Neo-Adjuvant (Pre-Operative) Therapy for Breast Cancer
- General Considerations -

Effective Date: December, 2014

The recommendations contained in this guideline are a consensus of the Alberta Provincial Breast Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
BACKGROUND

Breast cancer is the most frequently diagnosed cancer amongst Canadian women. One in nine Canadian women will develop breast cancer in their lifetime. In 2013 alone, approximately 24,000 Canadian women, including 2,100 of Alberta’s women were diagnosed with breast cancer. Advances in early detection, local therapy, and systemic therapy have led to a steady decline in mortality rates since the 1986 peak. Despite these advances, however, approximately 400 of Alberta’s women will still die from the disease this year (1). Breast cancer occurs primarily in females aged 50-69 (52%), and women over 69 (30%). The remaining 18% of breast cancer diagnosis occur in women under the age of 50 (1).

In the majority of cases, patients with non-metastatic breast cancer are treated with surgery initially followed by adjuvant therapy thereafter, as indicated. Neo-adjuvant (or pre-operative) therapy may be appropriate in some circumstances, particularly when surgical options are limited at the time of initial diagnosis.

This guideline is intended to highlight the general considerations for treatment of patients who are potentially eligible for neo-adjuvant therapy (NAT). Specific information regarding systemic therapy details will be reported in a separate neo-adjuvant systemic therapy guideline.

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Breast Tumour Team. Members of the Alberta Provincial Breast Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Breast Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in December, 2014.

SEARCH STRATEGY

The MEDLINE and Pubmed databases were searched for literature relevant to this topic from 2000-2014 (July). The reference sections of relevant articles were scanned for additional resources. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials. The search terms included: breast or mammary, cancer, carcinoma or neoplasm(s), neo-adjuvant and chemotherapy or endocrine therapy or radiotherapy or surgery. Only article written or translated into English were reviewed.

TARGET POPULATION

This guideline is targeted at females, who are at least 18 years of age and have been diagnosed with non-metastatic breast cancer.
GUIDELINE QUESTIONS

1. Who is an appropriate candidate for neo-adjuvant (pre-operative) therapy for breast cancer?
2. What are the potential advantages / disadvantages of NAT for breast cancer?
3. What types of NAT are available and when are they indicated, in general?
4. What is the ideal modality and frequency to determine treatment response to NAT?
5. Additional surgical considerations for patients undergoing NAT:
   a. How should axillary nodal involvement be evaluated?
   b. Which type of breast surgery is appropriate after NAT?
6. What is the role for radiation therapy in the NAT setting?

RECOMMENDATIONS

1. Eligibility for neo-adjuvant systemic therapy.
   A. Inoperable or Locally Advanced Breast Cancer:
      i. There is sufficient and consistent evidence, from well-designed studies to recommend NAT as an appropriate treatment option for patients with inoperable or locally advanced breast cancer (LABC) without distant metastasis.
      ii. All patients with inflammatory breast cancer (Stage IIIB) should be considered for NAT.
   B. Operable Breast Cancer:
      i. Patients with operable or early-stage breast cancer whereby additional tumour shrinkage is required to perform appropriate breast conservation surgery are potential candidates for NAT.

2. Potential advantages and disadvantages to neo-adjuvant systemic therapy.
   A. Advantages
      i. There is no detriment of NAT in terms of survival
         1. In the clinical trial setting, there is no difference in terms of overall survival (OS) outcomes for non-metastatic, operable candidates treated with NAT vs. standard adjuvant therapy for breast cancer.
      ii. Surgical advantages
         1. NAT may convert previously inoperable disease to operable disease
         2. NAT may allow for conversion of mastectomy (M) only candidates to breast conserving surgery (BCS) candidates.
         3. In BCS candidates with cancers >2 cm, NAT can potentially further reduce the extent of surgical resection, and improve on cosmesis.
      iii. Disease response assessment
         1. NAT allows for the ability to monitor response to therapy (*in vivo* therapeutic assessment), and the ability to change therapy if response is inadequate in the neo-adjuvant treatment setting (66-68).
         2. Pathologic complete response (pCR) has been noted in some studies to be a good prognostic feature. pCR as a potential surrogate for OS for certain breast cancer populations remains controversial at this time.
      iv. Research
1. In a research setting, NAT provides researchers with an opportunity to study the impact of therapeutic treatments on the in situ tumour on the basis of sequential sampling (e.g. imaging, tumour biology, etc.) (58).

B. Potential disadvantages of NAT
   i. The potential disadvantages to NAT are generally limited. In a minority of cases, progressive disease while on NAT may limit surgical options (i.e. treatment delays caused by ineffective NAT may not make surgical resection possible). As patients are monitored closely during NAT, this happens infrequently, however.

3. What types of neo-adjuvant therapies are available, and when are they indicated in general?
   A. Neo-adjuvant chemotherapy (NC)
      i. Factors that are associated with favorable response to NC include:
         1. Younger age, non-lobular histology, higher grade, negative hormone receptor (HR) status and Human epidermal growth factor 2 (HER2)-positive disease.
      ii. Choice of NC regimen
         1. In general, patients who would be eligible for adjuvant chemotherapy based on initial clinical-pathological features would also be eligible to receive the same or similar chemotherapy regimen in the NAT setting.
         2. Outside of the clinical trial research setting, there is no routine role for neo-adjuvant platinum-based chemotherapy regimen at this time.
         3. Ideally, NC should be given in its entirety before definitive surgery
   B. Neo-adjuvant biologic or targeted therapy:
      i. Patients with HER2-positive breast cancer should receive HER2-positive directed therapy as part of the neo-adjuvant systemic therapy regimen.
         1. This treatment may also extend into the postoperative (or adjuvant) setting as per standard treatment duration.
      ii. Where available, dual HER2-positive directed therapy has demonstrated greater response rates and higher pCR rates when compared to single agent HER2-positive directed therapy.
      iii. Outside of the clinical trial research setting, there is no routine role for neo-adjuvant bevacizumab at this time.
   C. Neo-adjuvant endocrine therapy (NET)
      i. HR positivity remains the single most important criterion for eligibility for NET.
      ii. Both pre- and post-menopausal women with HR-positive breast cancer may be technically eligible for NET.
      iii. Although evidence exists, NET is not standardly used in North American treatment settings.
      iv. NET is a particularly attractive option in post-menopausal patients with HR-positive breast cancer who would not be expected to easily tolerate chemotherapy (absolute or relative contraindication to chemotherapy) or in those patients who decline NC.
      v. Response to NET is typically slower than with NC (i.e. takes longer to see disease response), and the probability of achieving pCR is typically lower in patients treated with NET compared to NC.
vi. For patients treated with NET, endocrine therapy (ET) would continue after definitive surgical resection (adjuvant ET), as per standard treatment duration/guidelines.

4. Optimal treatment monitoring
   A. Clinical Examination
      i. Clinical exam should be performed and documented at baseline and at follow-up assessments
   B. Imaging
      i. The available evidence is insufficient to conclusively recommend one monitoring modality over another.
         1. There is evidence for the utility of physical exam (PE), ultrasonography (US), mammography (MG) and magnetic resonance imaging (MRI) for monitoring response to NAT.
      ii. Baseline imaging:
         1. Breast imaging should be performed at baseline
      iii. Follow up imaging:
         1. May be repeated in the NAT setting to help clarify clinical treatment response.
         2. Repeat imaging may be avoided if clear tumour size decreases are noted clinically during treatment.
         3. If follow-up imaging is used, preference should be made to the most cost-effective imaging modality that most easily and consistently identifies the breast cancer.
         4. When repeat imaging is used, the same method should be used as was performed at baseline.
         5. Caution should be exercised in interpretation of imaging as there may be discordance between radiologic imaging, clinical findings and definitive breast surgical pathology
      iv. Timing of imaging:
         1. The available evidence is insufficient to conclusively recommend exact timing of disease monitoring with radiologic imaging.
         2. Imaging should be done when a change in management is expected due to lack of clinical response particularly in the setting of planned or desired BCS. If disease progression is clinically suspected, imaging may be performed to confirm clinical impression.
         3. If a total M is planned, and clinical improvement during NAT is noted repeat imaging is not always necessary prior to surgery
   C. Serial tissue biopsy (e.g. Ki-67)
      i. This is not routinely performed outside of the research or clinical trial setting
5. Surgical Considerations

A. Breast – pre NAT
   i. Baseline breast imaging (MG and US of the breast and axilla) is recommended – to document baseline breast and axillary involvement.
   ii. Core needle biopsy (not FNA) of the breast lesion in question should be performed for standard pathological confirmation of breast cancer and tumour receptor assessment (HR and HER2 receptor assessment)
   iii. All patients (irrespective of planned surgery – BCS or M) undergoing NAT should have breast clips inserted prior to the start of NAT for tumour localization to allow for easier identification of the breast cancer site after NAT. This is of particular importance in patients where by BCS is planned.

B. Management of the Axilla in the Neo-adjuvant Setting.
   i. Lymph node (LN) negative breast cancer (negative LN on clinical examination and imaging):
      1. There is sufficient evidence to recommend the use of sentinel lymph node dissection after NAT for staging and management of patients presenting with a clinically negative axilla.
   ii. Lymph node positive breast cancer (clinically LN positive or imaging LN positive):
      1. Pathologic confirmation of lymph node positive status with fine needle aspiration or core needle biopsy is recommended prior to initiation of NAT.
      2. Irrespective of response to NAT, at the present time, standard axillary lymph node dissection (ALND) should be performed at the time of definitive breast surgery until more evidence is available to support the use of SLN biopsy alone.

C. Surgical Management of the Breast after NAT
   i. Breast Conserving Surgery
      1. There is sufficient evidence to support BCS as acceptable for most patients after NAT
   ii. Mastectomy (M)
      1. Patients who have contraindications to radiation, or have multi-centric breast cancer (disease located in different quadrants of the breast) or large tumour-to-breast ratios after NAT should be considered for M.
   iii. Post-mastectomy Breast Reconstruction
      1. Patients interested in reconstruction after M should be approached according to the recommendations of AHS Clinical Practice Guideline BR-016: Breast Reconstruction Following Prophylactic or Therapeutic Mastectomy for Breast Cancer
6. Role of radiation therapy
   A. Neo-adjuvant radiotherapy (RT)
      i. Although not generally recommended, there are some cases where neo-
         adjuvant RT may be indicated:
         1. Patients who have locally advanced disease but are not suitable to
            receive NC due to relative or absolute contraindication (i.e. frail elderly or
            multiple co-morbidities or poor performance status).
         2. Where neo-adjuvant systemic therapy failed to produce sufficient
            response to allow for definitive breast surgery (salvage RT)
      ii. If the decision to proceed with neo-adjuvant RT is made, where applicable,
          concurrent ET should be considered in patients with hormone receptor positive
          disease, and in patients with HER2-positive disease concurrent trastuzumab can
          be continued during RT if trastuzumab has already been initiated in the neo-
          adjuvant setting.
      iii. There is no current role for concurrent NC and neo-adjuvant RT outside of the
           clinical trial setting.
   
   B. Adjuvant radiotherapy
      i. See adjuvant breast RT BR-005 and BR-006
DISCUSSION

The use of NC (also called primary or pre-operative chemotherapy) dates back to the early 1970s when the Milan Cancer Institute began to test the effectiveness of NC in shrinking a breast cancer to facilitate irradiation or radical M in patients with LABC (2). Since then, many additional trials, both non-randomized and randomized, have studied the long-term impact of the NAT approach in women with locally advanced (inoperable) and early stage (operable) breast cancer.

Eligibility for neo-adjuvant systemic therapy

Traditionally, NAT has been given to patients with LABC (Stage IIIA-IIIC) where attempts at surgical resection are contraindicated due to the inability to fully resect all of the disease (i.e. unlikely to achieve negative margins), let alone BCS. The inability to obtain negative margins is associated with poorer outcomes (47).

NAT is also indicated in women with early stage, operable breast cancer (I-II) who desire improved cosmetic outcomes following surgery. For patients desiring BCS but would otherwise require M or in cases where up front BCS would be expected to have suboptimal cosmesis due to surgical reasons, the use of NAT to downsize the tumour can be attempted. NAT could also be considered for patients who have medical contraindications to surgery at diagnosis, but in whom surgery is anticipated at a later date.

Patients with low grade, HER2-negative, estrogen receptor (ER)-positive, breast cancers are less likely to have a significant clinical response or pCR to NC (9), and may be better suited for primary surgery followed by adjuvant therapy (3,10,11).

Elderly patients with locally advanced tumours that are ER-positive may respond well to neo-adjuvant endocrine treatment however response tends to be slower and the patients must be treated for a longer period of time prior to expecting significant response.

Potential advantages and disadvantages to neo-adjuvant systemic therapy

Advantages

NAT has been compared with adjuvant chemotherapy in the context of evaluating effects on patient survival and disease recurrence. Initially, it was hoped that NAT would increase survivability. Unfortunately, for all comers, no change in survival rates has been observed when NC is given versus chemotherapy given in the adjuvant setting (8, 59). However, NAT is capable of facilitating local treatment, including converting previously unresectable, LABC to a resectable tumour (3-5, 60-62), and in those with primary operable tumours, down-staging can result in an increased rate of BCS (6-8, 59, 63, 63).

Many studies have also looked at local recurrence rates (LRRs) of patients who have undergone NAT and most show no increase in the NAT group (4,12), but increased LRRs are found if radiation is used in the absence of surgery. Because of this, surgery is recommended as standard therapy even in the presence of an apparent complete clinical response (13).
Furthermore, NAT allows direct and early observation of response to treatment in the primary tumour. This provides the clinician with valuable information, allowing for modifications to the treatment plan in the event of poor response. This benefit may, however, be somewhat mitigated by the fact that clinical and radiographic monitoring in this setting may be somewhat inaccurate with respect to predicting pCR (65), and it remains unconfirmed whether changes in therapy after poor response can lead to improved clinical outcomes (66-68).

NAT also provides an opportunity to study the impact of systemic therapies on breast cancer biology in a research setting (58). NAT allows for the evaluation of tumour response, and the availability of tissue for biopsy and biomarker development. Pathologically detected residual disease after NC may provide valuable prognostic information, where pCR has been associated with better survival outcomes (8, 69-71).

Disadvantages

The response to NC is fairly high (approximately 80%), and the majority of non-responding cases have stable disease (8). However, in worst case scenarios, progressive disease can potentially convert an operable breast cancer into inoperable breast cancer. Progressive disease occurs in approximately 1-6% of patients receiving NAT (8, 72-74).

What factors should be examined when considering neo-adjuvant therapy?

Histopathologic confirmation and evaluation of receptor status (ER, progesterone receptor (PR), and HER2) must be obtained before initiating neo-adjuvant treatment. Patients should undergo appropriate initial staging work-up prior to NAT, and metastatic disease should be ruled out.

The main prognostic factors that should be considered (and are associated with increased risk of relapse (23)):

- Poor histological grade
- Negative ER status
- Lymphovascular involvement
- Higher number of involved lymph nodes

Patients with low grade, HER2-negative, ER-positive, breast cancers are less likely to have a significant clinical response or pCR to NC (9), and may be better suited for primary surgery followed by adjuvant therapy (3,10,11).

Neo-adjuvant Chemotherapy (NC)

In general, similar regimens can be used for NAT (including NC) as is used for adjuvant therapy. Ideally, chemotherapy should be provided before surgery in its entirety, and not split into pre-operative and post-operative phases. There is no one ideal NC for all breast cancers. Trastuzumab-based chemotherapy is indicated for patients with HER2-positive disease (14). There is no clear ideal NC regimen for “triple negative” breast cancer either. The role of neo-adjuvant platinum based therapy is still evolving. A more detailed evaluation of the evidence pertaining to chemotherapy in NAT setting is underway and will be reported in a separate neo-adjuvant systemic therapy guideline.

Neo-adjuvant Biological or Targeted Therapy
Patients with HER2-positive breast cancer, who are receiving systemic therapy in the neo-adjuvant setting, should receive HER2-positive directed therapy. HER2-positive patients have a higher rate of pCR to NC when combined with HER2-positive directed therapy, especially when the tumour is HR-negative (91). The addition of trastuzumab to chemotherapy improved the rate of pCR (42% versus 20%) reduced the relapse rate (26% vs 39%), and lowered mortality rates (13% versus 20%) in women with HER2-positive breast cancer (92). More recently, dual targeted HER2 directed therapies in combination with chemotherapy has been examined to improve on response rates and pCR. Pertuzumab combinations with chemotherapy and trastuzumab have been examined with the rationale to overcome potential trastuzumab resistance (caused by HER2/3 heterodimers), and have demonstrated limited/no apparent increases in toxicity (93). Lapatinib (oral tyrosine kinase inhibitor to HER 1/2) has also been investigated as an alternative to trastuzumab in the neo-adjuvant setting; and have demonstrated that pCR rates with lapatinib are either similar to, or inferior to trastuzumab, but with greater toxicity when compared to dual antibody directed therapy (94, 95). At the present time, dual targeted HER2 directed therapies in the NAT breast cancer setting are not funded for use in Canada. Outside of the clinical trial research setting, there is no routine role for neo-adjuvant bevacizumab at this time either.

**Neo-adjuvant Endocrine Therapy (NET)**

NC is typically the NAT of choice for younger, pre-menopausal patients with NAT eligible breast cancer. The NET therapy approach, however, is an option for patients with HR-positive breast cancer particularly in those patients who decline or could not tolerate NC.

NET treatment options for postmenopausal women are typically with aromatase inhibitors (AI). In premenopausal women, treatment options include either neo-adjuvant Tamoxifen +/- ovarian suppression, or AI + ovarian suppression. The phase III trial STAGE demonstrated that in premenopausal women receiving goserelin and anastrozole had higher rates of clinical complete and partial responses compared to Tamoxifen alone (70.4% vs 50.5%, respectively; p=0.004) (50). Of note, one needs to ensure that the patient remains biochemically post-menopausal in the setting of aromatase inhibition and serial hormonal monitoring may be required in younger women.

Response to NET is typically slower than with NC (i.e. it takes longer to see disease response), and the probability of achieving pCR is typically lower in patients treated with NET compared to NC.

For patients treated with NET, ET would continue after definitive surgical resection (adjuvant ET), as per standard treatment duration/guidelines.

A more detailed evaluation of the evidence pertaining to ET in this setting is underway and will be reported in a separate neo-adjuvant systemic therapy guideline.
NAT Treatment monitoring

Accurate prediction of residual pathologic tumour size after NC is critical in guiding surgical therapy. Many examinations have been proposed to monitor tumour size and evaluate response to NAT. The conventional, relatively inexpensive approach is to assess with PE, US, and/or mammogram evaluation. The major advantage to these conventional approaches is their cost, availability and ease of use, whereas the major disadvantage may be their accuracy, particularly when assessing smaller tumours. The alternative to conventional modalities is MRI. Much controversy in the utility of MRI in treatment monitoring exists, with some studies finding great utility, while others find no apparent advantage or inferiority over conventional modalities. Choice of imaging modality should be individualized.

The utility of PE, Mammogram, and US in accurately predicting tumour size both before and after NT has been examined in multiple studies since the early 1990’s. The major advantages to these approaches are their low cost, and the ease at which they can be administered. However, the accuracy of these modalities when compared to surgical specimens is relatively poor. In a retrospective study (n=189) of patients receiving NC, US, mammogram and PE all proved unpredictable in assessing post-treatment tumour size. False positives rates were as high as 65% (15), correlation coefficients compared to pathological specimen were low, 0.45, 0.36 and 0.42 for US, MG and PE respectively (To yield a prediction that is even 50% better than a random guess, the correlation must be at least 0.86). These correlation coefficients were relatively low compared to 5 other studies with smaller samples sizes, which varied from 0.29-0.96, 0.33-0.94 and 0.68-0.88 for US, MG and PE respectively (n= 16-141) (16-20).

Although much controversy exist surrounding the use of radiological tools in the assessment of response to NAT, the most recently studied method appears to be MRI. Some have argued that the use of all three methods (MG, US and MRI) may be useful as a means of increasing the likelihood of cPR, as early identification of patients who will respond to therapy versus those who will not may be critical, allowing for the substitution of ineffective therapy as quickly as possible (21), however, only limited evidence exists to support this hypothesis. Several studies have demonstrated MRI to be the most accurate diagnostic tool for the assessment of tumour response to NAT (22-27), while others show limited advantage when compared to conventional imaging (28,29).

A meta-analysis of 25 studies (total n=1,212) examined the utility of MRI to predict pathologic complete remission in breast cancer patients after NAT. The study demonstrated the high specificity (90.7%) but low sensitivity (63.1%) of MRI in predicting pathologic complete remission after preoperative therapy in patients with breast cancer (30). A number of smaller studies have demonstrated that MRI performance may be affected by several factors. In a small study (n=44), tumours treated with taxane-containing regimens caused MRI to underestimate residual disease and frequency (31). In another small study (n=51) HER2-status effected MRI performance, with high false-negative pCR predictions in HER2-negative patients being treated with antiangiogenic agents (32). In another small study (n=86), triple negative tumours were associated with enhanced MRI accuracy (33). Alternatively, a small study (n=81) found molecular subtype and non-taxane regimen type had minimal effect on MRI performance (34).

Serial positron emission tomography/ computed tomography (PET/CT) has also been utilized, but to a lesser extent and with less clinical utilization.

In practical terms, this means that patients who are clinical candidates for breast conserving therapy (BCT) should be aware of the potential inaccuracy of all assessment techniques, both positive and
negative, and that further surgery may be necessary if clear margins are not obtained. The choice of imaging modality that best complements the clinical exam is controversial.

**How often should imaging be done?**

Limited evidence exists on the ideal monitoring frequency during NAT. Clinical examination (CE) of the breast is appropriate before each cycle of therapy. After completion of NAT, imaging (CE, MG, US and in some cases MRI) may be appropriate before surgery. Many surgeons will forego post-treatment imaging in patients who are having a M in whom the imaging is not expected to change surgical management. Imaging may also be repeated sooner in order to either document tumour response or disease progression as required, however, no significant evidence exists to support or refute the use of serial imaging during NAT.

**Breast Cancer Biomarkers**

In general, breast cancer biomarkers are used in predictive and prognostic capacities that influence treatment decisions. HR-negative (ER-negative and PR-negative) tumours are more likely to achieve pCR with NC, but prognostically are more likely to recur, have a shorter time to recurrence and have a decreased OS compared to patients with HR-positive disease. However, beyond 5 years post-treatment, the advantage of ER-positivity in terms of relapse and death grows smaller, and ultimately disappears (51-55). HR-positive tumours are more likely to develop clinically apparent metastases in bone, soft tissue and the reproductive/genital tracts when compared to ER-negative tumours, whereas, HR-negative tumours are more likely to develop clinically apparent metastases in brain, and liver, which are associated with shorter survival (56.) In the absence of targeted treatment and chemotherapy, HER2-positivity is associated with an unfavorable prognosis (57). HER2-positive disease is however associated with a superior treatment response and outcome to NAT, particularly when trastuzumab is included as part of treatment with chemotherapy.

A meta-analysis of 14 studies (total n= 865) demonstrated a change in ER and PR status before versus after NAT with a variety of treatment regimens. In those patients with initial pre-NC ER-negative disease, conversion occurred to ER-positive disease post-NAT in 17.7% of patients (n=436), whereas ER-positive disease converted to ER-negative disease in 11.4% of patients (n=429); p=0.16. In PR-negative disease, conversion occurred to PR-positive disease post-NAT in 15.0% of patients (n=400), whereas PR-positive disease converted to PR-negative disease in 33.4% of patients (n=416); p<0.001. HER2 and Ki67 did not significantly change. It remains unclear whether changes in HR status after NAT affects predictive or prognostic parameters, and further investigation is required before a definitive conclusions can be made (35). That being said, clinically, consideration for repeat breast cancer biomarkers post NAT could be made for patients with initially HR negative disease.

**Surgical Considerations**

**Surgical Considerations Pre-NAT**

Baseline breast imaging is important to document baseline disease and for use in subsequent monitoring of tumour size and evaluation of treatment response. Mamography, US and CE are the monitoring modalities of choice, as these are relatively low cost, and easily administered, although accuracy remains less than desirable (15-20). As an alternative, MRI has been examined, but its’ high cost and low sensitivity (30) preclude it from being standard of care for all cases. MRI however is potentially
useful in cases whereby suboptimal/clinically discordant imaging is noted with MG and/or US. In either instance, the same imaging modality used at baseline, should be used to follow treatment response.

Breast cancer pathologic confirmation with fine needle aspiration (FNA) was originally used as a means to diagnose palpable breast masses (78) but has been essentially replaced with the core needle biopsy (CNB) in the 1990s, because of its superior sensitivity (94-99% vs 43.8-95%) and specificity (99-100% vs 89.8-100%) when compared to FNA (79, 80) for breast cancer diagnosis. Breast cancer biomarker assessments can also be performed on CNB as opposed to FNA and as such CNB is now regarded as the diagnostic method of choice for breast cancer pathologic assessment.

The utilization of breast clips allow for improved breast cancer lesion localization, which subsequently facilitates the removal of lower volume of breast during surgery post NAT. Before the introduction of biopsy clips, biopsy site hematoma would be identified with US (81) or MG imaging (82) was used to locate lesion. These outdated techniques result in lower clear margin rates (31-62%) (83-85) when compared to patients with breast clips, where clear margins can be achieved in approximately 90% of patients (86).

Axillary Lymph Node Evaluation and Management

Evaluation and management of the axilla is an area of much debate and interest in current breast cancer research. PE alone of the axilla is notoriously inaccurate to define whether or not axillary disease is present or not (particularly in smaller lesions); with one study demonstrating an overall error rate of 41%, and a false-positive rate of 53% (36). This exceptionally high rate of error necessitates more accurate imaging and biopsy of any suspicious lesions for more accurate assessment of axillary disease involvement.

In the last decade, sentinel lymph node biopsy (SLNB) has become established as the standard for nodal staging in patients with early-stage breast cancer, with staging accuracy rates in excess of 95% particularly when using blue dye and radioactive isotopes (37). This is due primarily to the fact that several randomized trials showed that SLNB and ALND had similar disease free survival (DFS) and OS (38,39). SLNB is preferred due to less morbidity and improved quality of life when compared to ALND (40,41).

The primary controversy surrounding SLNB in the NAT setting is in regards to timing of the procedure in relation to the NAT. In patients with a clinically and radiologically negative axilla, the SLN procedure appears to be equally accurate in predicting the status of the axilla at the time of surgery whether it is performed before or after NC (42). Previously, radiation and chemotherapy options were driven by the pre-treatment axillary status and this necessitated obtaining SLN information prior to NAT. Currently, the status of the pre-treatment axilla alone does not change the choice of chemotherapy regimens for NAT. RT treatment is administered based on the status of the post-chemotherapy axilla in these patients and therefore in the clinically/radiologically negative lymph node patient, SLNB can be performed post NAT.

For patients that have radiologically or clinically positive nodes prior to treatment there is much controversy (43) over ideal surgical treatment of the axilla post-treatment. Two major trials have investigated the role of SLNB in the NAT setting – the SENTINA and the ACOSOG Z1071 trials (44,45). In the SENTINA trial, patients with clinically or radiologically positive lymph nodes underwent SLNB and ALND after NAT if they became clinically/radiologically node negative. Detection rate of SLN was only 80% and the false negative rate was 14.2%. Interestingly, 47.7% of all of these patients were
pathologically node positive. They concluded that SLNB was not a reliable tool for use in patients who converted from clinically lymph node positive to negative with NAT. In the ACOSOG Z1071 trial, 701 patients who had confirmed axillary involvement then underwent NC followed by SLNB and ALND. At least 1 SLN was detected in 92.7% of patients, but only 2 or more in 80% of patients. If only 1 SLN was identified, the false negative rate was 31%. The predefined goal of a false negative rate of <10% was only achieved if 3 or more nodes were detected and dual agent mapping was performed (blue dye and technetium).

Currently it is unclear if patients require postoperative nodal RT if they achieve a pCR in the axilla after having positive nodes pre-NC. Currently the NSABP B-51 trial (NCT01872975) is recruiting patients with T1–3, biopsy-proven node positive cancer who are undergoing NC who have negative nodes at the time of surgery. Patients are randomized to nodal radiation vs no nodal radiation. SLNB without ALND is being allowed for the trial.

As such, until more information is available, for patients that have clinically/radiologically pathologically confirmed positive LN and are undergoing NAT, SLNB alone should not be performed outside of the research setting. These patients should undergo a standard ALND post NAT at the time of definitive surgery.

Surgical Management of the Breast after Neo-adjuvant Therapy

In every surgical evaluation, an individual patient’s needs and expectations should be discussed with the surgeon including an overview of potential benefits and risks of M when compared to BCS. Effects on long-term survival, the possibility and consequence of local recurrence, the impact on cosmetic outcome, and psychosocial impact should be thoroughly discussed.

In general, if negative margins can be achieved and there is no contraindication to RT, BCS is an option for most patients. Although tumour location can affect the cosmetic result associated with BCS, it should not be a contraindication to BCS (88). Patients with dense breast tissue were more likely to undergo M than patients with less dense tissue in a phase III trial of 1052 patients, however, it remained unclear whether this was due to surgeon/patient bias or the inability to fulfill BCS criteria (89). Patients with connective tissue disease may tolerate irradiation poorly; however, retrospective data has not indicated increases in acute toxicities in this patient population (90). Tumour-to-breast ratio post-NAT is important, as a high tumour to breast ratio is a relative contraindication to BCS. Of note, although patients harboring BRCA mutations have an increased lifetime risk of developing breast cancer (in either breast) and may opt for M, the presence of a BRCA mutation should not preclude a breast-conservation approach in patients who are otherwise appropriate candidates for BCS. Data also suggest that local-regional relapse (LRR) at baseline after BCS+RT appears to be comparable for triple negative breast cancer and the HER2-positive subgroups, but is about 50% greater than luminal tumours. LRR appears to be similarly increased after M; thus, TNBC should not be a contra-indication for BCS either (46).

Absolute contraindications to BCS include: multicentric disease with two or more primary tumours in separate quadrants of the breast such that they cannot be encompassed in a single excision, diffuse malignant microcalcifications on MG, a history of prior therapeutic RT that included a portion of the affected breast, pregnancy (however BCS can be considered in the third trimester, where RT can be deferred until after pregnancy), or persistent positive margins after multiple attempts at re-excision. M is indicated for patients who are not candidates for BCS, patients who prefer M to BCS (87), and for patients who choose M for prophylactic purposes to reduce breast cancer risk.
Role of radiation therapy

Neo-adjuvant radiotherapy

Neo-adjuvant RT is not typically recommended due to the high response rate associated with NC. However, neo-adjuvant RT may be indicated in patients with locally advanced disease who do not wish to receive chemotherapy, or in patients who have relative or absolute contraindications to chemotherapy. This population includes patients with multiple co-morbidities, poor performance status, frail patients, or elderly patients. Neo-adjuvant RT may also be considered after neo-adjuvant systemic (NC or NET) therapy has failed to produce a sufficient response to allow for definitive breast surgery (i.e. salvage RT). If radiotherapy is used there does not seem to be any major contraindications to either concurrent ET in patients with hormone receptor positive disease (92), or with concurrent trastuzumab in patients with HER2-positive disease where trastuzumab was already initiated in the neo-adjuvant setting(93).

Currently, there is no role for concurrent NC and RT outside of clinical trials.
TREATMENT ALGORITHM
Management of the Axilla

Radiologic and Clinical Assessment

Needle (FNA) Biopsy Axilla if Suspicion

Lymph Node Positive

Lymph Node Negative

Neo-adjuvant Chemotherapy

ALND

SLNB

Positive

ALND or Discussion in Multidisciplinary Rounds

Negative
Breast Cancer Diagnosis to Surgery

Non-Metastatic Breast Cancer

- Inoperable or LABC
  - NAT
    - Goal: Tumor Downsize M → BCS
    - Improve BCS cosmesis

- Operable
  - Operate BCS or M
    - Adjuvant Rx as Indicated
Eligible for Chemotherapy?

Yes   No

NAC   Eligible for Endocrine Therapy?

Yes   No

NET   Neo-Adjuvant Radiotherapy
Assess Disease Response to NAT

- Response
  - Continue Planned Rx until Surgery
    - Response
      - Adjuvant Rx as Indicated
    - No Response
      - Surgery
- No Response
  - Switch Therapy
    - Amenable to Surgery
      - Yes
        - Adjuvant Rx as Indicated
      - No
        - Neo-Adjuvant Radiotherapy
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>Doxorubicin plus cyclophosphamide</td>
</tr>
<tr>
<td>AI</td>
<td>Aromatase inhibitor</td>
</tr>
<tr>
<td>ALND</td>
<td>Axillary lymph node dissection</td>
</tr>
<tr>
<td>BCS</td>
<td>Breast conserving surgery</td>
</tr>
<tr>
<td>BCT</td>
<td>Breast conserving therapy</td>
</tr>
<tr>
<td>BRCA</td>
<td>Refers to genes BRCA1 and BRCA2</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>DFS</td>
<td>Disease free survival</td>
</tr>
<tr>
<td>ER</td>
<td>Estrogen receptor</td>
</tr>
<tr>
<td>ET</td>
<td>Endocrine therapy</td>
</tr>
<tr>
<td>FEC</td>
<td>Fluorouracil epirubicin cyclophosphamide</td>
</tr>
<tr>
<td>HER2</td>
<td>Human epidermal growth factor 2</td>
</tr>
<tr>
<td>HR</td>
<td>Hormone receptor</td>
</tr>
<tr>
<td>LABC</td>
<td>Locally advanced breast cancer</td>
</tr>
<tr>
<td>LRR</td>
<td>Local recurrence rate</td>
</tr>
<tr>
<td>MG</td>
<td>Mammograph</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>M</td>
<td>Mastectomy</td>
</tr>
<tr>
<td>NC</td>
<td>Neo-adjuvant chemotherapy</td>
</tr>
<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
</tr>
<tr>
<td>NAT</td>
<td>Neo-adjuvant therapy</td>
</tr>
<tr>
<td>NSABP</td>
<td>National surgical Adjuvant Breast and Bowel Project</td>
</tr>
<tr>
<td>NET</td>
<td>Neo-adjuvant endocrine therapy</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>pCR</td>
<td>Pathological complete response</td>
</tr>
<tr>
<td>PE</td>
<td>Physical exam</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PR</td>
<td>Progesterone receptor</td>
</tr>
<tr>
<td>RT</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>SLNB</td>
<td>Sentinel lymph node biopsy</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasonograph</td>
</tr>
</tbody>
</table>

**DISSEMINATION**

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

**MAINTENANCE**

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.
CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Breast Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Breast Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.
REFERENCES


(10) Hayes DF. Targeting adjuvant chemotherapy: a good idea that needs to be proven! J Clin Oncol 2012 Apr 20;30(12):1264-1267.


(53) Hilsenbeck SG, Ravdin PM, de Moor CA, Chamness GC, Osborne CK, et al. Time-dependence of hazard ratios for prognostic factors in primary breast cancer