe and feasible in the setting of recurrence. However, the data remains limited by short follow-up and is largely confined to the setting of invasive disease rather than DCIS [66–68] and this approach is, therefore, not universally accepted. Invasive recurrences should be treated according to principles outlined in the subsequent section "Invasive Breast Cancer" and will be dependent on previous DCIS treatment and whether radiotherapy has been previously administered.

DCIS and the Axilla

The incidence of axillary metastases in DCIS is <1%, and these are likely to represent missed invasive disease, rather than true DCIS metastases. For DCIS diagnosed preoperatively on core biopsy, 15% will subsequently be found to have invasive cancer on final postoperative pathology [18]. It should be borne in mind that the majority of reported sentinel lymph node (SLN) involvement in DCIS is revealed by immunohistochemical (IHC) techniques as isolated tumor cells or micrometastases, and the clinical significance of these is uncertain even in true invasive disease [52, 53].

The American Society of Clinical Oncology has recommended that axillary staging in patients with DCIS treated by BCS be reserved for those with invasive disease. For those undergoing mastectomy or immediate reconstruction for DCIS, sentinel lymph node biopsy (SLNB) is recommended, with a view to avoid axillary lymph node dissection in the event of an upgrade from DCIS to invasive carcinoma on final pathology of the mastectomy specimen, as SLNB is not possible after mastectomy [69]. The current NCCN guidelines also offer similar recommendations, reserving SLNB for DCIS treated with mastectomy or excised in an anatomic

location that may compromise the performance of a future SLNB (e.g., extreme upper outer quadrant lesions near the axilla and central lesions involving the nipple-areolar complex, both likely disrupting lymphatic drainage of the breast) [39].

Invasive Breast Cancer

In this section, the management of invasive breast cancer is discussed, focusing on tumors less than 5 cm with no evidence of matted or fixed axillary lymph nodes, corresponding to T0, T1, T2 and N0, N1 (stages 0, I, IIA, and IIB).

Work-up	Surgical management	Follow-up (F/U)
History and physical exam Imaging: Review bilateral mammogram and ultrasound (assess for multifocal/multicentric disease, as well as contralateral disease) Axillary US Breast MRI if indicated (see below) Core needle biopsy to confirm the diagnosis Apply clip if neoadjuvant therapy is considered CCO staging recommendations [70]: Routine bone scanning, liver ultrasonography, and chest radiography are not indicated before surgery Postoperatively: In women with stage I tumors, routine bone scanning, liver ultrasonography, and chest radiography are not indicated as part of baseline staging In women who have pathological stage II tumors, a postoperative bone scan is recommended as part of baseline staging In women who have pathological stage III tumors, bone scan, chest radiography, and liver ultrasound are recommended postoperatively	Breast (local): Breast-conservative surgery plus breast irradiation or mastectomy +/− postmastectomy radiation therapy [71] Axilla (regional): Sentinel lymph node biopsy for clinical N0 patients Axillary lymph node dissection for clinical N1 Consider and discuss neoadjuvant chemotherapy in the following cases: Triple-negative Young patients (<40) Her2/neu + Reducing the size of tumor to facilitate BCS Node-positive patients	Regular clinical breast exam Mammogram every 12 months

BCS breast-conserving surgery, *MRI* magnetic resonance imaging, *CCO* Cancer Care Ontario, *US* ultrasound

Special Notes

- It is standard of care to obtain the diagnosis of invasive breast cancer with core needle biopsy. While the primary use of core needle biopsy is to establish a diagnosis, it is also useful in providing receptor status if neoadjuvant chemotherapy is considered. Furthermore, positive margin rates and the need for reoperation are reduced in women who have been assessed with core needle biopsy preoperatively [72].

- In breast cancer of a more advanced stage, Cancer Care Ontario has recommended that in women with pathological stage III tumors, bone scanning, liver ultrasonography, or CT abdomen and chest radiography are recommended postoperatively as part of baseline staging. However, in women for whom treatment options are restricted to tamoxifen or hormone therapy, or for whom no further treatment is indicated because of age or other factors, routine bone scanning, liver ultrasonography, and chest radiography are not indicated as part of baseline staging [70].
- Mammography remains the mainstay of breast imaging. MRI of the breast is considered an adjunct to mammography. Preoperative diagnostic MRI detects additional ipsilateral lesions in up to 32% of patients and contralateral lesions in 7% of patients. Sensitivity ranges from 75 to 100% and specificity from 80 to 100% [73]. However, several studies have failed to show a decreased rate of positive margins in BCS for patients undergoing MRI [74, 75] while also showing an increased likelihood of mastectomy in such patients [75].
- According to the American College of Radiology, current indications for diagnostic MRI are as follows:
  - Axillary adenocarcinoma with unknown primary.
  - Evaluation of response to neoadjuvant chemotherapy.
  - Assessment of extent of DCIS and IDC.
  - Assessment of invasion of deep fascia.
  - Evaluation of possible recurrence.
- Diagnostic MRI can also be considered in patients with invasive lobular carcinoma, as there is some evidence that MRI reduces the need for re-excision surgery in this subset of patients, but at the cost of an increased likelihood of upfront mastectomy [74].
- Be aware that mucinous carcinomas often lack suspicious features on imaging and can be mistaken for fibroadenomas. Consider serial imaging or repeat core biopsies of breast lesions suggestive of fibroadenomas in older patients [76].
- The eighth edition of the AJCC introduced changes to breast cancer staging such that in addition to anatomic features, the biology of breast cancers are considered in determining prognosis [2]. In addition to TNM status, biologic markers of tumor grade and receptor status (estrogen receptor, progesterone receptor, and HER2/neu receptor) and results of genomic assays (including Oncotype DX® and EndoPredict) were included.

Breast-Conserving Surgery

The aim of breast conservation is to achieve a balance between complete resection of the tumor with negative margins and preservation of as much normal breast tissue as possible. Volume loss is the major determinant of cosmesis after BCS. A good cosmetic outcome maximizes the psychosocial benefits of breast preservation [77].

In patients with no contraindication to BCS, there are several points to be discussed with the patient	BCS includes the lumpectomy to a negative margin, margin revision being necessary in about 20% of cases If the margin is positive after appropriate attempts at therapeutic breast-conserving surgery, the patient should be considered for mastectomy
	BCS for DCIS and invasive breast cancer includes administration of radiotherapy
	When compared with mastectomy, BCS may have a slightly higher risk of local recurrence. Both approaches, however, have equivalent survival outcomes

Absolute Contraindications to BCS

1. Early pregnancy, if radiation deemed necessary to be performed during pregnancy.
2. Multicentric IDC—diffuse-appearing suspicious microcalcifications or inability to resect the evident disease with acceptable cosmetic results.
3. Any contraindication to radiation therapy (e.g., active collagen vascular disease with severe vasculitis, ataxia telangiectasia).

Relative Contraindications to BCS

1. A history of collagen vascular disease, in remission.
2. Large tumor size in relation to the breast size.
3. A history of prior therapeutic irradiation to the breast region.

For invasive cancer, another consideration in the choice of surgical treatment of the primary tumor is the management of the axilla after positive SLNB. The ACOSOG Z0011 trial—detailed in sect. IV of this chapter—supports omission of axillary lymph node dissection (ALND) after positive SLNB in many patients treated with BCS. However, patients treated with mastectomy were excluded and the current standard remains completion of ALND in those cases. This may factor into the decision-making process for the patient and surgeon.

Trials for BCS Versus Mastectomy

Study	Methods	Results
NSABP-B06 Fisher et al. [62]	*N* = 1851 RCT Patients in stages I and II were assigned total mastectomy/ALND, lumpectomy/ALND alone or lumpectomy/ALND + breast irradiation Margins—no cancer cell at the surgical margin	Follow-up—20 years No significant differences in disease-free survival and overall survival Recurrence rate in the ipsilateral breast was 14.3% in the lumpectomy/ALND plus breast irradiation group and 39.2% in the lumpectomy/ALND-alone group

Study	Methods	Results
Milan Group Veronesi et al. [23]	*N* = 701 RCT Patients with tumor <2 cm were assigned radical mastectomy vs. quadrantectomy/ALND + radiotherapy Margins—1.5–2.0 cm, with the overlying skin and deep fascia	Follow-up—20 years No statistical difference in overall survival Recurrence rate higher in the BCS group (8.8% vs. 2.3%)

RCT randomized controlled trial

Meta-analysis to Assess Surgical Margins in BCS for Early Breast Cancer

Study	Methods	Results
Houssami et al. [77]	33 studies *N* = 28,162 patients (1506 with LR) Impact of surgical margins on LR Model 1—effect of margin status in relation to LR Model 2—effect of margin distance to LR (1 mm vs. 2 mm vs. 5 mm)	Higher probability of LR associated with positive/close margins vs. negative margins (OR 1.97) No difference in LR with 1 mm vs. 2 mm vs. 5 mm margin distance Wider margins unlikely to increase long-term local control

LR local recurrence, *OR* odds ratio

This work by Houssami et al. formed the basis of the Society of Surgical Oncology-American Society for Radiation Oncology (SSO-ASTRO) consensus guidelines for breast-conserving surgery for early-stage breast cancer. Using this data, a multidisciplinary panel concluded that "no ink on tumor" should be adopted as the standard for an adequate margin for invasive breast cancer [78]. This guideline has since been endorsed by the American Society of Clinical Oncology (ASCO) and the American Society of Breast Surgeons (ASBrS) [79].

Genetic Testing

In Ontario, patients who qualify for government-funded genetic testing include the following [80]:

1. Male breast cancer patients.
2. Female breast cancer under age 35.
3. Ashkenazi Jewish patients with breast cancer < age 50 and/or ovarian cancer at any age.
4. Affected breast cancer patients with 2 cases of breast and/or ovarian cancer on the same side of the family.
5. Unaffected patient but has relative with known BRCA1 or BRCA2 mutation.

6. Unaffected Ashkenazi Jewish patient with first- or second-degree relative with breast or ovarian cancer.
7. Unaffected individual with a strong pedigree of breast or ovarian cancer (>10% chance of carrying a pathogenic mutation).

Note that NCCN offers similar guidelines on genetic testing, which includes individuals with triple-negative breast cancer diagnosed ≤60 years old [81]. The ASBrS has also recently published a consensus guideline recommending that genetic testing be considered and discussed for all patients with a new diagnosis of breast cancer [82].

The Axilla

Management of the axilla is arguably the most controversial aspect of the breast cancer treatment paradigm. Many changes have occurred in the past 20 years. From considering axillary lymph node dissection (ALND) as the standard of care for all breast cancer patients, to now omitting selected patients with proven axillary metastases from further surgery, it is a complex facet of the management of invasive breast cancer.

Authors such as Steele et al. [83] in the 1980s challenged the belief that all breast cancer patients should have an ALND. They endorsed a system of axillary node sampling, whereby four nodes were "cherry picked" from level one of the axilla, and if negative for disease, no further surgery was performed. This limited axillary node sampling may be seen as the grandfather of SLNB, a technique which has supplanted ALND as the standard of care in staging the clinically negative axilla.

Several key trials have demonstrated the efficacy of SLNB

Study	Methods	Results
Multicenter Validation Study Krag et al. [84] 1998	*N* = 443 All patients underwent both SLNB and then ALND	It demonstrated that this technique could be used by surgeons At least 1 SLN was identified in 98% of cases and the predictive value of a negative SLN was 96%, with a false-negative rate of 11%
ASCO Review Lyman et al. [85] 2005	*N* = 8059 Systematic review of 69 SLNB trials	SLN identification was successful in 95% of patients The false-negative rate was 7.3% (range 0–29%). Using both radiocolloid and blue dye was more successful than blue dye alone
ALMANAC Mansel et al. [86] 2006	*N* = 1031 RCT Patients randomly assigned to ALND vs. SLNB with delayed ALND if SLN positive	SLNB group had less arm morbidity SLNB group had better quality of life and arm functioning scores

Study	Methods	Results
NSABP B-32 Technical results Krag et al. [87] 2007 NSABP B-32 OS results Krag et al. [88] 2010	*N* = 5611 RCT Comparing SLNB, followed by ALND (group 1) vs. SLNB, followed by ALND for positive SLN (group 2)	Lymphatic mapping was successful in 97.2% when using both radioactive and blue dye The FNR was 9.8% in group 1. The FNR was inversely associated with the number of SLNs removed, such that the FNR was 17.7% when only one SLN was removed, 10% when 2 SLNs were removed, and so forth No significant differences were observed in regional control or OS between groups at follow-up of 8 years No significant differences in nodal recurrence as first event between the two groups

ALND axillary lymph node dissection, *ASCO* American Society of Clinical Oncology, *FNR* false-negative rate, *NSABP* National Surgical Adjuvant Breast and Bowel Project, *OS* overall survival, *SLN* sentinel lymph node, *SLNB* sentinel lymph node biopsy, *RCT* randomized controlled trial

Approach to the Axilla in Early-Stage Breast Cancer

The contribution of ALND to survival in women with breast cancer has been questioned since the publication of the NSABP B-04 [89] trial. It has often been the basis of argument against mandatory ALND. In this study, clinically node-negative patients were randomized to radical mastectomy (RM), total mastectomy (TM), plus postoperative axillary irradiation or TM alone. Forty percent of the RM group had subclinical lymph node involvement. One can assume that the TM plus irradiation and the TM alone groups also had 40% of subclinical axillary lymph involvement because of randomization. Despite not having any treatment to the axilla, the axillary recurrence rate, as a first failure, was only 19% in the TM alone group. Moreover, the three groups had a similar overall survival [90].

In the era of SLNB, the contribution of axillary dissection to survival was revisited in the ACOSOG Z0011 trial [91]. In this prospective randomized noninferiority trial, women with T1-T2 breast cancers who were clinically node negative (T1-T2cN0), receiving breast-conserving therapy with only one or two positive SLNs and with no gross extracapsular extension, were randomized to SNLB-alone versus ALND groups. All patients received adjuvant systemic therapy and opposing tangential field whole-breast irradiation. One criticism of this study was the relatively short follow-up (median: 6.3 years) period when it was first published in 2006. However, subsequent results published in 2017 still showed no difference in 10-year overall survival (86.3% in the SLND alone group vs. 83.6% in the ALND group with a noninferiority p = 0.02) [92]. Ten-year disease-free survival was also similar between groups, with 78.2% in the ALND group versus 80.2% in the SLNB-alone group. This study demonstrated the noninferiority of SLNB to ALND for patients with T1-T2 tumors, and 1 or 2 positive SLNs who are treated with lumpectomy, adjuvant radiation and systemic therapy, with a noninferiority hazard ratio of 1.3.

Studies in support of ALND *after positive SLNB*

Study	Methods	Results
SEER Database Analysis Joslyn. [93] 2002	Retrospective review *N* = 257,157 Women diagnosed with breast cancer in the SEER database between 1988 and 2000	Women undergoing ALND had an increased survival With an increasing ratio of positive nodes to total number removed, there was a consistent trend towards reduced survival
Truong et al. [94] 2002	Retrospective population-based cohort *N* = 8038 Patients treated for T1–2 breast cancer in British Columbia between 1989 and 1998	Overall and cancer-specific 5-year survival rates were significantly worse in those who had not undergone ALND (68% vs. 85% and 86% vs. 91%, respectively). Note that the much larger difference in overall survival suggests large heterogeneity between groups
Early Breast Cancer Trialists' Collaborative Group Analysis Clarke et al. [95] 2005	78 RCTs *N* = 42,000 Comparing the effect of different types of local treatment on recurrence and survival	While not directly examining ALND, the study showed that local control affects overall survival, a fact which is often used in support of ALND Local recurrence positively impacted on the 15-year survival

RCT randomized controlled trials, *ALND* axillary lymph node dissection, *SEER* surveillance epidemiology and end results (US National Cancer Institute)

Studies suggesting ALND does not affect overall survival

Study	Methods	Results
NSABP B-04 Fisher et al. [96] 1985	*N* = 1843 RCT Women were assigned to radical mastectomy vs. simple mastectomy plus local nodal irradiation, or simple mastectomy with delayed ALND if needed	There was no effect on survival of prophylactic ALND vs. nodal radiotherapy vs. no initial axillary treatment This study is criticized for being underpowered and also for including many women with simple mastectomy who had some nodes removed with the breast specimen
The Breast Carcinoma Collaborative Group of the Institut Curie Cabanes et al. [97] 1992	*N* = 658 RCT Patients assigned to lumpectomy alone or lumpectomy plus ALND All received RT, and women with positive LNs received chemotherapy	ALND was initially associated with significantly better 5-year survival (97% vs. 93%) However, after 10–15 years of follow-up, survival rates were similar (~75%). Regional recurrence was lower in women who had ALND. However, this needs to take into consideration the fact that the only women who received chemotherapy were in the ALND group

NSABP National Surgical Adjuvant Breast and Bowel Project, *RCT* randomized controlled trials, *ALND* axillary lymph node dissection, *RT* radiotherapy, *LN* lymph node

Studies in support of ALND omission *after limited positive SLNB*

Study	Methods	Results
Z0011 Guiliano et al. [91, 92] 2010, 2017	*N* = 891 RCT T1-T2cN0 invasive breast cancer ALND vs. no ALND for women with 1 or 2 positive SLNB Exclusion: 3 or more positive SLNs, matted nodes, gross extranodal extension, neoadjuvant treatment Planned adjuvant systemic therapy and opposing tangential field whole-breast irradiation to all patients	At median follow-up of 9.3 years, the 10-year overall survival was 83.6% in ALND and 86.3% in those with SLNB. Importantly, 10-year disease-free survival was also similar, with 78.2% in ALND and 80.2% with SLNB It is criticized for its low numbers and an approximately 20% lost to follow-up rate (unlike NSABP-B32 < 1%) Inconsistent field of adjuvant radiation therapy (from the radiation reports available for 605 patients, 89% received whole-breast radiation and 15% also received radiation to the supraclavicular region) [98] Powered for 1900 patients but closed earlier due to lower than expected mortality rate
AMAROS Donker et al. [99] 2014 IBCSG 23–01 Galimberti et al. [100] 2018	*N* = 4806 → 1425 (29.7%) found to have positive SLNB RCT, noninferiority trial From 2001 to 2010, patients with cT1–2 N0 invasive breast cancer were enrolled in the EORTC phase III noninferiority AMAROS trial. Patients with neoadjuvant systemic treatment were excluded from the study Protocol was amended in 2006 to include cT3 and multifocal disease Patients were randomized to ALND or ART prior to SLNB and breast-conserving surgery or mastectomy. Patients with positive SLNs were then included in analysis. ART included radiation to level I, II, III, and supraclavicular lymph nodes Primary endpoint was 5-year axillary recurrence rate RandomisedRandomized noninferiority phase 3 trial Primary endpoint: disease-free survival in T1-T2 tumors with only micrometastasis randomized to ALND or no ALND	5-year axillary recurrence was 0.43% after axillary lymph node dissection and 1.19% after axillary radiotherapy. Due to the accrual and low number of events, the noninferiority test was underpowered and the study was statistically inconclusive Clinical signs of lymphedema were noted more often following ALND than ART, 23% vs. 11% at 5 years ($p < 0.0001$). Rates of subjectively measured lymphedema were not different between groups. Range of motion and quality of life measurements were not significantly different between the two groups No significant difference in 10-year disease-free survival (74.9% in the ALND group vs. 76.8% in the no ALND group) with a hazard ratio of 0.85 (95% CI 0.65–1.11). This study showed noninferiority as a hazard ratio of less than 1.25 Higher rate of sensory neuropathy, motor neuropathy, and lymphedema in the ALND group

RCT randomized controlled trial, *ALND* axillary lymph node dissection, *LN* lymph node, *SLNB* sentinel lymph node biopsy, *RT* radiotherapy, *EORTC* European Organisation for Research and Treatment of Cancer, *AMAROS* the after-mapping of the axilla: radiotherapy or surgery?, *ART* axillary radiation therapy, *NSABP* National Surgical Adjuvant Breast and Bowel Project, T1 or T2 and clinically N0

Special Notes

- Although by no means an exhaustive examination of the literature, the above studies do help demonstrate the controversy surrounding ALND. It should be always remembered that with the rapid changes in adjuvant therapy for breast cancer, one must examine the older literature with a certain degree of care. Certainly, it seems that the benefit of extensive axillary surgery is questionable in this era of effective adjuvant therapy. Given the limitations of the Z0011 study, however, it is difficult at the present time to completely advocate a definitive move away from the procedure. Both NCCN guidelines and the American Society of Breast Surgeons endorse that if all Z0011 criteria are met, ALND is not required after SLNB.
- At the University of Toronto, we also forego axillary dissection in patients meeting the Z0011 inclusion criteria.

Isolated Tumor Cells and Micrometastases

Isolated tumor cells (ITCs)	Micrometastases
Defined by the eighth edition of AJCC as "small clusters of cells not greater than 0.2 mm, or nonconfluent or nearly confluent clusters of cells not exceeding 200 cells in a single histologic lymph node cross section are classified as isolated tumour cells" [2] (pN0(i+)) No further surgery, radiotherapy, or chemotherapy is indicated by their presence. However, in the neoadjuvant setting, their significance is less clear [101].	Defined by a separate designation of pN1mi (>0.2 mm and no greater than 2.0 mm) to indicate micrometastases alone [2] NSABP B-32 showed a 1.2% lower 5-year survival ($p = 0.03$) in patients with occult micrometastases, compared to those that were pathologically node-negative [88]. Thus, although larger than ITCs, micrometastasis are of limited clinical significance

Special Notes

- The literature is populated by much discussion regarding the significance of isolated tumor cells (ITCs) and micrometastases. This debate has been largely superseded by the publication of Z0011 and its findings relating to the significance of macrometastases [91], along with Weaver et al. who demonstrated statistical but no clinical significance to their presence [102].

Extranodal Extension

Extranodal extension (ENE) is defined as tumor breach outside of the lymph node capsule. In the literature, it has been associated with worse prognosis and involvement of further non-sentinel lymph nodes with disease [103, 104]. The ACOSOG Z0011 trial excluded patients with gross ENE but did not further analyze the presence of microscopic ENE [91]. In a study by Gooch et al., in 331 patients with ENE

out of 11,730 patients meeting ACOSOG Z0011 criteria, ENE was associated with increased axillary burden [105]. ENE > 2 mm was the strongest predictor of greater than 4 positive lymph nodes at completion ALND on multivariate analysis (33% of patients with ENE >2 mm vs 9% of patients with ENE ≤2 mm vs 3% of patients with no ENE had more than 4 positive LNs at completion ALND, $p < 0.0001$). Another smaller study demonstrated similar recurrence and mortality in patients with no ENE compared to patients with ENE ≤2 mm [106]. Therefore, one could consider avoiding ALND if only microscopic or focal ENE (≤ 2 mm) is identified on SLNB.

SLNB Following Neoadjuvant Systemic Therapy

- For patients undergoing neoadjuvant chemotherapy, studies such as SENTINA, ACOSOG Z1071, and SN FNAC have demonstrated the feasibility and accuracy of SLNB following neoadjuvant systemic therapy if dual-agent lymphatic mapping is used and more than 2 SLNs are retrieved. These studies are described in more detail in the *Locally Advanced Breast Cancer* section.

Summary: Management of the Clinically Node-Negative Axilla in Patients Who Have Not Received Neoadjuvant Chemotherapy

- SLNs are pathologically negative or contain only ITCs:
  - SLNB is the standard for staging and axillary surgery [107].
- SLNs contain micrometastatic disease on pathologic examination:
  - SLNB alone can safely manage burden of disease. However, case should be discussed at Multidisciplinary Cancer Conference (MCC) to determine if identification of macrometastases would alter adjuvant therapy recommendations. If so, completion ALND may be considered if the patient does not meet inclusion criteria for Z0011 [107].
- SLNs contain macrometastatic disease on pathologic examination:
  - If meets all inclusion criteria for Z0011 (T1 or T2 tumor, clinical N0, 1, or 2 positive SLNs, no gross extranodal extension, breast-conserving therapy, whole-breast radiotherapy planned, no neoadjuvant chemotherapy), no further ALND is required [107].

    If three or more positive SLNs and/or gross extranodal disease, consider completion ALND [107].
  - If patient has undergone mastectomy, has multicentric tumor, or is pregnant, a discussion at MCC is warranted to review the benefits/risks of completion ALND versus axillary radiotherapy.

Considerations of Adjuvant Treatment for Invasive Breast Cancer

Genomic Assays

In addition to providing prognostic information regarding breast cancers and the risk of recurrence, genomic assays are also being used to guide the recommendation for adjuvant therapies. Studies are ongoing to include node-positive patients.

TAILORx Study—Sparano et al. [108]

Methods	Results	Implications for clinical practice
N = 10, 273 RCT Patients aged 18–75 with hormone receptor-positive, HER2-negative, axillary node-negative breast cancers with mid-range Oncotype DX® recurrence scores (11–25) were randomly assigned to either chemoendocrine or endocrine therapy alone Noninferiority study to determine if chemotherapy can be safely omitted in patients with mid-range (intermediate) recurrence scores	Endocrine therapy was not inferior to chemotherapy in these patients with regard to: Invasive disease-free survival Freedom from recurrence of breast cancer at a distant or local-regional site Overall survival Chemotherapy was associated with some benefit in women 50 years old and younger with Oncotype DX® recurrence scores in the 16–25 range 9-year rate of distant recurrence: ~5% for women with recurrence scores of 11–25 ~3% for women with recurrence scores of 10 or less	Adjuvant chemotherapy can be omitted in patients with HR-positive, HER2-negative, node-negative breast cancers who have Oncotype DX® recurrence scores <25 if over the age of 50 Adjuvant chemotherapy should be discussed and offered to women under the age of 50 with HR-positive, HER2-negative, node-negative breast cancers who have Oncotype DX® recurrence scores in the 16–25 range

HR hormone receptor, *RCT* randomized controlled trial

Ovarian Function Suppression

Ovarian function suppression with LHRH (luteinizing hormone-releasing hormone) analogs (e.g., goserelin (Zoladex), leuprolide (Lupron)) should be considered in high-risk hormone receptor-positive premenopausal women requiring chemotherapy [109, 110]. Ovarian function suppression may also be considered to protect ovarian function in premenopausal women during chemotherapy [111, 112].

Locally Advanced Breast Cancer

Locally advanced breast cancer (LABC) is a heterogeneous entity. The term includes T3: tumors greater than 5 cm in maximum diameter, T4: tumors that directly invade skin or chest wall, as well as inflammatory breast cancer, and tumors that have extensive regional lymph node involvement (matted ipsilateral lymph nodes N2–N3) without evidence of distant metastatic disease at initial presentation. These tumors fall into the category of stage IIB (T3 N0) and III disease as per AJCC eighth edition staging. It is clinically useful to separate LABC into operable and inoperable (situations in which surgery is unlikely to remove all disease). This decision is made clinically based on physical examination and review of breast imaging. Approximately 25–30% of LABC are inoperable on presentation [113]. Up to 20% of patients with stage III disease are metastatic after staging [39]. Signs of questionable operable benefit or inoperability include the following [114]:

1. Extensive skin edema.
2. Satellite nodule in the skin.
3. Inflammatory breast cancer.
4. Involvement of supraclavicular or internal mammary lymph nodes.
5. Preoperative upper limb edema.
6. Skin ulceration.
7. Fixation to the chest wall.
8. Fixed, matted ALN.

Optimal management of LABC requires multimodality treatment [39]. The usual order of treatment varies according to the patient and the tumor clinical stage and characteristics:

Work-up	Inoperable LABC	Operable LABC	Follow-up (F/U)
Obtain the ER, PR, and HER2/neu status Imaging: Breast MRI CT scan chest, abdomen, and pelvis Bone scan PET/CT (optional) Apply a radiologic marker to breast cancer and biopsy-proven involved node preinitiation of chemotherapy Precise tumor measurement and documentation of skin changes Consider discussion in MCC Refer to Fertility, if premenopausal	Neoadjuvant systemic therapy and reassess response after each cycle If response—continue until completion of planned treatment or maximal response—then surgical management If no response—discuss again in MCC. Options: Alternate systemic therapy regimen If operable: Ssurgical management If nonoperable: radiotherapy +/− planned surgical treatment	Consider neoadjuvant chemotherapy in: Any patient who will need adjuvant chemotherapy [115] and in whom surgical pathology information is not required to determine regimen High-grade tumors [115, 116] HER2+ [116] Triple negative (ER/PR/HER2−) [117] Luminal B [115] – Young patients <35 years [118] Patient has large tumor and seeks breast conservation Patients with node-positive disease Surgical management of the breast (usually mastectomy unless downstaging with optional reconstruction) and axilla (see below: SLNB vs. axillary dissection)	Regular clinical breast exam 1–4 times a year for 5 years, then annual Mammogram every 12 months

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *MCC* Multidisciplinary Cancer Conference, *SLNB* sentinel lymph node biopsy

Special Notes

- Radiation therapy will be recommended postmastectomy or post-BCS to patients with LABC.
- Advantages of neoadjuvant chemotherapy:
  - Evaluation of in vivo response to chemotherapy.
  - Downstaging to facilitate breast conservation and omission of ALND in some cases.

    Conversion from mastectomy to BCS occurs in approximately 23% of patients [119]. The extent of conversion depends on the criteria for performing BCS set by the individual trial.
  - Local recurrence rates in this conversion group were slightly higher than in the mastectomy group (15.9% vs. 9.9%, not significant) in the NSABP B-18 study [120] and in a 2018 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of ten randomized trials from 1983 to 2002 [121]. A 2012 combined analysis of NSABP B-18 and B-27 found that the 10-year cumulative incidence of locoregional recurrence after NACT was 12.3% for

mastectomy (without radiation) versus 10.3% for BCS (with radiation) [122]. A more recent 2016 meta-analysis of eight trials from 2000 to 2015 with a total of 3215 patients found that following neoadjuvant chemotherapy, the prevalence of local recurrence was 9.2% in the BCS group versus 8.3% in the mastectomy group (not significant) [123].
  - Early introduction of chemotherapy to treat occult potential systemic metastases.

Neoadjuvant chemotherapy studies

Study	Methods	Results
NSABP B18 Wolmark et al. [120]	*N* = 1493 RCT Operable T1–3 N0–1 M0 patients assigned to preoperative chemo (4 cycles of AC) vs. postoperative chemo (4 cycles of AC)	Follow-up—9 years No differences in OS (70% and 69%) or DFS (53% and 55%) Marginally statistically significant treatment by age interactions appears to be emerging for survival and DFS, suggesting that younger patients may benefit from preoperative therapy, whereas the reverse may be true for older patients
EORTC Trial 10,902 van der Hage et al. [119]	*N* = 698 RCT Patients with T1c, T2, T3, T4b, N0 to 1, and M0 breast cancer were assigned to preoperative vs. postoperative chemotherapy (4 cycles—FEC)	Median follow-up—56 months No differences in terms of PFS, OS, and LRR Preoperative chemotherapy enabled more patients to be treated with breast-conserving surgery (rate of downstaging was 23%)
Fisher et al. 2011 [124]	*N* = 385 Retrospective chart review Patients with stage I, II, or III and triple-negative breast cancer treated with neoadjuvant or adjuvant chemotherapy	There is a trend towards survival benefit in patients with pCR following neoadjuvant chemotherapy However, patients undergoing neoadjuvant chemotherapy with residual disease had significantly worse survival compared to patients receiving adjuvant therapy, with a trend towards worse survival compared to patients receiving neoadjuvant chemotherapy with pCR

AC doxorubicin/adriamycin + cyclophosphamide, *RCT* randomized controlled trial, *DFS* disease-free survival, *FEC* fluorouracil, epirubicin, and cyclophosphamide, *OS* overall survival, *PFS* progression-free survival, *LRR* locoregional recurrence, *pCR* complete pathologic response

- Potential candidates for BCS after neoadjuvant chemotherapy:
  - Ideally unifocal disease (However, multifocal and even multicentric disease can now be removed using oncoplastic techniques, thus allowing for BCS. This is discussed further in the "Oncoplastics" section.)
  - No inflammatory skin involvement.
  - Radiographic abnormalities (e.g., suspicious calcifications) resectable with lumpectomy.
  - No contraindication to adjuvant radiotherapy.
- Neoadjuvant endocrine therapy may be considered for patients who are not candidates for systemic chemotherapy and have markers for endocrine responsive-

ness or chemotherapy unresponsiveness such as ER and PR positivity, low grade, invasive lobular histology, and low Ki67 [115].

- SLNB has been investigated both before and after the completion of neoadjuvant chemotherapy [125]. When performed before neoadjuvant chemotherapy, it is both accurate (identification rate between 93 and 100%) and safe, with a low rate of regional recurrence reported. However, it potentially delays the initiation of chemotherapy in an era where lymph node status does not influence the choice of chemotherapy. Conversely, SLN biopsy after neoadjuvant chemotherapy has the advantage of reducing the number of operative procedures needed, as well as being both accurate and safe [125]. A 2016 meta-analysis examining the accuracy rate of SLNB after neoadjuvant chemotherapy found that in 1456 patients with initially clinically node-negative breast cancer from 16 studies, the SLNB detection rate was 96% (95% CI: 95–97%), with a false-negative rate of 6% [126]. Furthermore, in comparison to performing SLNB prior to chemotherapy, SLNB performed after neoadjuvant chemotherapy has similar SLN identification and false-negative rates, has lower nodal positivity rates (with fewer subsequent axillary dissections for T2 and T3 disease), and does not lead to higher locoregional failure rates [127]. Thus, in patients whose initial ipsilateral axillary evaluation is negative (cN0), sentinel lymph node biopsy is preferably performed after neoadjuvant systemic therapy [39].
- Three clinical trials examined the accuracy and false-negative rates of SLNB performed after neoadjuvant chemotherapy in patients with cN1 disease. The ACOSOG Z1071 (Alliance) Trial had a SLNB identification rate of 92.7% (which was higher when using dual tracer vs. single tracer, 93.8% vs. 88.9%) with a false-negative rate of 12.6% when 2 or more sentinel lymph nodes were examined [128]. The Canadian SN FNAC study showed a SLN identification rate of 87.6% after chemotherapy (less than the predefined optimal SLN identification rate of 90%), but has shown an acceptable false-negative rate of 8.4% when immunohistochemistry (IHC) is used and sentinel node metastases of any size (thus including isolated tumor cells) are considered positive. After neoadjuvant therapy, accuracy of SLNB is further increased by the use of both blue dye and radiolabeled tracer, as well as harvesting more than one sentinel node if possible [101]. In the SENTINA study C arm (patients who converted from cN+ to clinically node negative after neoadjuvant chemotherapy), the SLN detection rate was 80.1% with an overall FNR of 14.2% (24.3% when one node removed vs. 18.5% when two sentinel nodes removed vs. consistently <10% when three or more sentinel nodes removed) [129]. A recent updated meta-analysis of 19 studies from 2016 demonstrated a pooled SLN identification rate of 91% for patients with clinically node-positive breast cancer treated with neoadjuvant chemotherapy, with a pooled FNR of 13% [130].
- Residual nodal disease in the axilla following neoadjuvant treatment is felt to represent chemoresistant disease, and chemoresistant disease is also felt to be

resistant to radiotherapy [131]. As a result, in patients who are node positive on presentation, axillary lymph node dissection should be performed if the axilla remains clinically positive following neoadjuvant systemic therapy. If the axilla becomes clinically negative after neoadjuvant systemic therapy, SLNB may be performed; otherwise, axillary lymph node dissection should be pursued. SLNB has a > 10% false-negative rate in this setting but this rate can be improved by: (1) targeted removal of clipped nodes that were biopsy-proven positive prior to neoadjuvant systemic therapy [132, 133], (2) use of dual tracer localization, (3) removal of two (as per SN FNAC) or more (as per ACOSOG Z1071) sentinel nodes [39], and (4) use of IHC and planned ALND for any persistent disease in sentinel nodes (including isolated tumor cells). Alternatively, intraoperative frozen section may be undertaken at the time of SLNB, with planned completion axillary lymph node dissection if any residual nodal disease is identified on frozen section. Axillary lymph node dissection should be pursued for any residual nodal disease following neoadjuvant systemic therapy on final pathology, including isolated tumor cells.

- Axillary imaging after neoadjuvant chemotherapy has not been found to be a reliable predictor of axillary pathology after neoadjuvant chemotherapy. In the SN FNAC study, the accuracy of axillary ultrasound post-NAC was 62%, with an 81% positive-predictive value and a 48% negative-predictive value [101]. In the ACOSOG Z1071 study, 57% of 430 patients with normal axillary ultrasounds had nodal positivity [128]. Radiologic response by MRI has also not been found to predict axillary response following neoadjuvant chemotherapy [134].
- Future Directions: Two ongoing randomized controlled trials are investigating the potential de-escalation of therapy for patients with initial clinical N1 disease who receive neoadjuvant chemotherapy. (1) In breast cancer patients with cT1-3 N1 disease who have positive sentinel lymph nodes after receiving neoadjuvant chemotherapy, the Alliance A11202 trial is a prospective randomized phase III trial that is randomizing them to either no further axillary surgery (with radiation to breast (if BCS)/chest wall (if mastectomy) and nodal basins including levels 1–3 of the axilla and supraclavicular fossa) or completion level 1–2 axillary lymph node dissection (with radiation to breast (if BCS)/chest wall (if mastectomy) and nodal basins including level 3 axillary nodes and supraclavicular fossa). The primary endpoint is invasive breast cancer recurrence-free survival. As of May 2019, the study has enrolled 2918 participants [135]. (2) In breast cancer patients with cT1-3 N1 disease who have negative axillary nodes following neoadjuvant chemotherapy (determined histologically negative either by ALND or SLNB +/− ALND), the B-51/RTOG 1304 (NRG 9353) trial is randomizing patients to receive either regional nodal radiotherapy (with radiation to breast (if BCS)/chest wall (if mastectomy)) or no regional nodal radiotherapy (with whole-breast radiotherapy if BCS but no chest wall radiotherapy if mastectomy). The primary endpoint is to determine if the addition of comprehensive regional nodal

radiotherapy significantly reduces breast cancer recurrence in this population, with secondary outcomes examining overall survival, locoregional recurrence, and distant recurrence. As of May 2019, this study has accrued 1231 patients (75.2% of anticipated sample size) with an estimated completion date of April 2020 [136].

- Following standard neoadjuvant chemotherapy for triple-negative breast cancer, adjuvant capecitabine is now offered for patients with residual disease at surgery (Create-X trial) [137]. For HER-2 positive patients with no residual disease after neoadjuvant chemotherapy, patients will complete up to 1 year of HER2-targeted therapy with trastuzumab (Herceptin) with or without pertuzumab [39]. For HER2-positive patients with residual invasive disease at surgery, 14 cycles of ado-trastuzumab emtansine (TDM-1) is now recommended (Katherine trial) [138].

Inflammatory Breast Cancer

Inflammatory breast cancer (IBC) is a rare clinicopathological entity (1–6% of all breast cancer) characterized by rapid progression and aggressive behavior, with higher metastatic potential. IBC presents with erythema and edema with exaggerated hair-follicle pits, causing a peau d'orange appearance of the skin [139]. Diffuse erythema of more than one-third of the skin overlying the breast distinguishes IBC (T4d) from neglected noninflammatory LABC with skin involvement (T4a-c) [139, 140]. Diagnostic criteria include rapid onset of erythema, edema and/or peau d'orange with or without a palpable mass occupying at least one-third of the breast, duration not greater than 6 months, and pathological confirmation of invasive cancer [141]. Skin biopsy can aid in diagnosis and was recommended by an international consensus [141]. Most IBC are ductal carcinoma of high nuclear grade; 17–30% are triple negative and 18–44% are HER2-positive [140]. Dermal lymphatic emboli are present in 75% of cases; their absence does not exclude the diagnosis [139, 140]. All women with IBC should undergo staging investigation with at least bone scan and CT scans of the chest, abdomen, and pelvis [141].

After ruling out metastasis, patients are treated with preoperative chemotherapy followed by modified radical mastectomy and radiation in those who clinically respond to chemotherapy [39, 139–143]. Nonresponders may be considered for palliative radiotherapy, as surgery does not appear to benefit this subgroup; mastectomy may be considered for symptom palliation [39, 139]. The trimodality approach of chemotherapy, surgery, and radiation improves the outcome of patients with IBC, as Li et al. in 2008 reported a 5-year survival rate of 40–50% [139].

Special Considerations

Pregnancy and Breast Cancer

Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy or within 1 year of delivery. It is one of the most common malignancies diagnosed during pregnancy. Incidence is estimated to be 1 in 3000–10,000 pregnancies, and 0.2–3.8% of all breast cancers are pregnancy-related [144].

PABC has been demonstrated to have worse prognosis in terms of recurrence and death when compared with non-pregnancy-related breast cancer. Suggested causes include the following:

1. Aggressive disease caused by hormonal and immune changes, and breast involution [145].
2. Diagnosis at an advanced stage, possibly due to a lack of awareness and difficulty in assessing the pregnant breast [145].
3. Use of suboptimal treatments [146].

Management of PABC requires multidisciplinary approach, ensuring best care both for the mother and the fetus. Of note, there is no evidence showing that termination of the pregnancy affects prognosis. However, termination during the first trimester should be discussed with the patient, as it can help avoid delays in treatments that are contraindicated during organogenesis [39].

Treatment of PABC depends on the stage of the cancer, and is similar to that of the non-pregnant patient, with modifications dependent on the gestational age of the pregnancy at diagnosis of PABC [147].

Work-up	Surgical management	Adjuvant therapy
Physical exam Breast and axillary ultrasound Mammogram (with fetal protection) Biopsy	BCT vs. mastectomy: same as for the non-pregnant patient Exception is a patient in the first trimester where chemotherapy is not indicated. Since radiation will be delayed to the postpartum period, mastectomy may offer maximal oncological safety SLNB vs. ALND: same as for the non-pregnant patient SLNB: technetium-99 lymphoscintigraphy is considered safe, but blue dye is contraindicated Reconstruction is usually delayed until after delivery, as achieving symmetry is difficult due to pregnancy-associated breast engorgement	Radiation: Wwhen indicated, should be delayed to the postpartum period Chemotherapy: can be administered, as adjuvant or neoadjuvant treatment, beginning after the first trimester and up to week 35 or 3 weeks before the planned delivery

ALND axillary lymph node dissection, *BCT* breast-conserving therapy, *SLNB* sentinel lymph node biopsy

Special Notes

- Breast MRI should not be performed during pregnancy due to inability to administer gadolinium.
- Fluorouracil, doxorubicin, and cyclophosphamide can be used during the second and third trimesters of pregnancy; paclitaxel may be acceptable if clinically indicated [39].
- The use of trastuzumab is contraindicated in all trimesters due to renal and pulmonary complications [39].
- Tamoxifen is associated with a 20% birth defect risk and, if indicated, should be initiated postpartum [147].

Breast Cancer in the Elderly

With improving life expectancy, the geriatric population is expected to become a significant proportion of the Canadian population. Cancer care decisions in the elderly is complicated by competing medical comorbidities.

Regarding screening, the Canadian Task Force on Preventative Health Breast Cancer Update in 2018 offered no recommendations on screening for patients age 75 and older [148]. A 2009 update from the United States Preventative Services Task Force on screening for breast cancer also acknowledged the lack of studies on the effectiveness of mammography screening in decreasing breast cancer mortality in women aged 70 years and older [149]. The lag time to benefit from screening for breast cancer with mammography is estimated to be 10 years, which should also factor into the consideration for screening the geriatric population [150]. In women over the age of 75, the American Geriatric Society has recommended that medical comorbidities, individual life expectancy and the risks of screening, overdiagnosis, and overtreatment should be considered when making the decision to screen for breast cancer [151].

Special Notes

- Breast cancers in the elderly are more likely to be hormone receptor-positive and less frequently HER2-positive.
- A Cochrane Review comparing surgery (with and without adjuvant endocrine therapy) versus endocrine therapy alone as primary treatment for hormone receptor-positive breast cancer in the elderly showed no difference in survival but increased local control with surgery [152]. Individual life expectancy, medical comorbidities, and the risks of overtreatment should be considered in treatment decisions for breast cancer in the elderly.
- A 2017 systematic review and meta-analysis found that elimination of axillary staging in the elderly affected regional control but did not impact survival [153]. The Society of Surgical Oncology Choosing Wisely campaign also recommends not routinely using axillary staging in clinically node-negative women over the age of 70 years old with hormone receptor-positive breast cancer [154].

- The CALGB 9343 randomized controlled trial showed that in women over 70 years of age with stage 1 (T1N0M0) estrogen receptor-positive breast cancer and clinically negative axilla treated with lumpectomy and endocrine therapy, the addition of adjuvant radiotherapy resulted in an 8% improvement in local-regional control but no additional benefit on survival after 12 years of median follow-up [155].
- Tools such as ePrognosis (eprognosis.ucsf.edu) or a comprehensive geriatric assessment [156] can help predict morbidity and mortality in older patients with cancer. These tools may help evaluate elderly patients in the consideration for surgical treatment of breast cancer.

Dense Breasts

Increased breast density is recognized as an independent risk factor for breast cancer [157]. Mammographic screening is less effective in detecting lesions in women with dense breast tissue. To avoid missing breast cancers on mammograms, supplemental screening modalities including ultrasonography and MRI have been used to increase breast cancer detection rates [158]. This is an area requiring further research. Additional breast imaging modalities increase false-positive rates [158, 159] and their effects on breast cancer outcomes remain unclear [159].

Paget's Disease of the Nipple

Paget's disease of the nipple is an uncommon presentation of breast cancer (1–3%). It presents as a scaly, raw, eczematous, or ulcerated lesion that begins on the nipple and then spreads to the areola. Bloody discharge is occasionally present and bilaterality has been described. An underlying breast cancer (DCIS or invasive disease) is present in 85–88% of cases, often without an associated mass on exam or mammographic finding [160].

Paget's disease is often mistaken in its initial assessment for eczema or dermatitis and treated with a short course of topical steroids. Lesions suspected of Paget's disease of the nipple and persistent nipple abnormalities following treatment with topical steroids should undergo skin punch biopsy. The histologic hallmark of Paget's disease of the nipple are Paget cells, which are malignant intraepithelial adenocarcinoma cells within the epidermis of the nipple. Following the diagnosis of Paget's disease of the nipple, bilateral mammography and ultrasound should be performed to identify an underlying cancer (with bilateral breast MRI if both mammogram and ultrasound are negative).

If an underlying cancer is identified preoperatively, both the cancer and the nipple-areolar complex require excision, either as BCS or mastectomy. In clinically node-negative patients, axillary SLNB should be performed if invasive disease is confirmed preoperatively or if undertaking mastectomy for DCIS. Patients with a clinically positive or suspicious axilla should undergo ultrasound-guided fine

needle aspiration or core needle biopsy of the palpable nodes. If FNA or core biopsy is positive, axillary lymph node dissection at the time of surgery is recommended. If FNA or core biopsy is negative, proceed to SLNB. For patients treated with neoadjuvant chemotherapy, SLNB may be considered for select patients with initial cN1 disease that convert to cN0.

For women with Paget's disease of the nipple without a palpable mass or mammographic abnormality, and where cancer is not identified preoperatively, central lumpectomy (removing the nipple-areolar complex) followed by whole-breast radiotherapy is appropriate. SLNB as a second operation may be pursued if invasive breast cancer is identified postoperatively [160].

Male Breast Cancer

Male breast cancer is a rare condition, with less than 1% of all breast cancers occurring in men [161]. The peak age of incidence is 71 for sporadic cancer and in the 50s for BRCA2-associated male breast [162]. Men tend to be 5–10 years older than women at diagnosis. The most frequent type is invasive ductal carcinoma, accounting for 90% of the cases [163]. The vast majority of male breast cancer is hormone receptor-positive.

The main risk factors for male breast cancer are a strong family history of breast cancer and BRCA mutation (men with BRCA2 mutation have a greater risk of breast cancer (6% absolute lifetime risk) than men with BRCA1 mutation, and an 80-fold increased risk over the general population) [164, 165]. Other conditions associated with increased levels of estrogen and/or decreased levels of androgen, such as Klinefelter syndrome, cirrhosis, gynecomastia, obesity, alcoholism, exogenous treatment with testosterone or estrogen-containing compounds, and testicular diseases (e.g., orchitis, cryptorchidism, testicular injury), are also risk factors.

The presentation (usually a subareolar painless, firm mass), diagnostic work-up (with mammography, ultrasound and biopsy), and staging of male breast cancer mirror that of breast cancer seen in women. One should keep in mind that a new diagnosis of male breast cancer should prompt genetic testing and counseling, as well as screening for prostate cancer.

The management of male breast cancer is similar to breast cancer seen in women. Treatment principles, including the indications for neoadjuvant and adjuvant systemic therapy and management of the axilla, are extrapolated from treatment principles in women, although most studies do not include men. Thus, male breast cancer cases should be discussed in the setting of a multidisciplinary conference.

Surgical management of male breast cancer is simple mastectomy and SLNB or ALND for invasive cancer. Adjuvant radiotherapy is recommended if there is involvement of the chest wall or lymph nodes. There is emerging data that BCS may be attempted for patient preference if there is sufficient breast tissue to obtain a clear margin. In this setting, adjuvant radiotherapy is also recommended, similar to women with breast cancer undergoing BCS [166].

For hormone-sensitive tumors, adjuvant endocrine therapy is recommended. In this setting, tamoxifen has been more studied and is recommended, given the insufficient evidence to support aromatase inhibitor therapy in men [167]. For men who cannot tolerate tamoxifen (e.g., hypercoagulable state), an aromatase inhibitor may be given in combination with an LHRH agonist (e.g., goserelin, leuprolide, buserelin). Later-line hormonal treatments include anti-androgen drugs (e.g., flutamide, bicalutamide). Bilateral orchiectomy can be used to lower estrogen/androgen levels but given its psychological and physical impact, medical options are preferred over this last resort [161, 166].

Following a personal history of breast cancer, men should be surveyed with annual mammography [165]. Screening recommendations for men with a strong family history or genetic predisposition for breast cancer include semiannual clinical exam starting at age 35 and baseline mammography at age 40, with further annual mammography if increased breast density is observed on baseline mammogram [165].

Until recently, it was thought that male breast cancer was associated with a worse prognosis than women. This may be related to male breast cancer being typically diagnosed at a later stage than female breast cancer, owing to a lack of awareness of male breast cancer and a lack of screening in this population [166]. A 2012 study reported a 5-year survival rate of 74% in men compared to 83% in women [168]. However, more contemporary studies of both male and female breast cancer with careful matching for age at diagnosis, grade, and stage are revealing an improvement in survival with time, such that survival is no longer significantly worse in men than women [166].

Metastatic Breast Cancer

Approximately 4.1% of newly diagnosed breast cancer patients will have metastases at presentation. Improved systemic therapy has seen an increase in the 5-year survival of such patients in the past 5 years [169].

Until recently, surgery had a limited role in the management of patients with metastasis [170, 171]. However, there is an emerging body of evidence to support the concept that removing the primary may provide a survival advantage for such patients [169–171]. A 2002 retrospective review of 16,023 patients from the National Cancer Data Base found that overall survival was improved in women with de novo stage IV breast cancer who underwent surgical resection, with 3-year survival rates of 17% for the no-surgery group, 26% for the partial mastectomy group, and 35% for the mastectomy group [170]. Multiple other retrospective studies have reported survival benefits following surgical resection of the breast primary in patients with metastases [172–180]. However, Cady et al. [181] in 2008 challenged this view through a case-matched retrospective analysis of 808 patients with metastatic breast cancer. They found that case matching either diminishes or eliminates the survival advantage obtained with surgery. This finding was further supported by a 2011 study by Dominici et al. [182]. These retrospective studies highlighted the need for randomized controlled trials to examine the benefit of surgery in the de novo metastatic population.

In a 2015 open-label randomized controlled trial of patients with de novo metastatic breast cancer who responded to frontline chemotherapy, Badwe et al. found that locoregional treatment of the primary tumor and axillary nodes in 173 women had no impact on overall survival, as compared to the 177 women who did not receive locoregional treatment [183]. In a 2018 multicenter, phase III RCT randomizing 138 patients to upfront surgery (following chemotherapy) and 136 patients to systemic therapy only, Soran et al. found that median survival was not different at 36 months but was improved at 40 months with upfront surgery (HR 0.66, 95% CI: 0.49–0.88). Subgroup analyses found that this benefit was seen for estrogen- or progesterone-receptor positivity, HER2 negativity, patients younger than 55 years of age, and patients with bone oligometastasis [184]. Additional trials are ongoing [185]. We believe that these cases constitute special situations that need a multidisciplinary approach. Each decision needs to be tailored according to patient symptoms (e.g., pain, bleeding, nonhealing wound), comorbidities, and life expectancy.

Locoregional Recurrence of Breast Cancer

Breast cancer recurrence can be divided into breast recurrence after breast-conserving therapy, recurrence after mastectomy, and axillary recurrences [186].

Breast recurrence after BCT	Recurrence after mastectomy	Axillary recurrence
Rate of LR after BCT—0.5–1% per year [187] Risk factors: Age < 45 years High grade Extensive DCIS Node positive HER2/neu overexpression Positive margins Lack of radiotherapy [188] Most recurrences occur in the same quadrant as the primary tumor Usually detected by physical examination and/or mammography Metastatic work-up is required to rule out systemic disease Due to previous radiotherapy, mastectomy is the standard of care, although data is beginning to emerge examining possible repeat excision and radiotherapy [67–68, 188]. Repeat SLNB may be attempted if ALND was not previously performed [39]	Rate of chest wall recurrence: 5–7% The main predicting factor of chest wall recurrence is tumor size >4 cm and 4 or more positive nodes [188] Usually the recurrence after mastectomy carries a worse outcome than that after BCT Metastatic work-up is indicated If systemic disease is ruled out, the local treatment involves wide local excision with or without radiotherapy (depending if previously received); repeat SLNB attempt is discouraged [39]	Rule out distant metastases and then patients treated with surgical excision of gross disease (i.e., completion axillary node dissection) have better regional control than those treated by radiation therapy [188, 189]. If not technically resectable, consider systemic therapy to gauge response, then resect if becomes feasible [39] Isolated axillary recurrence has a 5-year survival of 50% [190] There is limited data on repeat irradiation of a previously irradiated axilla, and it should be discussed in the setting of a multidisciplinary meeting [68] For supraclavicular and internal mammary node recurrence, NCCN recommends radiation therapy [39], while UpToDate recommends initial systemic therapy, with consideration for either surgery (if previous irradiation) or radiation or both if restaging does not show metastatic progression [191]

BCT breast-conserving therapy, *LR* local recurrence

Referral to Medical Oncology

1. All invasive breast cancers need to be evaluated by medical oncology or discussed in MCC for consideration of systemic therapy.

Referral to Radiation Oncology

1. In situ or invasive carcinoma treated with breast-conserving therapy.
2. Positive or very close margins after mastectomy.
3. Any tumor more than 5 cm irrespective of the surgical treatment offered.
4. Locally advanced and inflammatory breast cancer.
5. Node-positive breast cancer.
6. Paget's disease of the nipple treated with central lumpectomy.

Referring to Multidisciplinary Cancer Conference

Ideally all patients where time allows; however, the following should be discussed:

1. Any case in which a deviation from the standard of care is considered.
2. Axillary lymph node metastases.
3. To review imaging and assess the extent of the disease for the purpose of planning surgical therapy.
4. Disease progression on neoadjuvant chemotherapy with borderline resectability.
5. Patient with metastasis to contralateral axilla.
6. Patient with axillary metastasis and unknown primary cancer.
7. Locoregional recurrence.
8. Metastatic breast cancer in which surgery is being considered.

Technical Aspects of Breast Surgery

Oncoplastic Breast Surgery

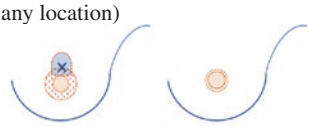
Oncoplastic breast surgery (OPBS) is defined as breast reshaping and breast volume displacement and replacement techniques that extend breast-conserving surgery (BCS) options in order to avoid mastectomy [192]. It aims to preserve aesthetic outcome as well as quality of life for breast cancer patients without compromising disease control. Longer term follow-up data confirms not only the oncologic safety of these techniques, but also a lower rate of positive margins when OPBS is utilized, given the wider area of resection [193, 194]. To date, OPBS has been widely accepted and utilized in Europe and the United Kingdom. In a recent MD Anderson Cancer Center analysis of 9861 patients with operable breast cancer, the addition of OPBS permitted a nearly fourfold increase in the percentage of all BCS performed (from 4% to 15%) between 2007 and 2014 [195].

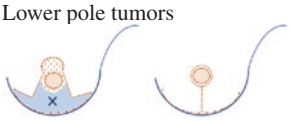
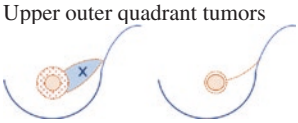
There are two levels of oncoplastic breast surgery [192]:

- Level I: Basic glandular reshaping with local glandular flaps. There is no skin excision and the nipple-areolar complex may be recentralized.
- Level II: Therapeutic mammoplasties, mastopexies and contralateral balancing procedures. The resulting breast is usually smaller, rounder, and higher.

Whenever there is an anticipated poor cosmetic outcome with standard BCS, OPBS should be considered. Excision volume, tumor location, and glandular density are three important elements that should be considered for the choice of the appropriate OPBS technique [196]. Up to 50% of the breast volume can be excised using OPBS. As a general rule, when resection of less than 20% of the breast is planned, Level I parenchymal reshaping can be used. Tumors located in the upper outer quadrant are in the most favorable location for larger volume resections, whereas the upper inner and lower quadrants are the least favorable and can result in significant deformity without OPBS. Regarding the breast glandular density, fatty and scattered fibroglandular breasts are at more risk of fat necrosis after extensive undermining. On the other hand, heterogeneously dense and extremely dense breasts are ideally suited for mobilizing during Level I OPBS.

Comparing Level I and Level II OPBS [196]

Level	Indications	Technique	Pitfalls/comments
I Parenchymal reshaping	Anticipated poor cosmetic outcome with standard BCS Resection of less than 20% of the breast volume is planned	Subcutaneous undermining following mastectomy plane up to ¼ to 2/3 of the breast envelope Excision of the tumor and mobilization from the pectoralis fascia NAC can be recentralized away from the lumpectomy area	Fat necrosis if extensive undermining in fatty breasts
II	Resection of 20–50% of the breast volume is planned		
Round-block	Upper pole and upper inner quadrant tumors (but virtually any location) 	Two concentric periareolar incisions followed by deepithelialization of the skin between the 2 incisions Skin undermining circumferentially starting from outer edge of incision and lumpectomy NAC recentralization	NAC is supplied by posterior glandular base This is a versatile technique and can be applied to tumors in any location

Level	Indications	Technique	Pitfalls/comments
Superior pedicle mammoplasty with inverted T scar	Lower pole tumors 	Periareolar and inferior quadrant incisions Deepithelialization and elevation of superior pedicle Lumpectomy and re-approximation of medial and lateral parenchymal flaps NAC recentralization	Foregoing deepithelialization of the area around the NAC and elevation of the NAC would result in "bird beak" deformity
Batwing	Upper inner quadrant tumors 	Batwing (or hemi-batwing) incision Lumpectomy with removal of skin between upper incision and NAC Re-approximation of batwing incision	The lateral drawing lines should be greater than the round central diameter in length for optimal results [197]
Racquet mammoplasty	Upper outer quadrant tumors 	Racquet incision periareolar and upper outer quadrant Periareolar deepithelialization, quadrant undermining, and lumpectomy Complete detachment of retroareolar gland to allow volume redistribution in lateral space NAC recentralization	An incomplete detachment of the retroareolar gland will not permit maximal mobility to fill the defect

BCS breast-conserving surgery, *NAC* nipple-areolar complex

This table illustrates some examples of level 2 oncoplastic techniques but is not exhaustive.

Technical Aspects of Breast Reconstruction aAfter Mastectomy

Breast reconstruction after mastectomy seeks to restore breast appearance and feel, and patient-reported outcome measures demonstrate its benefit in psychosocial and physical well-being [199]. Ultimately, the decision to pursue reconstruction is up to the patient's preference, but it is our goal to enable our patients to make an informed decision in a timely fashion. The possibility of breast reconstruction should be discussed with the patient who is undergoing mastectomy, and if immediate reconstruction is desired and appropriate, a timely referral to a plastic surgeon is encouraged.

Types of Reconstruction

After a skin-sparing or nipple-sparing mastectomy is performed, there are two main types of reconstruction: prosthetic (use of implants) versus autologous (use of one's own body tissue). The choice between these two options and the timing of the reconstruction (delayed vs. immediate) require a discussion based on the need for adjuvant chemotherapy or radiation, donor tissue availability, medical comorbidities, patient's preference, and lifestyle [200].

Implant-Based Reconstruction

Implant-based reconstruction can be performed two-staged (using a temporary tissue expander) or single-staged (via a direct-to-implant method).

The two-staged reconstruction is more commonly performed, and this process involves a tissue expander placement at the time of the mastectomy. In the immediate few weeks after the operation, the mastectomy skin envelope undergoes expansion as saline fluid is injected into the tissue expander via a syringe needle every 1–2 weeks in the office setting until the expander reaches the desired volume. The subsequent operation involves the tissue expander exchange for a permanent implant. The time between the initial operation to the exchange varies per individual but is generally around 6 months.

The direct-to-implant method involves placing the permanent implant at the time of the mastectomy. This single-staged reconstruction is more successful when there is good mastectomy flap vascularity and no significant stretch or tension in the mastectomy flaps after the implant placement. This method would be ideal for patients with native breasts that are non-ptotic and small with the desired volume that is similar or smaller than the native volume.

In implant-based reconstruction, acellular dermal matrix (ADM)—a processed cadaveric dermis—is commonly used to provide extra coverage of the device in the lower breast pole as an extension of the pectoralis major muscle [201, 202], improve definition of the inferior pole [203], and potentially reduce capsular contracture [204]. However, ADM is costly with a potentially added risk [205] and its selective use is encouraged. In a preoperative setting, ADM use is anticipated in patients with larger breast volumes, nipple-sparing procedures, and direct-to-implant reconstruction, and when postoperative radiation treatment is anticipated. In an intraoperative setting, ADM use is considered in patients with compromised pectoralis major muscle integrity, a high pectoralis insertion, relative skin excess in the setting of a well-perfused mastectomy skin flap, and positive sentinel lymph node status (increases the possibility of receiving adjuvant radiation therapy). Poor flap vascularity is a contraindication for acellular dermal matrix use because it will not incorporate and may lead to persistent seroma, infection, and ultimate loss of the reconstruction [206].

In the past two decades, a subpectoral (dual plane) placement of the implant has been commonly used [207] and remains widely used. In recent years, a prepectoral placement of the implants has also become an acceptable option as it allows the benefits of no animation deformity or absence of pectoralis major muscle spasm and

less discomfort [208]. However, for a prepectoral reconstruction to be successful, a reasonable thickness of the mastectomy flap ensuring the flap vascularity is critical [208]. Other considerations include BMI < 30, mild to moderate breast volume, nonsmokers, minimal ptosis, and prophylactic mastectomy patients in order to decrease the risk of delayed wound healing, mastectomy flap necrosis, infection, seroma, and reconstructive failure [209, 210].

Implant-based reconstruction requires a detailed discussion regarding the safety concerns of the implants. Both silicone and saline implants that are currently available in practice are deemed safe. However, it is important to discuss implant-related risks that include implant infection, rupture, extrusion, capsular contracture, the possible need for additional implant exchanges in the future, and the risk for breast implant-associated anaplastic large cell lymphoma (BIA-ALCL).

BIA-ALCL is a rare peripheral T cell lymphoma which recent evidence suggests an increased incidence with textured implants [211]. Patients may present with periprosthetic fluid collection years after the initial implant operation in these cases, or with a periprosthetic mass. The work-up would involve a cytological analysis of at least 50 cc of a periprosthetic aspirate for lymphoma protocol with flow cytometry, and immunohistochemistry checking for malignant cells that are CD30+ and ALK-negative. Confirmed cases of BIA-ALCL require total capsulectomy and implant removal, with the need for possible adjuvant therapy if there is lymph node or extracapsular involvement or systemic disease. At this time, there is no confirmed case of BIA-ALCL in a patient with a smooth implant-only history where the full implant history of the patient is known.

Autologous Reconstruction

Autologous reconstruction involves using one's own tissue. There are two types—pedicled and free flaps.

Pedicled flaps involve transposing regional tissue while keeping the blood supply intact, such as the pedicled latissimus dorsi (LD) flap or a pedicled transverse rectus abdominis myocutaneous (TRAM) flap that gets transposed to the chest. The pedicled LD flap is a faster operation than a free flap but likely requires additional volume using a prosthetic device (tissue expander changed to implant). This is an option for patients who have previously received radiation to the chest or those who are not candidates for a free flap due to inadequate tissue availability or medical comorbidities. The pedicled TRAM flap is less frequently used today as it increases the risk of abdominal bulge/hernia from having the entire rectus muscle taken but it remains an option in certain situations.

Free flaps involve a distant transfer of tissue that requires a reestablishment of the blood supply via the use of microsurgical techniques. The most commonly used flaps are the deep inferior epigastric perforator (DIEP) flap or muscle-sparing transverse rectus abdominus (MS-TRAM) free flap from the abdomen. Alternative free flaps use tissues from the buttocks and thighs in cases where there is insufficient abdominal tissue or the patient has already undergone abdominoplasty. Free flaps are generally longer operations (8–10 hours) that require a 3-day stay in the hospital to monitor the flap perfusion in the first few days. Patients with an autologous

reconstruction have been found to have a higher long-term satisfaction than those who underwent an implant-based reconstruction on patient-reported outcome measures [199].

Timing of Reconstruction

Reconstruction is offered in an immediate, delayed, or delayed-immediate time frame. An immediate reconstruction is performed at the time of the mastectomy and can include both autologous and implant-based reconstruction options. In an immediate reconstruction, adequate perfusion of the mastectomy flap is critical to obtain a successful reconstruction. Delayed reconstruction is often recommended in patients who are anticipated to undergo adjuvant radiation as the reconstruction failure and complication rate is increased in this population [212]. Delayed autologous reconstruction would allow breast reconstruction using healthy tissue and decrease reconstruction failure rates [200]. Delayed-immediate reconstruction is for patients who are at an increased risk for needing postmastectomy radiation therapy and who wish to have a breast form in place while waiting for final pathology and/or during the period of postmastectomy radiation therapy. A tissue expander is placed at the time of skin-sparing mastectomy and those who do not require postmastectomy radiation therapy, based on final pathology, can undergo a definitive breast reconstruction soon after the initial operation with an implant or a flap [213]. If radiation therapy is required, the expander can be radiated, and following a post-recovery period the expander can be replaced with autologous tissue. In this manner, more skin is preserved (but still not as much as with an immediate reconstruction), and radiation of the final reconstruction can be avoided. However, there may still be complications related to radiation of the expander so that it may require premature removal and place the patient back into the realm of delayed reconstruction.

Surveillance [214, 215]
Surveillance for breast cancer recurrence in the reconstructed breast is completed clinically. There is no evidence to support radiographic screening of the reconstructed breast unless the patient has palpable findings suggestive of recurrence. Suspicious masses or symptoms should be imaged and completely worked up. Fat necrosis is relatively common and benign following breast reconstruction.

Toronto Pearls

- When localizing a lesion for breast conservation, some radiologists will mark the site of the lesion on the skin, but this is not always true. It is helpful to remember that the point of entry and the nipple are the only fixed points. The cranial-caudal (CC) view of a preoperative mammogram defines medial versus lateral and lesion along the nipples line will be either 12′ or 6 o'clock. The medial-lateral

(ML) view defines upper versus lower half and lesions located at the nipple line will be located at either 3′ or 9 o'clock.

- Z0011 results are integrated into our surgical practice: clinically node-negative patients who have undergone lumpectomy and SLNB with positive nodes and who meet Z0011 criteria are not routinely offered completion axillary dissection.
- In cases of locally advanced breast cancer, we perform the SLNB after neoadjuvant chemotherapy if nodes were clinically and radiologically negative prior to treatment. FNA of any suspicious axillary nodes is attempted pretreatment. If nodes were positive and the axilla becomes clinically negative after neoadjuvant systemic therapy, SLNB may be performed; otherwise, axillary lymph node dissection should be pursued.
- Oncoplastic procedures in breast conservation are considered on a case-by-case basis, as are contralateral balancing procedures such as reduction mammoplasty (in conjunction with plastic surgery).
- Contralateral prophylactic mastectomy (CPM) is not routinely recommended in the absence of a genetic mutation resulting in increased lifetime risk of developing a new breast cancer. In discussing CPM for patients without a gene mutation, the following must be considered: CPM does not offer an overall survival benefit in comparison to clinical and radiographic surveillance [198]. It does decrease the risk of developing a contralateral breast cancer. CPM has no effect on local recurrence of the ipsilateral cancer. CPM may be considered in non-gene mutation carriers who are unable/unwilling to undergo continued surveillance and in those who wish to have immediate autologous flap-based reconstruction for optimal symmetry.

References

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2017. Toronto: Canadian Cancer Society; 2017.
2. Hortobagyi GN, Connolly JL, Edge SB, et al. American Joint Committee on Cancer cancer staging manual. 8th ed. New York: Springer International Publishing; 2017.
3. Sabel M, Collins L. Atypical and lobular carcinoma in situ: high-risk lesions of the breast. In: Chagpar AB, editor. UptoDate; 2017. Retrieved March 23, 2019 from https://www.uptodate.com/contents/atypia-and-lobular-carcinoma-in-situ-high-risk-lesions-of-the-breast.
4. American Society of Breast Surgeons. Consensus guideline on concordance assessment of image-guided breast biopsies and management of borderline or high-risk lesions. 2016. Retrieved from https://www.breastsurgeons.org/about/statements/PDF_Statements/Concordance_and_High%20RiskLesions.pdf.
5. Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. N Engl J Med. 2005;353:229–37.
6. National Comprehensive Cancer Network. Breast cancer screening and diagnosis (Version 3.2018). http://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf.
7. Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Mangetic resonance imaging screening of women at high risk for breast cancer. Warner E, Agbassi C, reviewers. Toronto (ON): Cancer Care Ontario; 2012 Aug 31 [Endorsed 2018 Jan]. Program in Evidence-based Care Evidence-based Guideline No.: 15–11 Version 3 ENDORSED. Accessed March 30, 2019 from https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2051.

8. Mastracci TL, Tjan S, Bane AL, et al. E-cadherin alterations in atypical lobular hyperplasia and lobular carcinoma in situ of the breast. Mod Pathol. 2015;18(6):741–51.
9. Collins LC, Baer HJ, Tamimi RM, et al. Magnitude and laterality of breast cancer risk according to histologic type of atypical hyperplasia: results from the Nurses' Health Study. Cancer. 2007;109:180–7.
10. Masannat YA, Bains SK, Pinder SE, et al. Challenges in the management of pleomorphic lobular carcinoma in situ of the breast. Breast. 2013;22(2):194–6.
11. Sabel M. Overview of benign breast disease. In: Chagpar AB, editor. UptoDate. 2018. Retrieved March 23, 2019 from https://www.uptodate.com/contents/overview-of-benign-breast-disease.
12. Sydnor MK, Wilson JD, Hijaz TA, et al. Underestimation of the presence of breast carcinoma in papillary lesions initially diagnosed at core-needle biopsy. Radiology. 2007;242:58–62.
13. Foley NM, Racz JM, Al-Hilli A, et al. An international multicenter review of the malignancy rate of excised papillomatous breast lesions. Ann Surg Oncol. 2015;22(Suppl 3):S385–90.
14. James BA, Cranor ML, Rosen PP. Carcinoma of the breast arising in microglandular adenosis. Am J Clin Pathol. 1993;100:507–13.
15. Koenig C, Dadmanesh F, Bratthauer GL, et al. Carcinoma arising in microglandular adenosis: an immunohistochemical analysis of 20 intraepithelial and invasive neoplasms. Int J Surg Pathol. 2000;8:303–15.
16. Racz JM, Carter JM, Degnim AC. Challenging atypical breast lesions including flat epithelial atypia, radial scar, and intraductal papilloma. Ann Surg Oncol. 2017;24(10):2842–7.
17. Spanheimer PM, Murray MP, Zabor EC, et al. Long-term outcomes after surgical treatment of malignant/borderline phyllodes tumors of the breast. Ann Surg Oncol. 2019;26(7):2136–43.
18. Virnig BA, Tuttle TM, Shamliyan T, et al. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. J Natl Cancer Inst. 2010;102(3):170.
19. Collins LC, Tamimi RM, Baer HJ, et al. Outcome of patients with ductal carcinoma in situ untreated after diagnostic biopsy: results from the Nurses' Health Study. Cancer. 2005;103:1778–84.
20. Sanders ME, Schuyler PA, Dupont WD, et al. The natural history of low-grade ductal carcinoma in situ of the breast in women treated by biopsy only revealed over 30 years of long-term follow-up. Cancer. 2005;103:2481–4.
21. Fisher ER, Anderson S, Redmond C, et al. Pathologic findings from the national surgical adjuvant breast project protocol B-06. 10-year pathologic and clinical prognostic discriminants. Cancer. 1993;71:2507–14.
22. Boland GP, Chan KC, Knox WF, et al. Value of the Van Nuys prognostic index in prediction of recurrence of ductal carcinoma in situ after breast-conserving surgery. Br J Surg. 2003;90:426–32.
23. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347(16):1227–32.
24. Kuerer HM, Smith BD, Chavez-MacGregor M, et al. DCIS margins and breast cancer: MD Anderson Cancer Center multidisciplinary practice guidelines and outcomes. J Cancer. 2017;8(14):2653–62.
25. Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. J Clin Oncol. 1998;16(2):441–52.
26. Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst. 2011;103(6):478–88.
27. Julien JP, Bijker N, Fentiman IS, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. Lancet. 2000;355(9203):528–33.
28. Donker M, Litière S, Werutsky G, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma in situ: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial. J Clin Oncol. 2013;31(32):4054–9.

29. Cuzick J, Sestak I, Pinder SE, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol. 2011;12:21–9.
30. Wärnberg F, Garmo H, Emdin S, et al. Effect of radiotherapy after breast-conserving surgery for ductal carcinoma in situ: 20 years follow-up in the randomized SweDCIS Trial. J Clin Oncol. 2014;32(32):3613–8.
31. Cutuli B, Bernier J, Poortmans P. Radiotherapy in DCIS, an underestimated benefit? Radiother Oncol. 2014;112(1):1–8.
32. Silverstein MJ, Lagios MD. Treatment selection for patients with ductal carcinoma in situ (DCIS) of the breast using the University of Southern California/Van Nuys (USC/VNPI) prognostic index. Breast J. 2015;21(2):127–32.
33. Hughes LL, Wang M, Page DL, et al. Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol. 2009;27(32):5319–24.
34. Wong JS, Chen YH, Gadd MA, et al. Eight-year update of a prospective study of wide excision alone for small low- or intermediate-grade ductal carcinoma in situ (DCIS). Breast Cancer Res Treat. 2014;143(2):343–50.
35. Solin LJ, Gray R, Hughes LL, et al. Surgical excision without radiation for ductal carcinoma in situ of the breast: 12-year results from the ECOG-ACRIN E5194 study. J Clin Oncol. 2015;33(33):3938–44.
36. Sagara Y, Freedman RA, Vaz-Luis I, et al. Patient prognostic score and associations with survival improvement offered by radiotherapy after breast-conserving surgery for ductal carcinoma in situ: a population-based longitudinal cohort study. J Clin Oncol. 2016;34(11):1190–6.
37. McCormick B, Winter K, Hudis C, et al. RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. J Clin Oncol. 2015;33(7):709–15.
38. Shah C, Vicini FA, Berry S, et al. Ductal carcinoma in situ of the breast: evaluating the role of radiation therapy in the management and attempts to identify low-risk patients. Am J Clin Oncol. 2015;38(5):526–33.
39. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 1.2019. 14/03/2019. Available at: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed 16 Mar 2019.
40. Smith BD, Bellon JR, Blitzblau R, et al. Radiation therapy for the whole breast: executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Pract Radiat Oncol. 2018;8(3):145–52.
41. Lalani N, Rakovitch E. Improving therapeutic ratios with the Oncotype DX® ductal carcinoma in situ (DCIS) score. Cureus. 2017;9(4):e1185. https://doi.org/10.7759/cureus.1185.
42. Evaluation of the DCIS score for decisions on radiotherapy in patients with low/intermediate risk DCIS (DUCHESS). ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US). 2016. Identifier NCT02766881. Cited 2018 Jan 27. Available from: http://clinicaltrials.gov/ct2/show/NCT02766881.
43. Klein J, Kong I, Paszat L, et al. Close or positive resection margins are not associated with an increased risk of chest wall recurrence in women with DCIS treated by mastectomy: a population-based analysis. Springerplus. 2015;4:335. https://doi.org/10.1186/s40064-015-1032-5.
44. Childs SK, Chen YH, Duggan MM, et al. Impact of margin status on local recurrence after mastectomy for ductal carcinoma in situ. Int J Radiat Oncol Biol Phys. 2013;85(4):948–52.
45. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: national surgical adjuvant breast and bowel project B-24 randomised controlled trial. Lancet. 1999;353:1993–2000.
46. Allred DC, Anderson SJ, Palk S, et al. Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP protocol B-24. J Clin Oncol. 2012;30(12):1268–73.

47. Forbes JF, Sestak I, Howell A, et al. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomized controlled trial. Lancet. 2016;387(10021):866–73.
48. Anderson C, Meyer AM, Wheeler SB, et al. Endocrine therapy initiation and medical oncologist utilization among women diagnosed with ductal carcinoma in situ. Oncologist. 2017;22(5):535–41.
49. Anderson C, Winn AN, Dusetzina SB, Nichols HB. Endocrine therapy initiation among older women with ductal carcinoma in situ. J Cancer Epidemiol. 2017;2017:6091709. https://doi.org/10.1155/2017/6091709.
50. Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. J Clin Oncol. 2016;34(33):4040–6.
51. Kell MR, Morrow M. An adequate margin of excision in ductal carcinoma in situ. BMJ. 2005;331:789–90.
52. Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. Pract Radiat Oncol. 2016;6(5):287–95.
53. Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. Ann Surg Oncol. 2016;23(12):3801–10.
54. Marinovich ML, Azizi L, Macaskill P, et al. The association of surgical margins and local recurrence in women with ductal carcinoma in situ treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol. 2016;23(12):3811–21.
55. Van Zee KJ, Subhedar P, Olcese C, et al. Relationship between margin width and recurrence of ductal carcinoma in situ: analysis of 2996 women treated with breast-conserving surgery for 30 years. Ann Surg. 2015;262(4):623–31.
56. Tadros AB, Smith BD, Shen Y, et al. Ductal carcinoma in situ and margins <2 mm: contemporary outcomes with breast conservation. Ann Surg. 2019;269(1):150–7.
57. Bijker N, Meijnen P, Peterse JL, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853 – a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol. 2006;24(21):3381–7. Epub 2006 Jun 26.
58. Collins LC, Achacoso N, Haque R, et al. Risk factors for non-invasive and invasive local recurrence in patients with ductal carcinoma in situ. Breast Cancer Res Treat. 2013;139(2):453–60.
59. Subhedar P, Olcese C, Patil S, et al. Decreasing recurrence rates for ductal carcinoma in situ: analysis of 2996 women treated with breast-conserving surgery over 30 years. Ann Surg Oncol. 2015;22(10):3273–81.
60. Rakovitch E, Gray R, Baehner FL, et al. Refined estimates of local recurrence risks by DCIS score adjusting for clinicopathological features: a combined analysis of ECOG-ACRIN E5194 and Ontario DCIS cohort studies. Breast Cancer Res Treat. 2018;169(2):359–69.
61. Wallis MG, Clements K, Kearins O, et al. The effect of DCIS grade on rate, type and time to recurrence after 15 years of follow-up of screen-detected DCIS. Br J Cancer. 2012;106(10):1611–7.
62. Fisher B, Land S, Mamounas E, et al. Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the national surgical adjuvant breast and bowel project experience. Semin Oncol. 2001;28:400–18.
63. Kong I, Narod SA, Taylor C, et al. Age at diagnosis predicts local recurrence in women treated with breast-conserving surgery and postoperative radiation therapy

for ductal carcinoma in situ: a population-based outcomes analysis. Curr Oncol. 2014;21(1):e96–e104.
64. Cronin PA, Olcese C, Patil S, et al. Impact of age on risk of recurrence of DCIS: outcomes of 2996 women treated with breast-conserving surgery over 30 years. Ann Surg Oncol. 2016;23(9):2816–24.
65. Solin LJ, Fourquet A, Vicini FA, et al. Salvage treatment for local recurrence after breast-conserving surgery and radiation as initial treatment for mammographically detected ductal carcinoma in situ of the breast. Cancer. 2001;91(6):1090–7.
66. Resch A, Fellner C, Mock U, et al. Locally recurrent breast cancer: pulse dose rate brachytherapy for repeat irradiation following lumpectomy- a second chance to preserve the breast. Radiology. 2002;225:713–8.
67. Arthur DW, Winter KA, Kuerer HM, et al. NRG Oncology-Radiation Therapy Oncology Group Study 1014: 1-year toxicity report from a phase 2 study of repeat breast-preserving surgery and 3-dimensional conformal partial-breast reirradiation for in-breast recurrence. Int J Radiat Oncol Biol Phys. 2017;98(5):1028–35.
68. Harms W, Budach W, Dunst J, et al. DEGRO practical guidelines for radiotherapy of breast cancer VI: therapy of locoregional breast cancer recurrences. Strahlenther Onkol. 2016;192(4):199–208.
69. Lyman GH, Temin S, Edge SB, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2014;32:1365–83.
70. Hamm C, Tey R, reviewers. Baseline staging tests in primary breast cancer. Toronto: Cancer Care Ontario; 2011. Available at: https://www.cancercare.on.ca/common/pages/UserFile.aspx?fi leId=13868.
71. Meric F, Mirza NQ, Vlastos G, et al. Positive surgical margins and ipsilateral breast tumor recurrence predict disease-specific survival after breast-conserving therapy. Cancer. 2003;97:926–33.
72. Hanley C, Kessaram R. Quality of diagnosis and surgical management of breast lesions in a community hospital: room for improvement? Can J Surg. 2006;49:185–92.
73. Warner E. Systematic review: using magnetic resonance imaging to screen for women at high risk for breast cancer. Ann Intern Med. 2008;148(9):671–9.
74. Sardanelli F, Boetes C, Borish B. Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer. 2010;46:1296–316.
75. Houssami N, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: meta-analysis of surgical outcomes. Ann Surg. 2013;257(2):249–55.
76. Tan JZY, Waugh J, Kumar B, et al. Mucinous carcinomas of the breast: imaging features and potential for misdiagnosis. J Med Imaging Radiat Oncol. 2013;57(1):25–31.
77. Houssami N, Macaskill P, Marinovich ML. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol. 2014;21(3):717–30.
78. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of surgical oncology-american society for radiation oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. Ann Surg Oncol. 2014;21(3):704–16.
79. Buchholz TA, Somerfield MR, Griggs JJ, et al. Margins for breast-conserving surgery with whole-breast irradiation in stage I and II invasive breast cancer: American Society of Clinical Oncology endorsement of the Society of Surgical Oncology/American Society for Radiation Oncology consensus guideline. J Clin Oncol. 2014;32(14):1502–6.
80. Ontario Ministry of Health and Long Term Care guidelines on breast cancer genetic counseling and testing. Available at: http://www.health.gov.on.ca/en/pro/programs/ohip/bulletins/4381/bul4381a.aspx.
81. NCCN clinical practice guidelines in oncology: genetic/familial high-risk assessment: breast and ovarian. Version 3.2019. 18/01/2019. Available at: http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed 12 May 2019.

82. American Society of Breast Surgeons. Consensus guideline on genetic testing for hereditary breast cancer. 2019. Retrieved from https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Genetic-Testing-for-Hereditary-Breast-Cancer.pdf. Accessed 12 May 2019.
83. Steele RJ, Forrest AP, Gibson T, et al. The efficacy of lower axillary sampling in obtaining lymph node status in breast cancer: a controlled randomized trial. Br J Surg. 1985;72:368–9.
84. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer—a multicenter validation study. N Engl J Med. 1998;339:941–6.
85. Lyman GH, Giuliano AE, Somerfield MR, et al. American society of clinical oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol. 2005;23:7703–20.
86. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC trial. J Natl Cancer Inst. 2006;98:599–609.
87. Krag DN, Anderson SJ, Julian TB, et al. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. Lancet Oncol. 2007 Oct;8(10):881–8.
88. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010;11(10):927–33.
89. Fisher B, Montague E, Redmond C, et al. Findings from NSABP protocol no. B-04-comparison of radical mastectomy with alternative treatments for primary breast cancer. I. Radiation compliance and its relation to treatment outcome. Cancer. 1980;46:1–13.
90. Newman LA, Mamounas EP. Review of breast cancer clinical trials conducted by the National Surgical Adjuvant Breast Project. Surg Clin North Am. 2007;87:279–305. Vii.
91. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg. 2010;252:426–32.
92. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA. 2017;318(10):918–26. https://doi.org/10.1001/jama.2017.11470.
93. Joslyn SA. Hormone receptors in breast cancer: racial differences in distribution and survival. Breast Cancer Res Treat. 2002;73:45–59.
94. Truong PT, Bernstein V, Wai E, et al. Age-related variations in the use of axillary dissection: a survival analysis of 8038 women with T1-ST2 breast cancer. Int J Radiat Oncol Biol Phys. 2002;54:794–803.
95. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;366:2087–106.
96. Fisher B, Bauer M, Margolese R, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med. 1985;312:665–73.
97. Cabanes PA, Salmon RJ, Vilcoq JR, et al. Value of axillary dissection in addition to lumpectomy and radiotherapy in early breast cancer. The Breast Carcinoma Collaborative Group of the Institut Curie. Lancet. 1992;339:1245–8.
98. Jagsi R, Chadha M, Moni J, et al. Radiation field design in the ACOSOG Z0011 (Alliance) trial. J Clin Oncol. 2014 Nov 10;32(32):3600–6.
99. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981–22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol. 2014;15:1303–10.

100. Galimberti V, Cole BF, Viale G, et al. International breast Cancer Study Group Trial 23-01. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01):10-year follow-up of a randomised, controlled phase 3 trial. Lancet Oncol. 2018;19(10):1385–93.
101. Boileau JF, Poirier B, Basik M, Holloway C, et al. Sentinel node biopsy following neoadjuvant chemotherapy in biopsy proven node positive breast cancer: the SN FNAC study. J Clin Oncol. 2015;33(3):258–64.
102. Weaver DL, Ashikaga T, Krag DN, et al. Effect of occult metastases on survival in node-negative breast cancer. N Engl J Med. 2011;364:412–21.
103. Altinyollar H, Berberoglu U, Gulben K, et al. The correlation of extranodal invasion with other prognostic parameters in lymph node positive breast cancer. J Surg Oncol. 2007;95(7):567–71.
104. Joseph KA, El-Tamer M, Komenaka I, et al. Predictors of nonsentinel node metastasis in patients with breast cancer after sentinel node metastasis. Arch Surg. 2004;139(6):648–51.
105. Gooch J, King TA, Eaton A, et al. The extent of extracapsular extension may influence the need for axillary lymph node dissection in patients with T1-T2 breast cancer. Ann Surg Oncol. 2014;21(9):2897–903.
106. Choi AH, Blount S, Perez MN, et al. Size of extranodal extension on sentinel lymph node dissection in the American College of Surgeons Oncology Group Z0011 Trial Era. JAMA Surg. 2015;150(12):1141–8.
107. Pilewskie ML, Morrow M. Management of the clinically node-negative axilla: what have we learned from the clinical trials? Oncology (Williston Park). 2014;28(5):371–8.
108. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med. 2018;379:111–21.
109. Francis PA, Regan MM, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med. 2015;372:436–66.
110. Pagani O, Regan MM, Waley MD, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med. 2014;371:107–18.
111. Moore HC, Unger JM, Phillips KA, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med. 2015;372:923–32.
112. Park WC. Role of ovarian function suppression in premenopausal women with early breast cancer. J Breast Cancer. 2016;19(4):341–8.
113. Kwon DS, Kelly CM, Ching CD. Chapter 2 Invasive breast cancer. In: Feig BW, Ching CD, editors. The MD Anderson surgical oncology handbook. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2012. p. 20–65. Print.
114. Chia S, Swain SM, Byrd DR, et al. Locally advanced and inflammatory breast cancer. J Clin Oncol. 2008;26:786–90.
115. Kaufmann M, von Minckwitz MG, Bear HD, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol. 2007;18:1927–34.
116. Colleoni M, Viale G, Zahrieh D, et al. Expression of ER, PgR, HER1, HER2, and response: a study of preoperative chemotherapy. Ann Oncol. 2008;19:465–72.
117. Rody A, Karn T, Solbach C, et al. The erbB2+ cluster of the intrinsic gene set predicts tumor response of breast cancer patients receiving neoadjuvant chemotherapy with docetaxel, doxorubicin and cyclophosphamide within the GEPARTRIO trial. Breast. 2007;16:235–40.
118. Spring L, Greenup R, Niemierko A, et al. Pathologic complete response after neoadjuvant chemotherapy and long-term outcomes among young women with breast cancer. J Natl Compr Cancer Netw. 2017;15(10):1216–23.
119. van der Hage JA, van de Velde CJ, Julien JP, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol. 2001;19:4224–37.
120. Wolmark N, Wang J, Mamounas E, et al. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr. 2001:96–102.

121. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomized trials. Lancet Oncol. 2018;19(1):27–39.
122. Mamounas EP, Anderson SJ, Dignam JJ, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J Clin Oncol. 2012;30(32):3960–6.
123. Zhou X, Li Y. Local recurrence after breast-conserving surgery and mastectomy following neoadjuvant chemotherapy for locally advanced breast cancer – a meta-analysis. Breast Care (Basel). 2016;11(5):345–51.
124. Fisher CS, Ma CX, Gillanders WE, et al. Neoadjuvant chemotherapy is associated with improved survival compared with adjuvant chemotherapy in patients with triple-negative breast cancer only after complete pathologic response. Ann Surg Oncol. 2012;19:253–8.
125. Sabel MS. Sentinel lymph node biopsy before or after neoadjuvant chemotherapy: pros and cons. Surg Oncol Clin N Am. 2010;19:519–38.
126. Geng C, Chen X, Pan X, et al. The feasibility and accuracy of sentinel lymph node biopsy in initially clinically node-negative breast cancer after neoadjuvant chemotherapy: a systematic review and meta-analysis. PLoS One. 2016;11(9):e0162605.
127. Hunt KK, Yi M, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy is accurate and reduces the need for axillary dissection in breast cancer patients. Ann Surg. 2009;250(4):558–66.
128. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer. The ACOSOG Z1071 (Alliance) clinical trial. JAMA. 2013;310(14):1455–61.
129. Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicenter cohort study. Lancet Oncol. 2013;14(7):609–18.
130. El Hage CH, Headon H, El Tokhy O, et al. Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following neoadjuvant chemotherapy in women with node-positive breast caner at diagnosis? An updated meta-analysis involving 3,398 patients. Am J Surg. 2016;212(5):969–81.
131. Rycaj K, Tang DG. Cancer stem cells and radioresistance. Int J Radiat Biol. 2014;90(8):615–21.
132. Boughey JC, Ballman KV, Le-Petross HT, et al. Identification and resection of clipped node decreases the false-negative rate of sentinel lymph node surgery in patients presenting with node-positive breast cancer (T0-T4, N1-N2) who receive neoadjuvant chemotherapy: results from ACOSOG Z1071 (Alliance). Ann Surg. 2016;263(4):802–7.
133. Caudle AS, Yang WT, Krishnamurthy S, et al. Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. J Clin Oncol. 2016;34(10):1072–8.
134. Weber JJ, Jochelson MS, Eaton A, et al. MRI and prediction of pathologic complete response in the breast and axilla after neoadjuvant chemotherapy for breast cancer. J Am Coll Surg. 2017;225(6):740–6.
135. ClinicalTrials.gov [Internet]. Comparison of axillary lymph node dissection with axillary radiation for patients with node-positive breast cancer treated with chemotherapy. Bethesda: National Library of Medicine (US); 2013. Identifier NCT01901094. 2019 Feb 20 [cited 2019 March 10]. Available from: http://clinicaltrials.gov/ct2/show/NCT01901094.
136. ClinicalTrials.gov [Internet]. Standard or comprehensive radiation therapy in treating patients with early-stage breast cancer previously treated with chemotherapy and surgery. Bethesda: National Library of Medicine (US); 2013. Identifier NCT01872975. 2017 May 16 [cited 2019 March 21]. Available from: http://clinicaltrials.gov/ct2/show/NCT01872975.
137. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med. 2017;376:2147–59.
138. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med. 2019;380:617–28.

139. Li BD, Sicard MA, Ampil F, et al. Trimodal therapy for inflammatory breast cancer: a surgeon's perspective. Oncology. 2010;79:3–12.
140. Mamouch F, Berrada N, Aoullay Z, et al. Inflammatory breast cancer: a review. World J Oncol. 2018;9(5–6):129–35.
141. Dawood S, Merajver SD, Viens P, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol. 2011;22(3):515–23.
142. Robertson FM, Bondy M, Yang W, et al. Inflammatory breast cancer: the disease, the biology, the treatment. CA Cancer J Clin. 2010;60:351–75.
143. Ueno NT, Espinosa Fernandez JR, Cristofanilli M, et al. International consensus on the clinical management of inflammatory breast cancer from the Morgan Welch Inflammatory Breast Cancer Research Program 10th Anniversary Conference. J Cancer. 2018;9(8):1437–47.
144. Hartman EK, Eslick GD. The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis. Breast Cancer Res Treat. 2016;160:347–60.
145. Ruiz R, Herrero C, Strasser-Weippl K, et al. Epidemiology and pathophysiology of pregnancy-associated breast cancer: a review. Breast. 2017;35:136–41.
146. Peccatori FA, Lambertini M, Scarfone G, et al. Biology, staging, and treatment of breast cancer during pregnancy: reassessing the evidences. Cancer Biol Med. 2018;15:6–13.
147. Cordeiro CN, Gemignani ML. Breast cancer in pregnancy: avoiding fetal harm when maternal treatment is necessary. Breast J. 2017;23(2):200–5.
148. Klarenbach S, Sims-Jones N, Lewin G, et al. Recommendations on screening for breast cancer in women aged 40-74 years who are not at increased risk for breast cancer. CMAJ. 2018;190(49):E1441–51.
149. Nelson HD, Tyne K, et al.; U.S. Preventive Services Task Force. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;151(10):727–37, W237–42.
150. Lee SJ, Boscardin WJ, Stijacic-Cenzer I, et al. Time lag to benefit after screening for breast and colorectal cancer: meta-analysis of survival data from the United States, Sweden, United Kingdom, and Denmark. BMJ. 2013;346:e8441.
151. American Geriatrics Society. Ten things clinicians and patients should question. 2014 [updated 2015 Apr 23]. Choosing Wisely. Accessed May 25, 2019 from https://www.choosingwisely.org/societies/american-geriatrics-society/.
152. Hind D, Wyld L, Reed MW. Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: cochrane review. Br J Cancer. 2007;96(7):1025–9.
153. Liang S, Hallet J, Simpson JS, et al. Omission of axillary staging in elderly patients with early stage breast cancer impacts regional control but not survival: a systematic review and meta-analysis. J Geriatr Oncol. 2017;8(2):140–7.
154. Choosing Wisely. The Socieyt of Surgical Oncology Encourages Doctors, Patients to question specific commonly-used tests and treatments as part of choosing wisely campaign. 2016. Accessed May 25, 2019 from http://www.choosingwisely.org/the-society-of-surgical-oncology-joins-choosing-wisely-campaign/.
155. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol. 2013;31(19):2382–7.
156. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol. 2007;25(14):1824–31.
157. Nazari SS, Mukherjee P. An overview of mammographic density and its association with breast cancer. Breast Cancer. 2018;25(3):259–67.
158. Melnikow J, Fenton JJ, Whitlock EP, et al. Supplemental screening for breast cancer in women with dense breasts: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2016;164(4):268–78.
159. Lee JM, Arao RF, Sprague BL, et al. Performance of screening ultrasonography as an adjunct to screening mammography in women across the spectrum of breast cancer risk. JAMA Intern Med. 2019; https://doi.org/10.1001/jamainternmed.2018.8372. [Epub ahead of print].

160. Sabel, M., & Weaver, D. L. (2018) Paget disease of the breast. In: Chagpar AB, Hayes DF, Pierce LJ, editors. UptoDate. Retrieved May 12, 2019 from https://www.uptodate.com/contents/paget-disease-of-the-breast.
161. Canadian Cancer Society. Breast cancer in men. Accessed March 29, 2019 from http://www.cancer.ca/en/cancer-information/cancer-type/breast/breast-cancer/breast-cancer-in-men/.
162. Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. Lancet. 2006;367(9510):595–604.
163. Serdy KM, Leone JP, Dabbs DJ, et al. Male breast Cancer. Am J Clin Pathol. 2017;147(1):110–9.
164. Pritzlaff M, Summerour P, McFarland R, et al. Male breast cancer in a multi-gene panel testing cohort: insights and unexpected results. Breast Cancer Res Treat. 2017;161(3):575–86.
165. Block WD, Muradali D. Breast cancer in men. CMAJ. 2013;185(14):1247. https://doi.org/10.1503/cmaj.122056.
166. Gradishar WJ, Ruddy KJ. Breast cancer in men. In: Chagpar AB, Hayes DF, editors. UpToDate. 2019. Retrieved April 20, 2019, from https://www.uptodate.com/contents/breast-cancer-in-men.
167. Zagouri F, Sergentanis TN, Azim HA Jr, et al. Aromatase inhibitors in male breast cancer: a pooled analysis. Breast Cancer Res Treat. 2015;151(1):141–7.
168. Greif JM, Pezzi CM, Klimberg VS, et al. Gender differences in breast cancer: analysis of 13,000 breast cancers in men from the National Cancer Data Base. Ann Surg Oncol. 2012;19(10):3199–204.
169. Pockaj BA, Wasif N, Dueck AC, et al. Metastasectomy and surgical resection of the primary tumor in patients with stage IV breast cancer: time for a second look? Ann Surg Oncol. 2010;17:2419–26.
170. Khan SA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? Surgery. 2002;132:620–6.
171. Beslija S, Bonneterre J, Burstein HJ, et al. Third consensus on medical treatment of metastatic breast cancer. Ann Oncol. 2009;20:1771–85.
172. Fields RC, Jeffe DB, Trinkaus K, et al. Surgical resection of the primary tumor is associated with increased long-term survival in patients with stage IV breast cancer after controlling for site of metastasis. Ann Surg Oncol. 2007;14:3345–51.
173. Babiera GV, Rao R, Feng L, et al. Effect of primary tumor extirpation in breast cancer patients who present with stage IV disease and an intact primary tumor. Ann Surg Oncol. 2006;13:776–82.
174. Blanchard DK, Shetty PB, Hilsenbeck SG, et al. Association of surgery with improved survival in stage IV breast cancer patients. Ann Surg. 2008;247:732–8.
175. Neuman HB, Morrogh M, Gonen M, et al. Stage IV breast cancer in the era of targeted therapy: does surgery of the primary tumor matter? Cancer. 2010;116:1226–33.
176. Bafford AC, Burstein HJ, Barkley CR, et al. Breast surgery in stage IV breast cancer: impact of staging and patient selection on overall survival. Breast Cancer Res Treat. 2009;115:7–12.
177. Hazard HW, Gorla SR, Scholtens D, et al. Surgical resection of the primary tumor, chest wall control, and survival in women with metastatic breast cancer. Cancer. 2008;113:2011–9.
178. Ly BH, Vlastos G, Rapiti E, et al. Local-regional radiotherapy and surgery is associated with a significant survival advantage in metastatic breast cancer patients. Tumori. 2010;96:947–54.
179. Gnerlich J, Jeffe DB, Deshpande AD, et al. Surgical removal of the primary tumor increases overall survival in patients with metastatic breast cancer: analysis of the 1988-2003 SEER data. Ann Surg Oncol. 2007;14:2187–94.
180. Rao R, Feng L, Kuerer HM, et al. Timing of surgical intervention for the intact primary in stage IV breast cancer patients. Ann Surg Oncol. 2008;15:1696–702.
181. Cady B, Nathan NR, Michaelson JS, et al. Matched pair analyses of stage IV breast cancer with or without resection of primary breast site. Ann Surg Oncol. 2008;15:3384–95.
182. Dominici L, Najita J, Hughes M, et al. Surgery of the primary tumor does not improve survival in stage IV breast cancer. Breast Cancer Res Treat. 2011;129(2):459–65.

183. Badwe R, Hawaldar R, Nair N, et al. Locoregional treatment versus no treatment of the primary tumor in metastatic breast cancer: an open-label randomized controlled trial. Lancet Oncol. 2015;16(13):1380–8.
184. Soran A, Ozmen V, Ozbas S, et al. Randomized trial comparing resection of primary tumor with no surgery in stage IV breast cancer at presentation: protocol MF07-01. Ann Surg Oncol. 2018;25(11):3141–9.
185. Khan SA. Early surgery or standard palliative therapy in treating patients with stage IV breast cancer. Available from: http://clinicaltrials.gov/show/NCT01242800. Updated 01 January 2019. Accessed 16 Mar 2019.
186. Easson AM, McCready DR. Management of local recurrence of breast cancer. Expert Rev Anticancer Ther. 2004;4:219–26.
187. Cabioglu N, Hunt KK, Buchholz TA, et al. Improving local control with breast-conserving therapy: a 27-year single-institution experience. Cancer. 2005;104:20–9.
188. Mahvi DA, Liu R, Grinstaff MW, et al. Local cancer recurrence: the realities, challenges, and opportunities for new therapies. CA Cancer J Clin. 2018;68(6):488–505.
189. Recht A, Pierce SM, Abner A, et al. Regional nodal failure after conservative surgery and radiotherapy for early-stage breast carcinoma. J Clin Oncol. 1991;9:988–96.
190. Willner J, Kiricuta IC, Kolbl O. Locoregional recurrence of breast cancer following mastectomy: always a fatal event? Results of univariate and multivariate analysis. Int J Radiat Oncol Biol Phys. 1997;37:853–63.
191. Hirsch A, Sabel MS, Hayes DF. Management of locoregional recurrence of breast cancer after mastectomy. In: Burstein HJ, editor. UpToDate. 2018. Retrieved March 16, 2019, from https://www.uptodate.com/contents/management-of-locoregional-recurrence-of-breast-cancer-after-mastectomy.
192. Campbell EJ, Romics L. Oncological safety and cosmetic outcomes in oncoplastic breast conservation surgery: a review of the best level of evidence literature. Breast Cancer (Dove Med Press). 2017;9:521–30.
193. Kaur N, Petit JY, Rietjens M, et al. Comparative study of surgical margins in oncoplastic surgery and quadrantectomy in breast cancer. Ann Surg Oncol. 2005;12(7):539–45.
194. Spear SL, Pelletiere CV, Wolfe AJ, et al. Experience with reduction mammaplasty combined with breast conservation therapy in the treatment of breast cancer. Plast Reconstr Surg. 2003;111(3):1102–9.
195. Carter SA, Lyons GR, Kuerer HM, et al. Operative and oncologic outcomes in 9861 patients with operable breast cancer: single-institution analysis of breast conservation with oncoplastic reconstruction. Ann Surg Oncol. 2016;23(10):3190–8.
196. Clough KB, Kaufman GJ, Nos C, et al. Improving breast cancer surgery: a classification and quadrant per quadrant atlas for oncoplastic surgery. Ann Surg Oncol. 2010;17(5):1375–91.
197. Sanidas EE, Schrenk P. Part II: breast conserving oncoplastic techniques: Batwing technique. In: Fitzal F, Schrenk P, editors. Oncoplastic breast surgery, a guide to clinical practice. 2nd ed. Vienna: Springer; 2015. p. 21–5. Print.
198. Wong SM, Freedman RA, Sagara Y, et al. Growing use of contralateral prophylactic mastectomy despite no improvement in long-term survival for invasive breast cancer. Ann Surg. 2017;265(3):581–9.
199. Santosa KB, Qi J, Kim HM, et al. Long-term patient-reported outcomes in postmastectomy breast reconstruction. JAMA Surg. 2018;153(10):891–9.
200. Lee CN-H, Deal AM, Huh R, et al. Quality of patient decisions about breast reconstruction after mastectomy. JAMA Surg. 2017;152(8):741–8.
201. Rawlani V, Buck DW II, Johnson SA, et al. Tissue expander breast reconstruction using prehydrated human acellular dermis. Ann Plast Surg. 2011;66:593–7.
202. Kim JY, Connor CM. Focus on technique: two-stage implant-based breast reconstruction. Plast Reconstr Surg. 2012;130(Suppl 2):104S–15S.
203. Spear SL, Sher SR, Al-Attar A. Focus on technique: supporting the soft-tissue envelope in breast reconstruction. Plast Reconstr Surg. 2012;130(Suppl 2):89S–94S.

204. Salzberg CA, Dunavant C, Nocera N. Immediate breast reconstruction using porcine acellular dermal matrix (Strattice) long-term outcomes and complications. J Plast Reconstr Aesthet Surg. 2013;66:323–8.
205. Ho G, Nguyen TJ, Shahabi A, et al. A systematic review and meta-analysis of complications associated with acellular dermal matrix-assisted breast reconstruction. Ann Plast Surg. 2012;68:346–56.
206. Jordan SW, Khavanin N, Fine NA, et al. An algorithmic approach for selective acellular dermal matrix use in immediate two-stage breast reconstruction: indications and outcomes. Plast Reconstr Surg. 2014;134:178–88.
207. Corderiro PG, Jazayeri L. Two-stage implant-based breast reconstruction: an evolution of the conceptual and technical approach over a two-decade period. Plast Reconstr Surg. 2016;138:1–11.
208. Nahabedian MY. Current approaches to prepectoral breast reconstruction. Plast Reconstr Surg. 2018;142:871–80.
209. Sigalove S, Maxwell GP, Sigalove NM, et al. Prepectoral implant-based breast reconstruction: rationale, indications, and preliminary results. Plast Reconstr Surg. 2017;139:287–94.
210. Sbitany H, Piper M, Lentz R. Prepectoral breast reconstruction: a safe alternative to submuscular prosthetic reconstruction following nipple-sparing mastectomy. Plast Reconstr Surg. 2017;140:432–43.
211. Leberfinger AN, Behar BJ, Williams NC, et al. Breast implant-associated anaplastic large cell lymphoma: a systematic review. JAMA Surg. 2017;152(12):1161–8.
212. Nelson JA, Disa JJ. Breast reconstruction and radiation therapy: an update. Plast Reconstr Surg. 2017;140(5S):60S–8S.
213. Kronowitz SJ. Delayed-immediate breast reconstruction: technical and timing considerations. Plast Reconstr Surg. 2010;125(2):463–74.
214. Shea-Budgell M, Quan ML, Mehling B, et al. Breast reconstruction following prophylactic or therapeutic mastectomy for breast cancer: recommendations from an evidence-based provincial guideline. Plast Surg. 2014;22(2):103–11.
215. Zakireh J, Fowble B, Esserman LJ. Application of screening principles to the reconstructed breast. J Clin Oncol. 2010;28:173–80.