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Neoadjuvant therapy for breast cancer: updates and proceedings from the Seventh Annual Meeting of the Canadian Consortium for Locally Advanced Breast Cancer

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ABSTRACT

Therapy for breast cancer involves a complex interplay of three main treatment modalities: surgery, systemic therapy, and radiation therapy. The Canadian Consortium for Locally Advanced Breast Cancer (LABC) was established with the goal to convene a strong multidisciplinary team of breast oncology clinicians and scientists who are dedicated to the advancement of LABC research and treatment, with a vision to drive progress through increased collaboration across disciplines and throughout Canada. The most recent meeting in May 2017 highlighted the latest evidence and literature about the optimal use of neoadjuvant systemic therapy in breast cancer. There is a need for increased clinical and scientific collaboration and the development of guidelines for the use of emerging treatment strategies. The interactive meeting sessions fostered unique opportunities for academic debate and nurtured collaboration between the attendees.

Key Words Breast cancer, diagnosis, treatment, neoadjuvant therapy, locally advanced disease, surgery, radiation

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INTRODUCTION

Therapy for early breast cancer (BCA) involves a complex interplay of three main treatment modalities: surgery, systemic therapy, and radiation therapy. Traditionally, chemotherapy has been administered to BCA patients after surgery, followed by radiation and hormonal therapy. Mounting evidence suggests that, in addition to advances in individualized systemic BCA therapy, a shift in the traditional sequencing of treatment modalities might also improve outcomes in patients with early BCA. Neoadjuvant systemic therapy (NST), which consists usually of neoadjuvant chemotherapy (NAC) delivered before surgery, has traditionally been reserved for women with locally advanced BCA (LABC), but is as effective as adjuvant chemotherapy for earlier-stage disease. However, the optimal use of NST and other treatment modalities is unclear, highlighting the need for increased clinical and scientific collaboration and the development of guidelines for the use of emerging treatment strategies.

The Canadian Consortium for Locally Advanced Breast Cancer was established in 2010 by Dr. Muriel Brackstone, a surgical oncologist from London Health Sciences Centre, London, Ontario, and Dr. Mark Clemons, a medical oncologist currently working at The Ottawa Hospital Cancer Centre, Ottawa, Ontario[1]. The goal of the Consortium was to convene a strong multidisciplinary team of breast oncology clinicians and scientists who are dedicated to the advancement of LABC research and treatment, with a vision to drive progress through increased collaboration across disciplines and throughout Canada. The Consortium has met annually since[2,3] and consists of a group that offers diverse expertise in basic and translational research, medical oncology, radiation oncology, pathology, surgery, and radiology. Specific goals of the Consortium are the development of clinical care pathways[3], including evidence-based consensus guidelines[3], and the promotion of high-quality basic, translational, and clinical collaborative research initiatives spanning various disciplines and centres.

The 7th annual Consortium meeting was held 30 April–1 May 2017 in Toronto. The meeting was co-chaired by Dr. Justin Lee, a radiation oncologist from the Odette Cancer Centre, Toronto, Ontario; Dr. Debjani Grenier, a

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medical oncologist from CancerCare Manitoba, Winnipeg, Manitoba; and Dr. Angel Arnaout, a surgical oncologist from The Ottawa Hospital Cancer Centre, Ottawa, Ontario. The keynote speaker, Dr. Karen Gelmon, a senior scientist and medical oncologist at BC Cancer, provided a comprehensive overview of neoadjuvant therapy in BCa. Her speech was followed by presentations from leading Canadian experts in the fields of medical oncology, surgical oncology, pathology, and radiation oncology, further detailing the established evidence and controversies pertaining to each specialty. Subsequently, group sessions specifically focused on reaching a national consensus about clinical care pathways and related treatment guidelines and about the organization of inter- and intra-institutional infrastructure to facilitate clinical and correlative research. The interactive meeting sessions fostered unique opportunities for academic debate and nurtured collaboration between the attendees, resulting in a concrete set of initiatives to further the goals of the Consortium. This meeting report also includes highlights from each presentation at the conference.

KEYNOTE SESSION: OVERVIEW OF NEOADJUVANT SYSTEMIC THERAPY IN BREAST CANCER

Dr. Karen Gelmon, BC Cancer, Vancouver, BC

Randomized clinical trials have found no significant differences in long-term outcomes when systemic chemotherapy is given before or after surgery[4], with the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 study being the most notable of those trials. Historically, the advantage of administering NAC has been surgical; however, a pathologic complete response (pCR) to NAC, defined as ypT0/is ypN0, is associated with favourable long-term clinical outcomes in early-stage BCa[5]. The correlation between pCR and favourable outcomes is strongest for patients with triple-negative BCa (TNBC), less so for those with HER2-positive (HER2+) disease, and least for those with hormone receptor–positive BCa. In women with HER2+ BCa, the incorporation of trastuzumab into NST results in a higher rate of pCR and better survival, as demonstrated in the NOAH trial[5,6]. However, despite the significant antitumour activity of trastuzumab combined with cytotoxic chemotherapy, resistance remains an issue, and further therapeutic options are needed. The Neo-ALTTO and NSABP B-41 clinical trials have assessed trastuzumab–lapatinib, and NeoSphere and TRYPHAENA have studied trastuzumab–pertuzumab[7]. Important findings in those trials demonstrate that dual HER2 blockade results in higher rates of pCR and can be can be safely combined with cytotoxic chemotherapy, with the therapeutic benefit seen primarily in patients with hormone receptor–negative tumours.

In TNBC, standard neoadjuvant therapy with an anthracycline and a taxane achieves pCR rates (breast and axilla) greater than 30%[8]. To improve outcomes in patients with TNBC, several approaches for increasing the efficacy of NAC have been pursued[9]. The NSABP B-40 trial demonstrated that adding capecitabine or gemcitabine to an anthracycline–taxane sequence did not improve the pCR rate[8]. The addition of a platinum to an anthracycline–taxane backbone improved pCR rates for patients with TNBC in the GeparSixto and Cancer and Leukemia Group B 40603 studies, as well as in other smaller trials[9]. However, it remains unclear whether that strategy is associated with a survival advantage. Even though pCR rates with carboplatin were highest in *BRCA* mutation carriers, the additional benefit from carboplatin was most noted in *BRCA* wild-type patients. Thus, the neoadjuvant data in TNBC so far do not support offering carboplatin only to *BRCA* mutation carriers.

Patients who undergo NAC and have residual disease upon its completion represent a high-risk population after standard treatment options; they are suitable candidates for the assessment of investigational therapeutic strategies. Clinical trials such as the KATHERINE study (NCT01772472 at http://ClinicalTrials.gov/) for HER2+ residual disease and the PENELOPE study (NSABP B-54-I), which is using the cyclin-dependent kinase 4/6 inhibitor palbociclib for residual estrogen receptor–positive (ER+) disease, are ongoing.

For postmenopausal women with a clinical stage II/III hormone receptor–positive BCa, neoadjuvant endocrine therapy (NETX) is an underutilized and low-toxicity potential alternative to chemotherapy for increasing breast conservation rates[10]. Individual responses to endocrine therapy can also be used to tailor systemic treatment[11]. During NETX, a change in the Ki-67 index can be a surrogate marker for treatment efficacy. In addition, the preoperative endocrine prognostic index was developed to identify patients at low risk of relapse after NETX such that adjuvant chemotherapy can be safely avoided[10]. For patients with an index of 0, the relapse risk over 5 years is extremely low without chemotherapy, such that continuing with endocrine therapy alone could be justifiable. In addition, several ongoing trials are investigating the combination of endocrine therapy and other targeted therapies. Using that approach, a parallel blockade of intracellular pathways and reversal of endocrine resistance could be achieved. The phosphatidylinositol 3-kinase/mechanistic target of rapamycin pathway, cyclin-dependent kinase 4/6, histone deacetylase, and immune checkpoints are promising and widely investigated targets[8,11].

Finally, NST serves as an excellent research platform to test novel therapies and predictive biomarkers by providing tumour specimens and blood samples before and during systemic treatment[12]. In addition, window-of-opportunity trials represent an innovative study design in which patients receive an investigational compound for a short period of time before surgery. Those studies can assess the biologic effects of investigational compounds by either molecular analysis or functional imaging of tumours. With the rapidly expanding arsenal of experimental targeted agents in BCa, new trial designs are needed to expedite the successful clinical development of those agents.

SURGICAL MANAGEMENT OF PATIENTS UNDERGOING NEOADJUVANT SYSTEMIC THERAPY

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From the surgeon's perspective, the primary goal of NST is tumour or nodal downstaging to increase tumour

resectability and decrease surgical morbidity[13–15]. Neoadjuvant systemic therapy can also be administered to increase the resectability of LABC and inflammatory BCa (stage III); to increase the feasibility of breast-conserving surgery (BCS) in mastectomy candidates with stage II and III disease with no significant increase in local recurrence rates[15]; to improve cosmesis for BCS candidates; to decrease the morbidity and extent of axillary surgery in bulky node-positive disease; and to increase the feasibility of sentinel lymph node biopsy (SLNB) in formerly node-positive disease. However, surgeons must carefully consider the extent of disease and the likelihood of adequate tumour response before recommending NST to improve the likelihood of a successfully downstaged surgery. Multidisciplinary care should be initiated as soon as possible, including referral to radiation oncology in connection with breast-conserving therapy or post-mastectomy radiotherapy (PMRT); to genetic counselling and testing, if indicated; and to early plastic surgery consultation if breast reconstruction is a consideration. It is important to clarify upfront not only the goals but also the expectations of NAC as it relates to post-NAC surgical decision-making so that the patient and the treating team are all on the same page.

Diagnostic Assessment of Extent of Disease in Breast and Axilla Before, During, and After Neoadjuvant Systemic Therapy

Important steps are required from the time of diagnosis until the time of surgical resection to ensure successful locoregional therapy outcomes in patients treated with NAC. Those steps include accurate assessment of the location and extent of the primary breast tumour and determination of the axillary nodal status before and after NAC—information that is critical for the successful execution of the surgical plan and optimization of the use of adjuvant radiotherapy after NAC[14]. Physical examination, mammography, and breast ultrasonography can help to delineate the size and configuration of the primary breast tumour. Mammography in particular can delineate the extent of any malignant microcalcifications whose presence might indicate an extensive intraductal component[15].

Tumour response during NST and the likelihood of pCR in BCa is strongly influenced by tumour biology and subtype[16]. After NST, reliable information that optimally reflects the extent of residual disease in the breast or axilla is crucial for an optimal surgery. Magnetic resonance imaging (MRI) can also contribute important information about the extent and configuration of primary breast tumours and their response to NAC[15]. By identifying patterns of tumour growth and response (concentric or dendritic), MRI can help to select appropriate candidates for BCS after NAC. However, the high sensitivity but generally lower specificity of MRI requires that histologic confirmation of MRI abnormalities be obtained before a decision to proceed with mastectomy.

Before NAC, careful consideration should be given to the exact identification of the original tumour location so that, if a complete clinical and radiologic response is achieved, the tumour bed can be targeted for resection. A radiopaque marker also allows the pathologist to scrutinize that particular area for residual tumour[15].

In the setting of NAC, a lack of knowledge at presentation of the pathologic axillary nodal status is often of concern[14,16]. Ultrasound-guided core-needle or fine-needle aspiration of a suspicious ipsilateral axillary node should be performed to document node-positive disease. Insertion of a tissue marker (for example, a radiopaque clip, ultrasound-visible clip, tattoo ink) into any percutaneously sampled axillary node will facilitate sentinel node identification if SLNB is a consideration after NAC.

Decision for Surgery

Patients undergoing NAC are usually evaluated at regular intervals by the treating medical or surgical oncologist (or both) according to standard cycle monitoring practices. Progression of disease on NAC has been reported in 4.3% of patients[14], and early surgical intervention could be considered in those patients.

In general, to allow the patient's immune system to recover, surgery is performed 3–6 weeks after NAC. The final recommendation for surgery depends on the extent of disease at presentation, patient choice, clinical response to NAC, the need for postoperative radiotherapy, and the results of genetic testing, if performed. A modified radical mastectomy remains the standard of care for inflammatory BCa regardless of the response to NAC. Patients who experience a clinical complete response still require breast and axillary surgery to exclude microscopic residual disease[14–16].

After NAC, a SLNB might be performed in women with clinically or needle-biopsy-negative axillary nodes at baseline[14,15,17]. In such patients, sentinel node identification and false-negative rates are comparable to those for SLNB performed in the adjuvant setting.

For patients with 1 or more biopsy-proven positive nodes at baseline, evidence suggests that NAC downstages the involved nodes in a considerable proportion of patients (up to 30% for anthracycline-containing regimens, up to 40% for anthracycline–taxane-containing regimens, and even greater when HER2-positive BCa is treated with NAC plus anti-HER2 therapy)[14,15,17]. Several clinical trials have evaluated the feasibility of SLNB after NST in patients with T1–3N1–3 disease at baseline[16]. The American College of Surgeons Oncology Group (ACOSOG) Z0171 single-arm multicentre trial enrolled almost 700 patients (T0–4N1–2M0) who underwent a SLNB and axillary node dissection after NAC[17]. The primary endpoint of the study was the false-negative rate (FNR) for clinically node-positive patients who had at least 2 sentinel nodes excised. The authors predefined an acceptable FNR as 10% or less. The sentinel node identification rate was 92.5%. When 2 sentinel nodes were excised, the FNR was 19.6%, which declined to 8.3% when 3 sentinel nodes were excised. In patients who received the dual tracer, the FNR was 10.8%. In addition, clip placement at diagnosis of node-positive disease, with removal of the clipped node during sentinel node surgery, lowered the FNR even further, to 6.8%[17]. The authors concluded that, in patients who convert to clinically node-negative after NAC, the SLNB will be more accurate if more than 2 sentinel nodes are removed, if the dual-dye technique is used, and if resection is guided by clip placement of the originally biopsy-proven positive node. A specimen radiograph of the resected nodes could then be obtained to document removal of the clipped node.

The Canadian SN FNAC study was carried out by many of the investigators at the LABC Consortium meeting several years ago[18]. It evaluated the feasibility and accuracy of SLNB after NAC in 153 patients with cytologically proven node-positive BCa. The sentinel node identification rate was 87.6%, and the overall FNR was 9.6%. When ypN0(i+) was considered to be a positive node, the FNR was 8.4%. As in the other studies, the FNR dropped to 4.9% when 2 or more sentinel nodes were removed. The SN FNAC study concluded that any size of metastasis in the sentinel node after NAC matters, and that the accuracy of the SLNB after NAC could be improved with the use of immunohistochemistry. That approach differs from the approach used in the adjuvant setting, in which immunohistochemistry staining of histologically negative sentinel nodes should not be considered the standard (as supported by the ACOSOG Z0010 trial)[19].

The third study, SENTINA[19], was a 4-arm prospective multicentre study for all women scheduled for NAC. Patients with clinically node-negative disease underwent SLNB before NAC (arm A). If the sentinel node was positive (pN1), a second SLNB was performed after NAC (arm B). Women with clinically node-positive disease upfront received NAC. Within the latter group, patients who converted to clinically node-negative disease after chemotherapy [ycN0 (arm C)] were treated with SLNB and axillary lymph node dissection (ALND). Only patients whose clinical nodal status remained positive (ycN1) underwent ALND without SLNB (arm D). The SLNB identification rates were 99.1% in arms A and B, 80.1% in arm C, and 60.8% for the repeat SLNB in arm B. The FNR in the repeat SLNB was 50%. The FNR in arm C depended on number of sentinel nodes excised: 24.3% for removal of 1 node, 18.5% for 2 nodes, and less than 10% for 3 or more nodes (similar to the data reported from ACOSOG Z0171). The authors found that the FNR was lower when dual tracer rather than radiocolloid only was used (8.6% vs. 16%). Because of the high FNR of the repeat SLNB, the authors recommended against the use of the repeat SLNB in the neoadjuvant setting.

In the SENTINA trial, patients had to be clinically node-negative after NAC to be included in the SLNB arm; in the ACOSOG Z0171 trial, all patients underwent a SLNB and ALND after NAC. Another important aspect that differentiates these two trials is that pathology confirmation of lymph node involvement before NAC was not mandatory in the SENTINA trial, and the definition of node-positive disease was based mainly on ultrasound appearance. Figure 1 summarizes the above-mentioned trials.

For patients with a large burden of disease before NAC, or for those who harbour residual disease in the axilla after a SLNB after NAC, the standard management of the axilla remains an ALND. However, that approach is an area of evolving research: two new trials have opened in Canada to investigate the role of SLNB and regional lymph node radiation in patients with upfront node-positive disease who are rendered clinically node-negative after NAC[15,16,20,21]. The NSABP B-51/Radiation Therapy Oncology Group 1304 trial and the Alliance A11202 trial are currently evaluating the role of regional nodal radiation after NAC (as an alternative to ALND) in SLNB-negative and SLNB-positive patients treated with BCS and mastectomy. Those trials are outlined in the section describing the radiotherapy session (next).

	ACOSOG	SENTINA	SN FNAC
N	649	592	153
ID	92.7%	80.1%	87.6%
Nodal PCR	41%	52%	25%
FNR%	12.6%	14.2%	8.4%
Single Tracer	15%	27%	16%
Dual Tracer	8.6%	12%	5.2%
1 SN	31.5%	24.3%	18.2%
2 SN	21.1%	18.5%	9.5%
3 SN	9.1%	7.3%	2.5%
Clipping node	6.8%		

FIGURE 1 Summary of clinical trials addressing axillary management, before neoadjuvant chemotherapy, of patients with upfront clinically positive axillary nodes. ACOSOG = American College of Surgeons Oncology Group[17]; SENTINA = sentinel lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy[19]; SN FNAC = sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer[18]; ID = node identification rate; PCR = pathologic complete response; FNR = false-negative rate; SN = sentinel node.

RADIATION THERAPY IN PATIENTS UNDERGOING NEOADJUVANT SYSTEMIC THERAPY

Dr. Mohamed Akra, CancerCare Manitoba, Winnipeg, MB

One of the most challenging problems facing BCa radiation oncologists today is deciding which BCa patients treated with NAC followed by mastectomy will benefit from post-mastectomy radiation therapy, particularly those who achieve a PCR[21]. That topic was the focus of a small-group discussion led by Dr. Justin Lee, radiation oncologist from the Odette Cancer Centre, about whether an adaptive radiotherapy approach is required based on response to neoadjuvant therapy.

The controversy about which BCa patients benefit from PMRT after NAC extends to women with clinically node-positive axillary disease that responds well and is downstaged to pathologically negative at surgery (ypN0). Dr. Mohamed Akra outlined the radiation oncology management on this topic. In general, the need for regional nodal radiation is controversial and has been guided primarily by the status of the axillary nodes before initiation of NAC, regardless of clinical response. Axillary radiotherapy should be considered if the patient is sentinel node–positive and has not experienced axillary clearance[14,15,20,22]. The question of whether completion ALND can be omitted in favour of axillary radiotherapy in patients with positive sentinel nodes after NAC is being addressed in the ongoing phase III A011202 trial conducted by the Alliance for Clinical Trials in Oncology (Figure 2). The trial is enrolling patients with 1 or more positive sentinel lymph nodes after NAC and is comparing the standard of ALND plus regional lymph node radiation (excluding the dissected axilla) to SLNB without a dissection plus regional lymph node radiation. A second randomized trial is the NSABP B-51/Radiation Therapy

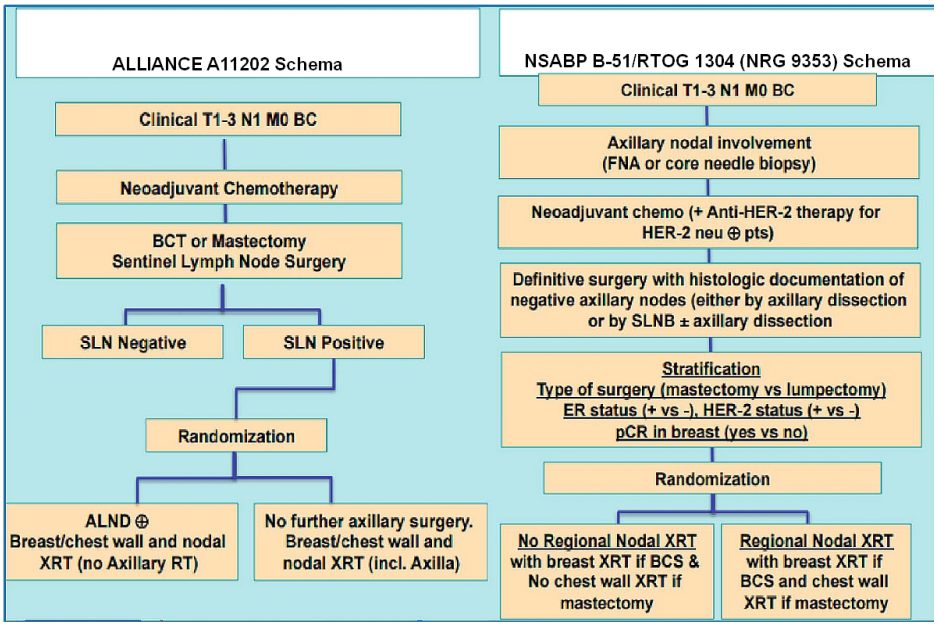

FIGURE 2 Schema of two currently open trials in Canada for the management of axillary nodes following sentinel node biopsy after neoadjuvant chemotherapy. NSABP = National Surgical Adjuvant Breast and Bowel Project; RTOG = Radiation Therapy Oncology Group; BC = breast cancer; FNA = fine-needle aspiration; BCT = breast-conserving therapy; HER2 = human epidermal growth factor receptor 2; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; ER = estrogen receptor; pCR = pathologic complete response; ALND = axillary lymph node dissection; XRT = external-beam radiotherapy; RT = radiation therapy; BCS = breast-conserving surgery.

Oncology Group 1304 study, which is evaluating patients with 1 or more positive axillary lymph nodes that are converted to histologically negative after NAC as documented by SLNB or ALND. The patients are then being randomized to PMRT with regional nodal irradiation (RNI) or no radiation, and in those who have undergone BCS, breast irradiation with or without RNI[14,15]. The study will help to determine which patients can safely omit PMRT or RNI (or both) in the setting of nodal PCR. It is clear that, in the absence of definitive data, achieving a balance between the potential risks of overtreatment and the risks of undertreatment (for example, increased rates of locoregional recurrence and decreased survival) is not straightforward. Outside of a clinical trial, current recommendations are to consider PMRT and RNI, and breast radiotherapy with or without a boost and RNI, in patients with positive nodes after chemotherapy. Decisions are made on an individualized basis for patients who were node-positive before chemotherapy and who were rendered node-negative and are also not enrolled in the clinical trial. The above-mentioned trials are currently open in Ottawa, London, Montreal, Toronto, Winnipeg, and Quebec City.

PATHOLOGY ASSESSMENT IN PATIENTS RECEIVING NEOADJUVANT CHEMOTHERAPY

Dr. Fang-I Lu, Sunnybrook Health Sciences Centre, Toronto, ON

The opportunity to learn about tumour response to chemotherapy *in vivo* provides meaningful prognostic information for individual patients. Multidisciplinary interaction is therefore essential in the neoadjuvant setting. A careful, systematic pathology evaluation of the post-NAC specimen in the context of clinical and imaging findings is required for accurate diagnosis[23–25]. At a minimum, the pathologist should be informed that the surgical sample was obtained after NST and should have information about the pretreatment tumour location, size, and focality readily available. Clearly labelling the surgical specimen as a post-neoadjuvant specimen is very helpful. Clip placement at the time of the diagnostic biopsy of the breast tumour and axillary lymph nodes is strongly recommended. In patients with an excellent tumour response, ensuring that the correct area in the breast or the correct axillary lymph nodes were excised could be difficult if no clip were placed[23,24]. When dealing with post-NAC specimens, the selection of representative sections is crucial. For small specimens, the tumour bed should be submitted *in toto*. When the specimen is large (for example, a large lumpectomy or mastectomy), at least 1 tissue block should be submitted per 1 cm of the largest cross-section of the tumour bed. Radiologic, photographic, or pictorial imaging of the sliced specimen is recommended to map the tissue sections and to reconcile macroscopic and microscopic findings.

Post-NAC changes are complex, and several different classification systems for post-NAC specimens are available[23–25]. Although those systems collectively have advantages and disadvantages, the most commonly cited method for quantifying residual disease that is simple to apply, reproducible, and clinically validated to have long-term correlation with outcomes (overall survival, event-free survival, and distant relapse-free survival) is the residual cancer burden (RCB)[24,25]. This online tool standardizes the sampling of specimens and interprets the average invasive

cancer cellularity by area for the entire residual tumour bed. The residual tumour bed area is initially determined from the macroscopic evaluation combined with any specimen radiography and is then revised after the corresponding tissue sections from that area have been studied under the microscope. The RCB score incorporates gross and microscopic findings in the breast tumour bed and regional lymph nodes. It is calculated from the two-dimensional size of the largest residual tumour bed, the proportion of that residual tumour bed that is invasive cancer, the number of positive lymph nodes, and the diameter of the largest metastasis. The formula to calculate RCB combines those variables with adjustment and weighting factors to balance the contributions from various variables and to normalize the distribution of the RCB. The continuous RCB score is divided into 4 classes (0, I, II, and III). An RCB score of 0 corresponds to PCR. The RCB score is prognostic beyond 10 years overall and in phenotypic subgroups.

Reassessment of hormone receptor and HER2 status in residual cancer after NST varies with the individual centre, with no consensus about if and when retesting of markers is advisable. The clinical utility of reassessing marker status in the surgical specimen can depend on the results from the core biopsies taken before NST. Generally, retesting is performed if the hormone receptor or HER2 status was deemed negative or equivocal on the pre-treatment biopsy, because a positive result for the post-NAC specimen could change clinical management. If retesting is performed, it could use either the residual primary tumour or residual nodal disease (if the latter specimen contains a better representation of residual tumour cells)[23–25].

SMALL-GROUP DISCUSSIONS

Adaptive Radiotherapy After Incomplete Response to Neoadjuvant Chemotherapy

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When surgery is the first line of BCA treatment, numerous randomized clinical trials and meta-analyses have demonstrated that PMRT improves locoregional control and survival for many women with axillary lymph node–positive disease[20]. For patients who undergo BCS after neoadjuvant therapy, whole-breast external-beam radiation remains the standard of care whether a PCR is achieved or not, as is the case for patients who undergo upfront surgery. The data are insufficient to support the use of partial breast irradiation or hypofractionated radiation after NAC[21].

The use of NAC before mastectomy has created substantial controversy with respect to identifying the subgroups of women who would benefit from PMRT. Unlike the data for PMRT when mastectomy is performed in the upfront setting (for which numerous randomized trials and meta-analyses are available to guide decision-making), the current literature on PMRT after NAC is limited. For patients who undergo mastectomy, the roles of PMRT and RNI are more controversial, particularly for patients who achieve a PCR[21]. Another complicating matter is that women who receive NAC today represent a heterogeneous group ranging from locally advanced and even inoperable disease to operable early-stage disease. In the absence of clear guidelines, concerns have been raised about whether to base radiotherapy decisions on the tumour parameters before or after NAC. In addition, there is concern that the patient might have had a heavier lymph node burden at baseline, despite the downstaging achieved with NAC. In general, PMRT is associated with a reduction in locoregional recurrence and improvement in disease-free and overall survival for stages IIB–III disease. The recent meta-analysis of post-mastectomy patients from the Early Breast Cancer Trialists' Collaborative Group showed that chest-wall radiotherapy reduces the rates of both recurrence and mortality for node-positive patients, even after adjuvant systemic chemotherapy[20], suggesting that chest wall radiotherapy is appropriate in post-NAC patients who remain node-positive. For patients who achieve a PCR in the breast and nodes after NAC, the results from the NSABP B-18 and B-27 studies show very low rates (<10%) of locoregional recurrence after mastectomy in the absence of radiotherapy[20,22], suggesting that radiotherapy might be able to be omitted in some groups of patients. Conversely, a recent meta-analysis of patients treated in German Gepar trials found that, among patients who achieved PCR, the use of PMRT was an independent prognostic factor for local locoregional relapse-free survival[20].

In practice, most radiation oncologists continue to adopt a conservative approach, basing indications for radiotherapy on the maximum or worst stage from the pre- and post-treatment pathologic stage and tumour characteristics. Biopsy-proven nodal disease at presentation is typically considered to be an indication for PMRT, and patients who achieve PCR should ideally be offered participation in clinical trials. Current indications for PMRT include inflammatory BCA, positive surgical margins, residual positive nodes after NST, and T3 or T4 disease at baseline.

The discussion also addressed the use of clinical target contouring compared with standard anatomic borders. Practices and opinions about whether target contouring should be part of routine practice vary among Canadian radiation oncology sites. The use of post-mastectomy boost was discussed as a potential means of dose escalation in very high-risk scenarios (extensive residual disease after NAC, chemotherapy-refractory TNBC, inflammatory BCA). It was agreed that, although the evidence to recommend routine use of PMRT boost is insufficient, that approach could be considered on an individual basis.

Optimal Neoadjuvant Systemic Therapy for Triple-Negative Breast Cancer

Dr. Jean-Francois Boileau, Segal Cancer Centre, Montreal, QC, and Dr. Debjani Grenier, CancerCare Manitoba, Winnipeg, MB

To improve outcomes for patients with TNBC, several NAC approaches have been pursued. The preferred chemotherapy in this subgroup is a sequential regimen of an anthracycline combination followed by a taxane, although reversing the sequence achieves comparable response rates (Neo-tAnGo and SWOG 0800). The sequence of those agents has, in practice, varied across Canada, with BC Cancer reporting more frequent use of upfront taxanes. The group was undecided about the routine use of dose-dense chemotherapy,

although it is the standard in the United States. The group recognized the potential benefit of adding a platinum agent associated with an increased pCR rate in the TNBC group and also with a potential benefit for women without a germline *BRCA* mutation, as demonstrated in GeparSixto (which also demonstrated improved disease-free survival) and Cancer and Leukemia Group B trials (which did not demonstrate improved survival and used a standard chemotherapy backbone). However, the addition of carboplatin is associated with more toxicities. Funding can also be an issue. Cancer Care Ontario does not currently fund carboplatin if a taxane is used in the neoadjuvant setting, but Alberta and Quebec do fund the drug for that indication. In summary, no consensus was reached in terms of the routine use of a platinum agent in women with TNBC. More long-term follow-up from the relevant trials is required.

Neoadjuvant Endocrine Therapy

Dr. Katia Tonkin, Cross Cancer Institute, Edmonton, AB, and Dr. Debjani Grenier, CancerCare Manitoba, Winnipeg, MB

Historically, NETX has been selected in postmenopausal women who have large ER+ tumours and whose frailty or significant commodities make upfront surgery less desirable. This patient population is often older (mean age: 70 years) than that in other BCA trials, which might account for the limited long-term follow-up. More recently, the use of NETX has diversified beyond frail patients to a more general ER+ BCA population. Patients with strongly ER+, HER2-negative disease might not benefit as much from upfront chemotherapy: lower pCR rates limit the value of pCR as a surrogate endpoint for the effectiveness of systemic treatment in this population. Thus, NETX is a reasonable option, particularly in postmenopausal women with high levels of ER expression[10,11,26].

Large randomized trials comparing NETX with NAC are few. The NEOCENT trial (NAC vs. endocrine therapy) was a randomized phase III study designed to compare NAC (FEC100: epirubicin–5-fluorouracil–cyclophosphamide) with NETX (letrozole) in postmenopausal women with strongly hormone receptor–positive primary BCA. Unfortunately, the trial was prematurely closed because of slow accrual. In a smaller randomized study of luminal breast tumours, NAC (4 cycles) was compared with 6 months of NETX (exemestane and goserelin for premenopausal patients), resulting in clinical tumour response rates of 66% and 48% respectively ($p = 0.075$)[11].

In addition, few data on NETX in premenopausal women are available. Premenopausal patients have largely been excluded from NETX trials, predominantly because of an expectation that younger woman with large cancers require chemotherapy. The largest premenopausal study of NETX, STAGE, randomized 204 woman with ER+ operable BCA to 24 weeks of goserelin plus either anastrozole or tamoxifen[10,11]. The primary endpoint of best overall tumour response was analyzed for noninferiority. In the anastrozole arm, 70.4% of the patients had a complete or partial response; only 50.5% of those in the tamoxifen arm responded, the difference being statistically significant [95% confidence interval (CI): 6.5 to 33.3; $p = 0.004$].

In advance of surgery, NETX can downstage breast tumours, converting an otherwise inoperable patient into an operable one or enabling BCS[10–12,26,27]. Downstaging rates vary, but up to 45%–50% of patients who would require an upfront mastectomy can be converted to BCS after NETX[27]. A recent meta-analysis demonstrated that aromatase inhibitors are superior to tamoxifen when used as NETX, with improved clinical objective tumour response (response rate: 1.29; 95% CI: 1.14 to 1.47; $p < 0.001$), ultrasound response (response rate: 1.29; 95% CI: 1.10 to 1.51; $p = 0.002$), and BCS rate (response rate: 1.36; 95% CI: 1.16 to 1.59; $p < 0.001$)[11,27]. Notably, the duration of NETX was usually 3–4 months in most clinical trials—for example, P024, IMPACT, and PROACT[11]. However, evidence from other studies suggests that a 3- to 4-month duration of NETX is insufficient to achieve maximum reduction in tumour volume[27]. Emerging literature suggests that maximal tumour response might well be reached beyond the 4-month duration, and that 6–7 months of exposure to endocrine therapy will likely maximize tumour shrinkage.

Because a pCR after NETX is rare, that variable has not been routinely used as a predictor of long-term survival. Immunohistochemical assessment of the Ki-67 index in core biopsies of tumour taken before, during, and at the end of NETX might be a more clinically useful and valid surrogate for outcome in patients with ER+ BCA. The Ki-67 index measures the proportion of cells proliferating in a tumour and could be a marker of treatment benefit and long-term outcome[10–12], although its routine use in clinical practice has not yet been formally recommended because of a lack of standardization in its assessment and cut-off values. The Ki-67 index was used as the primary biomarker endpoint in the IMPACT trial[11]. The on-treatment Ki-67 index, even after only 2 weeks of presurgical therapy, is a more accurate marker of long-term prognosis than the baseline Ki-67 index. In the IMPACT trial, a higher Ki-67 index after 2 weeks of endocrine therapy (that is, on treatment) was significantly associated with lower recurrence-free survival ($p = 0.004$); a higher baseline Ki-67 index was not[11]. Ellis[10] similarly found a significant association between relapse-free survival and the post-treatment Ki-67 index, but not the pre-treatment Ki-67 index (hazard ratio: 1.4; $p < 0.001$). Given the prognostic significance of early changes in the Ki-67 index, the number of short-course preoperative "window of opportunity" endocrine studies has grown rapidly. The largest of them is the POETIC trial, in which more than 4000 postmenopausal patients with ER+ BCA were randomized to a nonsteroidal aromatase inhibitor or to no treatment for 2 weeks before and after surgery. The results of POETIC were presented at the 2017 San Antonio Breast Cancer Symposium and suggested a similar prognostic function for the Ki-67 index[11].

NEW AND PROPOSED CLINICAL TRIALS FOR PATIENTS UNDERGOING NEOADJUVANT THERAPY IN CANADA

Dr. Mark Basik of the Sir Mortimer B. Davis Jewish General Hospital proposed a trial in which patients with a clinical complete response confirmed by imaging and a biopsy demonstrating no residual disease after NAC would be randomized to radiation with or without preceding surgery.

Drs. Muriel Brackstone and Francesco Perera of the London Health Sciences Centre both discussed clinical trials focused on preoperative radiation, either concurrently or after NAC. Specifically, Brackstone discussed harnessing the immunomodulatory effects of preoperative radiation for high-risk nonmetastatic TNBC. Dr. Mark Clemons of The Ottawa Hospital discussed the success of the REACT (Rethinking Clinical Trials) platform as a model for designing and implementing pragmatic clinical trials to answer clinical care questions that demonstrate equipoise. Drs. William Tran and Maureen Trudeau of the Odette Cancer Centre both proposed potential methods of predicting early response, PCR, and long-term outcomes in patients undergoing NAC. Tran discussed using high-tech imaging features such as those in Snapchat (Snap Inc., Venice, CA, U.S.A.), and Trudeau proposed a trial using the RNA disruption assay.

This multidisciplinary group were quite interested in pursuing a NETX-compared-with-chemotherapy trial in Canada, specifically in women with locally advanced, but low-risk ER+ BCA (luminal A). Key methodology questions such as the potential stratification of the ER+ BCAs into different molecular subtypes before treatment [using genomic tests such as Oncotype DX (Genomic Health, Redwood City, CA, U.S.A.) or the PAM50 (NanoString Technologies, Seattle, WA, U.S.A.)], the duration of NETX (4 vs. 6 months), and the potential additional use of a cyclin-dependent kinase 4/6 inhibitor in addition to NETX were discussed.

Interested individuals thus had opportunities to work together to develop a clinical trial protocol that would be eligible for future external funding applications and feasible within the current Canadian oncology practice environment.

SUMMARY

The 2017 Canadian Consortium for LABC meeting highlighted the latest evidence and literature on the use of NST in BCA. Increased clinical and scientific collaboration and the development of guidelines for the use of emerging treatment strategies are need. The interactive meeting sessions fostered unique opportunities for academic debate and nurtured collaboration between the attendees.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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