# Chapter 13
# Surgical Approach in Invasive Breast Cancer


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## Historical Background

Beginning in the twentieth century, breast cancer was thought to arise in the breast and progress to other sides centrifugally. At that time more extensive procedures were performed to prevent disease spread to distant sites. Halsted radical mastectomy was the primary surgery with demonstrated improvements in survival. The procedure included removal of breast tissue with the overlying skin, underlying pectoral muscle and regional lymph nodes along the axillary vein. Halsted radical mastectomy remained the mainstay of breast surgical therapy until the 1970s. The modern era brought the hypothesis of both centrifugal spread to adjacent structures and lymphatic and blood vessel spread to distant sites, as many patients continued to suffer disease despite such large resections.

Breast cancer treatment now includes local and regional approaches together with medical therapies designed to treat systemic disease. The combination of multimodality treatment options has brought improvements in survival rates.

## Planning Surgery

Before surgical treatment, the initial stage is to diagnose the disease. The primary choice for diagnosis is core biopsy. Excisional biopsy should be reserved for lesions

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that are not amenable to core biopsy. Fine needle aspiration (FNA) is one choice but has high false-negative rates. In addition, FNA cannot distinguish invasive from in situ lesions with high reliability. The biopsy should provide information about the tumor type, histological grade, lymphovascular invasion and hormone receptor status (ER, PR, HER2). The history of the patient should be taken, and a proper physical examination should be performed. Adequate and appropriate imaging studies are necessary to establish the extent of disease and to assign clinical stage. Patients with abnormal blood tests or chest radiographs and patients with locally advanced or inflammatory breast cancer should undergo further investigation for distant metastases.

The choice of treatment strategy is based on the tumor features (location and size of tumor, number of lesions, extent of lymph node involvement) and biology (pathology including biomarkers and gene expression) and on the age, general health status, and personal preferences of the patient. Patients should be actively involved in all management decisions. The possibility of hereditary cancer should be explored, and if needed, prophylactic procedures should be discussed following appropriate genetic counseling and testing of the patient. In younger premenopausal patients, possible fertility issues should be discussed, and guidance on fertility-preservation techniques should be provided before initiation of treatment [1–11].

The primary aim of breast cancer surgery is to eradicate the tumor and any local disease to achieve local control. Well-defined procedures in breast surgery include the following (Figs. 13.1 and 13.2):

Mastectomy
Breast-conserving surgery (followed by radiotherapy)
Contralateral mastectomy
Axillary staging
Surgical approach after systemic therapy
Breast reconstruction

## Mastectomy

Mastectomy is required for tumors that are large compared to breast size, concomitant with large microcalcifications on mammography, or large with a lack of clear margins and for patients with contraindications for radiotherapy. Patient preference for mastectomy and a desire not to receive radiotherapy are also acceptable indications for mastectomy. Contraindications for radiotherapy are previous breast or chest wall irradiation, active lupus or scleroderma at the skin and pregnancy.

Simple and modified radical mastectomy both include removal of the gland together with the nipple and areola. Complete axillary lymph node dissection is part of modified radical mastectomy. An elliptical incision is planned for proper closure of future skin flaps and to contain the nipple areola complex and previous biopsy scars. Skin flaps are prepared, and glandular tissue is relieved. Breast tissue is separated from the underlying pectoral muscle with the pectoral fascia left on the breast specimen. In case of modified radical mastectomy, dissection is continued towards the axilla, and the specimen involves level I and II axillary lymph nodes. Level I

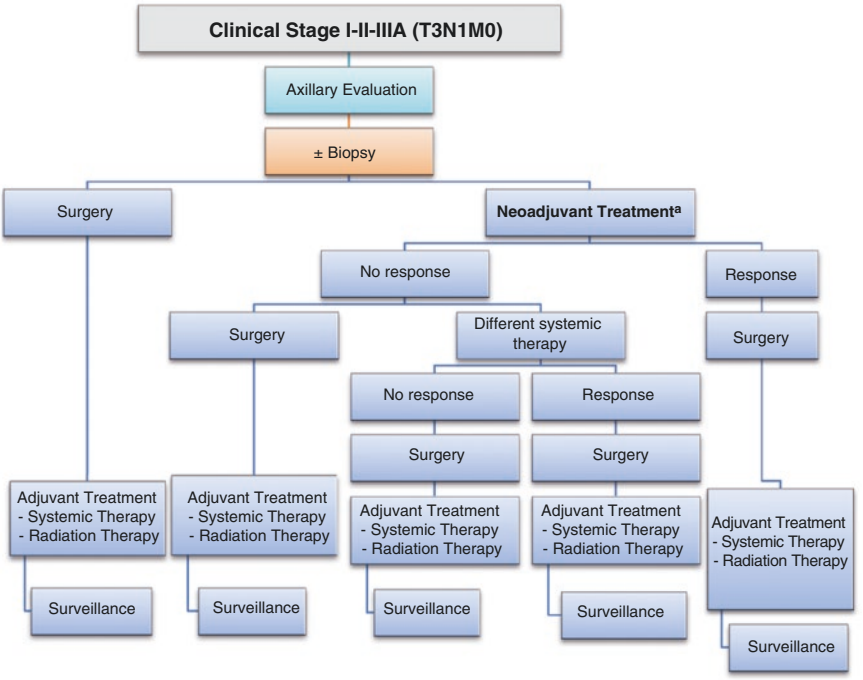


**Fig. 13.1** Management of patients for stage I–II–IIIA (T3N1M0) breast cancer. [a]Neoadjuvant chemotherapy should be administered to T2 and T3 tumors (N0–N1) meeting BCS criteria except tumor diameter, or to triple negative and HER-2-positive patients

lymph nodes are inferior to the pectoralis minor muscle, whereas level II lymph nodes are posterior to the muscle.

If immediate reconstruction is planned, skin-sparing mastectomy may be performed. This procedure leaves the maximum skin possible by removing only the nipple areola complex with the breast tissue. If immediate reconstruction is not planned, sufficient skin is left for closure of the flaps. When performing prophylactic mastectomy, the nipple areola complex may be spared.

## Breast-Conserving Surgery

Breast-conserving surgery (BCS) removes the tumor with clear margins, defined as no ink on tumor. More extensive procedures, such as quadrantectomy, that remove the tumor with wider margins have not been shown to improve survival. The removed specimen is oriented, and margins are inked prior to sectioning. Specimen mammogram is recommended if the tumor is not palpable or marked with a guide wire or if there is coexistence of microcalcifications. If margins are positive in perioperative pathological evaluation, re-excision should be performed to obtain clear margins. Wider excisions will lead to worse cosmetic outcomes. The defect is closed

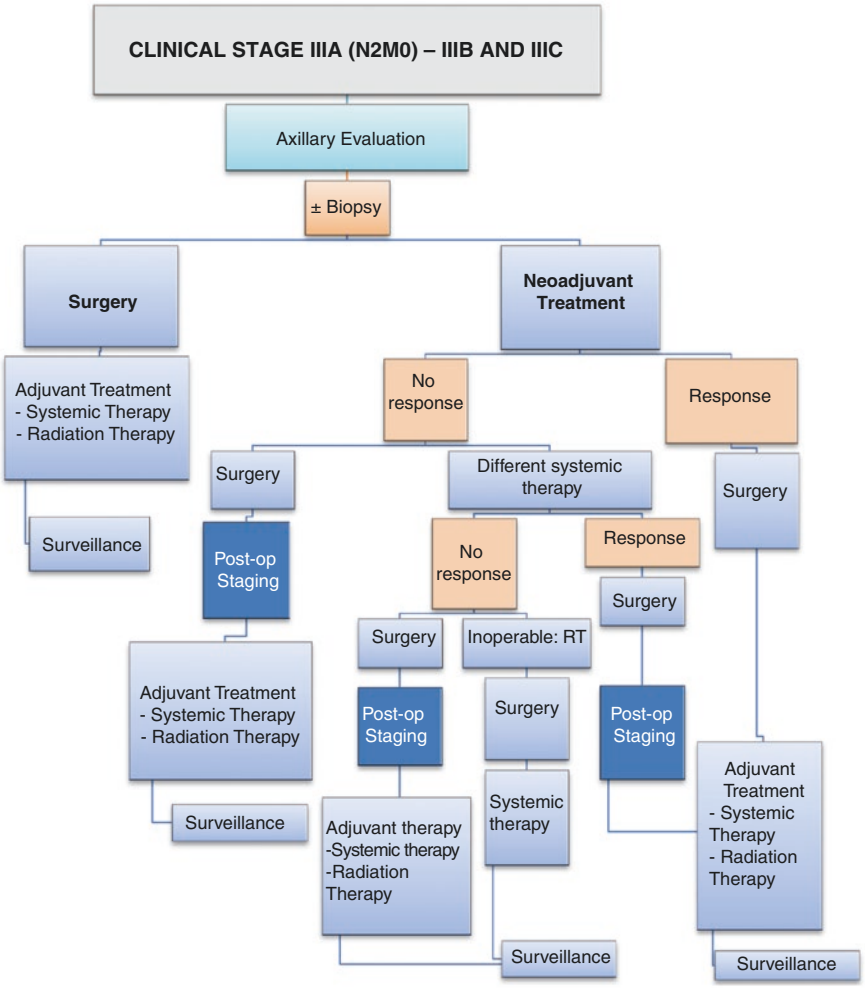


**Fig. 13.2** Locoregional and adjuvant systemic treatment for clinical stage IIIA (N2M0)—IIIB and IIIC disease (non-inflammatory)

in a cosmetic fashion. There is an increasing trend of combining plastic surgery techniques with breast cancer surgery to maximize cosmetic results. This so-called "oncoplastic surgery" has been popularized to achieve the best aesthetic results with adequate oncologic margins. The primary aim is to preserve breast appearance and symmetry as much as possible. Several deformities may occur after BCS depending on the location of the tumor and the amount of excised tissue. The final aesthetic outcome may worsen with administration of radiotherapy, which may increase the deformity and make it more challenging to correct.

Axillary staging is usually performed through a separate incision. Sentinel lymph node biopsy is replacing axillary lymph node dissection in clinically node-negative patients. Axillary dissection is similar for those requiring modified radical mastectomy.

Breast-conserving therapy, axillary lymph node dissection, and whole-breast irradiation are equivalent to mastectomy with axillary lymph node dissection as the primary treatment for most women with stage I and stage II breast cancers *(Proposal 1)* [12–15]. Both procedures result in similar overall survival and disease-free survival.

Breast-conserving surgery is contraindicated for patients who are pregnant and would require radiotherapy during pregnancy; have diffuse disease that cannot be removed locally via a single incision with an acceptable cosmetic result; have widespread suspicious or malignant-appearing microcalcifications on mammography; or have positive pathologic margins after surgery. Patients with pathologically positive margins should generally undergo re-excision to achieve negative pathologic margins. If the margins remain positive after re-excision, mastectomy should be performed for optimal local control of the disease.

Relative contraindications to BCS include previous radiation therapy to the breast or chest wall; active connective tissue disease such as scleroderma and lupus involving the skin; tumors greater than 5 cm, and focally positive pathologic margins. Those patients with focally positive pathologic margins who do not undergo re-excision should be considered for a higher radiation boost dose to the tumor bed. To adequately assess margins following lumpectomy, surgical specimens should be oriented, and the pathologist should provide descriptions of the gross and microscopic margin status and the distance, orientation, and type of tumor in relation to the closest margin. Careful histological assessment of resection margins is essential, with no tumor at the inked margin required. Marking the tumor bed with clips facilitates accurate planning of the radiation boost field where appropriate. Acceptably low local recurrence rates remain the major quality assurance target. Current guidelines recommend local recurrence rates after wide excision and radiotherapy of <1% per year (with a target of <0.5%) and not exceeding 10% overall.

Women undergoing BCS plus radiotherapy have been shown to have better body self-image than those undergone mastectomy, but postoperative psychological well-being has not been shown to differ between these groups [16].

## *Recommendations*

All patients with stage I or II breast cancer should be offered BCS or mastectomy *(Proposal 1).*

The surgery type should be tailored to the individual patient, who should be informed of all options and made aware that radiotherapy is required following BCS and that further surgery is necessary in case of positive margins *(Proposal 1).*

The patient should be aware of the advantages and harms of radiotherapy following BCS *(Proposal 1).*

Mastectomy should be preferred to BCS in case of the following *(Proposal 1)*:

Inappropriate tumor-breast size ratio or tumor location interfering with cosmetic outcome after BCS;

Multifocal-multicentric disease that cannot be properly manipulated with acceptable cosmetic results after BCS;
Contraindication to radiotherapy

Due to adverse cosmetic outcomes, quadrantectomy is not recommended as BCS.

BCS should maintain total excision of the tumor with clear margins with acceptable cosmetic outcome following both surgery and radiotherapy**.**

A detailed pathological assessment should be made.

No ink on tumor should be assessed as clear margins.

Patients with positive margins should be considered for re-excision.

Categories indicate the strength of the supporting evidence rather than the importance of the recommendations.

## Contralateral Mastectomy

Hereditary breast cancer is thought to represent only 5% of all breast cancer cases. Hereditary breast cancer is mainly caused by mutations in the BRCA1 and BRCA2 genes, which are located on chromosomes 17 and 13, respectively. Mutations in these genes predispose carriers to breast and ovarian cancer as well as melanoma and prostate, bile duct and pancreatic cancers. They are inherited in an autosomal dominant pattern and considered tumor suppressor genes. Rarer cases arise due to Li Fraumeni Syndrome (p53 mutation), Peutz-Jeghers Syndrome (STK11/LKB1 gene), Cowden Syndrome (PTEN gene), Hereditary Diffuse Gastric Cancer (HDGC; CDJ-1 gene) and Ataxia Telangiectasia (ATM gene) and consist of less than 1% of all breast cancer cases.

Both BRCA genes are very large, and more than one hundred different mutations have been reported, including for which clinical significance has not been established. Patients with these clinically unidentified significant mutations may or may not be at risk for cancer. In addition, not all mutations in certain sequences of BRCA1 and 2 are identified by screening methods. Technically, negative screening results do not exclude the possibility of the presence of a mutation. Consequently, several estimation models have been developed to aid clinicians in genetic counseling.

The complexity of genetic testing necessitates clinical guidance from a special health practitioner trained in and familiar with the field. A mutation is most likely to be identified in a family that includes patients who have already been diagnosed with breast or ovarian cancer. The screening method should be performed based on the patient with the youngest age of onset and who is less likely to have developed sporadic cancer. If a mutation is identified, the remaining relatives and offspring can be screened with high accuracy. Relatives found not to carry the mutation bear the same risk as the general population, whereas unaffected relatives with the mutation have a greater risk than the general population and require surveillance and prophylactic measures.

Prophylactic strategies consist of prophylactic mastectomy, salpingo-oophorectomy and chemoprevention.

Only limited data are available on the survival impact of contralateral mastectomy in unilateral breast cancer [17]. Women with breast cancer who are ≤35 years or premenopausal and carriers of a known BRCA1/2 mutation may be recommended additional risk-reduction strategies following appropriate risk assessment and counseling. The lifetime risk of breast cancer in a BRCA1 carrier is 80–85%, with a 10-year actuarial risk of contralateral breast cancer ranging from 25% to 31%. With bilateral mastectomy, the risks for both subsequent breast cancer incidence and mortality are reduced by 90–95%. The decision should be made with a multidisciplinary team before the surgery and should include a discussion of the risks associated with development of a contralateral breast cancer compared with the risks of recurrent disease from the primary cancer. Except as specifically outlined in some situations, prophylactic mastectomy of a breast contralateral to a known unilateral breast cancer treated with mastectomy is discouraged. The use of prophylactic mastectomy contralateral to a breast treated with breast-conserving surgery is very strongly discouraged in all patients.

Despite the overall trend toward breast conservation, increasing numbers of breast cancer patients are opting for bilateral mastectomy (incorporating contralateral risk-reducing surgery) in preference to breast conservation and mammographic surveillance of the irradiated breast. These patients should be counseled properly and should be informed of the finding that patients with early-stage breast cancer might have even better outcomes after breast-conserving therapy compared with after mastectomy.

### *Recommendations*

Patients from high-risk families (multiple affected family members, male breast cancer, bilateral breast cancer, concomitant ovarian cancer, Ashkenazi Jewish, early onset of breast cancer) should be referred to genetic counseling.

Genetic counselling should be undertaken by physicians with specific training.

Patients with a family history of breast cancer or known BRCA1 or 2 gene mutations should be offered optional prophylactic mastectomy.

Prophylactic salpingo-oophorectomy should also be offered.

## Axillary Staging

Axillary surgery is required for adequate staging and proper treatment of breast cancer. The primary aim is to eradicate local disease. Axillary surgery minimizes local recurrence and influences survival and prognosis by guiding adjuvant therapy. Axillary lymph node dissection (ALND) was a routine surgical procedure for breast cancer treatment. ALND provides useful information for staging of disease while eradicating local disease. The procedure involves removal of lymph nodes in the axillary fossa posterior to the pectoral minor muscle up to the axillary vein. The

level of axillary lymph node dissection is defined as I, II or III according to the location of the lymph node basins removed relative to the pectoralis minor muscle. Unfortunately, ALND is associated with serious morbidities, such as placement of axillary drainage, longer hospitalization, recovery, postoperative pain and limitations in arm and shoulder movement due to lymphedema.

Sentinel lymph node biopsy (SLNB) was developed to reduce these morbidities associated with ALND while providing similar information on axillary status. The sentinel lymph node is defined as the first lymph node to which tumor cells are likely to spread from the primary breast tumor. Patients with positive SLNB may benefit from ALND, and negative patients that will avoid the morbidities of ALND. The sentinel lymph node is localized via lymph node mapping. Mapping may be performed with blue dye (methylene blue or isosulfan blue) or technetium-labeled sulfur colloid either alone or in combination. Several studies have demonstrated that the combination technique may result in lower false-negative rates. The mapping agents may be injected in the subdermal, periareolar or peritumoral region. The mapping agent(s) passes through the lymphatics and accumulates at the draining node. Then, the sentinel lymph node(s) are harvested if they are identified and then pathologically evaluated.

Preoperative lymphoscintigraphy may provide information on draining basins and sentinel lymph node number. The procedure may be performed the day prior to surgery or on the day of surgery. Peritumoral injection may provide an image of drainage to the axillary, internal mammillary, or both nodal basins. If subareolar or subdermal injection is used, only axillary drainage is revealed. A lack of lymph node detection on lymphoscintigraphy prior to operation does not preclude success of intraoperative detection. Preoperatively, blue dye is injected prior to incision in a volume of 3–5 ml, and massage is performed to facilitate drainage. A handheld gamma probe is used to detect radioactivity transcutaneously and guide incision. After the incision is made, the increased radioactivity and blue lymphatic channel guide the surgeon to the sentinel lymph node(s). After harvesting the node, the region is checked to confirm that the radioactivity has decreased. If not, the search continues to other sentinel lymph node(s).

Trained physicians have been reported to identify sentinel lymph nodes in 95% of cases with a less than 10% false-negative rate. Patients with clinically positive lymph nodes should be evaluated with ultrasound and FNA biopsy prior to surgery. In case of confirmed axillary metastasis, patients may be directed to ALND or considered for neoadjuvant chemotherapy. If no axillary metastasis is demonstrated, patients can proceed to SLNB.

Sentinel lymph node (SLN) mapping and surgical excision of clinically lymph node negative axilla are recommended to evaluate the pathologic status of the axillary lymph nodes in patients with stage I or stage II breast cancer [18–24]. This recommendation is supported by the results of randomized clinical trials showing decreased arm and shoulder morbidity such as pain, lymphedema and sensory loss in patients with breast cancer undergoing SLNB compared with patients undergoing standard ALND [24, 25]. An experienced SLN team is mandatory for the use of SLN mapping and excision [26, 27]. With appropriate training in the dual

radiocolloid/blue dye or indocyanine green fluorescence technique, acceptably low false-negative rates and favorable axillary recurrence rates following SLNB are achievable. Women who have invasive breast cancer and do not have access to an experienced SLN team should be referred to an experienced SLN team for definitive surgical treatment of the breast and surgical axillary lymph node staging. Candidates for SLN mapping should have clinically negative axillary lymph nodes or a negative fine-needle aspiration (FNA) biopsy of any clinically suspicious axillary lymph nodes. There is no consensus for the pathologic assessment of SLNB. The significance of occult micrometastases in terms of surgical management and patient outcome appears to be negligible. Thus, routine IHC or PCR is not recommended for the evaluation of sentinel lymph nodes, and treatment decisions should be made based on H&E staining [28].

Multiple attempts have been made to identify cohorts of women with involved SLNs who have a sufficiently low risk of non-SLN involvement that complete axillary dissection might be avoided if the SLN is positive. None of the early studies identified a low-risk group of patients with positive SLN biopsies but consistently negative non-sentinel nodes [29–34]. Nonetheless, a randomized trial (ACOSOG Z0011) compared SLN resection alone with ALN dissection in women ≥18 years of age with T1/T2 tumors, fewer than 3 positive SLNs, and undergoing breast-conserving surgery and whole-breast irradiation. In this study, there was no difference in local recurrence, DFS, or OS between the two treatment groups. Only ER-negative status, age <50, and lack of adjuvant systemic therapy were associated with decreased OS. At a median follow-up of 9.3 years, 10-year locoregional recurrence did not differ significantly between the 2 groups. The 10-year OS was 86.3% in the SLND alone group and 83.6% in the ALND group ($p = 0.02$) [35]. In addition to this study, based on the results of the IBCSG 23–01 trial, further axillary treatment does not seem to be required when a sentinel node has micrometastasis (0.2–2 mm) [36]. Therefore, according to these results, patients with T1 or T2 tumors with 1–2 positive SLNs and undergoing BCS plus tangential breast irradiation may not require further axillary procedures. However, these results need to be confirmed and cannot be extended to patients with characteristics other than those of the trial's patient population.

Level I or II axillary dissection should be recommended when (1) patients have clinically positive nodes at the time of diagnosis that are confirmed by FNA or core biopsy or (2) sentinel nodes are not identified. Traditional level I and level II evaluation of axillary lymph nodes requires that at least 10 lymph nodes be removed for pathologic evaluation to accurately stage the axilla [37, 38]. Level III ALND should be performed only if gross disease is apparent in the level II nodes. Level I–II lymph node dissection should include tissue inferior to the axillary vein from the latissimus dorsi muscle laterally to the medial border of the pectoralis minor muscle.

Furthermore, without definitive data demonstrating superior survival with ALND or SLNB, these procedures may be considered optional in patients who have particularly favorable tumors, patients for whom the selection of adjuvant systemic therapy will not be affected by the results of the procedure, elderly patients, and patients with serious comorbid conditions. Patients with SLN metastasis and no

ALND or axillary lymph node irradiation are at increased risk for ipsilateral lymph node recurrence [39].

There are some unanswered questions regarding sentinel lymph node biopsy in early breast cancer:

accuracy in neoadjuvant chemotherapy;
accuracy in recurrent breast cancer;
the appropriate approach for non-axillary positive lymph nodes;
the optimal pathological method for evaluating sentinel nodes;
the role of intraoperative assessment and the proper method.

### *Recommendations*

All patients with stage I or II breast cancer should be assessed for axillary lymph node status.

Axillary lymph node dissection should be offered for all patients with clinically positive lymph nodes, multifocal disease or non-successful SLNB.

Sentinel lymph node biopsy should be offered instead of ALND for all patients with clinically negative lymph nodes and stage I or II unifocal disease.

All patients should be informed of complications of ALND *(Proposal 1).*

ALND should be performed in all women with more than 3 proven metastatic axillary lymph nodes.

Patients should be informed of probable unsuccessful SLNB or false-negative results and procedure consequences.

The SLNB procedure should be performed by appropriately trained and experienced physicians.

If available, preoperative lymphoscintigraphy combined with the intraoperative double technique (blue dye and radioisotope labeled tracers) should be performed.

If the double technique is not available, a single method is appropriate.

Sentinel lymph node evaluation should be definitive for proper tailoring.

Definitive histopathological analysis of SLNB should be performed to reduce the false-negative rate.

If the initial assessment of SLNB is negative, each 2-mm slice should be cut into 4 sections of 0.5-mm thickness, with 3 sections randomly evaluated with hematoxylin and eosin and one with cytokeratin immunohistochemistry.

Patients with positive non-axillary lymph nodes (internal mammillary, supra/infra clavicular) should be considered for appropriate radiotherapy.

## Surgical Approach After Systemic Therapy

Neoadjuvant chemotherapy is recommended for patients with T4 tumors, axillary lymph node-positive T1–T3 tumors and axillary lymph node-negative T2–T3 tumors with triple-negative or HER2-positive tumors. In other cases, axillary lymph

node positivity alone is not sufficient to make a decision regarding neoadjuvant treatment. In Luminal B tumors, chemotherapy can be considered a priority. Neoadjuvant hormone therapy alone may be considered to avoid mastectomy in node-negative select patients (i.e., patients with strong hormone receptor positivity, advanced age, or poor performance status) (Figs. 13.2 and 13.3). Patients with inoperable locally advanced breast cancer have large, fixed or erosive lesions that are not

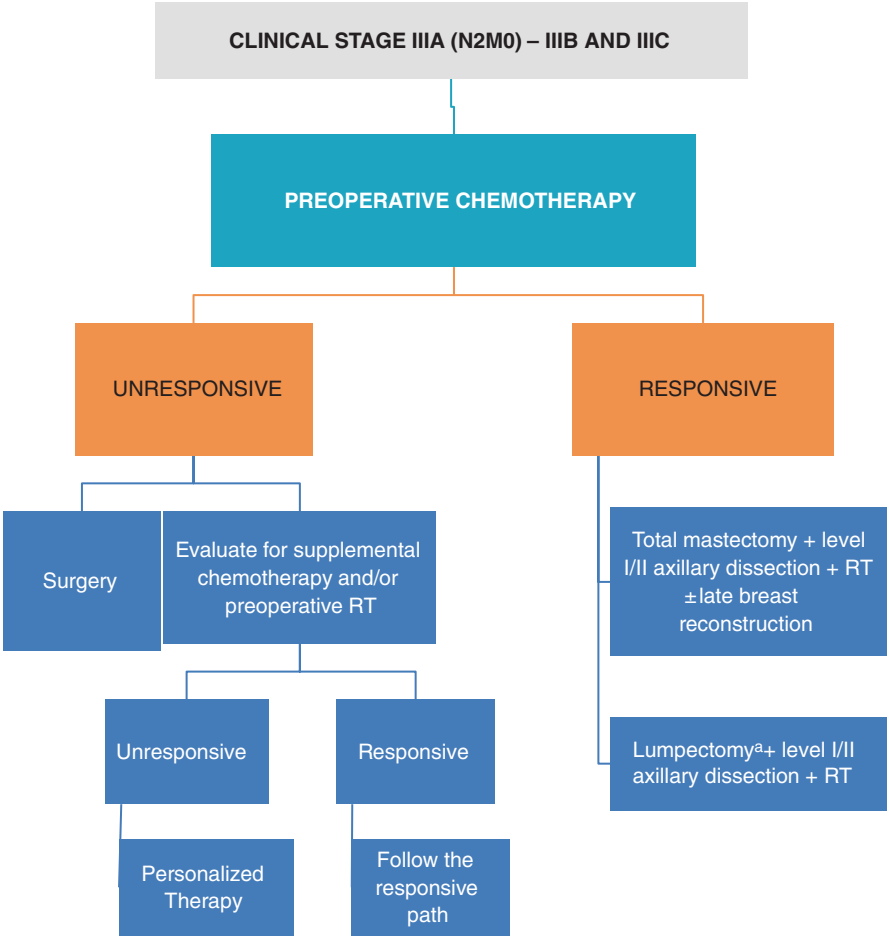


**Fig. 13.3** Surgical approach after neoadjuvant systemic treatment for patients with clinical stage IIIA (N2M0)—IIIB and IIIC breast cancer. [a]After downstaging with systemic treatment, resection of the entire area of the original primary tumor is not necessary (if there is shrinkage in the tumor). MR imaging is recommended in patients who will undergo BCS after neoadjuvant therapy. Clinical examination and radiological imaging modalities (USG, MMG, MR imaging) are used to evaluate the tissue to be excised (shrinking or patching). However, if the tumor response is patchy, the original tumor area should be removed with clean surgical margins. If diffuse live tumor cells are observed in the excised lumpectomy specimen after neoadjuvant chemotherapy, re-excision should be performed, even if there is no surgical margin involvement

amenable to mastectomy; advanced nodal disease with arm edema due to fixed lymph nodes at the axilla; and inflammatory breast cancer. Systemic chemotherapy or hormonal therapy can result in breast tumor size reduction in nearly 80% of patients with locally advanced breast cancer. Systemic therapy can convert inoperable tumors to operable ones and convert the need for a surgical procedure from mastectomy to breast-conserving surgery, which will enable favorable cosmesis. Clinical trials are reporting better aesthetic results in early-stage breast cancer patients. This approach also permits the study of tumor biology before surgery and the evaluation of the tumor response to chemotherapy regimens. At the end of systemic therapy, many patients may achieve complete pathological response in both clinical examination and imaging studies. Consequently, the primary tumor site should be marked with a metallic clip prior to the initiation of chemotherapy to indicate the original tumor site.

Preoperative systemic chemotherapy trials have gathered some informative definitions and knowledge of breast cancer in recent years. This knowledge has revealed tumor and patient characteristics that can predict the response to therapy. Consequently, patients can be better defined and selected for appropriate drug regimens, and patients are obtaining greater benefit from the chemotherapy. Targeted therapies, such as the treatment of HER2-positive breast cancer patients with trastuzumab and pertuzumab in combination with chemotherapy, have led to increased rates of pathologic complete response.

Primary systemic chemotherapy (preoperative chemotherapy) should be considered for women with large clinical stage IIA, stage IIB, and T3N1 tumors who meet the criteria for breast-conserving therapy except for tumor size and who wish to undergo breast-conserving therapy (Figs. 13.1 and 13.4). In patients anticipated to

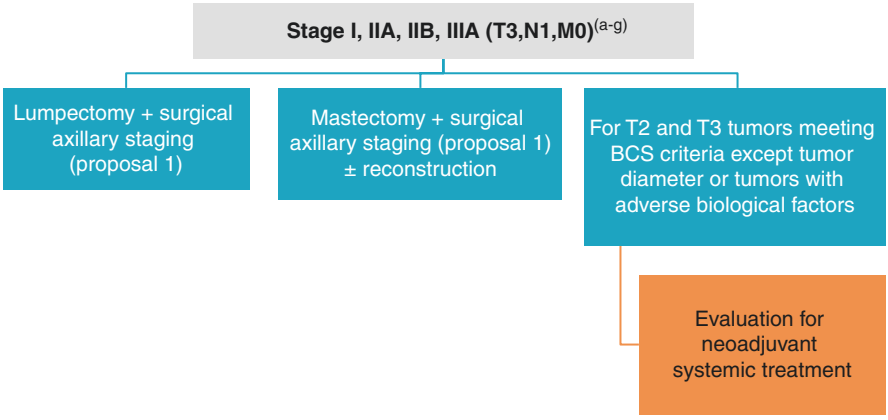


**Fig. 13.4** Surgical treatment of patients with clinical stage I, II or IIIA (T3N1M0) disease[a–g]. [a]Absolute contraindications to breast-conserving surgery (BCS) include diffuse suspicious microcalcifications, widespread disease, and persistent positive pathological margins. Relative contraindications include tumor size >5 cm, prior radiation therapy, active connective tissue disease, focally positive margins, and a known or suspected genetic predisposition to breast cancer. Nipple-conserving surgery can be performed in patients with hereditary BRCA1/2 mutations if the

retroareolar tissue is determined to be clean by a pathologist. [b]In women undergoing BCS for invasive BC and proceeding to standard RT and adjuvant systemic therapy, the minimum acceptable surgical margin is "no ink on invasive tumor". Tumor biology or patient age (<40) does not change the minimum acceptable surgical margins. [c]For BCS: If adjuvant whole-breast RT and systemic treatment will be given to the patient with macrometastasis in 1–2 sentinel lymph nodes, complete axillary dissection may not be performed regardless of tumor biology. [d]For mastectomy: Complete axillary dissection should be performed in patients with macrometastases in 1–2 sentinel lymph nodes if adjuvant RT is not planned. However, there is no complete consensus regarding the omission of axillary dissection in patients for whom RT has been planned. [e]Positive margins (ink on invasive carcinoma or ductal carcinoma in situ) were associated with a twofold increase in the risk of ipsilateral breast tumor recurrence (IBTR) compared with negative margins. This increased risk was not mitigated by favorable biology, endocrine therapy, or a radiation boost. More widely clear margins than no ink on tumor do not significantly decrease the rate of IBTR compared with "no ink on tumor". No evidence indicates that more widely clear margins reduce IBTR in young patients or in those with unfavorable biology, lobular cancers, or cancers with an extensive intraductal component. The use of "no ink on tumor" is the standard for adequate margins in invasive cancer but not in DCIS. During the operation, it is best to perform the incision macroscopically 1 cm around the tumor. Postoperative MR imaging is appropriate for patients with tumors in close proximity to the surgical margin. In cases undergoing BCS, a surgical margin of 2 mm or greater is considered safe only in those with DCIS. If the invasive tumor is <1 mm in DCIS, the surgical border safety is evaluated according to DCIS. If the invasive focus is >1 mm in DCIS, the surgical margin width should be evaluated according to the invasive cancer. An adequate surgical margin should be decided by clinical, radiological and pathological evaluation. A "sufficient surgical margin" should be decided according to findings such as radiological additional foci (multifocal disease, microcalcification), invasive lobular carcinoma, multiple surgical margin involvement and persistent proximity of surgical margins in re-excision. [f]Neoadjuvant chemotherapy is recommended for patients with axillary lymph node-positive T1–T3 tumors and axillary lymph node-negative T2–T3 tumors with triple-negative or HER2-positive tumors. In other cases, axillary lymph node positivity alone is not sufficient to make a decision regarding neoadjuvant treatment. In Luminal B tumors, chemotherapy can be considered a priority. Neoadjuvant hormone therapy alone may be considered to avoid mastectomy in node-negative select patients (i.e., patients with strong hormone receptor positivity, advanced age, or poor performance status). Neoadjuvant hormonotherapy should last for 6–8 months, as long as the patient responds. The addition of hormonal agents to neoadjuvant chemotherapy can be made with a low level of evidence. Importantly, the guidelines emphasize that addition of endocrine therapy is not based on direct evidence. Additionally, they provide no reason why endocrine therapy should be delayed until completion of cytotoxic treatment. Tamoxifen as endocrine therapy should not be given with chemotherapy. When neoadjuvant chemotherapy is given, the use of chemotherapy in high-risk patients with very strong hormone-receptor positivity, aromatase inhibitors in the postmenopausal stage, and medical oophorectomy in the premenopausal stage [± aromatase inhibitor, especially in HER2-positive patients] may be considered (proposal 3). [g]In a patient who is clinically node positive (N1) at presentation and is downstaged after chemotherapy, sentinel lymph node (SLN) biopsy is appropriate. Marking of positive axillary nodes with a clip in the beginning of the chemotherapy should be considered to permit verification that the biopsy-positive lymph node has been removed at the time of definitive surgery. Among in these subgroup of patients, SLNB has a >10% false-negative rate when performed after preoperative systemic therapy. This false negative rate can be improved by marking biopsied lymph nodes to document their removal, using dual tracer, and by removing more than 2 sentinel nodes. If SLN is positive, axillary lymph node dissection must be performed. After downstaging, resection of the entire area of the original primary tumor is not necessary (if there is shrinkage in the tumor). MR imaging is recommended in patients who will undergo BCS after neoadjuvant therapy. Clinical examination and radiological imaging modalities (USG, MMG, MR imaging) are used to evaluate the tissue to be excised (shrinking or patching). However, if the tumor response is patchy, the original tumor area should be removed with clean surgical margins. If diffuse live tumor cells are observed in the excised lumpectomy specimen after neoadjuvant chemotherapy, re-excision should be performed, even if there is no surgical margin involvement

receive preoperative systemic therapy, core biopsy of the breast tumor and placement of image-detectable marker should be considered to demarcate the tumor bed for any future post-chemotherapy surgical management. Clinically positive ALN should be sampled by FNA or core biopsy, and positive nodes can be removed following preoperative systemic therapy at the time of definitive operation. Patients with clinically negative ALNs should undergo axillary ultrasound prior to neoadjuvant treatment. For those with clinically suspicious ALNs, core biopsy or FNA of these nodes is indicated [40].

Sentinel node biopsy or level I/II dissection can be performed as axillary staging after preoperative systemic therapy. Level I/II dissection should be performed when patients are proven node positive prior to neoadjuvant therapy. The false-negative rate of SLNB in either the pre- or post-chemotherapy settings is low [41–44]. Nevertheless, a pathologic complete response (pCR) following chemotherapy is possible in lymph node metastases previously undetected by clinical exam. An SLN excision can be considered before administering preoperative systemic therapy because it provides additional information to guide local and systemic treatment decisions. Close communication between members of the multidisciplinary team, including the pathologist, is particularly important when any treatment strategy involving preoperative systemic therapy is planned.

Because complete or near-complete clinical responses are common, the use of percutaneously placed clips in the breast under mammographic or ultrasound guidance aids post-chemotherapy resection of the original area of the tumor and is encouraged. Breast conservation rates are higher after preoperative systemic therapy [45].

Local therapy following a complete or partial response to preoperative systemic therapy is usually breast-conserving surgery if possible along with surgical axillary staging. If breast-conserving surgery is not possible or progressive disease is confirmed, mastectomy is performed along with surgical axillary staging with or without breast reconstruction. Surgical axillary staging may include SLN biopsy or level I/II dissection. If SLN biopsy was performed before administering preoperative systemic therapy and the findings were negative, then further ALN staging is not necessary. If an SLN procedure was performed before administering preoperative systemic therapy and the findings were positive, then a level I/II ALN dissection should be performed.

Patients with stage III disease may be further divided into (1) those in whom an initial surgical approach is unlikely to successfully remove all disease or to provide long-term local control; and (2) those in whom a reasonable initial surgical approach is likely to achieve pathologically negative margins and provide long-term local control. Thus, stage IIIA patients are divided into those with clinical T3N1 disease and those who have clinical T anyN2M0 disease based on evaluation by a multidisciplinary team.

In patients with inoperable, locally advanced non-inflammatory disease, anthracycline-based preoperative systemic therapy is standard therapy. Local therapy following a clinical response to preoperative systemic therapy usually consists of mastectomy or breast-conserving surgery with level I/II ALN dissection [45–47]. Delayed breast reconstruction can be considered in mastectomy patients.

Patients with a clinical/pathologic diagnosis of inflammatory breast cancer (IBC) should always be treated with preoperative chemotherapy [48, 49]. Primary surgery

and SLN dissection is not a reliable approach in patients with IBC [50]. Breast-conserving surgery is not recommended in IBC patients due to poor cosmesis and higher local recurrence rates compared with mastectomy.

The use of breast-conserving surgery in patients with IBC has been associated with poor cosmesis, and limited data suggest that rates of local recurrence may be higher compared with mastectomy. Breast-conserving therapy is not recommended for patients with IBC.

Mastectomy with level I/II ALN dissection is the recommended surgical procedure for patients who respond to neoadjuvant chemotherapy. Delayed breast reconstruction is an option for patients with IBC who have undergone a modified radical mastectomy. Early/immediate reconstruction after mastectomy may compromise post-mastectomy radiotherapy outcomes [51].

For patients with IBC who do not respond to preoperative systemic therapy, mastectomy is not generally recommended. Additional systemic chemotherapy and/or preoperative radiation should be considered for these patients, and patients responding to this secondary therapy should undergo mastectomy and subsequent treatment as described above.

## Breast Reconstruction

Breast reconstruction may be an option for any woman receiving surgical treatment for breast cancer. Therefore, all women undergoing breast cancer treatment should be educated about breast reconstructive options adapted to their individual clinical situation. However, breast reconstruction should not interfere with the appropriate surgical management of the cancer.

Breast reconstruction consists of several surgical techniques utilizing either prosthesis or tissue from elsewhere in the body to rebuild breast shape. The use of implants, pedicled flaps or free flaps are the most commonly applied procedures. Breast reconstruction can be immediate at the time of primary surgery or delayed to allow time to recover from the primary surgery and subsequent adjuvant treatments.

The decision regarding the type of reconstruction involves patient preference, body habitus, smoking history, comorbidities, plans for irradiation, and expertise and experience of the reconstruction team. Reconstruction is an optional procedure that does not impact the probability of recurrence or death but is associated with an improved quality of life for many patients. It is sometimes necessary to perform surgery on the contralateral breast (e.g., breast reduction, implantation) to achieve optimal symmetry between the ipsilateral reconstructed breast and the contralateral breast.

The loss of the breast for cosmetic, body image, and psychosocial issues may be partially overcome through the performance of breast reconstruction. Reconstruction can be performed either immediately following mastectomy and under the same anesthetic or in a delayed fashion following mastectomy. Breast reconstruction usually involves a staged approach requiring more than one procedure.

Many factors must be considered in decision making about breast reconstruction following mastectomy. Several different types of breast reconstruction, such as autogenous tissues, implants, or both, can be performed following mastectomy [52–54]. Reconstruction with implants can be performed either by immediate placement of a permanent subpectoral implant or initial placement of a subpectoral expander followed by replacement of the expander with a permanent implant. At 1 year after mastectomy, patients who underwent autologous reconstruction were more satisfied with their breasts and had greater psychosocial and sexual well-being than those who underwent implant reconstruction. Although satisfaction with breasts was equal to or greater than baseline levels, physical well-being was not fully restored [54]. Autogenous tissue methods of reconstruction use various combinations of donor sites (e.g., abdomen, buttock) that may be brought to the chest wall with their original blood supply or as free flaps with microvascular anastomoses to supply blood from the chest wall/thorax. Several procedures using autologous tissue are available, including transverse rectus abdominis myocutaneous flap, latissimus dorsi flap, and gluteus maximus myocutaneous flap reconstruction. Composite reconstruction techniques use implants in combination with autogenous tissue reconstruction to provide volume and symmetry. Patients with underlying diabetes or who smoke tobacco have increased rates of complications following autogenous tissue breast cancer reconstruction, presumably because of underlying microvascular disease.

## *Skin-Sparing Mastectomy*

The possible advantages of skin-sparing mastectomy include improvements in breast cosmesis, body image, and nipple sensation following mastectomy, although the impact of this procedure on these quality-of-life issues has not been well studied [55–57]. There are limited data from surgical series with short follow-up suggesting that nipple-areolar complex (NAC)-sparing mastectomy in selected patients is associated with low rates of occult involvement of the NAC with breast cancer and local disease recurrence. NAC-sparing procedures may be an option in patients who are carefully selected by experienced multidisciplinary teams. Assessment of retroareolar margins is mandatory in patients considering an NAC-sparing procedure [56, 58, 59]. Retrospective studies validate the use of NAC-sparing procedures for patients with breast cancer with low rates of nipple involvement and low rates of local recurrence due to early-stage, biologically favorable tumors that are located >2 cm from the nipple [60, 61]. Contraindications for nipple preservation include findings of nipple involvement such as Paget's disease or bloody nipple discharge. Ongoing prospective trials to assess NAC-sparing mastectomy in the setting of malignancy will answer many questions, and participation in such trials is encouraged.

Although no randomized studies have been performed, the results of several retrospective studies have indicated that the risk of local recurrence is not increased among patients receiving skin-sparing mastectomies compared with those undergo-

ing non-skin–sparing procedures. However, strong selection biases almost certainly exist in the identification of patients appropriate for skin-sparing procedures [62–66]. Reconstruction of the NAC may also be performed in a delayed fashion if desired by the patient. Reconstructed nipples are devoid of sensation. Skin-sparing mastectomy should be performed by an experienced breast surgery team working in a coordinated, multidisciplinary fashion to guide proper patient selection for skin-sparing mastectomy, determine optimal sequencing of the reconstructive procedure in relation to adjuvant therapies, and perform a resection that achieves appropriate surgical margins. Post-mastectomy radiation should still be applied for patients treated by skin-sparing mastectomy following the same selection criteria as for standard mastectomy.

## *Post-Mastectomy Radiation and Breast Reconstruction*

The decision for post-mastectomy radiation therapy can affect reconstruction strategies because of the increased risk of complications, such as capsular contracture, following irradiation of the implant. Postmastectomy radiation therapy may also have a negative impact on breast cosmesis when autologous tissue is used in immediate breast reconstruction [67, 68]. Some studies, however, have not found a significant compromise in reconstruction cosmesis following irradiation [69]. While some experienced breast cancer teams have employed protocols in which immediate tissue reconstructions are followed by radiation therapy, it is generally preferred that radiation therapy precede the placement of autologous tissue because of reported loss of reconstruction cosmesis.

When implant reconstruction is planned in a patient requiring radiation therapy, a two-stage approach with immediate tissue expander placement followed by implant placement is recommended. Exchange of the tissue expanders with permanent implants can be performed prior to radiation or after completion of radiation therapy. The expansion of irradiated skin can result in an increased risk of malposition, capsular contracture, poor cosmesis, and implant exposure. The use of tissue expanders/implants is relatively contraindicated in patients who have been previously irradiated. Immediate placement of an implant in patients requiring postoperative radiation has an increased rate of complications such as capsular contracture, malposition, poor cosmesis, and implant exposure.

## *Recommendations*

Breast reconstruction options should be offered for all patients undergoing mastectomy.

Immediate and delayed reconstruction should be discussed prior to mastectomy due to the importance of self-confidence and body image perception.

## Breast Reconstruction Following BCS (Oncoplastic Approach)

The optimization of the cosmetic and oncologic outcomes of breast-conserving surgery has been addressed in recent years by the emergence of the field of oncoplastic surgery. The possible cosmetic outcome of lumpectomy should be evaluated prior to surgery. Oncoplastic techniques for breast conservation can extend breast-conserving surgical options in situations where the resection itself would likely yield an unacceptable cosmetic outcome [70]. The definition of oncoplastic surgery has been recently expanded to include a wide range of volume displacement or volume redistribution procedures performed by breast surgeons and general surgeons to optimize breast shape and breast volume following breast cancer surgery [71]. Oncoplastic volume displacement procedures combine the removal of generous regions of breast tissue with "mastopexy" techniques in which the remaining breast tissues are shifted together within the breast envelope to fill the resulting surgical defect, thus avoiding the creation of a significant breast deformity. Volume displacement techniques are generally performed during the same operative setting as the breast-conserving lumpectomy by the same surgeon who is performing the cancer resection [70–73].

The advantages of oncoplastic volume displacement techniques include the ability to remove larger regions of breast tissue, thus facilitating wider surgical margins around the cancer, while better preserving the natural shape and appearance of the breast compared to standard breast resections [73].

The limitations of oncoplastic volume displacement techniques include the lack of standardization among centers, performance at only a limited number of sites, and the possible need for subsequent mastectomy if pathologic margins are positive. Patients should be informed of the possibility of positive margins and the potential need for secondary surgery, which could include re-excision segmental resection or require mastectomy with or without loss of the nipple. Oncoplastic procedures can be combined with surgery on the contralateral unaffected breast to minimize long-term asymmetry.

Finally, it is important to note that the primary focus should be on treating the tumor and that such treatment should not be compromised when decisions regarding breast reconstruction are made. In the first international consensus conference on standardization of oncoplastic breast conserving surgery the panelists considered oncoplastic breast conserving surgery safe and effective for improving aesthetic outcomes and broadening the indication for breast conserving surgery towards larger tumors [74]. A slim majority believed that oncoplastic breast conserving surgery reduces the rate of positive margins; however, there was consensus that oncoplastic breast conserving surgery is associated with an increased risk of complications compared to conventional breast conserving surgery. The panel strongly endorsed patient-reported outcomes measurement, and recommended selected scales of the Breast-Q™-Breast Conserving Therapy Module for that purpose. The Clough bi-level classification was recommended for standard use in clinical practice for indicating, planning and performing oncoplastic breast conserving surgery, and the Hoffmann classification for surgical reports and billing

purposes. Mastopexy and reduction mammoplasty were the only two recognized oncoplastic breast conserving surgery procedure categories supported by a majority of the panel. Finally, the experts unanimously supported the statement that every oncoplastic breast conserving surgery procedure should be tailored to each individual patient [74].

## Surgery for Metastatic Breast Cancer

The primary treatment approach for women with metastatic breast cancer and an intact primary tumor is systemic therapy, with consideration of surgery after initial systemic treatment for those women requiring palliation of symptoms or with impending complications, such as skin ulceration, bleeding, fungation, and pain [75]. Generally, such surgery should be undertaken only if complete local clearance of the tumor may be obtained and if other sites of disease are not immediately threatening to life. Radiation therapy may be considered as an alternative to surgery. Surgery often requires collaboration between the breast surgeon and the reconstructive surgeon to provide optimal cancer control and wound closure.

Retrospective studies suggest a potential survival benefit from complete excision of the primary tumor in select patients with metastatic breast cancer [76–81]. Substantial selection biases exist in all of these studies and are likely to confound the study results. Two recent prospective, randomized studies assessed whether or not surgery on the primary tumor in the breast is necessary for women who are diagnosed with metastatic breast cancer. The results from both studies were similar and showed that surgical treatment of primary tumors in woman presenting with stage IV disease does not produce an increase in OS in general [82, 83]. However, a survival advantage for primary tumor excision was observed only in patients with solitary bone metastasis in the Turkish study [83].

Randomized clinical trials addressing the advantages and disadvantages of local therapy for patients with stage IV disease while eliminating selection biases are necessary. Patient enrollment in such trials is encouraged.

## Conclusion

The use of no ink on the tumor as the standard for an adequate margin in invasive cancer in the era of multidisciplinary therapy is associated with low rates of IBTR and has the potential to decrease re-excision rates, improve cosmetic outcomes, and decrease health care costs. Patients without sentinel lymph node (SLN) metastases should not receive axillary lymph node dissection (ALND). Patients with one to two metastatic SLNs planning to undergo breast-conserving surgery with whole-breast radiotherapy should not undergo ALND (in most cases). Patients with SLN metastases who will undergo mastectomy should be offered ALND according to randomized

controlled studies. Patients with operable breast cancer and multicentric tumors, with ductal carcinoma in situ (DCIS) who will undergo mastectomy, who previously underwent breast and/or axillary surgery, or who received preoperative/neoadjuvant systemic therapy may be offered SLN biopsy. Women who have large or locally advanced invasive breast cancer (tumor size T3/T4), inflammatory breast cancer, or DCIS (when breast-conserving surgery is planned) or are pregnant should not undergo SLN biopsy. All women undergoing breast cancer treatment should be educated about breast reconstructive options, as adapted to their individual clinical situation. These recommendations are based on cohort studies and/or informal consensus.

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