CancerCare Manitoba
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Practice Guideline: Disease Management

Provincial Consensus Recommendations for Adjuvant Systemic Therapy for Breast Cancer

Effective Date: July 2017

CancerCare Manitoba Guideline
Disease Management – Breast Cancer
Developed by: Breast Disease Site Group

Preface

At CancerCare Manitoba (CCMB) the Clinical Practice Guidelines Initiative (CPGI) seeks to improve patient outcomes through the development, dissemination, implementation and evaluation of guidelines for the management of common clinical scenarios encountered by cancer patients throughout the province.

This clinical practice guideline was created through the efforts of a large interdisciplinary group from CCMB in collaboration with community partners. Members of the CCMB Breast Disease Site Group (DSG), the Department of Surgery at the University of Manitoba, the CCMB Department of Nursing, the CCMB Department of Epidemiology, general surgeons from the community, and oncologists from the Winnipeg Regional Health Authority (WRHA) Community Oncology Program, and the Community Cancer Program Network (CCPN) sites have participated in its development.

The Breast DSG will review and update this document every two years, unless emerging evidence from scientific research, or practice issues requiring urgent resolution dictate a need for immediate change in content.

Purpose

This document is intended as a guide to facilitate a common approach to the treatment of breast cancer patients with adjuvant systemic therapy.

For this purpose, it may be used by qualified and licensed healthcare practitioners involved with the care of oncology patients, which may include (but is not limited to): physicians, surgeons, nurses, radiation therapists, pharmacists, psychosocial oncology caregivers, and dieticians at CCMB, and Community Oncology Program sites (CCPN sites, Uniting Primary Care and Oncology (UPCON) clinics and WRHA Community Oncology Program sites).

Disclaimer

This guideline document should be viewed as an evidence-based practice tool, and as such, it does not represent an exhaustive text on the subject of adjuvant systemic therapy for breast cancer. Clinicians are advised to use it in their practice concomitantly with information from other evidence-based sources.

Use of this guideline in the clinical setting should not preclude use of the practitioner's independent clinical judgement, nor should it replace consultation with the appropriate oncology specialist when indicated (example: medical oncologist, radiation oncologist, family practitioner in oncology (FPO), hematologist, nurse practitioner/clinical nurse specialist, pharmacist, psychosocial oncology professional, and dietician).

It is the responsibility of the practitioner to develop an individualized disease or symptom management plan for each patient under his/her care, and ideally, this should take place within the context of a multidisciplinary team. The needs and preferences of the patient and the family should always be reflected in the plan of care.

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Provincial Consensus Recommendations for Adjuvant Systemic Therapy for Breast Cancer

I. Introduction: Breast Cancer in Manitoba

Breast cancer is the most common malignancy in women in Manitoba with an estimated 850 cases and 190 estimated deaths due to breast cancer in 2014. Adjuvant systemic chemotherapy, biologic therapy and endocrine therapy is known to reduce the incidence of recurrence of disease in many early breast cancer patients dependent on the specific morphology of the cancer diagnosis and its staging.

The options available to patients are directly linked to the biology of the tumours and the estrogen receptor (ER), progesterone receptor (PR) and HER2/neu expression which truly does direct 'personalized medicine' for breast cancer. The rate of ER and/or PR positivity in breast cancer is approximately 75%; HER2/neu positivity is approximately 15% (both in ER positive and ER negative); while 15% are triple negative for ER, PR and HER2/neu.[1] This directly impacts treatment options and therapeutic decision making. In order to standardize therapy to ensure treatment is evidence-based and that the best possible recommended care is given, the use of evidence-based guidelines, where available, is considered a standard of care. In 1989, prior to use of current evidence-based adjuvant systemic therapy for breast cancer, the age standardized mortality rate (ASMR) for breast cancer was above 30 per 100,000, and this has fallen dramatically to less than 20 per 100,000 population in 2014.[2]

The literature around adjuvant therapy for breast cancer spans a number of decades and the absolute volume of practice changing trials is vast, which has sparked interest by a number of sites into performing systematic reviews and creating guidelines around the management of these cancers to improve outcomes in terms of the risk of recurrence and mortality from breast cancer. Because this work has already been completed by a number of groups, we elected to review the existing guidelines to determine if we could identify guidelines that meet the needs of our population in order to inform treatment in the adjuvant setting in an evidence-based manner.

References

1. Cosetti RJ, Tyldesley SK, Speers CH, et al. Comparison of breast cancer recurrence and outcome patterns between patients treated from 1986 to 1992 and from 2004 to 2008. *J Clin Oncol* 2015;33(1):65-73.
2. Canadian Cancer Society's Advisory Committee on Cancer Statistics. *Canadian Cancer Statistics 2014*. Toronto, ON: Canadian Cancer Society; 2014.

II. Scope of Guideline

Aim and Purpose

Development of this guideline was undertaken for the purpose of knowledge translation of the current standards in practice for adjuvant systemic therapy of breast cancer in Manitoba. The overall aim of the development is to improve the standard of care received by this patient population, through application of evidence-based interventions and promotion of best practices.

Development Panel

Development Panel

Oncology Subspecialties CancerCare Manitoba/University of Manitoba	4 Medical Oncologists, Breast DSG 1 Surgical Oncologist, Breast DSG 1 Medical Oncology Resident 1 Physician, Community Oncology Program

Development Process

A multidisciplinary group of medical professionals organized a conference to establish management consensus for patients with early breast cancer. Attendees were experts and practitioners from across the province as well as an external expert (for impartiality). Presentations included evidence-based recommendations, as well as local expertise. The guidelines were developed using a modified Delphi consensus method (*See Section III, Guideline Methodology, for description*).

Patient Population and Healthcare Setting

The recommendations in this guideline are applicable to the care of patients with early breast cancer. *(See Section III, Guideline Methodology, for clinical scenarios).*These recommendations are intended for use in both inpatient and outpatient settings.

End-Users

This guideline is written for use by healthcare professionals providing care for the above mentioned patient population. Intended primarily for use by oncology clinicians, the guideline may be of interest to trainees, physician extenders, allied healthcare staff, healthcare administrators, policy-makers and possibly members of the general public.

III. Guideline Methodology

Clinical Research Question Development

Prior to beginning a literature search, the working group developed clinical research questions using the PICOT method (**P**opulation; **I**ntervention; **C**omparison; **O**utcome; **T**ime Frame). Discussion and consensus narrowed the clinical research questions to:

Clinical Question #1

In women with stage ≥T1cNo HER2+ breast cancer, what is the benefit of adjuvant trastuzumab in recurrence reduction and improvement in overall survival?

In women with stage T1bNo HER2+ breast cancer, what is the benefit of adjuvant trastuzumab in recurrence reduction and improvement in overall survival?

In women with stage T1aNo HER2+ breast cancer, what is the benefit of adjuvant trastuzumab in recurrence reduction and improvement in overall survival?

Clinical Question #2

In women with early HER2+ breast cancer, what is the optimal treatment duration and choice of chemotherapy/biological therapy?

Clinical Question #3

In women with high risk (node positive and/or triple negative breast cancer), what is the reduction in the risk of cancer recurrence and mortality with the use of third generation adjuvant chemotherapy compared to previous standard of care? What are the optimal chemotherapy regimens to be used in this setting?

Clinical Question #4

In women with early stage lymph node negative breast cancer, does the use of adjuvant chemotherapy improve overall survival compared to no chemotherapy?

Clinical Question #5

In premenopausal women with non-metastatic resected hormone receptor positive breast cancer, what adjuvant endocrine therapies are of benefit for prevention of breast cancer recurrence and improved survival after surgical resection in comparison to no endocrine therapy?

Clinical Question #6

In premenopausal women with non-metastatic resected hormone receptor positive breast cancer who become postmenopausal 2-3 years after chemotherapy, what adjuvant endocrine therapy, and in what sequence, is the most beneficial in reduction of risk of recurrence of breast cancer and improved survival?

Clinical Question #7

In postmenopausal women with non-metastatic resected hormone receptor positive breast cancer, what adjuvant endocrine therapy is most beneficial for risk reduction of recurrence of breast cancer and for overall survival benefit? If sequential therapy is used, what is the optimal sequence?

Clinical Question #8

What is the indication for use of ovarian suppression in premenopausal women for adjuvant therapy to prevent breast cancer recurrence and improve survival?

Clinical Question #9

What is the optimal and/or acceptable timeframe from surgery date to initiate adjuvant therapy?

Clinical Question #10

In patients requiring additional surgery and adjuvant chemotherapy, when should surgery be performed to allow for more prompt delivery of chemotherapy?

Literature Search

Clinical Practice Guidelines

PubMed, SAGE (Search Standards and Guidelines Evidence) Guideline Database, Google Scholar, and Google (environmental search) were systematically searched for clinical practice guidelines. In SAGE, 12 results were found for breast cancer. The following strategy was used to search for clinical practice guidelines in PubMed with humans as a limit, after 2009 (5 years) and English, yielding 3 results:

> *("Practice Guidelines as Topic"[Mesh] OR "Guideline" [Publication Type]) AND ("Breast neoplasm" [Mesh] OR (Breast [Title/Abstract] AND (Neoplasm*[Title/Abstract] OR Cancer*[Title/Abstract]))) AND ("Adjuvant chemotherapy"[Mesh])*

Guidelines were also searched environmentally by guideline developer, including Cancer Care Ontario (CCO), Alberta Health Services (AHS), BC Cancer Agency (BCCA), Saskatchewan Cancer Agency (SCA), Cancer Care Nova Scotia (CCNS), National Comprehensive Cancer Network (NCCN), New Zealand Guidelines Group (NZGG), Scottish Intercollegiate Guideline Network (SIGN), Guideline International Network (GIN), European Society of Medical Oncology (ESMO), Belgian Health Care Knowledge Centre (KCE), Cancer Australia, National Guideline Clearinghouse (NGC), American Society of Clinical Oncology (ASCO), National Health and Medical Research Council (NHMRC), National Cancer Institute (NCI) at the National Institutes of Health (NIH), American Cancer Society (ACS), and National Institute for Health and Care Excellence (NICE).

Literature Review of Primary Evidence

Primary evidence was searched *via* PubMed, ClinicalKey and Scopus in order to obtain evidence for the clinical questions that were not substantially addressed in existing guidelines. Separate literature reviews were completed for the clinical questions. Combinations of the keywords shown in Table 1 were used for the searches. Identification of additional articles was completed using a snowballing technique, which involved moving backwards by following references of eligible papers and forward through citation chasing. Environmental searches of Google and Google Scholar were completed but were of limited value.

Table 1. Literature Review Search Terms

Clinical Research Question	Search Terms
Adjuvant Ovarian Suppression	(MESH = Breast Neoplasms OR TIAB = breast cancer OR breast tumor* OR tumour*) AND (TIAB = adjuvant ovarian suppression OR adjuvant ovarian ablation OR adjuvant ovarian protection OR gonadotropin releasing hormone agonist OR LH-RH agonist) AND (TIAB = premenopausal) Limits: previous 5 years, humans, English
Timing of Adjuvant Therapy	(MESH = Breast Neoplasms OR TI/AB = breast cancer OR tumor* OR tumour*) AND (MESH = surgery OR surgical OR TIAB = surgery OR surgical OR mastectomy OR breast-conserving surgery) AND (MESH = chemotherapy OR TIAB = adjuvant chemotherapy OR adjuvant chemotherapeutic OR adjuvant therapy) AND (TIAB = timing OR time OR delay)

Quality Appraisal of Relevant Guidelines

All relevant guidelines were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE II instrument).[1] This standardized instrument is used to assess the quality of the guideline based on methodological rigour and transparency of the development process. Further, the working group considered the currency of the guideline, rapidity of updates, relevance to the PICOT questions and applicability for the Manitoba context when considering whether to adopt or adapt an existing guideline.

2015 Adjuvant Systemic Therapy for Breast Cancer Provincial Consensus Meeting

A Provincial Consensus Meeting was held in Winnipeg, Manitoba on February 28, 2015. The working group met on nine prior occasions to propose the current evidence and develop the agenda, budget, consensus statements and algorithm for this consensus meeting. The agenda included presentations of current evidence, a debate of current literature and group discussions. Logistical organization of the conference was completed by the CCMB Clinical Practice Guidelines Initiative.

The working group determined that a Modified Delphi Consensus Process would be used during discussion of the consensus statements at the conference. The Delphi Consensus Process is defined as "…a method for structuring a group communication process so that the process is effective in allowing a group of individuals, as a whole, to deal with a complex problem."[2] Guiding assumptions were adapted from those used at the 2011 CCMB provincial Rectal Cancer Consensus Conference. *(See Appendix 3)*. Voting and discussion on the consensus statements followed each presentation. Consensus was reached and following each presentation was then presented and discussed again at the conclusion of the meeting. Consensus was reached with 75% agreement. *(See Appendix 2)*.

The conference was attended by medical oncologists, primary care providers, family physicians, general surgeons/surgical oncologists, residents, nurses and allied staff from CancerCare Manitoba and other urban and

rural provincial health institutions. Individuals from the region and other parts of the country (for impartiality) were invited to speak on the guideline topics of interest. *(See Appendix 4).* Attendees received accreditation through the Royal College of Physicians and Surgeons of Canada, the College of Family Physicians of Canada and the Manitoba College of Family Physicians.

Working Group Meetings

The working group developed this guideline in response to the consensus statements developed at the 2015 Adjuvant Systemic Therapy for Breast Cancer Provincial Consensus Meeting. The consensus statements formed the framework of the guideline. Using the consensus statements for guidance, working group members drafted each of the guideline sections or made the necessary modifications to the chosen guideline to adapt. Each section was reviewed by the working group and revised according to consensus decisions.

Internal and External Review

Internal and external peer reviews were pursued, the results of which are appended to these guidelines. *(See Appendix 6).* The internal review process was consensus-based and completed by the working group. An external review was completed by a Family Physician in Oncology and a Medical Oncologist. All reviewers completed a full review of the guideline document using a standardized practitioner feedback form (adapted from Brouwers and colleagues).[3] Feedback was reviewed and discussed by the working group. Decisions to incorporate any changes into the guideline were consensus-based (acceptance, rejection or acceptance with modifications).

Maintenance

At CancerCare Manitoba clinical practice guidelines are considered 'living' documents which require ongoing evaluation, review and updating. Re-evaluation of this guideline is planned for 2017 (2 years). The working group will revise and update the document if necessary, with any critical new evidence brought forward before this scheduled review.

References

1. AGREE Next Steps Consortium. The AGREE II instrument [electronic version]. Updated 2009. Available online at: http://www.agreetrust.org [Accessed 25 March 2015].

2. Linstone HA & Turnoff M. The Delphi method: Techniques and applications. Reading, MA: Addison-Wesley Publishing Company; 1975.

3. Brouwers MC, Graham ID, Hanna SE, et al. Clinicians' assessments of practice guidelines in oncology: the CAPGO survey. *Int J Technol Assess Health Care* 2004;20(4):421-6.

IV. HER2 Positive

Background – HER2/neu

The human epidermal growth factor receptor 2 (HER2) oncogene is overexpressed in approximately 20% of breast cancers and is associated with aggressive tumour biology.[1] The development of rationally designed HER2-targeted therapies has dramatically improved outcomes among women with HER2-positive breast cancers. Trastuzumab is a humanized monoclonal antibody against HER2, which inhibits tumour cell growth.[2] It was first approved for the treatment of metastatic breast cancer in 1999[3], and was subsequently proven to reduce recurrence rates and mortality in early HER2-positive disease.[4-6] As such, women with early stage breast cancers that are HER2 positive are advised adjuvant chemotherapy and trastuzumab.[7] In this population, adjuvant trastuzumab approximately halves the risk of breast cancer recurrence and reduces mortality by one third when compared to adjuvant chemotherapy alone.[8,9]

Key Evidence

Relevant guidelines evaluated:

1. American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) 2013[7]
2. Scottish Intercollegiate Guidelines Network (SIGN) 2013[10]
3. European Society for Medical Oncology (ESMO) 2013[11]
4. Belgian Health Care Knowledge Centre (KCE) 2013[12]
5. Alberta Health Services (AHS) 2014[13]
6. National Comprehensive Cancer Network (NCCN) 2014[14]

Decisive factors considered in selecting guideline:

1. Quality of recommendations
2. Recommendations broken down by T-stage
3. Up to date evidence (and regular future updates)
4. Suggestions are acceptable chemotherapy regimens

The joint ASCO/CAP guideline recommendations for assessment of HER2 status have been widely endorsed and adopted. The consensus of the group was to **ADOPT** the 2013 ASCO/CAP HER2 testing guideline.

Many of the identified guidelines could not be rated using the AGREE II tool due to format of presentation. While NCCN guidelines clearly incorporate an element of expert consensus, they best address all PICOT questions and are the most comprehensive and frequently updated guidelines available. As such, the consensus of the group was to **ADAPT** the 2014 NCCN guideline.

Recommendations

HER2 Testing in Breast Cancer

Recommendations for HER2 testing in breast cancer are the consensus-based opinion of the members of the Working Group and are adopted from the ASCO/College of American Pathologists (CAP) 2013 guideline.

Key recommendations for Oncologists:

- Must request HER2 testing on every primary invasive breast cancer (and on metastatic site, if stage IV and if specimen available) from a patient with breast cancer to guide decision to pursue HER2-targeted therapy. This should be equally considered for a patient who previously tested HER2 negative in a primary tumour and presents with disease recurrence with clinical behaviour suggestive of HER2-positive or triple-negative disease.
- Should recommend HER2-targeted therapy if HER2 test result is positive, if there is no apparent histopathological discordance with HER2 testing, and if clinically appropriate. If the pathologist or oncologist observes an apparent histopathologic discordance after HER2 testing, the need for additional HER2 testing should be discussed.
- Must delay decision to recommend HER2-targeted therapy if initial HER2-test result is equivocal. Reflex testing should be performed on the same specimen using the alternative test if initial HER2 test result is equivocal or on an alternative specimen.
- Must not recommend HER2-targeted therapy if HER2 test result is negative and there is no apparent histopathologic discordance with HER2 testing. If the pathologist or oncologist observes an apparent histopathologic discordance after HER2 testing, the need for additional HER2 testing should be discussed.
- Should delay decision to recommend HER2-targeted therapy if HER2 status cannot be confirmed as positive or negative after separate HER2 tests (HER2 test result or results equivocal). The oncologist should confer with the pathologist regarding the need for additional HER2 testing on the same or another tumour specimen.
- If the HER2 test result is ultimately deemed to be equivocal, even after reflex testing with an alternative assay (i.e., if neither test is unequivocally positive), the oncologist may consider HER2-targeted therapy. The oncologist should consider the feasibility of testing another tumour specimen to attempt to definitely establish the tumour HER2 status and guide therapeutic decisions. A clinical decision to ultimately consider HER2-targeted therapy in such cases should be individualized on the basis of patient status (comorbidities, prognosis, and so on) and patient preferences after discussing available clinical evidence.

Key recommendations for Pathologists:

- Must ensure that at least one tumour sample from all patients with breast cancer (early-stage or metastatic disease) are tested for either HER2 protein expression (IHC assay) or *HER2* gene expression (ISH assay) using a validated HER2 test.
- In the United States, the ASCO/CAP Guideline Update Committee preferentially recommends the use of an assay that has received FDA approval, although a CLIA-certified laboratory may choose instead to use a laboratory-developed test (LDT). In this case, the analytic performance of the LDT must be prospectively

validated in the same clinical laboratory that will perform it, and the test must have documented analytic validity (CAP guidance document). Bright-field ISH assays must be initially validated by comparing them with an FDA-approved FISH assay.

- Must report HER2 test result as positive if: a) IHC 3+ positive or b) ISH positive using either a single-probe ISH or dual-probe ISH. This assumes that there is no apparent histopathologic discordance observed by the pathologist.
- Must report HER2 test result as equivocal and order reflex test on the same specimen (unless the pathologist has concerns about the specimen) using the alternative test if: a) IHC 2+ equivocal or b) ISH equivocal using single-probe ISH or dual-probe ISH. This assumes that there is no apparent histopathologic discordance observed by the pathologist. Note that there are some rare breast cancers (e.g., gland-forming tumours, micropapillary carcinomas) that show IHC 1+ staining that is intense but incomplete (basolateral or U shaped) and that are found to be *HER2* amplified. The pathologist should consider also reporting these specimens equivocal and request reflex testing using the alternative test.
- Must report HER2 test result as negative if a single test (or all tests) performed in a tumour specimen show: a) IHC 1+ negative or IHC 0 negative or b) ISH negative using single-probe ISH or dual-probe ISH. This assumes that there is no apparent histopathologic discordance observed by the pathologist.
- Must report HER2 test result as indeterminate if technical issues prevent one or both tests (IHC and ISH) performed in a tumour specimen from being reported as positive, negative, or equivocal. This may occur if specimen handling was inadequate, if artifacts (crush or edge artifacts) make interpretation difficult, or if the analytic testing failed. Another specimen should be requested for testing, if possible, and a comment should be included in the pathology report documenting intended action.
- Must ensure that interpretation and reporting guidelines for HER2 testing are followed.
- Should interpret bright-field ISH on the basis of a comparison between patterns in normal breast and tumour cells, because artifactual patterns may be seen that are difficult to interpret. If tumour cell pattern is neither normal nor clearly amplified, test should be submitted for expert opinion.
- Should ensure that any specimen used for HER2 testing (cytologic specimens, need biopsies, or resection specimens) begins the fixation process quickly (time to fixative within 1 hour) and is fixed in 100% neutral buffered formalin for 6 to 72 hours and that routine processing, as well as staining or probing, is performed according to standardized analytically validated protocols.
- Should ensure that the laboratory conforms to standards set for CAP accreditation or an equivalent accreditation authority, including initial test validation, ongoing internal quality assurance, ongoing external proficiency testing, and routine periodic performance monitoring.
- If an apparent histopathologic discordance is observed in any HER2 testing situation, the pathologist should consider ordering additional HER2 testing and conferring with the oncologist. Proper documentation regarding the decision-making process with results are to be included in the pathology report. As part of the HER2 testing process, the pathologist may pursue additional HER2 testing without conferring with the oncologist.
- Although categories of HER2 status by IHC or ISH can be created that are not covered by these definitions, in practice they are uncommon and if encountered should be considered IHC equivocal or ISH equivocal.

Adjuvant Therapy for HER2 Positive Breast Cancer

Recommendations for HER2 positive breast cancer are the consensus-based opinion of attendees at the consensus meeting and are adapted from the NCCN 2014 guideline.

Adjuvant Therapy for HER2 Positive Breast Cancer

TNM Stage	Recommendation	Category*
T ≤ 0.5 cm and N0	No adjuvant chemotherapy or trastuzumab	2A
T ≤ 0.5 cm and N1mi (≤ 2 mm)	Consider adjuvant chemotherapy with trastuzumab[i]	2A
T 0.6-1.0 cm and N0	Consider adjuvant chemotherapy with trastuzumab[i]	2A
T > 1 cm and N0	Adjuvant chemotherapy with trastuzumab	1
Any T and Node positive (> 2 mm)	Adjuvant chemotherapy with trastuzumab	1

[i] The prognosis of patients with T1a and T1b tumours that are node negative is uncertain even when HER2 is amplified or overexpressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.

*See appendix V for NCCN category definitions

Regimens: [ii,iii,iv]

1. AC (doxorubicin/cyclophosphamide) followed by T (paclitaxel) + trastuzumab	6. Paclitaxel + trastuzumab[v]
2. TCH (DOCEtaxel/carboplatin/trastuzumab)	7. Trastuzumab + DOCEtaxel followed by FEC
3. AC followed by DOCEtaxel + trastuzumab	8. Trastuzumab + paclitaxel followed by FEC
4. FEC (fluorouracil/epirubicin/cyclophosphamide) followed by DOCEtaxel + trastuzumab	9. DOCEtaxel/cyclophosphamide + trastuzumab (given concurrently)
5. FEC followed by paclitaxel + trastuzumab	

[ii] Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2-positive tumours.

[iii] Trastuzumab should optimally be given concurrently with the taxane, and should be given for one-year total duration.

[iv] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab with an anthracycline should be avoided.

[v] Paclitaxel + trastuzumab may be considered for patients with low-risk stage I, HER2 positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.

Clinical Considerations

In the absence of long-term outcome data, dual anti-HER2 blockade using pertuzumab **with** trastuzumab is **NOT** recommended in the adjuvant setting outside of clinical trials.

References

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V. High Risk Breast Cancer (HER2 negative)

Background

This guideline defines high risk breast cancer as those with either:

1. Involvement of at least one regional lymph node **(node-positive disease)**; ***OR***
2. Negative estrogen, progesterone and HER2 receptor status **(triple-negative)**

Node positive breast cancer represents approximately 40-45% of newly diagnosed breast cancers and triple negative breast cancers represent approximately 10-15% of newly diagnosed breast cancers in Manitoba. High risk breast cancer is associated with the greatest risk for cancer recurrence and deaths from breast cancer. Therefore, it is important to recognize this category of breast cancer early, and treat it adequately.

Key Evidence

The initial search strategy revealed 70 potentially useful guidelines. After excluding duplicate guidelines and those posing questions not directly related to the relevant question, a list of 25 guidelines on adjuvant systemic treatment of breast cancer were identified. Of the 25 guidelines identified, 16 did not precisely include recommendations for high risk breast cancer. Therefore, 9 guidelines met the inclusion criteria and were deemed relevant to management of high risk breast cancer in the adjuvant setting with cytotoxic chemotherapy. These included the following:

1. New Zealand Guideline Group (NZGG) 2009[1]
2. National Institute of Clinical Excellence (NICE) 2009[2]
3. Scottish Intercollegiate Guidelines Network (SIGN) 2013[3]
4. National Comprehensive Cancer Network (NCCN) 2014[4]
5. European Society for Medical Oncology (ESMO) 2013[5]
6. Ministry of Health (MOH) Malaysia 2010[6]
7. Belgian Health Care Knowledge Centre (KCE) 2013[7]
8. Alberta Health Services (AHS)2014[8]
9. Cancer Australia 2011[9]

Decisive factors considered in selecting guideline:

- Quality of recommendations
- Up to date evidence (and regular future updates)
- Explicit recommendations for both node positive (including micro metastasis) and triple negative populations
- Recommendations broken down by T-stage
- Suggestions on acceptable chemotherapy regimens

**Although the NCCN guideline was not amenable to assessment using the AGREE II tool, the consensus of the group was that it was of sufficient quality and that it best met the needs of our group based on its rapidity of evaluation and updating.*

Recommendations

Recommendations for high risk breast cancer are the consensus-based opinion of attendees at the consensus meeting and are adopted from the NCCN 2014 guideline.[4]

Adjuvant Chemotherapy for High Risk Breast Cancer

TNM Stage	Recommendation	Category**
Hormone Receptor Positive and Node Positive		
(Any T and)* N1mi	Consider adjuvant chemotherapy	2B
(Any T and)* ≥ N1*	Recommend adjuvant chemotherapy	1
Triple Negative		
T ≤ 0.5 cm and pN0	No adjuvant chemotherapy	2A
T ≤ 0.5 cm and pN1mi	Consider adjuvant chemotherapy	2A
T 0.6-1.0 cm (and N0)*	Consider adjuvant chemotherapy	1
T > 1 cm (and N0)*	Recommend adjuvant chemotherapy	1
(Any T and)* ≥ N1	Recommend adjuvant chemotherapy	1

*Added for clarification purposes.

**See Appendix V for NCCN definition of categories.

Recommended chemotherapy regimens:

- FEC/CEF-D
- Dose-Dense AC – Paclitaxel
- AC-Paclitaxel
- AC-DOCEtaxel
- FAC-T
- TAC
- TC
- EC/FEC
- FAC/CAF
- Dose-Dense AC
- CMF

References

1. New Zealand Guidelines Group. Management of early breast cancer. Wellington: New Zealand Guidelines Group; 2009. Available at: http://www.health.govt.nz/. Accessed on 10 September 2014.
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VI. Lymph Node Negative

Background

Lymph node negative breast cancer is common, representing approximately 55% of all newly diagnosed breast cancers in Manitoba. Adjuvant treatment recommendations are based on a risk:benefit comparison of the treatment under discussion. With respect to chemotherapy, the recommendation to use chemotherapy is given when the estimated benefits of chemotherapy in reducing risk of recurrence and/or death exceed the expected risks of chemotherapy treatment. Commonly used features that portend a lower risk of recurrence include the hormone receptor positive and HER2/neu negative phenotype, a tumour size < 1 cm. Features typically considered high risk include hormone receptor negative, HER2 positive, triple negative (ER, PR, and HER2/neu negative), histological grade III, lymphovascular invasion, and age at diagnosis < 35 years.

Key Evidence

Applicable guidelines evaluated and used:

- Alberta Health Services (AHS) 2014[1]
- European Society for Medical Oncology (ESMO) 2013[2]
- National Comprehensive Cancer Network (NCCN) 2014[3]

The attendees of the consensus meeting found the Alberta Health Services (AHS) guideline most applicable to developing guidelines in determining the role of chemotherapy in women with lymph node negative breast cancer because it was risk-based and referenced contemporary high-quality publications.[1] The ESMO guideline used a risk-based approach but was felt to be difficult to interpret given the inexact categorization of cancers by molecular subtype using typical risk factors.[2] The guidelines did appear to generally correlate well with the recommendations in the AHS guideline. The NCCN guideline was not selected because it did not consider some of the commonly regarded risk factors, instead using the OncotypeDx® (21-gene recurrence score) to stratify patients for treatment.[3] Currently, the OncotypeDx® assay is not funded in Manitoba.

Due to the aforementioned reasons, the Working Group has chosen to **ADAPT** the **Alberta Health Services (AHS) 2014** guideline recommendations pertaining to lymph node negative breast cancer as outlined below.

Recommendations

Recommendations for lymph node negative breast cancer are the consensus-based opinion of attendees at the consensus meeting and are adapted from the AHS 2014 guideline.[1]

Adverse Prognostic Factors

- Age < 35 years
- HER2 over-expression (HER2+)
- Presence of lymphovascular invasion
- Grade 3
- Hormone receptor negative disease
- OncotypeDx® Recurrence Score > 30
- ER- or PR-negativity

Table 1. Alberta Health Services - Risk Groups[1]

Risk Category	Risk Factor	Preferred Adjuvant Therapy
Lower Risk	• ≤ 2 cm, grade 1, with no other adverse prognostic factors • < 0.5 cm with any other feature • OncotypeDx® Recurrence Score < 18	Endocrine therapy alone
Intermediate Risk	• All other combinations of factors that do not fit into either the low or high risk criteria • OncotypeDx® Recurrence Score 18-30	Consider 2nd generation TC (DOCEtaxel/cyclophosphamide)
High Risk	• > 1 cm with any adverse prognostic factor • > 3 cm • HER2+ breast cancer* • OncotypeDx® Recurrence Score > 30	Consider 3rd generation anthracycline + taxane

*Refer to the specific guideline recommendations for HER2+ or triple negative breast cancer *(see Section IV and V)*

References

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VII. Adjuvant Endocrine Therapy

Background

Adjuvant endocrine therapy has been used to treat breast cancer and has shown effectiveness in the subgroup of breast cancer patients with estrogen (ER) and/or progesterone (PR) receptor positivity with approximately 60-75% of patients having this subtype of breast cancer. Using the following terms, a literature search was performed to identify relevant guidelines: 'breast', 'adjuvant endocrine therapy', and 'systemic therapy'. The search was originally limited to articles published after January 1, 2009, identifying 15 guideline documents. Upon reviewing the data it was decided that only guidelines presented and published in late 2013 had relevance in this area. Subsequently, adjusted search parameters identified 5 relevant guidelines for inclusion.

Key Evidence

Identified guidelines relevant to Manitoba's population include the ASCO 2014 guideline, SIGN 2013, ESMO 2013, Belgian guideline 2013 as well as the NCCN 2014 guideline.[1-5] These guidelines were assessed for quality using the AGREE II tool, and after comparing the AGREE II tool scores for each, the guidelines were evaluated for their applicability to Manitoba's population. The NCCN 2014 guideline was difficult to interpret with the AGREE II tool, and was felt to have a less rigorous process for its development. Due to its formatting, it was a very difficult guideline to evaluate, which led to its exclusion. Given the ESMO guideline is similarly difficult to evaluate, it was also felt to less adequately meet our needs and be less amenable to critical appraisal. The SIGN guideline scored lower in some key domains than the ASCO guideline in terms of the AGREE II tool assessment, as did the Belgian guideline. For these reasons, the attendees of the consensus meeting chose to adopt the recommendations from the ASCO 2014 guideline.

Recommendations

Recommendations for adjuvant endocrine therapy are adopted from the ASCO 2014 guideline.[1]

1. Women diagnosed with hormone receptor-positive breast cancer who are pre- or perimenopausal should be offered adjuvant endocrine therapy with:
    a. Tamoxifen for an initial duration of 5 years (*Evidence Grade: High)*
    b. After 5 years, women should receive additional therapy based on menopausal status (*Evidence Grade: High)*
        i. If women are pre- or perimenopausal, or if menopausal status is unknown and cannot be determined, they should be offered continued tamoxifen for a total duration of 10 years. (*Evidence Grade: High)*
        ii. If women have become definitively postmenopausal, they should be offered continued tamoxifen for a total duration of 10 years or switching to up to 5 years of an aromatase inhibitor (AI), for a total duration of up to 10 years of adjuvant endocrine therapy. (*Evidence Grade: High)*

2. Women diagnosed with hormone receptor-positive breast cancer who are postmenopausal should be offered adjuvant endocrine therapy with one of the following options:

    a. Tamoxifen for a duration of 10 years. (*Evidence Grade: High)*; **OR**

    b. An AI for a duration of 5 years. There are insufficient data currently to recommend an AI for a duration of greater than 5 years. (*Evidence Grade: High)*; **OR**

    c. Tamoxifen for an initial duration of 5 years, then switching to an AI for up to 5 years, for a total duration of up to 10 years of adjuvant therapy. (*Evidence Grade: High)*; **OR**

    d. Tamoxifen for a duration of 2 to 3 years and switching to an AI for up to 5 years for a total duration of up to 7 to 8 years of adjuvant endocrine therapy. (*Evidence Grade: High)*

3. Women who are postmenopausal and are intolerant of either tamoxifen or an AI should be offered the alternative type of adjuvant endocrine therapy.

    a. If women have received an AI but discontinued treatment at less than 5 years, they may be offered tamoxifen for a total of 5 years. *(Evidence Grade: Low (consensus)*

    b. If women have received tamoxifen for 2 to 3 years, they should be offered switching to an AI for up to 5 years, for a total duration of up to 7 to 8 years of adjuvant endocrine therapy. (*Evidence Grade: High)*

4. Women who have received 5 years of tamoxifen as adjuvant endocrine therapy should be offered additional adjuvant endocrine treatment.

    a. If women are postmenopausal, they should be offered continued tamoxifen for a total duration of 10 years or switching to up to 5 years AI, for a total duration of up to 10 years of adjuvant endocrine therapy. (*Evidence Grade: High)*

    b. If women are pre- or perimenopausal, or menopausal status cannot be ascertained, they should be offered 5 additional years of tamoxifen, for a total duration of 10 years of adjuvant endocrine therapy. (*Evidence Grade: High)*

References

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VIII. Ovarian Suppression

Background

Suppression of ovarian function as adjuvant treatment for breast cancer in premenopausal women has been studied extensively. Women who remain premenopausal after treatment with adjuvant chemotherapy have inferior outcomes when compared stage for stage with those that achieve menopause after adjuvant chemotherapy. This has led to clinical trials investigating the benefit of adjuvant ovarian suppression (OS) to improve disease free and overall survival in patients that do not experience chemotherapy-induced amenorrhea. A literature search was undertaken, with the goal of identifying relevant trials that answer the question as to whether OS is feasible and improves outcomes. Twenty-one potentially relevant trials were identified. Four randomized phase III clinical trials and one retrospective analysis met criteria for inclusion in this review. No guidelines were identified that answered relevant clinical questions on this topic. Data from these trials were used to perform a meta-analysis to assess the benefit of OS with endocrine therapy in this population.

Key Evidence

The key published trials that met the search criteria with relevant outcomes included the Suppression of Ovarian Function Trial (SOFT) trial, INT-0142 trial, IBCSG VIII trial, and the Zoladex in Premenopausal Patients (ZIPP trial). The SOFT trial randomized patients to Tamoxifen vs. Tamoxifen with Ovarian Suppression (OS), or Exemestane with OS. OS was achieved by LHRH agonist or oophorectomy, or radiation therapy to ovaries.[1] Overall this was a negative trial, however an unplanned subgroup analysis of premenopausal women that remained premenopausal post-chemotherapy and were treated with OS + exemestane had a superior disease free survival and reduced recurrence compared to those in the Tamoxifen alone or Tamoxifen + OS groups.[1] The INT 0142 trial did not accrue as hoped, and early closure limited the ability to make conclusions regarding the impact of OS with Tamoxifen on survival in comparison with Tamoxifen alone.[2] The IBCSG VIII randomized women to CMF, CMF + Goserelin or Goserelin alone.[3] The combination of CMF + Goserelin was superior to either treatment alone in patients with lymph node negative and hormone receptor positive breast cancer.[3] The ZIPP trial randomized patients to Tamoxifen vs. Combination Tamoxifen + Goserelin vs. no endocrine therapy.[4] The trial was underpowered to demonstrate a survival advantage between the arms; however the time to first recurrence was lower in the OS groups.[4] Using hazard ratios of the data from these trials, there are superior disease free survival outcomes seen in the patients treated with LHRH agonists with a HR of 0.77, p = 0.002 (unpublished).

Recommendations

For a guideline regarding the role of adjuvant ovarian suppression therapy:

- There is insufficient evidence of benefit to routinely recommend adjuvant ovarian suppression for premenopausal patients with breast cancer
- In high risk premenopausal patients with premenopausal estradiol levels within 8 months after adjuvant chemotherapy, it is acceptable to present the option for use of ovarian suppression therapy concurrently

with exemestane or other aromatase inhibitor therapy OR tamoxifen if poor tolerance to aromatase inhibitor therapy, for a total duration of 5 years

- Options for ovarian suppression include monthly LH-RH agonist therapy or oophorectomy

References

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IX. Timing of Adjuvant Chemotherapy

Background

The expeditious timing of adjuvant therapy is an important consideration in the multimodal treatment plan of all breast cancer patients. Treatment delays can have important implications for the psychosocial health of patients as well as their financial wellbeing if they are off work during this time. A potential negative impact on the success rate of adjuvant therapy is plausible but not adequately studied. It is for those reasons that addressing the timeline for therapy is crucial.

While prompt delivery of adjuvant therapy is important, some time is required to collate all necessary patient information and to make sound therapy decisions. In this window of time, the following occurs: reporting of pathology, staging investigations (for advanced stage disease), medical oncology consultation, line placement and chemotherapy scheduling.

In addition to the above considerations, there is a group of patients, who after their first surgery will require both further surgery and adjuvant chemotherapy. This group of patients provides a complex challenge to coordinate care. This care is further complicated by the fact that it occurs both outside and within the cancer centre. Clarification on priorities and order of treatment is likely to better streamline care and to avoid delays and confusion, both for the patient and treating physicians.

Key Evidence

Two guidelines addressed the issue of optimal timing of the delivery of adjuvant chemotherapy. The UK National Health Service NICE guideline reviewed timing of adjuvant therapy in its breast cancer diagnosis and treatment guideline.[1] It recommends starting adjuvant therapy "as soon as clinically possible within 31 days of completion of surgery." The guideline's authors acknowledge that this is a consensus statement in the absence of strong scientific study. The Belgian Healthcare Knowledge Centre also addressed this issue in its 2013 guideline.[2] This group set a timeline of eight weeks to the initiation of adjuvant chemotherapy or radiotherapy. The strength of this recommendation is based on a robust literature on the timing of radiotherapy, as opposed to the limited evidence on timing of chemotherapy.

With limited and conflicting recommendations from existing guidelines, it was felt that a review of the primary literature would be beneficial for this topic. Two recent systematic reviews were identified. One highly pertinent retrospective study published in 2014 was also included. Balduzzi and colleagues reviewed the literature in 2010 and identified five studies where early administration of chemotherapy was compared to later initiation of chemotherapy.[3] What defined early and late initiation was different in each study; early onset ranged from 1 to 34 days post-operatively, while late was anywhere from 21 days to 12 weeks. Each study did however find a statistically significant improvement in disease free survival with early delivery of chemotherapy. Yu and colleagues expanded on this analysis in 2013 by performing a formal meta-analysis on these studies as well as more recent ones tackling this topic.[4] They too found a benefit to the early administration of chemotherapy and quantified the impact with a hazard ratio of 1.15 for every 4 weeks of delay in chemotherapy. The third study reviewed was a

retrospective review of almost 7000 patients treated with adjuvant chemotherapy at the MD Anderson Cancer Centre.[5] Findings showed an improved survival in patients receiving chemotherapy in less than 30 days compared to those delayed 61 days or more. Interestingly, this study found the benefit of early chemotherapy was limited to certain high risk groups, namely those with stage III disease, those who were triple negative, and HER2 positive patients treated with trastuzumab.

A word of caution must be given when interpreting the above mentioned studies, as they do come with significant limitations. All of these studies were retrospective in nature and by that very method are prone to potential bias. In particular, there may be factors in poor prognosis patients that lead to a delay in starting chemotherapy. For example, more advanced tumours require staging investigations in the post-operative period which may delay chemotherapy administration. The other caution in this literature is almost all patients in these studies received chemotherapy that we would currently deem outdated and suboptimal. We do not know whether these results would be replicated in our current treatment era; it is equally possible that modern chemotherapy may negate or exaggerate these findings.

The CCMB guideline working group was also interested in making recommendations around the coordinated timing of additional surgery and chemotherapy when both treatments are required. The scenario where this most frequently occurs is when an attempt at breast conserving surgery (i.e., lumpectomy) has not achieved microscopically negative margins at the initial operation. No other published guidelines addressed this scenario. Historically, adjuvant therapy trials defined the time to treatment, from the date of the last surgery not the first. At the consensus meeting the audience viewed flow diagrams that illustrate how, in our current Manitoba system, performing a second surgery can delay the onset of chemotherapy to 18 weeks or more from the date of diagnosis. With this in mind, we do recognize the expanded role for neoadjuvant chemotherapy in operable breast cancer. The BC Cancer Agency summarizes this philosophy well in the following guideline statement: “If on the basis of a core biopsy and patient characteristics, there is sufficient information to recommend chemotherapy, it is acceptable to proceed with chemotherapy first, even when a cancer is not locally advanced.”[6] By extension, if chemotherapy can be delivered prior to any surgery, it must be safe to place it juxtaposed between a first and subsequent surgery. A consensus discussion agreed with this philosophy in the absence of studies to address this clinical concern directly.

Recommendations

1. It is generally recommended to start adjuvant chemotherapy within 8 weeks of surgery. When feasible, patients with stage III disease, triple negative tumours, or HER2 positivity should start chemotherapy as soon as possible after surgery.

Note: The above statement does not imply that all patients require surgery first; some patients may be better suited for neoadjuvant chemotherapy.

2. In the setting where the first surgical pathology reveals the need for further surgery and shows clear indication for adjuvant chemotherapy:
    - It is reasonable to proceed with adjuvant chemotherapy and delay the second surgery until chemotherapy completion.

- Medical oncology referral and consultation may occur concurrently with further surgical plans to limit time delays.

Recommendations for Future Development

The amount of time that it takes to transition a patient from surgery to chemotherapy is dependent on many steps. A working group is required to find time savings in the referral, triage and consultation processes. Pathology delays, triage processes, manpower shortages and limited access to line insertion and chemotherapy delivery sites are just some examples for potential reasons for delay. The working group should look at processes to accept and triage high risk referrals at earlier time points in the patient's journey and shortening the time from receipt of referral to first appointment in most cases. Improving manpower and resources in the province to expedite reporting pathology, shorten wait times for staging investigations and medical oncology consultation, and increasing the number of chemotherapy "chairs" at our delivery sites is also important, but beyond the scope of this guideline. The discussion did acknowledge that the overuse of staging investigations against current CCMB breast cancer staging guidelines should be discouraged.

The group did discuss the use of neoadjuvant chemotherapy for high risk but operable breast cancer. The current practice environment employs this strategy in limited cases and there was much interest in expanding this role. There was much interest in exploring this topic further and a dedicated neoadjuvant chemotherapy guideline will be developed by this group at a future date. If a surgeon or treating physician is uncertain if a patient should be considered for neoadjuvant or early adjuvant approach, then discussion with a medical oncologist or the Breast DSG is encouraged. Similarly, if a surgeon is uncertain about whether to schedule a second (or third) surgery, or to refer on for medical oncology assessment, then prompt contact with this group is encouraged.

References

1. National Institute for Health and Care Excellence. Early and locally advanced breast cancer: diagnosis and treatment (Clinical Guideline 80). London: National Institute of Clinical Excellence, 2009. Available at: https://www.nice.org.uk/guidance/cg80. Accessed on 8 September 2014.
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X. Implementation of Guideline

The value of guidelines truly lies in their implementation and use. For that purpose, consideration was given to implementation during the planning of the consensus meeting, at the meeting, and during the drafting of this guideline document.

Local Consensus and Leader Support

As part of the knowledge translation approach, all physicians for whom these guidelines are applicable were invited to participate in the consensus meeting. There was an impressive response and good attendance. An outside expert was invited to speak and this was well appreciated by the attendees. Continuing Medical Education (CME) credits were provided.

Attendees from the meeting are expected to act as local opinion leaders disseminating and providing guidance to their colleagues on the recommendations developed at the consensus meeting.

Dissemination

It was recognized during the meeting that resources would be needed to distribute these guidelines to the community. For that purpose, the guideline will be accessible online through the CancerCare Manitoba website. Online availability will be preceded by an e-blast notification with the website embedded. Announcement of the guideline and updates will be through established provincial communication channels; the Community Oncology Program to CCPN rural sites, UPCON clinics and WRHA Community Oncology Program sites. This guideline will also be provided to partner organizations and guidelines reviewers in other provinces. Use of the guideline in clinics will be through the online version.

Educational Events

Presentation of the guideline's recommendations will be made available at rounds and conferences; Breast DSG rounds, CCMB Haematology/Oncology Regional Grand rounds, Allied Health rounds (Patient Services rounds), CCPN Community Cancer Care annual educational conference and at UPCON education and training events.

XI. Contact Physician and Contributors

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XII. Conflict of Interest

In accordance with the CancerCare Manitoba (CCMB) policy no. 01.001, “Conflict of Interest”, the authors of this guideline have disclosed conflicts of interest. Relationships with commercial interests were declared by three working group members; a Merck Honorarium (Dr. Pamela Hebbard), attendance at a Roche Advisory Board meeting (Dr. Vallerie Gordon) and attendance at a Novartis, Bristol-Myers Squibb Advisory Board meeting (Dr. Debjani Grenier). As members have adhered to the CCMB policy no. 01.014, “Interaction with Industry Representatives”, the developers are satisfied this guideline has been developed without bias and is based on best evidence and best practice. The authors of this guideline declare that no commercial support was received for their presentations at the 2015 Breast Consensus Meeting or during development of this guideline.

XIII. Appendices

Appendix 1

Levels of Evidence	
Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed, quasi- experimental study
III	Evidence obtained from well-designed, non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities
British Committee for Standards in Haematology 2007 http://www.bcshguidelines.com	

Appendix 2

2015 Breast Cancer Provincial Consensus Meeting
Group Discussion

Statement	Decision	Consensus / Comments
1. *For women with HER2+ breast cancer, recommendation is to **ADAPT** the **2014 NCCN** guideline for adjuvant therapy. Changes proposed:* • *In the absence of long-term outcome data, dual anti-HER2 blockade using pertuzumab is* **not recommended** *in the adjuvant setting outside of clinical trials* • *No preference given to AC → T over other anthracycline + taxane containing regimens*	Support	12
	Do Not Support	
	Support with Modification	1
	Modification	Include DOCEtaxel/cyclophosphamide + trastuzumab (given concurrently) as an acceptable regimen. Add qualifier statement: *Although the NCCN guideline was not amenable to assessment using the AGREE II tool, the consensus of the group was that it was of sufficient quality and that it best met the needs of our group based on its rapidity of evaluation and updating.*
2. *Recommendation to **ADOPT** the **ASCO/CAP** HER2 testing guideline*	Support	13
	Do Not Support	
	Support with Modification	
	Modification	
3. *Recommendation for cytotoxic adjuvant chemotherapy for node positive and triple negative breast cancer is to **ADOPT** the **NCCN 2014 guideline***	Support	12
	Do Not Support	
	Support with Modification	1
	Modification	Add qualifier statement: *Although the NCCN guideline was not amenable to assessment using the AGREE II tool, the consensus of the group was that it was of sufficient quality and that it best met the needs of our group based on its rapidity of evaluation and updating.*
4. *Recommendation to **ADAPT** the **AHS 2014 guideline** with modification of:* • *Risk Groups:* ○ *ER- or PR-negativity are adverse prognostic factors* ○ *High risk: HER2+, or RS >30, or >3 cm, or >1 cm and any adverse prognostic factor* • *Preferred chemotherapy regimen:* ○ *Low risk: endocrine therapy alone* ○ *Intermediate risk: consider 2nd generation [TC]* ○ *High risk: consider 3rd generation (anthracycline + taxane)* ○ *HER2+ or triple negative breast cancer to follow those specific guideline statements*	Support	15
	Do Not Support	
	Support with Modification	
	Modification	

Statement	Decision	Consensus / Comments
5. For premenopausal and postmenopausal women with hormone receptor positive breast cancer recommendation is to: • ***ADOPT** the **ASCO guideline** for adjuvant endocrine therapy of hormone receptor positive breast cancer* *vs.* • ***ADOPT** the **2014 NCCN guideline***	Support	15 support **ADOPT** the **ASCO guideline**
	Do Not Support	
	Support with Modification	
	Modification	
6. For a guideline regarding the role of adjuvant ovarian suppression therapy: • *There is insufficient evidence of benefit to routinely recommend adjuvant ovarian suppression for premenopausal patients with breast cancer* • *In high risk premenopausal patients with premenopausal estradiol levels within 8 months after adjuvant chemotherapy, it is acceptable to present the option for use of ovarian suppression therapy concurrently with exemestane* • *Preferred options for ovarian suppression include monthly LH-RH agonist therapy or oophorectomy (or ovarian radiation therapy)*	Support	
	Do Not Support	1
	Support with Modification	15
	Modification	In high risk premenopausal patients with premenopausal estradiol levels within 8 months after adjuvant chemotherapy, it is acceptable to present the option for use of ovarian suppression therapy concurrently with exemestane or other aromatase inhibitor therapy OR tamoxifen if poor tolerance to aromatase inhibitor therapy, for a total duration of 5 years Options for ovarian suppression include monthly LH-RH agonist therapy or oophorectomy ***Level of Evidence IIb***
7. It is generally recommended to start adjuvant chemotherapy within 8 weeks of surgery. When feasible, patients with advanced disease, triple negative tumours, and HER2 positivity should start chemotherapy as soon as possible after surgery.	Support	
	Do Not Support	
	Support with Modification	16
	Modification	When feasible, patients with stage III disease, triple negative tumours or HER2 positivity should start chemotherapy as soon as possible after surgery. The above statement does not imply that all patients require surgery first; some patients may be better suited for neoadjuvant therapy.
8. In the setting where the first surgical pathology reveals the need for further surgery and shows clear indication for adjuvant chemotherapy: • *It is reasonable to proceed with adjuvant chemotherapy and delay the second surgery until chemotherapy completion* • *Medical oncology referral and consultation may also occur concurrently with further surgical plans to limit time delays* ***Level of Evidence V***	Support	16
	Do Not Support	
	Support with Modification	
	Modification	

Appendix 3

2015 Breast Cancer Provincial Consensus Meeting
Guiding Assumptions

- Presenters' recommendations are based upon best available evidence
- Presenters are unbiased in their presentation of the best available literature
- Participants will use the data to assess the validity and appropriateness of the consensus statement
- Participants will remain unbiased and attempt to make decisions based on the best available evidence as presented
- All consensus items will be reviewed prior to discussion of any particular items where consensus has not been reached
- Consensus will be reached as a product of the discussion groups, first individually and then as a consortium
- Consensus is defined as 'agreement of 75% of participants in attendance at the afternoon session'
- If any participant leaves the conference before the end of the day, it will be assumed that he/she is in agreement with all of the final consensus statements
- Participants are expected to act as local opinion leaders and provide guidance to their clinical peers concerning the consensus information generated by this conference

Appendix 4

2015 Breast Cancer Provincial Consensus Meeting Agenda

Consensus Meeting Agenda

7:45 BREAKFAST		
8.15 – 8.30 **LECTURE THEATRE** **Moderator: Dr. Vallerie Gordon – Welcome, Introductions and Opening Remarks**		
8.30 – 9.15 **LECTURE THEATRE** **Keynote Address**	**Dr. Maureen Trudeau** The Importance of Guideline/ Evidence Based Therapy in Breast Cancer	• Familiarize the audience with the guideline development cycle • To highlight how guidelines result in improved cancer related outcomes • To explain how guidelines are used in Canada to support drug funding for systemic cancer therapy
9.15 – 9.45 **Presentation**	**Dr. Vallerie Gordon** Status of Breast Cancer Guidelines in Manitoba/Rationale for Guidelines Based Treatment in Manitoba	• Be familiar with the relevant current guidelines directing adjuvant systemic therapy in early breast cancer for adjuvant curative intent • Have an understanding of the Agree Tool method to evaluate systematic reviews and guidelines • Assist with selection of the relevant guideline for adjuvant treatment for our population consisting of women with early breast cancer
9:45 – 10:00 NUTRITION BREAK		
10:00 – 12:15 **LECTURE THEATRE** **Clinical Question, Literature Review and Recommendations**	**Dr. Danielle Desautels** Under the supervision of **Dr. Debjani Grenier** "Adjuvant HER2 – Targeted Therapy for Breast Cancer"	• Be familiar with the population presenting with early HER2+ breast cancer and the potential benefit for adjuvant HER2-targeted therapies in this population • Be familiar with the relevant guidelines directing HER2-targeted therapy in early breast cancer for adjuvant curative intent • Assist with selecting the relevant guideline for our population consisting of women with HER2+ breast cancers that are: » Node-positive, or node-negative with tumour size > 1 cm » Node-negative with tumour size > 5 mm but ≤ 10 mm (ie, T1b) » Node-negative with tumour size > 1 mm but ≤ 5 mm (ie, T1a)
	Dr. Saroj Niraula "Cytotoxic Chemotherapy of Adjuvant Treatment of Breast Cancer with Involvement of Regional Node(s) and/or with Triple Negative Phenotype"	• Familiarize audience with population who present with potentially curable breast cancer with high risk features that includes involvement of regional node(s) or triple negative histology • Familiarize audience with current guidelines regarding treatment of node positive and triple negative breast cancer with cytotoxic chemotherapy in the adjuvant setting • Familiarize audience with the major evidence underlying treatment of high risk breast cancer • Explain selection of a guideline appropriate for implementation in Manitoba to treat node positive and triple negative breast cancer
	Dr. Marshall Pitz "Node Negative Breast Cancer – Adjuvant Chemotherapy"	• Be familiar with the population currently presenting with early node negative breast cancer and the potential benefit for adjuvant chemotherapy in this population • Be familiar with the relevant guidelines directing chemotherapy in early breast cancer for adjuvant curative intent • Assist with selecting the relevant guideline for our population consisting of women with lymph node negative breast cancer
12:15 – 1:00 LUNCH		
1:00 – 1:15	**Dr. Mark Kristjanson – Direct Referral for Breast Imaging Go Live Announcement**	
1:15 – 2:45 **LECTURE THEATRE** **Clinical Question, Literature Review and Recommendations**	**Dr. Vallerie Gordon** "Adjuvant Endocrine Therapy"	• Be familiar with the population currently presenting with early hormone responsive breast cancer and the potential benefit for adjuvant endocrine manipulation in this population • Be familiar with the relevant current guidelines directing endocrine therapy in early breast cancer for adjuvant curative intent • Assist with selecting the relevant guideline for our population consisting of women with breast cancer with ER and/or PR positive status that are: » Premenopausal » Postmenopausal » Initially premenopausal but become postmenopausal following chemotherapy or during endocrine therapy
	Dr. Pamela Hebbard "Adjuvant Therapy: Timing Considerations"	• To determine what is an acceptable time frame for patients to receive adjuvant therapy • To understand the negative impacts that may occur if there are delays in treatment • To highlight times when adjuvant systemic therapy should precede further surgery for positive margins
2:45 – 3:00 – NUTRITION BREAK		
3:00 – 4:00	**Review of Consensus Recommendations**	

Appendix 5

NCCN Category Definitions

Category	Definition
1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

Appendix 6

Internal/External Guideline Review Results	
Dr. Cornelius Woelk *CW Wiebe Medical Centre* *Winkler, MB*	• I am not familiar enough with the entire literature to comment on missed trials. The review noted seems complete. • As a Family Physician in Oncology I feel less able to comment on the wider literature and data. • Applying the treatment plans will not be challenging in my area of work at the Community Cancer Program level • In general, I would be following the guidelines, but it is the Medical Oncologist who determines the treatment plan, which we then carry out. Hopefully they would be following the guidelines. Sometimes patients ask questions of PFOs regarding treatment benefit and options. It is good to have guidelines such as these to refer to when speaking with patients. • Please note my comments, as embedded into the guideline document. • Overall, this guideline is a welcome addition to those already in place, and my comments are mostly of clarification, etc.
Dr. Dean Reuther *Alberta Health*	• Overall very well done • Clear, detailed description of the questions to be addressed, methodology for review and the resultant recommendations • Glad to see that addressing neoadjuvant treatment will be the topic of another guideline • **Very important** that the "companion work" of assessment of practice against the guideline recommendations is undertaken • Guidelines are of limited volume if not used as a tool for benchmarking and practice improvement • Interesting that a radiation oncologist was not involved in the development of these guidelines • Another important "companion" work piece is the development of clinical care pathways that speak to these guidelines • Also interested to see if Manitoba is tackling issues around breast reconstruction
Dr. David Dawe *CancerCare MB*	• There are widely different opinions of NCCN 2014 guidelines in this guideline, from "less rigorous" (p.22) to "best met needs" (p16). ○ Why would needs change by section? • The recommendations in various places to "consider adjuvant chemotherapy" are not very helpful, though I realize they mean it's at physician and patient discretion.

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CCMB Clinical Practice Guideline: Disease Management
Breast Cancer