



Performance and Practice Guidelines for the Use of Neoadjuvant Systemic Therapy in the Management of Breast Cancer

Article I – INTRODUCTION

This American Society of Breast Surgeons (ASBrS) Performance and Practice Guideline summarizes the indications and management considerations for neoadjuvant chemotherapy and neoadjuvant endocrine therapy, collectively referred to as neoadjuvant systemic therapy. The Guideline reflects the consensus of a panel comprising members of the Education Committee, the Board of Directors and the Executive Committee, and is based on multiple sources from the peer-reviewed literature. This Guideline is not a systematic review of the literature but a consensus statement. This Guideline reflects what ASBrS considers to be optimal practice, but may require modification based on the clinical circumstance, the physicians' judgment, the patient's preference, and the consideration that scientific evidence continues to evolve.

Article II – Indications

Neoadjuvant (pre-operative) systemic therapy (NST) comprises today cytotoxic, endocrine and biological targeted and non-targeted agents administered to premenopausal and post menopausal patients. Neoadjuvant chemotherapy (NAC) has been shown to be equivalent to adjuvant (post-operative) chemotherapy in terms of disease-free and overall survival¹⁻³. As a cancer biology research tool, NST provides a platform to efficiently evaluate the safety and efficacy of novel therapeutic agents while monitoring the physical and/or biological response of the tumor. From a surgical perspective, the primary goal of NST is to achieve tumor or nodal downstaging in order to increase tumor resectability and decrease surgical morbidity.

The purpose of NST is to:

- A. Increase resectability of locally advanced breast cancer and inflammatory breast cancer (stage IIIA-IIIC) and enable early administration of systemic therapy to individuals at highest risk of systemic occult disease.
- B. Increase the feasibility of breast conserving surgery among women with Stage II-III invasive breast cancer who would otherwise require mastectomy due to unfavorable breast-to-tumor ratio.
- C. Increase the cosmesis of breast conserving surgery among breast conserving surgery candidates who might otherwise achieve inferior cosmetic results due to unfavorable breast-to-tumor ratio.
- D. Decrease the morbidity and extent of axillary surgery in women with significant axillary nodal disease^{1,2,4,5}.
- E. In the case of NAC, downstage the axilla in node positive patients who might benefit from

sentinel node biopsy.

F. NST may be considered an option for anyone for whom adjuvant systemic therapy is indicated.

Article III – Contraindication

A. Pure ductal carcinoma in situ is the only absolute contraindication to NST. NST is typically reserved for patients with T1b or higher disease.

Article IV -- Nomenclature

A. RECIST (Response Evaluation Criteria In Solid Tumors) Criteria are the most widely used international standard for reporting tumor clinical response to NST⁶. Four (4) RECIST categories are described:

1. Complete response (lesion not detectable),
2. Partial response ($\geq 30\%$ reduction in the maximal lesion diameter),
3. Stable disease ($< 30\%$ reduction in maximal lesion diameter)
4. Progressive disease ($\geq 20\%$ increase in the maximal lesion diameter)

B. The RECIST categories are further divided into *clinical* response (denoted by a lowercase “c”) in reference to measurements made by physical examination or radiological imaging or *pathological* response (denoted by a lower case “p”) based on histological assessment following lesion resection.

C. The optimal tumor response to NST is a clinical complete response (cCR) in which there is no palpable or imaging evidence of residual disease and pathological complete response (pCR) where no residual viable invasive disease is detected in the resection specimen.

D. The FDA preferred definition of pCR is no residual invasive disease in the breast *and* axillary nodes. Residual DCIS is allowed. However, from a surgical perspective, the presence and extent of residual DCIS are important for complete resection and local control.

E. At the individual trial level, there is no correlation between pCR and disease free or overall survival. However, a recent meta-analysis suggested improved disease free and overall survival when pCR was achieved in triple negative invasive breast cancer and HER2/neu-amplified invasive breast cancer treated with anti/HER2-neu therapy⁷.

Article V. The following tests and procedure should be completed prior to or near the time of referral to medical oncology:

A. Breast cancer staging should include diagnostic mammograms and ultrasound of the ipsilateral breast and axilla

B. Pre-treatment contrast-enhanced MRI is optional, but may aid in identifying tumor growth patterns (e.g., concentric or stellate configuration, tumor dimensions, multifocal or multicentric disease) that may influence the surgical approach and/or impact decisions

regarding breast conserving surgery. Contrast-enhanced MRI is also the most accurate breast imaging study for determination of the extent of residual disease post-NST⁸.

- C. Core needle or vacuum-assisted biopsy of the breast primary as well as additional sites of multi-centric disease and axillary sites are needed to establish the diagnosis of invasive cancer and to rule out multicentric disease, if suspected. Although percutaneous biopsy is preferred to establish a diagnosis, incisional biopsy does not preclude use of NST.

Placement of a detectable tissue marker (e.g., radiopaque clip, ultrasound-visible clip, or tattoo ink) into the breast primary and any additional sites of disease as well as any axillary sites, to document the lesion's location in case all radiographic features of the malignancy disappear following NST⁹.

- D. Documentation of invasive breast cancer and determination of tumor biomarkers (ER, PR, and HER2/neu) in the core needle biopsy specimen obtained from the breast or axillary node. Although Ki-67 is commonly reported, lack of reproducibility of Ki-67 scoring limits its utility for treatment decision-making.
- E. In the absence of systemic symptoms, systemic staging, physical exam findings, or abnormal liver function testing, NCCN guidelines recommend systemic staging for distant metastasis only in patients with Stage III breast cancer¹⁰. Staging for visceral metastasis may be performed using CT scan of the chest and abdomen +/- pelvis **or** FDG PET/CT scan. Staging for a bone metastasis is accomplished using bone scan or sodium fluoride PET/CT unless an obvious bone metastasis is demonstrated by FDG PET/CT. Symptom-guided imaging should also be performed (e.g., brain MRI for headaches).
- F. Discuss the optional placement of a vascular access port to facilitate NAC.
- G. Enroll patient in breast cancer "navigation" program, if available.
- H. Communicate with referring and/or primary care physician regarding treatment plan.
- I. Measure patient "distress" with available tools and initiate early referral for counseling and support as needed.
- J. Before treatment starts or during treatment, the following issues should also be considered:
 - a. Risk assessment for germ-line mutation status, which if positive, may change surgical treatment from breast conservation to mastectomy
 - b. Consideration of early plastic surgical consultation if patient would benefit from an oncoplastic partial mastectomy, a symmetry procedure, or post-mastectomy reconstruction.
 - c. Consideration of radiation oncology consultation regarding breast conserving therapy or PMRT

Article VI. Treatment Regimens

- A. Neoadjuvant chemotherapy. Multiple chemotherapy regimens are used for administration of neoadjuvant chemotherapy. In general, the neoadjuvant chemotherapy regimen is administered preoperatively over a span of 3-6 months, followed by appropriate adjuvant endocrine therapy, anti-HER2/neu targeted therapy, and in some cases additional chemotherapy¹¹. Clinical trial participation should be considered.
- B. Neoadjuvant anti-HER/neu therapy. Patients with HER2/neu-amplified, Stage IB or higher stage invasive breast cancer (including N1mic) should be evaluated for dual anti-HER2/neu targeted therapy using combination chemotherapy, trastuzumab, and pertuzumab. Pertuzumab is a novel anti-HER2/neu agent that is FDA-approved only for administration in the neoadjuvant (and metastatic) setting outside a clinical trial. Dual anti-HER2/neu targeted therapy has been shown to achieve high rates of tumor downstaging^{12, 13}.
- C. Neoadjuvant endocrine therapy (NET) produces the best response rates in postmenopausal women with clinical stage II through III breast cancer with Luminal A phenotype^{14, 15}. Significant tumor downstaging using NET usually requires 4-6 months of continuous therapy, but pCRs are rarely observed. There is no established role for NET in premenopausal women and it is contraindicated for inflammatory breast cancer. NAC and NET are generally not administered concurrently.

Article VII. Treatment Monitoring

- A. Patients undergoing NST are typically reevaluated by the treating medical oncologist every 2-4 weeks according to standard cycle monitoring practices for administration of therapy, symptom management and assessment of treatment response, including routine tumor measurements. In the absence of progression or other patient-related factors (intolerable side effects, etc.), the entire program of NST is delivered. Progression of disease on NST has been reported in 4.3% of patients¹⁶. Early surgical intervention may be considered in these patients.
- B. Many surgeons find interval follow-up to be a beneficial method of maintaining patient contact during the 4-6 month long course of NST. Surgical follow-up near the end of NST facilitates surgery scheduling and planning for post-NST imaging (e.g., mammography, ultrasound, and/or MRI) and scheduling of surgery. Post-NST breast and axillary imaging is unnecessary if the findings will not impact the surgical plan, e.g, if mastectomy and ALND are planned.

Article VIII. Decision for Surgery

- A. Surgery is usually performed 3-6 weeks after NST to allow time for improvement in blood counts.
- B. Final recommendations for surgery following NST depend on the extent of disease at presentation, patient choice, tumor response to NST, and genetic testing, if performed. Modified radical mastectomy remains the standard of care for inflammatory breast

cancer regardless of the response to NST.

- C. Surgeons must also anticipate that a patient's surgical desires regarding BCS, mastectomy, or breast reconstruction might change while receiving NST.
- D. Surgical planning regarding breast conserving surgery, mastectomy, or breast reconstruction should also consider the need for radiotherapy.
- E. Patients that experience a clinical complete response require breast and axillary surgery to exclude the presence of residual malignancy

Article IX. Surgical Planning – Breast Conserving Surgery

- A. Repeat Mammogram and Ultrasound of the breast to evaluate the extent of residual locoregional disease following NST.
- B. Breast MRI may be performed to estimate the extent of residual locoregional disease. MRI is superior to clinical breast examination, mammography, and ultrasound for assessing the extent of residual breast disease after NST, whereas axillary ultrasound is superior to MRI and PET/CT for detection of residual axillary disease¹⁷
- C. The extent of microcalcifications impacts eligibility for BCS, but correlates poorly with the extent of residual disease¹⁸.
- D. Patients with non-palpable disease following NST should undergo a localization procedure of the residual lesion or tissue marker. Localization techniques include single or bracket wire-localization, intraoperative ultrasound, and radioguided seed localization.
- E. Two-view specimen radiography is recommended to document removal of the tissue marker and any associated imaging abnormality, followed by selective cavity side-wall shaves
- F. Resection of the original tumor volume is not required following a partial or complete clinical response to NST. The resection volume should be limited to any residual imaging or palpable findings. If no visible or palpable component remains, the resection volume may be limited to the tissue in the immediate vicinity of the biopsy site marker.
- G. Specimen radiography during surgery is essential to document removal of the biopsy site marker and any associated radiographically apparent microcalcifications, architectural distortions, or masses. Resection of all suspicious microcalcifications is strongly recommended even though they correlate poorly with the extent of residual disease¹⁸.
- H. Touch prep or frozen section are optional, but may be used for intraoperative margin assessment.

- I. Placement of multiple surgical clips along the lumpectomy cavity will aid administration of breast radiotherapy.
- J. The pathology report should document the extent of residual invasive and in situ disease, the invasive and in situ surgical margins, the total number of negative and positive nodes, and the presence of extranodal extension. In the case of a pCR in the breast and/or axilla, the pathology report should document the presence of the biopsy site as well as any evidence of residual necrotic tumor or treatment effects.
- K. Re-excision of surgical margins following breast conserving surgery is indicated for patients with “tumor on ink” for either the invasive or in situ component. The minimum required margin width should be discussed in a multidisciplinary setting to determine if wider margins are needed. SSO/ASTRO guidelines do not provide guidance regarding optimal margin width following NST¹⁹.

Article X. Surgical Planning – Mastectomy

- A. Skin and nipple sparing mastectomy may be safely attempted after NST if the preserved skin and/or nipple remain clinically uninvolved by cancer, provided that negative margins are achieved^{20,21}.
- B. The surgeon should inform the pathologist of the tumor location and that the patient received NST to facilitate accurate identification and characterization of the surgical pathology findings.

Article XI. Surgical Planning – Axillary Staging

- A. Locoregional management of the axilla following NST may be influenced by the status of the axilla at baseline.
- B. Retrospective studies support the use of sentinel node biopsy (SNB) after NST among with women with cN0 or needle biopsy negative axillary nodes²²⁻²⁴. Among such individuals, sentinel node identification and false negative rates are comparable to SNB performed in the adjuvant setting. ALND is performed if SNB post-NST detects axillary metastasis or if the sentinel nodes are not identifiable.
- C. SNB also be performed prior to NST in clinically node negative patients if knowledge of the pre-treatment SN histology is critical to treatment decision-making. However, data from the SENTINA Trial do not support the use of repeat SNB after NST due to an unacceptably low sentinel node identification rate and an exceedingly high false negative rate²⁵.
- D. Several clinical trials have evaluated the feasibility of SNB after NST in patients with T1-3, N1-3 disease at baseline²⁵⁻²⁸. Currently, NCCN guidelines support use of the SNB procedure after NST among previously node-positive patients converted to clinically node-negative¹⁰. Acceptable SN false negative rates may be obtained when dual tracers (i.e., blue dye and radioisotope) are used for SN mapping, a minimum of three SN are removed, and when specimen radiography of the SN confirms removal

of the original biopsy-positive axillary node. Under such circumstances, SNB-negative patients may avoid ALND whereas SNB-positive patients should undergo ALND.

- E. Identification of the originally biopsied node may be facilitated by wire-guided or ultrasound-guided dissection. There may be a role for emerging nodal localization techniques, e.g., tattoo ink-guided or radioguided seed localization^{9,29}. A specimen radiograph should be obtained of the resected node(s) to document removal of any radio-opaque marker placed within a biopsy-positive node.

Article XII. Surgical Planning – Breast Reconstruction

- A. Breast reconstruction remains an option for patients managed with NST. Complicating the decision regarding the technique and timing of breast construction is the potential need for post-mastectomy radiotherapy (PMRT), which increases the acute and chronic morbidity of breast reconstruction and produces inferior cosmesis³⁰⁻³⁴.
- B. Patients for whom PMRT is unnecessary may contemplate all options for immediate and delayed breast reconstruction [immediate implant, tissue expander/implant, and autologous myocutaneous flap reconstruction] with a relatively low risk of surgical complications.
- C. Patients for whom PMRT is necessary may be managed with immediate or delayed autologous myocutaneous flap reconstruction (e.g., DIEP, TRAM) with fewer complications compared to implant-based reconstructions³³. However, selected patients may undergo immediate or delayed-immediate implant-based reconstruction, which allows preservation of the entire skin envelope for optimal cosmesis³⁵.
- D. Delayed-immediate breast construction involves placement of a tissue expander at the time of mastectomy prior to PMRT followed by expander-implant exchange or autologous myocutaneous flap reconstruction after PMRT³⁵.
- E. When the need for PMRT is uncertain, delayed-immediate reconstruction allows to completion of implant reconstruction or conversion to autologous myocutaneous flap reconstruction depending on the decision regarding PMRT.
- F. Although more tolerant of radiation than implant-based reconstructions, autologous myocutaneous flap reconstructions treated with irradiation commonly experience a higher risk of fat necrosis, volume loss, and flap contracture compared to non-irradiated autologous myocutaneous flap reconstruction³⁶.
- G. Mastectomy and immediate breast reconstruction are usually performed 3-6 weeks after completion of NST if PRMT is not planned.
- H. If PMRT is planned, delayed breast reconstruction is usually performed 3-6 months after PMRT.

- I. Patient should be counseled that BMI >30, smoking history, and diabetes increase the risk of complications of breast reconstruction^{37,38}.

Article XIII. Surgical Planning – Radiation therapy

A. Post-Breast Conserving Surgery

- a. Whole breast external beam radiation remains the standard of care for patients treated with breast conserving surgery after NST. A tumor bed boost is usually employed.
- b. In general, the need for regional nodal radiation is controversial and has been guided primarily by the status of the axillary nodes prior to NST, regardless of clinical response. The NSABP B-51/RTOG1304 and Alliance A11202 clinical trials are currently evaluating the role of regional nodal radiation post-NST (as an alternative to ALND) in SN negative and SN positive patients treated with BCS and mastectomy.
- c. There are insufficient data to support the use of partial breast irradiation or hypofractionated radiation therapy following NST.

B. Post-Mastectomy RT

- a. In general, indications for PMRT are based on the clinical stage prior to initiation of NST regardless of the response to NST³⁹. In general, PMRT is associated with a reduction in the LRR and improvement in disease-free and overall survival for Stage IIB-III disease⁴⁰. Relative indications for PMRT include patient age <45-50 years, lymphovascular invasion, positive surgical margins, residual positive nodes after NST, T3 or T4 disease at baseline, and pre-NST tumor size >4cm⁴¹⁻⁴³. There is insufficient evidence to support the omission of PMRT following a pCR.
- b. The need for PMRT should be discussed with a radiation oncologist to determine the current recommendations for this treatment approach.
- d. PMRT is usually initiated within 6 weeks of mastectomy.

Article XIV – Surgeon qualifications

Surgeons must have successfully completed an American Board of Medical Specialties-approved surgical residency program and must have attained, or be admissible for, board certification by the American Board of Surgery or its equivalent.

Article XV – Documentation

Documentation prior to surgery should include an informed consent, encompassing all treatment options and a full discussion of risks and benefits. The operative report should include all appropriate patient identifiers, the name of the operation, the type of anesthesia, and a succinct description of the clinical setting, indication for surgery, and operative findings. The steps of the

operative procedure should be described in detail, noting in particular any complications and how they were managed. The presence of clinical residual disease as well as the number/location/type of surgical drains should be noted. A copy of the operative report should go to all treating physicians and should be part of the permanent medical record. A plan for follow-up, including discussion of pathology results, wound care, drain management, and arm exercises should be part of the overall survivorship program.

Article XVI – Equipment specification and quality control

Standard general surgical instruments and operating room equipment are required.

Article XVII – Quality assessment and improvement

- A. The adequacy of breast conserving surgery is assessed by achieving complete tumor removal with negative surgical margins.
- B. Specimen orientation should be performed and documented in the event that margin re-excision is required.
- C. There should be a policy to review the emerging evidence in a systematic fashion to allow for changing indications and incorporation of new data with a multidisciplinary approach.
- D. Patients should be counseled regarding the potential need for re-excision of positive margins or mastectomy if margin clearance is not achievable.
- E. Complications, both acute (e.g., hemorrhage, infection) and chronic (e.g., seromas, breast lymphedema) should be discussed and recorded if they should occur. A plan for management of such complications should exist.

Approved March 2, 2017

Board of Directors

The American Society of Breast Surgeons

References:

1. 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.
2. 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;19:4224–4237.

3. Gianni L, Baselga J, Eirmann W, et al. European Cooperative Trial in Operable Breast Cancer (ECTO): improved freedom from progression (FFP) from adding paclitaxel (T) to doxorubicin (A) followed by cyclophosphamide methotrexate and fluorouracil (CMF). *J Clin Oncol*. 2005;23:7s abstract 513.
4. Bear HD, Anderson S, Brown A, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol*. 2003;21:4165–4174.
5. Gianni L, Baselga J, Eiermann W, et al. First report of the European Cooperative Trial in Operable Breast Cancer (ECTO): effect of primary systemic therapy. *Proc Am Soc Clin Oncol*. 2002;21:34a abstract 132.
6. Eisenhauer EA, Therasse P, Bogaerts J, et al. New Response evaluation criteria in solid tumors: revised RECIST guidelines (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.
7. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384(9938):164–172.
8. Jochelson MS, Lampen-Sachar K, Gibbons G, et al. Do MRI and mammography reliably identify candidates for breast conservation after neoadjuvant chemotherapy. *Ann Surg Oncol*. 2015;22:1490-1495.

9. Choy N, Lipson J, Porter C, et al. Initial results with preoperative tattooing of biopsied axillary lymph nodes and correlation to sentinel lymph nodes in breast cancer patients. *Ann Surg Onc.* 2015;22(2):377-382.
10. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (Breast Cancer). (Version 2.2015).
http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed May 24, 2015.
11. Mieog JSD, van der Hage JA, van de Velde CJH. Neoadjuvant chemotherapy for operative breast cancer. *Br J Surg.* 2007;94:1189–1200.
12. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol.* 2013;24:2278–2284.
13. Gianni L, Pienkowski T, Im Y-H, et al. Efficacy and safety of neoadjuvant pertuzamab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (Neosphere): a randomized multicentre, open-label, Phase 2 trial. *Lancet Oncol* 2012;13:25-32.
14. Saleh RR, Bouganim N, Hilton J, Arnaout A, Clemons M. Neoadjuvant endocrine treatment for breast cancer: from bedside to bench and back again? *Current Oncology.* 2014;21(1):e122-e128. doi:10.3747/co.21.1627.

15. Haddad, TC, Goetz MP. Landscape of neoadjuvant therapy for breast cancer. *Ann Surg Oncol.* 2015;22:1408-1415.
16. Dialani V, Chadashvili T, Slanetz PJ. Role of imaging in neoadjuvant therapy for breast cancer. *Ann Surg Oncol* 2015;22:1416-1424.
17. Bosch AM, Kessels AG, Beets GL, et al. Preoperative estimation of the pathological breast tumour size by physical examination, mammography and ultrasound: a prospective study on 105 invasive tumours. *Eur J Radiol.* 2003;48:285–292.
18. Weiss A, Lee KC, Romero Y, et al. Calcifications on mammography do not correlate with tumor size after neoadjuvant chemotherapy. *Ann Surg Oncol.* 2014;21:3310-3316.
19. Moran M, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology—American Society of Radiation Oncology consensus guidelines on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *Inj J Radiat Oncol Biol Phys.* 2014;88(3):553-564.
20. Wang F, Peled AW, Garwood E, et al. Total skin-sparing mastectomy and immediate breast reconstruction: an evolution of technique and assessment of outcomes. *Ann Surg Oncol.* 2014;21(10):3223-3230.
21. Radovanovic Z, Radovanovic D, Golubovic A, et al. Early complications after nipple-sparing mastectomy and immediate breast reconstruction with silicone prosthesis: results of 214 procedures. *Scand J Surg.* 2010;99(3):115-118.

22. Kelly AM, Dwamena B, Cronin, et al. Breast cancer sentinel node identification and classification after neoadjuvant chemotherapy—a systemic review and meta-analysis. *Acad Radiol.* 2009;16(5):551-563.
23. Xing Y, Foy M, Cox DD, et al. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. *Br J Surg.* 2006;93:539–546.
24. Mamounas EP, Brown A, Anderson S, et al. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol.* 2005;23:2694–2702.
25. 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, multicentre cohort study. *Lancet Oncol.* 2013;14:609–618.
26. Boguey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA.* 2013;310:1455–1461.
27. NSABP B-51/RTOG 1304. [ClinicalTrials.gov Identifier: NCT01872975](https://clinicaltrials.gov/ct2/show/study/NCT01872975)
28. Alliance A112020. [ClinicalTrials.gov Identifier: NCT01901094](https://clinicaltrials.gov/ct2/show/study/NCT01901094)

29. Vidal-Sicart S, Giammarile F, Mariani G, et al. Pre- and intra-operative imaging techniques for sentinel node localization in breast cancer. *Imaging In Medicine*. 2013;5(3):275-291.
30. Ascherman JA, Hanasono MW, Newman MI, et al. Implant reconstruction in breast cancer patients with radiation therapy. *Plast Reconstr Surg*. 2006;117:359–365.
31. Benediktsson K, Perbeck L. Capsular contracture around saline-filled and textured subcutaneously placed implants in irradiated and non-irradiated breast cancer patients: Five years of monitoring of a prospective trial. *J Plast Reconstr Aesthet Surg*. 2006;59:27–34.
32. Behranwala KA, Dua RS, Ross GM, et al. The influence of radiotherapy on capsule formation and aesthetic outcome after immediate breast reconstruction using bidimensional anatomical expander implants. *J Plast Reconstr Aesthet Surg*. 2006;59:1043–1051.
33. Barry M, Kelly MR. Radiotherapy and breast reconstruction: a meta-analysis. *Breast Cancer Res Treat*. 2011;27:15–22.
34. Lam TC, Hsieh F, Boyages J. The effects of postmastectomy adjuvant Radiotherapy on immediate two-stage prosthetic breast reconstruction: a systematic review. *Plast Reconstr Surg*. 2013;132:511-518.
35. Kronowitz SJ, Robb GL. Radiation therapy and breast reconstruction: a critical review of the literature. *Plast Reconstr Surg*. 2009;124:395-408.

36. Garvey PB, Clemens MW, Hoy AE, et al. Muscle-sparing TRAM flap does not protect breast reconstruction from postmastectomy radiation damage compared with the DIEP flap. *Plast Reconstr Surg.* 2014;133:223-233.
37. Chang DW, Wang B, Robb GL et al. Effect of obesity on flap and donor site complications in free transverse rectus abdominis myocutaneous flap breast reconstruction. *Plast Reconstr Surg.* 2000;105:1640–1648.
38. Chang DW, Reece GP, Wang B. Effect of smoking on complications in patients undergoing free TRAM flap breast reconstruction. *Plast Reconstr Surg.* 2000;105:2374–2380.
39. Garg AK, Buchholz TA. Influence of neoadjuvant chemotherapy on radiotherapy for breast cancer. *Ann Surg Oncol.* 2015;22:1434-1440.
40. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): 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 randomized trials. *Lancet* 2005;336(9503):2087-2106.
41. 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;30:3960–3966.
42. Buchholz TA, Katz A, Strom EA, et al. Pathologic tumor size and lymph node status

predict for different rates of locoregional recurrence after mastectomy for breast cancer patients treated with neoadjuvant versus adjuvant chemotherapy. *Int J Radiat Oncol Biol Phys.* 2002;53:880–888.

43. Katz A, Strom EA, Buchholz TA, et al. Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: Implications for postoperative irradiation. *J. Clin Oncol.* 2000;18(15):2817-2817.