



A Canadian national expert consensus on neoadjuvant therapy for breast cancer: linking practice to evidence and beyond

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ABSTRACT

Background

Use of the neoadjuvant approach to treat breast cancer patients has increased since the early 2000s, but the overall pathway of care for such patients can be highly variable. The aim of our project was to establish a multidisciplinary consensus among clinicians with expertise in neoadjuvant therapy (NAT) for breast cancer and to determine if that consensus reflects published methods used in randomized controlled trials (RCTs) in this area.

Methods

A modified Delphi protocol, which used iterative surveys administered to 85 experts across Canada, was established to obtain expert consensus concerning all aspects of the care pathway for patients undergoing NAT for breast cancer. All RCTs published between January 1, 1967, and December 1, 2012, were systematically reviewed. Data extracted from the RCTs were analyzed to determine if the methods used matched the expert consensus for specific areas of NAT management. A scoring system determined the strength of the agreement between the literature and the expert consensus.

Results

Consensus was achieved for all areas of the pathway of care for patients undergoing NAT for breast cancer, with the exception of the role of magnetic resonance imaging in the pre-treatment or preoperative setting. The levels of agreement between the consensus statements and the published RCTs varied, primarily because specific aspects of the pathway of care were not well described in the reviewed literature.

Conclusions

A true consensus of expert opinion concerning the pathway of care appropriate for patients receiving NAT for breast cancer has been achieved. A review of the literature illuminated gaps in the evidence about some elements of NAT management. Where evidence is available, agreement with expert opinion is strong overall. Our study is unique in its approach to establishing consensus among medical experts in this field and has established a pathway of care that can be applied in practice for patients receiving NAT.

KEY WORDS

Breast cancer, locally advanced breast cancer, neoadjuvant chemotherapy, neoadjuvant endocrine therapy, consensus, pathway of care

1. INTRODUCTION

Adjuvant therapy for breast cancer has improved breast cancer outcomes in operable disease¹, but in recent years, the use of preoperative [“neoadjuvant therapy” (NAT)] in breast cancer patients has been increasing. Long considered a standard treatment option for inoperable locally advanced breast cancer (LABC), NAT has been used in several clinical trials for earlier-stage operable breast cancers^{2–41}. In fact, some clinical practice guidelines now suggest that NAT should be considered for any patient who would be a candidate for adjuvant systemic therapy⁴². Although some trial data demonstrate that NAT is at least equivalent to adjuvant therapy in terms of breast cancer outcomes⁴¹, the evidence across the entire spectrum of neoadjuvant treatment contains gaps. Those gaps range from the criteria for selecting patients for NAT and the optimal pre-treatment work-up, to defining ideal patient outcomes such

as pathologic complete response (pCR). Indeed, the full care pathway for patients treated with NAT is generally not captured in individual clinical trials or clinical practice guidelines, and that pathway is an important consideration, given the complex needs of those patients, who usually require comprehensive management and multidisciplinary collaboration.

Evidence-based guidelines are important tools for knowledge dissemination and establishment of best practice⁴³. However, when the evidence contains gaps, expert consensus is an important avenue by which practice can be informed, and consensus statements can supplement evidence and practice guidelines. The methods used to create many consensus statements are unfortunately not always well described. Consensus meetings held with groups of medical experts develop recommendations that often rely on agreement by attendees with certain statements or principles. It is well established that true consensus can sometimes be difficult to achieve in such meetings, because the opinions of individuals can influence or bias the decisions of the group—a challenge that has been clearly documented in the business literature⁴⁴. In the 1950s, the Delphi consensus methodology was developed as a means of overcoming such obstacles^{44,45}. Several specific methods for the Delphi model have been studied and published, and they vary based on the area of study⁴⁵. The overall process involves asking a question, sharing the majority answer with the respondents, and then continually re-asking the question until a predefined level of consensus is achieved. Using that approach, respondents who have strong opinions will likely leave their answers unchanged, but those who have less established beliefs on a particular topic might alter their answers to align with the majority opinion.

The Canadian neoadjuvant breast cancer national consensus group was developed with a goal for multidisciplinary experts in the neoadjuvant therapy of breast cancer (both LABC and earlier-stage disease) to meet annually, review data, and discuss best practices. Over the course of several meetings, the earlier-mentioned gaps in the evidence concerning important facets of neoadjuvant management of breast cancer were identified. The rationale for the present study was to establish statements addressing evidence gaps or controversy in the NAT care spectrum and to use a true expert consensus process to reach agreement for those statements. In addition, the literature was reviewed to determine whether the statements relating to the care pathway aligned with the methods or care pathways used in randomized controlled trials (RCTs) of NAT. The ultimate output is a true consensus statement with clear links to the evidence, where available. This consensus statement can be used to create a comprehensive approach to NAT in breast cancer, including areas that are controversial or lacking in evidence.

The intended users of this consensus statement are clinicians who treat breast cancer, particularly with NAT. The statement is probably most applicable to higher-resource health care settings. The stakeholders involved in the expert consensus panel included medical, radiation, and surgical oncologists; pathologists; and radiologists.

2. METHODS

2.1 Defining the Consensus Statements

Four main areas of controversy were identified in the overall spectrum of clinical care for breast cancer patients offered NAT:

- Definition of the most appropriate candidates
- Types of investigations to conduct before starting NAT
- Ways to monitor NAT
- Type and timing of therapies

A small group further explored these controversial areas. A set of survey questions developed in each of the areas was pilot-tested for face and content validity with a sample of 6 clinicians. The project received no external funding, and it depended on the voluntary participation of all co-investigators. Survey participants were not remunerated for participation. Ethics approval was granted by the Research Ethics Board of St. Michael's Hospital, Toronto, Ontario.

2.2 Consensus Process

A modified Delphi protocol was developed and used to establish consensus about the developed statements among Canadian oncologists with expertise in the relevant areas. Experts were identified using these criteria: at least 50% of practice dedicated to breast cancer, participation in expert panels in the subject area, publication record in the area, and expertise identified by peers. Medical trainees were not included. Because the purpose of our project was to determine consensus across the whole pathway of care for patients with LABC or those receiving NAT, experts were asked to answer questions related to each aspect of the care pathway (Appendix A). The consensus statements were disseminated using e-mail links to the Web-based survey platform SurveyMonkey (<http://www.surveymonkey.com>). Addresses of participants were gathered from oncology group membership or personal correspondence with the investigators, and 85 experts from across Canada were contacted. Careful consideration was given to ensuring that representation was sought from all provinces. Responses were kept anonymous during tabulation.

"Consensus" was prespecified as 80% agreement among the experts. Per the Delphi protocol, if fewer

than 80% of experts agreed on a given statement, the results were provided to the entire respondent pool, the survey statement was modified to reflect the aspect of non-agreement, and the survey with the modified statement was re-distributed. The process was repeated until all statements achieved at least 80% agreement (Figure 1).

2.3 Systematic Review of RCTs

The systematic review of all RCTs of NAT for breast cancer (early or LABC) was completed using the PubMed citation index. The search terms used were “locally advanced breast cancer” OR “breast cancer” AND “neoadjuvant therapy” OR “neoadjuvant systemic therapy” OR “neoadjuvant chemotherapy.” Trials were included if they were phase III RCTs published between January 1, 1980, and December 1, 2012, that assessed the use of systemic therapy for the neoadjuvant treatment of breast cancer. The rationale for including only phase III RCTs was that we sought to determine whether expert recommendations for the ideal pathway of care in clinical practice reflected the care pathway used for relevant patients in clinical trials. We included trials only if the main focus was an outcome: breast cancer response, recurrence, or survival. Trials were excluded if they focused on pharmacodynamics or pharmacokinetics as primary endpoints, or if they were chiefly concerned with validating tools that measure mid-treatment response (imaging modalities or

biomarkers). If more than one publication was identified for the same trial, the publication that described the methodology most completely was used.

Data extracted from relevant journal articles were used to determine whether the methodology and clinical care models in the trials addressed concepts evaluated in the consensus statements. The specific information abstracted included the study’s definition of LABC and of pCR, the investigations performed before initiation of NAT, the chemotherapy regimen or regimens used, the techniques and procedures for addressing suspicious axillary lymph nodes before treatment, the protocol for determining tumour receptor status, the protocol for progressive disease (salvage treatment), the use of breast-conserving surgery, the protocol for residual disease at the time of surgery, and the time between NAT and surgery. Number of patients enrolled, pCR rate, and survival outcomes (if available) were also captured for each of the trials. Extracted data were summarized in tabular form.

3. RESULTS

3.1 Consensus Survey

The initial iteration of the survey attracted 56 responses from among the 85 experts contacted (for a response rate of 66%). Although all specialties (medical, radiation, and surgical oncologists; pathologists) were represented in the study, most respondents were medical

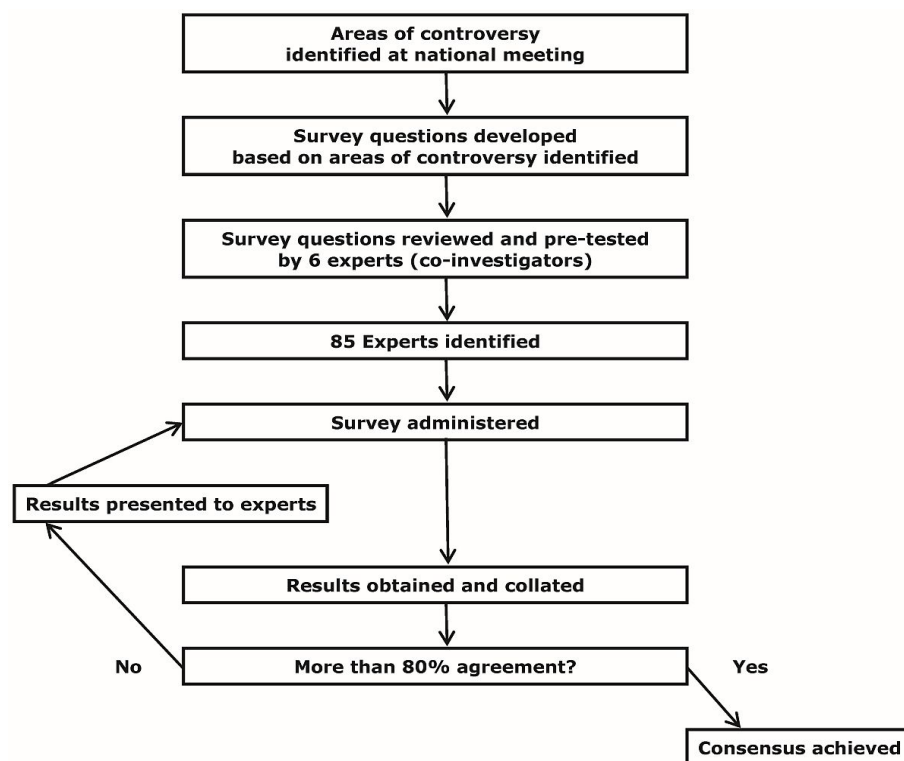


FIGURE 1 Delphi model for development of the expert consensus.

oncologists (Figure 2). Most geographic jurisdictions were also represented; the exceptions were the three territories (Yukon, Nunavut, Northwest Territories), Prince Edward Island, and New Brunswick. The largest number of respondents had practices in Ontario, but when the total number of registered medical oncologists practicing in each province was considered, responses from Ontario, Manitoba, Nova Scotia, and Newfoundland and Labrador were close to proportionately distributed (Figure 3).

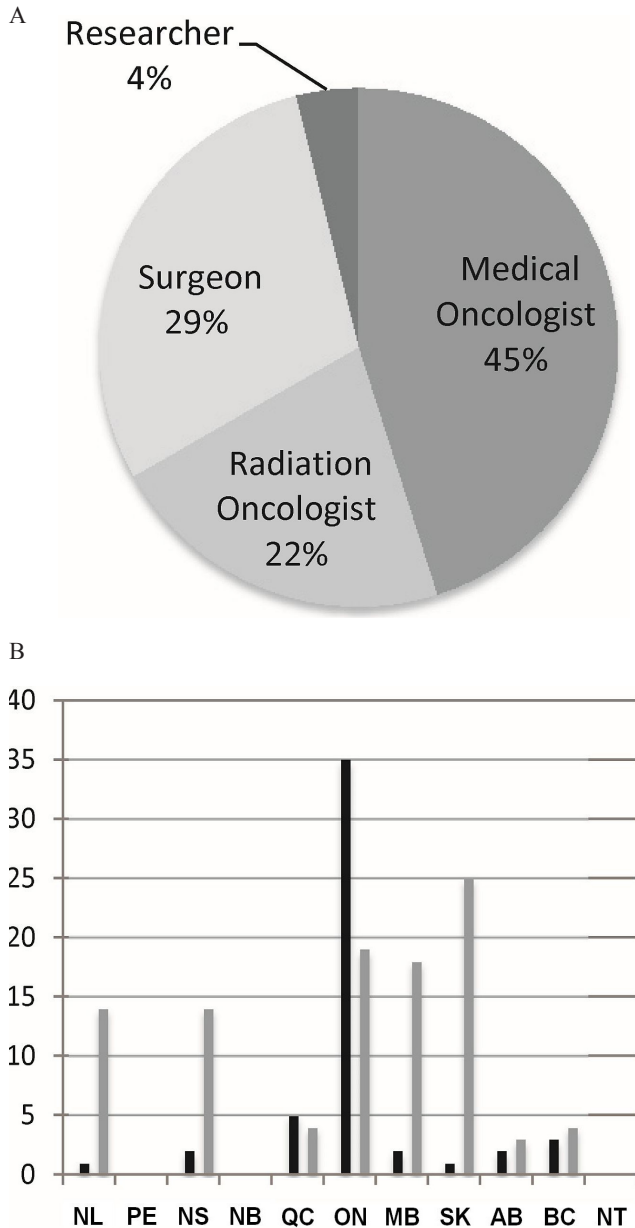


FIGURE 2 Experts involved in the consensus process, by (A) area of specialty and (B) province (dark bars indicate the number of respondents, light bars indicate the proportion that the respondents represent of all practising medical oncologists in the given province). NT = all three northern territories combined.

Reaching consensus required 3 iterations of the survey. Overall consensus was achieved for almost all statements about the NAT care pathway; the exception concerned the use of magnetic resonance imaging (MRI) in the neoadjuvant setting for early-stage (non-LABC) breast cancer. For such patients, only 52.2% of the experts agreed that MRI is required before initiation of neoadjuvant chemotherapy; 54.3% felt that MRI is required after completion of neoadjuvant chemotherapy. With respect to LABC patients who are candidates for breast-conserving surgery (instead of complete mastectomy), 81.3% of the experts agreed that MRI should be used before initiation of neoadjuvant chemotherapy, and 68.1% agreed that MRI is required after completion of NAT. Because the experts were still far from reaching consensus on this issue after 3 iterations and because it seemed unlikely that further iterations would lead to consensus, the investigators stopped the iterative process for this one element of the care pathway. Otherwise, more than 80% agreement was achieved on all other consensus statements (Table 1).

For the remaining aspects of the care pathway for patients treated with NAT, the experts were quite consistent and showed a high degree of agreement. The lowest consensus percentage was 83.7%. Among

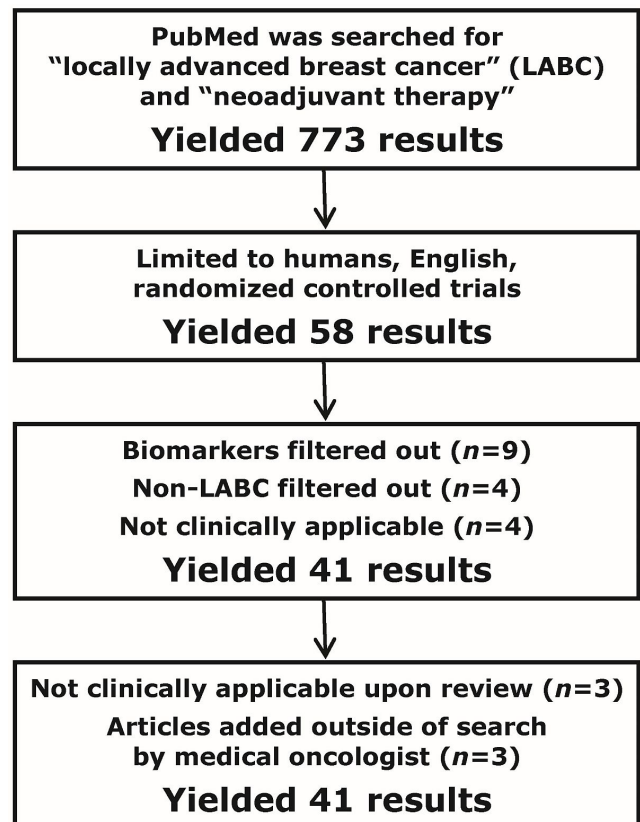


FIGURE 3 Expert respondents as proportion of practicing oncologists, by province.

TABLE 1 Consensus statements and alignment with the literature

Statement	Expert consensus agreement		Alignment ^a
	(%)	(n/N)	
<i>Definitions and patient selection</i>			
Locally advanced breast cancer (LABC) is often defined as T3 or T4 tumours of any clinical N status, or any size tumour classified N2 or N3. The definition includes inflammatory breast cancer, and the tumour can be operable or inoperable upon presentation.	95.7	45/47	Evidence more conservative
Patients should preferably be offered neoadjuvant therapy (NAT) if they have LABC by the given definition.	100.0	46/46	Perfectly aligned
Pathologic complete response is defined as noninvasive disease in the breast and axilla.	83.7	41/49	Evidence less conservative
<i>Pre-NAT work-up</i>			
Clinically or radiographically suspicious lymph nodes should undergo fine-needle aspiration or core biopsy before initiation of NAT.	96	49/50	No supporting evidence found
In LABC patients, magnetic resonance imaging (MRI) is required before initiation of NAT if the patient ...			
is a potential candidate for breast-conserving surgery (BCS).	81.3	39/48	No supporting evidence found
is <i>not</i> a potential candidate for BCS.	15.2	7/46	No supporting evidence found
For LABC patients, MRI is required after completion of neoadjuvant chemotherapy if the patient ...			
is a candidate for BCS.	68.1	32/47	No supporting evidence found
is <i>not</i> a candidate for BCS.	10.9	5/46	No supporting evidence found
In non-LABC patients, MRI is required before initiation of NAT if the patient ...			
is a candidate for BCS.	52.2	24/46	No supporting evidence found
is <i>not</i> a candidate for BCS.	4.4	2/45	No supporting evidence found
In non-LABC patients, MRI is required after completion of NAT if the patient ...			
is a candidate for BCS.	54.3	25/46	No supporting evidence found
is <i>not</i> a candidate for BCS.	95.6	43/45	No supporting evidence found
The work-up required before initial neoadjuvant treatment should preferably include receptor status on core biopsy [estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2)], bilateral mammogram, clinical staging (accurate tumour measurement on clinical exam), imaging of chest and abdomen, and bone scan.	100.0	47/47	Evidence more conservative
Sentinel lymph node biopsy surgery before neoadjuvant treatment is not a preferred option for LABC patients.	84	2/50	No supporting evidence found
ER and PR status should preferably be checked on the core biopsy; the check should be repeated on the final pathology specimen <i>only</i> if initial result was ER- or PR-negative or low ER- or PR-positive.	100.0	46/46	Evidence less conservative
HER2 status should preferably be checked on the core biopsy; the check should be repeated on the final pathology specimen only if initial result was negative or low positive (that is, fluorescence <i>in situ</i> hybridization ratio of 1.8–2.0).	93.5	43/46	No supporting evidence found
<i>Selection and management of NAT</i>			
Sequential anthracycline and taxane is the neoadjuvant chemotherapy regimen of choice for ER-positive, PR-positive, HER2-negative patients.	100.0	46/46	Evidence less conservative
Sequential anthracycline and taxane combined with anti-HER2 blockade is the neoadjuvant chemotherapy regimen of choice for ER-negative, PR-negative, HER2-positive patients.	93.3	42/45	No specific studies assessing chemotherapy backbone based on subtype were found

TABLE 1 Continued

Statement	Expert consensus agreement		Alignment ^a
	(%)	(n/N)	
<i>Selection and management of NAT (continued)</i>			
Sequential anthracycline and taxane is the neoadjuvant chemotherapy regimen of choice for triple-negative patients.	93.0	40/43	No specific studies assessing chemotherapy backbone based on subtype were found
Neoadjuvant endocrine therapy is preferred to chemotherapy for patients that are ER-positive or PR-positive (or both) with multiple comorbidities before surgery.	95.6	43/45	No supporting evidence found
Neoadjuvant endocrine therapy is preferred to chemotherapy for patients that are ER-positive or PR-positive (or both) and more than 80 years of age before surgery.	93.6	44/47	No supporting evidence found
Radiotherapy (with or without hormonal therapy or trastuzumab) should be preferred as the next treatment approach for patients who continue to have inoperable LABC after anthracycline–taxane-based chemotherapy.	100.0	47/47	No supporting evidence found
Patients with clinically node-positive LABC at diagnosis should preferably receive adjuvant radiotherapy including regional lymph nodes (infraclavicular or supraclavicular) regardless of pathologic response.	97.9	46/47	No supporting evidence found
Lumpectomy is an option for the surgical management of patients who receive NAT.	97.9	46/47	Evidence more conservative
Patients should preferably receive chest wall and regional nodal irradiation if there is clinical evidence of node involvement before NAT.	95.7	45/47	No supporting evidence found
In the setting of residual disease at the time of surgery, no further therapy beyond adjuvant radiation therapy and targeted therapy (endocrine therapy or trastuzumab, based on receptor status) is needed outside of clinical trials.	100.0	47/47	No supporting evidence found
<i>Monitoring response to NAT</i>			
Patients should preferably be assessed at each neoadjuvant treatment cycle for their clinical response to the neoadjuvant chemotherapy.	100.0	46/46	Evidence less conservative
Assessment of a patient’s clinical response should preferably occur monthly if they are on neoadjuvant endocrine therapy instead of chemotherapy.	93.5	43/46	No supporting evidence found
Accurate clinical measurement with a tape measure or calipers should be preferred for the assessment of clinical response to NAT.	95.7	45/47	No supporting evidence found
All patients who experience disease progression on NAT should preferably be reviewed at multidisciplinary tumour rounds to determine the next appropriate management option.	97.9	46/47	Evidence contrary to consensus statement

^a Based on median score. Less conservative = reviewed literature had less stringent or specific criteria or definitions pertaining to the statement; Perfectly aligned = reviewed literature had similar or identical criteria or definitions pertaining to the statement; More conservative = reviewed literature had more stringent or specific criteria or definitions pertaining to the statement; Evidence contrary to consensus statement = reviewed literature had criteria or definitions in direct contrast to the statement; No supporting evidence found = reviewed literature did not address the pertinent content.

these responding Canadian experts, there was 98% consensus that pCR is defined as having no invasive disease in the breast and axilla. There was also 95.7% consensus that LABC should be defined as a T3 or T4 tumour of any clinical N status, or an N2

or N3 tumour of any size, which might be operable or inoperable upon presentation and which includes inflammatory breast cancer. It was unanimously agreed that sequential anthracycline- and taxane-based regimens are the optimal choice of neoadjuvant

chemotherapy. Lastly, 98% of the experts agreed that clinically or radiographically suspicious lymph nodes should preferably undergo fine-needle aspiration or core biopsy before initiation of NAT.

3.2 Comparison to Available Evidence

The initial search of PubMed yielded 773 publications. After the search was limited to human studies and RCTs in the English language, fifty-eight articles remained. The abstracts of those articles were then hand-searched by CES (the principal investigator and a medical oncologist). Publications considered not applicable—including nine on biomarkers, four that did not include patients receiving NAT, and four pertaining to subjects deemed out of scope—were removed. The remaining forty-one articles were assessed by 3 independent reviewers, and three more articles addressing only biomarker outcomes were eliminated. Cross-referencing citation lists in the relevant clinical trials added three other papers. The final review therefore included forty-one articles.

3.3 Comparing Consensus Statements with the Evidence

The assessed RCTs were evaluated for their alignment with each consensus statement, and an overall assessment of the degree of congruity was established for most of the studies; a formal scoring system was used to establish the most prevalent degree of alignment for each statement (data not shown).

Overall, variability between the Canadian consensus statements and the corresponding aspects of care as found in the reviewed RCTs was significant (Table 1). For example, the definition of pCR was rather heterogeneous in the assessed RCTs; in contrast, the Canadian experts almost uniformly defined pCR as no invasive disease in the breast and axilla. Overall, we determined that the trials were “less conservative” (Table 1) than the expert consensus^{2–42}. However, of the assessed publications, eleven^{2,5,6,8,11,13,14,17,18,25,26,41,42} used definitions of pCR that completely aligned with the expert survey. In contrast, the definition of LABC was found to be “more conservative” in the trials than in the consensus survey. However, of the assessed RCTs, twelve^{5,8,9,11,13,14,21,32,34,36,38,39,42} showed complete concordance with the expert consensus. The experts reached a strong consensus that lumpectomy be considered an option for surgical management after NAT. However, that view was not reflected in the assessed RCTs. The literature review also found that few of the reviewed studies specifically mentioned whether the ipsilateral axillary lymph nodes were assessed before systemic therapy. No level of agreement between the expert consensus and the RCTs with respect to the preoperative assessment of lymph nodes could therefore be ascertained. Similarly, the use of MRI was seldom described in the clinical trial protocols^{2–42}. Finally,

the only aspect of NAT for which a perfect match was found between most of the assessed RCTs and the expert consensus was that NAT should be considered the standard of care for patients with LABC.

4. DISCUSSION

A rigorous process achieved a true consensus of expert opinion on the pathway of care for NAT in breast cancer patients (Table 1). The consensus statements were also compared with published clinical trials to help establish the areas that in fact have supporting evidence and the areas that do not. However, it is notable that several of the areas considered by the consensus panel were in fact not addressed explicitly in clinical trial protocols at all. That observation does not necessarily mean that the expert consensus in those areas is not evidence-based, but simply that, for NAT in breast cancer, evidence is not clearly defined in RCTs. Expert consensus might therefore be the only source of guidance for clinical care in those areas. In addition, the reviewed RCTs themselves showed considerable variability in how well they aligned with individual consensus statements, such that a smaller number of studies sometimes perfectly aligned with the experts, but most did not. The comparisons therefore represent general trends of expert consensus compared with the published literature. Some practice statements might have been influenced by a few RCTs that might not be representative of most studies.

Ultimately, the Canadian experts agreed on most facets of NAT management. This compilation of consensus statements can be disseminated as a comprehensive Canadian approach to NAT in breast cancer, being more inclusive of the entire patient care journey in a real-world setting.

It is notable that any recommendation for MRI in the neoadjuvant care pathway still lacks an expert consensus after 3 iterations of our survey. Indeed, the issue of imaging was also not clearly addressed in the assessed RCTs. Although strong evidence supports the high sensitivity and specificity of MRI compared with mammography, ultrasonography, or clinical exam for assessing disease volume, consideration of that volume in the breast before NAT is probably of clinical significance only in patients who are considered candidates for breast-conserving surgery. Even in that scenario, it is unclear whether MRI changes cancer outcomes in terms of locoregional recurrence. Several studies have suggested that routine preoperative use of MRI results in higher rates of mastectomy, but the translation of those data into recurrence risk is unclear, especially considering contemporary recommendations for locoregional and systemic management. Our consensus survey sought to address that area of controversy, but was unable to establish agreement among the experts. Future prospective studies focusing on this issue

TABLE II Pathway of care for breast cancer patients undergoing neoadjuvant therapy (NAT)

Who should receive NAT?

Patients with locally advanced breast cancer (LABC) should preferentially be treated using NAT. These patients have T3 or T4 tumours of any clinical N status, or any size tumour classified N2 or N3. This definition includes inflammatory breast cancer, and the tumour can be operable or inoperable upon presentation.

Which tests and procedures should a patient undergo before starting NAT for breast cancer?

Receptor status [estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2)] on core biopsy

Bilateral mammography

Clinical staging (accurate tumour measurement on clinical exam)

Imaging of chest and abdomen

Bone scan

Clinically or radiographically suspicious lymph nodes should undergo fine-needle aspiration or core biopsy before initiation of NAT.

Sentinel lymph node biopsy surgery before NAT is not a preferred option for LABC patients.

Should a patient undergo breast magnetic resonance imaging (MRI)?

If the patient is not a candidate for breast-conserving surgery, there is no clear need for MRI.

If the patient is a candidate for breast-conserving surgery, MRI might be appropriate, but consensus was not achieved.

Which chemotherapy regimen should be used?

An anthracycline- and taxane-containing regimen, with the addition of targeted therapy based on receptor status, is, overall, the agreed-upon regimen.

Who should be considered for neoadjuvant endocrine therapy?

Neoadjuvant endocrine therapy is preferred to chemotherapy for patients who are ER-positive or PR-positive (or both) and more than 80 years of age before surgery, and for patients with ER-positive disease and significant comorbidities.

How should patients be followed while on NAT?

Patients should preferably be assessed at each neoadjuvant treatment cycle for clinical response to neoadjuvant chemotherapy.

A patient's clinical response should preferably be assessed monthly if they are receiving neoadjuvant endocrine therapy instead of chemotherapy.

Accurate clinical measurement with a tape measure or calipers should preferably be used to assess clinical response to NAT.

What should be done if the patient is still inoperable or progresses while on treatment?

Radiotherapy (with or without hormonal therapy or trastuzumab) should be the preferred next treatment approach for patients who continue to have inoperable LABC after anthracycline- and taxane-based chemotherapy.

All patients who experience disease progression while on NAT should preferably be reviewed at multidisciplinary tumour rounds to determine the next appropriate management option.

Which locoregional treatments should be used?

Patients with clinically node-positive LABC at diagnosis should preferably receive adjuvant radiotherapy to include the regional lymph nodes (infraclavicular or supraclavicular) regardless of pathologic response.

Lumpectomy is an option for the surgical management of patients who receive NAT.

Should a patient receive further treatment if residual disease is found at the time of surgery?

In the setting of residual disease at the time of surgery, no further therapy beyond adjuvant radiation therapy and targeted therapy (endocrine therapy or trastuzumab, based on receptor status) is needed outside of clinical trials.

will be important to establish whether preoperative MRI could lower the risk of locoregional recurrence or improve other outcomes after NAT.

The expert consensus supported the use of chemotherapy regimens that include both an anthracycline and a taxane as the standard of care in eligible patients, including specific subtypes of breast cancer. That recommendation was somewhat reflected in the reviewed RCTs, although the use of those chemotherapy agents was not specifically stratified by tumour receptor status in most trials. Many of the assessed RCTs aimed to evaluate novel neoadjuvant therapies, but use of an anthracycline and a taxane as the standard chemotherapy backbone for some of the protocols could be considered to imply that an anthracycline–taxane approach is favoured; those trials would then be considered to align with our expert consensus. As newer studies continue to evaluate other therapeutic strategies in the neoadjuvant setting, updated data could affect future consensus about this aspect of NAT in breast cancer care.

Our project is unique in its establishment of consensus among experts in the field of NAT for breast cancer and in the explicit linking of the practice recommendations back to the literature. Many of the consensus statements address areas of care that are not well defined in published RCTs and that reflect important knowledge gaps in the evidence. The present work constitutes a real-world illustration of what Canadian experts promote as the standard pathway of care for NAT in breast cancer, including appropriate reflection of clinical trial data where they exist.

Although a 60%–70% response rate to the consensus survey (over all iterations) was achieved, the opinions of the respondents might not reflect the views of all experts in the field. In addition, 68.6% of the respondents practiced in Ontario and their views might not accurately reflect the opinions of clinicians from other Canadian provinces. Finally, the search strategy used during the literature review might have limited the number of relevant articles, because only RCTs were included. A full systematic review including other publications (such as guidelines and review articles) and the grey literature (unpublished studies and academic meeting proceedings) was not completed. Finally, several of the included studies evaluated older NAT protocols, which, no longer being reflective of newer treatment approaches, might have resulted in discordance with the expert consensus statements.

5. IMPLEMENTATION AND FUTURE WORK

A complementary study evaluating current practice patterns of NAT in breast cancer by Canadian clinicians is also being conducted to identify areas that could potentially be targeted for directed knowledge translation interventions. That study might help to better align practice across Canada and, by capturing data on

pathway implementation, also serve as a mechanism for measuring best practice. As evidence changes, expert consensus could also evolve, and future work would therefore involve repeating the consensus process. The process is expected to be repeated every 3 years at a minimum to ensure that the content of the recommendations remains current.

As NAT for breast cancer continues to move beyond locally advanced disease, efforts such as this one will be imperative to help direct practice, embracing both the available high-level evidence and expert consensus to address the finer nuances of a complex care pathway.

6. ACKNOWLEDGMENTS

The Canadian Locally Advanced Breast Cancer Network is an established group of academic and clinical experts who review evidence and practice in the realm of LABC and NAT for breast cancer. The participating breast cancer experts strictly establish the content and output of the related meetings.

7. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: CES has received honoraria from Roche, Novartis, Amgen, and AstraZeneca; has participated in advisory committees and received travel grants from Roche, Novartis, and Amgen; and has received unrestricted research grant funding from Roche, Amgen, and Novartis. JFB has received speaking honoraria from Genomic Health and Roche, has participated in Roche advisory committees, and has received scientific meeting travel grants from Roche. His institution has received research funding from RNA Diagnostics and Roche. SG has received speaking honoraria from Novartis with respect to oral cancer treatments not specific to NAT. SH, RL, YR, DH, AW, JL, and MB declare that they have no conflicts.

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