Princess Margaret Hospital
University Health Network

PRINCESS MARGARET CANCER PROGRAM
CLINICAL PRACTICE GUIDELINES

BREAST SITE GROUP
May 2017

Revision dated December 2015

FIRST PRODUCTION EDITOR
Dr Eitan Amir

FIRST REVISION EDITOR
Dr Erin Cordeiro

SECTION EDITORS

Section 1 & 2
Introduction & Prevention …… Ruth Heisey, Bridgette Lord
Section 3 & 4.1
Screening and Early Detection & Diagnostic Imaging……Anabel Scaranelo, Pavel Crystal, Supriya Kulkarni
Section 4.2
Pathology…….Hal Berman, Susan Done, Anna Marie Mulligan, Naomi Miller, Bruce Youngson
Section 5 & 5.1.1
Management Algorithm & Surgical management…….....Wey Leong, David McCready, Alexandra Easson, Michael Reedijk
Section 5.1.1
Reconstructive Surgery ……..Stefan Hofer, Toni Zhong, Agnes Wisniewski
Section 5.1.2
Systemic therapy……Eitan Amir, Philippe Bedard, David Warr
Section 5.1.3
Radiation therapy ……Anthony Fyles, Anne Koch, Fei-Fei Liu, Jennifer Croke
Section 5.2
Locally Advanced Breast Cancer ……Nancy Gregorio, Barbara Fitzgerald
Section 5.3
Metastatic Disease……Eitan Amir, Philippe Bedard, David Warr
Section 5.4
Special Scenarios……..Wey Leong
Section 6.1
Symptom Management……. ……..Eitan Amir, David Warr
Section 6.2
Psychosocial Oncology ……Lori Bernstein, Norma D'agostino
Section 6.3
Oncology Social Work ……Robin Forbes
Section 6.4
Survivorship self-care Clinics……...Aleksandra Chafranskaia, Stephanie Phan, Jennifer Jones
Section 6.5
Clinical Nutrition…….……Daniela Fierini, Susan Haines
Section 6.6
Cancer Genetics Support Program……..Mary Jane Esplen
Section 7
Follow-up care …….....Nela Bene

Revision dated December 2015

TABLE OF CONTENTS

1. INTRODUCTION

Genetic and familial factors can significantly increase the lifetime risk of developing breast cancer and women with known genetic mutations such as BRCA1 and 2 mutation carriers have a substantially increased risk of cancer as well as a propensity to present with cancer at a younger age. Evidence shows that strategies to reduce risk of cancer in these populations are effective.

An accurate individualized risk assessment is necessary to make meaningful recommendations. These recommendations may include: lifestyle changes, referral for consideration of genetic testing, enhanced screening, chemoprevention or risk-reducing surgery.

Identification of potential BRCA mutation carriers followed by a thorough qualitative and in some cases quantitative risk assessment allows for a more tailored approach to care.

2. PREVENTION

(This section was last updated February 2017)

QUALITATIVE RISK ASSESSMENT

Multiple factors are known to influence a woman's risk of developing breast cancer.

Risk Factors

Age

The single greatest risk factor for breast cancer is age. The risk of a 60 year old woman being diagnosed with breast cancer in the next ten years (3.45%) is eight times that of a 30 year-old woman (0.43%) (1).

Hormonal Factors

Prolonged exposure to ovarian hormones appears to increase breast cancer occurrence (2, 3). Combined hormone replacement therapy (HRT) increases breast cancer risk with risk increasing the longer it is used. If 10,000 women took combined HRT for one year there would be 8 more cases of breast cancer per year (Beral V, Million Women Study Collaborators. Lancet 2003; 362(9382):419-27, Chlebowski RT, Manson JE, Anderson GL, et al. J Natl Cancer Inst 2013;105(8):526-35.) The risk returns to usual risk 3 years after stopping combined HRT.

Risk Factor	Comparison Category	Relative Risk
Early menarche (before age 12)	Menarche after age 15	1.3
Late menopause (after age 55)	Menopause age 45 or younger	1.2-1.5

Nulliparous or first child after age 30	First live birth before age 20	1.7-1.9
Combined hormone replacement therapy (HRT) for 10 or more years	No history of HRT use	1.5

Ionizing Radiation
Exposure of the breast to therapeutic levels of ionizing radiation is associated with an increase in breast cancer risk, especially if the exposure occurs between 10 to16 years of age. The risk in these patients seems to rise at around 8-10 years after they received their radiation treatment. For example, a female diagnosed with Hodgkin lymphoma at age 20 years and treated with 40 Gray of chest irradiation and no alkylating agents has an estimated cumulative breast cancer risk of 19.1% (95 % CI, 13.0% to 27.4%) over the next 30 years(4). It is recommended that screening programs to detect breast cancer should be initiated within 9 years after mantle radiation (5).

Breast Density
The relative risk associated with increased mammographic density is substantially larger than the relative risk of breast cancer associated any menstrual and/or reproductive risk factors. Women with very dense breasts (density of > 75%) have over four times the risk of developing breast cancer compared those with fatty breasts (breast density <10%) (6).

Dietary Factors
One of the most studied lifestyle factors related to breast cancer risk has been diet. However, many of the findings are inconclusive due to difficulties in study design and long-term follow-up. Regular Vitamin D intake (1000 IU daily) during the winter months and a healthy diet with no more than three servings of red meat per week might provide some protection against breast cancer (7, 8).

Alcohol Consumption
Alcohol intake is associated with a small increased risk for developing breast cancer (9). Consumption of two or more alcoholic drinks per day is thought to convey a relative risk of 1.3 of developing breast cancer (10).

Increased Body Mass
Increased body mass appears to be a more important risk factor in postmenopausal women than in premenopausal women. An increased body mass index in postmenopausal women demonstrated a relative risk of 1.2-1.9 (3).

Exercise
A sedentary lifestyle may make women more prone to developing breast cancer compared to an active lifestyle (11, 12). Women who engaged in the equivalent of 1.25 to 2.5 hours per week of brisk walking had an 18% decreased risk of postmenopausal breast cancer (RR, 0.82; 95% CI, 0.68-0.97) compared with inactive women (13). Regular exercise, such as taking a brisk walk for

30 minutes 5 days of the week could assist with weight loss, reduce breast cancer risk (13) and improve cardiovascular health (14).

Race and Ethnicity
White women are slightly more likely to develop breast cancer than African-American women however, in women under the age of 45, breast cancer is more common in African- American women. Asian/Pacific Islanders, Hispanic, and Native-American women have a lower risk of developing breast cancer (15).

History of Previous Breast Biopsy with Atypia
A previous breast biopsy demonstrating atypical ductal or lobular hyperplasia is thought to convey a relative risk as high as 5.3 for developing breast cancer. Other studies have found the relative risk associated with atypia to be slightly lower at 4.24 (95 percent confidence interval, 3.26 to 5.41), This increased risk is expected to persist for 25 years post-biopsy (16). A woman with a previous biopsy demonstrating LCIS is thought have up to a 16 fold increased relative risk (2, 17).

Personal history of breast cancer
A woman with a personal history of breast cancer has a 0.5-1% risk per year of developing a contralateral breast cancer in the 10 years following diagnosis (18).

Family History of Breast Cancer
Other than age, the presence of a significant family history is probably the most important risk factor for the development of breast cancer. About 5 to 10% of breast cancers are considered to be hereditary. The relative risk (RR) for developing breast cancer depends on the number of relatives affected and the age of diagnosis of the respective relatives. The RR for woman with a first degree relative aged 50 years or older with postmenopausal breast cancer is 1.8 whereas the RR for woman with a first-relative with premenopausal breast cancer is 3.3. The RR for a woman with a second-degree relative with breast cancer is 1.5; and the RR for woman with 2 first-degree relatives with breast cancer is 3.6 (2)

In families with genetic mutations the risk is much higher (19). The identification of candidates appropriate for referral for consideration of specific germ-line genetic susceptibility such as mutations in the BRCA family of tumor suppression genes is of utmost importance in risk assessment (19). Genetic testing for potential mutation carriers is important not only due to the potential increased risk of breast cancer but also due to the increased risk of developing ovarian cancer for which there is currently no effective early detection strategy.

Women with BRCA mutations have a propensity to have cancer at a younger age. These women should be offered more intensive surveillance or prophylactic measures such as surgery or chemoprevention (see section referring to OBSP high risk program).

Referral Guidelines

The following are current referral criteria for consideration of genetic testing (20).

	Any Ethnicity	Ashkenazi Jewish
Patient only	Breast cancer (<35) **Triple negative** breast cancer (<60) Bilateral breast cancer (1st case <50) Breast **and** ovarian cancer (any ages) Male breast cancer (any age)	Breast cancer (<50)
Patient + Family History	Breast cancer (<50) + 1st/2nd degree relative with breast cancer (<50) Breast cancer (<60) + 1st/2nd degree relative with ovarian cancer Breast cancer (<60) + 1st/2nd degree relative with male breast cancer Breast cancer (any age) + >2 relatives with breast **or** ovarian cancer	Breast cancer (any age) + **any** family history of breast **or** ovarian cancer
Unaffected + Family History	Relative with a BRCA1/2 mutation Strong family history of breast **or** ovarian cancer	1st/2nd degree relative with breast cancer (<50) 1st/2nd degree relative with ovarian cancer 1st/2nd degree relative with male breast cancer 1st/2nd degree relative with breast cancer (any age) + any family history of breast **or** ovarian cancer

References

1. Altekruse SF, Kosary CL, Krapcho M et al. SEER Cancer Statistics Review, 1975-2007. National Cancer Institute. Bethesda, Maryland, based on November 2009 SEER data submission, posted to the SEER WEB site, 2010. Accessed October 17, 2011 at http;//www.cdc.gov/cancer/breast/statistics/age.htm.

2. Singletary SE. Rating the risk factors for breast cancer. Annals of Surgery 2003;237:474-82.

3. Warner E. Breast-cancer screening. N Engl J Med 2011:365(11):1025-32.

4. Travis LB, Hill D,Dores GM, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. J Natl Cancer Inst 2005;97:1428–1437.

5. Basu SK, Schwartz C, Fisher SG et al. Unilateral and bilateral breast cancer in women surviving pediatric Hodgkin's disease. Int J Radiation Oncology Biol Phys 2008;72:34-40.

6. Boyd NF, Guo H, Martin JL, et al. Mammographic density and the risk of and detection of breast cancer. N Engl J Med 2007;356:227-36.

7. Garland CF, Gorham ED, Mohr SB et al. Vitamin D and prevention of breast cancer: pooled analysis. J.Steroid Biochem. Mol. Biol. 103(3-5), 708-711 (2007).

8. Cho E, Chen WY, Hunter DJ et al. red meat intake and risk of breast cancer among premenopausal women. Arch. Intern. Med. 166(20), 2253-2259 (2006).

9. Chen WY, et al. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. JAMA. 2011;306:1884.

10. Zhang SM, Lee I, Manson JE. Alcohol consumption and breast cancer risk in the Women's Health Study. Am J Epidemiol 2007;165:667-76.

11. Mahoney MC, Bevers T, Linos E et al. Opportunities and strategies for breast cancer prevention through risk reduction. J Clin 2008;58:347-71.

12. Friedenreich CM, Cust AE. Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects. Br J Sports Med 2008;42:636-47.

13. Anne McTiernan, MD, PhD; Charles Kooperberg, PhD; Emily White, PhD; Sara Wilcox, PhD; Ralph Coates, PhD; Lucile L. Adams-Campbell, PhD; Nancy Woods, PhD; Judith Ockene, PhD. Recreational Physical Activity and the Risk of Breast Cancer in Postmenopausal Women. The Women's Health Initiative Cohort Study.*JAMA.* 2003;290(10):1331-1336. doi:10.1001/jama.290.10.1331.

14. U.S. Department of Health and Human services. Physical activity and health: a report of the surgeon general. Atlanta,GA,USA, U.S. Department of Health and Human Services, centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion (1996). www.cdc.gov/nccdphp/sgr/pdf/sgrfull.pdf.

15. Chlebowski RT, Chen Z, Anderson GL et al. Ethnicity and breast cancer: factors influencing differences in incidence and outcome. JNCI J Natl Cancer Inst (2005) 97 (6): 439-448. doi: 10.1093/jnci/dji064.

16. Hartmann LC, et al. Benign breast disease and the risk of breast cancer. The New England Journal of Medicine. 2005;353:229.
17. Hooks M. Breast Cancer: Risk Assessment and prevention. Southern Medical Journal 2010;103:333-38.

18. Fowble B, Hanlon A, Freedman G et al. Second cancers after conservative surgery and radiation for stages 1-11 breast cancer: identifying a subset of women at increased risk. Int J Radiat OncolBiol Phys 2001;51:679-90.

19. Caroll, JC, Heisey, R, Warner, E. Family history and breast cancer. CMAJ. 2012 DOI:101.1503/cmaj.111670.

20. US Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation statement. Ann Intern Med. 2005;143(5):355–61.

QUANTITATIVE RISK ASSESSMENT

A number of statistical models have been developed that integrate a variety of risk factors for breast cancer to calculate an overall "risk score".

The Gail Model estimates breast cancer 5-year and lifetime risk and is most effectively used in women with a limited family history of breast cancer. It is commonly used to determine if women qualify for chemoprevention (see Section 3). This model has recently been modified to provide accurate risk assessments for African American, Hispanic and Asian women in addition to Caucasian women (1, 2). This modified Gail Model called the Breast Cancer Risk Assessment Tool can be found on the National Cancer Institute website at http://www.cancer.gov/bcrisktool

The IBIS model (also known as the Tyrer-Cuzick model) is also frequently used and includes several variables to calculate both the risk of developing breast cancer as well as the risk of carrying a BRCA1 or BRCA2 mutation. The IBIS model can be used to determine lifetime risk and is an accepted tool for determining suitability for enhanced screening (annual MRI in addition to mammographic screening -see Section 4).This can be found at http://www.ems-trials.org/riskevaluator/.

Additional risk models which estimate the probability that genetic testing will detect a BRCA1 or BRCA2 include: BRCAPRO, and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA). Patients with risk estimates of >10% to be a gene mutation carrier should be offered genetic testing.

References

1. Gail MH, Costantino JP, Pee D et al. Projecting individualized absolute invasive breast cáncer risk in African American women. J. Natl Cancer Inst. 99 (23), 1782-1792 (2007).

2. Matsuno RK, Constantino JP, Zeigler RG et al. Projecting individualized absolute invasive breast cáncer risk in Asian and Pacific Islander American women. J Natl Cancer Inst. 103(12), 951-961 (2011).

3. Amir E, Freedman O, Seruga B, et al. Assessing women at high risk of breast cancer: a review of risk assessment models. JNCI 2010;102:680-91.

4. Smith R, Cokkindides V, Brooks D et al. Cancer screening in the United States, 2011: a review of current American Cancer Society guidelines and issues in cancer screening. CA: Cancer J Clin 2011;61:8-30.

5. Tice JA, Kerlikowske K. Screening and prevention of breast cancer in primary care. Prim Care 2009;36:533-58.

RISK-REDUCING STRATEGIES

Lifestyle Changes

Lifestyle changes such as increasing exercise and reducing alcohol intake may have a small impact on breast cancer risk. Patients should be encouraged to maintain a healthy lifestyle for their overall well-being.

There is also some evidence to suggest that Vitamin D has a protective effect against breast cancer (1). Currently the Canadian Cancer Society recommends that Canadian adults consider taking a vitamin D supplement of 1000 international units (IU) a day during fall and winter months (2).

Chemoprevention/ Preventive Therapy

The Canadian Task Force on Preventative Health Care recommends that women at higher risk of developing breast cancer (Gail index ≥1.66% at 5 years) be counseled on the potential benefits and risks of chemoprevention (3). The U.S Preventive Services Task Force concludes that women with an estimated 5-year breast cancer risk of ≥3% are likely to have more benefit than harm and that these women should be targeted for consideration of treatment (4). Tamoxifen and raloxifene have both been shown to decrease the risk of developing invasive breast cancer in high risk women (5-8). Tamoxifen is the only breast cancer prevention agent appropriate for use in both pre and post-menopausal women and is prescribed for five years for prevention. Raloxifene has been approved for post-menopausal women only. Although approved for use as breast cancer preventive agents in many other countries, all these agents are "off label" for breast cancer prevention in Canada.

In general, women with a history of atypical hyperplasia, or women under the age of 50 with a strong family history are more likely to benefit from chemoprevention (9).

The aromatase inhibitors exemestane and anastrozole have also been shown to reduce breast cancer incidence in high risk post-menopausal women (10, 11). Early data suggests that exemestane has superior efficacy to tamoxifen and raloxifene, however these have not yet been approved by Health Canada and would also be an "off label" use. There are many physician and patient barriers to breast cancer preventive therapy (Hum S, Wu M, Pruthi S, Heisey R. Physician and Patient Barriers to Breast Cancer Preventive Therapy. Curr Breast Cancer Rep 2016;8(3):158-164.) and current uptake is low.

Risk-reducing Surgery

Due to the significant physical and emotional impact, surgical approaches are reserved for women at very high risk for developing breast cancer such as BRCA mutation carriers. Bilateral prophylactic mastectomies are known to reduce the risk of breast cancer by 90% in high risk women (12, 13). Six high risk women need to undergo prophylactic mastectomies to prevent one incidence of breast cancer (13). All these women should be offered breast reconstruction.

Women with BRCA gene mutations may also be offered a prophylactic bilateral salpingo-oophorectomy. A preventative oopherectomy in BRCA1 and BRCA2 mutation carriers decreases

the overall risk of death by 77% (14). Undergoing an oophorectomy impart a 50% reduced risk for developing breast cancer and up to a 96% reduced risk for developing ovarian cancer (15). It has been suggested that BRCA carriers consider undergoing a salpingo-oophorectomy after childbearing is complete. However, women should be counseled regarding the timing of the surgery as recent recommendations suggest that BRCA1 mutations carriers consider undergoing a salpingo-oophorectomy at age 35 years (14).

References

1. Goodwin PJ. Vitamin D in cancer patients: above all, do no harm. J Clin Oncol 2009:27(13); 2117-19.

2. Canadian Cancer Society. Vitamin D Fact Sheet. July, 2001. http://www.cancer.ca/ Accessed October 8, 2011.

3. Canadian Task Force on Preventative Health Care http://www.canadiantaskforce.ca

4. Moyer VA. Medications to decrease the risk for breast cancer in women: recommendations from the U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2013; 159:698-708.

5. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 1998;90:1371–88.

6. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 2005;97:1652–62.

7. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial [published errata appear in in JAMA. 2006;296(25):2926, and JAMA. 2007;298(9):973]. JAMA. 2006;295:2727–41.

8. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 trial: preventing breast cancer. Cancer Prev Res (Phila). 2010;3:696–706

9. Pruthi S, Heisey R, Bevers T. Chemoprevention for Breast Cancer. Ann Surg Oncol (2015); 22:3230-3235.

10. Goss PE, Ingle JN, Ales-Martinez JE et al. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med 2011;364:2381-91.

11. Cuzick J, Sestak I, Forbes JF et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): aninternational, double-blind, randomised, placebo-controlled trial (published erratum appears in Lancet. 2014;383(9922):1040)
    a. Lancet 2014;383:1041-8.

12. Rebbeck TR, Friebel T, Lynch HT. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol. 2004;22:1055-62.

13. Hartmann LC, Sellers TA, Schaid DJ, et al .Efficacy of bilateral prophylactic mastectomy in BRCA1 or BRCA2 mutations carriers. J Natl Cancer Inst 2001;93:1633-37.

14. Finch A, Lubinski, J, Moller, P, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014:32:1547-53.

15. Rebbeck TR, Lynch HT, Neuhausen SL et al. Prophylactic oophorectomy in carriers of BRAC1 or BRCA2 mutations. N Engl J Med 2002;346:1616-22.

3. SCREENING AND EARLY DETECTION

Breast Self Examination and Clinical Breast Exam

There is currently no evidence that performance of either breast self-examination or clinical breast examination reduces overall or breast cancer specific mortality in the average risk patient (1). However, it is important for a woman to be familiar with her own breasts and currently the practice of self-examination is neither encouraged nor discouraged.

Mammography (DM) and Tomosynthesis (DBT)

Mammography is the only breast imaging modality demonstrated in randomized controlled trials to decrease breast cancer mortality (2). Digital breast tomosynthesis (DBT) is a new technology available as supplemental add-on equipment option on new mammography systems. DBT allows to acquire individual images of thin layers of breast tissue producing clearer images than conventional mammography. DBT imaging enable detection of some cancers that may be obscured by overlapping breast tissue on conventional mammography. Furthermore, DBT diminishes number of false-positive interpretation and thus reduces number of additional tests and associated costs and anxiety. Several prospective studies have demonstrated benefits of DBT. The reported increase in cancer detection rate is between 20-40%, and decrease recall in recall rate by 15-30% using DBT (3-5).

The Ontario Breast Screening Program (OBSP) recommends screening mammography once every 1-2 years in women at an average risk to develop breast cancer, aged 50-69 and every year in women at a high risk to develop breast cancer, aged 30-69. The interval and age for average risk population is supported by a not updated (2006) Cochrane review on mammography screening for breast cancer (6). The Society of Breast Imaging and American College of Radiology recommend annual screening from age 40 for women at average risk for breast cancer (7).

The evidence for mammography screening in women without increased lifetime risk aged 40-49 or inferior age is less clear, prompting the need for individual patient risk/benefit assessment. Currently both the American Cancer Society and the National Cancer Institute suggest annual mammography for women over the age 40 however not all organizations support annual mammography in this age group (7). The recently updated Canadian Task Force on Preventative Health Care no longer recommends screening mammography for average risk women aged 40-49 years (8). The lower incidence of breast cancer combined with the difficulties with detection in younger women with increased breast density make it less likely that large scale population organized mammographic screening program of unselected women less than 50 years of age will be beneficial. Therefore, the decision whether or not to use mammography in women between the ages of 40 and 49 years should be an individual one taking into account patient preferences and a personalized risk assessment. Should mammography be offered to a woman under the age of 50, there is some evidence to suggest that women in this younger age group should be screened annually as opposed to biannually due to faster breast cancer doubling-time in younger women.

Recommendations:

Screening Mammography with tomosynthesis for initial screen (baseline exam) in women at any risk either symptomatic or asymptomatic.
Screening Mammography once every 1-2 years in asymptomatic women, no previous breast cancer and no breast implants women aged ≥ 40.
Screening Mammography annually in asymptomatic high risk women aged ≥25-30y (but not before age 25).
Consider screening mammography once every 1-year in asymptomatic women with breast implants aged ≥ 40.
Consider screening mammography with tomosynthesis once every 1-year in asymptomatic women with dense breast tissue aged ≥ 40.
Screening Mammography once every 1-2 years in low risk women aged 50-74. (20-30y, ≥40y)
Intermediate risk High risk

Ultrasonography

Breast ultrasound is primarily used as a diagnostic tool and is not recommended for screening in low risk population. The use of breast ultrasound as stand-alone screening test is not appropriate. The use of ultrasound as a screening tool in conjunction with mammography was found to only moderately increase sensitivity while significantly increasing the number of false-positives (7).

Recommendation:

Breast ultrasound in addition to mammography can be considered in women for whom MRI screening may be appropriate but MRI can't be done.

Breast ultrasound may be considered as an adjunctive to mammography screening test in women with dense breast tissue and risk factors (e.g. family history of breast cancer) only if they don't qualify for breast MRI.

Breast Magnetic Resonance Imaging (MRI)

The use of breast MRI has increased substantially in recent years. It is expensive and should only be used when it is indicated. In 2014, 'Choosing Wisely Canada' was launched in an effort to encourage physicians and patients to engage in conversations about unnecessary tests, treatments and procedures while helping physicians and patients make smart and effective choices to ensure patients receive the highest quality care (9). There is controversy regarding the use of MRI in some scenarios currently faced during clinical practice. MRI screening for breast cancer is not recommended in the general population. However, annual MRI screening in addition to annual mammography has been recommended for those at high risk. Several groups to date have issued recommendations about the best use of MRI in the screening scenario: the American Cancer Society (ACS) published one of the first guidelines in March-April 2007 (10); the European Society of Breast Imaging (EUSOBI) Guidelines (11) were published in April 2008 to address standards of breast MRI technique as well as indications. The Canadian Breast Cancer Foundation (CBCF) provided recommendations for early detection and diagnosis of breast cancer at a consensus conference entitled, "It's About Time", held in Toronto in October 2009 (12). The European Society of Breast Cancer Specialists (EUSOMA) organized a workshop in Milan in October 2008 with 23 experts including epidemiologists, geneticists, oncologists, radiologists, radiation oncologists, and surgeons to discuss the evidence for the use of MRI and

issued guidelines in May 2010 (13). The Society of Breast Imaging (SBI) and American College of Radiology (ACR) published usage guidelines (7) in the same year. In March 2011 the Ontario Government in collaboration with Cancer Care Ontario announced the introduction of a provincial high-risk screening program that started in July 2011. The High Risk Screening Centres offers breast MRI in addition to mammography and referrals for genetic assessment and testing to women aged 30 to 69 that meet the following criteria: a) known mutation carriers (e.g. BRCA1 & BRCA2) and their untested first-degree relatives, b) women with a history of chest irradiation before age 30 and at least 8 years previously or c) women with a lifetime risk of 25% or greater as calculated using the IBIS or BOADICEA risk assessment tool (14).

Recommendations:
Screening with MRI in patients ***without a prior history of breast cancer*** should be offered to:

1. Known BRCA mutation carriers starting at age 25.

2. Untested first-degree relatives of proven BRCA mutation carriers starting at age 25 to 30.

3. Women with a history of chest irradiation before age 30 years, starting 8 years after radiation or at age 25 (whichever is sooner)

4. Women with rare genetic syndromes like Li-Fraumeni, Cowden, or Bannayan-Riley-Ruvalcaba syndrome and their first-degree relatives starting at age 25 to 30.

5. Women with a lifetime risk of breast cancer of 25% or greater, as defined by models* that are largely dependent on family history starting at age 30.
Information about Tyrer-Cuzick (IBIS) model risk calculator available at
http://www.ems.trials.org/riskevaluator

6. Women with diagnosis of lobular carcinoma in situ (LCIS) or atypical hyperplasia and dense breast tissue on mammography (defined as ACR density 3 or 4)

7. Screening MRI should be considered in women with a lifetime risk of breast carcinoma between 20-25% and mammographically dense breast tissue.

Screening in women ***with a prior history of breast cance***r (surveillance MRI) may be considered in (15):

- Women who meet the criteria #1-7 for MRI screening (described above).
- Women with extremely dense breast tissue on mammography (defined as ACR density 4) at the discretion of clinician/radiologist.

Timing of breast MRI screening/surveillance:

- Screening should be done annually in conjunction with mammography. Surveillance in women with a prior history of breast cancer may be offered every 1-2 years in

conjunction with surveillance mammography and preferentially at the discretion of the clinician/radiologist.

- Screening or surveillance should stop around 69-70 years. Patients more than 70 years do not benefit from intensive use of screening/ surveillance MRI. Young patients or pre-menopausal women with regular cycle may benefit to have breast MRI scheduled between day 7 to 13 of the menstrual cycle.

- Patients currently on chemoprevention (tamoxifen) and without dense breast tissue may not benefit from supplemental screening/surveillance with breast MRI.

References

1. Mark K, Temkin SM, Terplan M. Breast self-awareness: the evidence behind the euphemism. Obstet Gynecol. 2014 Apr;123(4):734-6. doi:10.1097/AOG.0000000000000139. PubMed PMID: 24785598.

2. Tabár L, Yen AM, Wu WY, Chen SL, Chiu SY, Fann JC, Ku MM, Smith RA, Duffy SW, Chen TH. Insights from the breast cancer screening trials: how screening affects the natural history of breast cancer and implications for evaluating service screening programs. Breast J. 2015 Jan;21(1):13-20. doi: 10.1111/tbj.12354. Epub 2014 Nov 20. PubMed PMID: 25413699.

3. Houssami N, Skaane P. Overview of the evidence on digital breast tomosynthesis in breast cancer detection. Breast. 2013 Apr;22(2):101-8. doi: 10.1016/j.breast.2013.01.017. Epub 2013 Feb 16. Review. PubMed PMID: 23422255.

4. Kopans DB. Digital breast tomosynthesis from concept to clinical care. AJR Am J Roentgenol. 2014 Feb;202(2):299-308. doi: 10.2214/AJR.13.11520. Review. PubMed PMID: 24450669.

5. Gilbert FJ, Tucker L, Gillan MG, Willsher P, Cooke J, Duncan KA, Michell MJ, Dobson HM, Lim YY, Purushothaman H, Strudley C, Astley SM, Morrish O, Young KC, Duffy SW. The TOMMY trial: a comparison of TOMosynthesis with digital MammographY in the UK NHS Breast Screening Programme - a multicentre retrospective reading study comparing the diagnostic performance of digital breast tomosynthesis and digital mammography with digital mammography alone. Health Technol Assess. 2015 Jan;19(4):1-136. doi: 10.3310/hta19040. PubMed PMID: 25599513.

6. Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD001877. Review.

7. Lee CH, Dershaw DD, Kopans D, et al. Breast cancer screening with imaging: recommendations from the Society of Breast Imaging and the ACR on the use of

mammography, breast MRI, breast ultrasound, and other technologies for the detection of clinically occult breast cancer. J Am Coll Radiol. 2010 Jan;7(1):18-27.

8. Canadian Task Force on Preventive Health Care, Tonelli M, Connor Gorber S, Joffres M, Dickinson J, Singh H, Lewin G, Birtwhistle R, Fitzpatrick-Lewis D, Hodgson N, Ciliska D, Gauld M, Liu YY. Recommendations on screening for breast cancer in average-risk women aged 40-74 years. CMAJ. 2011 Nov 22;183(17):1991-2001. doi: 10.1503/cmaj.110334. Erratum in: CMAJ. 2011 Dec 13;183(18):2147. PubMed PMID: 22106103; PubMed Central PMCID: PMC3225421.

9. Levinson W, & Canadian Medical Assocation. Choosing Wisely Canada 2014. Available from: http://www.choosingwiselycanada.org/.

10. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007 Mar-Apr;57(2):75-89

11. Mann RM, Kuhl CK, Kinkel K, et al. Breast MRI: guidelines from the European Society of Breast Imaging. Eur Radiol. 2008 Jul;18(7):1307-18.

12. Yaffe M, Jong R, Pisano E, et al. Earlier Detection and Diagnosis of Breast Cancer: Recommendations and Scientific Review from It's About Time! A Consensus Conference. Available at URL http://www.cbcf.org/en-US/Ontario assessed11 Nov 2010.

13. Sardanelli F, Boetes C, Borisch B, et al. Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer. 2010May;46(8):1296-316.

14. Amir E, Freedman OC, Seruga B, Evans DG. Assessing women at high risk of breast cancer: a review of risk assessment models. J Natl Cancer Inst. 2010 May 19;102(10):680-91.

15. Solin LJ, Orel SG, Hwang WT, Harris EE, Schnall MD. Relationship of breast magnetic resonance imaging to outcome after breast-conservation treatment with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ. J Clin Oncol. 2008 Jan 20; 26 (3):386-91.

4. DIAGNOSIS AND PATHOLOGY

(This section was last updated February 2017)

4.1 DIAGNOSTIC IMAGING

Mammography, Ductography and Tomosynthesis

Mammography remains a standard part of the assessment of clinically palpable lesions within the breast or in the initial assessment of nipple discharge from one single orifice that is spontaneous with clear or bloody colour which is further investigated with ductography with or without tomosynthesis slices. Additional mammography views with or without spot compression/ magnification views and digital breast tomosynthesis may be of benefit in cases of focal asymmetric tissue to differentiate between a true lesion (either benign or potentially malignant) versus summation of breast densities that could mimic a worrisome feature.

Recommendation:

Diagnostic Mammography. Additional views at the discretion of the breast radiologist. Ductography if spontaneous suspicious nipple discharge present.

Breast ultrasonography

Breast ultrasound is a valid method adjunct to mammography in the investigation of a mass lesion, ultrasound of the breast can aid in determining the nature of a mass (solid versus cystic), and may also aid in the diagnosis and biopsy of palpable or non-palpable lesions; guidance in drainage of collections, abscess and to aspirate symptomatic large cysts. Therefore, breast ultrasonography could be utilized in the workup of a breast mass with interventional procedure at the discretion of the breast radiologist.

Recommendation:

Breast ultrasound of the affected side plus or minus biopsy at the discretion of the breast radiologist.

Axillary ultrasound

The pathological status of the axillary lymph node remains one of the most vital factors in determining prognosis and treatment in patients with invasive breast cancer. Axillary ultrasound should be considered a part of the overall assessment of new breast cancer patients. Ultrasound guided assessment of axillary nodes with fine needle aspiration of radiological abnormal axillary nodes has been a fundamental step in planning care.

Recommendation:

Axillary ultrasound of the affected side as complementary to the breast sonography work-up. Axillary ultrasound with fine needle aspiration (FNA) of a palpable node or radiological abnormal lymph node.

Breast Magnetic Resonance Imaging (MRI)

The use of diagnostic breast MRI has grown for the past decade and has been shown a valuable additional tool for breast imagers to use to provide optimal patient care. MRI is a highly sensitive

method to depict cancers and the ability to obtain accurate tissue diagnosis of areas of enhancement in a timely fashion demonstrates the benefit that MRI can provide.

The technology is now being used for a wide variety of indications:

1. In patients with metastatic axillary adenocarcinoma of unknown primary if conventional breast imaging (mammography and ultrasound) is negative.

2. Locally advanced breast cancer. Breast MRI should be performed before and if after neoadjuvant chemotherapy. Some exams can be done during the treatment in order to provide monitoring only if less expensive tests are insufficient.

3. Women newly diagnosed with invasive breast cancer with either of the following:

• Invasive lobular cancer
• Dense breasts (defined as ACR density 3 or 4 at the discretion of the clinician/radiologist)
• Known BRCA carrier

4. To assist pre-op in determining extent of disease e.g. patients with dense breast tissue and a biopsy proven invasive breast cancer or high-grade in situ carcinoma where MRI results may produce changes in the planned surgery (at the discretion of the surgeon/radiologist). If changes in surgery are suggested based on the MRI finding this new suspicious areas should be confirmed by a core biopsy before making the change. MRI-guided core biopsy should be available.

5. Women who will need re-excision post-lumpectomy due to positive surgical margins (at the discretion of the surgeon/radiologist)

6. Insufficient conventional breast imaging for diagnosis (at the discretion of the clinician/radiologist)

7. To evaluate silicone implant integrity

Recommendations:
Diagnostic breast MRI whenever is required as per indications above. MRI-guided biopsy if suspicious areas of enhancement not identified by conventional breast imaging (mammography/tomosynthesis or ultrasound)

Positron Emission Tomography (PET) and Computed Tomography (CT)

Recommendations:
Currently PET scan is not a part of the work up in the diagnosis or staging of breast cancer patients.

Staging

PMH follows the guideline recommendations for post-operative staging of breast cancer patients as outlined by the Cancer Care Ontario Program in Evidence Based Care and summarized below.

Recommendations in asymptomatic patients:

- Stage I: In women with intraductal and pathological stage I tumours, routine bone scanning, liver ultrasonography and chest radiography are NOT indicated as part of baseline staging.
- Stage II: In women who have pathological stage II tumours, a postoperative bone scan is recommended as part of baseline staging. Routine CT scanning of thorax, abdomen and pelvis (or liver ultrasonography and chest radiography) are NOT indicated in this group but may be considered for patients with four or more positive lymph nodes.
- Stage III: In women with pathological stage III tumours, bone scanning, and CT scanning of thorax, abdomen and pelvis (or liver ultrasonography and chest radiography) are recommended postoperatively as part of baseline staging.
- In women for whom treatment options are restricted or for whom no further treatment is indicated because of age or other factors, routine bone scanning, liver ultrasonography and chest radiography may not be indicated as part of baseline staging.

Patients with symptomatic disease should be investigated as guided by the nature of their symptoms.

Pre-operative staging investigations including a bone scan as well as a CT scan of the thorax, abdomen and pelvis may be appropriate in the workup of a women with known lymph node positivity pre-operatively (based on FNA biopsy) or a high clinical suspicion of metastatic disease (e.g. T3-4 disease).

4.2 PATHOLOGY

Clinical / imaging information:
Pathology and cytology specimens are reviewed in the context of clinical/imaging findings. If full clinical and imaging information is available in EPR to the reporting pathologist, this does not have to be made available by the responsible physician, however if this is not available in EPR - the responsible physician must provide this
e.g. RDC case with no imaging reported at the time the slides are reviewed by the pathologist - the responsible radiologist must provide appropriate information in the clinical history section of the ordered specimen
e.g. excision specimen with prior biopsy external to UHN and no details in EPR - the responsible surgeon must submit clinical and imaging printed reports with the specimen for the responsible pathologist.

Cytology Fine needle aspirate of breast, lymph node, other

This is the most common cytology specimen received in the evaluation of patients with breast disease, other types of cytology samples include: nipple discharge, fluid samples (pleural, peritoneal)

- Cytologic interpretation occurs within a clinical context: The tissue type being sampled must be accurately stipulated (i.e. it is essential to indicate if specimen is from breast tissue or lymph node, if it is not possible to tell - this should be indicated). Accurate, relevant clinical information must be provided (such as current pregnancy, lactation status, previous surgery, chemotherapy/radiation etc.)

- A fine needle aspirate of a breast lesion cannot differentiate in situ from invasive carcinoma. A diagnosis of malignancy on an FNA of the breast should always be confirmed by either definitive clinical findings, other cytologic findings (eg. aspirate of breast and ipsilateral lymph node both malignant documenting metastases), or confirmatory tissue biopsy before major treatment decisions such as mastectomy or chemotherapy.

- ER, PgR, HER2 assessment: Assessment of ER, PgR and HER2 status is usually performed on tissue samples. If this assessment is required clinically and it is not feasible to obtain a tissue sample, it may be possible to perform the assessment on a cytology specimen - the responsible cytopathologist should be contacted directly.

Tissue Samples

Small Biopsy Specimens

The most common small sample is a needle core biopsy of breast which may range in size from 14G to 7G, may be vacuum assisted or not, and is usually obtained under stereotactic, ultrasound or MRI guidance. Other small samples may include: punch biopsies of skin or nipple, or 14G core biopsy of lymph node.
ER, PgR and HER2 status may be assessed by immunohistochemical stain, HER2 status may also be assessed by ISH (in situ hybridization)- see later section.

In order to achieve appropriate fixation for ER, PgR, HER2 assessment, core biopsies received Monday to Thursday after 11:30 will be held in formalin overnight and submitted for routine processing the following day. Core biopsies received on Fridays before 4pm will be submitted for routine processing on Friday evening)

Gattuso Rapid Diagnostic Clinic

- Diagnostic breast core biopsies are expedited through the Gattuso Rapid Diagnostic clinic
- Same day diagnosis is possible on 14G core biopsy specimens only, larger core biopsies (>14g) cannot be processed for same day diagnosis.

- Preliminary Reports:
  It is frequently necessary to perform additional studies (evaluate deeper levels and/or assess immunostains) on a breast core biopsy specimen in order to render a final diagnosis. These studies will not be completed before a patient returns for same day follow up, and may not be completed by the follow up appointment if it is within a few days of the biopsy being taken - in these situations the biopsy will be reported in "interim" or "preliminary diagnosis" form with final diagnosis issued following completion of all necessary studies

- ER,PgR, HER2on rapid diagnostic biopsies
  The tissue samples handled for same day diagnosis have limited fixation and are unsuitable for assessment of ER, PgR, HER2 status.
  If assessment of ER, PgR, HER2 status is required as well as same day diagnosis - the sample taken must be split into 2 parts at source so that one specimen part can be processed rapidly for same day diagnosis and the other part processed routinely will be suitable for ER, PgR, HER2 assessment. In this situation the electronic order must designate the split specimen as two parts and must clearly indicate that the two specimen parts are of the same lesion and that one part is to be processed routinely.

Operative Breast Specimens

Possible specimens include: lumpectomy (typically for palpable mass), wire localization specimen (typically for non- palpable lesion - mass or calcification), mastectomy, and duct excision specimens.

Specimen Orientation:

All surgical breast specimens submitted to pathology must be orientated by surgical staff. If there is no attached skin the routine orientation involves two sutures, if there is attached skin - the skin and one suture may suffice for orientation. The details of the suture and skin orientation must be provided in the electronic order or on the requisition (usually short suture anterior, long suture lateral for 2 sutures: skin anterior, suture lateral for specimen with skin.)

Specimen Preservation / Fixation:

During the hours of operation of the surgical pathology laboratory (8:30 am- 4: 30 pm Mon. to Fri.), breast specimens are sent to pathology fresh (without fixative), outside these hours the specimen should be submitted in adequate formalin (see below).

Under no exception should tissue be left unfixed (i.e. not in formalin) outside regular pathology hours - this may result in irretrievable loss of cell detail which may render the tissue histologically uninterpretable.

Specimens larger than small biopsy samples require particular attention to fixation and handling to ensure optimal tissue preservation for pathologic evaluation and for assessment of tumour markers (such as ER, PgR and HER2).

Tissue must be fixed, therefore should be sent to pathology, as rapidly as possible after removal from a patient. The time from surgical excision to fixation should be kept to $\leq$ 1 hour.
The time of tissue collection (the time the tissue is handed from the surgical field) should be documented on the pathology requisition by operating room staff.

Immediately following receipt of the tissue in Pathology, the tissue must be:

a) Surface painted to mark margins in a manner that will allow for orientation and assessment of all specimen margins during microscopic examination
b) Measured in three dimensions
c) Serially sliced in an appropriate plane (may be parasagittal, transverse or coronal depending on the specimen dimensions or lesion present, usually sliced perpendicular to the longest axis of the specimen, all slices taken perpendicularly to specimen margins unless otherwise instructed) for optimal fixation
d) Examined and sampled for tissue banking if feasible (see later)
e) Immersed in fixative as rapidly as possible

- The standard fixative is 10% neutral buffered formalin (NBF). Specimens should be fixed as rapidly as possible in an adequate volume of formalin (i.e. a volume of formalin at least 10 times greater than the volume of the specimen).
- The time the tissue is received in pathology and the time it is immersed in formalin is recorded on the pathology paperwork(usually the specimen diagram) by pathology staff.
- For specimens larger than small biopsies - adequate fixation before sampling (see later) requires overnight fixation. Where a weekend follows the day of specimen removal, that will necessitate fixation over the weekend.

Specimen Imaging:

- Specimens resected under imaging guidance for a non- palpable lesion are sent to Imaging to confirm resection of the lesion prior to the patient leaving the operating room and before the specimen is submitted to pathology.
- Depending on the nature of the lesion and the specimen, further imaging of the pathology specimen may be necessary to direct sampling of the specimen for histologic examination. (For example a specimen resected for a lesion that is not grossly apparent must either be

submitted in full for histologic evaluation, or must be sampled under imaging guidance if too large to submit in full).
- Depending on the nature of the specimen further imaging of the tissue blocks may be necessary

Intraoperative Consultation (frozen section):

- Intraoperative consultation on a target breast lesion is rarely indicated since preoperative diagnostic core biopsy is usually performed.
- In the rare situation in which this is necessary, since freezing results in permanent loss of cell detail, this should only be performed on breast lesions that are > 1cm size so that sufficient lesional tissue is not frozen to allow for accurate histologic evaluation.(This usually means that non- palpable lesions are unsuitable for frozen section evaluation).

Tissue Sampling by Pathology:

- Tissue sampling in pathology must be conducted in the context of known clinical and imaging information. Depending on the clinical context, findings on imaging, and the nature of the specimen, it may be appropriate to selectively sample the specimen or to submit the specimen in total for histologic evaluation. Sampling of the pathology specimen is conducted according to Pathology Departmental Guidelines, and the majority of breast specimens are sampled under the direct supervision of a staff pathologist.

- Directed sampling may require imaging of the sliced and fixed specimen (as detailed above).

- Staff in Pathology attempt to ensure that when ER, PgR, HER2 assessment is required on a specimen, that a sample of tumor is submitted with time in fixative between the recommended guidelines of 6 and 72 hours - see later section on ER,PgR, HER2 testing.

Tissue Banking:

- Consistent with UHN Biobanking guidelines, tissue is banked for research on as many fresh (unfixed) breast specimens as possible as long as that banking will not interfere with the pathological assessment and diagnosis of the specimen. Non lesional fresh tissue is also banked on as many cases as feasible following banking guidelines.(Banked tissue is frozen and /or formalin fixed)

- Enhanced banking of formalin fixed tumour/ non lesional tissue is performed on as many specimens as possible following review of the fixed specimen by the pathologist. Histologic sections of the material put aside at this time for banking are reviewed by the reporting pathologist before sign out, if necessary this material can be repatriated to patient care blocks.

Other Operative Specimens

Sentinel Lymph Node in the setting of invasive carcinoma:

- Intraoperative evaluation by frozen section may be requested as clinically indicated

- In Pathology, sentinel nodes should be sliced parallel to the longitudinal axis into slices of not more than 2mm thickness in order to detect macrometastatic disease.
- Sentinel nodes are evaluated with a single H&E section per block
  If metastatic carcinoma is identified on microscopic examination of the frozen section block(s), the reporting pathologist will attempt to report the size of the metastatic focus (≤ 0.2mm, 0.2 to 2mm, >2mm)

Sentinel Lymph Node in the setting of in situ duct carcinoma:

- Intraoperative evaluation by frozen section will not be requested unless there is a specific indication
- Sentinel lymph node slicing and evaluation are as for invasive carcinoma

Axillary dissection:

The number of lymph nodes reported on depends on the number removed in the specimen by the surgeon, and the number identified in the specimen by the pathology staff. Lymph nodes that are grossly identified in the specimen are usually submitted in toto for histologic examination (exception lymph nodes grossly involved by metastatic carcinoma may be sampled rather than submitted in total).

Reporting of Surgical Pathology Breast Specimens

Small Biopsy Specimens

The small size of these pathology specimens may limit accuracy of grading/typing of cancers. The grade may be reported and special stains performed for subtyping of the carcinoma at the discretion of the reporting pathologist, depending on the nature of the specimen and the clinical context. If not initially reported and necessary for clinical management, this information can be reported after initial sign out as an addendum.

Operative Breast Specimens

These specimens are reported in such a manner that the requirements of Cancer Care Ontario (CCO) (which has adopted the College of American Pathologists (CAP) Guidelines) are met or exceeded.
The usual reporting format includes a synoptic report unless this is not appropriate for the specimen or in the opinion of the reporting pathologist the nature of the pathologic entity and specimen are such that synoptic reporting either cannot be achieved or may result in inaccurate or misleading information.

Estrogen Receptor (ER), Progesterone Receptor (PgR), HER2 Testing

Type of specimen assessed

1) ER, PgR, HER2 assessment is routinely performed for all patients newly diagnosed with invasive carcinoma of the breast.
- Reliable test results require adherence to current guidelines for tissue handling and fixation. As a result of this some samples are unsuitable for testing - this is noted in the appropriate section.

- ER, PgR, HER 2 testing is usually performed on an operative (excised) breast specimen but may be performed on a small biopsy such as a core biopsy if clinically indicated and if the sample is appropriate.

2) Patients with diagnosed metastatic disease (stage IV) if specimen available

3) Repeat testing on excision specimen if testing performed on core biopsy
- Repeat testing should be considered in the context of the details of the invasive carcinoma and the test result. If HER2 testing is equivocal on a core - HER2 testing should be repeated on an excision specimen. Repeat biomarker testing on an excision specimen should be conducted if there is concern with the results obtained on testing the core biopsy
- Repeat testing on the excision specimen following neoadjuvant chemotherapy may be performed

Details of fixation

1) ER and PgR testing is by immunohistochemical stain. HER2 testing is initially by immunohistochemical stain with ISH performed as required in the setting of an equivocal immunohistochemical result.

2) Current guidelines for testing recognize the importance of fixation in accuracy and reproducibility of results and require reporting of: the fixative used, the interval between resection and fixation, and length of time in fixative. The aim is rapid fixation (i.e. immediate immersion in 10% neutral buffered formalin for a small specimen e.g. core, and an interval of ≤ 1hour between resection and fixation for a larger specimen). Tissue must be fixed in formalin for a minimum of 6 hours, the optimal time for fixation in formalin is between 6 and 72 hours.

3) Procedures in Pathology are created to maximize the number of breast specimens in which the fixation falls within the above guidelines. However Pathology staff cannot ensure this for all specimens e.g.:
- Core biopsies processed in the Xpress Tissue Processor for same day diagnosis receive only 1.5 hours fixation and are not suitable for ER, PgR, HER2 assessment

- Some core biopsy specimens and surgical specimens will be in formalin >72 hours before processing starts (eg core biopsies from Thursday afternoon, surgical specimens from Thursday - held in formalin till tissue processing proceeds on Sunday evening)

- For samples fixed > 72 hours - the ER/PgR/HER 2 results should be considered in the context of the fixation interval.

Oncotype DX assay

- 21-gene recurrence score assay
- Pathology will send recut unstained slides of tissue block of invasive for this assessment on clinical request (a request is made by sending the completed appropriate form to

Pathology). Usually the tissue block selected for recutting of unstained slides is the block used initially for assessment of ER. PgR and HER2.

References:

1. College of American Pathologists cancer checklists. http://www.cap.org

2. National Health Service (NHS) Breast Screening Programme - Pathology Reporting of Breast Disease Jan 2005 (NHSBS Publication No 58). www.cancerscreening.nhs.uk/breastscreen/publications

3. Association of Directors of Anatomic and Surgical Pathology. http://www.adasp.org/

4. Wolff AC, Hammond EH, Hicks DG et al. Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. J Clin Oncol 2013;31(31):3997-4013.

5. Updated Recommendations from the Canadian National Consensus Meeting on HER2/neu Testing in Breast Cancer. Current Oncology 14(4):149-153. Canadian Consensus for HER2/neu Testing Guidelines in Breast Cancer May 2007

6. Laboratory Medicine Program Pathology Operating Procedure Documents - Surgical Pathology.

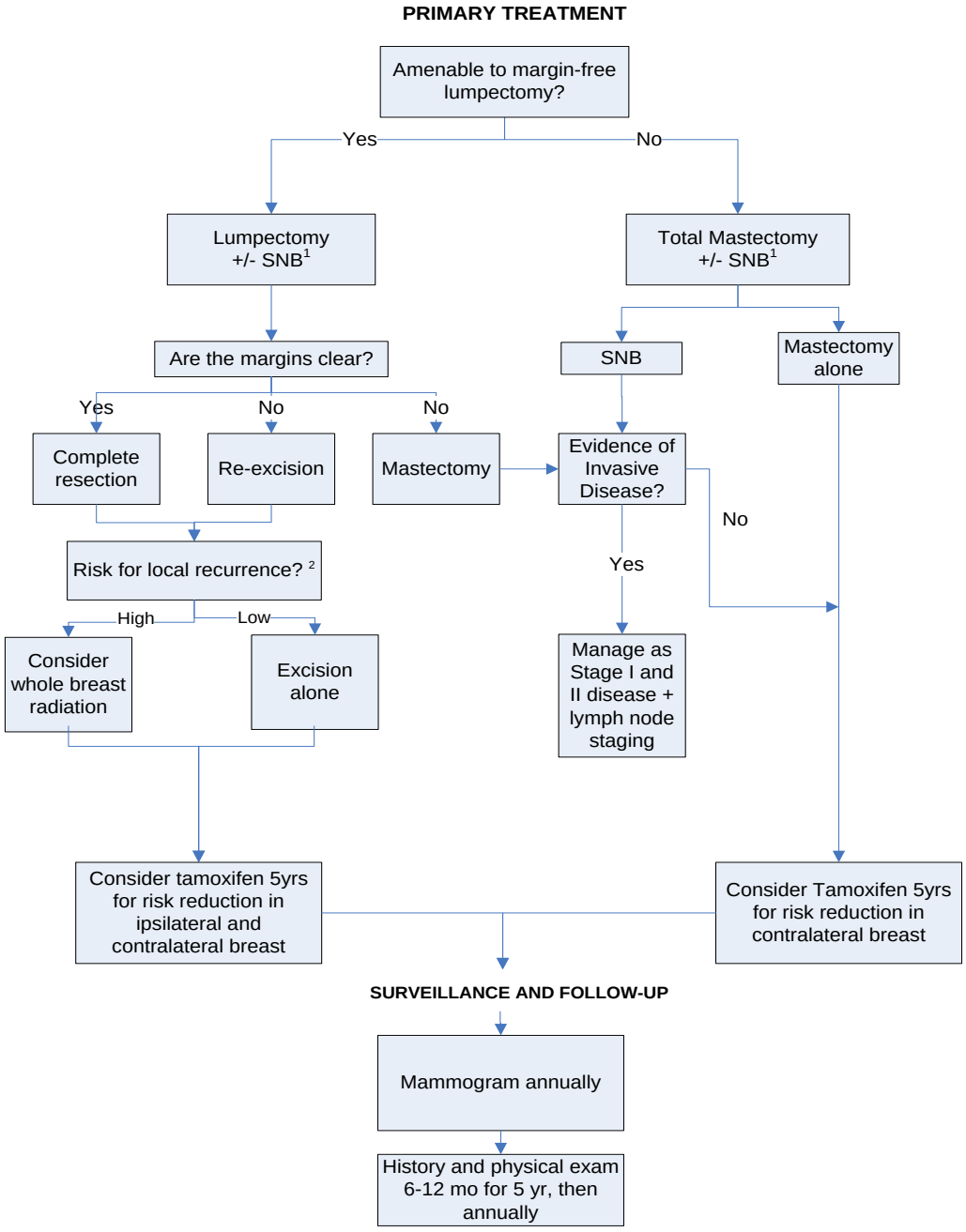
7. Hammond et al, American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer, J. Clin. Oncol. 28 (16): 2784-2795, 2010.

8. CCO convened panel 2014 (Dr. Martin Chang, Dr. Sharon Nofech-Mozes, Dr. Wedad Hanna, Dr. Susan Robertson, and Dr. Aaron Pollett) Summary Statement 2013 ASCO/CAP HER2 Guidelines: Building a Consensus for Ontario

5. MANAGEMENT ALGORITHMS

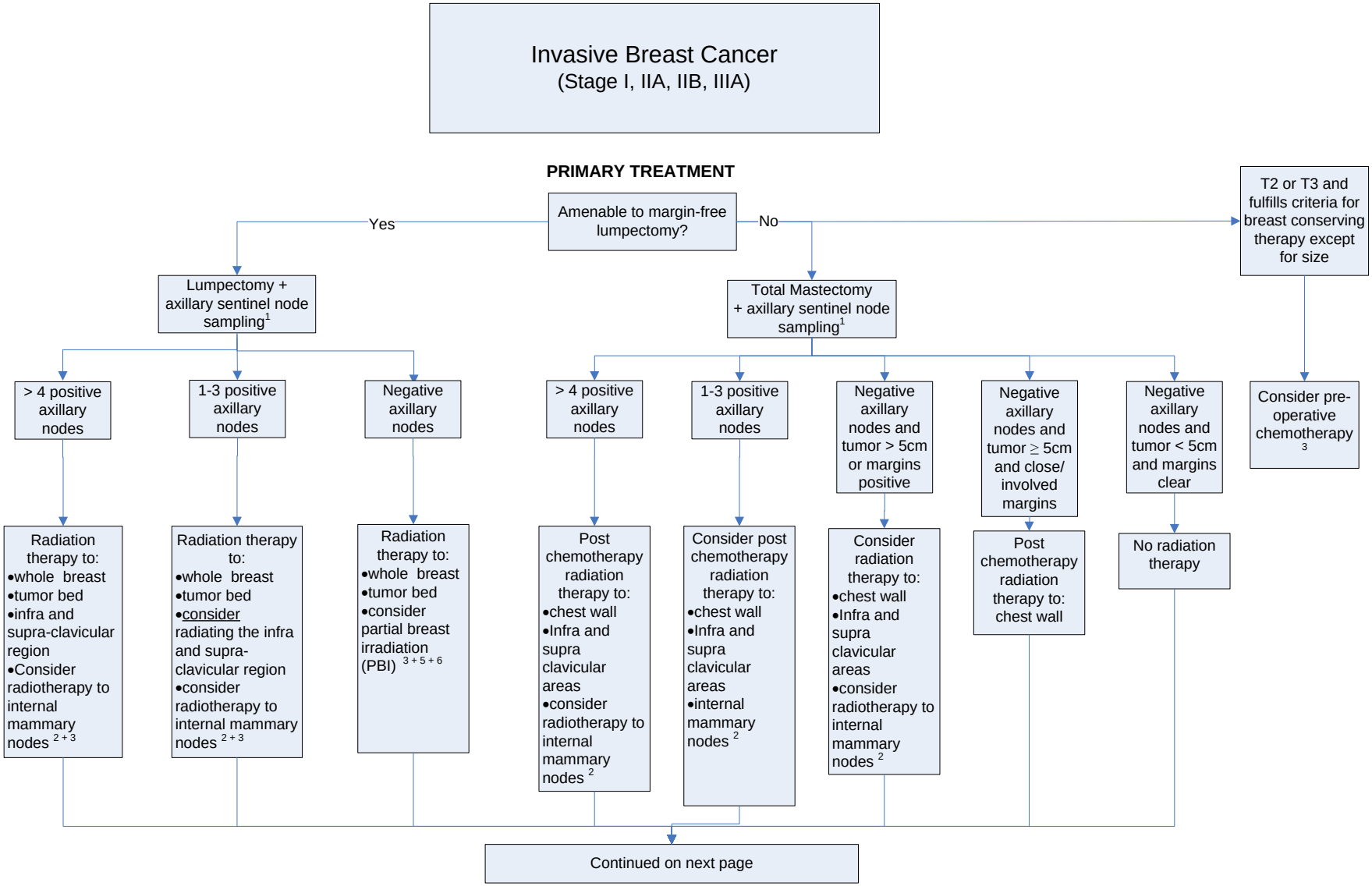
(This section was last updated December 2015)

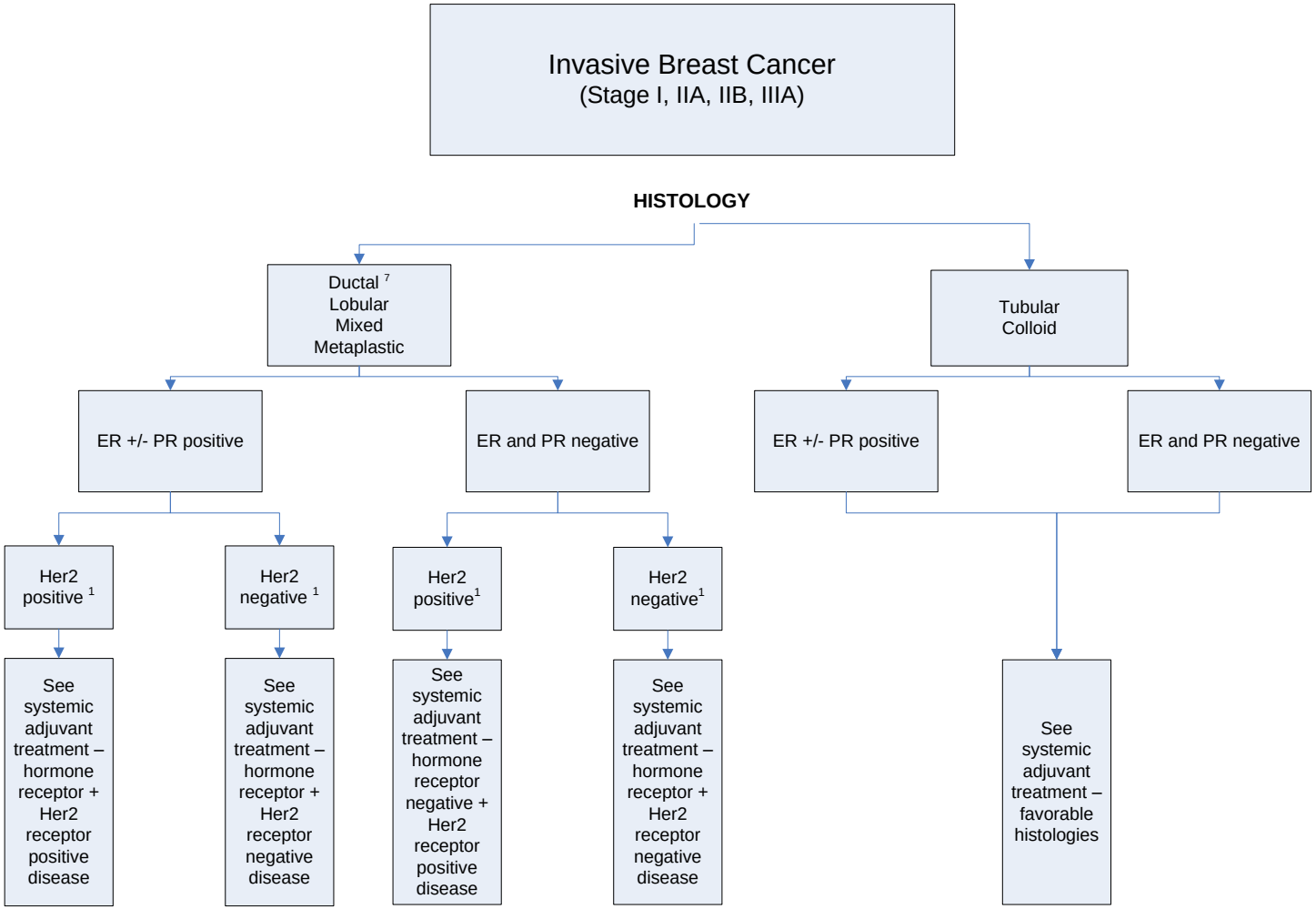
In-situ breast cancer



[1] Sentinel node biopsy (SNB) should be performed with suspicion of invasive disease
[2] A number of factors determine local recurrence risk: palpable mass, large size, high grade, close or involved margins, age < 50 years.

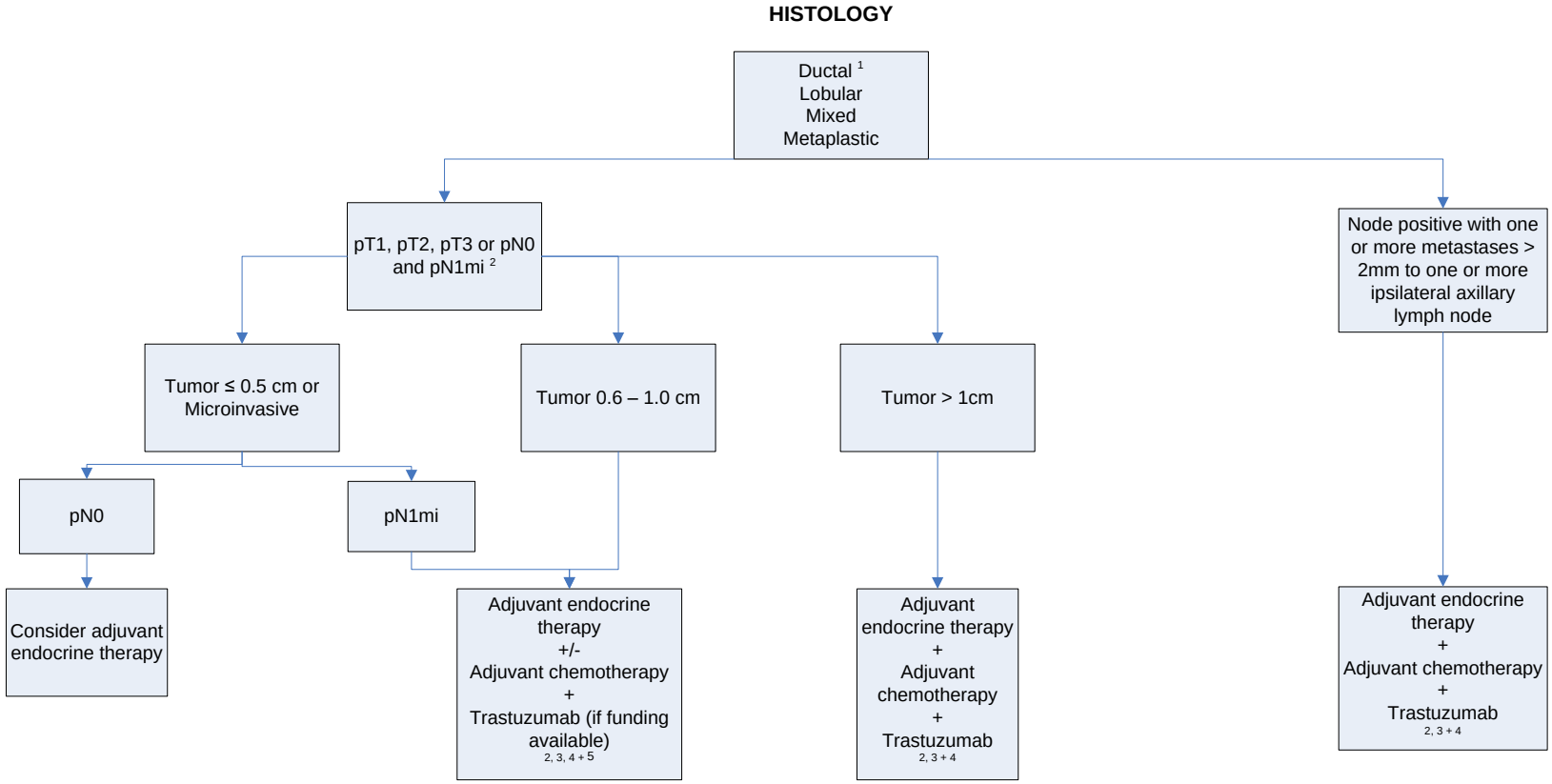
Operable Invasive Breast Cancer



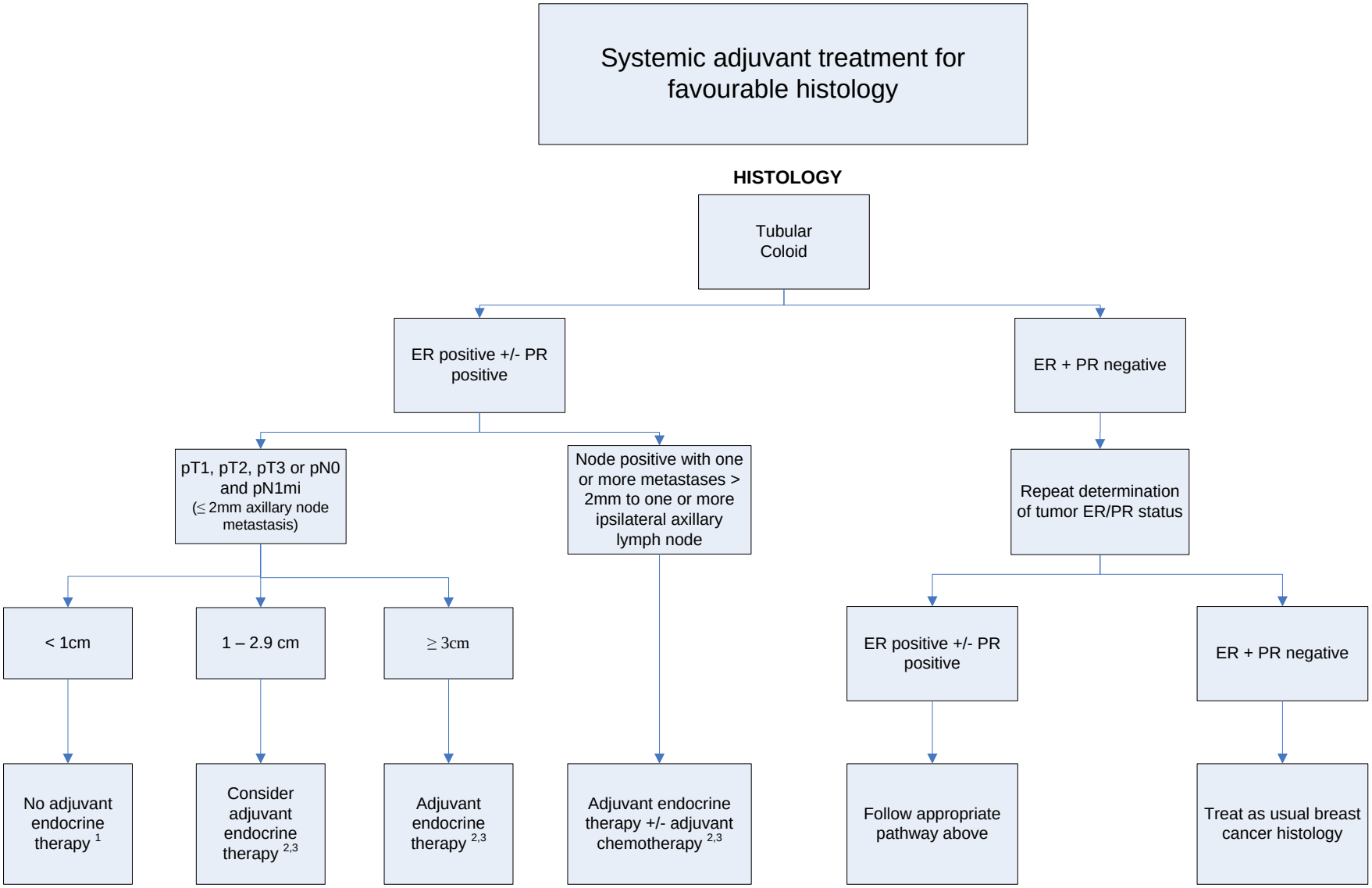


[1] See surgical axillary staging
[2] Radiation therapy should be given to internal mammary lymph nodes if they are clinically and pathologically positive. CT planning should be utilised in all cases where radiation therapy is being delivered.
[3] Radiation therapy should follow chemotherapy when indicated
[4] See preoperative chemotherapy guidelines
[5] PBI can be delivered prior to chemotherapy
[6] Consider omitting breast irradiation in patients > 70 year, estrogen receptor position, clinically node negative, T1 tumors receiving adjuvant endocrine therapy
[7] This includes medullary and micropapillary types

Systemic Adjuvant Treatment: Hormone Receptor and Her2 Positive

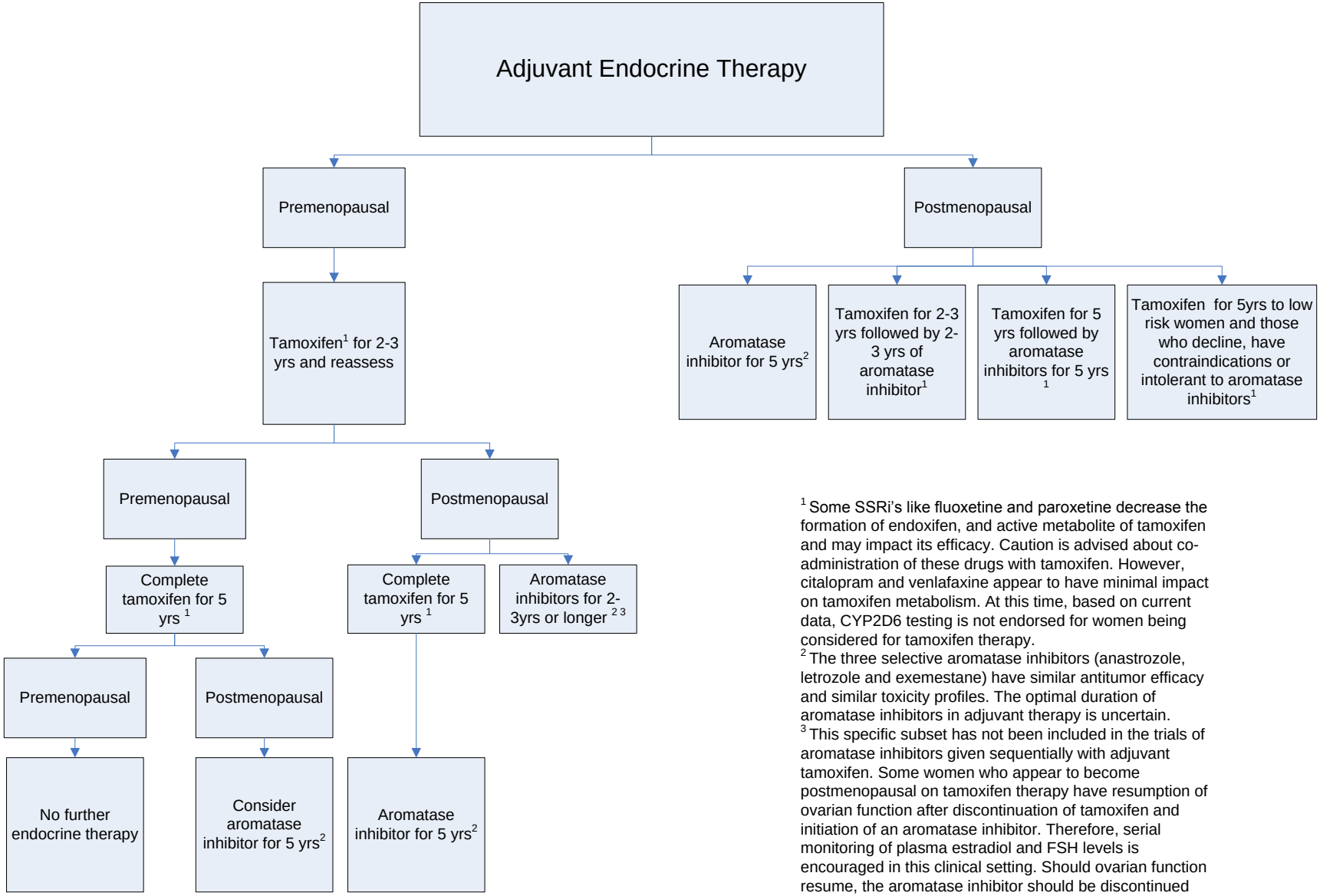


[1] Grading and treatment of mixed lobular and ductal carcinoma as well as metastatic carcinoma should be based on the ductal component. The metastatic or mixed component does not alter the prognosis.
[2] Premenopausal women with hormone receptor positive breast cancer receive similar benefits from surgical or radiation ovarian ablation compared with CMF alone. Early evidence suggests similar benefits from ovarian suppression (LHRH agonists) as ovarian ablation. Combining ablation/suppression and endocrine therapy may be superior than suppression alone. There is uncertainty regarding the benefit of ablation/suppression in premenopausal women who have received adjuvant chemotherapy.
[3] Adjuvant chemotherapy and endocrine therapy should be given sequentially, with endocrine following chemotherapy. The benefits of adjuvant chemotherapy and endocrine therapy are additive. However, the benefit from chemotherapy may be small, Therefore, the decision to chemotherapy should be individualised according to the prognostic factors of each case. Evidence supports use of sequential or concurrent use of endocrine and radiation therapy.
[4] There is limited data for chemotherapy in those over 70yrs. Treatment should be individualized with consideration of comorbid conditions.
[5] The benefit of trastuzumab in hormone receptor positive T1a and T1b disease has not been studied in the available literature.



[1] If ER-positive consider endocrine therapy for risk reduction and to diminish the small risk of disease recurrence
[2] Premenopausal women with hormone receptor positive breast cancer receive similar benefit from surgical or radiation ovarian ablation compared with CMF alone. Early evidence suggests similar benefits from ovarian suppression (LHRH agonists) as ovarian ablation. Combining ablation/suppression and endocrine therapy may be superior than suppression alone. There is uncertainty regarding the benefit of ablation/ suppression in premenopausal women who have received adjuvant chemotherapy.
[3] There is limited data for chemotherapy in those over 70yrs. Treatment should be individualized with consideration of comorbid conditions.

Adjuvant Endocrine Therapy

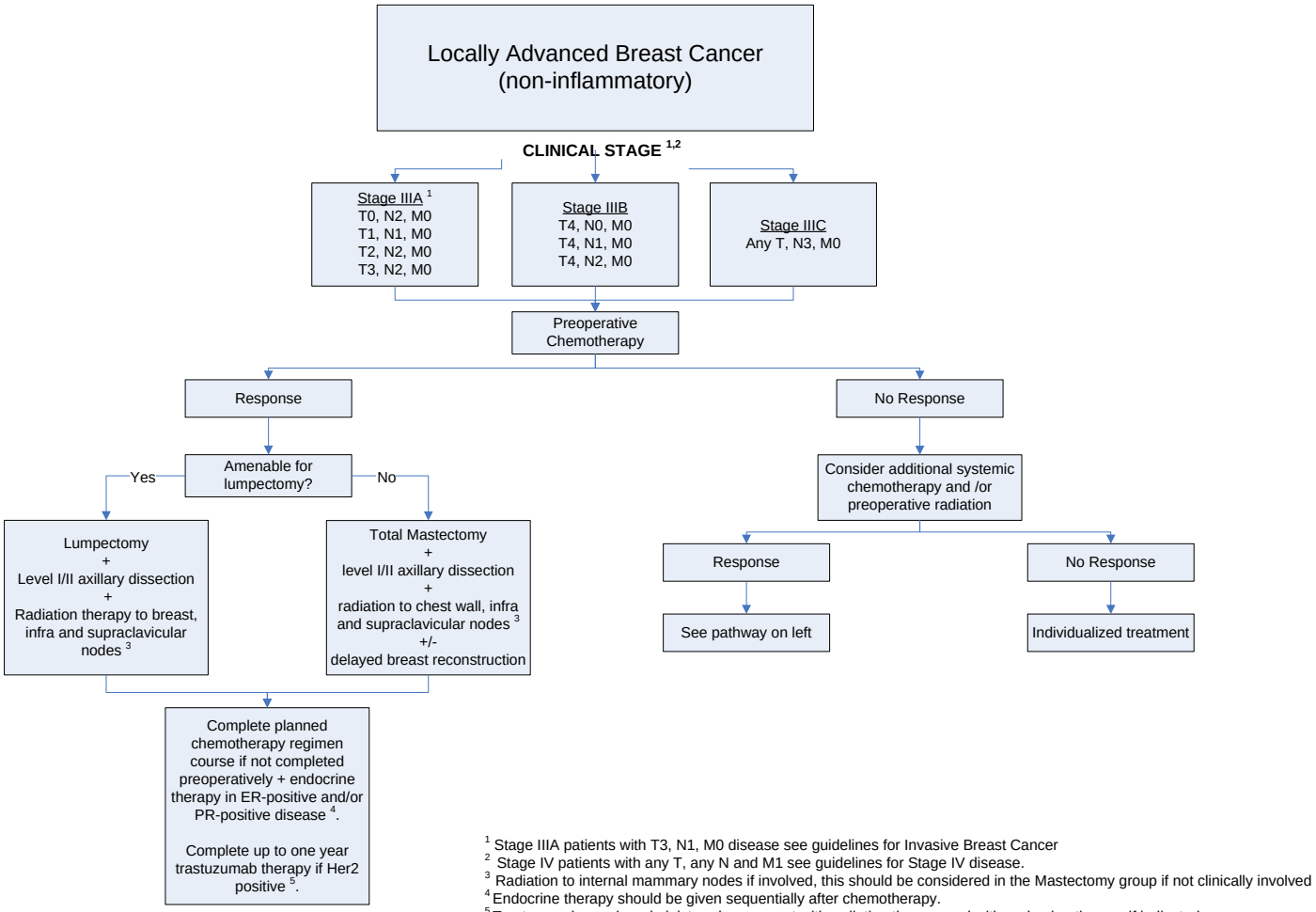


[1] Some SSRi's like fluoxetine and paroxetine decrease the formation of endoxifen, and active metabolite of tamoxifen and may impact its efficacy. Caution is advised about co-administration of these drugs with tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. At this time, based on current data, CYP2D6 testing is not endorsed for women being considered for tamoxifen therapy.

[2] The three selective aromatase inhibitors (anastrozole, letrozole and exemestane) have similar antitumor efficacy and similar toxicity profiles. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.

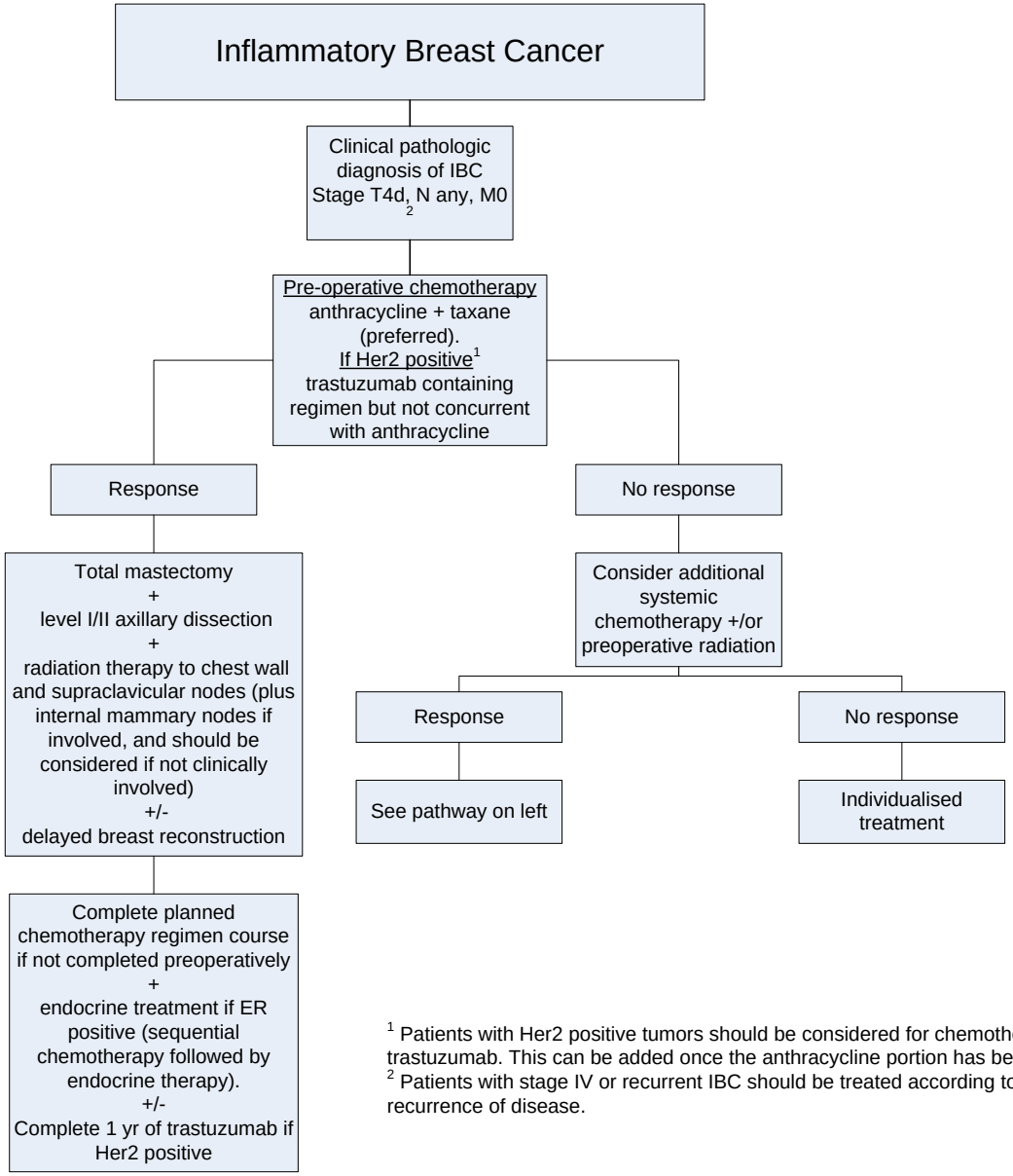
[3] This specific subset has not been included in the trials of aromatase inhibitors given sequentially with adjuvant tamoxifen. Some women who appear to become postmenopausal on tamoxifen therapy have resumption of ovarian function after discontinuation of tamoxifen and initiation of an aromatase inhibitor. Therefore, serial monitoring of plasma estradiol and FSH levels is encouraged in this clinical setting. Should ovarian function resume, the aromatase inhibitor should be discontinued and tamoxifen resumed.

Inoperable Invasive Breast Cancer (Locally Advanced)



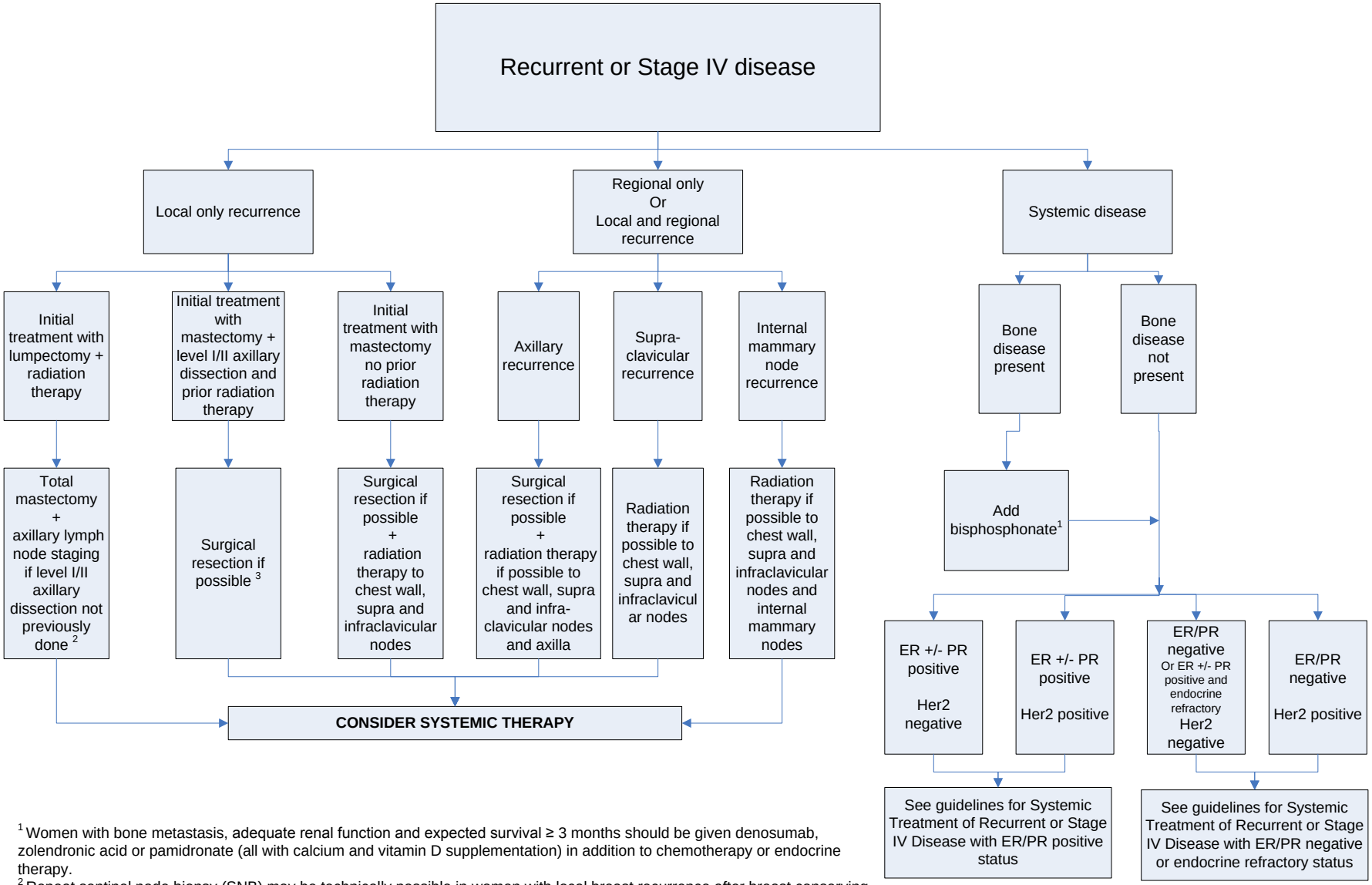
[1] Stage IIIA patients with T3, N1, M0 disease see guidelines for Invasive Breast Cancer
[2] Stage IV patients with any T, any N and M1 see guidelines for Stage IV disease.
[3] Radiation to internal mammary nodes if involved, this should be considered in the Mastectomy group if not clinically involved
[4] Endocrine therapy should be given sequentially after chemotherapy.
[5] Trastuzumab may be administered concurrent with radiation therapy and with endocrine therapy if indicated.

Inoperable Invasive Breast Cancer (Inflammatory)

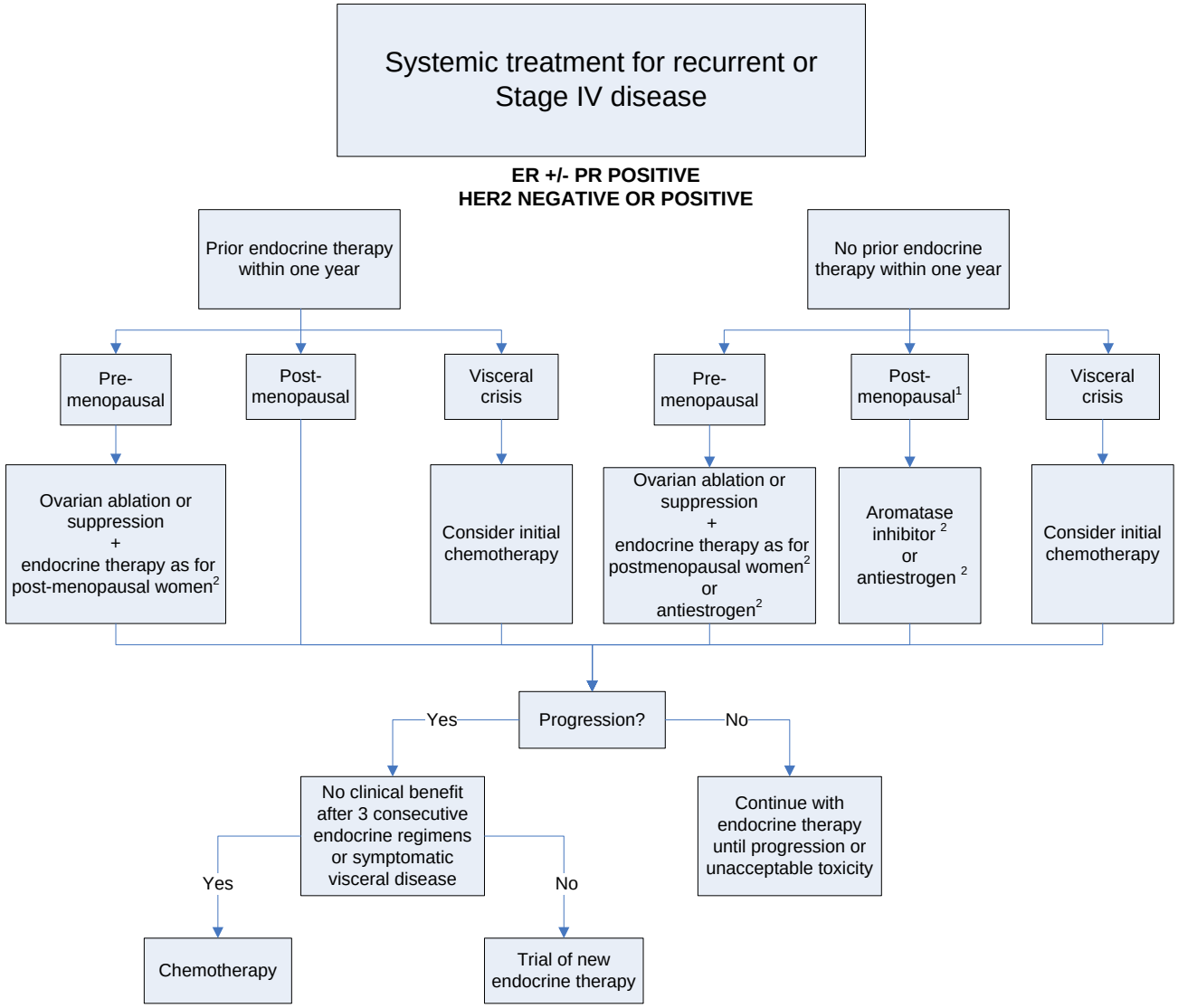


[1] Patients with Her2 positive tumors should be considered for chemotherapy incorporating trastuzumab. This can be added once the anthracycline portion has been completed
[2] Patients with stage IV or recurrent IBC should be treated according to the guidelines for stage IV and recurrence of disease.

Recurrent Breast Cancer

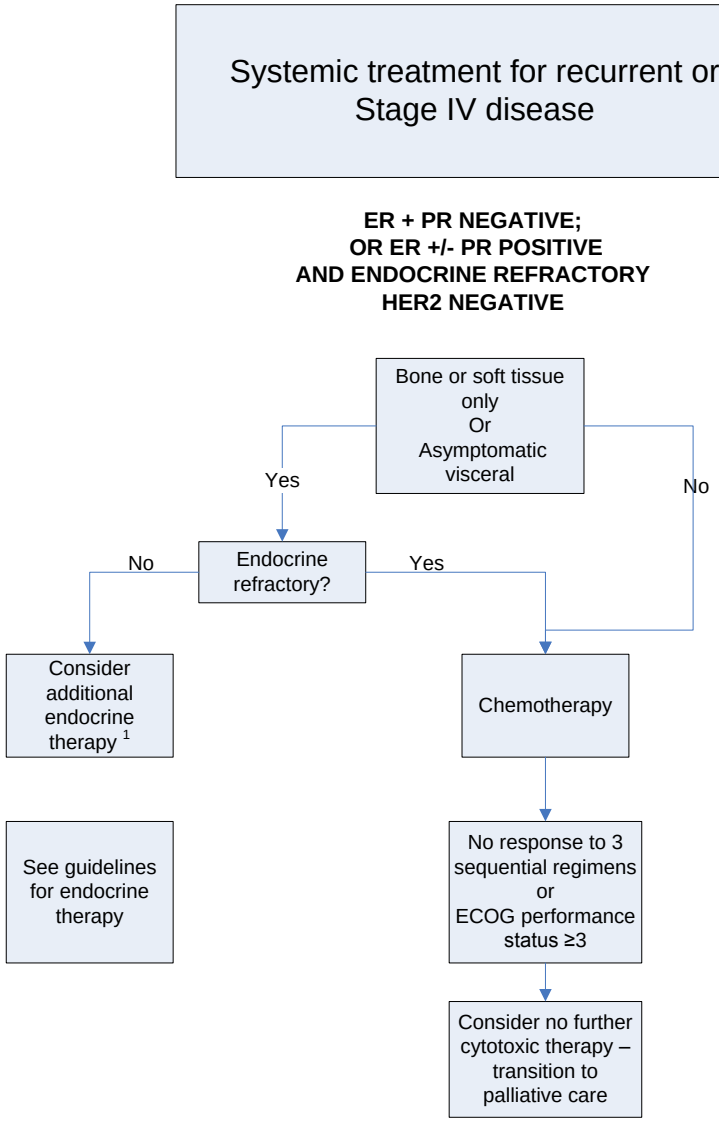


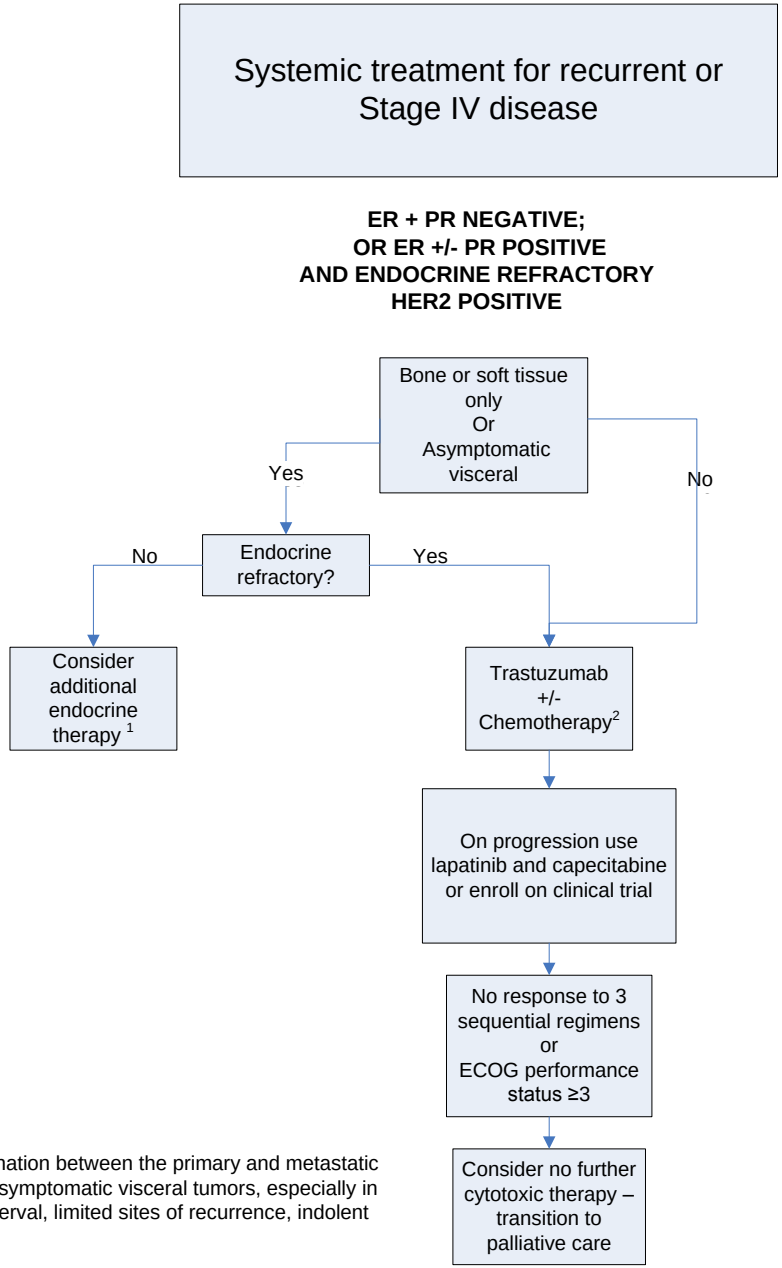
[1] Women with bone metastasis, adequate renal function and expected survival ≥ 3 months should be given denosumab, zolendronic acid or pamidronate (all with calcium and vitamin D supplementation) in addition to chemotherapy or endocrine therapy.
[2] Repeat sentinel node biopsy (SNB) may be technically possible in women with local breast recurrence after breast conserving surgery with prior SNB. The accuracy is unproven and the prognostic significant of repeat SNB after mastectomy is unknown and its use is discouraged.
[3] If not technically resectable, consider systemic therapy to best response, then resect if possible.



[1] Limited studies document a progression free survival advantage by adding trastuzumab or lapatinib to aromatase inhibition in postmenopausal women with ER-positive + Her2 positive disease. However, no overall survival advantage has been demonstrated.

[2] Women presenting at the time of initial diagnosis with metastatic disease may benefit from the performance of local breast surgery +/- radiation therapy. Generally this palliative local therapy should be considered only after response to initial systemic therapy





[1] False negative ER +/- PR determinations occur. There may also be discordance between ER +/- PR determination between the primary and metastatic tumor(s). Endocrine therapy with its low attendant toxicity may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor positive tumor (e.g. long disease free interval, limited sites of recurrence, indolent disease or older age).

[2] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity.

5.1 EARLY STAGE CANCER

5.1.1 Surgical Management of Invasive Breast Cancer

Mastectomy versus Breast Conserving Surgery

Long term follow up of randomized clinical trials have reported similar survival rates for women treated by mastectomy or breast conservation surgery. However all of these studies had specific selection criteria and indeed the vast majority of patients in these studies presented with tumours <2.5 cm.

Accurate pre-operative assessment of the size and extent of the tumour is essential for deciding whether breast conservation surgery is an alternative option to mastectomy.

Routine methods for assessing the extent of disease in the breast are clinical examination, mammography, ultrasound and MRI. In a significant number of cases the true extent of disease is underestimated, particularly with invasive lobular cancer and therefore the use of magnetic resonance imaging (MRI) is indicated in planning surgical treatment and in particular if there is a discrepancy between the clinical and mammographic or sonographic estimated extent of disease; if there is a dense breast pattern on mammography; or the diagnostic core biopsy is of an invasive breast cancer. MRI showed the best imaging pathology correlation in terms of size of disease.

Whilst many women may be suitable for breast conservation surgery, various factors (e.g. biological, patient choice) may lead to some women being advised or choosing to have a mastectomy for their disease. Wherever possible, patients should be offered an informed choice between breast conservation surgery and mastectomy. In women opting for prophylactic mastectomy, a pre-operative breast MRI is advised. When possible, the MRI should be done in mid- phase of the menstrual cycle in pre-menopausal women.

Patients choosing or advised to have mastectomy for invasive breast cancer should have the opportunity to discuss whether breast reconstruction (either at the time of mastectomy or delayed after adjuvant treatment) is appropriate and feasible.

Surgical Margins

Patients undergoing breast conservation surgery should have malignant tumours excised with microscopically clear radial margins (no ink on tumour). Close margins at the chest wall or near the skin may be less important provided the resection goes down to the chest wall and right under the skin.
Shaving of margins at the time of the lumpectomy can be considered and is now recommended based on new evidence that shows a significant reduction on the need for re-resection (NEJM).

Intra-operative specimen radiography is mandatory for non-palpable lesions requiring radiological localization (wire-guidance).

Pathologically involved margins lead to a higher risk of local recurrence, even if adjuvant radiotherapy is given. Historical data suggest that approximately one in four patients with later local recurrence will die of breast cancer, although this is likely an over-estimate in a setting of modern systemic therapy.

- Our group endorses the consensus statement issued by SSO and ASRO (March 2014 Ref: Moran et al. 2014 Int J Rad Onc Biol Phys 88(3).553e564.) which recommended the definition of a negative surgical margin as no ink on tumours. It also recommended that wider surgical margins are not necessary as there is no demonstrable reduction in the recurrence rate within the same breast (Ipsilateral breast tumour recurrence).

Axillary Node Surgery

The presence of axillary node metastases is a powerful prognostic determinant in primary operable breast cancer and its assessment requires histological examination of excised axillary lymph nodes. Appropriate management of the axilla is also important in the prevention of uncontrolled axillary relapse.

Sentinel node biopsy (SNB)

Axillary staging is usually performed by sentinel node biopsy. This is recommended in the majority of patients with clinical and/or radiologically negative axillary lymph nodes. The combined technique (blue dye and radio-isotope) is the recommended method. Case series show that surgeons can achieve >90% sentinel node identification rates and <10% false negative rates. Intraoperative pathological consultation with frozen section can be considered where there is clinical or radiological concern for involved lymph nodes and there is a need for completion axillary dissection.

In general, where the sentinel node is positive (macrometastasis or micrometastasis), further axillary treatment (axillary dissection) should be considered on a case by case analysis in specific circumstances.

The routine undertaking of axillary dissection in patients with 1 or 2 positive sentinel lymph nodes is not necessary in patients that fulfill the criteria of the Z0011 trial. (American College of Surgeons Oncology Group reported on the Z0011clinical trial which randomized patients with early-stage breast cancer and positive sentinel lymph nodes to completion axillary dissection or no further surgery. In this trial, eligible patients had tumour sizes less than 5 cm and no more than 2 positive sentinel nodes. Patients received lumpectomy, adjuvant radiation therapy and most were treated with adjuvant systemic therapy. Further involved axillary lymph nodes were detected in more than 27% of those who underwent completion axillary node dissection. Despite this, after about 6

years of follow-up, there was no significant difference in either disease-free or overall survival between the study arms.)

The significance of isolated tumour cells in axillary lymph nodes is currently uncertain. These should be regarded as lymph node negative and routine axillary treatment is not recommended.

Axillary Dissection

Some patients with invasive breast cancers are diagnosed with axillary disease prior to definitive surgery. The use of pre-operative ultrasound axillary assessment and appropriate fine needle aspiration (or core biopsy if feasible) can yield a diagnosis of involved nodes in some cases. If a positive non-operative diagnosis of axillary nodal metastasis is made in a patient with early breast cancer, that patient would usually proceed to an axillary dissection.

FNA of the axillary node is not always indicated, patient can still have the SNB and the decision on completion axillary dissection made based on an individual bases according to the discussion of each case at the Multidiscipplinary Clinical Conference

If an axillary dissection is carried out, all axillary lymph node posterior and lateral to pectoralis minor and inferior to the level of the axillary vein (level I, II) are removed. Level III resections are reserved for patients with gross nodal disease medial to pectoralis minor. The number of nodes retrieved from axillary node clearance histology specimens will be patient, surgeon and pathologist dependent. However, for a full axillary clearance at least 10 nodes should be retrieved in >90% of cases.

RECONSTRUCTIVE SURGERY

(This section was updated February 2017)

Management Philosophy

All patients, in whom mastectomy is a treatment option, should have the opportunity to receive advice on breast reconstructive surgery. Not all patients will be good candidates, or wish to consider reconstruction.

Timely access for patients considering reconstruction is important so that they are not discouraged by the process. The timing of the reconstruction should be discussed, such as the risks and benefits of immediate versus delayed reconstruction. In general, delayed reconstruction is preferred for patient in whom post-mastectomy radiation therapy is a likely required following their mastectomy (see section on radiation therapy below). For patients undergoing mastectomy without immediate reconstruction, a service should be provided to supply and fit them for external breast prostheses.

(i) Introduction

Breast reconstruction is well recognized to improve some adverse psychosocial effects of mastectomy, which can result in anxiety and depression with consequent negative effects on self-esteem and sexual function. Studies demonstrate that breast reconstruction can enhance vitality and femininity while restoring a sense of well-being and improved quality of life.

Breast reconstruction is now well accepted component of standard cancer treatment. The reconstructive surgeon works in collaboration with the surgical oncologist, medical oncologist and radiation oncologist to provide patients with optimal and personalized multi-disciplinary care with due consideration of both aesthetic goals and oncologic safety. Patients are provided with the opportunity to meet with a reconstructive surgeon who can offer a full range of surgical options for breast restoration.

(ii) Oncological safety of Breast Reconstruction

In spite of initial concerns, the safety of both immediate and delayed reconstruction has been widely established. Breast reconstruction has not been found to affect either the incidence or detection of local recurrences. Similarly immediate reconstruction has not been found to cause significant delays for post-operative adjuvant cancer therapies.

(iii)Timing of Reconstruction

Patients who are likely to require postmastectomy radiotherapy are generally advised to defer reconstruction. Similarly patients with particularly aggressive forms of breast cancer may be advised to delay reconstructive procedures.

In many cases however, the timing of reconstruction is the patient's personal choice. In the past it was believed that patients should undergo reconstruction as a delayed procedure as it would allow them time to come to terms with their mastectomy defect and ultimately have a better appreciation of their reconstructed breast. Studies however failed to demonstrate a psychological advantage of delaying the procedure, and the benefits of immediate reconstruction are now increasingly recognized. A recent Cochrane review reports an absence of quality trials investigating the benefits of immediate versus delayed reconstruction. A single randomized controlled trial reported a reduction in psychiatric morbidity with immediate reconstruction. Immediate reconstruction may offer superior cosmetic results as a large proportion of the native breast skin can be retained in skin sparing approaches, reducing the amount of scarring on the breast and avoiding the patch-like appearance of delayed reconstructions that import significant distant skin paddles. In addition essential aesthetic landmarks such as the inframammary fold can be retained.

Risk-reducing (prophylactic) Mastectomy

Risk-reducing surgery with prophylactic mastectomy and reconstruction may be offered to women at a high lifetime risk of developing breast cancer, such as those who carry

mutations implicated in specific familial cancer syndromes, specifically in BRCA1 or BRCA2 genes, those with a strong family history without an identifiable mutation, or where invasive carcinoma is associated with widespread LCIS or hyperplasia with atypia in the surrounding breast tissue. Patients who previously received a significant dose of radiation to the breasts for an unrelated reasons, such as lymphoma, especially when the radiation was given at a young age of (< 30) should be offered the option of prophylactic mastectomy.

In these high-risk populations, pre-operative work-ups include a careful history and physical, screening mammogram and MRI, appropriate genetic assessment, family planning and psychological counseling are mandatory.

Skin-sparing mastectomy is most often employed for prophylactic mastectomy, and nipple-sparing mastectomy may be used in some patients who have the appropriate indications and anatomy. The use of nipple-sparing mastectomy must be decided upon by the patient, and both the breast and plastic surgeons on an individual patient basis. The indications for sentinel node biopsy should be individualized, especially in patients with some indeterminate findings on screening. The risk of developing breast cancer is reduced by 90-95% but prevention of developing breast cancer in the future cannot be guaranteed.

Radiotherapy and Reconstruction

Patients who require radiotherapy as part of their breast cancer regime present significant challenges for the reconstructive surgeon. Tissue expansion is problematic in the setting of previous irradiation as the tissues are tight and thickened limiting the degree of stretching that can be achieved. In addition the risk of infection and subsequent implant extrusion is increased.

Radiotherapy following breast reconstruction has unpredictable effects on both implant based and autologous reconstruction. It is associated with the development of severe capsular contractures in implant based reconstructions and atrophy and fibrosis of autologous tissue flaps, both of which may severely compromise aesthetic outcome. Previous or anticipated radiotherapy is therefore a major consideration when planning both the type and timing of reconstructive surgery.

(iv) Implant based Reconstruction

Implant based reconstruction is performed in two stages. In the first stage a tissue expander is placed in a submuscular pocket created by pectoralis major and serratus anterior muscles. Following an initial delay of two to three weeks, patients commence the expansion process. This is performed in the clinic setting with saline injections through the integrated port every one to two weeks and continues until the desired size is achieved. Three months after the final expansion the patient returns to the operating room

for the second stage of reconstruction where the expander is replaced with a permanent silicone implant. Adjustments to improve shape and symmetry can be made at this point.

The main advantage of implant-based reconstruction is that the procedures required are shorter and relatively simple. As it does not require harvest of additional tissues distant scarring is avoided. The recovery period is shorter and patients can return to work approximately two weeks post-operatively. The process is however protracted, involving multiple procedures and clinic attendances, with an approximate interval of 6 months between the initial surgery and completion of breast mound reconstruction. The breast shape that can be achieved with use of implants is limited and means that in unilateral reconstructions there may be significant asymmetry between the breasts, which may require additional balancing procedures.

Patients should also be informed of the potential problems associated with tissue expanders and implants including infection, extrusion and capsular contracture. As the lifetime of the current generation of implants is unknown patients should also be aware that they might require further surgery at a later stage for maintenance of their implants. Silicone implants are used at our unit. Patients are reassured the in spite of past controversies regarding the association of silicone implants with autoimmune disease no evidence exists to support a causal relationship. The association between silicone breast implants and anaplastic large cell lymphoma is limited but unclear and cause of current investigation.

Single Stage Implant Reconstruction

Implant based reconstruction is conventionally performed in two stage as the pectoralis major muscle is insufficient to provide full coverage of an implant. Acellular Dermal Matrix is a decellularized human dermal matrix which is commercially available. It can provide additional coverage for the lower pole of breast implants allowing immediate placement of a permanent implant without the need for tissue expansion. This technique simplifies the process of implant based reconstruction, but seems associated with slightly higher complication rates, which makes is more suitable for carefully selected patients meeting specific physical criteria.

(v) Latissimus Dorsi Reconstruction

The latissimus dorsi (LAT) flap transfers muscle and skin on a vascular pedicle from the back to the chest wall. The tissue volume is generally insufficient to recreate a breast mound of adequate size and so this technique is most commonly combined with an implant. The most common application of this reconstructive method is in patients who do not wish to undergo autologous reconstruction but have had previous chest wall irradiation making them poor candidates for tissue expansion of the sub-pectoral pocket. The LAT flap provides a well vascularized muscular pocket and healthy skin, which can be readily expanded. The extra overlying tissue may create a more natural looking breast than an implant alone as it provides additional volume in the lower pole. Patients undergoing this procedure follow a similar time course to those undergoing

reconstruction with expanders and implants alone. In addition however, they have a scar at the donor site, which may be visible in some clothing. Hematoma or seroma formation may occur at the donor site. Although the latissimus dorsi is considered an expendable muscle patients may experience variable degrees of disability following its harvest. This may include stiffness and reduced range of movement at the shoulder.

(vi) Autologous tissue Reconstruction

Autologous tissue transfer is the current gold-standard for breast reconstruction. It permits the reconstruction of a breast that feels and looks natural without the use of implants. The abdomen is the most common source of autologous tissue for breast reconstruction and it may be transferred using a variety of techniques. The pedicled transverse rectus abdominis myocutaneous (TRAM) flap is based on the superior epigastric artery and mobilizes abdominal fat and skin on a vascular pedicle that includes a unilateral rectus abdominis muscle. The muscle is divided distally and mobilized through a subcutaneous tunnel, transporting fat and skin to the chest wall defect. Tissue transferred in this manner may have sub-optimal blood supply resulting in necrosis of some of the fat component. Fat necrosis may present as small hard areas or lumps, which can compromise the aesthetic appearance of the reconstructed breast and may cause significant anxiety for patients with a history of breast cancer. The vascularity of the flap can be improved by disconnecting the muscle completely in the abdomen and reconnecting the inferior dominant vascular pedicle (deep inferior epigastric vessels) to blood vessels in the chest using microvascular techniques. The removal of the entire rectus abdominus muscle however weakens the abdominal wall, increasing the risk of bulges or hernia formation. The defect generally requires reconstruction with a synthetic mesh, which carries an associated risk of infection.

The deep inferior epigastric artery perforator (DIEP) flap harvests large quantities of abdominal fat and skin while maintaining the integrity of the abdominal wall and is therefore our flap of choice for breast reconstruction. Considered the current state-of-the-art, the small perforating vessels that pass from the main pedicle to the abdominal fat and skin are identified and dissected free of the surrounding muscle. In the majority of patients the entire rectus abdominis muscle can be left in situ, maintaining normal abdominal strength and minimizing the risk of bulges or hernia. In approximately 10% of patients the perforators are inadequate to support the fat and skin of the flap and in these cases a small portion of the muscle may need to be harvested to enhance the vascularity of the flap.

Microvascular free tissue transfer is a complex, technically demanding technique and unilateral breast reconstruction procedures take four to five hours to complete. The length of the procedure and the small inherent risk of free flap failure (approximately 1% at our unit) constitute the main disadvantages of the DIEP flap. The risk of flap failure may be increased in patients with a history of smoking, clotting disorders or previous radiotherapy. In addition there is a large scar at the donor site but as the harvest procedure is similar to an abdominoplasty the appearance of the abdomen is usually quite pleasing to the patient.

Autologous reconstructions are not constrained by implant shape and so offer enhanced versatility and enable superior symmetry with the contralateral natural breast in unilateral reconstructions. In spite of the increased operative time a pleasing breast reconstruction with good symmetry can be achieved in a single procedure. The transferred tissue will adapt to any changes in the patient's body habitus so maintenance surgery is unlikely to be needed later in life. A pre-operative CT angiogram of the abdominal wall vasculature is performed to determine the presence of perforators of appropriate caliber. Patients are given 5,000iu of subcutaneous heparin on the morning of surgery and thromboembolic deterrent stockings are also used. In bilateral cases sequential compression devices are also added. Aspirin (81mg OD) is commenced post-operatively and continued for a six-week period. Patients may be provided with an abdominal binder to support the abdominal wall for up to 6 weeks. The average hospital stay is three days after the procedure. Patients are advised that physical activities must be curtailed post-operatively.

(vii) Other Autologous Options

Although the abdomen is our first choice for autologous tissue reconstruction it is not always an available option. The most common factors precluding harvest of abdominal tissue include extensive previous surgical scarring and inadequate abdominal pannus. In these cases patients may be offered alternative procedures for microvascular transfer of tissues to the breast defect.

The ample soft tissue of the gluteal region makes the free gluteal flap a reasonable second or third line option for creating a breast mound. Although this method is more limited in its ability to create a breast that is large or sags, the reconstructed breast will be soft and have a natural shape. There is flattening at the buttock donor site, which can be noticeable in normal clothing.

The TMG (Transverse Myocutaneous Gracilis) flap is taken from the inner thigh region, the same distribution as in a cosmetic inner thigh lift. Part of the gracilis muscle is taken to provide the blood supply to this flap. This is usually not missed following its removal. This flap is used to create a smaller sized breast and almost no contour abnormality can be expected in the inner thigh following this flap.

In both the free gluteal and thigh flaps, the amount of skin that can be taken is limited so that these techniques are mostly used only in immediate breast reconstruction at the same time as the mastectomy. The cosmetic outcome of these procedures are moderate to good, and over 60% of patients will require a second revision surgery to improve the breast mound.

(viii) Selecting a Reconstructive Technique

At the initial consultation the options are outlined and the relative advantages and disadvantages of each method are discussed at length. Patients are examined and advised of which specific techniques would be appropriate for them. They are then provided with

relevant literature reiterating what has been discussed and asked to take some time to consider their options. If they wish to proceed with reconstruction, they return to the clinic to further discuss their chosen reconstructive technique.

	Implant/Expander	Tissue flap
Surgery	2 separate shorter surgeries (2 hr each)	1 longer procedure (4-5 hrs)
Hospitalization	Day surgery or overnight stay	Average 3 days
Recovery	2-4 weeks following tissue expander insertion	6-10 weeks
Scars	Mastectomy scar only	Mastectomy scar + scar at donor site
Shape and feel	No natural sag, firm over time	Very natural feel, soft
Opposite breast	More changes needed to match implant	Fewer changes needed to match natural breast
Complications	Breast feels more firm + less natural appearing with time	~1 % risk of microsurgical failure with complete flap loss abdominal weakness, bulge, hernia

(ix) Postoperative Rehabilitation

Following reconstruction physical activities are restricted. The nature and duration of these limitations depend on the method of reconstruction used. The post-operative rehabilitation protocols are outlined below.

Rehabilitation Protocol post Tissue Expanders and Implants

0-2 weeks	Healing of incision	No exercise **ROM to 90** for light self-care activities No lifting > 5 pounds

2-6 weeks	Expansion	May follow same instructions as post-mastectomy: AAROM, AROM as tolerated; **no PROM** Increase self care activities Postural training Start scar massage once incisions are completely healed – 3 weeks – (surgeon's approval) No lifting > 10 pounds
Over 6 weeks		No pectoralis strengthening PROM Light activities only 24 hours after expansion Gradual increase in weights and return to activities

Rehabilitation Protocol post Latissimus Dorsi Flap with Tissue Expanders/ Implant

0-2 week	Healing of Incision	No exercise **ROM to 90** for light self-care activities No lifting > 5 pounds
2-8 weeks	Expansion	May follow same instructions as post-mastectomy: AAROM, AROM as tolerated; **no PROM** Increase self care activities Postural training Teach patient manual lymph drainage around incision (surgeon's approval) Teach patient gentle breast massage (surgeon's approval) Start scar massage once incisions are completely healed – 3 weeks – (surgeon's approval) No lifting > 10 pounds
Over 8 weeks		PROM Light activities only 24 hours after expansion Gradual increase in weights and return to activities

Rehabilitation Protocol post DIEP Flap Reconstruction

0-2 week	Healing of Incision	Wear binder & stockings, deep abdominal breathing, ankle pumping & log rolling No exercise **ROM to 90** for light self-care activities No lifting > 5 pounds
2-6 weeks		AAROM, AROM arm exercise and trunk flexibility 1 week post -op as tolerated; **no PROM** No lifting > 10 pounds PROM after 3 wks post-op Increase self care activities Postural training Teach patient manual lymph drainage around incision (surgeon's approval) Start scar massage once incisions are completely healed – usually 3 weeks post-op – (surgeon's approval)
Over 6 weeks	6-8 weeks 8-12 weeks 12-16 weeks	No abdominal exercise for 6 weeks No sit ups No lifting > 10 pounds for 6 weeks Progressive UE PROM Increased Postural exercise and training Core stability exercises Increase trunk flexibility (prone lying, prone on elbows, prone press ups) Reverse sit ups 10-12 weeks
Return to Gym	6-8 weeks 8-12 weeks 12-16 weeks	25% of what you used to do 50% of what you used to do 75% of what you used to do

References

Arriagada R, Le MG, Rochard F, et al. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up. J Clin Oncol 1996;14:1558.

Cordeiro PG Breast Reconstruction for Breast Cancer. NEJM 2008; 359(15): 1590-1601

D'Souza N, Darmanin G, Fedorowicz Z. Immediate versus delayed reconstruction following surgery for breast cancer. Cochrane Database Syst Rev. 2011; 6(7).

Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15 year survival: an overview of randomized trials. Lancet 2005;366:2087–106

Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347(16):1233–41.

Geffrelot, J, F. Toudic Emily, C. Levy, C. Blanc Fournier, C. Segura, O. Switsers, D. Allouache, C. Delcambre, S. Martin, T. Delozier Determination of clear margin in breast-conserving surgery: Is 1 mm needed? J Clin Oncol 28:15s, 2010 (suppl; 515)

Damen TH, Timman R, Kunst EH, Gopie JP, Bresser PJ, Seynaeve C, Menke-Pluijmers MB, Mureau MA, Hofer SOP, Tibben A: High satisfaction rates in women after DIEP flap breast reconstruction. J Plast Reconstr Aesthet Surg: January 2010: 63(1): pp 93-100.

Holland R, Veling SH, Mravunac M, et al. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. Cancer 1985;56(5):979–90.

McCarthy Cm, Pusic AL, Sclafani L. Breast cancer recurrence following prosthetic post mastectomy reconstruction, incidence detection and treatment. Plas and Recon Surg. 2088; 121:381-8

McCready DR, Yong WS, Ng AKT, et al.: Influence of the New AJCC Breast Cancer Staging System on Sentinel Lymph Node Positivity and False-Negative Rates. Journal of the National Cancer Institute 96:873-875, 2004

Olson JA Jr, McCall LM, Beitsch P, Whitworth PW, Reintgen DS, Blumencranz PW, Leitch AM, Saha S, Hunt KK, Giuliano AE; American College of Surgeons Oncology Group Trials Z0010 and Z0011. Impact of immediate versus delayed axillary node dissection on surgical outcomes in breast cancer patients with positive sentinel nodes: results from American College of Surgeons Oncology Group Trials Z0010 and Z0011.J Clin Oncol. 2008 Jul 20; 26(21):3530-5.

Veronesi U, Saccozzi R,Vecchio Del, et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. N Engl J Med 1981;305(1):6–11.

Winters ZE, Benson JR, Pusic AL. A systematic review of the clinical evidence to guide treatment recommendations in breast reconstruction based on reported outcome measures and health related quality of life. Annals of Surgery 2010; 252(6): 929-942

Zhong T, Hofer SO, McCready DR, Jacks LM, Cook FE, Baxter N: A Comparison of Surgical Complications between Immediate Breast Reconstruction and Mastectomy: The Impact on Delivery of Chemotherapy-An Analysis of 391 Procedures. 2011 Jul 27. [Epub ahead of print]. Annals of Surgical Oncology: 2011.

Zhong T, McCarthy C, Min S, Zhang J, Beber B, Pusic A, Hofer SOP: Satisfaction and Health-Related Quality of Life Following Autologous Tissue Breast Reconstruction: A Prospective Analysis of Early Postoperative Outcomes. Cancer, published online Oct 24, 2011.

5.1.2 Systemic Therapy

(This section was updated February 2017)

Adjuvant Systemic Therapy

Overview

Adjuvant systemic therapy includes:

- **Endocrine Therapy** (for ER/PgR positive tumours)
    - Postmenopausal women
        - Tamoxifen
        - Aromatase Inhibitors
    - Premenopausal women
        - Tamoxifen
        - Ovarian ablation/suppression
- **Chemotherapy**
- **Targeted therapy**

The choice of adjuvant systemic therapy must take into account the potential benefits and possible side effects of treatment

Risk Assessment

- Node negative (N-)

Low Risk	Moderate Risk	High Risk
• 10 year risk of recurrence < 10% • Hormone receptor (ER/PgR) positive • Grade 1 • Size ≤ 2 cm • Lymphovascular invasion absent • Her 2-negative • Age > 35	• Not low or high risk	• Hormone receptor negative • Grade 3 • Size > 2 cm • Age ≤ 35 • Her 2-positive

- Node positive (N+)

Recommendations

Node Negative Disease

- Low Risk – No treatment or Endocrine therapy alone (ER/+)
- Moderate Risk – Endocrine therapy (ER/PgR+) ± chemotherapy. Consider Oncotype DX.
- High Risk – As for N+ disease

Node Positive Disease

- Chemotherapy + Endocrine therapy (ER/PgR+)
- 3rd generation regimens (taxane-containing) shown to be most effective regimens in node-positive/high-risk node negative patients
- Benefit of chemotherapy greater in premenopausal, compared to postmenopausal women

Endocrine Therapy

Pre/peri-menopausal	Postmenopausal
• Tamoxifen (T) x5-10yrs • Ovarian ablation/suppression (OA/OS) • T + OA/OS	• T x5-10 yrs • T (2-3 yrs) then aromatase inhibitor (AI) (complete 5 yrs) • AI x 5 yrs • T (5 yrs) then AI (x 5 yrs)

Tamoxifen

- Tamoxifen may be used in pre/peri/postmenopausal ER/PgR + women
- Tamoxifen reduces the risk of local recurrence after lumpectomy (tamoxifen + radiotherapy to the breast is superior to radiation alone) and reduces risk of distant disease recurrence
- Tamoxifen reduces the risk of contralateral breast cancer (47% risk reduction)
- Tamoxifen for 5 years is more effective than for 2 or 3 years
- Compared with 5 years of therapy, 10 years has been shown to improve recurrence rate and survival although the absolute improvement is small in women at lower risk (e.g. T1N0).
- Tamoxifen plus chemotherapy is superior to either tamoxifen or chemotherapy alone in reducing the recurrence of breast cancer and improving overall survival

- As chemoprevention, tamoxifen reduces the risk of developing ER positive breast cancer in high-risk women

- Main side effects are menopausal symptoms (hot flashes, urogenital atrophy), increased risk of thromboembolism, endometrial cancer

Ovarian Ablation/Suppression (OA/OS)

- OA/OS only effective for premenopausal ER/PgR + women

- OA/OS decrease the risk of contralateral breast cancer (40-50% risk reduction)

- OA/OS increases survival in premenopausal women (25% improvement in survival)

- OA/OS = CMF-like chemotherapies in early disease (ZEBRA)

- Choice of OA vs OS in adjuvant setting unclear

- Duration recommended for OS – unknown ?2-3 years

- Addition of OA/OS to tamoxifen has no additional benefit in unselected pre-menopausal women in adjuvant setting. However, in women <35 who have high risk disease requiring chemotherapy and in whom menses return, the addition of OA/OS appears to reduce the risk of recurrence. Note should be made that this is based on a small subgroup analysis of the SOFT trial. In women receiving OA/OS, consideration can be given to the use of an aromatase inhibitor rather than tamoxifen as it appears to further reduce risk of recurrence. However, two independent studies (SOFT/TEXT and ABCSG12) have shown excess deaths in women receiving OA/OS and aromatase inhibitor compared with OA/OS and tamoxifen.

- OA = OS in metastatic disease

- Main side effects are menopausal symptoms (hot flashes, urogenital atrophy), increased risk of osteoporosis and cardiovascular events. Quality of life especially sexual functioning is dramatically reduced with use of OA/OS

Aromatase Inhibitors (AIs)

- AIs are only effective in postmenopausal ER/PgR + women

- AIs should NOT be used in pre/perimenopausal women; amenorrhea due to chemotherapy or tamoxifen is unreliable for assessing patient as postmenopausal (see below). FSH and LH may be suppressed by tamoxifen and may be high in patients with a high estradiol level. If in doubt, aromatase inhibitors should suppress estradiol levels by 95% i.e. undetectable within 4 weeks of initiation of

aromatase inhibitor therapy.

- AIs improve disease free survival over tamoxifen alone, however have no impact on overall survival
- AIs may be given after 2-3 years of tamoxifen, to complete 5 years of endocrine therapy

- AIs may be given as 'up-front' adjuvant therapy for 5years (ATAC, BIG 1-98)

- AIs may be given as 'extended therapy' after 5 years of tamoxifen (MA.17,B33)

- Main side effects are menopausal symptoms (hot flashes, urogenital atrophy), musculoskeletal symptoms, increased risk of osteoporosis and cardiovascular events

Chemotherapy

- Chemotherapy is an option for both hormone receptor positive and hormone receptor negative women

- Recent trials have reported improvement in disease-free survival for women assigned to tamoxifen plus chemotherapy compared with tamoxifen alone

- Chemotherapy regimen types
    - 1st generation regimens include CMF, AC
    - 2nd generation regimens include FEC100, AC-Taxol
    - 3rd generation regimens include FEC-Docetaxel, dose-dense AC-Paclitaxel

- 3rd generation more effective than 2nd generation which are more effective than 1st generation regimes, usually with added toxicity

- In terms of breast cancer outcomes
    - CMFx6 and ACx4 are equivalent (NSABP B23)
    - CEF is superior to CMF (MA.5)
    - FEC-Docetaxel is superior to FEC100 (PACS01)
    - AC-Paclitaxel is superior to AC (NSABP B28)
    - AC-Paclitaxel 3-weekly is inferior to dose-dense EC-paclitaxel and CEF (NCIC-CTG MA.21)
    - FEC100 is superior to FEC50 (FASG)
    - TC (docetaxel and cyclophosphamide) has superior efficacy and toxicity compared to AC (US ONC 9735)

- There is increasing interest in the role of Oncotype DX for women with hormone receptor positive, node negative tumors who may not benefit from the addition of chemo to endocrine therapy

- There is increasing interest in reduced benefit of more potent chemotherapy regimens in patients with hormone positive, Her2 negative disease

Recommendation

Intermediate risk women who receive chemotherapy can be treated with short course regimens. TC is preferable to AC in this setting due to improved efficacy and improved long-term toxicity (fewer cardiac events and no known risk of leukemia).
High risk women should be treated with long-course regimens such as FEC-Docetaxel or dose-dense AC-Paclitaxel. The latter of these is better tolerated, but requires the need for growth factor support and cannot be easily combined with trastuzumab if given q3weekly.
Note: the PACS 01 trial compared 6 cycles of 5-Fluoro-uracil (500 mg/m2), epirubicin (100 mg/m2) and cyclophosphamide (500 mg/m2) (FEC) with 3 cycles of FEC followed by 3 cycles of docetaxel (100 mg/m2) (FEC-D). Results showed that the taxane containing regimen led to improvement in both DFS and OS with an acceptable toxicity profile, including a febrile neutropenia rate of 11.2%. However, two subsequent reports of unselected patients treated at cancer centres showed febrile neutropenia rates in excess of 25%. Therefore concomitant use of growth factor support should be considered for patients having FEC-Docetaxel.
For regimen details see belowbelow – Adjuvant Chemotherapy Regimens.
Adjuvant Online!

- Prediction tool for risk of relapse, breast cancer mortality, benefit of endocrine therapy, chemotherapy and combined therapy
- Risk / benefit calculation based on patient age, comorbidities, tumour size, grade, nodal status, ER/PgR status. Current version (*version* 8.0) does not take Her2 status or LVI into account. This can be improved by using a 1.5x incremental risk increase through the "Prognostic" option.

Predict is an alternative tool to Adjuvant Online and provides assessment of HER2 status. However, it has not been well validated in a North American population.

Oncotype DX assay

- 21-gene recurrence score assay
- may consider use in ER/PgR+, node-negative, intermediate-risk women who may not benefit from chemotherapy if low recurrence risk
- low-risk RS <18; intermediate-risk RS ≥18 and <31; high-risk RS≥ 31

Adjuvant Bone-targeted therapy

- Bone targeted therapy (either zoledronic acid 4mg every 6 months or clodronate 800mg bid daily) is associated with a reduction in the risk of bone metastases and breast cancer-related mortality. The effect is seen only in patients who are definitively menopausal and is independent of other factors such as hormone receptor status.
- As the effect size is modest (relative risk reduction ~15-20%), this will only translate into significant absolute effects in higher risk post-menopausal women

(e.g. large tumour size, lymph node involvement or failure to receive chemotherapy which is considered otherwise appropriate).

- In women receiving an aromatase inhibitor, an alternative to zoledronic acid or clodronate is q6 month denosumab (60mg SC). However, data for this are limited to a single trial with bone mineral density outcomes. Additionally, the optimal dose and schedule of denosumab in this setting is unknown.

References

1. Jonat W, Kaufmann M, Sauerbrei W et al; Zoladex Early Breast Cancer Research Association Study. Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: The Zoladex Early Breast Cancer Research Association Study. J Clin Oncol. 2002 Dec 15;20 24):4628-35
2. Coates AS, Keshaviah A, Thürlimann Bet al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol. 2007 Feb 10;25(5):486-92
3. Howell A, Cuzick J, Baum M et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet. 2005 Jan 1-7;365(9453):60-2
4. Roché H, Fumoleau P, Spielmann M, Canon JL et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. J Clin Oncol. 2006 Dec 20;24(36):5664-71
5. Trudeau ME. Optimizing adjuvant breast cancer chemotherapy: rationale for the MA.21 study. Oncology (Williston Park). 2001 May;15(5 Suppl 7):7-13.
6. Mamounas EP, Bryant J, Lembersky B et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. J Clin Oncol. 2005 Jun 1;23(16):3686-96
7. Jones SE, Savin MA, Holmes FA et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol. 2006 Dec 1;24(34):5381-7
8. Clemons M, Simmons C. Identifying menopause in breast cancer patients – considerations and implications. Breast Cancer Research and Treatment 2007 Aug;104(2):115-20
9. www.adjuvantonline.com
10. www.predict.nhs.uk/

11. Early Breast Cancer Trialists' Collaborative Group (EBCTCG)., Coleman R, Powles T, Paterson A, Gnant M, Anderson S, Diel I, Gralow J, von Minckwitz G, Moebus V, Bergh J, Pritchard KI, Bliss J, Cameron D, Evans V, Pan H, Peto R, Bradley R, Gray R. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet. 2015 Oct 3;386(10001):1353-61.

12. Gnant M, Pfeiler G, Dubsky PC, Hubalek M, Greil R, Jakesz R, Wette V, Balic M, Haslbauer F, Melbinger E, Bjelic-Radisic V, Artner-Matuschek S, Fitzal F, Marth C, Sevelda P, Mlineritsch B, Steger GG, Manfreda D, Exner R, Egle D, Bergh J, Kainberger F, Talbot S, Warner D, Fesl C, Singer CF; Austrian Breast and Colorectal Cancer Study Group..Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2015 Aug 1;386(9992):433-43

Adjuvant Chemotherapy Regimens

FEC-Docetaxel

Proceed with chemo if ANC equal to or greater than 1.2 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L
If parameters are outside of acceptable range, contact the physician for further orders.

On Days 1, 22 and 43				
Dexamethasone	8mg	po		
Ondansetron	16mg	po		
Aprepitant	125/80/80 mg	po		
Epirubicin hcl	100mg/m2	iv	push	
Fluorouracil	500mg/m2	iv	push	
Cyclophosphamide	500mg/m2	iv	250ml N saline	infuse iv over 30 min
Dexamethasone	4mg	po	bid	2 days
Starting on the day after chemotherapy (days 2-3)				
Prochlorperazine maleate	10mg	po	q6h prn	30 tablets
Every 6 hours as needed for nausea or vomiting Alternative: olanzapine 2.5 mg once to twice po daily prn 30 tabs (more effective than prochlorperazine)				
Starting day 2 of cycle, give filgrastim 300 mcg subcutaneously daily for 7-10 days. If drug coverage, pegfilgrastim 6mg single dose on day 2 of regimen is preferred				

On Days 64, 85 and 106				
Dexamethasone	8mg	po	bid	3 days
Twice a day with food for 3 days starting the day before docetaxel. Must have 3 doses prior to docetaxel				
Docetaxel	100mg/m2	iv	250ml N Saline	
Use non-PVC excel bag and tubing. Use graduated rate for first infusion. If no reaction, infuse subsequent doses over 1hr				
Diphenhydramine	50mg	iv	50ml N Saline	q4h prn
Infuse iv over 15-30 minutes every 4 hours as required. Maximum daily dose of diphenhydramine allowed in chemo daycare for allergic reactions is 200 mg.				

Oxycocet 1 po qid PRN for pain 30 tablets *for refractory pain either prednisone 10 mg bid po x 5 days or dexamethasone 4 mg po daily x 5 days
Starting day 2 of cycle, give filgrastim 300 mcg subcutaneously daily for 7-10 days. If drug coverage, pegfilgrastim 6mg single dose on day 2 of regimen is preferred

Dose dense AC-Paclitaxel

Proceed with chemo if ANC equal to or greater than 1.0 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L
If parameters are outside of acceptable range, contact the physician for further orders.

On Days 1, 15, 29 and 43					
Ondansetron	8mg	po			
Dexamethasone	8mg	po			
Aprepitant	125/80/80 mg	po			
Doxorubicin HCl	60mg/m2	iv	IV push		
Cyclophosphamide	600mg/m2	iv	250ml N Saline	Infuse IV over 30min	
Filgrastim	300mcg	sc	qd	7 days	
Starting day 3 of cycle, give subcutaneously daily for days. If drug coveragepegfilgrastim 6mg single dose on day 2 of regimen is preferred					
Dexamethasone	4mg	po	qd	2 days	
Starting on the day after chemotherapy (days 2-3)					
Prochlorperazine maleate	10mg	po	q6h prn	30 tablets	
Every 6 hours as needed for nausea or vomiting Alternative: olanzapine 2.5 mg once to twice daily is probably more effective					

On Days 57, 71, 85 and 99					
Dexamethasone	20mg	iv	50ml	N Saline	Infuse iv over 15 minutes pre-paclitaxel (45 mins before paclitaxel) Note: if no infusion reaction after two paclitaxel infusions, pharmacy will discontinue premedication
Diphenhydramine	50mg	iv	50ml	5% Glucose	Infuse iv over 20 minutes
Famotidine	20mg	iv	50ml	5% Glucose	Infuse iv over 15 minutes

Paclitaxel	175mg/m2	iv	500ml	N Saline	
Use graduated rate for first two cycles. If no reaction, infuse subsequent doses over 3 hours. Use non-PVC excel bag and tubing with 0.22 micron in-line filter.					
Diphenhydramine	50mg	iv	50ml	N Saline	q4h prn
Administer iv over 15-30 minutes every 4 hours as needed. Maximum daily dose of diphenhydramine allowed in chemo daycare for allergic reactions is 200 mg.					
Filgrastim	300mcg	sc	qd	7 days	
Starting day 2 of cycle, give subcutaneously daily for 8 days. If drug coverage, pegfilgrastim 6mg single dose on day 2 of regimen is preferred.					
Oxycocet 1 qid PO prn for pain For refractory pain, prednisone 10 mg bid po x 5 days or dexamethasone 4 mg qd po x 5 days					

Trastuzumab

On Day 1					
Trastuzumab	8mg/kg	iv	250ml	N Saline	Infuse iv over 90 minutes
Diphenhydramine	50mg	iv	50ml	N Saline	
Administer iv over 15-30 minutes every 4 hours as needed. Maximum daily dose of diphenhydramine allowed in chemo daycare for allergic reactions is 200 mg.					
Acetaminophen	650mg	po	PRN headache		
Meperidine	25mg	iv	50ml	N Saline	
One time dose as required for rigors/chills. Infuse iv over 10-15 minutes.					
Dimenhydrinate	50mg	iv	50ml	N Saline	
One time dose as needed for nausea or vomiting due to meperidine. Infuse iv over 15 min.					

On Days 22 and q21 days for 17-18 cycles					
Trastuzumab	6mg/kg	iv	250ml	N Saline	Infuse iv over 30 minutes
Diphenhydramine	50mg	iv	50ml	N Saline	
Administer iv over 15-30 minutes every 4 hours as needed. Maximum daily dose of diphenhydramine allowed in chemo daycare for allergic reactions is 200 mg.					

Acetaminophen	650mg	po		PRN headache
Meperidine	25mg	iv	50ml	N Saline
One time dose as required for rigors/chills. Infuse iv over 10-15 minutes.				
Dimenhydrinate	50mg	iv	50ml	N Saline
One time dose as needed for nausea or vomiting due to meperidine. Infuse iv over 15 min.				

Docetaxel and Cyclophosphamide

Proceed with chemo if ANC equal to or greater than 1.2 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L
If parameters are outside of acceptable range, contact the physician for further orders.

On Day 1, 22, 43 and 64					
Ondansetron	16mg	po			
Dexamethasone	8mg	po	bid	3 days	
Twice a day with food for 3 days. Patient must have 3 doses prior to receiving docetaxel.					
Pt. Must receive 3 doses of 8mg dexamethasone po prior to docetaxel infusion					
Docetaxel	75mg/m2	iv	250ml	N Saline	
Use non-PVC excel bag and tubing. Use graduated rate for first infusion. If no reaction, infuse subsequent doses over 1hr					
Diphenhydramine	50mg	iv	50ml	N Saline	q4h prn
Administer iv over 15-30 minutes every 4 hours as needed.					
Maximum daily dose of diphenhydramine allowed in chemo daycare for allergic reactions is 200 mg.					
Cyclophosphamide	600mg/m2	iv	250ml	N Saline	Infuse iv over 30 min
Filgrastim 300 mg sc daily x 7-10 days.If drug coverage, pegfilgrastim 6 mg sc x1 on day 2 is preferred					
Or,					
Ciprofloxacin	500mg	po	bid	10 days	
Twice a day for 10 days, on days 5 to 14.					
Prochlorperazine maleate	10mg	po	q6h prn	30 tablets	
Every 6 hours as needed for nausea or vomiting					
Oxycocet 1 qid po prn for pain 40 tabs					
For refractory pain, prednisone 10 mg bid po or dexamethasone 4 mg qd po x 5 day					

Doxorubicin and Cyclophosphamide

Proceed with chemo if ANC equal to or greater than 1.2 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L
If parameters are outside of acceptable range, contact the physician for further orders.

On Days 1, 22, 43 and 64					
Ondansetron	16mg	po			
Dexamethasone	8mg	po			
Aprepitant	125/80/80 mg	po			
Doxorubicin HCl	60mg/m2	iv	IV push		
Cyclophosphamide	600mg/m2	iv	250ml N Saline	Infuse IV over 30min	
Dexamethasone	4mg	po	qd	2 days	
Starting on the day after chemotherapy (days 2-3).					
Prochlorperazine maleate	10mg	po	q6h prn	30 tablets	
Every 6 hours as needed for nausea or vomiting Olanzapine 2.5 mg qd to bid po is probably a more effective alternative					

Docetaxel and Carboplatin and Traztuzumab (6 cycles)

On Day 1					
Dexamethasone	8mg	po	bid	3 days	
Twice a day with food for 3 days. Patient must have 3 doses prior to receiving docetaxel					
Ondansetron	16mg	po			
Trastuzumab	8mg/kg	iv	250ml N Saline	Infuse iv over 90 minutes	
Pt. Must receive 3 doses of 8mg dexamethasone po prior to docetaxel infusion					
Docetaxel	75mg/m2	iv	250ml N Saline		
Use non-PVC excel bag and tubing. Use graduated rate for first infusion. If no reaction, infuse subsequent doses over 1hr					
Carboplatin	AUC=6	iv	250ml 5% Glucose	Infuse iv over 30 minutes	
Diphenhydramine	50mg	iv	50ml N Saline		
Administer iv over 15-30 minutes every 4 hours as needed. Maximum daily dose of diphenhydramine allowed in chemo daycare for allergic reactions is 200 mg.					

Acetaminophen	650mg	po		PRN headache
Meperidine	25mg	iv	50ml	N Saline
One time dose as required for rigors/chills. Infuse iv over 10-15 minutes.				
Dimenhydrinate	50mg	iv	50ml	N Saline
One time dose as needed for nausea or vomiting due to meperidine. Infuse iv over 15 min.				
Filgrastim 300 mcg daily sc x 7-10 days starting on day 2 If drug coverage, pegfilgrastim 6 mg sc on day 2 is preferred				

Bisphosphonates for early breast cancer

Adjuvant Bisphosphonates

This policy is currently under review. There is evidence that women who are postmenopausal at time of treatment will experience a reduction in mortality with use in the adjuvant setting.

Role of Bisphosphonates for Cancer Therapy-induced Bone Loss

Women who are osteoporotic and on adjuvant endocrine therapy that enhances loss of bone density or who have undergone premature treatment-induced menopause should receive a bisphosphonate.

Women who are osteopenic and on adjuvant therapy which enhances loss of bone density, or who have undergone premature treatment-induced menopause should be considered for a bisphosphonate, especially in the presence of other risk factors: prior non-traumatic (fragility) fracture, aged over 65 years, family history of osteoporosis, tobacco use, low body weight.

Postmenopausal women taking aromatase inhibitors are recommended to commence treatment with bisphosphonates if the T-score is <-2.0, or in the presence of a fragility fracture.

Secondary causes of osteoporosis should be excluded and standard lifestyle advice on smoking, exercise, calcium supplementation and adequacy of vitamin D intake should also be provided.

Women with premature menopause due to chemotherapy, ovarian function suppression or oophorectomy and postmenopausal women receiving adjuvant therapy with an aromatase inhibitor should have bone density monitored at least every 2 years following a baseline DEXA (dual energy x-ray absorptiometry) scan of the spine and hip.

Frequency of bone mineral density monitoring should be tailored to the individual. If baseline T-score >-1.0 further monitoring of bone density may not be necessary
A woman with early breast cancer at risk of bone mineral loss should be provided with appropriate advice for good bone health. This includes, but is not limited to:

- A healthy diet
- Cessation or continuing abstinence from smoking
- Maintenance of a healthy body mass index
- Regular exercise
- Calcium

Adequate vitamin D levels

5.1.3 RADIATION THERAPY

(This section was last updated December 2015)

The following are considered to be contraindications to whole breast radiation, in some cases partial breast radiation may be possible:

- 1st/2nd trimester of pregnancy,
- history of prior radiation to the breast region (e.g., Hodgkins Disease),
- history of collagen vascular disease,
- diffuse indeterminate or malignant appearing calcifications on mammography.

Tis: Non Invasive Carcinoma

Non-invasive carcinoma includes ductal carcinoma in-situ (DCIS), lobular carcinoma in situ, and Paget's disease without an invasive component.

DUCTAL CARCINOMA IN SITU (DCIS)

(Please see Chapter 5.4.1 DCIS Page 101 For DCIS background, Diagnotic Evaluation and Surgical Management)

(a) Breast irradiation

The majority of women treated with breast-conserving surgery should be considered for adjuvant radiotherapy (6, 7). The radiotherapy regimen has historically consisted of 50 Gy in 25 fractions over 5 weeks. There is now data supporting the therapeutic equivalency of hypofractionated regimens , which is offered to appropriately selected women (8, 9). Attempts should be made to minimize cardiac exposure with left-sided lesions.

The role of a boost for patients with DCIS has not been well established and is currently being investigated in the MA-33 randomized trial (11). For now, a boost should not be routinely administered, as there are no data supporting the efficacy of higher radiation doses in DCIS.

(b) Chest wall irradiation

Chest wall radiotherapy is appropriate for consideration in the setting of positive margins following mastectomy. For close margins (<2mm), recently published data indicates that chest wall recurrence is not increased, therefore post-mastectomy radiotherapy may be omitted (5).

(c) Regional nodal irradiation

No clinical indications.

References

1. Solin et al. Fifteen-year results of breast-conserving surgery and definitive breast irradiation for the treatment of ductal carcinoma in situ of the breast. J Clin Oncol 1996;14:754-63.

2. Sloane et al. Consistency achieved by 23 European pathologists in categorizing ductal carcinoma in situ of the breast using five classifications. European Commission Working Group on Breast Screening Pathology. Hum Pathol 1998;29:1056-62.

3. Winchester et al. Treatment trends for ductal carcinoma in situ of the breast. Ann Surg Oncol 1995;2:207-13.

4. Holland et al. Extent, distribution, and mammographic/histological correlations of breast ductal carcinoma in situ. Lancet 1990;335:519-22.

5. Klein J et al. Close or positive resection margins are not associated with an increased risk of chest wall recurrence in women with DCIS treated by mastectomy: a population-based analysis. Springerplus. 2015 Jul 10;4:335.

6. Fisher et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. Journal of Clinical Oncology 1998;16:441-52.

7. Julien et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet. 2000;355:528-33.

8. Lalani N et al. Long-term outcomes of hypofractionation versus conventional radiation therapy after breast-conserving surgery for ductal carcinoma in situ of the breast. Int J Radiat Oncol Biol Phys. 2014 Dec 1;90(5):1017-24.

9. Williamson D et al. Local control with conventional and hypofractionated adjuvant radiotherapy after breast-conserving surgery for ductal carcinoma in-situ. Radiother Oncol. 2010 Jun;95(3):317-20.

10. Kong I et al. Age at diagnosis predicts local recurrence in women treated with breast-conserving surgery and postoperative radiation therapy for ductal carcinoma in situ: a population-based outcomes analysis. Curr Oncol. 2014 Feb;21(1):e96-e104.

11. https://clinicaltrials.gov/ct2/show/NCT00470236

12. Julien JP et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet. 2000 Feb 12;355(9203):528-33.

13. Houghton J et al. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. Lancet. 2003 Jul 12;362(9378):95-102.

14. Emdin SO et al. SweDCIS: Radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. Acta Oncol. 2006;45(5):536-43.

15. Wong JS et al. Prospective study of wide excision alone for ductal carcinoma in situ of the breast. J Clin Oncol. 2006 Mar 1;24(7):1031-6.

16. Rakovitch E, et al. A population-based validation study of the DCIS Score predicting recurrence risk in individuals treated by breast-conserving surgery alone. Breast Cancer Res Treat. 2015 Jul;152(2):389-98.

17. McCormick B et al. RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. J Clin Oncol. 2015 Mar 1;33(7):709-15.

18. Fisher et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial [see comments]. Lancet 1999;353:1993-2000.

19. W. Shelley et al. Management of ductal carcinoma in situ of the breast: A clinical practice guideline. Evidence-based series #1-10 (Version 2.2006) http://www.cancercare.on.ca/pdf/pebc1-10s.pdf

LOBULAR CARCINOMA IN SITU

Management of this lesion has varied from bilateral mastectomy to increased surveillance. LCIS has a propensity to be multifocal, multicentric and bilateral with a 9-fold relative risk of subsequent invasive breast carcinoma in either breast. Following a biopsy diagnosis, the absolute risk of developing invasive breast cancer is 17% at 15 years.

A conservative approach with routine clinical examination and screening mammography is appropriate. The role of breast irradiation is not clear.

T1 T2 or T3 N0 M0 Axillary Node Negative

Following Breast Conserving Surgery (BCS) and an axillary node dissection, the likelihood of loco-regional recurrence (LRR) at 10 years is in the range of 25-30%. Factors such as young age, margin status, tumor size, lymphovascular infiltration (LVI) and Extensive In Situ Carcinoma (EIC, defined as more than 25% DCIS) may affect the probability of a recurrence further. A 66% relative risk reduction in local recurrence is achieved with the use of adjuvant radiotherapy and may even confer a small survival benefit.

(a) Breast irradiation

All node negative patients undergoing lumpectomy should receive whole breast irradiation to reduce the incidence of local recurrence. Evidence from several large RCTs with long-term follow-up supports the therapeutic equivalency of BCS and adjuvant whole breast radiotherapy to mastectomy with regards to survival (1-6). The radiotherapy regimens in common use consist of 50 Gy in 25 fractions over 5 weeks or 42.5 Gy in 16 fractions over 3.5 weeks.

Boost

Certain patients should be considered for a boost to the tumour bed:

- patients < 50-60 years (definitely if < 40)
- close margins
- patients with positive margins who decline further surgery and/or multiple LRR risk factors

(b) Chest wall irradiation

This is indicated for patients who have tumours greater than 5 cm in diameter, multifocal disease, node positive, extension to the chest wall or positive/close (less than 2 mm) margins of resection following mastectomy. A combination of features such as: young age, margins close grade III and/or LVI warrants consideration of chest wall irradiation.

(c) Regional node irradiation

There is no indication for routine regional nodal radiation in this group.

(d) Partial breast radiation (including Brachytherapy)

This may be considered in the setting of a clinical trial.

T1 T2 N1 M0 Axillary Node Positive but Not Locally Advanced

(a) Breast irradiation

Following lumpectomy, all patients should be considered for whole breast irradiation. In patients with tumors less than 5 cm and 1-3 axillary nodes positive, radiotherapy to the breast with or without regional nodal irradiation may be considered(see Regional nodal irradiation). The role of a boost is similar to node negative patients.

(b) Chest wall irradiation

Patients with 1-3 nodes positive with clear resection margins, no evidence of chest wall invasion and primary tumors less than 5 cm do not routinely receive radiation. Chest wall radiation is indicated for patients who have extension to the chest wall, or less than 2 mm of positive resection margins after mastectomy. Regional nodal radiotherapy may be considered with the presence of adverse features, such as premenopausal status, presence of extranodal extension, lymphovascular space invasion, and inadequate axillary dissection (<10 lymph nodes). The radiotherapy regimen in common use consists of 50 Gy in 25 fractions over5 wks.

(c) Regional nodal irradiation

In the clinical setting of four or more positive axillary nodes, there is evidence to support the utility of regional nodal radiotherapy (RNI). In patients with 1-3 nodes positive, RNI may also be consideredafter breast conserving therapy or mastectomy. (7-11).

The recently reported MA-20 trial investigated the role of RNI (including IMNs) in patients with high-risk node-negative or node positive (although the majority had 1-3 positive nodes) breast cancer following breast-conserving therapy (12). The 10 year results were recently published and demonstrated a reduction in locoregional recurrence, systemic recurrence and improved disease-free survival with the inclusion of RNI. There was no significant difference in the primary endpoint of overall survival. Patients in the RNI group had higher rates of grade ≥2 acute pneumonitis (1.2% vs. 0.2%, p=0.01) and lymphedema (8.4% vs. 4.5%, p=0.001). EORTC 22922 investigated elective IMN and medial supraclavicular lymph node irradiation on overall survival for women with centrally or medially located tumors, irrespective of axillary involvement, or externally located tumors with axillary involvement. At 10-year follow up, irradiation of the IMNs provided no significant improvement on overall survival. Disease-free survival and

distant disease-free survival were improved, and breast-cancer mortality was reduced. The rate of death from causes other than breast cancer was not increased with regional node irradiation (13). The only trial that has specifically addressed the value of IMN RT was designed to detect a very large survival difference (10%) with IMN treatment in post-mastectomy patients with node positive disease, or node negative disease but with central or medial primary tumors (14). A statistically significant benefit for IMN RT was not found, but subgroup analyses suggested that node-positive patients may derive a benefit from IMN treatment.

The recently published AMAROS trial evaluated whether axillary radiotherapy provided comparable regional control with fewer side-effects compared to completion axillary dissection in patients with a positive sentinel lymph node (15). Axillary radiotherapy included the contents of all three levels of the axilla and the medial aspect of the supraclavicular fossa. After a median follow-up of over 6 years there was no significant difference in the rates of 5-year axillary recurrence. Ipsilateral arm lymphedema was noted significantly more often after axillary lymph node dissection than after axillary radiotherapy.

References:

1. Fisher B et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002 Oct 17;347(16):1233-41.

2. Veronesi U et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002 Oct 17;347(16):1227-32.

3. Blichert-Toft M, Rose C, Andersen JA, et al. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of lifetable analysis. In: Consensus development conference on the treatment of early-stage breast cancer. Journal of the National Cancer Institute monographs. No. 11. Bethesda, Md.: National Cancer Institute, 1992:19-25.

4. van Dongen JA et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. J Natl Cancer Inst. 2000 Jul 19;92(14):1143-50.

5. Jacobson JA et al. Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. N Engl J Med. 1995 Apr 6;332(14):907-11.

6. Arriagada R et al. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. J Clin Oncol. 1996 May;14(5):1558-64.

7. Overgaard M et al. Postoperative radiotherapy in highrisk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial . Lancet 1999 ; 353 : 1641 – 8.

8. Overgaard M et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial . N Engl J Med 1997 ; 337 : 949 – 55.

9. Ragaz J et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med. 1997 Oct 2;337(14):956-62.

10. EBCTCG (Early Breast Cancer Trialists' Collaborative Group) et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.

11. Whelan TJ et al. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. J Clin Oncol. 2000 Mar;18(6):1220-9.

12. Whelan TJ et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):307-16.

13. Poortmans PM et al. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):317-27

14. Hennequin C et al. Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. Int J Radiat Oncol Biol Phys. 2013 Aug 1;86(5):860-6.

15. Donker M et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol. 2014 Nov;15(12):1303-10.

5.2 Locally Advanced and Inflammatory Breast Cancer

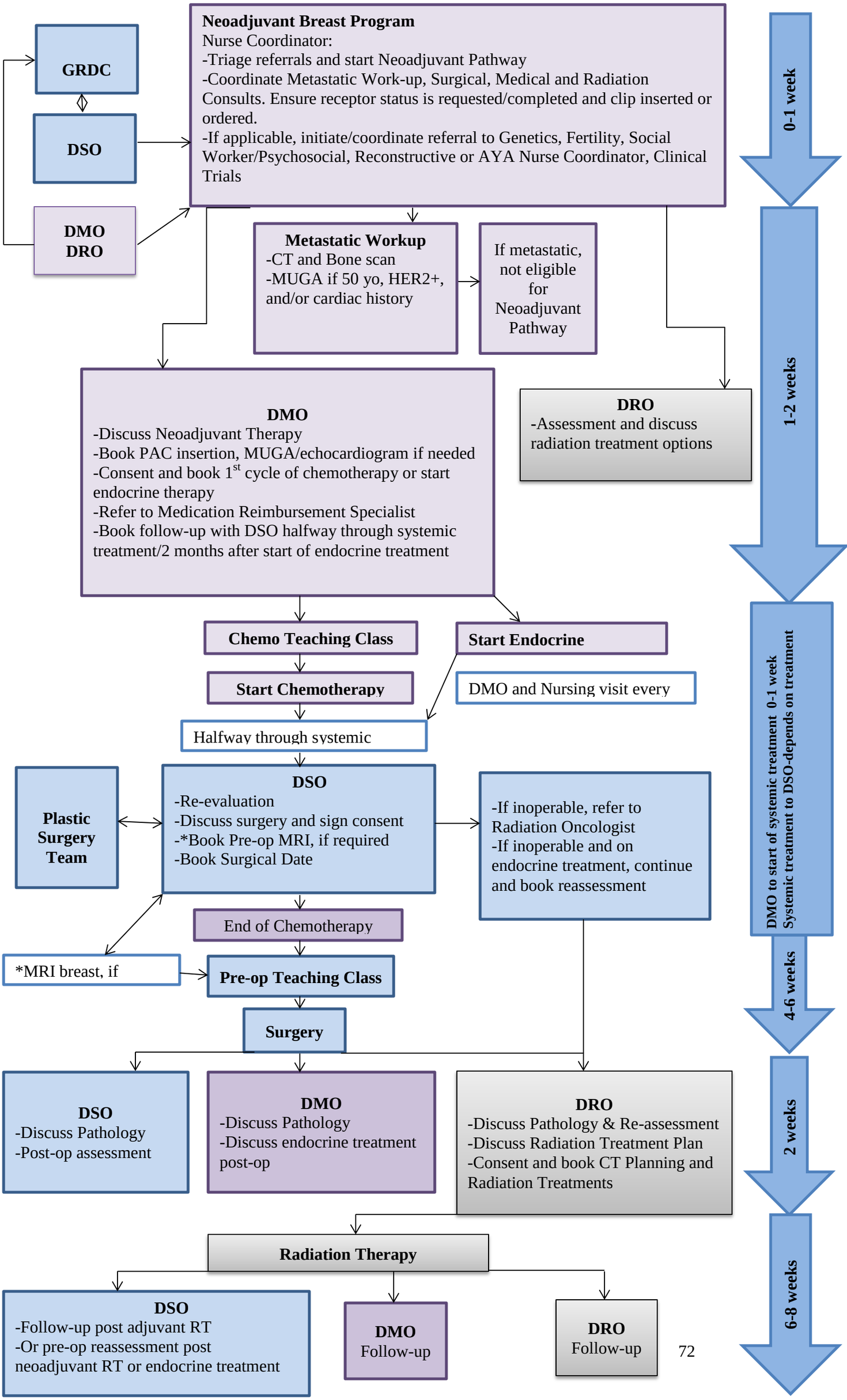
(This section was last updated December 2015)

Introduction

Locally advanced breast cancer (LABC) and inflammatory breast cancer (IBC) were both initially commonly defined as breast cancers that were inoperable at presentation and/or as having extremely poor survival with locoregional treatments alone (Chia et al., 2008).

Locally advanced breast cancer is a clinically heterogeneous disease that includes a wide variety of clinical scenarios. These include tumours greater than 5 cm or that involves the skin or chest wall. It also includes patients with fixed axillary lymph nodes or ipsilateral supraclavicular, infraclavicular, or internal mammary nodal involvement (Giordano, 2003)

IBC is the most aggressive manifestation of breast cancer. Patients usually present with rapid onset of swelling of the involved breast, diffuse erythema, peau d'orange, tenderness, induration and warmth (Cristofanilli et al 2003). Pathologically there is extensive lymphovascular invasion by tumor emboli that involves the superficial dermal plexus of vessels in the papillary and high reticular dermis. IBC has a greater association with younger age at diagnosis, higher tumor grade, negative estrogen receptor status and HER2/neu amplification (Panades et al., 2005).


GRDC
DSO
DMO
DRO
Neoadjuvant Breast Program
Nurse Coordinator:
-Triage referrals and start Neoadjuvant Pathway
-Coordinate Metastatic Work-up, Surgical, Medical and Radiation Consults. Ensure receptor status is requested/completed and clip inserted or ordered.
-If applicable, initiate/coordinate referral to Genetics, Fertility, Social Worker/Psychosocial, Reconstructive or AYA Nurse Coordinator, Clinical Trials
0-1 week
Metastatic Workup
-CT and Bone scan
-MUGA if 50 yo, HER2+, and/or cardiac history
If metastatic, not eligible for Neoadjuvant Pathway
1-2 weeks
DMO
-Discuss Neoadjuvant Therapy
-Book PAC insertion, MUGA/echocardiogram if needed
-Consent and book 1st cycle of chemotherapy or start endocrine therapy
-Refer to Medication Reimbursement Specialist
-Book follow-up with DSO halfway through systemic treatment/2 months after start of endocrine treatment
DRO
-Assessment and discuss radiation treatment options
Chemo Teaching Class
Start Chemotherapy
Start Endocrine
DMO and Nursing visit every
Halfway through systemic
DMO to start of systemic treatment 0-1 week
Systemic treatment to DSO-depends on treatment
Plastic Surgery Team
DSO
-Re-evaluation
-Discuss surgery and sign consent
-*Book Pre-op MRI, if required
-Book Surgical Date
-If inoperable, refer to Radiation Oncologist
-If inoperable and on endocrine treatment, continue and book reassessment
End of Chemotherapy
*MRI breast, if
Pre-op Teaching Class
4-6 weeks
Surgery
DSO
-Discuss Pathology
-Post-op assessment
DMO
-Discuss Pathology
-Discuss endocrine treatment post-op
DRO
-Discuss Pathology & Re-assessment
-Discuss Radiation Treatment Plan
-Consent and book CT Planning and Radiation Treatments
2 weeks
Radiation Therapy
6-8 weeks
DSO
-Follow-up post adjuvant RT
-Or pre-op reassessment post neoadjuvant RT or endocrine treatment
DMO
Follow-up
DRO
Follow-up

Definition

Inoperable LABC and IBC at presentation:

- Stage IIIB: T4a-c and T4d inflammatory carcinoma, N0-2
- Stage IIIC: Any T, N3a to c.

Although often grouped together, locally advanced and inflammatory breast cancer have different biological features. The common thread regarding LABC/IBC is the consideration of neoadjuvant systemic therapy (NST) as the initial management of choice. The intent of NST is to improve surgical options and to improve breast cancer survival (Kaufman et al., 2006). The advantages of NST specifically in the LABC and IBC cohorts include earlier treatment of subclinical distant micrometastases, down staging of the primary tumour, and the ability for an in vivo assessment of response to specific systemic agents (Chia et al., 2008). Systemic therapy is also administered with the clear goal of improving disease-free and overall survival.

Optimal management of LABC/IBC encompasses combined-modality therapy with NST followed by locoregional therapy (surgery and radiation). Involvement of the multidisciplinary team from the onset and throughout the course NST is crucial (Gralow et al., 2008)

Prognosis depends on tumour size, extent of lymph node involvement and presence of IBC. Some of the best results are from MD Anderson, where the median overall survival for IBC is 40 months and 30% of patients reach 10 year survival (Buzdar 1995).

Workup

Chance of distant metastases is considerably higher, and systemic staging is indicated to rule out stage IV disease, which would change treatment goals considerably.

It is critical that all patients be carefully staged to accurately quantify the original disease extent.

Physical examination with measurement of the primary tumour size and a clinical assessment of regional lymph node status.

Pretreatment photographs of T4 tumours can be helpful to document the extent of skin involvement.

Breast imaging

- evaluate lymph nodes spread, extension of breast disease, chest wall invasion or skin/ nipple involvement,
- evaluate for multifocal or multicentric disease, screen for the presence of synchronous contralateral breast cancer,

- provide an initial assessment of whether a patient may be a candidate for breast conserving surgery.

Includes bilateral diagnostic mammography, breast MRI, targeted axillary ultrasound and diagnostic breast ultrasound.

Reports should provide location and size measurements in three dimensions (superior-inferior, anterior-posterior and transverse) of the known tumour with volume.

MRI – routine use is indicated before and after the neo-adjuvant chemotherapy in cases where breast conservative surgery may be performed. The use of MRI during the treatment remains controversial. It may play a role in evaluating size, location, extension of the known tumour, describing chest wall integrity and lymph nodes appearance as well detecting occult contralateral cancers .

Pathology

Core biopsy on all suspicious abnormalities found within the ipsilateral or contralateral breast before treatment starts. Fine needle aspirate of palpable lymph nodes to confirm disease (Buchholz et al. 2008). Receptor status (ER, PgR, Her2) is required prior to neoadjuvant systemic therapy.

Neoadjuvant Systemic Therapy

Chemotherapy

Evidence supports the use of combination of anthracycline/taxane based preoperative regimens (Smith et al., 2002; Heys et al., 2002; G von Minckwitz et al., 2005).

Treatment recommendation:

- Fluoruracil + Epirubicin + Cyclophosphomide x 3 cycles followed by Docetaxel x 3 cycles +/- Trastuzumab.
- Adriamycin + Cyclophosphomide x 4 cycles (given every 2 weeks) followed by Paclitaxel x 4 cycles (not for HER2-positive).

(***For regimen details see Chapter 5.1.2***

Appendix 1: Revised Referral to Cancer Rehabilitation and Survivorship Program

Toronto General
Toronto Western
Princess Margaret
Toronto Rehab

Cancer Rehabilitation & Survivorship
Fax: 416 946-4549
Phone: 416 946-4501 ext. 2363

MRN_____

Name_____

DOB _____

Tel: (home) _____ (cell) _____

Referral to Cancer Rehabilitation and Survivorship

Eligibility Requirements:

- Patient must be on active follow-up for cancer at Princess Margaret Cancer Centre
- Reason for referral ***must*** be cancer related

Cancer Diagnosis: _____ Date: _____

Form Completed by: _____ Other Information: _____

Staff Physician Name: _____ Requires Interpreter: Language: _____

Staff Physician Signature:_____

Reason for Referral

Physical

☐ Musculoskeletal (ROM, strength)
_____

☐ Neurological
_____

☐ Balance
☐ Deconditioning
☐ Exercise Contraindications/Precautions
_____

_____

_____

☐ Lymphedema:
Location: _____
Active Cellulitis: Y N
Ruled out DVT: Y N

Functional

☐ Fatigue
☐ Difficulty with ADLs
☐ Return to Work/School
☐ Sexuality

Cognitive

☐ Brain Fog (memory, attention, concentration)

Other

_____

_____

This referral includes a consultation from Dr. Eugene Chang (Physiatry) as needed. Patients will also be screened for nutrition and psychosocial issues as part of our comprehensive assessment. All services are provided by a transdisciplinary team (occupational therapy, physiotherapy, social work, massage therapy, kinesiologist, dietitian, psychology, neuropsychology and nursing).

Revision date May 2017

Appendix 1: Revised Referral to Cancer Rehabilitation and Survivorship Program

Toronto General
Toronto Western
Princess Margaret
Toronto Rehab

Cancer Rehabilitation & Survivorship
Fax: 416 946-4549
Phone: 416 946-4501 ext. 2363

MRN_____

Name_____

DOB _____

Tel: (home) _____ (cell) _____

Referral to Cancer Rehabilitation and Survivorship

Eligibility Requirements:

- Patient must be on active follow-up for cancer at Princess Margaret Cancer Centre
- Reason for referral ***must*** be cancer related

Cancer Diagnosis: _____ Date: _____

Form Completed by: _____ Other Information: _____

Staff Physician Name: _____ Requires Interpreter: Language: _____

Staff Physician Signature:_____

Reason for Referral

Physical

☐ Musculoskeletal (ROM, strength)
_____

☐ Neurological
_____

☐ Balance
☐ Deconditioning
☐ Exercise Contraindications/Precautions
_____
_____
_____

☐ Lymphedema:
Location: _____
Active Cellulitis: Y N
Ruled out DVT: Y N

Functional

☐ Fatigue
☐ Difficulty with ADLs
☐ Return to Work/School
☐ Sexuality

Cognitive

☐ Brain Fog (memory, attention, concentration)

Other

_____
_____

This referral includes a consultation from Dr. Eugene Chang (Physiatry) as needed. Patients will also be screened for nutrition and psychosocial issues as part of our comprehensive assessment. All services are provided by a transdisciplinary team (occupational therapy, physiotherapy, social work, massage therapy, kinesiologist, dietitian, psychology, neuropsychology and nursing).

Revision date May 2017

Appendix 1: Revised Referral to Cancer Rehabilitation and Survivorship Program

Toronto General
Toronto Western
Princess Margaret
Toronto Rehab

Cancer Rehabilitation & Survivorship
Fax: 416 946-4549
Phone: 416 946-4501 ext. 2363

MRN_____

Name_____

DOB _____

Tel: (home) _____ (cell) _____

Referral to Cancer Rehabilitation and Survivorship

Eligibility Requirements:

- Patient must be on active follow-up for cancer at Princess Margaret Cancer Centre
- Reason for referral ***must*** be cancer related

Cancer Diagnosis: _____ Date: _____

Form Completed by: _____ Other Information: _____

Staff Physician Name: _____ Requires Interpreter: Language: _____

Staff Physician Signature:_____

Reason for Referral

Physical

☐ Musculoskeletal (ROM, strength)
_____

☐ Neurological
_____

☐ Balance
☐ Deconditioning
☐ Exercise Contraindications/Precautions
_____

_____

_____

☐ Lymphedema:
Location: _____
Active Cellulitis: Y N
Ruled out DVT: Y N

Functional

☐ Fatigue
☐ Difficulty with ADLs
☐ Return to Work/School
☐ Sexuality

Cognitive

☐ Brain Fog (memory, attention, concentration)

Other

_____

_____

This referral includes a consultation from Dr. Eugene Chang (Physiatry) as needed. Patients will also be screened for nutrition and psychosocial issues as part of our comprehensive assessment. All services are provided by a transdisciplinary team (occupational therapy, physiotherapy, social work, massage therapy, kinesiologist, dietitian, psychology, neuropsychology and nursing).

Revision date May 2017

Adjuvant Chemotherapy Regime ***Page 57***)

Preoperative chemotherapy response rates:
Initial disease in the lymph nodes can be eradicated in 20-40% of patients receiving preoperative chemotherapy (Rastogi et al., 2008). Dose intensification of an anthracycline regimen was not superior to a standard anthracycline regimens. (Therasse et al., 2003; Ellis et al., 2006)

Targeted Therapy

The main pathway for therapeutic targeting at present is the HER-2 pathway. In HER2 positive operable disease, Buzdar et al (2005) showed significantly higher pCR rates in the trastuzumab plus chemotherapy arm of his study.

Up until now, a part from trastuzumab, none of the targeted therapies can be considered a standard therapeutic option.

Parameters associated with a higher likelihood of pCR include smaller tumor size, histology (ductal > lobular), tumor intrinsic subtype (basaloid or HER2 > luminal), hormone receptor status (ER negative > positive) and grade (high > low) (Garlow et al., 2008).

Patients with disease progression during the initial course of treatment should be switched to an alternate regimen, offered local therapy or considered candidates for investigational approaches particularly if their disease is unresectable. Crossing over to alternative chemotherapy in nonresponders seems to offer minimal benefit in terms of pCR

In addition, to date no trial has shown that additional chemotherapy after a modern preoperative chemotherapy (generally antracycline and taxane based therapy) has shown improvement in outcomes.

Endocrine Therapy

A little more than 20% of all breast cancers occur in women younger than age 50 years and 60% are estrogen receptor (ER) positive compared to 80% being positive in women older than the age of 50 years (Parton & Smith, 2008).

Neoadjuvant hormonal therapy, in particular with aromatase inhibitors, can be considered a safe option for patients with endocrine sensitive tumours not suitable for chemotherapy and a reasonable alternative to chemotherapy for aged or unfit patients (Smith et al., 2005; Semiglazov et al., 2004).

Neoadjuvant hormone therapy versus chemotherapy: one concern with hormone therapy is that it yields a low pathological complete response, however neoadjuvant chemotherapy induces similar low rate of pCR in ER+ population (Ring et al., 2004).

The only randomized trial comparing neoadjuvant chemotherapy and endocrine therapy has been published only in abstract form and therefore should be interpreted with caution (Semiglazov et al., 2004). Before conducting such a study, questions remain; they include choice of the aromatase inhibitor and the identification of the patient population that derives the most benefit from neoadjuvant endocrine therapy.

From a premenopausal perspective, there is a trend that ovarian suppression may be of benefit in younger women not achieving this with chemotherapy (Walshe et al., 2007). Patients with positive estrogen and/or progesterone receptors should be placed on Tamoxifen 20mg po daily for five years.

Note:
pCR – short-term end point is not sufficiently robust to change clinical practice or lead to drug approval, however, studies incorporating this can generate important preliminary data that can inform the design of larger, definitive trials and hopefully will lead to greater individualization of breast cancer treatment.

Using other biologic measures as study end points in addition to pCR, new drugs and regimens can be tested in rapid sequence, providing an early indication of drug activity and the ability to identify novel prognostic and predictive factors (Gralow et al., 2008; Guarneri et al., 2006).

Locoregional Therapy

Surgery

LABC - Patients whose disease has been rendered resectable should undergo either breast conserving surgery (BCS) and axillary lymph node dissection (ALND) if clinically positive or FNA positive lymph nodes, if not Sentinel Node Biopsy can be considered with possible frozen section, it is to be noted that in this scenario at least 3 sentinel nodes should be retrieved or modified radical mastectomy. When considering surgical approach, must note that four factors were independently associated with LRR: clinical N2 orN3 disease, lymphovascular space invasion noted at the time of biopsy or in the surgical specimen, multifocal or break-up pattern of residual disease, and residual disease larger than 2 cm (Buchholz et al., 2008). If the patient is a potential candidate for BCS, the primary tumour location should be marked early in the course of preoperative chemotherapy, radiographic evaluation and biopsy of suspicious areas before chemotherapy initiation are required, and restaging of the disease should be done before surgical procedure.

Inflammatory – patients should have modified radical mastectomy.
In appropriately selected patients with LABC, selection criteria for breast conserving surgery:

Role of sentinel lymph node dissection in patients receiving NST is evolving. Long term regional control rate and overall survival is unknown for this patient population. Not

recommended in both the inoperable LABC and IBC population (Mamounas et al., 2005).

Recurrence rates: The Ipsilateral breast recurrence rate in patients who were converted from a proposed mastectomy to a lumpectomy after neo-adjuvant chemotherapy was statistically significantly increased (15.9% vs 9.9%) compared to patients in whom it was proposed they had a lumpectomy prior to neo-adjuvant therapy and did have a lumpectomy after neo-adjuvant treatment (NSABP 18).

Reconstructive Surgery

Postsurgical radiation can have significant adverse effects on the aesthetic outcome. Implants tend to develop significant capsular fibrosis after radiation therapy. Autologous tissue reconstruction seems to tolerate radiation better than implants, but some report there can be some degree of skin contraction, volume loss, or other adverse effects (Tran et al., 2000). Reconstruction is not recommended until 1-2 years following the completion of treatment.

Radiation

Plays a critical role for all patients treated with preoperative chemotherapy and breast conservation. Locoregional RT should be recommended postmastectomy to reduce rates of LRR. Initial clinical stage and the final pathologic extent of disease independently predicted the risk of a LRR (Buchholz et al., 2002; McGuire et al., 2005; Bristol et al., 2001); Mamounas EP, et al. J Clin Oncol. 2012 Nov 10;30(32):3960-6.). After mastectomy XRT to the chest wall and regional nodes to a dose of 5000 cGy in 25 fractions.

Patients whose disease cannot be resected should undergo irradiation of the involved breast, chest wall and regional nodes to a dose of 5000 cGy in 25 fractions. The patient should be reconsidered for surgery four weeks thereafter. Those with resectable disease should undergo a mastectomy and axillary lymph node dissection. Those with unresectable disease should continue with radiotherapy. Sites of gross disease should be boosted with no less than 1000 cGy in 5 fractions and no more than 1600 cGy in 8 fractions, depending on the target volume.

Clinical And Radiographic Evaluation Of The Disease

Mid-treatment Response

In patients undergoing neoadjuvant therapy for locally advanced breast cancer, repeat imaging after 2-3 cycles of treatment may be considered to determine response, especially in cases where clinical response is questionable and an early change in therapy is being considered.(von Minckwitz et al., 2006). Imaging studies employed to determine the extent of response in the literature include ultrasound and MRI (Myers et al.,

2006). There is evidence supporting that MRI alone is the best modality (ACRIN study) to evaluate response.

Recommendations: MRI (or ultrasound when MRI is not possible) is indicated especially for patients with locally advanced breast cancer. Mammography with tomosynthesis may be of benefit for assessment if cancer is identified on this modality.

Post-treatment Response

At completion of neoadjuvant chemotherapy, patients undergo repeat breast imaging to determine the extent of disease left within the breast. The tri-modality approach of ultrasound, mammogram, and MRI allows for the most accurate prediction of disease extent and thus allows for appropriate surgical planning.

Recommendations: MRI is indicated especially for those patients with locally advanced breast cancer. Mammography with or without tomosynthesis remains the standard for assessment. Ultrasound as an adjunct to mammography, can aid in determining the nature of a residual mass, particular in cases where calcifications remain on mammography.

Follow-Up

Breast Imaging

Annual mammography is the standard for follow up of women who have had a previous diagnosis of breast cancer. Breast MRI may be considered for follow up in patients with dense breasts and are standard for certain high-risk populations (i.e. BRCA1/2 carriers) or at the recommendation of radiology. For those patients in whom annual screening MRI is recommended, there is currently no evidence as to the optimal interval of follow up for mammography and MRI if both exams done together or staged in six-months interval time.

Breast imaging at any higher frequency than yearly test is not recommended, but may be warranted for the follow up of abnormalities within the breast.

Recommendations: Annual mammogram and breast MRI in certain high-risk populations. Breast MRI may be considered in dense breasts, at the recommendation of radiology guidelines, or if clinically indicated.

Follow up imaging for metastases: Follow up imaging with the intention of early detection of metastases is not indicated in breast cancer survivors (Meyers et al., 2006). Patient symptoms should guide any further testing or investigations, and there is no role for routine testing in the absence of symptoms or signs of metastatic disease. Excessive testing leads to unwarranted investigations.

References:

1. Chia S, Sandra M, Swain DR et al. Locally advanced and inflammatory breast cancer, J Clin Oncol 26 (5): 786-790, 2008.

2. NCCN: Clinical Practice Guidelines in Oncology Breast Cancer, 2007.

3. 6th edition American Joint Commission on Cancer Criteria – Singletary SE, Allred C, Ashley P et al. Revision of the American joint committee on cancer staging system for breast cancer. J Clin Oncol 20: 3628-3636, 2002

4. Kaufman M, Hortobagyi GN, Goldhirsch A et al. Recommendations from an international expert panel on the use of neoadjuvant systemic treatment of operable breast cance.r An update. J Clin Oncol 24: 1940-1949, 2006.

5. Esserman L, Kaplan E, Patridge S et al. MRI phenotype is associated with response to doxorubicin and cyclophosphomide neoadjuvant chemotherapy in stage III breast cancer. Ann Surg Oncol 8: 549-559, 2001.

6. Gralow J, Zujewski J, Winer E. Preoperative therapy in invasive breast cancer: reviewing the state of the science and exploring new research directions, J of Clin Oncol 26: 696-697, 2008.

7. Giordano, SH. Update on locally advanced breast cancer. The oncologist 8: 521-530, 2003.

8. Cristofanilli M, Buzdar AU, Hortobagyi GN. Update on the management of inflammatory breast cancer. The oncologist 8: 141-148, 2003.

9. 9. Panades M, Olivotto IA, Speers CH et al. Evolving treatment strategies for inflammatory breast cancer: a population-based survival analysis. J Clin Oncol 23: 1941-1950, 2005.

10. Buzdar et al. Combined Modality Treatment of Stage III and Inflammatory Breast Cancer. Surgical Oncology Clinics of North America. 1995; 5(5): 715-734.

11. Rastogi P, Stewart J, Anderson HD et al. Preoperative chemotherapy: updates of NSABP Protocols B-18 and B-27. J Clin Oncol 26(5), 778-785, 2008.

12. Guarneri V, Broglio K, Kau SW et al. Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors. J Clin Oncol. 24: 1037-1044, 2006.

13. Smith IC, Heys SD, Hutcheon ID et al. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol. 20: 1456-1466, 2002.

14. Heys SD, Hutcheon ID, Sarkar TK et al., Neoadjvuant docetaxel in breast cancer: 3 year survival results from the Aberdeen trial, Clin Breast Cancer 3: S69-S74,

2002.

15. G von Minckwitz, Blohmer JU, Raab G et al., In vivo chemosensitivity-adapted preoperative chemotherapy in patients with early stage breast cancer: the GEPARTRIO pilot study. Ann Oncol. 16: 56-63, 2005.

16. Parton & Smith, Controversies in the Management of Patients with Breast Cancer: Adjuvant Endocrine Therapy in Premenopausal Women, J of Clin Oncol 26: 745-752, 2008.

17. Smith IE, Dowsett M, Ebbs SR et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen or both in combination: the immediate preoperative anastrozole, tamoxifen, or combined with tamoxifen (IMPACT) multicenter double-blind randomized trial. J of Clin Oncol. 23: 5108-5116, 2005.

18. Semiglazov VF, Ivanov VG, Semiglazov VV et al. Neoadjuvant endocrine therapy vs chemotherapy for postmenopausal ER- positive breast cancer patients. Breast Cancer Res Treat. 88: (abs 2090), 2004.

19. Ring AE, Smith IE, Ashley S et al.: Oestrogen receptor status, pathological complete response and prognosis in patients receiving neoadjuvant chemotherapy for early breast cancer. Br J Cancer 91: 2012-2017, 2004.

20. Semiglazov VF, Semiglzov VV, Ivanov V et al. The relative efficacy of neoadjuvant endocrine therapy versus chemotherapy in postmenopausal women with ER positive breast cancer. J Clin Oncol ASCO Proceedings (post meeting edition) 22: 519, 2004 (abstr).

21. Walshe JM, Denduluri N, Swain SM: Amernorrhea in premenopausal women after adjuvant chemotherapy for breast cancer. J Clin Oncol 24: 5769- 5779, 1996.

22. Adjuvant Breast Cancer Trials Collaborative Group: Ovarian ablation or suppression in premenopausal early breast cancer ovarian ablation or suppression randomized trial. J Natl Cancer Inst 99: 516-525, 2007.

23. Therasse P, Mauriac L, Welnicka-Jaskiewica M et al. Final results of a randomized phase III trial comparing cyclophophamide, epirubicin and fluorouracil with a dose intensified epirubicin and cyclo plus filgrastim as neoadjuvant treamtn in labc: An EORTCNCIC-SAKK Multicenter study. J Clin Oncol 21: 843-850, 2003.

24. Ellis GK, Green SJ, Russell CA et al. SWOG 0012, a randomized phase III comparison of standard doxorubicin and cyclo followed by weekly paclitaxel versus weekly doxorubicin and daily oral cyclo plus G-CSF followed by weekly paclitaxel as neoadjuvant therapy for inflammatory and labc. J Clin Oncol 24:

12s, 2006(abstr 5375779, 1996.

25. Garlow JR, Burstein HJ, Wood W et al. Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease, J of Clin Oncol 26: 814-819, 2008.

26. Gralow JR, Zujewski J, Winer E, Preoperative therapy in invasive breast cancer: reviewing the state of the science and exploring new research directions, J of Clin Oncol. 26(5). 696-697, 2008.

27. Guarneri V, Frassoldati A, Giovannelli S. et al. Primary systemic therapy for operable breast cancer: A review of clinical trials and perspective. Cancer Letters, 2006, doi:10.1016/j.canlet.2006.07.001.

28. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission reate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 23: 3676-3685, 2005.

29. Mamounas EP, Brown A, Anderson S et al. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: Results form national surgical adjuvant breast and bowel project protocol B-27. J Clin Oncol 23: 2694-2702, 2005.

30. Buchholz TA, Lehman CD, Harris JR, et al. Statement of the science concerning locoregional treatments after preoperative chemotherapy for breast cancer: A national cancer institute conference. J Clin Oncol, 26(5), 791-797, 2008.

31. Tran NV, Evans GR, Kroll SS: Postoperative adjuvant irradiation: Effects on transverse rectus abdominis muscle flap breast reconstruction. Plast Reconstr Surg 106: 313-317, 2000.

32. Buchholz TA, Tucker SL, Masullo L, et al. Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. J Clin Oncol. 20: 17-23, 2002)

33. McGuire SE, Gonzalez-Angulo AM, Tucker SL et al. Radiation is an important component of therapy for patients with stage III breast cancer who achieve a pathological complete response after neoadjuvant chemotherapy. Int J Radiat OncolBiol Phys 63: 85, 2005 (abstr, suppl 2.

34. Bristol IJ, Strom EA, Domain D et al. Long term locoregional treatment outcomes for patients with inflammatory breast cancer. Int J Radiat OncolBiol Phys 66: 2001., 2006 (abstr, suppl 3).

35. Meyers, R., Minuk, T., Johnston, M. and the Diagnostic Imaging Guidelines Panel. (2006). Diagnostic Imaging in Breast Cancer: Recommendations Report.

36. v Minckwitz G et al. Individualized treatment strategies according to in vivo-chemosensitivity assessed by response after 2 cycles of neoadjuvant chemotherapy. Final results of the Gepartrio study of German breast group. San Antonio Breast Cancer Symposium December 2006. Abstract 42.

Patridge AH, Wang PS, Winer EP et al: Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. J Clin ONcol 21: 602-606, 2003

5.3 METASTATIC DISEASE

5.3.1 Systemic Therapy for Metastatic Disease

(This sections was updated February 2017)

Introduction

Advanced breast or Stage IV disease is unfortunately incurable, therefore the goal of therapy is to optimize quality of life and, if possible, prolong time to progression of disease and death. Management of these patients is best conducted within a multidisciplinary team, including medical, radiation and surgical oncologists, and a palliative care team.

Systemic treatment of advanced breast cancer includes:

- endocrine therapy
- chemotherapy ± novel targeted therapies, including monoclonal antibodies and small molecules
- supportive measures

Endocrine Therapy

In view of its preferable toxicity profile, initial palliation with endocrine therapy should be the primary consideration for patients with:

- Endocrine sensitive disease: hormone receptor-positive disease (ER and/or PgR positive),
- Absence of rapidly progressing visceral disease.

Commonly used endocrine agents:

- Selective Estrogen-Receptor Modulator (SERM): tamoxifen
- Third generation aromatase inhibitors (AIs):
    - Non-steroid AIs: anastrazole, letrozole
    - Steroid AI: exemestane
- LHRH agonist: goserelin
- Selective Estrogen-Receptor Downregulator (SERD): fulvestrant
- Progestational agent: megestrol acetate

Due to data in the adjuvant setting suggesting that concurrent chemotherapy and tamoxifen may be inferior to sequential use of these modalities, it is recommended that endocrine treatment not be given concurrent with chemotherapy.

There is little evidence regarding the optimal sequence of endocrine therapy; the choice should be based on the previous use of endocrine agents in the adjuvant setting. Most patients will be treated sequentially with available endocrine agents, although the chance of response to a second or third agent is low if there has been no response to the prior endocrine treatment.

Premenopausal setting	Postmenopausal setting

• Tamoxifen +/- ovarian ablation • Ovarian ablation: LHRH agonist, oophorectomy, irradiation of ovaries • Anastrozole or Letrozole + Ovarian ablation • Exemestane + Ovarian ablation • Megestrol acetate • Fulvestrant + Ovarian ablation	• Anastrozole or Letrozole • Tamoxifen • Exemestane • Megestrol • Fulvestrant

Premenopausal patients

In premenopausal patients commonly used endocrine agents are tamoxifen and LHRH agonists.

- Tamoxifen remains the preferred treatment if not used previously as adjuvant therapy, or if relapse has occurred at least one year after stopping adjuvant tamoxifen.
- A combination of ovarian ablation (LHRH agonist) and tamoxifen is associated with improved outcome as compared to treatment of LHRH agonist alone.
- AIs as monotherapy are contraindicated in premenopausal patients.
- If women are rendered postmenopausal by ovarian ablation AIs may be used, but limited data are available regarding the effectiveness of an LHRH agonist in combination with an AI in premenopausal women.

Postmenopausal patients

In postmenopausal patients commonly used endocrine agents are: tamoxifen, AIs, fulvestrant and megestrol acetate.

- AIs are appropriate as first or second line treatment; they have shown superior outcome as compared to tamoxifen in first line therapy and to megestrol acetate in second line therapy.

- Tamoxifen remains an appropriate initial treatment in women who received no adjuvant therapy, AIs as adjuvant therapy, or if relapse has occurred at least one year after stopping adjuvant tamoxifen.

- Exemestane can be effective treatment if progression of disease on non-steroid AIs.

- Fulvestranthas historically been considered after sequential use of tamoxifen and an AI; it has comparable activity to tamoxifen as first line therapy and to AIs in the second line therapy. However, recent data suggest that it may be superior to an

AI in first line among patients who are endocrine therapy naïve (HR 0.80).

- Fulvestrant and the steroid AI exemestane are equally effective after progression on non-steroid AIs.

- Megestrol remains an appropriate option after progression of disease on tamoxifen and an AI.

- There is increasing interest in the addition of CDK4/6 inhibitors such as palbociclib to endocrine therapy. Data support their use in combination with letrozole in first line or with fulvestrant in subsequent lines of therapy. However, data are based on improvement in progression-free survival only. There is no evidence of improvement in overall survival. There is manageable toxicity, predominantly neutropenia, fatigue and GI disturbance. Additionally, these agents are not reimbursed by the Ontario Drug Benefits and initial assessment by the pan-Canadian Oncology Drug Review provided a negative recommendation for funding. The drug is accessible through selected private insurance plans and through a temporary compassionate program.

Evidence base:

- A recent meta-analysis of 4 randomized clinical trials (RCTs) showed improvement in overall survival (OS) (HR=0.78, p=0.02) and progression-free survival (PFS) (HR=0.7, p=0.003) with combined tamoxifen and LHRH agonist as compared to LHRH alone.
- The combination of anastrozole and LHRH goserelin in 35 premenopausal patients revealed a promising median time-to-progression (TTP) of 8 months, a median OS of 26 months and a clinical benefit of 72%
- For first line therapy:
    - RCTs comparing anastrozole, letrozole and exemestane to tamoxifen, respectively, showed higher objective response rates (RRs) and prolonged TTP for AIs as compared to tamoxifen.
    - A meta-analysis showed an OS benefit (HR=0.87, p<0.001) for third-generation AIs as compared to tamoxifen or progestational agents in the first or second line of therapy.
    - RCTs comparing fulvestrant to tamoxifen in the first-line hormone therapy did not show an advantage for fulvestrant in TTP and objective RR as compared to tamoxifen.
    - The PALOMA-2 trial showed an improvement in progression-free survival with the addition of palbociclib to letrozole (HR 0.58). Overall survival data are immature, however, no signal of survival benefit was observed in the preceding PALOMA-1 trial (HR 0.81).
- For second/third line therapy:
    - RCT's comparing letrozole, anastrozole and exemestane to megestrol, respetively,showed equivalent or better objective RRs and TTP; toxicity was less with AI's compared to megestrol.

- A RCT comparing letrozole to anastrozole showed increased RR for letrozole as second line treatment, but no difference in TTP.
- RCTs showed fulvestrant to be at least as effective as anastrozole in terms of RR, TTP and OS after progression on tamoxifen.
- A RCT comparing fulvestrant with exemestane after progression on non-steroid AIs showed no difference between the drugs in regard to objective RR, clinical benefit and TTP.

Cytotoxic Chemotherapy

Cytotoxic chemotherapy is appropriate for women with:

- Endocrine insensitive disease: ER and PgR negative or hormone receptor-positive disease, which is refractory to endocrine manipulations or
- Short disease-free interval (< 6 months) following adjuvant treatment or
- Rapidly progressive visceral disease regardless of endocrine sensitivity

Commonly used chemotherapy regimens

Single agents

- Anthracyclines (doxorubicin, epirubicin)
- Taxanes (paclitaxel, docetaxel, nab-paclitaxel)
- Vinorelbine
- Capecitabine
- Eribulin
- Platinum

Chemotherapy combinations:

- AC (doxorubicin, cyclophosphamide)
- CMF (cyclophosphamide, methotrexate, 5-FU)
- CM (metronomic cyclophosphamide/methotrexate)
- Gemcitabine and platinum (cisplatin or carboplatin)

Preferred agents with Trastuzumab:

- Paclitaxel
- Docetaxel
- Vinorelbine

For regimen details see – Metastatic Chemotherapy Regimens Page 94 .

Treatment

- Combination chemotherapy is best reserved for select, fit patients with rapidly progressing disease; administering agents sequentially has the advantage of giving each drug at its maximum tolerated dose without overlapping toxicities.

- Anthracyclines and taxanes are the most active chemotherapeutic agents in advanced breast cancer; many women with recurrent disease will already have received anthracyclines and/or taxanes in adjuvant setting and treatment of advanced disease should be tailored accordingly.

- Doxorubicin and epirubicin are comparable in efficacy; anthracyclines are used in multiple dosings and scheduling formats.
- The optimal schedules of taxanes are weekly paclitaxel and 3-weekly docetaxel.

- In tumours overexpressing HER-2/neu, trastuzumab should be used, preferably in combination with single-agent chemotherapy; excessive cardiac toxicity limits the ability to combine trastuzumab with regimens containing anthracyclines.
  - The preferred first line treatment is a taxane (paclitaxel weekly or docetaxel q3weekly) with trastuzumab and pertuzumab.
  - On progression option include trastuzumab emtansine or an alternate chemotherapy with trastuzumab (e.g. vinorelbine). Capecitabine and lapatinib are alternatives and may have differentially greater activity in patients with brain metastases.
  - Trastuzumab emtansine is available in 3rd or subsequent lines for patients who have not been previously treated with it.
  - Trastuzumab in combination with an aromatase inhibitor can be considered for carefully selected women with low- bulk endocrine sensitive tumours, which express HER-2/neu.

- Capecitabine has useful single-agent activity in pretreated advanced breast cancer; the combination of capecitabine and docetaxel may be an option in pretreated rapidly progressing, fit women with advanced breast cancer. Associated with dose related hand-foot syndrome. Vinorelbine monotherapy is active in newly diagnosed advanced breast cancer and effective as salvage therapy in pretreated advanced breast cancer.

Other Treatments

- Gemcitabine is a drug with modest activity in breast cancer and can be considered in women who have responded to multiple prior lines of chemotherapy.

- Nanoparticle albumin-bound (nab)-paclitaxel either in 3-weekly or weekly regimen has less toxicity as compared to conventional 3-weekly paclitaxel and docetaxel (avoidance of steroid premedication is a key feature). Albumin-bound paclitaxel (Abraxane) is appropriate for women who have a reaction to paclitaxel.

- Lapatinib, a tyrosine kinase inhibitor of HER-1 and HER-2, in combination with capecitabine may be treatment option in patients with HER-2 positive disease, which progressed after trastuzumab-based therapy. This unfunded drug is covered by most private plans.

- Bevacizumab, an anti-angiogenic humanized monoclonal antibody targeting VEGF, in combination with paclitaxel remains licensed, but not approved for use. It's inclusion with first line chemotherapy is currently not recommended due to unclear efficacy and increased toxicity.

Evidence base:

- A meta-analysis of 12 RCTs showed that taxanes do not improve survival when compared with anthracyclines, either as single agents (HR=1.01), or in anthracycline combinations (HR=0.95); taxanes in combination with anthracyclines modestly improve RRs and progression-free survival (PFS) (HR=0.92, p=0.031).

- According to a meta-analysis of 13 RCTs epirubicin and doxorubicin showed no difference in efficacy.

- A RCT comparing pegylated liposomal doxorubicin to conventional doxorubicin showed comparable efficacy but significantly less cardiotoxicity for pegylated-liposomal doxorubicin.

- In a RCT comparing weekly and 3-weekly paclitaxel, weekly paclitaxel was superior in RR (OR=1.75, p=0.0004), TTP (HR=1.43, p<0.0001) and OS (HR=1.28, p=0.0092) with neurotoxicity as dose-limiting toxicity.

- In a RCT comparing 3-weekly docetaxel (100 mg/m2) to 3-weekly paclitaxel (175 mg/m2) 3-weekly docetaxel was superior in regard to TTP (HR=1.64, p<0.0001) and OS (HR=1.41, p=0.03) but with more haematological and non-haematological toxicities.

- In a RCT nanoparticle 3-weekly albumin-bound (nab) paclitaxel demonstrated higher RR and longer TTP (HR=0.75, p=0.006) and improved OS (0.73, p=0.024) in second-line and higher therapy; in comparison to 3-weekly conventional paclitaxel; nab-paclitaxel showed favourable safety profile.

- In a randomized phase II trial all three nab-paclitaxel dosage levels (weekly and 3-weekly) were superior to 3-weekly docetaxel in regard to PFS when used as first line therapy.

- In a pivotal RCT, treatment with trastuzumab plus A (or E)/C in combination or given with 3-weekly paclitaxel was associated with superior RR, TTP and OS as compared to chemotherapy alone as first line therapy; a high proportion of cardiac events was observed in the women treated with anthracyclines.

- As second-line treatment for HER2 positive disease, trastuzumab as a single agent showed a RR of 12 to 15% in phase II trials; however, phase II trials of trastuzumab in combination with weekly paclitaxel, vinorelbine or docetaxel have shown response rates of 60 to 83%.

- In RCTs trastuzumab with paclitaxel and carboplatin was superior in regard to RR and PFS as compared to trastuzumab and paclitaxel alone; in a similar RCT trastuzumab with docetaxel and carboplatin was not more efficaous as compared

to trastuzumab and docetaxel alone.

- The combinations of trastuzumab, carboplatin, and docetaxel or paclitaxel were associated with a higher toxicity profile compared to trastuzumab and docetaxel or paclitaxel, respectively.

- In a RCT addition of trastuzumab to anastrozole was associated with superior RR and PFS as compared to anastrazole alone; however PFS in both arms was disappointingly low and there was no improvement in OS.

- A RCT showed superior efficacy of lapatinib in combination with capecitabine in regard to TTP (HR=0.49, p<0.001) but not for OS when compared to capecitabine alone in women previously treated with anthracyclines, taxanes and trastuzumab.

- A phase II study of capecitabine in taxane-pretreated patients showed a RR of 26%.

- In a RCT capecitabine combined with taxotere was superior to capecitabine alone in regard to RR, TTP (HR=0.65, p=0.001) and OS (HR=0.77, p=0.01) in anthracycline-pretreated women but more toxic.

- In a phase II study of non-pretreated advanced breast cancer vinorelbine mononotherapy showed RR of 35% and median OS of about 16 months; in a phase II study of anthracycline- and taxane-pretreated women vinorelbine monotherapy showed RR of 25% and median survival of 6 months.

- A RCT showed superior efficacy of bevacizumab in combination with paclitaxel in regard to TTP (HR=0.6, p<0.001) but not OS when compared to paclitaxel alone.

- Oral cyclophosphamide plus methotrexate produced 2 complete responses and 12 partial responses in 63 patients with metastatic breast cancer who progressed on first line therapy, with 26% of patients still responding after 12 months.

Supportive Care

*(See Symptom Management **Page 106**)*

References:

1. Klijn JG, Blamey RW, Boccardo F, et al: Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol 19:343-53, 2001

2. Carlson RW SC, Rivera E, et al. : Goserelin plus anastrazole in treatment of premenopausal hormone receptor positive, recurrent or metastatic breast cancer. J

Clin Oncol 25:18S, 2007 (suppl, abstr 1030).

3. Eisen A PK, Johnston M, et al. : The role of aromatase inhibitors in the treatment of postmenopausal women with metastatic breast cancer. Cancer Care Ontario Practice Guideline Initiative, September 2002.

4. Mauri D, Pavlidis N, Polyzos NP, et al: Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. J Natl Cancer Inst 98:1285-91, 2006

5. Howell A, Robertson JF, Abram P, et al: Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial. J Clin Oncol 22:1605-13, 2004

6. Osborne CK, Pippen J, Jones SE, et al: Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol 20:3386-95, 2002

7. Howell A, Robertson JF, Quaresma Albano J, et al: Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol 20:3396-403, 2002

8. Chia S, Gradishar W, Mauriac L, et al: Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol 26:1664-70, 2008

9. Carrick S, Parker S, Wilcken N, et al: Single agent versus combination chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev:CD003372, 2005

10. Piccart-Gebhart MJ, Burzykowski T, Buyse M, et al: Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. J Clin Oncol 26:1980-6, 2008

11. Findlay BP, Walker-Dilks C: Epirubicin, alone or in combination chemotherapy, for metastatic breast cancer. Provincial Breast Cancer Disease Site Group and the Provincial Systemic Treatment Disease Site Group. Cancer Prev Control 2:140-6, 1998

12. Harris L, Batist G, Belt R, et al: Liposome-encapsulated doxorubicin compared with conventional doxorubicin in a randomized multicenter trial as first-line

therapy of metastatic breast carcinoma. Cancer 94:25-36, 2002

13. Seidman AD, Berry D, Cirrincione C, et al: Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol 26:1642-9, 2008

14. Jones SE, Erban J, Overmoyer B, et al: Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol 23:5542-51, 2005

15. Gradishar WJ, Tjulandin S, Davidson N, et al: Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 23:7794-803, 2005

16. Gradishar W KD, Cheporov S, et al. : Randomized comparison of weekly or every-3-week (q3w) nab-paclitaxel compared to q3w docetaxel as first-line therapy in patients (pts) with metastatic breast cancer (MBC). J Clin Oncol; 25:18S, 2007(suppl, abstr 1032).

17. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783-92, 2001

18. Tomiak E VS, Levine m, et al.: Use of trastuzumab (Herceptin) in metastatic breast cancer. CCO Practice Guideline Initiative, January 2002.

19. Seidman AD, Fornier MN, Esteva FJ, et al: Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. J Clin Oncol 19:2587-95, 2001

20. Esteva FJ, Valero V, Booser D, et al: Phase II study of weekly docetaxel and trastuzumab for patients with HER-2-overexpressing metastatic breast cancer. J Clin Oncol 20:1800-8, 2002

21. Burstein HJ, Kuter I, Campos SM, et al: Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. J Clin Oncol 19:2722-30, 2001

22. Perez EA: Carboplatin in combination therapy for metastatic breast cancer. Oncologist 9:518-27, 2004

23. Robert N, Leyland-Jones B, Asmar L, et al: Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. J Clin

Oncol 24:2786-92, 2006

24. Pegram M FJ, Pienkowski V, et al.: BCIRG 007: First overall survival analysis of randomized phase III trial of trastuzumab plus docetaxel with or without carboplatin as first line therapy in HER-2 amplified metastatic breast cancer. J Clin Oncol 25:18S, 2007 (suppl, abstr 1008).

25. Mackey JR KB, Clemens M, et al.: Trastuzumab prolongs progression-free survival in hormone-depenent and HER2-positive metastatic breast cancer. Breast Cancer Res Treat 100: S5, 2006 (suppl 1, abstr 3).

26. Geyer CE, Forster J, Lindquist D, et al: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 355:2733-43, 2006

27. Blum JL, Dieras V, Lo Russo PM, et al: Multicenter, Phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients. Cancer 92:1759-68, 2001

28. O'Shaughnessy J, Miles D, Vukelja S, et al: Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 20:2812-23, 2002

29. Weber BL, Vogel C, Jones S, et al: Intravenous vinorelbine as first-line and second-line therapy in advanced breast cancer. J Clin Oncol 13:2722-30, 1995

30. Zelek L, Barthier S, Riofrio M, et al: Weekly vinorelbine is an effective palliative regimen after failure with anthracyclines and taxanes in metastatic breast carcinoma. Cancer 92:2267-72, 2001

31. Miller K, Wang M, Gralow J, et al: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 357:2666-76, 2007

32. Colleoni M, Rocca A, Sandri MT, et al: Low-dose oral methotrexate and cyclophosphamide in metastatic breast cancer: antitumor activity and correlation with vascular endothelial growth factor levels. Ann Oncol 13:73-80, 2002

33. Pavlakis N, Schmidt R, Stockler M: Bisphosphonates for breast cancer. Cochrane Database Syst Rev:CD003474, 2005

34. Hillner BE, Ingle JN, Chlebowski RT, et al: American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 21:4042-57, 2003

35. Rizzo JD, Somerfield MR, Hagerty KL, et al: Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American

Society of Hematology clinical practice guideline update. J Clin Oncol 26:132-49, 2008

36. Leyland-Jones B, Semiglazov V, Pawlicki M, et al: Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. J Clin Oncol 23:5960-72, 2005

37. Amadori D. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial. Lancet Oncol. 2013 Jun;14(7):663-70

38. Sideras K. Nonhormonal management of hot flashes for women on risk reduction therapy.J Natl Compr Canc Netw. 2010 Oct;8(10):1171-9.

39. Briot K. Effect of a switch of aromatase inhibitors on musculoskeletal symptoms in postmenopausal women with hormone-receptor-positive breast cancer: the ATOLL (articular tolerance of letrozole) study. Breast Cancer Res Treat. 2010 Feb;120(1):127-34

40. Irwin ML. Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors. J Clin Oncol. 2015 Apr 1;33(10):1104-11

41. Hershman DL. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014 Jun 20;32(18):1941-67

42. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, Harbeck N, Lipatov ON, Walshe JM, Moulder S, Gauthier E, Lu DR, Randolph S, Diéras V, Slamon DJ. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016 Nov 17;375(20):1925-1936.

43. Robertson JF, Bondarenko IM, Trishkina E, Dvorkin M, Panasci L, Manikhas A, Shparyk Y, Cardona-Huerta S, Cheung KL, Philco-Salas MJ, Ruiz-Borrego M, Shao Z, Noguchi S, Rowbottom J, Stuart M, Grinsted LM, Fazal M, Ellis MJ. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. Lancet. 2016 Dec 17;388(10063):2997-3005

5.3.2 Metastatic Chemotherapy Regimens

Doxorubicin q3wk

Proceed with chemo if ANC equal to or greater than 1.2 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L
If parameters are outside of acceptable range, contact the physician for further orders.

Every 21 days for 4-6 cycles				
Ondansetron	16mg	po		
Dexamethasone	8mg	po		
Doxorubicin HCl	60mg/m2	iv	IV push	
Dexamethasone	4mg	po	bid	2 days
Starting on the day after chemotherapy (days 2-3).				
Prochlorperazine maleate	10mg	po	q6h prn	30 tablets
Every 6 hours as needed for nausea or vomiting				

Doxorubicin q1wk

Proceed with chemo if ANC equal to or greater than 1.2 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L
If parameters are outside of acceptable range, contact the physician for further orders.

Every 7 days for 12-18 cycles				
Ondansetron	16mg	po		
Dexamethasone	8mg	po		
Doxorubicin HCl	20mg/m2	iv	IV push	
Dexamethasone	4mg	po	bid	2 days
Starting on the day after chemotherapy (days 2-3).				
Prochlorperazine maleate	10mg	po	q6h prn	30 tablets
Every 6 hours as needed for nausea or vomiting				

Doxorubicin and Cyclophosphamide

Proceed with chemo if ANC equal to or greater than 1.2 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L
If parameters are outside of acceptable range, contact the physician for further orders.

Every 21 days for 4-6 cycles					
Ondansetron	16mg	po			
Dexamethasone	8mg	po			
Aprepitant	125/80/80 mg	po			
Doxorubicin HCl	60mg/m2	iv	IV push		
Cyclophosphamide	600mg/m2	iv	250ml N Saline		Infuse IV over 30min
Dexamethasone	4mg	po	qd	2 days	Starting on the day after chemotherapy (days 2-3).
Prochlorperazine maleate	10mg	po	q6h prn	30 tablets	Every 6 hours as needed for nausea or vomiting Olanzapine 2.5 mg qd to bid po is a more effective alternative

Capecitabine

Capecitabine	1250mg/m2	po	bid	14 days
Prochlorperazine maleate	10mg	po	q6h prn	
Dispense an appropriate combination of 500 mg and 150 mg tablets to make up each dose				

Intravenous CMF

Proceed with chemo if ANC equal to or greater than 1.2 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L
If parameters are outside of acceptable range, contact the physician for further orders

Dexamethasone	8mg	po	once prn		
Prochlorperazine maleate	10mg	po	once prn		
Methotrexate sodium	40mg/m2	iv	once	iv push	
Fluorouracil	600mg/m2	iv	once	iv push	
Cyclophosphamide	600mg/m2	iv	250ml	N Saline	infuse iv over 30min
Prochlorperazine maleate	10mg	po	q6h prn		

Docetaxel q3wk

Proceed with chemo if ANC equal to or greater than 1.2 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L
If parameters are outside of acceptable range, contact the physician for further orders

Dexamethasone	8mg	po	bid	3 days	
Twice a day with food for 3 days starting the day before docetaxel. Must have 3 doses prior to docetaxel					
Docetaxel	100mg/m2	iv	250ml	N Saline	
Use non-PVC excel bag and tubing. Use graduated rate for first infusion. If no reaction, infuse subsequent doses over 1hr					
Diphenhydramine	50mg	iv	50ml	N Saline	q4h prn
Infuse iv over 15-30 minutes every 4 hours as required. Maximum daily dose of diphenhydramine allowed in chemo daycare for allergic reactions is 200 mg.					

Paclitaxel q1wk

Proceed with chemo if ANC equal to or greater than 1.2 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L
If parameters are outside of acceptable range, contact the physician for further orders

Dexamethasone	20mg	iv	50ml	N Saline	Infuse iv over 15 minutes pre-paclitaxel (45 mins before paclitaxel) Note: if no infusion reaction after two paclitaxel infusions pharmacy will discontinue premedications
Diphenhydramine	50mg	iv	50ml	5% Glucose	Infuse iv over 20 minutes
Famotidine	20mg	iv	50ml	5% Glucose	Infuse iv over 15 minutes
Paclitaxel	80mg/m2	iv	250ml	N Saline	Use graduated rate for first two cycles. If no reaction, infuse subsequent doses over 3 hours. Use non-PVC excel bag and tubing with 0.22 micron in-line filter.
Diphenhydramine	50mg	iv	50ml	N Saline	q4h prn Administer iv over 15-30 minutes every 4 hours as needed. Maximum daily dose of diphenhydramine allowed in chemo daycare for allergic reactions is 200 mg.

Trastuzumab

First cycle					
Trastuzumab	8mg/kg 6 mg/kg	iv load iv maintenance	250ml	N Saline	iv over 90 minutes
Diphenhydramine	50mg	iv	50ml	N Saline	Administer iv over 15-30 minutes every 4 hours as needed. Maximum daily dose of diphenhydramine allowed in chemo daycare for allergic reactions is 200 mg.
Acetaminophen	650mg	po	PRN headache		
Meperidine	25mg	iv	50ml	N Saline	One time dose as required for rigors/chills. Infuse iv over 10-15 minutes.
Dimenhydrinate	50mg	iv	50ml	N Saline	One time dose as needed for nausea or vomiting due to meperidine. Infuse iv over 15 min.

Vinorelbine

Give on Days 1 and 8 of a 21 day schedule					
On Day 1: Proceed with chemo if ANC equal to or greater than 1.5 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L If parameters are outside of acceptable range, contact the physician for further orders.					
On Day 8: Adjust Vinorelbine Dose Based on The Following Treatment Day Parameters: ANC equal to or greater than 1.5 x 10^9/L and Platelets equal to or greater than 100 x 10^9/L: Give 100% of dose ANC = 1.0-1.4 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L: Give 50% of dose If parameters are outside of acceptable range, contact the physician for further orders.					
Dexamethasone	8mg	po	once		
Vinorelbine tartrate	25mg/m2	iv	50ml	N Saline	Iv push over 6-10 minutes
Prochlorperazine maleate	10mg	po	q6h prn		

Nano albumin bound paclitaxel (q3wk)

Proceed with chemo if ANC equal to or greater than 1.2 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L If parameters are outside of acceptable range, contact the physician for further orders				
nab-paclitaxel (Abraxane)	260mg/m2	iv	infuse iv over 30 minutes. Do not use in-line filter.	
Prochlorperazine maleate	10mg	po	q6h prn	

Nano albumin bound paclitaxel (q1wk)

Proceed with chemo if ANC equal to or greater than 1.2 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L
If parameters are outside of acceptable range, contact the physician for further orders

nab-paclitaxel (Abraxane) Do not use in-line filter.	100mg/m2	iv	infuse iv over 30 minutes.
Prochlorperazine maleate	10mg	po	q6h prn

Gemcitabine

Proceed with chemo if ANC equal to or greater than 1.2 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L
If parameters are outside of acceptable range, contact the physician for further orders

On Days 1 and 8 of a 21-day cycle					
Dexamethasone	8mg	po			
Gemcitabine	1000mg/m2	iv	250ml	N Saline	Infuse iv over 30 minutes

Gemcitabine and Cisplatin

Proceed with chemo if ANC equal to or greater than 1.2 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L
If parameters are outside of acceptable range, contact the physician for further orders

On Day 1					
Ondansetron	16mg	po			
Dexamethasone	8mg	po			
Aprepitant	125/80/80 mg	po			
Gemcitabine	1000mg/m2	iv	250ml	N Saline	Infuse iv over 30 minutes
Magnesium sulfate 1g cisplatin (pre-hydration)	iv	500ml	N Saline	Infuse iv over 1 hour pre	
Mannitol	20g	iv	Infuse iv over 5-10min immediately before		

cisplatin. Use in-line filter.					
Cisplatin	70mg/m2	iv	500ml	N Saline	Infuse iv over 1 hour
Mannitol cisplatin. Use in-line filter.	20g	iv	Infuse iv over 5-10min immediately before		
Magnesium sulfate cisplatin (post-hydration)	1g	iv	500ml	N Saline	Infuse iv over 1 hour pre
Dexamethasone	4 mg po daily on days 2 and 3				
Prochlorperazine maleate Every 6 hours as needed for nausea or vomiting Olanzapine 2.5 mg qd to bid is a more effective alternative	10mg	po	q6h prn	30 tablets	
On Day 8					
Dexamethasone	8mg	po			
Gemcitabine	1000mg/m2	iv	250ml	N Saline	Infuse iv over 30 minutes

Gemcitabine and Carboplatin

Proceed with chemo if ANC equal to or greater than 1.2 x 10^9/L AND Platelets equal to or greater than 100 x 10^9/L
If parameters are outside of acceptable range, contact the physician for further orders

On Day 1					
Ondansetron	16mg	po			
Dexamethasone	8mg	po			
Gemcitabine minutes	1000mg/m2	iv	250ml	N Saline	Infuse iv over 30
Carboplatin minutes	AUC=5	iv	250ml	5% Glucose	Infuse iv over 30
Prochlorperazine maleate Every 6 hours as needed for nausea or vomiting Olanzapine 2.5 qd to bid prn is a more effective alternative	10mg	po	q6h prn	30 tablets	
On Day 8					
Dexamethasone	8mg	po			
Gemcitabine minutes	1000mg/m2	iv	250ml	N Saline	Infuse iv over 30

5.4 SPECIAL SCENARIOS RELEVANT TO BREAST CANCER

5.4.1 Ductal Carcinoma in-situ (DCIS)

(This section was last updated December 2015)

Background

In ductal carcinoma in situ (DCIS), by definition, the abnormal cells have not invaded through the wall of the ducts into the surrounding tissue. Therefore the risk of metastasis is low (< 1%). Relevant clinical endpoint in the management of DCIS is therefore the risk of local recurrence, not survival. Local recurrence may either in situ or invasive disease, and there is the risk of breast cancer-related mortality if there is an invasive recurrence (1).

Due to screening mammography, DCIS is most often present as suspicious calcifications. It can also present with painless palpable mass, nipple discharge and changes of the nipple (Paget's disease).

Diagnostic Evaluation

Breast Imaging

Standard bilateral mammography with mediolateral oblique (MLO) and craniocaudal (CC) views are recommended. Additional spot-compression magnification views are standard to assess the extent and character of the microcalcifications and to identify calcifications that might not otherwise be evident. MRI is helpful to assess the extent of the disease and to identify an invasive component. Large areas of microcalcifications detected on mammography should have additional assessment with MRI. MRI has high sensitivity and specificity to evaluate axillary nodes. MRI may identify other lesions in the same or the opposite breast because is highly sensitive but is not very specific, hence capabilities of MRI-guided biopsy are necessary. Management should not change unless there is tissue confirmation that further disease is present. Low to intermediate grade DCIS may be missed on MRI. Ultrasound imaging is an integral part of the radiological assessment to evaluate palpable masses, axillary nodes, and any indeterminate MRI findings.

Core Biopsy

For mammographic lesions, stereotactic core biopsy should be used for evaluation of suspicious or indeterminate microcalcifications that are not associated with a mass lesion, otherwise ultrasound-guided core biopsy is indicated. Multiple samples using a vacuum assisted device should be performed, and intra-operative specimen radiography performed to confirm that the abnormal microcalcifications have been adequately sampled. Stereotactic core biopsy may not be possible in certain circumstances:

1. In patients whose breast thickness is too small (usually less than 2 or 2.5 cm) to allow for the safe use of the biopsy needle.
2. Lesions located just under the skin or close to chest wall

3. When the microcalcifications cannot be visualized in the stereo pair ("faint microcalcifications")

Ultrasound-guided biopsy may be used if the lesion is visible by ultrasound and is advised to perform a needle localization to demonstrate the imaging correlation from one modality to another.

Alternatively, when stereotatic core biopsy is not feasible and target not identified by sonography, an MRI in BIRADS 4A /4B lesions or a surgical excision of the area after mammographic placed needle-localization may be required in BIRADS 4B/ 4C lesions.

Pathologic Reporting

Pathology review by a pathologist with expertise in breast cancer is recommended due to reports of significant variability in pathologic reporting of DCIS (2). Standard surgical pathology synoptic reporting with the following pathologic features should be reported to determine the optimal treatment:

1. Size of the specimen in three dimensions
2. Whether the entire specimen was submitted for evaluation
3. Whether the entire specimen was submitted in one piece or in multiple fragments
4. A synoptic report of the following histological features of DCIS
    a. Nuclear grade
    b. Presence and extent of comedo necrosis
    c. Architectural pattern
    d. Tumour size or extent
    e. Presence and location of microcalcifications (within tumour, in surrounding parenchyma)
    f. Margin status and width and location of the closest resection margin.

Management

The goal of surgery includes the removal of all suspicious areas of disease with minimal cosmetic deformity. When there is any question about the completeness of surgical removal, a post-operative mammogram should be considered.

Lymph nodes

Axillary node dissection: The incidence of positive axillary nodes with isolated DCIS is negligible (3). Therefore, routine axillary node assessment is not recommended. Sentinel node biopsy may be considered when there is:

1. Extensive high grade DCIS
2. DCIS with microinvasion
3. Suspicious findings on core biopsy that suggest invasion may be an indication for SLNB in selected patients.
4. A planned mastectomy since sentinel node biopsy cannot be performed following mastectomy.

Mastectomy

DCIS is highly curable with mastectomy however, most women with DCIS present with asymptomatic disease confined to a single quadrant of the breast (4). Such patients can be adequately treated with breast-conserving surgery and radiation. Mastectomy with the option for reconstruction should be discussed with all women, however for most women this will represent excessive treatment.

Indications for mastectomy include:

1. Presence of multicentric DCIS
2. Presence of diffuse microcalcifications.
3. Persistent positive resection margins after two attempts at breast preservation.
4. History of previous chest wall, nodal, or breast irradiation
5. When adequate excision would produce in an unacceptable cosmetic result.
6. Presence of contra-indications to breast radiotherapy (e.g. pregnancy, collagen vascular disease).

Breast-conserving surgery

The majority of lesions detected in the current era will be non-palpable and will require needle-localization either under stereotactic or ultrasound guidance prior to removal. Every effort should be made to remove the lesion in one piece. Removal of the lesion in multiple fragments should be avoided as it precludes pathologic evaluation of tumour size and margin status. Surgical clips outlining the excision cavity should be considered to facilitate radiotherapy planning and to demarcate the tumour bed for future imaging studies. Intraoperative specimen radiography is essential and should be compared to the preoperative mammogram to ensure complete excision of the lesion. The presence of the lesion in close proximity to the specimen margin may provide the opportunity for further resection along that margin to ensure adequate excision of the lesion at the time of the initial surgery.

Indications for Re-excision

- Post-operative mammogram with positive, suspicious or indeterminate microcalcifications.
- Positive resection margins.
- Resection margins (medial, lateral, superior, inferior, or posterior if resection to pectoralis fascia not performed) < 1 mm should be strongly considered.

Radiotherapy

(Please see chapter 5.1.3 Radiation Therapy Page 64)

Breast-Conserving Surgery Alone

Three randomized controlled trials have demonstrated a reduction in local recurrence with the addition of radiotherapy following breast-conserving surgery for DCIS. A subset of patients who do not benefit from radiotherapy has not been clearly identified. However, data from retrospective series suggest that a subset of patients may exist in whom the risk of recurrence is low such that omission of radiotherapy may be discussed with the patient.

1. Tumour size < 2.5 cm

2. Unicentric, non-palpable
3. Nuclear grade 1 or 2
4. No or focal comedo necrosis (< 1 ducts)
5. Margins > 1 cm

Systemic Therapy

The role of tamoxifen continues to evolve. Two trials (7, 8) investigated the role of tamoxifen versus no tamoxifen in addition to breast conserving surgery and radiotherapy in the treatment of DCIS. While there is some evidence to suggest that tamoxifen is effective in the reduction of ipsilateral recurrence and contralateral incidence in women with DCIS, the absolute benefit is small and the evidence is conflicting. Women should be informed of the option of five years of tamoxifen therapy and of the potential toxicities and benefits associated with tamoxifen (9).

References:

1. Solin et al. Fifteen-year results of breast-conserving surgery and definitive breast irradiation for the treatment of ductal carcinoma in situ of the breast. J Clin Oncol 1996;14:754-63.

2. Sloane et al. Consistency achieved by 23 European pathologists in categorizing ductal carcinoma in situ of the breast using five classifications. European Commission Working Group on Breast Screening Pathology. Hum Pathol 1998;29:1056-62.

3. Winchester et al. Treatment trends for ductal carcinoma in situ of the breast. Ann Surg Oncol 1995;2:207-13.

4. Holland et al. Extent, distribution, and mammographic/histological correlations of breast ductal carcinoma in situ. Lancet 1990;335:519-22.

5. Fisher et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. Journal of Clinical Oncology 1998;16:441-52.

6. Julien et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet. 2000;355:528-33.

7. Fisher et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial [see comments]. Lancet 1999;353:1993-2000.

8. Houghton J et al. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomized controlled trial. Lancet. 2003;362(9378):95-102.

9. W. Shelley et al. Management of ductal carcinoma in situ of the breast: A clinical practice guideline. Evidence-based series #1-10 (Version 2.2006) http://www.cancercare.on.ca/pdf/pebc1-10s.pdf

6. SUPPORTIVE CARE

6.1 SYMPTOM MANAGEMENT

(This section was last updated December 2015)

Bisphosphonates

In advanced breast cancer with bone metastases, bisphosphonates have been shown to reduce the incidence of skeletal-related events and may be a useful adjunct to conventional measures for control of bone pain. Zoledronic acid 4 mg iv q 4 weeks is our current standard. After 2 years or therapy the frequency may be decreased to q 12 weeks. Patients with a poor life expectancy should have their bisphosphonates stopped unless they were used for hypercalcemia. Prior to initiating therapy, patients should be asked about whether they have any current dental problems and whether they have seen a dentist in the past year.

Erythropoiesis-stimulating agents (ESAs)

- ESA can be considered in patients with chemotherapy-induced anemia (Hgb<11).
- A decreased rate of transfusion is the only proven benefit of ESA use.
- Data are not sufficient to exclude the possibility of shortened tumour progression and survival as a result of use of ESAs in advanced breast cancer.
- ESAs can be considered for select patients, but their routine use is not recommended.

Drug induced toxicities

Hot flashes

Venlafaxine SR 37.5 mg qd po x 1 week then 75 mg qd po thereafter
If not tolerated, already on an antidepressant or ineffective:
Gabapentin 300 mg bid po x 1 week then tid thereafter (higher doses may be more effective) or Pregabalin 75 mg po bid x 1 week then tid thereafter

Aromatase inhibitor induced bone pain

In some patients, the pain will improve spontaneously over several months.
Switch to an alternative aromatase inhibitor
A combined program of aerobic and resistance exercise was shown in one trial to reduce pain.

Pain due to peripheral neuropathy

If not on an antidepressant:
Duloxetine 30 mg daily po x 1 week then 60 mg qd thereafter. Nausea or sedation prevent ongoing use in 20% of paients

Evidence base:

- A meta-analysis of bisphosphonates for women with breast cancer reported that they reduce the risk of developing skeletal events (RR=0.83, p<0.00001) and significantly improve bone pain.
- In a double blind RCT comparing epoetin alpha and placebo in women undergoing first-line treatment with chemotherapy, the OS was inferior in the arm with epoetin alpha (HR=1.37, p=0.01).

Chemotherapy-induced Nausea and Vomiting

Introduction

Following exposure to emetogenic cancer chemotherapy, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT_3 receptors, located peripherally on vagal nerve terminals and centrally in the nucleus tactus solitarus. (1) A group of drugs called "5-HT_3 Selective Serotonin Receptor Antagonists" exert their antiemetic effects by blocking the serotonin-induced stimulation of vagal afferent nerve.

Prevention of Chemotherapy Induced Acute Emesis

Acute emesis is defined as nausea and vomiting that occurs within the first 24 hours post chemotherapy. It may begin within a few minutes to several hours after administration of chemotherapy and commonly resolves within the first 24 hours. For chemotherapy with mildly emetogenic potential (see Table 1), the use of prochlorperazine or/and dexamethasone as acute prophylactic antiemetic therapy is often sufficient. To effectively control emesis induced by agents with moderately or highly emetogenic potentials (see Table 1), a 5-HT_3 serotonin receptor antagonist is required. (2) Presently, there are three 5-HT_3 serotonin receptor antagonists on the market: granisetron, ondansetron, and dolasetron. All three demonstrate equivalent therapeutic efficacy in prevention of chemotherapy induced ACUTE emesis. Granisetron is the only 5-HT_3 serotonin receptor antagonist in the UHN formulary; therefore, any orders for ondansetron will automatically be substituted with granisetron. Ondansetron however, may be dispensed by UHN's retail pharmacies.

A single dose of 5-HT_3 serotonin receptor antagonist is as effective as multiple doses. (2) For single day chemotherapy, granisetron 1 mg intravenous (IV) single dose, 30 minutes before chemotherapy is recommended. For multiple days chemotherapy regimen, granisetron 1mg IV q24h on each chemotherapy day is recommended. The granisetron dose should be administered at the same time each day in relation to the chemotherapy. Vomiting may still occur in some patients within the first 24 hours, despite administration of granisetron. Since additional doses of granisetron will not be beneficial, and other neuroreceptors are involved in emesis, a prudent approach to manage this problem is to add a different class of antiemetics such as a dopamine receptor antagonist, an antipsychotic-antiemetic, and/or steroids. Combining granisetron with dexamethasone has shown enhanced antiemetic effectiveness in acute emesis. The standard dexamethasone dose is 20mg for cisplatin, and 10mg for doxorubicin based

chemotherapy. (2) A randomized double blind study supported the use of a higher dose in that 20 mg dexamethasone was statistically superior to an 8 mg dose and numerically (but not statistically significant) superior to 12mg. (3)

Prevention of Nausea and Vomiting from Highly-Emetogenic Chemotherapy

In addition to the use of a 5HT3-receptor antagonist and dexamethasone, it has been shown that by additionally blocking the tachykinin, substance P, at NK1-receptors with aprepitant (EmendÒ), one can reduce the risk of emesis from highly-emetogenic chemotherapy by 17%.(4) Moreover, women with breast cancer receiving an anthracycline+cyclophosphamide had a 9% improvement in vomiting risk (although with no impact on nausea) when a 5HT3 antagonist and dexamethasone were supplemented with aprepitant (EmendÒ) (5).

Aprepitant is a moderate inhibitor of the CYP3A4 isoenzyme and could decrease the metabolism of corticosteroids (substrates); thus, dexamethasone, *when employed as part of an antiemetic regimen,* should have dosages reduced (i.e. halved) if given orally. Prednisone, *as part of an anticancer protocol,* should not have its dose reduced if aprepitant is used concomitantly. Chemotherapeutic agents known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. In clinical trials where aprepitant has been used with some of these agents, doses were *not* adjusted Pharmacokinetic studies with vinorelbine and docetaxel have shown no increase in the area under the curve.(6,7) The explanation for this appears to be that the interaction is primarily with orally administered medication where there is extensive metabolism by CYP3A4 in the bowel wall.

Prevention of Chemotherapy Induced Delayed Emesis

Delayed emesis is defined as the period beyond 24 hours post chemotherapy. It occurs commonly with the administration of cisplatin, carboplatin, cyclophosphamide or doxorubicin. Cisplatin related emesis reaches its maximal intensity from 48-72 hours following chemotherapy and can last 6 –7 days. While treatment for delayed emesis may be prescribed; prevention of its occurrence is preferable. (2) To prevent delayed onset emesis, it is recommended to incorporate extended administration (2-5 days) of dexamethasone. (2)

Treatment of Chemotherapy Induced Delayed Emesis

Once the patient experiences delayed onset emesis, there is little use for 5-HT_3 serotonin receptor antagonists at later points in time. Urine collections during the first 24 hours have shown a substantial release of serotonin metabolites following the administration of cisplatin but beyond that time, the concentrations are near baseline. Nine randomized double-blind studies (more than 3,700 patients) have evaluated the prolonged use of 5-HT_3 serotonin receptor antagonists. (8-15) CCOPGI's meta-analysis reported a 4.5% improvement in the complete response rate of delayed emesis for prolonged used of 5-HT_3 serotonin receptor antagonists (i.e., 22 patients would have to be treated with

prolonged 5-HT_3 serotonin receptor antagonist in order to prevent emesis in one additional patient) (2). This benefit is considered too small to warrant the routine use of prolonged 5-HT_3 serotonin receptor antagonists. Therefore, the use of 5-HT_3 serotonin receptor antagonists for more than 24 hours following chemotherapy should be reserved for patients who do not respond to other antiemetics in a prior course of chemotherapy.

As demonstrated in randomized trials, corticosteroids are probably the single most effective drug class for delayed onset emesis. Usually given as 4-8 mg BID to TID IV or by mouth (PO) for 2-5 days. There are other drugs to consider:

1. **Prochlorperazine****, 10 mg IV/PO/PR q6h routine/prn. Watch for extrapyramidal reactions, treat with benztropine.
2. **Metoclopramide**, 10-40mg q4-6 hours prn x 3-4 days with dexamethasone. (16, 17)
3. **Domperidone**, 20 mg qid (ac & hs) has demonstrated efficacy in a non-blinded study. (18) In addition, several studies showed that metopimazine (a dopamine receptor antagonist that, like domperidone, infrequently causes extrapyramidal side effects) significantly reduces both acute and delayed onset emesis when combined with ondansetron or when combined with ondansetron plus corticosteroids (19-22) and reduces delayed onset emesis when combined with corticosteroids (23). Combinations of domperidone with either a 5HT3 serotonin receptor antagonist and/or corticosteroids may therefore enhance control of chemotherapy-induced nausea and vomiting.
4. **Haloperidol****, 0.5-2 mg PO/subcutaneously (SC) q8-12h routine/prn (with benztropine prn).
5. Nabilone 0.5-1 mg PO BID routine/prn. This drug should be used with caution due to its commonly experienced CNS/psychiatric and cardiovascular adverse effects. For patients who experience positive response, Nabilone should be considered as part of the pre-chemo antiemetic regimen in subsequent cycles.
6. **Olanzapine**, 5-10mg once prior to chemotherapy has been shown to be effective in acute and delayed emesis in a phase II trial. (24) It has also been used successfully in the prevention and treatment of refractory nausea and vomiting. (25)

** Prochlorperazine, olanzapine and metoclopramide must not be used in combination.

TABLE - The Antiemetic Guidelines for Chemotherapy Induced Emesis

	Mildly Emetogenic Agents or Protocols	Moderately to Highly Emetogenic Agents or Protocols
	Use Non-5-HT_3 antagonist premed	Use 5-HT_3 antagonist premed for all in-hospital 5-HT_3 antagonists Rx
Pre-chemo$^{\Psi}$	No prophylaxis if emesis not anticipated ***OR*** Dexamethasone 10 mg PO/IV$^{\#}$	Out-patient* Granisetron 1 mg IV or PO In-patient Granisetron 1 mg IV ***PLUS*** Dexamethasone 20 mg PO/IV$^{\#}$ ***PLUS (for high risk patient only)*** Metoclopramide 0.5 mg/kg q6h IV/PO (plus Diphenhydramine 50 mg PO q4h prn for restlessness and dystonic reactions) ***OR*** Domperidone 20 mg PO qid
Post-chemo (1st 24 hrs)	If dexamethasone alone continue to provide inadequate acute emesis prophylaxis ***Add*** Metoclopramide 10-20 mg IV/PO q6h ***OR*** Domperidone 20 mg po qid (ac & hs) ***OR*** Prochlorperazine 10 mg IV/PO q6h	Out-patient Rx: Granisetron 1 mg PO (or other 5-HT_3 antagonists equivalent) 12 hrs post chemo if oral granisetron was used pre-chemo ***Add PRN*** Metoclopramide 0.5 mg/kg IV/PO q6h (plus Diphenhydramine 50 mg IV/PO q4h prn for restlessness or acute dystonic reactions) ***OR*** Domperidone 20 mg PO qid ***OR*** Prochlorperazine 10mg IV/PO q6h In-patient: Have the same *PRN* medications as out-patients (IV or PO). In rescue situation, use IV Metoclopramide (0.5 mg/kg q6h) (plus Diphenhydramine) ***OR*** Prochlorperazine 10 mg IV/PO q6h

	Mildly Emetogenic Agents or Protocols	Moderately to Highly Emetogenic Agents or Protocols
Delayed Emesis (24 hrs post chemo to 3-5 days)	Dexamethasone 4-8 mg PO bid for 3-5 days if delayed emesis is anticipated [#] ***add*** PRN Metoclopramide 0.5 mg/kg PO/IV q6h (plus Diphenhydramine 50 mg PO q4h prn for restlessness or acute dystonic reactions) ***OR*** Domperidone 20 mg PO qid ***OR*** Prochlorperazine 10 mg IV q6h ***OR*** Haloperidol 0.5-2 mg SC q8-12h Consider: Nabilone 1 mg PO BID Note: 5-HT_3 antagonists reserved for patients who do not respond to the above	Dexamethasone 4-8 mg PO bid for 3-5 days if delayed emesis is anticipated [#] ***add*** PRN Metoclopramide 0.5 mg/kg IV/PO q6h (plus Diphenhydramine 50 mg PO q4h prn for restlessness or acute dystonic reactions) ***OR*** Domperidone 20 mg PO qid ***OR*** Prochlorperazine 10 mg IV q6h ***OR*** Haloperidol 0.5-2 mg SC q8-12h Consider: Nabilone 1 mg PO BID Note: 5-HT_3 antagonists reserved for patients who do not respond to the above

Ψ For anticipatory nausea/vomiting, add lorazepam 1 to 2 mg SL/PO pre-chemotherapy.
Ψ Pre-chemotherapy antiemetics may be given any time within 30 minutes before chemotherapy
The use of steroids is usually avoided in AML patients
***** Pre-chemotherapy recommendation applicable only to patients who have not been pre- medicated with 5-HT_3 at home

6.2 PSYCHOSOCIAL ONCOLOGY

(This section was updated February 2017)

Facing a serious illness such as cancer can be very distressing. At Princess Margaret Cancer Centre, help is available for patients and family members having difficulty coping with their illness or treatment. Staff in the Department of Psychosocial Oncology have expertise in providing supportive care and assistance through this difficult time. This multidisciplinary program is focused on the psychosocial and psychological aspects of cancer.

The program includes staff in the disciplines of social work, psychiatry, psychology, palliative care, , music therapy chaplaincy and occupational therapy. It provides outpatient and consultative services to patients with cancer and their families. Research is being conducted on such issues as quality of life, self-concept, death and dying, cognitive effects of cancer and its treatment, and psychotherapeutic interventions in patients with cancer.

The primary role of Psychosocial Oncology is to provide care for patients who have had contact with their Princess Margaret physician within the last year.

Contact information

Psychosocial Oncology Reception 416 946-4525
Fax referral requests for Psychsocial Oncology Clinicians to 416 946-2047

Psychiatry
Patients, family members, POPC staff or oncology staff may **initiate** a consult request. However:

- The patient must be informed that they are to see a clinician
- The attending physician must make a **written** referral

When there is a request for an **emergency or urgent referral,** such a request and the reasons for its urgency need to come directly from a **physician** familiar with the patient's clinical situation. This ensures that there has been appropriate screening and, more importantly, that **a physician responsible for the patient is aware of the level of their patient's distress.** The attending physician's involvement will be ensured without delaying the consultation. Most often it will be appropriate for these requests to go to the Psychiatrist On-Call.

For urgent referrals contact Psychosocial Oncology directly x 4525

Who to Refer:

Psychiatry consultation should be considered if the following concerns/issues are identified:

- Suicidal risk
- Threat to others
- Question of certification
- Ability to consent to treatment or to refuse treatment (competency assessment)
- Indecision about treatment
- Altered or unusual behaviour (suspected delirium)
- Psychosis
- Depressive or anxiety symptoms (requests indicate major symptomatology/ medications)
- Prior history of psychiatric illness
- Assistance in symptom management
- Substance abuse
- Prolonged hospitalization (may be identified as apathetic, lacking motivation, etc.)

You may consider a Psychiatry Consultation for:

1. Coping and/or stress
    - Anxiety: genetic risk (alongside a cancer diagnosis), phase of illness, treatment related, end of life
    - Reaction to illness depression or anxiety
    - Family/marital coping needs related to the cancer diagnosis or treatment

Request for specific intervention: cognitive therapy, Mindfulness Based Cognitive Therapy, family or marital therapy

2. Trauma
3. Personality disorder affecting treatment compliance
4. Compliance/capacity assessment
5. Sexual disorders /dysfunction
6. Substance abuse
7. Advocacy
8. Psychological issues: body image, self-esteem, identity, fear, phase of treatment crisis, developmental issues
9. Existential issues

The primary role of the Psychiatry Consult and Clinic Service is to provide care for current PMH patients. Family members are seen when the family member impacts the care of the PMH patient. Family members of PMH patients need a written referral of the attending physician caring for the PMH patient (for them to provide the best care to the family unit they need to understand the stresses in the family). Requests for bereavement consults and follow-up are decided on a case-by-case basis.

When to refer:

Referrals can be made to Psychiatry at any stage of a patient's treatment, patients who have no evidence of disease and whose treatment (including aromatase inhibitors)

occurred longer than 3 years ago will be referred to the community unless there is a unique need requiring a psychosocial oncology clinician.

6.3 ONCOLOGY SOCIAL WORK

Oncology social workers provide psychosocial support to patients who are diagnosed with breast cancer and are receiving active treatment for their illness. Social workers intervene to facilitate patient and family participation in treatment, and the discharge of patients following inpatient care. Social workers help patients and families adjust to the illness, reduce stress and improve their quality of life.

Patients, family members, Psychosocial Oncology staff or oncology staff may initiate a Social Work referral. If the Oncology Team initiates the referral it is preferable that the patient is advised of the referral by the Team member prior to the Social Worker making contact, and that the Psychosocial Oncology Referral Form is used (attached

CRS Program Referral_FINAL_July 7).

Patients and families who have needs or concerns unrelated to their cancer care are referred to resources in their community for assistance as appropriate.

Who to Refer:
Patients diagnosed with and receiving treatment for breast cancer, and their families.

When to Refer:
Referrals can be made to Social Work at any stage of a patient's treatment, with a focus on removing barriers impeding access to treatment. Referrals are accepted for both patients and family members. Referrals can be made to Social Work at any stage of a patient's treatment, patients who have no evidence of disease and whose treatment (including aromatase inhibitors) occurred longer than 3 years ago will be referred to the community unless there is a unique need requiring a psychosocial oncology clinician.

Short term counseling Services provided by Social Work may include:

- Treatment-related decision making
- Individual/family coping and/or stress, regarding impact of diagnosis, treatments, illness
- Individual/family safety concerns
- Disclosing a parent's cancer diagnosis to children
- Complex discharge planning
- Palliative care planning
- Advance care planning (e.g. power of attorney, wills, funeral arrangements)
- Individual/family safety concerns

- Advocacy
- Information and/or referrals for community resources; resource lists for fee for service home support services (e.g. home supports)
- Substance abuse assessment and referral
- Practical assistance such as transportation planning
- Financial matters (e.g. Income support, programs and disability pensions)
- Assessment of financial need for PMH Lodge, Wig Salon
- Assistance in obtaining a priority access letter for Toronto Community Housing for patients with a prognosis of less than 2 years (priority criteria as determined by Toronto Community Housing)

6.3.1 Distress Assessment and Response Tool (DART)

Merging efforts with Cancer Care Ontario's (CCO) Ontario Cancer Symptom Management Collaborative, and in collaboration with the Canadian Partnership Against Cancer (CPAC) Screening for Distress initiative, the Psychosocial Oncology and Palliative Care department at Princess Margaret Hospital (PMH), has developed the Distress Assessment and Response Tool (DART).

DART is comprised of a web-based electronic distress screening tool, linked to an inter-professional distress response Care Path, graded to the individual patient's level of distress. DART is currently being implemented in a customized, graded fashion clinic by clinic, with nurses aligned to play a key leadership role.

Every patient attending ambulatory cancer clinics at PMH will eventually have an opportunity to complete this self assessment tool on touch screen kiosks in waiting areas prior to their clinic appointment. A summary report is created and placed on the patient's chart and a copy is given to the patient. The DART report highlights the social, emotional, spiritual, informational, physical and practical needs of each patient.

Low distress items are highlighted to the specially trained DART volunteer for provision of basic information, peer support and linkage to resources. Items of moderate to high distress are highlighted to the nurse and oncologist for further assessment and intervention. Persistently high distress items are flagged for referral to specialty services such as social work and psychiatry.

DART thus provides health care teams with an individualized, targeted and holistic approach to enhance communication and meet patients' cancer-related needs. This process of standardized distress screening and triaged intervention promotes interprofessional practice, supports patient-centered care, and efficiently delivers appropriate health services to enhance quality of life for all cancer patients.

6.4 CANCER REHABILITATION & SURVIVORSHIP PROGRAM

(This section was updated February 2017)

I. Background

The Cancer Survivorship Program has been renamed the Cancer Rehabilitation and Survivorship (CRS) Program (Program Director: Dr. Jennifer M Jones; Medical Director: Dr. Eugene Chang) and is now part of the newly developed Supportive Care Department (Head: Dr. Gary Rodin) at Princess Margaret Cancer Centre.

The CRS program is built on principles of self-management to support survivors living with late and long-term effects of cancer treatment and provides a comprehensive on-going care across the age spectrum. The CRS program adopts a consultative nature of service delivery grounded on clinical practice guidelines and based on the chronic disease model with principles of self-management that emphasizes medical, role and emotional management of the chronic condition. The program has a focus on improving health and quality of life, maximizing function and health promotion. Care is provided by an inter-disciplinary team which consists of physiatry, occupational therapy, physiotherapy, nursing, kinesiology, massage therapy, nutrition, social work, psychology.

Historically, the Cancer Survivorship Program has served primarily the breast, gynecology and head and neck cancer sites at Princess Margaret. Beginning in 2016 our mandate will change to provide programs and services to all cancer sites. Consequently, using a consultative and collaborative approach, our team has worked to redesign our clinical program to improve efficiency of care, timely and appropriate access to care, and to accommodate the increased number of referrals. The newly designed CRS Program includes strong partnerships and triage streams with community and patient education programs and the Toronto Rehabilitation Institute and an 8 week structured rehabilitation program.

II. Target Population

Physicians can use our new referral (***see Appendix 1 Page 121***) to refer patients that have been seen for active follow-up ≤2 years post treatment at Princess Margaret Cancer Centre for the following cancer-related impairments:

Physical

- Musculoskeletal (ROM, strength)
- Neuropathy
- Balance
- Deconditioning
- Lymphedema

Functional

- Difficulty with ADLs

- Fatigue
- Return to work/school
- Sexuality

Cognitive
- Brain fog (memory, attention, concentration)

III. Description of Services

All patients referred to our program will receive a Comprehensive Assessment (CA) with an inter-disciplinary team consisting of a physiatrist (rehabilitation medicine), occupational therapist, physiotherapist, kinesiologist and social work (as needed). The inter-disciplinary team will make an informed, collaborative decision about the patient's plan of care at the end of the visit in a team huddle case review. Depending on the severity of symptoms assessed and the patients' goals, the patient will be triaged into one of three potential streams: (1) none- mild impairment; (2) mild-moderate impairment; (3) moderate-high impairment. ***See Appendix 2 Page 122*** for process map illustrating how a patient moves through our program.

1) **None-Mild**: Patients who are in the none-mild stream, will be referred to community supports such as Wellspring, Gilda's club, to hospital-based group wellness and exercise classes (WE-Can home based exercise program, Healthy Steps, Yoga, Tai Chi, Mindfulness Meditation) or patient education classes (Getting Back on Track, Lymphedema Awareness, Reclaim your Energy, What you can do about Brain Fog, Sex and Intimacy, Cancer Exercise). Ideally, patients who are classified as none-mild impairment can be referred directly to community or hospital-based supports directly from the referring physician.

   Criteria to classify patients as none-mild stream include the following:

   - Range of motion within normal limits, may have some pulling/tightness on end range
   - Lymphedema prevention (no observable or palpable swelling)
   - No complaints of pain
   - DART score between 0-3 for all items
   - Sexuality (vaginal dryness, questions about lubricants, body image)
   - Return to work/school (no prior job or program they are returning to)

2) **Mild-Moderate:** Patients in the mild-moderate stream, who are deemed medically clear to exercise, will be offered an 8-week group-based Structured Cancer Rehabilitation (SR) Program. ***See Appendix 3 Page 123*** for detailed information on the curriculum delivered in this program. We anticipate that the comprehensive nature of this program will eliminate the need to bring patients back to clinic for multiple one-to-one follow up appointments, thus enabling us to maintain a reasonable wait-

list and to accommodate the needs of all cancer patients at UHN. In addition, the group-based format provides a supportive environment for peers to connect and to normalize their experiences.

Components of the Structured Rehabilitation Program:

i. An exercise prescription session (1hr) by a registered Kinesiologist (RKin) followed by 8 weekly group exercise classes and a home based exercise program. These sessions will be supervised by a physiotherapist (PT) and an RKin and can address potential impairment with ROM, strength and deconditioning. Patients who require further 1:1 support for their physical impairment can access PT, OT or physiatry services as appropriate.

ii. An 8-week (1hour session per week) supported self-management skills program addressing the following topics: Mood, Diet and Nutrition, Brain Health, Fatigue, Stress Reduction.

If a patient has a diagnosis of lymphedema, a specific return to work or sexuality concern, they will be seen for individual follow-up appointment which may be scheduled during their SR visits (***See Appendix 4 Page 124*** for a description of Management of Lymphedema Issues).

Criteria to classify patients as mild-moderate stream include the following:

- Impaired range of motion
- Diagnosis of lymphedema
- Pain, neuropathy, decreased strength
- DART score greater than 3 for more than 1 area
- Sexuality (incontinence, pain with intercourse)
- Return to work or school concerns (if patient has a job or program they are returning to)

3) **Moderate-High:** Patients who are classified in the moderate-high stream will require 1:1 follow-ups with various members of the inter-disciplinary team before they can be considered for enrollment in the SR program. During the comprehensive assessment, the inter-disciplinary team and physiatrist will screen and triage appropriateness of referral to TRI In-patient and/or Out-patient MSK Oncology Program for patients with high complexity issues. Once a patient has received the support required and is medically clear and appropriate to participate in SR program they can be triaged back into CRS program.

Criteria to classify patients as moderate-high stream include the following:

- DART score of 7-10 on 3 or more impairment areas
- Medical concerns that require more in-depth physiatrist assessment/intervention (i.e., severe pain of unknown etiology, rule out mets etc.)

- Direct therapy and referral to OHIP PT/OT, private PT/OT, TRI or CCAC warranted
- Consultative services not appropriate at this time.

IV. Research

A strong program of research is being introduced alongside the new rollout of the CRS program to help us evaluate and continue to improve the way we are providing services. Every patient that is referred to the CRS program will complete a baseline questionnaire package to assess quality of life, disability, mood, social and work functioning, physical activity, and symptoms. In addition every patient referred to the CRS program will also complete a series of clinical measures/metrics administered by an RKin: height, weight, waist circumference, blood pressure, heart rate, grip strength, 6 Minute Walk Test (6MWT), and balance. Patients who have agreed to participate in the SR program will complete these measures again in the last week of the program and again at 3 months-post program. ***See Appendix 5 Page 136*** for data collection time points for patients who enroll in SR. Patients who do not enroll in SR for a variety of reasons, will complete the measure 3 months post-d/c from the CRS program. ***See Appendix 6 Page 137*** for data collection time points for patients who are referred to our program but do not enter SR. These patients may or may not have follow-up appointments in our clinic; in this scenario it will be three months after their last point of contact with a professional on our team. Consent for use of these clinical tools for research purposes will be obtained.

Appendix 1: Revised Referral to Cancer Rehabilitation and Survivorship Program

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab

Cancer Rehabilitation & Survivorship
Fax: 416 946-4549
Phone: 416 946-4501 ext. 2363

MRN_____

Name_____

DOB _____

Tel: (home) _____ (cell) _____

Referral to Cancer Rehabilitation and Survivorship

Eligibility Requirements:

- Patient must be on active follow-up for cancer at Princess Margaret Cancer Centre
- Reason for referral ***must*** be cancer related

Cancer Diagnosis: _____ Date: _____

Form Completed by: _____ Other Information: _____

Staff Physician Name: _____ Requires Interpreter: Language: _____

Staff Physician Signature:_____

Reason for Referral

Physical

☐ Musculoskeletal (ROM, strength) _____

☐ Neurological _____

☐ Balance
☐ Deconditioning
☐ Exercise Contraindications/Precautions _____ _____ _____

☐ Lymphedema:
Location: _____
Active Cellulitis: Y N
Ruled out DVT: Y N

Functional

☐ Fatigue
☐ Difficulty with ADLs
☐ Return to Work/School
☐ Sexuality

Cognitive

☐ Brain Fog (memory, attention, concentration)

Other

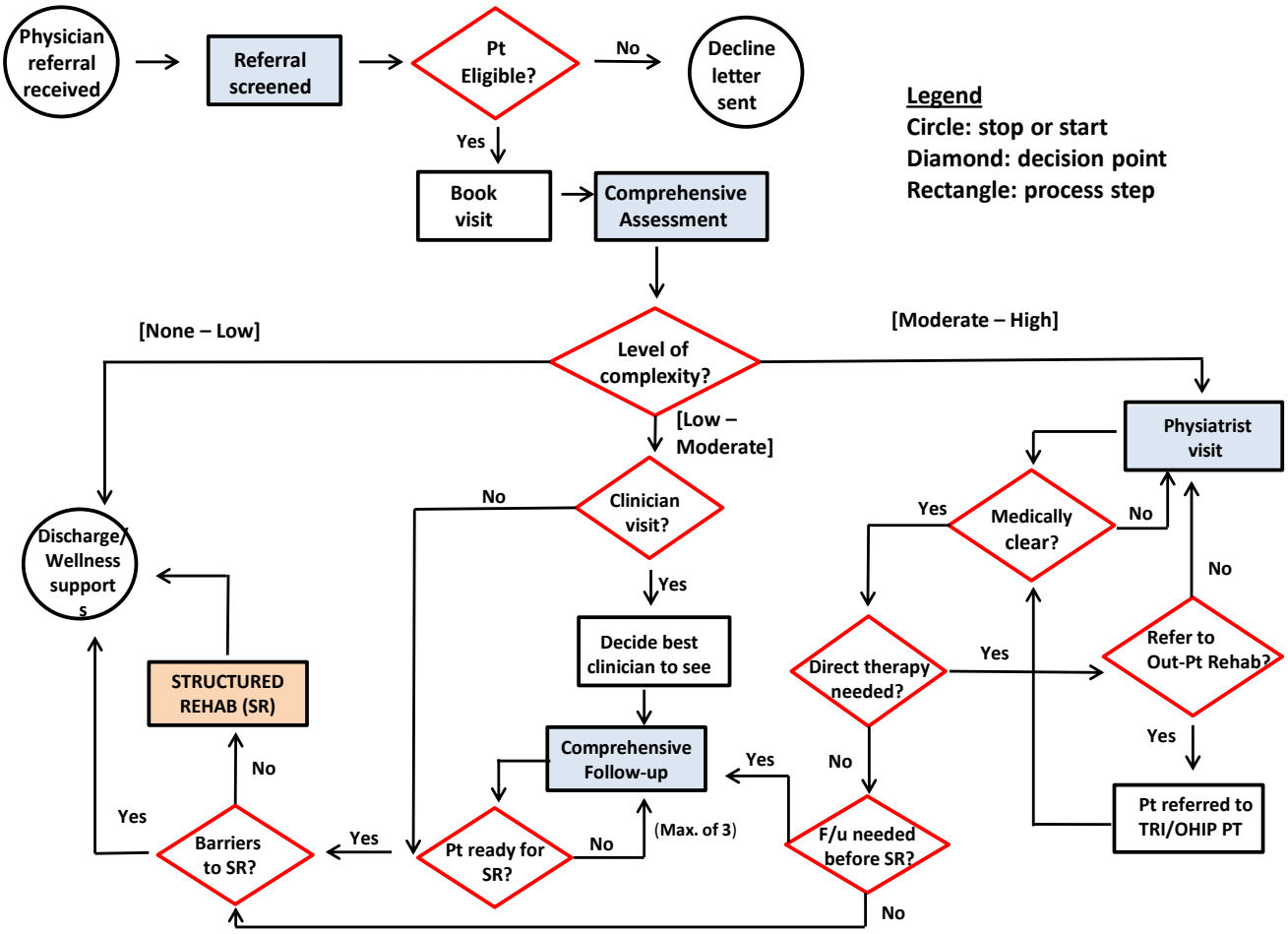
_____

_____

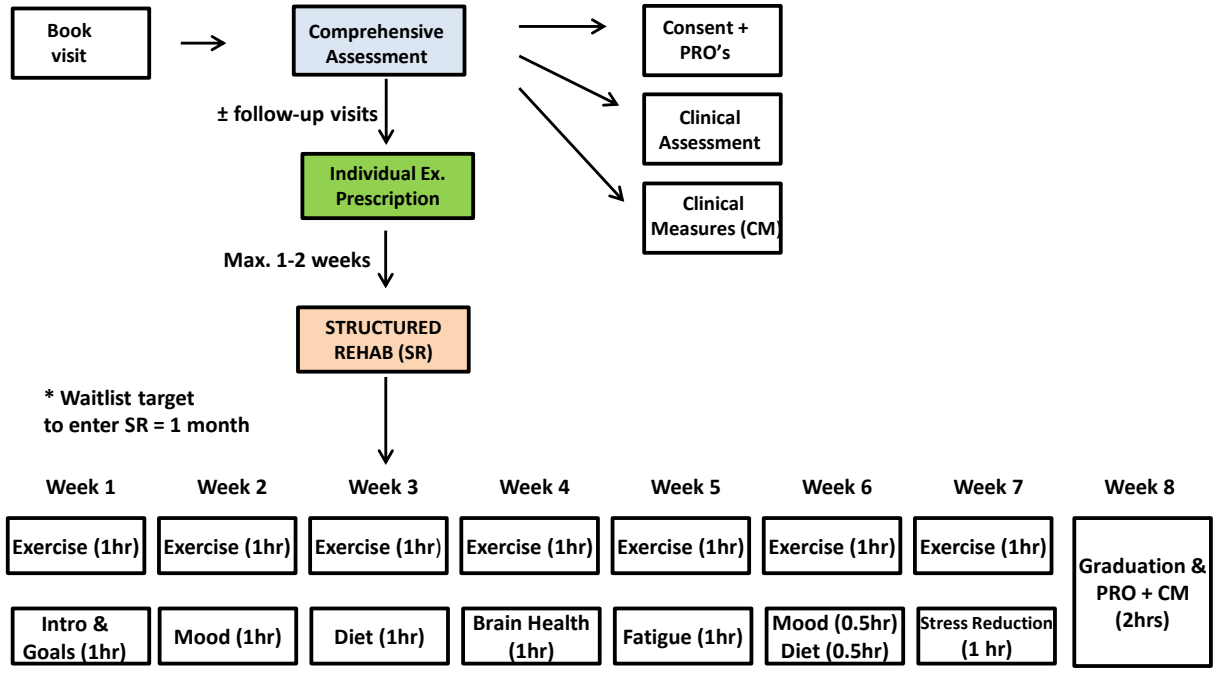
This referral includes a consultation from Dr. Eugene Chang (Physiatry) as needed. Patients will also be screened for nutrition and psychosocial issues as part of our comprehensive assessment. All services are provided by a transdisciplinary team (occupational therapy, physiotherapy, social work, massage therapy, kinesiologist, dietitian, psychology, neuropsychology and nursing).

Revision date May 2017

Appendix 2: High Level Process Map of Cancer Rehabilitation and Survivorship Program



Appendix 3: 8 Week, Group-based, Structured Rehab (SR) Program Curriculum



Appendix 4: Management of Lymphedema Issues

Lymphedema is a swelling of a body part caused by a build up of protein rich fluid in the tissues. The build up of fluid happens because of damage to your lymphatic system. Lymphedema can affect areas of your body that are not being properly drained because lymphatic nodes are missing or the lymphatic system is damaged. Lymphatic system can be damaged if you were treated for cancer by having:

- surgery that involved removal of lymph nodes
- radiation to lymph nodes or an area of your body where lymph nodes were removed.

All of the lymphedema seen in our program is secondary lymphedema, which occurs from damage of the lymphatic system secondary to cancer and its treatment. The overall risk of lymphedema for all cancers is reported to be 15.5% (Chang, S et al., 2010). Progressive lymphedema is complicated by recurrent infections, non-healing wounds, discomfort or pain, difficulty with daily tasks, emotional and social distress (Ridner, 2009; Ahmed 2008, Shih, 2009). Lymphedema is a chronic condition and can be successfully managed when properly diagnosed and treated.

Treatment of Lymphedema:

Review of the literature, International Lymphedema Framework consensus, National Lymphedema Network position statement on diagnosis and treatment of lymphedema all refer to Complete Decongestive Therapy. This is also sometimes called Combined, Complex or Comprehensive Decongestive Therapy. CDT is the main treatment for lymphedema. NLN position statement indicates experts who treat lymphedema consider CDT the "gold standard" of treatment (Mayrovitz, 2009; Szuba, 2000). CDT has been shown to be effective (Shah and Vicini, 2011; Mayrovitz, 2009).

Standards of care for lymphedema encompasses risk reduction, early detection, phase-I CDT in clinical setting and phase-II self-management at home (Mayrovitz, 2009). Risk reduction strategies and practices aims at: minimizing injury, chances of infection of at-risk limbs; reducing activities/behaviours linked to triggering lymphedema; promoting informed self-monitoring of changes suggestive of early-onset lymphedema; facilitating immediate medical evaluation if lymphedema is suspected. To facilitate early diagnosis, Lymphedema Awareness education sessions are offered once/month to patients and their caregiver who are at risk of developing lymphedema following cancer treatment.

Obesity is a risk factor for developing lymphedema or worsening lymphedema once it is diagnosed. Maintaining healthy weight is part of the education provided to patients. Patients are informed about importance of healthy lifestyle, getting back to exercise and healthy eating. Patients are encouraged to attend ELLICSR Kitchen cooking demonstrations and patient education sessions provided by the dietician on Healthy Eating During Breast Cancer Treatment, Eating Well After Breast Cancer Treatment, and What to Eat When You Don't Feel Like Eating. They are informed about exercise programs at UHN as well as the community such as, Taking Charge program, Healthy

Steps, H.E.A.L.Th program, Wellness and Exercise for Cancer Survivors (WE-Can) and other community exercise programs.

Goals of Phase-I (Reductive) CDT: to arrest disease progression; reduce lymphedema volume; prevent infections; restore mobility and ROM, train patients for life-long, self-management at home. Standard of care for Phase-I CDT includes Manual Lymph Drainage (MLD) to reduce edema volume), Short Stretch Compression Bandaging (SSCB) sustains reduced volume by decreasing trans-capillary ultrafiltration rate, decongestive exercises (influences lymph flow through body movement and transient muscle contraction especially when combined with SSCB), and skin care. Phase-I care concludes when plateau has been reached. Optimal outcome is a near normalization of the affected limb in terms of limb volume, tissue health, pain reduction and improved ROM and mobility.

In the CRS program patients who are referred for lymphedema will receive one-on-one skills coaching or teaching on lymphatic self-massage techniques, SSCB, skin care, exercise, maintaining a healthy lifestyle, wear and care of compression garments.

After Phase I, patients with lymphedema continue with Phase-II (maintenance), to help maintain gains made in Phase I longer term. Self-management at home includes: self MLD, skin care, self-examination to detect signs of infection, appropriate fitting and consistent wear and care of compression garments, bandages or other compression system, weight control and exercise and in some cases use of Intermittent Pneumatic Compression (IPC) device. Compression garments may be replaced every 4-6 months as necessary to optimize effectiveness.

Lymphedema Standards of Care for New Patients

- Encourage Manual Lymph Drainage in the community &/or have family member to learn massage/kinesiotaping/bandaging.
- High risk factors: post-op complications (seroma, infection, cellulitis), BMI> 30, AND, positive lymph nodes, radiation treatment especially in supraclavicular area, poor upper extremity function.

	Subclinical	**0-10% or 0-2 cm**	**10-20% or 2-4 cm**	**>20% or >4 cm**	**Breast/Trunk +/– arm**
Compression	20-30mmHg sleeve and gauntlet worn daily for 4 weeks; 1 mo FU, if decrease in limb volume, just for strenuous ex, flying and if there is heaviness or swelling	20-30 mmHg sleeve only for high risk patients (3 out of 6) to be worn for 4 wks; Just for ex/PA and flying after that	Compression garment (flat knit, custom) 20-30 mmHg. To be worn all day	1.Bandaging for 2-4 weeks followed by ADP for 30-40 mmHg flat knit, custom compression garments, if swelling still >20% 2. OR compression garments 30-40mmHg -- worn all day	Bra – assess current and discuss proper fit such as Bellisse bra; Start with bodywear or other light compression garments such as Spanx or active wear; ADP for sleeveless vest as last resort.
Lymphatic Self Massage		30 min sessions X 1 Follow-up as needed with patient attending group Skills Refresher Class	30 min sessions X 1 Follow-up as needed with patient attending group Skills Refresher Class	30 min sessions X 1 Follow-up as needed with patient attending group Skills Refresher Class	Discuss/offer kinesiotaping: 30 min sessions 1 week apart X 2
Bandaging coaching		NA - unless there is fibrosis or pitting edema	Only if treating fibrosis or pitting edema: 30 min sessions	30 min sessions 1 week apart X 2 Follow-up as needed	Large swollen breast

			1 week apart X 2 Follow-up as needed with bandaging review class	with bandaging review class	
Follow up appointment	Re-measurement in 1 mo, 3, 6	Re-measurement in 1 mo, 3 mo, 6 mo	Re-measurement in 1 mo following bandaging, 3 mo, 6 mo	Re-measurement in 2-4 weeks following bandaging, 3 mo (Garments ADP as a FU), 6 mo	Reassess after 1 mo of kinesiotaping or 3 mo, 6 mo

LYMPHEDEMA FOLLOW UP STANDARDS OF CARE
(In the absence of recurring/ongoing disease)

Increase since last visit	**Stable <2%**	**2%-7%**	**7%-15%**	**>15%**	**Trunk/Breast New or increased**
Compression	Continue present practice—encourage optimum use	Encourage optimum use of compression garments and times replacements (4-6 months)	Encourage bandaging until plateau is reached -- then compression garment. OR consider increasing level of compression. Encourage optimum use.	Strongly encourage bandaging until plateau is reached followed by optimum use of compression garments. Consider increasing	Discuss Bellisse Bra, compression vest, light compression garments such as Spanx or Joe Fresh
Lymphatic Self Massage And Scar Massage	Encourage to continue present practice	Offer massage review class Encourage optimum practice	Offer individual massage review Encourage optimum practice, MLD in the community	Offer individual massage review Encourage optimum practice, MLD in the community	Book individual massage review to instruct or review breast and or trunk massage MLD in the community
Bandaging coaching			Review bandaging x2 following massage—pt to come to clinic with bandages on and reapply bandages in clinic	Review bandaging x3 following massage—pt to come to clinic with bandages on and reapply bandages in clinic	Reassess after 1 month of kinesiotaping or 3 months without, 6 mo FU, annual
Decongestive exercises	Continue present practice—encourage optimum	Demonstrate decongestive exercises and encourage	Demonstrate decongestive exercises and encourage	Demonstrate decongestive exercises and encourage	Encourage decongestive exercises esp. deep breathing

	practice	optimum practice	optimum practice	optimum practice	
Follow up appointment	1 year; if stable at 2nd annual inform pt that she can call for **F/U appt for ADP** when fitter informs new ADP is needed	Re-measurement in 3-6 months	Re-measurement in 2 months (Garments ADP as a FU for bandaging or continue with bandaging)	Re-measurement in 2 months (Garments ADP as a FU for bandaging or continue with bandaging)	

NOTE: any patient can call at any time and request to attend Skills Refresher class (Thursdays 3-4)

Compression Bandaging:

Short-stretch compression bandaging is usually recommended whenever the swelling is new and/or changing. Bandages can also be used for a short period of time if you are being fitted for a new set of compression garments.

A compression garment (a sleeve, glove, gauntlet or vest) is recommended when the swelling stays the same for a period of time.

- Offer bandaging, if patient has fibrosis, pitting edema, >20% or > 4 cm difference, distorted limb shape, limb too large to fit compression garment, tissue thickening, fragile, damaged and ulcerated skin, pronounced skin folds, lymphorrhoea.
- Have to be able to offer 2 appointments one week apart– to teach/check bandaging technique (please see below)
- Contraindications for lymphatic compression bandage are severe arterial insufficiency, uncontrolled heart failure and severe peripheral sensitive neuropathy.
- Only short-stretch bandages are used (e.g. Comprilan).
- Patients and/or their caregivers are taught how to wrap the arm.
- If patients are unable to do the bandaging themselves, CCAC community nurses may be able to help and referrals are initiated.
- Daily activities and exercises are encouraged: bandages work best when they help support the action of the arm muscles pumping on the lymph vessels.

Frequency of bandage change

There is no evidence to indicate how frequency of bandage change affects speed of swelling reduction. Bandages should be reapplied when they become too loose to keep the level of compression in an effective range. Clinical experience recommends that during intensive treatment, bandages should be changed at least daily during the first week of treatment.

When tolerability of the bandages is optimum, then bandage frequency should be continuously adapted toward the best volume reduction and fewer bandage changes.

Duration of the bandaging

Daily bandaging is usually undertaken for one to four weeks of treatment. The duration should be adapted to the obtained swelling reduction. The reduction of the volume excess is mainly obtained during the first week of the treatment whatever the bandage and then slows.

Night application

During the initial phase, and when the objective is to have a reduction of swelling, bandages are usually kept on during the night. During long-term treatment, bandages are often used as a complement to compression garments and are recommended during the night.

Bandaging Standards

WEEK 1

Initial bandaging appointment—

- Practitioner applies bandages so patient will know how it feels
- Give written instructions for bandaging
- Instruct patient to remove before going to bed that day
- Encourage patient to practise daily until next bandaging appointment—do not leave on longer than 2 hours to start
- Return to clinic with bandages on for next appointment.

WEEK 2

First subsequent appointment—

- Assess quality of bandaging when patient arrives at clinic
- Have patient reapply bandages with coaching and supervision

If completely unable to manage or is choosing not to continue bandaging:

- Suggest compression garment as soon as possible (initiate ADP)

If patient is struggling but wants to continue and it appears that she will be able to master skill:

- Have patients reapply bandages with coaching from clinician

- Patient to return in one week for more assessment re skill and ability

If patient appears to have grasped the skill:

- Re-measure to see response to bandaging
- Have patient reapply bandages with clinician present
- Have patient return in two weeks for re-measurement to see if swelling has plateaued.

WEEK 4

If patient has not attained required skill level for therapeutic bandaging:

- Suggest compression as soon as possible (initiate ADP)

If patient appears to have grasped the skill:

- Re-measure to see if swelling has plateaued
- Transition to compression garment. Continue with bandaging until garment arrives.

Kinesio Taping

Kinesio taping is a treatment technique which uses a specialized elastic tape that is helpful in reducing localized swelling. The tape was developed by Dr. Kenzo Kase and has been used effectively for over 20 years.

The tape is cut into strips and applied to the skin in a wavelike pattern. The tape can be worn for 3 to 5 days before it needs to be replaced. The tape is light and waterproof and people are able to shower and swim with the tape on. Most people find the tape very comfortable but some individuals react to the adhesive on the tape.

Kinesio taping works with the lymphatic system in several ways. The tape helps lift the skin, and as a result, aids lymph drainage. The tape is also applied in a manner which directs lymph fluid away from an area of lymphedema. The tape acts on sensory receptors in the skin and can improve muscle contraction which can enhance lymph drainage and blood circulation.

Kinesio taping can be very helpful in the treatment of neck and trunk lymphedema. It can also be used in combination with self-massage. A trained lymphedema therapist can teach patients or their family members how to apply and remove the tape.

Consideration for Kinesiotape:

1. Patient has breast, trunk, chest or shoulder lymphedema
2. Patient is able to afford kinesiotape

3. Patient has help to apply it
4. Patient interested

Process:

Clinician recommending kinesiotape applies test strip.

Visit 1: If no allergy – apply kinesiotape, explain how it is done to the patient and family Provide them with a hand-out
Visit 2: In one week -- bring the patient a family member back and ask the family member to apply the tape, correct as needed
Visit 3: In one week -- re-assess the ability to apply the tape correctly and ask if patient finds it helps the swelling. Provide patient/family with contact info as to where to purchase the tape.

Exercise & Physical Activity: General Tips for Exercise

Exercise is an essential part of your treatment program for lymphedema. Exercise positively affects the lymphatic system through the influence of muscle contractions and deep breathing that lead to an increase in lymphatic fluid flow. It has been estimated that during exercise the rate of lymph fluid flow increases 15 times.

Flexibility, aerobic training, and strengthening in combination with compression bandaging or garment are known to benefit patients with lymphedema.
Exercise programs should be individualized based upon patient's health history, prior activity level, lifestyle, and exercise preferences.

Types of Exercise

I. Exercises that facilitate lymphatic flow (Decongestive Exercises)
Non-resistive active motions in sequence that mimics the MLD (manual lymphatic drainage) or lymphatic self-massage sequence: the patient starts deep breathing exercises to stimulate larger lymph vessels in the trunk. Progress to exercises of the neck and trunk, then moves to the muscles of the arm, forearm and then hand and down into the lower extremities.

II. Muscle Strengthening (Resistance Training)
Progressive resistive exercise (exercise performed with gradually increasing weight resistance) has been found to be beneficial in the treatment of lymphedema when used together with compression therapy. The primary goal of strength training and resistive exercise is to improve muscle power, stamina, tone, and preventing injuries. Improved muscle strength allows body to respond to every day demands while staying in balance.

III. Flexibility (Stretching)

The goal of flexibility exercises is to stretch soft tissues thereby minimizing tightness and the effects of scarring which can block lymph fluid flow. In addition, flexibility for normal movement is maintained and improved. Improved flexibility allows lymph vessel system to function better

IV. Cardiorespiratory Training

Aerobic exercise is beneficial for individuals with lymphedema. By improving cardiovascular fitness, overall health is improved. Increased deep respiration (deep breathing) enhances venous and lymphatic return. Improved cardio function allows for less fluctuation of blood volumes thereby decreasing need for lymph vessel system to respond to "emergency floods" (Langfield and McFarland, 2005). Exercises such as walking decrease side effects of chemotherapy and radiation (Mock, et al., 2001).

Please refer to Guideline 19-5 from Cancer Care Ontario (CCO) (June 20, 2015), A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO) Exercise for People with Cancer below:

Recommendations

1. People living with cancer can safely engage in moderate amounts of exercise (see Recommendation 3) while on active treatment or post completion of treatment.
2. Moderate amounts of exercise (see Recommendation 3) are recommended to improve the QoL, as well as the muscular and aerobic fitness of people living with cancer.
3. Clinicians should advise their patients to engage in exercise consistent with the recommendations outlined by the Canadian Society of Exercise Physiology and the American College of Sports Medicine. The recommended duration, frequency, and/or intensity are the following:
    - 150 minutes of moderate-intensity aerobic exercise spread over three to five days and resistance training at least two days per week;
    - Resistance sessions should involve major muscle groups two to three days per week (eight to 10 muscle groups, eight to 10 repetitions, two sets); and
    - Each session should include a warm up and cool down.
4. A pre-exercise assessment for all people living with cancer before starting an exercise intervention is recommended to evaluate for any effects of disease, treatments and/or comorbidities.
5. It is recommended, where possible, that people living with cancer exercise in a group or supervised setting as it may provide a superior benefit/outcome in QoL and muscular and aerobic fitness.
6. It is recommended, where possible, that people living with cancer perform exercise at a moderate intensity (three to six times the baseline resting state) on an ongoing basis as a part of their lifestyle so that improvements in QoL and muscular and aerobic fitness can be maintained for the long term.

Overall effects of exercise also improved mood and enjoyment of life, allows one to participate in life more fully including household tasks and recreational activities and reduces fatigue (Langfield and McFarland, 2005).

References:

Chang, S et al. (2010) Prospective assessment of postoperative complications and associated costs following inguinal lymph node dissection (ILND) in melanoma patients. *Ann Surg Oncol*, 17, 2764-72.

Ridner S. (2009) The PsychoSocial Impact of Lymphedema. *Lymphat Res Biol*, 7, 109–112.

Ahmed RJ. (2008) Lymphedema and Quality of Life in Breast Cancer. Survivors: The Iowa Women's Health Study. *Clin Oncol,* 26, 5689-5696.

Shih Y. (2009) Incidence,Treatment Costs, and Complications of Lymphedema After Breast Cancer Among Women of Working Age: A 2-Year Follow-Up Study. *JCO,* 27, 2007-2014.

Mayrovitz HN. (2009) The standard of care for lymphedema: current concepts and physiological considerations. *Lymphat Res Biol,* 7,101-8.

Szuba A. (2000) Decongestive lymphatic therapy for patients with cancer-related or primary lymphedema. *American Journal of Medicine.* 109, 296-300.

Silver JK, Baima J. (2013) Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. *American Journal of Physical Medicine & Rehabilitation,* 92:715-727.

Stout NL, Binkley JM, Schmitz KH, et al. (2012) A Prospective Surveillance Model for Rehabilitation for Women with Breast Cancer. *Cancer,* 2012 Apr 15; 118 (8 Suppl): 2191 – 2200.

Wagner EH, Austin BT, Von Korff M. (1996) Organizing care for patients with chronic illness. *Milbank Q,* 74(4): 511-544.

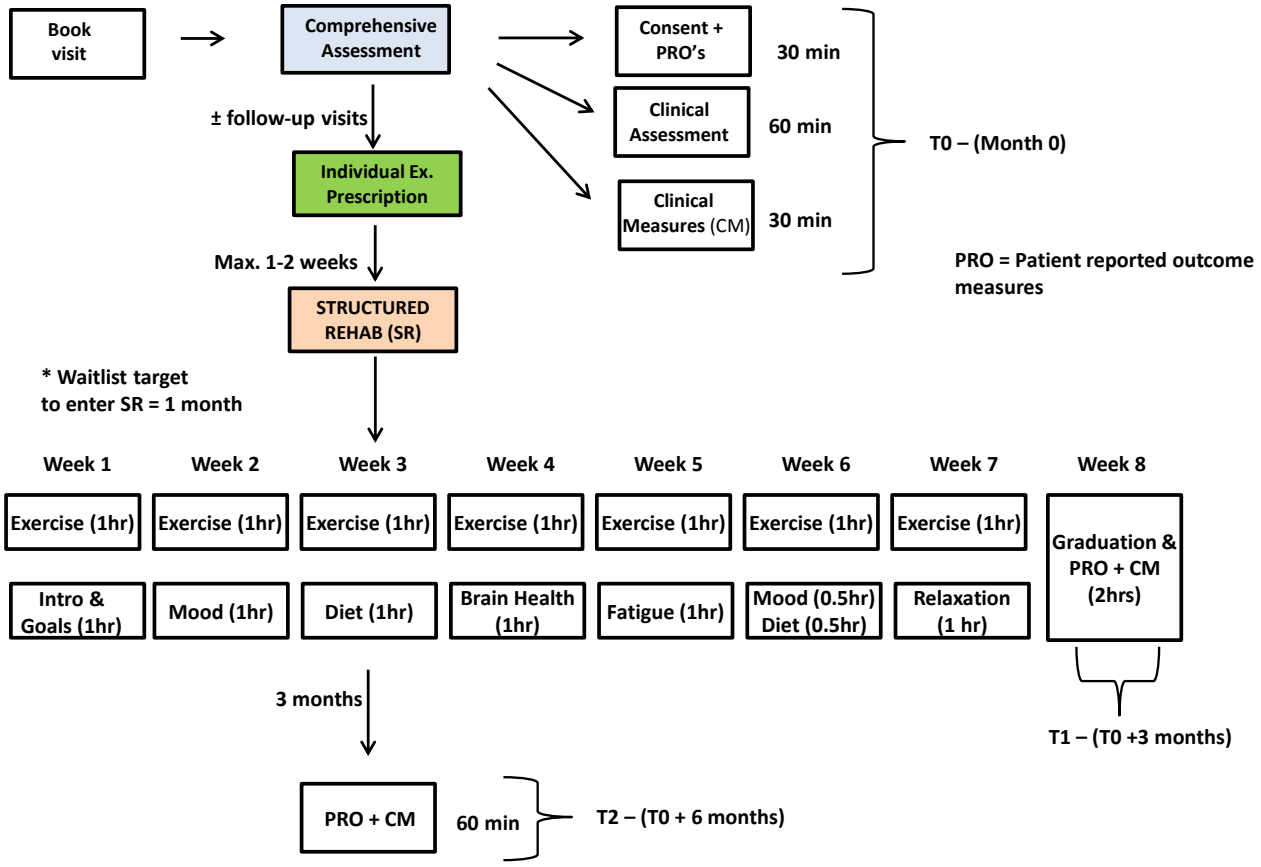
Shah C, Vicini F. (2011) Breast Cancer Related Lymphedema: Incidence rates, diagnostic techniques, optimal management and risk reduction strategies. *Int. J. Radiation Oncology Biol. Phy,* 81(4): 907 – 914.

Langfield S, McFarland J. (2005) Exercising with Lymphedema is a Balancing Act. *Lymphovenous News*, 8(3): 1-7.

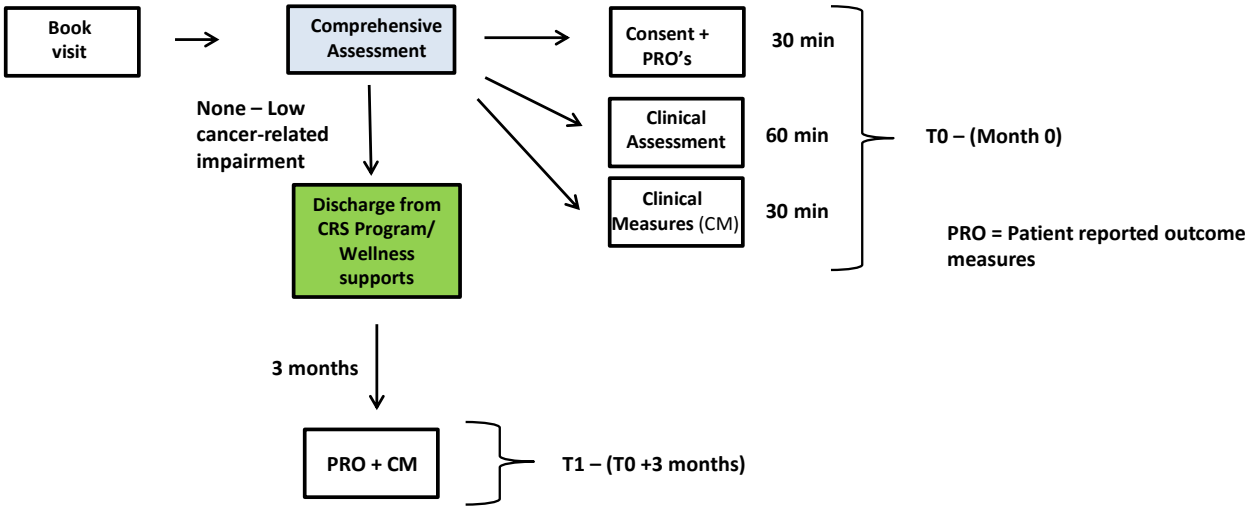
Mock V, Pickett M, Ropka M, Muscari Lin E, Stewart KJ, Rhodes VS, McDaniel R, Grimm PM, Krumm S, McCorkle R. (2001) Fatigue and Quality of Life Outcomes of Exercise during Cancer
Treatment. *Cancer Practice*, 9:3, 119-127.

Segal R, Zwaal C, Green E, Tomasone J, Loblaw A, Petrella T and the Exercise for People with Cancer Guideline Development Group. (2015) Guideline 19-5: A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO), Exercise for People with Cancer.

Appendix 5: Data collection time points for patients who enroll in Structured Rehab



Appendix 6: Data collection time points for patients who are referred to CRS Program but do not enter Structured Rebab



6.5 CLINICAL NUTRITION

(This section was updated February 2017)

A registered dietitian specializing in oncology is available to patients in the Breast Cancer site. **Please note** that patients with questions on healthy eating, who are eating well and have no nutrition impact symptoms, are at low nutrition risk and are seen in a group setting, not individually.

For patients at high and moderate nutrition risk, the dietitian can provide individual medical nutrition therapy. The dietitian assesses patients' nutritional status and develops an individualized care plan to meet patients' nutritional needs. Assessments include consideration of patients' comorbidities and medical history. Care plans are developed taking patients' cultural, social and financial circumstances into account. The dietitian also assesses any complementary nutrition therapies that patients are taking or considering and provides education on contraindications and potential for harm.

High nutrition risk patients are those with any of the following conditions, and are contacted within 2 working days of receipt of consultation:

- currently experiencing side effects related to disease/treatment resulting in significantly decreased intake x 2-3 days
- dehydration secondary to poor fluid intake, treatment side effects such as nausea, vomiting, diarrhea, dysphagia, mucositis, odynophagia etc.
- unintentional weight loss > 10 % of usual body weight in 6 months
- unintentional weight loss > 5 % of usual body weight in 1 month
- BMI < 18.5 undergoing active treatment

Patients at moderate nutritional risk are those with any of the following, and are contacted within 5 working days of receipt of consultation:

- anticipated side effects of treatment that will significantly reduce intake
- use of alternate/complementary therapy, i.e. megadosing of vitamins/minerals

Patients at low nutritional risk can be seen in a group setting at Princess Margaret or one-to-one at TWH.

At Princess Margaret, the two sessions offered for this low risk patient group are:

Healthy Eating During Breast Cancer Treatment

Topics include:

- healthy eating in preparation for treatment
- review of risk of weight gain during treatment and methods to reduce this risk
- coping with fatigue
- FAQs (frequently asked questions), such as ‘Should I take vitamins during treatment?’

Nutrition for Wellness – Healthy Eating After Breast Cancer Treatment

Topics include:

- healthy eating to reduce risk of recurrence
- healthy eating habits and patterns to reduce risk of weight gain
- wellness issues
- community resources

To refer **a high or moderate risk patient** to the Breast Cancer site dietitian, please call 416-946-4501 ext. 5343. Leave the patient's name, MRN and the reason for the referral.

To refer a patient to one of the Healthy Eating sessions, have them register by calling 416-946-4501 ext. 2363. Dates and times of the sessions are listed in the Patient Education calendar.

To refer a patient for **weight loss counselling**, print and complete the attached referral form and fax to TWH ambulatory care dietitians. Once the referral is faxed, inform the patient to contact the TWH ambulatory care dietitians to make an appointment. The number to call is 416-603-5800 ext. 5007.

TWH Dietitian Referral Form.pdf - A

6.6 CANCER GENETICS SUPPORTS PROGRAM

(This section was last updated February 2017)

Individuals and their families undergoing genetic testing or who have received genetic test results can be referred for support during decision-making around genetic testing or prophylactic surgery/ preventive options or to support them in their adjustment to test results.

Referrals can be made by patients directly or by health professionals to the Psychosocial Oncology Program

Contact information
PSYCHOSOCIAL ONCOLOGY Reception 416 946-4525
Fax referral requests for PSYCHOSOCIAL ONCOLOGY Clinicians to 416 946-2047

The Canadian Breast Cancer Foundation (formerly Willow) is a community-based organization that provides support to hereditary breast/ ovarian cancer families and can assist individuals undergoing testing or following their test results. CBCF has many excellent videos, self-management tools to assist individuals in making decisions and provides peer support services as well as updated information on hereditary cancer. CBCF's website is: http://support.cbcf.org/

7. POST CANCER TREATMENT FOLLOW-UP CARE

(This section was last updated December 2015)

Patients treated for cancer who are in their post treatment phase of care have unique needs which include both periodic surveillance to detect cancer recurrence, secondary primary cancers and, assessing for long/late term side effects of treatments.

In patients with early breast cancer (EBC) there is good evidence demonstrating similar outcomes when post cancer treatment follow-up care for survivors is provided by primary care practitioners in comparison to oncology specialty follow up care. A review of randomized controlled trials (RTCs) carried out from 1966 to 2004 confirmed that follow-up programs based on regular physical examination and annual mammography alone were as effective as more intense follow approaches (Rojas et al., 2004). In a study from the UK, care provided by primary care was not associated with an increase in time to diagnosis, anxiety or with deterioration in health-related quality of life (QOL) when compared to care in an acute care setting (Grunfeld et al., 1996).

More recent RCTs conducted at several regional cancer centres in Ontario, with women with EBC, 9-15 months post diagnosis and followed for 5 years confirmed there is no significant difference between specialist and family practitioner care when looking at detection of recurrence-related serious clinical events and health related QOL (Grunfeld et al., 2006).

NCCN Practice Guidelines (2010) recommend interval history and physical exam (including clinical breast exam) at minimum every 6 months for 5 years then annually for breast cancer survivors.

Mammography is recommended every 12 months or as determined by radiology. More information on surveillance MRIs and other imaging tests can be found in the Screening and Early Detection section of this document (p. 11-13).

Female breast cancer survivors on Tamoxifen require a gynecologic assessment every 3 years with PAP smear if uterus is present. Unusual vaginal bleeding should be clinically assessed and investigated as needed.

Women on aromatase inhibitors or who have experienced ovarian failure secondary to treatment should have monitoring of bone health with bone mineral density testing at baseline and periodically thereafter. The use of estrogen, progesterone, or selective estrogen receptor modulators to treat osteoporosis or low bone mass in women with breast cancer is discouraged. The use of bisphosphonates is generally the preferred intervention to improve bone mineral density. Management of bone health and therapy can be safely managed by primary care providers and/or osteoporosis/bone health clinics if available. Breast cancer survivors treated with a bisphosphonate should undergo an annual dental examination.

For bone health, 1000-1200 mg of Calcium/day and Vitamin D 1000IU /day (especially during fall and winter) are recommended. Calcium is best ingested through diet. Supplemental calcium should be adjusted based on daily calcium intake obtained through diet. For additional information on Vitamin D and breast cancer, see Risk Reduction Strategies Lifestyle Changes section on pg. 8.

Most cancer survivors are over the age of 60 and often have a variety of other health problems associated with aging. Screening for secondary cancers and other chronic diseases is important in cancer survivorship and should be continued by primary care practitioners. Sexually active women between the age of 21 years and 70 years need to have a PAP test every 3 years. Colon cancer screening starts at age of 50 years and involves a Fecal Occult Blood Test (FOBT) every 2 years until the age of 74 years. Colonoscopy every 10 years or sigmoidoscopy every 5 years are also available if recommended. For cardiac health, blood pressure should be measured at all appropriate visits and blood lipids should be evaluated every 1-5 years in postmenopausal women over the age of 50 years and men after the age of 40 years. Cancer survivors over age 55 (male) or 60 (female) who received systemic therapy involving anthracyclines, Trastuzumab, left chest radiation theray and/or aromatase inhibitors and have other risk factors for cardiac disease (hypertension, diabetes, dyslipidemia, smoking, family history of cardiac disease) could benefit from a specialized cardiology risk assessment. Screening for diabetes requires a blood glucose level every 3 years in people aged over 40 years.

The After Cancer Treatment Transition Clinic (ACTT) is a dedicated follow-up clinic for patients who finished their primary cancer treatment. Patients receive ongoing screening for recurrence and post treatment side effects, as well as education about screening for other cancers and chronic diseases. The clinic was established as a partnership between Princess Margaret Cancer Centre and Women's College Hospital and it is located at Women's College Hospital, 5th floor. Patients who completed active treatment for breast cancer stage 1-3 (excepting hormone therapy) at Princess Margaret Cancer Centre are eligible to be transferred to ACTT. A referral from an oncologist at Princess Margaret is needed. After reaching the 5 years post treatment landmark, recurrence free cancer survivors are transitioned from ACTT back to their family health practitioners with specific recommendations for ongoing screening and surveillance.

Reference:

Grunfeld E, Levine MN, Julian JA, et al. Randomized trial of long-term follow-up for early-stage breast cancer: a comparison of family physician versus specialist care. J Clin Oncol. 2006 Feb 20;24(6):848-55. Epub 2006 Jan 17.

Grunfeld E, Mant D, Yudkin P, et al. Routine follow-up of breast cancer in primary care: a randomised trial. Br Med J 1996; 313:665–669.

NCCN: Clinical Practice Guidelines in Oncology Breast Cancer, 2010

Rojas MP, Telaro E, Russo A, et al. Follow-up strategies for women treated for early breast cancer. Cochrane Database Syst Rev. 2005 Jan 25;(1):CD001768.