LRCP MANAGEMENT GUIDELINES
BREAST DISEASE SITE GROUP

CHAIR: Dr. T. Vandenberg (Medical Oncology)

PHYSICIAN MEMBERS

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RADIOLOGY
Dr. Anat Kornecki

GENETICS
Dr. J. Jung

RECONSTRUCTIVE PLASTIC SURG.

Stage II guidelines        1988 (January) Updated 2000 (June)
Complete guidelines, 1st Edition 1990 (March) Updated 2002 (June)
Updated                     1992 (February) Updated 2005 (June)
Updated                     1993 (May) Updated 2006 (June)
Updated                     1993 (October) Updated 2007 (June)
Updated                     1995 (December) Updated 2010 (Nov)
Updated                     1996 (May) Updated 2011 (Oct)
Updated                     1998 (March)
Updated                     1998 (November)
Updated                     1999 (January)
PREAMBLE
The management of patients with breast cancer is complex and involves input from many health care disciplines. In the last decade there have been many changes in the primary management, with increasing use of breast conserving procedures and systemic adjuvant therapy.

These guidelines reflect treatment policies adopted by the London Regional Cancer Program, and current clinical trials activity in this disease site. They will be revised and updated as appropriate. They have been devised as a working manual for use within the LRCP, and as a source of information to physicians and other health care professionals within our referral area of Southwestern Ontario. While ensuring a uniform high standard of patient care, they do not preclude adaptation of treatment to meet individual patient needs or unusual clinical circumstances.

Management is described under the TNM classification.

EARLY BREAST CANCER TRIAGE ALGORITHM (May 2011)

Due to the complexity of disease management and the importance of being certain that all patients with breast cancer have access to radiation and medical oncologists to discuss treatment options, all patients as noted below will be triaged to the appropriate specialty.

<table>
<thead>
<tr>
<th>EARLY BREAST CANCER TRIAGE ALGORITHM*</th>
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<tr>
<td>STAGE</td>
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<td>Any T4, 3</td>
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<td>Clinical or Path N+ (including Nmic)</td>
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<td>T2/N0</td>
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<tr>
<td>T1cN0 Intermediate/High Grade</td>
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<td>T1b any grade and LVI+</td>
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<td>T1b high grade</td>
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<td>Any T and HER2+ or TN</td>
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<td>Any lumpectomy</td>
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<td>Any positive or close (&lt;2mm) margins</td>
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<td>Any DCIS with lumpectomy</td>
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Exceptions to disposition may be considered due to medical co-morbidities/extreme age

*All referrals to MO or RO go through New patient referral at LRCP

Detailed information regarding techniques for staging, histological grading, breast imaging, surgery, radiotherapy, chemotherapy/hormone therapy is provided in 7 appendices, which will not be circulated outside the LRCP other than to members of the breast team (except on request). Appendix 8 and 9 will be included.

Appendix 1: TNM Staging
Appendix 2: Pathology
Appendix 3: Breast Imaging
Appendix 4: Surgery
Appendix 5: Radiotherapy
MENOPAUSAL STATUS

Determination of menopausal status is critical when using aromatase inhibitors (AIs). The definition of postmenopausal status is not clear. For three aromatase inhibitor adjuvant trials published to date, menopausal status is defined in differing ways as follows:

- **ATAC:** Bilateral oophorectomy; greater than 60 years of age; 45-59 years of age with intact uterus and amenorrheic for at least 12 months; or for those amenorrheic less than 12 months follicle stimulating hormone (FSH) concentrations within the postmenopausal range.

- **IES:** greater than or equal to 55 years of age with amenorrhea for more than two years, or amenorrhea for more than one year at the time of diagnosis.

- **MA.17:** No explicit definition, but eligibility criteria were, greater than or equal to 50 years of age; less than 50 years of age but postmenopausal at tamoxifen initiation; less than 50 years of age but bilateral oophorectomy; less than 50 years of age at the start of tamoxifen but became amenorrheic during chemotherapy or treatment with tamoxifen; or postmenopausal levels of FSH or LH.

Determination of menopausal status following adjuvant chemotherapy can be problematic, as temporary cessation of menstruation may occur for two or more years and resume. Cessation of menstruation also does not necessarily mean cessation of ovarian function. Ovarian function may interfere with the efficacy of AIs. Until a more accurate method of determining menopausal status can be found, it is recommended that the definitions from these trials be used to determine menopausal status when using AIs as initial adjuvant therapy, after two or three years of tamoxifen or as extended adjuvant therapy after five years of tamoxifen. Tamoxifen can interfere with functional assessment of menopausal status.

If uncertain regarding the postmenopausal status of a patient on tamoxifen, functional assessment should be measured by FSH/LH and estradiol levels and transvaginal ultrasound at baseline and every 3 months for one year. Functional assessment should be performed in all situations where menopausal status is not clear.

RECEPTOR STATUS

For all patients presenting with early stage breast cancer, in whom tumour ER/PR status has not been determined by the biochemical method, immunocytochemical determination of ER is recommended if this will influence management. All first excisions will have ER and PR as well as HER2/neu. Pathologic criteria for positive receptor includes greater than or equal to 1% nuclear staining for estrogen or progesterone receptor.

HER2/neu will be done on all patients with metastases who do not have prior known HER2 status and on all patients with early invasive breast cancer one mm or greater in size. HER2 status may also be requested on metastatic lesions at the discretion of a medical oncologist.
Tis
NONINVASIVE CARCINOMA

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

INVESTIGATIONS

**Biopsy:** for histopathology
(see Surgery Appendix 4)
pathology slides/blocks should be reviewed at one of the London teaching hospitals if it affects treatment decision

**Assessment:** history and physical, biochemical profile, bilateral mammography (preferably before surgery) chest radiograph. Bone and liver imaging are not required.

LOCAL THERAPY

**Surgery**
(1) Partial mastectomy (or lumpectomy)
(2) Simple mastectomy

Patients with intraductal tumor at or within 0.2 cm of the margins of resection should have surgical revision.

**Radiotherapy**
(a) **Breast irradiation**
Patients with completely resected DCIS should be offered breast radiation. Older frailer patients with small (less than 1 cm), low grade DCIS excised with adequate margins (1-2 cm), may not need radiation. **Patients with DCIS should be considered for the NCIC MA-33 protocol randomizing patients between a radiation boost and standard treatment.**

(b) **Chest wall irradiation**
This is indicated if there are positive or close (less than 2 mm) margins of resection after mastectomy (see Radiotherapy Appendix 5).

(c) **Regional nodal irradiation**
No indications.

**Mastectomy versus lumpectomy + breast irradiation**
With the trend towards less radical surgery for invasive breast cancer, it seems logical to consider breast conserving procedures for noninvasive cancer. For intraductal cancer there are data from several retrospective studies, as well as a subset of patients in the NSABP06 trial, suggesting that lumpectomy plus breast irradiation yields equivalent results to simple mastectomy. This is confirmed by the recently published results of the NSABP-17 trial. These options may be discussed with the individual patient, however, mastectomy is recommended for patients with pathologic evidence of extensive (ie. 4-5 cm or more) high grade (comedo) DCIS especially with close or with pathologic positive margins.

**Boost irradiation**
There are no published DCIS studies where an additional boost dose was given to the tumour bed, and no study has compared breast radiation alone to breast radiation plus a boost in DCIS. Such studies have, however, been done in patients with invasive breast cancer. There have been four randomized trials in patients with resectable invasive disease, comparing whole...
breast irradiation to whole breast radiation plus a boost to the tumour bed. Three of these studies were in patients with microscopically clear resection margins, and the fourth included some patients with positive resection margins. Three of the studies showed a statistically significant decrease in local recurrence with the addition of the boost and this technique is commonly used in patients with invasive breast cancer. The NCIC MA-33 study will address the question of using a boost in patients after lumpectomy for DCIS.

**Lobular carcinoma in situ**
Management of this lesion has varied widely from bilateral mastectomy to increased surveillance. LCIS tends to be multifocal, multicentric and bilateral. Women with LCIS have a 9-fold relative risk of developing subsequent invasive breast carcinoma. The risk is the same for both breasts. The absolute risk of developing invasive breast cancer after a biopsy diagnosis of LCIS is 17% at 15 years. The presence of a family history of breast cancer in a sister, mother or daughter does not appear to further affect the risk.

Initially a conservative approach is recommended ie. careful clinical and mammographic followup. In particularly anxious patients the option of bilateral mastectomy plus or minus reconstruction may be discussed. There is no data on the role of breast irradiation.

**SYSTEMIC THERAPY**

The only reported clinical trial to address this topic is the NSABP B-24 trial (Lancet 1999; 353(169): 1993-2000). Updated results on the 1804 women enrolled in this study are presented in Semin Oncol 2001; 28(4): 400-418. The absolute benefit in improvement of any breast cancer recurrence by the addition of tamoxifen was 6.9% (16.9% recurrence in controls versus 10% in the tamoxifen group). No differences in survival have been reported. In a multivariate analysis of this study, age less than 50 years, comedonecrosis, positive margins, and clinical (versus mammographic) presentation were significantly associated with increased risk of breast cancer recurrence (relative risks 2.17, 1.82, 1.84, and 1.90). While the B-17 and EORTC trials only tested the value of radiation in addition to conservative surgery, multivariate analyses of these studies identified comedonecrosis and positive margins (B-17; relative risks greater than 2) and age 40 or younger, positive margins, clinical presentation, and solid or cribriform histology (EORTC; relative risks 2.14, 2.07, 1.8, and 2.67) to be associated with increased recurrence (J Clin Oncol 1998; 16: 441-452, Lancet 2000; 366(9203): 528-533).

Both the Canadian National Practice Guideline and the Cancer Care Ontario Guideline for DCIS do not recommend routinely placing women with DCIS on tamoxifen. Instead, they recommend that the benefits and risks from tamoxifen be discussed with these women and that their other risk factors for breast cancer development be taken into account (i.e. assess the risk/benefit of tamoxifen as a breast cancer prevention agent). Randomized studies suggest that women who are most likely to have a positive benefit/risk ratio with tamoxifen are those who are less than 50 years of age or who have positive resection margins and refuse further surgery. Women who have a contraindication to radiation or who refuse this treatment but still want to avoid mastectomy should also be considered for tamoxifen therapy.

Fisher et al has examined the risks of breast cancer development in women enrolled on B-17 and B-24 and compared these risks with that of women with LCIS or ADH in the P-1 prevention study (Semin Oncol 2001; 28(4): 400-418). Women with DCIS managed by lumpectomy alone in B-17 developed invasive breast cancer at a rate of 125 per thousand women per five years (12.5% per five years or estimated 25% at ten years). This risk is, by itself, not insignificant and approximately twice the risk of women with LCIS. The addition of breast radiation reduced this risk of invasive breast cancer only to the level of women with LCIS (just over 60 per thousand...
per five years or 6 % per five years). At seven years follow-up in the B-24 trial, tamoxifen reduced the risk of both invasive and DCIS recurrences. While the absolute benefit is small at 7 years, the curves are still diverging, suggesting a larger absolute benefit over time. A similar effect was noted in B-17, from the addition of radiation, with a 19.5 % absolute benefit (47.7 % versus 28.2%) in reduction of any breast recurrence at 12 years versus a smaller absolute benefit in the initial report. If one estimates a 40 to 50 % further reduction in any breast recurrence by the addition of tamoxifen to breast radiation, then the projected absolute benefit at 12 years of follow-up on B-24 would be 7.8 to 9.75 %.

It is not known if there are subsets of women with DCIS who could be managed by local surgery with or without radiation and without tamoxifen. Silverstein et al reported that women with DCIS resected with more than 1 cm margins did well without any additional treatment (N Engl J Med 1999; 340: 1455-1461). Pathology techniques in this study were extremely detailed and not available at most cancer centres. A more recent UKCCCR trial (Lancet. 2003;362(9378):95-102) randomized over 1700 patients between radiation and no radiation and tamoxifen and no tamoxifen in a 2x2 design. Of the 523 patients who received radiation and tamoxifen, no difference was observed in the incidence of subsequent invasive cancer or DCIS. In the 1,053 patients who did not receive radiation, the only difference was seen in the incidence of the combination of ipsilateral and contralateral DCIS in the tamoxifen group. Furthermore, the RTOG has an ongoing study of women with low risk DCIS based on size less than 2.5 cm, low nuclear grade, and 1 cm margins, testing the value of tamoxifen and of radiation.

The MAP.3 trial (N Engl J Med 2011; 364:2381-91) randomized postmenopausal women with one or more of the following risk factors: Gail score >1.66%, prior atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS) or ductal carcinoma in situ (DCIS) with mastectomy, age > 60 to placebo (P) or exemestane (E). The annual incidence rate of IBC or DCIS was 0.35% for E and 0.77% for P (HR=0.47;95% CI 0.27-0.79; p = 0.004) based on 64 IBCs or DCISs (20E/44P). Clinical bone fractures, osteoporosis, hypercholesterolemia or cardiovascular events were equal in both arms. No clinically meaningful differences in QOL were detected.

Interprative Summary:

This is the first trial evaluating an aromatase inhibitor/inactivator for breast cancer prevention. E, a steroidal inactivator, was chosen based on its bone-sparing anabolic effects, compared to the non-steroidal aromatase inhibitors, letrozole and anastrozole. Its strengths include a blinded, placebo-controlled design, rapid recruitment, a simple method to calculate risk (www.cancer.gov/bcrisktool) and monitoring for toxicity. For those concerned about bone effects, the MA.27 bone sub-study comparing adjuvant anastrozole v E provides some reassurance. It is practice changing in that it offers an alternative to tamoxifen and raloxifene with less toxicity. There are some weaknesses including short-term follow up. Also, women on placebo will be offered the option of cross-over to E which will prevent longer term assessment for efficacy and toxicity. We do not know the ideal duration of therapy. The benefits of E for breast cancer prevention are similar to that for Rosuvistatin (Number needed to treat after five years 26 v 25 for Rosuvistatin in Jupiter trial) for patients at high risk for major cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes). Since primary prevention has significantly reduced cardiovascular deaths, one could argue that now is the time to discuss the E option with high risk patients as defined by this trial. Women with BRCA positive status were not eligible for this trial and should be considered separately. This drug is also contraindicated in pre or perimenopausal women. There are several challenges. Many women will be reluctant to take E, partly
because early breast cancer still has a very good prognosis, and there is no discernable impact on mortality. Other important issues will be long-term compliance, particularly considering the poor results with adjuvant therapy for those with a prior breast cancer where there is a much larger benefit. Another is cost when we are already spending a tremendous amount on health care and have to make choices between existing effective treatments. However, for some the reduction in breast cancer may still be important. The IBIS II trial testing anastrazole vs placebo will provide validation for MA.27. The NSABP is also conducting a trial of letrozole v tamoxifen for women with DCIS. Because the vast majority will not develop breast cancer, it would be helpful if higher risk subgroups could be identified and that a predictive marker for effectiveness could be found. One possible marker could be changes in breast density on mammography. Other options for prevention, in view of the association with increased breast cancer risk, should also be considered. These include exercise, weight control and reduction in alcohol intake. Even though the effectiveness of these interventions has not yet been proven, there is a strong biological rationale and these all carry health benefits beyond cancer prevention.

A balanced discussion of breast cancer prevention should be the role of family physician, based on the risks, benefits and underlying medical condition of individual patients. Oncologists in Canada will have an important role in providing educational support.

Postmenopausal women with DCIS could be offered the option of exemestane after a full discussion of the risks and benefits as well as alternative strategies as discussed above.

Premenopausal women with DCIS are at increased risk of breast cancer development. Women should be informed of clinical trials at the LRCP for DCIS. In women who receive breast conservation and radiation, the role of Tamoxifen would be reasonable in the following subgroups:

1. women younger than 50 years of age
2. women with positive surgical margins or when re-excision is not an option.
3. women with comedonecrosis
4. women with clinical presentation (palpable lump, nipple discharge)
5. women with ADH, LCIS, or first degree relatives with breast cancer.

In women who have had a mastectomy, the role of tamoxifen in reducing contralateral breast cancer should be discussed with each woman, weighing the risks and benefits. Tamoxifen would be reasonable for subgroups 1, 2, and 5 above.

SUGGESTED FOLLOWUP

Time interval
Year 1-5: 4-6 months

Followup by GP/surgeon for systemic therapy patients will generally occur after initiation of adjuvant hormonal therapy. Exceptions may occur for patients on clinical trials. Patients could also be followed by trained nurse practitioners.

FOLLOW-UP INVESTIGATIONS

Mammogram yearly (discretionary age greater than 70, depending on general medical condition).
T1, T2 or T3 N0M0 AXILLARY NODE NEGATIVE

INVESTIGATIONS

Biopsy: for histopathology and ER/PR status or HER2/neu status (see Surgery Appendix 4)

Assessment: history and physical, bilateral mammogram, breast and axillary ultrasound and core needle biopsy. Staging is not required for these stage patients pre-operatively unless distant disease is suspected.

LOCAL THERAPY

Surgery
Types of surgery
(1) Partial mastectomy (or lumpectomy) sentinel node biopsy for clinically lymph node negative patients, and axillary node dissection for suspected lymph node positive patients. Note that sentinel lymph node biopsy is the standard for axillary staging in early breast cancer patients.
(2) Simple mastectomy and sentinel node biopsy or axillary dissection as above

The indications and techniques for these procedures are outlined in detail (Surgery Appendix 4). Non-palpable tumors may be removed using needle localization.

Partial mastectomy (=lumpectomy) versus total mastectomy and sentinel lymph node biopsy
The ratio of the size of tumor to that of the breast is important in determining the procedure used. In general tumors less than 4 cms may be removed with breast conservation with good cosmetic results. Partial mastectomy may be performed for tumors underneath the nipple, but the whole nipple should be removed in continuity, with later reconstruction. Two or more infiltrating cancers or associated extensive intraductal carcinoma component with margin involvement, are usually indications for mastectomy. All resected margins should be histologically free of tumor. A minimum margin of 2-5 mm is preferred (see Surgery Appendix 4 for further details).

Surgical clips placed within the margins of the lumpectomy bed at the time of surgery greatly facilitate the adjuvant radiation planning. Negative pathological margins are recommended. Recommendations for close surgical margins are not currently well defined but will be forthcoming in the next few years (see Surgery Appendix 4 for further details).

N.B. Patients with positive resection margin(s) after lumpectomy should be referred back for further surgery, mastectomy or further local resection.

Axillary node assessment
Currently sentinel lymph node biopsy (SLNB) is recommended as the standard of care. Axillary node dissection is recommended for all patients with early stage breast cancer if SLNB cannot be done or is clinically or sonographically positive on pre-operative assessment. In those cases, a. full dissection of level 1 & 2 nodes is indicated, even if the first node identified is positive. Most clinical trials involving patients with T1 or T2 N0 or N1 breast cancer require identification of a minimum of 4 nodes in the axillary contents.

Pathological examination of all nodes in the axillary specimen is mandatory. Prognosis can be related to the number of positive nodes, and in some studies to the total number of nodes identified as the risk of missing occult nodal positivity relates to the number of nodes removed (see Surgery Appendix 4 for further details).
• All patients with macrometastases should be referred to radiation and medical oncology.

SENTINEL NODE BIOPSY IN THE MANAGEMENT & TREATMENT OF BREAST CANCER
(See Surgical Appendix 4)

Radiotherapy (see Radiotherapy Appendix 5 for details)
The following are contraindications to whole breast radiation: 1st/2nd trimester of pregnancy, history of prior radiation to the breast region (eg., HD), history of collagen vascular disease, diffuse indeterminate or malignant appearing calcifications on mammography.

(a) Breast irradiation
All node negative patients undergoing lumpectomy should receive whole breast irradiation to reduce the incidence of local recurrence. It is supported by the evidence from several large RCT’s (OCOG, NSABP-B6, Uppsala-Orebro, Milan). Whole breast irradiation has been used for decades, however there has been interest in the use of accelerated partial breast radiation (APBI). It has a shorter overall treatment time (typically one week) and decreases the dose of radiation to uninvolved breast tissue and adjacent organs. There are theoretical disadvantages such as not treating occult foci elsewhere in the breast and there are several multicenter randomized clinical trials comparing whole breast irradiation to APBI. Outside the framework of clinical trials, the use of APBI has rapidly increased and a consensus document was developed on APBI. Based on this report, APBI may be offered to women in the “suitable” group:

• Age ≥60
• BRCA 1 or 2 negative
• Tumor size ≤2cm
• Margins of at least 2mm
• Invasive ductal or other favourable histology
• Any grade
• LVSI negative
• ER/PR +
• Unifocal and clinically unicentric
• EIC negative
• SLNB or AND done and pN0 (i+ or i-)

Other patients are strongly encouraged to consider enrollment in ongoing clinical trials of APBI.

Certain patients should receive a boost to the tumor bed:
♦ Patients with close margins (less than 2 mm).
♦ Patients with positive margins who decline further surgery.
♦ In patients with negative margins, a boost will be used in patients age less than 40 and considered in selected patients aged 40-50 where it has been shown to decrease local recurrence significantly (NEJM 2001; 345: 1378-87). If systemic adjuvant chemotherapy is given, radiation will be delayed until the end of chemotherapy (usually 6 months) however the optimum sequencing of therapy remains unknown (Bellon J JCO Mar 2005 and of NEJM 1996; 334: 1356-61).

(b) Chest wall irradiation
This is indicated for patients who have extension to the chest wall, positive/close (less than 2 mm) margins of resection after mastectomy. It will be generally followed by a boost phase.

(c) Regional node irradiation
In general, there is no indication for routine regional nodal radiation in this group. However, patients with LVI positive disease in combination with age younger than 50, premenopausal status, grade III, or ER negative disease may be considered for nodal irradiation (Truong PT. J Am Coll Surg 2005 Jun; 200(6): 912-21).

(d) Partial breast irradiation (including Brachytherapy)
May be considered for patients that are considered "suitable" by the ASTRO Consensus Statement (Smith BD, IJROBP 2009) or in the setting of a clinical trial.

SYSTEMIC THERAPY

The use of adjuvant systemic therapy for patients with axillary node negative breast cancer is based on information from the Early Breast Cancer Trialist’s Collaborative Group (EBCTCG) meta-analyses 1995 of the use of tamoxifen (Lancet 1998; 351: 1451), and chemotherapy (Lancet 1998; 352: 930) These results are now updated at fifteen years follow up (Lancet 2005; 365:1687-1717). For women with high-risk node negative or node positive breast cancer, anthracycline chemotherapy should be considered unless there are contraindications such as poor cardiac function. Six months of anthracycline-based chemotherapy reduces annual breast cancer death rate by 38% for women less than age 50 and by about 20% for those age 50-69, irrespective of the use of tamoxifen, ER status or nodal status. Used with tamoxifen in receptor positive women, the mortality reductions approach 57% and 45% respectively. Other information resources include National guidelines (CMAJ 1998; 158(3): 543, and updated CMAJ 2001; 164: 213, and http://www.cmaj.ca/cmaj/ guidelines.htm), and Cancer Care Ontario Practice Guidelines Initiative, PG 1.8: Adjuvant Systemic Therapy for Node Negative Breast Cancer (http://www.cancercare.on.ca/ccopgi).

Patients are divided into risk categories based on tumor size, grade and the presence of lymphovascular invasion (LVI). Menopausal status, age and ER/PR status are considered in determining the type of systemic therapy recommended.

Patients are grouped into three risk categories.

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<th>RISK STATUS</th>
<th>DESCRIPTION</th>
<th>TREATMENT</th>
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| Low Risk     | - Tumour size less than 1cm.  
   - Tumour size 1-2 cm and all prognostic factors favourable (grade 1, no LVI).  
   Not triple negative or HER2+ | Pre and postmenopausal  
   No systemic treatment |
| High Risk    | - Tumour size greater than 3 cm irrespective of other factors.  
   - Tumour size 1-3 cm and grade 3 or LVI +ve. | All premenopausal, or ER and PR -ve less than 70 postmenopausal  
   Chemotherapy |
|              |             | Postmenopausal ER or PR +ve  
   Tamoxifen or AI  
   Chemotherapy may be added after discussion of |
Intermediate Risk
Risk of recurrence (10 yrs) 10-20%
-T greater than 1 cm and other combinations of risk factors than above.

Premenopausal
ER or PR +ve Tamoxifen
Option to discuss risks and benefits of chemotherapy ER / PR –ve Chemotherapy

Postmenopausal
ER or PR +ve
Tamoxifen or AI
ER / PR -ve discuss chemotherapy option

Oncotype Dx may be useful in intermediate grade ER or PR+ to assist in deciding on the role of chemotherapy

A more nuanced approach is followed by the St. Gallen's Group and the National Comprehensive Cancer Network Guidelines (Fig.1).

Fig.1: Howell A. Adjuvant Therapy for Breast Cancer: Does Stage Matter in the Era of Tailored Therapy? Educational Book. ASCO, 2010.

*As an alternative, Adjuvant! Online http://www.adjuvantonline.com may be used to determine 10 year risk of relapse and appropriate treatment determined according to risk status. The accuracy of this program was validated using the BCCA population database (Proc ASCO 2004; 22:8s). If Adjuvant! Online is used to determine recurrence risk, it is important to assess whether the recurrence risk correlates with clinical estimates. Although it may be reasonable to discuss adjuvant therapy with patients having T1b high grade or LVI+ cancers, there is no information on whether similar T1a cancers fall into the intermediate or higher risk groups.

The increased heterogeneity and complexity of breast cancer is accepted on the basis of clinically significant molecular subgroups. In certain situations, biology may trump size.

Some low-risk one to three node positive breast cancers may not require chemotherapy (Lancet Oncol 2010; 11: 55–65). Small HER2 positive node negative breast cancers may have a clinically significant risk of relapse and benefit from trastuzumab. However, no prospective clinical trials have evaluated this subgroup. The CCO Evidence Building
Program [http://www.cancercare.on.ca/cms/one.aspx?portalId=1377&pageId=96671](http://www.cancercare.on.ca/cms/one.aspx?portalId=1377&pageId=96671) is available to fund drugs for which there is evolving but incomplete evidence of efficacy to allow funding and gathering of real-world data pending final funding. Trastuzumab is now funded through this mechanism for small HER2 positive tumours less than or equal to one cm in size.

**Triple negative cancer** (N Engl J Med 2010;363:1938-48) is generally defined as HER2, ER and PR negative disease and usually characterized as basal subtype. It usually occurs in younger women more frequently of African descent. 70% of BRCA1 carriers have triple negative disease. Although aggressive, with a generally poorer prognosis, some triple negative subtypes have a good prognosis (adenoid cystic, low grade adenosquamous, myoepithelioma). As well, pCR with neoadjuvant therapy confers a similar good prognosis as breast cancer in general. Although there may be some differences in chemotherapy sensitivity for this entity, data are still sparse and it is too early to recommend specific therapy. A promising gene expression signature cluster analysis has been used to identify new cell line triple negative subgroups to model for effective biologic targets based on signaling pathways (SABCS 2010, Abs PD01-07). Accrual to clinical trials is strongly encouraged to determine effectiveness and to validate predictive biologic markers.

Pure tubular and mucinous/colloid tumors have a more favourable prognosis and management of these should be considered on a case by case basis. **Slides should be reviewed by a pathologist experienced in breast cancer.**

**Hormone therapy**

**Non-trial patients**

All premenopausal patients in intermediate and high risk categories, with ER and/or PR positive tumors, should receive adjuvant tamoxifen 20 mg daily for five years. There is strong evidence from the 1995 Oxford Meta-analysis (Lancet 1998; 351: 1451-67) to support the use of tamoxifen in all hormone receptor positive postmenopausal patients, and in premenopausal patients who will not receive chemotherapy. There are very limited data concerning the use of tamoxifen in premenopausal patients with or after adjuvant chemotherapy. Several trials have been completed but not yet published. Nevertheless it is now common practice to offer these patients adjuvant tamoxifen, after a discussion of the likelihood of benefit, based on extrapolation from other situations and the relatively low toxicity of tamoxifen. The timing of tamoxifen is also important. The ten year disease-free survival results were reported for INT 0100 (MA.9) (St. Galen, 2003), showing superiority for sequential over concurrent CAF and tamoxifen at ten years (60% v 53%).

The 1995 Meta-analysis (Lancet 1998; 351: 1451-67), showed a marginal disease free and no overall survival benefit for the use of adjuvant tamoxifen in patients with ER poor (negative) cancers. The 2000 Meta-analysis (Lancet 2005; 365:1687-1717) no longer showed any benefit in recurrence free survival for this group of patients. Therefore patients with hormone receptor negative tumors should not receive adjuvant tamoxifen.

Currently tamoxifen is recommended for a total duration of five years. In two trials, patients completing five years of tamoxifen were randomized to continue for an additional five years or to stop. The NSABP B14 trial (J Natl Cancer Inst 2001; 93: 684) suggested a poorer outcome for those receiving greater than 5 years of tamoxifen and the Scottish trial (J Natl Cancer Inst 2001; 93: 456) showed no additional benefit. In exceptional cases, if Tamoxifen needs to be continued beyond 5 years, it should be discussed carefully with the patients and two trials that have shown only modest benefits (Peto R, ATLAS trial, SABCS 2007 and Gary RG, Attom Trial, ASCO 2008, abstract 513). **In the Cancer Research UK trial, after a median follow-up of**
10.1 years of women aged 50-59 on five vs two years of adjuvant tamoxifen had a statistically and clinically significant reduction in HR of cardiovascular events (0.65, \(p=0.005\)) and deaths (0.41, \(p=0.02\)) (J Clin Oncol 29:1657-63. 2011). Tamoxifen should therefore also be considered as an alternative to AIs for women aged 50-59 who have higher risk factors for cardiovascular disease.

Prospective data from ATAC and BIG 1-98 do not support use of genotyping for CYP2D6 or the use of hot flashes as an indicator of effectiveness of tamoxifen as there was no correlation of these indicators with efficacy (SABCS 2010). Although SSRIs reduce hot flashes, this may be occurring through the reduction of endoxifen, the most important tamoxifen metabolite, via inhibition of CYP2D6. The NCCN 2007 Breast Cancer Guideline includes the cautionary note that some SSRIs decrease the formation of endoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. The clinical impact of these observations, however, is not known. Until further information is available, venlafaxine and citaloprim should be considered the SSRIs of choice.

**Aromatase Inhibitors**

Five major randomized trials have reported results of adjuvant aromatase inhibitors or inactivators (AIs) in postmenopausal women with hormone receptor positive stage 1 or 2 breast cancer.

- The ATAC Trial (Lancet 2005; 365: 60-62) showed a hazard ratio (HR) for disease-free survival (DFS) of 0.87 (0.78-0.97) at 68 months for anastrozole versus tamoxifen over five years.

- The BIG 1-98 trial (BIG 1-98 Collaborative Group, Mouridsen H, et al. N Engl J Med. 2009;361(8):766) showed that Letrozole up front had an improved DFS (HR: 0.83) compared to Tamoxifen at a median follow up of 68 months. However, DFS was not significantly improved with either Letrozole initially followed by Tamoxifen or vice versa compared to Letrozole upfront. There were some early relapses seen with Tamoxifen upfront treated patients versus Letrozole alone. A non-significant overall survival improvement (HR:0.87, 95%CI:0.75-1.02) was observed with upfront Letrozole treatment. The International Exemestane (IES) trial (N Engl J Med 2004; 350: 1081-90) showed a HR for DFS of 0.73 (0.62-0.86) for 2-3 years of exemestane after 2-3 years of tamoxifen versus 5 years of tamoxifen after 37.4 months of follow-up. Update at 58 months of follow-up showed a HR for DFS of 0.76 (0.66-0.88). There is a strong trend but not yet statistically significant survival benefit based on intention to treat. Preplanned supplementary analysis omitting ER negative tumors (regardless of PR status) but retaining ER unknown showed a statistically significant survival benefit HR 0.83 (0.69-0.99) (Lancet 2007 Feb 17;369(9561):559-706). There is a statistically significant improvement in distant disease free survival HR 0.83 (0.70-0.98)

- The ABCSG/ARNO trial (Lancet 2005; 366: 455-62) showed a HR for DFS of 0.59 (0.42-0.82) with 26 months of follow up.

- The NCIC MA.17 trial, with a median follow-up of 2.4 years, showed a HR of 0.58 (0.45-0.76). Subgroup analysis of MA.17 (JNCI 2005; 97:1262-71) shows an OS benefit in the N+ subgroup.

- ABCSG-12 (Gnant M et al. NEJM 2009;360(7):679-91) utilizing medical ovarian ablation with goserlin in premenopausal women with EBC compaed Tamoxifen versus Anastrazole. Patients were further randomized to receive Zoledronic acid or placebo once every 6 months for 3 years. With median follow up of nearly 4 years, no significant difference in DFS is seen between Tamoxifen and Anasrazole. However, patients treated with Zoledronic acid showed a 36% reduction in the risk of recurrence. While AIs are superior to Tamoxifen in post-menopausal women with EBC, this trial begs the...
question of whether goserlin or medical ovarian suppression is not as optimal as surgical oophorectomy in premenopausal women. There is also concern about the optimal dose of AI in premenopausal women with a high BMI since in the ATAC Trial, women with a higher BMI had a trend to higher recurrence than in thin women (J Clin Oncol 28:3411-15. 2010). An Italian study (abs 515, ASCO 2011) showed no influence of BMI on serum estrone sulphate levels. It is not advisable to increase AIs based on BMI based on current knowledge.

There is a consistent statistically significant finding of benefit for DFS in all five trials. The IES trial has shown a statistically significant benefit in distant DFS. In addition, letrozole after five years of tamoxifen has demonstrated an OS benefit in the N+ subgroup (ASCO)/04). Because these trials have employed different timing and schedules in the use of AIs, have varying use of adjuvant chemotherapy, studied different populations and have varying proportions of receptor positive cancers, it is impossible to tell which strategy of AI use is most appropriate. We also lack long-term side effect information, particularly with regards to osteoporosis and vascular events.

The TEAM trial (SABCS Dec 2010) showed no difference in the outcome between exemestane versus anastrozole when used upfront as an adjuvant treatment for early breast cancer.

In view of the lack of long term toxicity and efficacy data, the following strategies for use of AIs are suggested:

- Contraindications to tamoxifen (thromboembolic events, endometrial cancer, intolerable side effects). Consider AI:
  - Anastrozole or letrozole if up front.
  - Exemestane or anastrozole after 2-3 years of tamoxifen.

- Considering up front AI, letrozole, exemestane or anastrozole.
- Considering AI switch after 2-3 years of tamoxifen, suggest 2-3 years exemestane. Anastrozole may be a reasonable alternative.
- Considering AI after 5 years of tamoxifen, suggest 4-5 years of letrozole.
- Women stopping tamoxifen after less than 2 years or after 3-4.5 years should discuss options with their oncologist.

None of these treatments should be prescribed without consultation with an oncologist or an experienced GP oncologist. A decision should only be made after a full discussion of the benefits and risks of treatment and an appropriate plan of follow up. All women starting adjuvant AIs should have a baseline bone density test with follow up testing every one or two years. Those without osteopenia or fragility fracture should be started on calcium 1500 mg and Vit. D 800 U daily and at least 30 minutes of physical activity three times a week is recommended. Those with osteopenia or osteoporosis or with prior fragility fracture should be started on an oral bisphosphonate (alendronate and risedronate are the only ones shown to reduce hip fractures).

Tamoxifen is still an appropriate standard, especially for those suffering from musculoskeletal problems or with osteopenia/osteoporosis or symptomatic atrophic vaginitis. Those women who elect to start on tamoxifen should be reassessed after 2-3 years for switch to an AI.

**Ovarian Ablation**

Ovarian ablation is not recommended in addition to any systemic therapy in premenopausal women with hormone receptor positive early breast cancer. Ovarian ablation may be considered only in rare cases where patients will not be able to receive any systemic treatment. For ovarian ablation, surgery, radiation therapy and medical treatment are all effective. The use of once a month LHRH analogue for ovarian
suppression is preferable since clinical trials have most commonly used this schedule (Griff JJ et al. J Clin Oncol Sept 2011)

Chemotherapy

The 2000 Meta-analysis results (Lancet 2005; 365: 1687-1717) are now updated at fifteen years follow up. For women with high-risk node negative or node positive breast cancer, anthracycline chemotherapy should be considered unless there are contraindications such as poor cardiac function. Six months of anthracycline-based chemotherapy reduces annual breast cancer death rate by 38% for women less than age 50 and by about 20% for those age 50-69, irrespective of the use of tamoxifen, ER status or nodal status. Used with tamoxifen in receptor positive women, the mortality reductions approach 57% and 45% respectively. The long-term risks of anthracycline based chemotherapy (cardiotoxicity, leukemia) should be fully discussed with patients. Cyclophosphamide and docetaxel has been compared to AC and shows improved disease-free (87% v 82% at five years- (J Clin Oncol 2009;27:1177-83) and overall survival (87% v 82% at seven years-SABCS, 2007). Importantly, this benefit was also seen in elderly women. This chemotherapy should be considered especially for women at higher risk of cardiac toxicity or who are candidates for trastuzumab adjuvant therapy.

For patients with high risk tumors, there are many options including CEF, TAC, FEC100,CAF-po and ddAC→Paclitaxel (see Appendix 6). The NCIC MA.21 trial reported a 5% absolute improvement in DFS of CEF over AC→paclitaxel (SABCS 2006). The PACS 01 trial for women with T1-3, N+ breast cancer demonstrated a DFS benefit of 78.3% v 73.2% (p=0.014) and an OS benefit of 90.7% v 86.7% (p=0.05) at 60 months in favour of F500E100C600 x 3→Docetaxel100 x 3 over F500E100C600 x 6. This regimen is now funded for N+ or high risk N- breast cancer and should be considered over FEC100 if improved DFS is the primary consideration (J Clin Oncol 2006;24:5664-71). For patients with intermediate risk tumors requiring chemotherapy or any woman who would prefer a slightly less effective but less toxic regimen, CMF and AC are reasonable adjuvant chemotherapy regimens (see Appendix 6). We do not recommend the use of CEF in patients above the age of 60 because of the high risk of toxicity. AC→ paclitaxel should be avoided or used with caution if pre-existing neuropathy. A meta-analysis of taxanes as adjuvant therapy (ASCO, 2007 Abs 545) favours taxane use with an overall survival benefit (HR 0.81 (0.75-0.88) independent of nodal status and the duration of therapy. All women with node positive and high-risk node negative breast cancer who are candidates for adjuvant chemotherapy have their tumour assessed for HER2/Neu oncogene at diagnosis by an experienced regional pathology lab. Those staining positive by IHC or FISH should have a discussion of the risks and benefits of adjuvant chemotherapy. Prophylactic G-CSF should be considered where the risk of FN is 20% or more (ASCO Guidelines, 2006 http://jco.ascopubs.org/cgi/reprint/JCO.2006.06.4451v2.pdf).

FN rates for docetaxel-based adjuvant regimens are likely underestimated in the literature due to undocumented use of primary prophylaxis. Ontario experience documents FN rates well in excess of 20% (Curr Oncol. 2010 Apr;17(2):2-3, SABCS, 2009). Primary prophylaxis is strongly recommended for all patients treated with adjuvant docetaxel-based regimens. Because ddAC-Paclitaxel or the docetaxel portion of FEC-D are the only taxane regimens that include coverage for GCSF with the taxane, if a taxane-based regimen is being considered, and there is no private insurance coverage for GCSF, ddAC-Paclitaxel or FEC-D are recommended for this group. Prophylactic antibiotics are an alternative strategy if there are problems with GCSF.

Adjuvant chemotherapy may be discussed with healthy women greater than or equal to 70 years old, especially with hormone receptor negative disease, but should be considered with caution because of the paucity of data concerning benefits, and the greater potential for co-
morbidity and greater toxicity. Recently, the CALGB 49907 Trial compared capecitabine vs classic CMF or AC x 4 in women 65 or older (2/3 were 70 or older). The results show a highly significant disease-free and overall survival advantage for CMF or AC with a major benefit for hormone receptor negative tumours. N Engl J Med. 2009 May 14;360(20):2055-65.

Not all chemotherapy regimens in the preceding paragraph are funded in Ontario. Core and core restricted chemotherapy regimens approved for funding can be accessed at http://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=11137

Bisphosphonates

The use of bisphosphonates the adjuvant setting is explored through various clinical trials. Z-fast/Zofast combined data showed a reduction in the risk of recurrence of breast cancer initially. However, after longer follow up there appears to be no improvement (Brufsky AM, et al. Clin Breast Cancer 2009;9(2):77). ABCSG-12 study did show an improvement in DFS by about 36% with the use of adjuvant Zoledronic acid. However, more recently, AZURE trial (SABC 2010) reported no improvement in risk of breast cancer recurrence with the use of adjuvant zoledronic acid. A pre-specified data analysis showed that risk reduction similar to ABCSG-12 was seen in post-menopausal women in this trial. At present, the data is not supportive of routine use of adjuvant bisphosphonate therapy in patients with early breast cancer.

FOLLOW-UP PROTOCOL

As for non-invasive cancer. All high risk patients with node negative disease suitable for chemotherapy should be seen by a medical and/or a radiation oncologist.

A recent randomised study in Ontario of women who had completed adjuvant chemotherapy (plus or minus tamoxifen) and were either followed by their family doctor or the cancer centre, was presented at ASCO in June 2004 and showed no differences in outcomes after 3.5 years of followup.

Follow-up by GP/surgeon for systemic therapy patients will generally occur after adjuvant chemotherapy or initiation of adjuvant hormonal therapy. Exceptions may occur for patients on clinical trials.
INVESTIGATIONS

Biopsy: for histopathology and ER/PR status
(see Surgery Appendix 4)

Assessment: history and physical, complete blood count, biochemical profile, bilateral mammography before surgery if possible, chest radiograph, bone scan (optional). Although the true positive rate on bone scan is low for stage II disease, subsequent bone metastasis is common, and a baseline scan for subsequent comparison is useful.

Stage III patients (TXN2 or T3 or more) are recommended to undergo baseline staging prior to consultation for chemotherapy using bone scan and either chest x-ray and ultrasound of the abdomen and pelvis or CT chest, abdomen and pelvis.

LOCAL THERAPY

Surgery
Types of surgery:
(1) Partial mastectomy (or lumpectomy) and axillary node dissection
(2) Modified radical mastectomy and axillary node dissection

The indications and techniques for these procedures are outlined in detail (Surgery Appendix 4). Non-palpable tumors may be removed using needle localisation (Appendix 3).

Partial mastectomy versus total mastectomy
See details in section stage I.

N.B. Patients with positive resection margin(s) after lumpectomy should be referred back for further surgery, mastectomy or further local resection.

Axillary node dissection
See details in section stage I.

Radiotherapy
See prior section for contraindications to breast radiation.

(a) Breast irradiation
All patients undergoing lumpectomy, regardless of adjuvant therapy, should receive whole breast irradiation. Tumor less than 5 cm AND 1-3 axillary nodes positive receive breast radiation alone unless there are adverse features (see below). The role of a boost is similar to node negative patients. Radiation is usually delayed until the completion of adjuvant chemotherapy (approx. 6 months) but the optimal sequencing is unknown (ASTRO 2001; Plenary 4 update of NEJM 1996; 334: 1356-61).

(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 receive radiation unless there are adverse features (see below). 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. A boost phase is usually given as well. See below for indications for regional nodal irradiation.

(c) **Regional nodal irradiation** (Adapted in part from ASTRO Consensus Statement on Postmastectomy Radiation Therapy, IJROBP 1999; 44: 5).

For women with four or more positive axillary nodes there is clear benefit.

For those with 1-3 nodes positive, there is evidence of disease free and overall survival benefit from Danish and British Columbia randomized trials in post mastectomy patients. These may be criticized because they were conducted in an era when anthracycline, taxane, trastuzumab and aromatase inhibitor therapies, which have all been shown to reduce loco-regional recurrence, were not given. Also, some women may have had suboptimal axillary node dissection. Nevertheless, the benefit persists when women with suboptimal dissection are excluded. Furthermore, the 2005 Oxford meta-analysis confirm evidence of locoregional recurrence and overall survival benefit. Similar benefits have been reported in the MA.20 study for post lumpectomy patients presented in abstract (ASCO 2011). Patients with sentinel lymph node dissection (SLND) or limited axillary node dissection should also be considered if the positive to resected node ratio exceeds 0.2. A positive node on SLND should preferably be treated with complete axillary node dissection if the nodal metastasis is >0.2 mm on H&E (see Surgery Appendix 4 for further details). Locoregional radiation should therefore be considered in women with 1-3 nodes positive.

For women with 1-3 nodes where locoregional radiation is not recommended, it should still be given under the following conditions:
1) gross residual disease after Level I and II axillary dissection
2) T3 tumors
3) indicators of extensive axillary disease (large nodal disease, gross extranodal disease)

Additional factors that may be considered include: number of nodes sampled, patient age, grade of tumor.

A meta-analysis showed that locoregional radiation after surgery in patients treated with systemic therapy reduced mortality (JCO 2000; 18: 6). Although three RCT’s (Lancet 1999; 353: 1641-48, NEJM 1997; 337: 949-55, NEJM 1997; 337: 956-62) demonstrating a survival benefit with postmastectomy radiation included treatment to the chest wall, axilla, supraclavicular area and the internal mammary nodes (IMNs), there is controversy about what sites require treatment. In all patients, the chest wall/breast should be treated. The value of including the IMNs is uncertain and is currently being studied in a large European trial. In patients with positive axillary nodes, the IMNs are known to be also involved in about 30% of cases. Therefore, treatment of this area is worthy of serious consideration, provided it can be done with acceptable morbidity. Following a Level I and II axillary dissection, the use of a third field to treat the axillary apex and supraclavicular area is appropriate for selected node positive patients. A posterior axillary field is not routinely indicated after a Level I and II axillary dissection. However, if there is concern about the completeness of surgery (eg. less than 10 nodes removed), the addition of a posterior axillary field may be appropriate (see Radiotherapy Appendix 5 for details).
MANAGEMENT OF PATIENTS WITH 1-2 POSITIVE SENTINEL NODES

ACOSOG Z0011 (Giuliano AE, JAMA 2011) which showed no difference in local control, distant metastases or survival with no further ALND versus completion ALND, has changed the standard of practice in many jurisdictions, particularly in the U.S. However, this clinical trial has several methodological problems: Registration of 32% of patients occurred after surgery and there are no details on how radiation was delivered. 99/856 patients had no information on lymph node metastases, including 77/420 (18%) in the ALND group. 103/891 patients (11.5%) were ineligible for analysis. There was an imbalance in positive between groups. 166/991 (20%) were either lost to follow up or excluded from analysis. An intention to treat analysis in a non-inferiority trial is more likely to add bias. Furthermore, there is a logical inconsistency that less aggressive surgical treatment of axillary metastases would have no impact on relapse, whereas radiation treatment as per the MA.20 trial would have the opposite effect. There is enough uncertainty that a German group is planning to redo this trial. Therefore, if patients are informed of this trial, they should be aware of its weaknesses and that completion axillary lymph node dissection is still the standard of care.

If a patient still does not wish completion ALND, only patients fulfilling the eligibility criteria of ACOSOG Z0011 should be considered. These include all the below:

- Clinically T1-2 and N0.
- Pathologically, negative tumour margins and not more than 2 positive SLNs.
- No matted nodes or gross extranodal extension.
- No prior neoadjuvant therapy.

The NCIC CTG MA.20 trial compared breast radiation v the addition of locoregional radiation including upper internal mammary nodes. This trial has shown after a median 62 months follow up a significant improvement in locoregional disease free recurrence (96.8 v 94.5%, p=0.02), distant disease free survival (92.4 v 87.0%, p=0.002), DFS (89.7 v 84.0%, p=0.003) and a strong trend to improved OS (92.3 v 90.7%, p=0.07). Although there is an increased risk of pneumonitis (1.3 v 0.2%) and lymphedema (7.3 v 4.1%).

Combining the information from both trials, it is difficult to be certain how to manage these patients. In view of the lack of other data, a pragmatic approach is recommended:

- SLNs detected on IHC only or less than 0.2 mm do not require further surgery or radiation to the regional nodes.
- Sentinel lymph nodes with micro or macro-metastases should have the MSKCC breast additional non-SLN metastases nomogram calculation done (see http://nomograms.mskcc.org/Breast/BreastAdditionalNonSLNMetastasesPage.aspx). If the probability of additional spread is greater than 20%, a full ALND should be offered. For those with a lower risk, discussion on further care should be held with the multidisciplinary team as outlined below.
- All patients with pathology showing 1-2 nodes positive for micro-metastases regardless of further surgery must be referred to radiation and medical oncology and discussed at the tumour board. Consideration should be given to nodal radiation for any high risk features (high grade, LVI positive, ER and PR negative, triple negative or age less than 50).
- All patients with macrometastases should be referred to radiation and medical oncology.
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Hormone therapy

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**Chemotherapy**

The 2000 Meta-analysis results (Lancet 2005; 365: 1687-1717) are now updated at fifteen years follow up. For women with high-risk node negative or node positive breast cancer, anthracycline chemotherapy should be considered unless there are contraindications such as poor cardiac function. Six months of anthracycline-based chemotherapy reduces annual breast cancer death rate by 38% for women less than age 50 and by about 20% for those age 50-69, irrespective of the use of tamoxifen, ER status or nodal status. Used with tamoxifen in receptor positive women, the mortality reductions approach 57% and 45% respectively. The long-term risks of anthracycline based chemotherapy (cardiotoxicity, leukemia) should be fully discussed with patients.
Non-trial patients

For patients with high risk tumors, there are many options including CEF, TAC, FEC100, FEC-D and CAF-po (see Appendix 6). The NCIC MA.21 trial reported a 5% absolute improvement in DFS of CEF over AC→Paclitaxel (Proc ASCO 2007;25:18S,p15s). BCIRG trial 001 (New Engl J Med 2005: 352; 2302) has shown superiority in DFS for TAC versus FAC, and, in ten year follow up survival benefit (Martin, SABCS, 2010). Results are independent of ER and HER2 status. The febrile neutropenia rate is comparable to CEF, but it is unclear how TAC compares with MA.21 CEF. NSABP B-28 and CALGB trial 9344 demonstrate a DFS benefit of adding paclitaxel to doxorubicin-containing chemotherapy. It is unclear whether adding a taxane to more aggressive regimens (CAF, CEF d1 & 8 with oral cyclophosphamide) will provide a comparable result. Dose dense chemotherapy with q 2 wk AC→T seems to offer a DFS and OS over standard AC→T (CALGB 9741, updated Abs 517, ASCO, 2007), has acceptable toxicity when combined with GCSF and may be completed over a shorter time. However, another trial of weekly taxane after standard AC did not show a significant improvement in either outcome measure or between docetaxel and paclitaxel. Weekly paclitaxel had similar efficacy to q 3 wk docetaxel for DFS with increased neuropathy for weekly P and increased febrile neutropenia for q 3 wk D (INTERGROUP E1199, updated Abs 516, ASCO, 2007).

The PACS 01 trial for women with T1-3, N+ breast cancer demonstrated a DFS benefit of 78.3% v 73.2% (p=0.014) and an OS benefit of 90.7% v 86.7% (p=0.05) at 60 months in favour of F→E→C→Docetaxel→x 3 over F→E→C→x 6. This regimen is now funded for N+ or high risk N- breast cancer and should be considered over FEC100 if improved DFS is the primary consideration (J Clin Oncol 2006;24:5664-71). Docetaxel at 100 mg/m2 is associated with a high risk of febrile neutropenia. Primary prophylaxis with G-CSF should be considered in any situation where the risk of febrile neutropenia exceeds 20%. A meta-analysis of taxanes as adjuvant therapy (ASCO, 2007 Abs 545) favours taxane use with an overall survival benefit (HR 0.81 (0.75-0.88) independent of nodal status and the duration of therapy. Therefore, all women for whom improved survival is the primary consideration and for whom there are no contraindications to taxane therapy should receive a taxane-based regimen or CEF. All women with node positive breast cancer who are candidates for adjuvant chemotherapy must have their tumour assessed for HER2/Neu oncogene at diagnosis by an experienced regional pathology lab unless there are contraindications to herceptin. Those staining positive by IHC or FISH should have a discussion of the risks and benefits of adjuvant herceptin therapy. Cyclophosphamide and docetaxel has been compared to AC and shows improved disease-free (87% v 82% at five years- (J Clin Oncol 2009;27:1177-83) and overall survival (87% v 82% at seven years-SABCS, 2007). Importantly, this benefit was also seen in elderly women. This chemotherapy should be considered especially for women at higher risk of cardiac toxicity or who are candidates for trastuzumab adjuvant therapy.

For postmenopausal women with hormone receptor positive tumors less than or equal to 60 years, or those greater than 60 years who are candidates for an aggressive anthracycline-based chemotherapy, CAF po (see Appendix 6) as used in Intergroup 0100 (SWOG 8814, NCIC-CTG MA.9) is another option (Proc ASCO 2001; 20: 24a). This study showed an improved five year disease free and overall survival for patients receiving CAF + tamoxifen versus tamoxifen alone. In this trial, women were also randomized for sequential versus concurrent tamoxifen. Early results show a DFS benefit for sequential therapy (Proc ASCO 2002; 143: 37a). The ten year disease-free survival results were reported for INT 0100 (MA.9) (St. Galen, 2003), showing superiority for sequential over concurrent CAF and tamoxifen at ten years (60% versus 53%). An alternative regimen for women with high risk disease, who may not tolerate CAF or CEF, is FEC 100 IV every 3 weeks x 6 cycles as described by a French group (J Clin Oncol 2001; 19: 602) which was superior, in terms of five year disease free and overall survival, to FEC 50 (half
the dose of epirubicin). For older patients with few positive lymph nodes, or women who wish to minimize toxicity, CMF po or AC or DC are also reasonable options.

Adjuvant chemotherapy may be discussed with healthy women greater than or equal to 70 years old, especially with hormone receptor negative disease, but should be considered with caution because of the paucity of data concerning benefits, and the greater potential for co-morbidity and greater toxicity. Recently, the CALGB 49907 Trial compared capecitabine v classic CMF or AC x 4 in women 65 or older (2/3 were 70 or older). The results show a highly significant disease-free and overall survival advantage for CMF or AC with a major benefit for hormone receptor negative tumours. (N Engl J Med. 2009 May 14;360(20):2055-65).

Preoperative chemotherapy
A randomized NSABP trial (B18) involving 1,525 women with clinical T1-3, N0-1, M0 breast cancer, compared preoperative AC x 4 and the same chemotherapy given postoperatively, and showed no differences in 5 year disease free, distant disease free and overall survivals (J Clin Oncol 1998; 16: 2672). Slightly more patients treated preoperatively were able to undergo lumpectomy and radiation therapy rather than mastectomy (67.8% versus 59.8%). The ipsilateral breast tumor recurrence (IBTR) rate was marginally higher in the preoperative chemotherapy arm (7.9% versus 5.8%, p=0.23). An EORTC randomized trial of 698 patients receiving pre vs postoperative FEC x 4 showed similar results (J Clin Oncol 2001; 19: 4224). In this study, 57 (23%) of 246 patients planned for mastectomy had breast conserving surgery (BCS) whereas 14 (18%) of 77 needed a mastectomy rather than the planned BCS. However, overall survival was significantly worse (Hazard ratio 2.53) for patients who underwent BCS after downstaging of the tumor, compared with that of patients planned for BCS and who received this treatment. A study by Rouzier et al (J Clin Oncol 2001; 19: 3828) determined the incidence and prognostic significance of IBTR in 257 women with T1-3 breast cancers treated with preoperative chemotherapy, lumpectomy and radiation therapy. The IBTR rates were 16% at 5 years and 21.5% at 10 years. Multivariate analysis showed that the probability of local control was decreased by: age less than or equal to 40 years, excision margin less than 2 mm, S phase fraction greater than 4%, clinical tumor size greater than 2 cm. IBTR was a strong predictor for distant metastasis (59.7% at 5 years).

With preoperative chemotherapy, there is a concern that in the longterm IBTR may be greater, particularly in those patients with larger tumors “converted” from mastectomy to lumpectomy and that this may even adversely affect survival. Therefore, the Breast Team does not recommend preoperative chemotherapy for these patients, outside a clinical trial setting. Preoperative chemotherapy is indicated for locally advanced (tethered to chest wall or axilla) and inflammatory cancers (see next section). If preoperative chemotherapy is given, response to chemotherapy should not alter the initial surgical plan. Surgeons should place clips at the site of the biopsy so that localization for radiation planning can be optimized if there is a significant partial or complete pathological response.

When neoadjuvant therapy is planned, a taxane should be considered. Paclitaxel, 80 mg/m² weekly x 12 weeks prior to FAC produced a higher pCR rate in women with T1-3, N01-, M0 breast cancer versus q 3 wk paclitaxel followed by FAC (29% versus 15%, p less than 0.01) (ASCO/02, 35a). There is insufficient evidence to recommend weekly docetaxel. The Aberdeen Trial randomized patients to CVAP x 8 or CVAP x 4 followed by docetaxel 100mg/m² (San Antonio/03). Patients randomized to the docetaxel-containing arm achieved a strong trend to improved pCR (31% versus 15%, p=0.06), were more likely to undergo breast conservation (67% versus 48%, p less than 0.01), had higher DFS (90% versus 77%, p=0.03) and had higher overall survival rates at a median follow-up of 65 months (93% versus 78%, p=0.04).
Based on the above, when neoadjuvant chemotherapy is planned for a woman with non-metastatic cancer (including locally advanced or inflammatory cancer), if taxane chemotherapy is used, the following should be considered:

- Paclitaxel weekly x 12 weeks prior to a standard anthracycline containing regimen such as FAC, AC or FEC100.
- FAC, FEC100 or AC followed by four cycles of docetaxel (100 mg/m²) every three weeks.
- Trastuzumab will be added to neoadjuvant therapy as per adjuvant guidelines.

There is no evidence at this time to suggest that one taxane is superior to the other in this setting. More detailed information on neoadjuvant chemotherapy can be obtained by visiting the Cancer Care Ontario Practice Guidelines website for Breast Cancer at http://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=10760

**Trastuzumab Therapy in HER2/Neu Positive Breast Cancers**

Combined data from NSABP B31 and NCCTG 9831 (N=3351), with a median follow up of two years show a HR for DFS of 0.48 (2p=3x10⁻¹²) and 0.67 (2p=0.015) for OS for trastuzumab (H) given for one year starting concurrently with paclitaxel in the AC→T regimen when compared with AC→T alone (New Engl J Med 2005; 353: 1673-84). **Four-year results show HR for DFS of 0.49 (0.41-0.58) and OS of 0.63 (0.49-0.81).**

This is despite 21% of patients subsequently crossing over to trastuzumab (Abs 512, ASCO 2007). This has been corroborated in the HERA trial (N=3387) in which, with a median follow up of one year, using sequential trastuzumab, the estimated HR for DFS at two years was 0.54 (0.43-0.67) (New Engl J Med 2005; 353: 1659-72). OS benefit has now been reported with two years follow-up at 0.64 (0.45-0.87) absolute benefit 2.7%. Benefit appeared similar in all subgroups (nodal, receptor status, grade or type of chemotherapy given). Clinical cardiotoxicity is 4.1% with AC→T + H versus 0.7% with AC→T alone and 2.1% with H versus 0.2% without H in the HERA Trial. **A five-year update on cardiac dysfunction from NSABP B-31, using blinded assessment shows no change in cardiac toxicity at five years v three years follow-up.** Patients at increased risk of CHF include those 50 or older (5%), on antihypertensive medication (6.8%) or whose baseline LVEF is <54% (13%) (AbsLBA513). Further data are required to determine the efficacy and safety of two years versus one year of trastuzumab. There may be increased benefit with concurrent versus sequential H, but this may come at the price of increased cardiotoxicity. Women should be followed every three months for cardiac toxicity with an echocardiogram or MUGA scan, while on treatment. Most cardiac toxicity seems to occur early, often while still on therapy. (See monitoring for cardiotoxicity-Appendix 6).

In view of the magnitude of these results, it is recommended that all women with node positive and high risk node negative breast cancer who are candidates for adjuvant chemotherapy have their tumour assessed for HER2/Neu oncogene at diagnosis by an experienced regional pathology lab. Those staining 3+ by IHC or FISH+ should have a discussion of the risks and benefits of adjuvant herceptin therapy. Similar efficacy of herceptin has been confirmed in the BCIRG 006 trial as well as in the FINHER trial (San Antonio, 2005), but in view of the lack of confirmatory studies, one year of herceptin is the current standard.

**Neoadjuvant therapies in HER2+ cancer:**

The GeparQuattro study has confirmed a high pCR rate with trastuzumab and docetaxel but with more FN (J Clin Oncol 28:2024-31.2010). The GeparQuinto trial suggests inferior pCR rates with lapatinib plus chemotherapy vs trastuzumab and chemotherapy with more GI toxicity. The NeoALTTO trial suggests a superior pCR rate with both lapatinib and trastuzumab and chemotherapy compared to either agent alone with chemotherapy. DFS and OS data are not yet available for either trial (SABCS 2010).
Bisphosphonates

The use of bisphosphonate in an adjuvant setting is explored through various clinical trials. Z-fast/Zofast combined data showed a reduction in the risk of recurrence of breast cancer initially. However, after longer follow up there appears to be no improvement (Brufsky AM, et al. Clin Breast Cancer 2009;9(2):77). ABCSG-12 study did show an improvement in DFS by about 36% with the use of adjuvant Zoledronic acid. However, more recently, AZURE trial (SABC 2010) reported no improvement in risk of breast cancer recurrence with the use of adjuvant zoledronic acid. A pre-specified data analysis showed that risk reduction similar to ABCSG-12 was seen in post-menopausal women in this trial. At present, the data is not supportive of routine use of adjuvant bisphosphonate therapy in patients with early breast cancer.

SUGGESTED FOLLOW-UP

Time interval

During chemotherapy
2-4 weekly intervals according to regimen

After completion chemotherapy + radiotherapy
Year 1,2 4 months
Year 3,4,5 6 months
then yearly

Adjuvant hormone / no systemic treatment
Year 1,2 4 months
Year 3,4,5 6 months

A recent randomised study in Ontario of women who had completed adjuvant chemotherapy (plus or minus tamoxifen) and were either followed by their family doctor or the cancer centre was presented at ASCO in June, 2004 and showed no differences in outcomes after 3.5 years of followup.

Follow-up by GP/surgeon for systemic therapy patients will generally occur after adjuvant chemotherapy or initiation of adjuvant hormonal therapy. Exceptions may occur for patients on clinical trials.

FOLLOW-UP INVESTIGATIONS

Mammogram yearly (discretionary age greater than 70 depending on general medical condition)
Other investigations as clinically indicated
Routine bone and liver scans are not recommended.
ALL T4 LOCALLY ADVANCED/INFLAMMATORY

This section generally refers to stage T2B AND N2 or higher, T3Nx, T4Nx or any T AND N3. Thus this locally advanced staging includes N3 (supraclavicular metastases) and inflammatory carcinomas. Patients presenting with concurrent positive ipsilateral supraclavicular node(s) may be managed in a similar way although recognized to be N3. Note that patients presenting with contralateral axillary lymph node positivity must be assumed to have bilateral breast cancer until an MRI of the contralateral breast together with mammogram and ultrasound have ruled out a contralateral primary, at which point this patient will be considered to be metastatic (see section on treatment of patients with metastatic breast cancer).

Recommendation: Patients should be seen by a medical oncologist within one week of pathological and clinical confirmation of a locally advanced, non-metastatic malignancy. This implies that staging investigations (see below) must be expedited by the referring physician to meet these targets. The aim is that chemotherapy should start within a week of assessment by a medical oncologist.

INVESTIGATIONS

Biopsy: Core needle biopsy by image guidance is preferred but will accept tru-cut or incisional if core biopsy access is not available (see Surgery Appendix 4). A punch biopsy of the skin to diagnose inflammatory cancer should only be done in patients who have failed therapy for mastitis over 1 week and have had a mammogram, ultrasound and MRI that have failed to identify a breast mass to target for accurate biopsy (due to poor sensitivity of punch biopsy and inability to assess accurate Her2, ER/PR status on tumour emboli cells in lymphatics).

Assessment: as for stage II disease
- Bone scan, CT chest/abdomen and pelvis is preferred for these high risk patients due to high risk of distant metastases
- When possible, patients with locally advanced tumors should initially be reviewed jointly by a surgeon, radiation and medical oncologist.

LOCAL THERAPY

Surgery

Initial systemic treatment (usually chemotherapy but sometimes hormone) is recommended. Following neoadjuvant systemic therapy, modified radical mastectomy should be performed, if technically feasible. Sentinel lymph node biopsy following neoadjuvant chemotherapy for locally advanced breast cancer is currently not considered standard of care. Local excision of tumours (ie. T4 at diagnosis) by breast conserving surgery can be offered to patients where clinically feasible and appropriate, provided that pre-chemotherapy image-guided clips have been placed to identify the tumours in case of complete clinical response. In order to minimize local recurrence risk associated with this approach, complete excision of the initial tumour bed should be undertaken even if good clinical response is seen. Skin-sparing mastectomy or breast conserving surgery is contra-indicated for inflammatory breast cancer.

Radiotherapy

Patients with locally advanced/inflammatory disease should have irradiation of the breast/chest wall and the regional nodes (see prior section for description of regional nodes treated). The timing of radiotherapy should be following surgery unless patients are participating in a clinical
trial offering preoperative chemo/radiation, if this takes place, or at the completion of chemotherapy. Progression on chemotherapy would be an indication to proceed to immediate radiotherapy. Positive margins would be an indication for a boost to the chest wall.

**SYSTEMIC THERAPY** (possible regimens include AC-D, FEC-D, ddAC-T)

**Chemotherapy**

Patients should be treated with anthracyline and taxane-based primary chemotherapy (see Chemotherapy Appendix 6) although there is emerging evidence supporting platinum-based regimens for patients who are triple negative and this should be decided by the medical oncologist in the setting of a case by case tumour board discussion. The total number of courses is generally 6-8, and local treatment with surgery and/or radiotherapy (see Radiotherapy Appendix 5) may be instituted at the time of maximal or plateau of response, or at the end of chemotherapy. Patients progressing on chemotherapy may need early radiotherapy for local control.

Taxane therapy should be part of neoadjuvant chemotherapy for non-metastatic locally advanced or inflammatory cancer. If taxane chemotherapy is used, the following should be considered:

- FEC x 3 followed by docetaxel (100 mg/m²) x 3
- Paclitaxel weekly x 12 weeks following a standard anthracyline containing regimen such as FAC or AC. FEC100 could also be considered.
- AC x 4 followed by four cycles of docetaxel (100 mg/m²) every three weeks.
- ddAC x4 followed by dd paclitaxel x4 (q 2 wks).
- A current clinical trial for locally advanced breast cancer at the LRCP offers FEC x 3 followed by weekly docetaxel (35 mg/m²) x 9 with concurrent radiation in the setting of the clinical trial only

*It is recommended that all women with locally advanced disease or with node positive or high risk node negative breast cancer who are candidates for neoadjuvant chemotherapy have their tumour assessed for HER2/Neu oncogene at diagnosis by an experienced regional pathology lab. Those staining positive by IHC or FISH should have a discussion of the risks and benefits of neoadjuvant herceptin therapy.

**Hormone therapy**

At the completion of surgery following neoadjuvant chemotherapy, premenopausal patients with hormone receptor positive tumors should be given tamoxifen 20 mg/day for 5 years. These patients can also be referred to the premenopausal ovarian ablation clinic for consideration of ablation and aromatase inhibitor. Postmenopausal patients who are elderly or medically unfit for chemotherapy, with hormone receptor positive tumors, may be treated neoadjuvantly with an aromatase inhibitor. Local treatment with radiotherapy alone may be more appropriate than surgery, especially in elderly patients, and may be given at presentation or after response to hormonal therapy has been documented. For patients who are fit for surgery, a less aggressive or breast –conserving surgery can be considered in discussion with the patient if the life expectancy and local recurrence risk have been considered on an individual basis. Patients progressing on hormonal therapy should receive immediate radiotherapy.

**Bisphosponates**

Although bisphosphonates reduce the risk bone fracture in osteoporotic women, and are indicated for osteoporosis induced by aromatase inhibitors, the role for adjuvant
bisphosphonates is not supported by clinical trials at this time. Results of other clinical trials are awaited.

**SUGGESTED FOLLOW-UP**

**Time interval**

_During chemotherapy_
3-4 weekly intervals according to regimen

_During hormone therapy_
Monthly until documentation of response
then as for stage II

_After completion chemotherapy + local treatment_
As for stage II disease

**FOLLOW-UP INVESTIGATIONS**

As for stage II disease.
LOCOREGIONAL RECURRENCE AND DISTANT METASTASES

INVESTIGATIONS

Biopsy: Generally recommended at first relapse especially for low risk (node negative, small primary) individuals and those with solitary abnormality (lung or liver lesion, one lesion on bone scan) to confirm diagnosis of malignancy and rule out second primary. Biopsy of the metastatic site should be considered to reassess ER, PR and HER2 status.

Assessment: Complete blood count, biochemical profile (including liver function studies and calcium), chest radiograph, bone scan, liver US or CT scan. All other investigations only if patient complaining of symptoms. In the case of a positive bone scan, x-rays should be performed to assess critical areas at risk for pathological fracture that are positive on scan (spinal column, pelvis, proximal humeri and femora).

LOCAL THERAPY

Surgery

Indications:
(a) To confirm metastatic disease.
(b) For initial removal or debulking of locally recurrent disease prior to or as an alternative to radiotherapy
(c) For prophylactic pinning in patients at high risk of pathological fracture.
(d) In selected cases, for treatment of cord compression in patients with cannot receive further radiation therapy.
(e) Solitary brain metastasis.
(f) The role for resection of solitary metastases at other sites has not been formally evaluated in randomized trials. If this is being considered, this should be reviewed at the weekly breast team meeting and only after there has been complete re-staging to rule out metastases elsewhere.

Radiotherapy

Indications:
(a) For the treatment of locally recurrent chest wall disease as an alternative or in conjunction with surgery. In cases presenting with small volume chest wall disease completely resected, chest wall irradiation may be omitted.
(b) For control of isolated regional nodes, which are not amenable to surgical dissection. Symptomatic regional nodes may also be treated, even in the presence of distant metastases.
(c) For control of symptomatic disease to bone:
- for rapid relief of pain, not controlled by analgesics, in one or two sites. Patients with one site may be considered for RTOG 9714.
- as an alternative to systemic therapy if patient refuses such therapy or is likely to suffer unacceptable toxicity.
- for control of disease in sites felt to be at risk for pathological fracture, if further disease progression occurs, but who are not yet candidates for prophylactic pinning.
- after prophylactic pinning of bone for metastatic disease
(d) For control of brain metastases
(e) For control of other sites of soft tissue disease (eg. scalp, orbit)

Chemotherapy
Indications:
(a) Chemotherapy should be considered for all patients with any of the following characteristics:
   i) hormone receptor negative disease causing moderate or severe symptoms
   ii) disease involving multiple sites and with rapid progression
   iii) symptomatic disease progressive on hormonal therapy
   iv) lymphangitis carcinomatosis of lung
   v) liver metastases
   vi) hypercalcemia
(b) Avoid methotrexate in patients with moderate or large pleural effusions or ascites. Consider pleurodesis in the former case.
(c) Intrathecal chemotherapy is of questionable benefit for meningeal carcinomatosis. Generally, cauda equina syndrome and intracranial meningeal carcinomatosis are best treated with radiation.

In general, anthracycline chemotherapy is recommended for use outside a clinical trial (Chemotherapy Appendix 6). CMF combination chemotherapy is a suitable alternative in certain situations (see Appendix 6). Although combination chemotherapy is widely given as first line treatment, the superiority of this approach has not been well validated and there is evidence to suggest that single agent therapy may provide improved quality of life, although the response rate might be somewhat lower (J Clin Oncol 1998; 16: 3720-30). There is no evidence to suggest a detrimental effect on survival. An anthracycline (doxorubicin, epirubicin or, in the frail or elderly, mitoxantrone) should be used if first line therapy with a single agent is given. Abraxane can also be considered if there is a previous adverse reaction to another taxane. Combination chemotherapy with docetaxel and capecitabine should be considered front line if there are life-threatening metastases (J Clin Oncol 2002; 12: 2812-23). Gemcitabine and docetaxel should be considered for those with previous significant mucositis toxicity. Duration of chemotherapy should be tailored according to effectiveness and toxicity in consultation with the patient (J Clin Oncol 29:2144-49, 2011).

Second line chemotherapy may be given after response (including disease stabilization) and relapse on first line treatment, or in a young fit patient anxious for further therapy despite progression on first line chemotherapy. Outside a clinical trial, if anthracycline-based chemotherapy is given, taxanes are the next most effective therapy, even in anthracycline resistant disease. Docetaxel has shown a small survival benefit when compared to mitomycin C and vinblastine. There is a high rate of febrile neutropenia (35%) with this agent. This can be partially avoided by starting with a 25% dose reduction or by giving a low dose weekly schedule in patients with poor bone marrow reserve (heavily pretreated including radiation or radiopharmaceutical therapy or extensive bone marrow involvement). Vinorelbine is another active agent that could be considered, particularly in elderly patients.

Oral capecitabine may be considered in patients who have progressed on or are unable to tolerate prior anthracycline or taxane therapy. Severe toxicities may occur unless patients immediately stop the medication at the first sign of discomfort associated with mucositis or hand/foot syndrome, more than four loose bowel movements in 24 hours or any nocturnal diarrhea. Interaction with even small doses of warfarin can result in an increase in INR and occasionally, hemorrhage. Patients on this drug should be closely supervised. Demonstration of a survival benefit of capecitabine over CMF (Abs 1031, ASCO 2007) should be considered when selecting this agent, especially in populations where anthracyclines or taxanes are refused by the patient or contraindicated.

Demonstration of a survival benefit of capecitabine over CMF (Abs 1031, ASCO 2007) should be considered when selecting this agent, especially in populations where anthracyclines or taxanes are refused by the patient or contraindicated. Eribulin has shown a survival benefit in
heavily pretreated patients and is expected to be reviewed by Health Canada soon (Lancet; 377:9769.914 - 923, 2011).

Trastuzumab therapy can be considered for those who have positive testing performed by an accredited pathology lab. Besides a positive test, individuals must have metastatic cancer, have failed first-line therapy for metastatic disease and have anthracycline resistant disease (progression within 6 months of anthracycline therapy for early or metastatic disease) or have unacceptable toxicity. All patients receiving trastuzumab should have a baseline MUGA scan or echocardiogram. Trastuzumab may be given alone or with a taxane if there has been no prior taxane therapy.

Trastuzumab has activity as a single agent (response rates 12-15% if prior chemotherapy) and in combination with chemotherapy has an improved response rate (45% versus 29%, p less than 0.001), time to progression (7.2 versus 4.5 months, p less than 0.0001) one year survival rate (79% versus 68%, p less than 0.01) and median survival (25.4 versus 20.9 months, p less than 0.045). Grade ¾ cardiac toxicity was found in 5% of patients treated with single agent trastuzumab, 4% when combined with paclitaxel and 19% when combined with an anthracycline + cyclophosphamide. A small number of deaths have been reported. Trastuzumab + docetaxel is also superior to docetaxel alone for response (61% versus 34%), overall survival (31.2 versus 22.7 months) and time to treatment failure (9.8 versus 5.3 months). Although it is unclear whether a sequential approach would provide similar benefit and there is more toxicity with the combination, combined therapy should be considered in patients with rapidly progressive or life-threatening disease (J Clin Oncol 2005; 23: 4265-74). Vinorelbine plus trastuzumab is similar in efficacy to docetaxel plus trastuzumab in a non-inferiority trial but has less febrile neutropenia and neuropathy and no nail changes or edema ( J Clin Oncol 29:264-71, 2010).

Lapatinib: Lapatinib is indicated in combination with capecitabine for patients with progressive metastatic breast cancer, with prior exposure to anthracycline, taxane and herceptin. Lapatinib at the dose of 1250 mg/day orally with 2000 mg/m2 days 1-14 of capecitabine (Cameron D et al., Br Ca Res Treat 2008;112:533)demonstrated prolonged TTP (HR 0.57, p<0.001) and a trend towards improved OS (HR 0.78, p=0.177). Interestingly, Lapatinib arm had fewer cases of CNS metastatic involvement (4 vs 13, p<0.045). In addition, Lapatinib is now indicated in combination with letrozole, as first-line treatment for post-menopausal patients with metastatic breast cancer, over-expressing Her-2neu. This combination versus letrozole alone (Johnston S et al., J Clin Oncol 2009;27:5538) showed better clinical benefit rate and PFS (HR 0.71, p<0.019, 8.2 vs 3 months).

Hormone Therapy
Indications:
(a) As first line therapy for patients with symptomatic metastatic disease who do not fit the criteria, outlined above, for immediate chemotherapy.
(b) Hormone therapy may be delayed in patients with asymptomatic metastatic disease (eg. positive bone scan only, surgical removal of metastasis without residual disease) until symptoms develop.
(c) In elderly patients with ER+ tumors, hormone therapy under close supervision may be considered for liver metastases.
(d) Patients receiving initial chemotherapy for metastatic disease who subsequently fail, may be considered for a trial of hormone therapy, regardless of receptor status.
(e) In patients with receptor positive tumors who have a locoregional recurrence. Two published trials describe a significantly prolonged disease free survival benefit from tamoxifen in addition to locoregional treatment in this situation.
In general, outside of a clinical trial, preference is given to using tamoxifen initially in premenopausal patients. In postmenopausal patients, an aromatase inhibitor should be considered as first line therapy although tamoxifen is an acceptable alternative. The other agent should then be considered as second line. Third line therapy should consist either of exemestane or megestrol acetate. Choice may be dependent on toxicity profile (weight gain, increased thromboembolic complications with megestrol acetate; fewer problems with exemestane). Fulvestrant is another option. Premenopausal patients with receptor positive disease may be considered for laparoscopic oophorectomy or radiation induced menopause or LHRH agonists as first line treatment, although tamoxifen may also be used in this group. Patients who have previously received adjuvant tamoxifen should have this drug restarted if their disease recurs more than 1 year after cessation of tamoxifen adjuvant therapy. Aromatase inhibitors should not be used in premenopausal patients as they can cause increased estrogen production by the ovaries. A meta-analysis suggests survival benefit for the combination of LHRH agonist + tamoxifen and a phase II trial has also shown significant clinical activity with anastrazole and Zoladex for metastatic disease in premenopausal women.

If patients fail to respond or stabilize on first line hormone therapy they should be considered for palliative radiation or chemotherapy, unless the disease is very indolent. If they respond to first line therapy but fail second line treatment, third line therapy may still be considered.

Hormone therapy, particularly estrogens or tamoxifen, may precipitate hypercalcemia (see below, follow-up investigations).

Patients with predominantly bony disease with poor pain control might also benefit from bisphosphonate therapy. Clodronate po is suggested for the prevention of complications associated with bone metastases. Patients most likely to benefit are those with purely or predominantly osseous metastases. The timing of treatment is controversial and should be considered on an individual basis. If the patient is unable to tolerate po clodronate, an intravenous bisphosphonate should be given. Pamidronate is recommended, although either pamidronate or clodronate may be useful adjuncts for pain control. Physicians should be aware of the possibility of osteonecrosis of the jaw and refer for dental assessment if there are concerns. Increasing reports of ONJ, especially after two years of treatment, should prompt consideration of either stopping bisphosphonate therapy or reducing the interval to every three months. However, the clinical approach to each patient should be individualized. Some patients with morbidity from widespread bone metastases may require a more aggressive approach to therapy, whereas those with solitary or few metastases that are not particularly symptomatic could be considered for less intense or prolonged therapy.

Intravenous bisphosphonates should be limited to the following situations:
- Patients with documented bone metastases.
- Patients intolerant of oral clodronate or unlikely to tolerate oral bisphosphonates.
- No significant metastases elsewhere (exceptions include prior excellent response of liver/brain metastases/lymphangitic lung metastases to therapy).
- Urgent treatment for severe pain not responsive to other measures.
- Treatment should be given at local hospitals or via home IV program.
- Patients on home IV program should first be given treatment under supervision and then transferred to the home IV program if tolerated.
- Treatment should be given indefinitely. Because of concerns regarding longer term toxicities, creatinine should be assessed periodically and after two years, if bone disease is stable, consideration could be given to reducing the frequency to every
three months. If bone disease is a significant concern, then monthly administration may be more appropriate.

Zoledronic acid should be considered for patients who cannot tolerate pamidronate or who develop hypercalcemia refractory to pamidronate. Denosumab, may be considered for patients with renal failure, or who cannot tolerate bisphosphonates. Radiopharmaceutical therapy may also be considered for patients who are not candidates for chemotherapy.

SUGGESTED FOLLOW-UP

Time interval

During chemotherapy
3-4 week intervals according to regimen.

During hormone therapy
every 6 weeks for 2 visits, then q 3 months if stable or responding.

After completion treatment
As indicated by clinical condition.

FOLLOW-UP INVESTIGATIONS

Patients with widespread bone metastases and not on clodronate should have serum calcium checked 10 days after starting tamoxifen. Other investigations will be dictated by the patient's condition, and treatment regimen. Patients with metastatic disease should be frequently assessed regarding possible referral to VON, home care, palliative care, nutritional and chaplaincy services.

Patients for whom all therapeutic options, except palliative care, are exhausted, should be considered for further follow-up by family physician or palliative care services.
MALE BREAST CANCER (See J Clin Oncol. 2010; 28:2114-22)

In general, this will be treated according to the same principles as female breast cancer, but with the following exceptions.

(1) Primary treatment
Due to the small size of the male breast, surgery should normally take the form of a simple mastectomy and SLNB if negative axillary ultrasound. Even with this procedure treatment margins will often be close, and chest wall irradiation is recommended. See genetics section 8.

(2) Systemic treatment
Virtually all these tumors are ER+. Adjuvant Tamoxifen treatment should be given to all patients with node positive disease. At present, hormone therapy is not recommended for node negative disease. It seems reasonable to apply similar principles as those found for breast cancer in women.

Hormone therapy is recommended first line for patients with symptomatic metastatic disease, unless it is immediately life threatening.

Chemotherapy should be recommended according to the same recommendations for women.
APPENDIX 1

CCO requires dictation of clinical and pathological stage (I, II, III, IV) as well as TNM stage at the time of consultation. (To be added)

TNM STAGING
(J Clin Oncol 2002; 20: 3628-36)

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>Tis (DCIS)</td>
<td>Ductal carcinoma in situ</td>
</tr>
<tr>
<td>Tis (LCIS)</td>
<td>Lobular carcinoma in situ</td>
</tr>
<tr>
<td>Tis (Paget)</td>
<td>Paget's disease of the nipple with no tumor</td>
</tr>
</tbody>
</table>

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

| T1                | Tumor less than or equal to in greatest dimension |
| T1mic             | Microinvasion less than or equal to 0.1 cm in greatest dimension |
| T1a               | Tumor greater than 0.1 cm but not greater than 0.5 cm in greatest dimension |
| T1b               | Tumor greater than 0.5 cm but not greater than 1 cm in greatest dimension |

| T1c               | Tumor greater than 1 cm but not greater than 2 cm in greatest dimension |
| T2                | Tumor greater than 2 cm but not greater than 5 cm in greatest dimension |

| T3                | Tumor greater than 5 cm in greatest dimension |

| T4                | Tumor of any size with direct extension to: |
| (a) chest wall, or | |
| (b) skin, only as described below |

| T4a               | Extension to chest wall, not including pectoralis muscle |
| T4b               | Edema (including peau d’ orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast |
| T4c               | Both T4a and T4b |
| T4d               | Inflammatory carcinoma |

Regional lymph nodes (N)

| NX                | Regional lymph nodes cannot be assessed (eg. previously removed) |
| N0                | No regional lymph node metastasis |
| N1                | Metastasis in movable ipsilateral axillary lymph node(s) |
| N2                | Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis |
| N2a               | Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures |
| N2b               | Metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis. |
| N3                | Metastasis in ipsilateral infraclavicular lymph node(s), or in clinically apparent ipsilateral internal mammary lymph node(s) and in the absence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement |
| N3a               | Metastasis in ipsilateral infraclavicular lymph node(s) and axillary lymph node(s) |
| N3b               | Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s) |
lymph node(s)
N3c Metastasis in ipsilateral supraclavicular lymph node(s)

Regional lymph nodes (pN)*

pNX Regional lymph nodes cannot be assessed (eg. previously removed or not removed for pathological study)
pN0 No regional lymph node metastasis histologically, no additional examination for isolated tumor cells
pN0 (i -) No regional lymph node metastasis histologically, negative IHC
pN0 (i +) No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
pN0 (mol -) No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)
pN0 (mol +) No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)
pN1mi Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
pN1 Metastasis in one to three axillary lymph nodes and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
pN1a Metastasis in one to three axillary lymph nodes
pN1b Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
pN1c Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
pN2 Metastasis in four to nine axillary lymph nodes, or in clinically apparent internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN2a Metastasis in four to nine axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b Metastasis in clinically apparent internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN3 Metastasis in 10 or more axillary lymph nodes, or in infracavicular lymph nodes, or in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infracavicular lymph nodes
pN3b Metastasis in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
pN3c Metastasis in ipsilateral supraclavicular lymph nodes

Distant metastasis (M)
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
* “Clinically apparent” is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.
+ Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated for “sentinel node” (eg. pN0 (i +)(sn))
~ Isolated tumor cells are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical or molecular methods but which may be verified on hematoxylin and eosin stains. Isolated tumor cells do not usually show evidence of metastatic activity (eg. proliferation or stromal reaction)
# “Not clinically apparent” is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination
^ Associated with more than three positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden

**Stage Grouping (UICC, 7th ed, 2009)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tm</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
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<tr>
<td>Stage IB</td>
<td>T0,T1*</td>
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<td>Stage IIA</td>
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</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Note: *T1 includes T1mic
APPENDIX 2

PATHOLOGY CHECKLIST
APPENDIX 3

BREAST IMAGING

* The following are modified guidelines recommended by the American College of radiology, used at St Joseph Health Care

Mammography

Mammography is the diagnostic examination of the breast using low-dose x-rays. Digital mammography also uses x-rays but captures the image on a computer, where it can be viewed and manipulated for contrast. While finding no significant difference between the two techniques when applied to the general population and for most women over 50, studies have shown that digital mammograms detected more tumors in three specific groups: women under 50, women with dense breasts, and women not yet in menopause. The radiation-induced cancer risk associated with breast screening for a woman attending mammographic screening (two views) is about 1 in 20,000 per visit. Screening every two years from age 50 shows 80 lives saved for every life lost due to radiation-induced cancers. The goal of all mammography is the detection and evaluation of breast cancer and other breast diseases. The goal of diagnostic mammography is to obtain information that leads to specific interpretive conclusions and/or further diagnostic and management recommendations or courses of action. The patient's history, symptoms, and signs, the reported findings on physical examination, and results of any prior mammography will focus the diagnostic breast evaluation.

1. Screening mammography

There is unequivocal evidence from randomised controlled trials that population screening of women over the age of 50 by mammography alone can, by early detection, reduce mortality from breast cancer. The OBSP provides screening by invitation every 2 years for women over 50. Two-view mammography (mediolateral oblique and craniocaudal projections of each breast) is required at each attendance.

Screening of asymptomatic women between the ages of 40 and 49 years

Screening in this age group remains controversial as there are doubts regarding the risks and cost-effectiveness of population screening in this age group. Individual women in this age group who seek or are referred for mammographic screening should be made fully aware of the theoretical radiation risks and the increased rates of false reassurance, false-positive and false-negative results and benign surgical biopsies compared to screening in older women, as well as the possible benefits. Two-view mammography at each screening visit is recommended.

Screening women under the age of 40 years

There is no evidence of any mortality benefit from mammographic screening of women under the age of 30 years. There are also greater theoretical risks of radiation-induced breast cancer from the use of mammography in young women. For these reasons, routine screening of women in this age group in the absence of any significant breast cancer risk factors is not recommended.
Mammographic screening of patients at increased risk of breast cancer

- Family history of breast cancer (i.e. one first-degree relative -- a parent or sibling -- who had breast cancer)
- Diagnosis of atypia, also known as atypical hyperplasia (a form of benign breast disease), or lobular carcinoma in situ
- History of having been treated with mantle radiation before the age of 32
- Only a small proportion of breast cancer is hereditary and linked to highly penetrant dominant genes.

* Annual mammography starting ten years prior to the age of the youngest family member with breast cancer (but not earlier than age 25 and not later than age 40) Consider annual MRI

Women with a Diagnosis of Atypical Hyperplasia or Lobular Carcinoma In Situ

* Annual mammography beginning at the time of diagnosis. Consider annual MRI.

Women with a History of Chest Radiation

* Annual mammography starting eight years after radiation treatment. Consider annual MRI.

Mammography in women receiving HRT

Studies had demonstrated a higher risk of having breast cancer in women using HRT and this is dependent on the duration of use. There is a subsequent fall in sensitivity and specificity and an increased recall rate from mammographic screening. In this age group, there is no evidence to support more frequent screening. A decreased sensitivity and specificity of screening mammography have been reported.

Mammography in the follow-up of patients with breast cancer

Patients who have been treated for breast cancer may develop recurrence of the primary cancer or distant metastatic disease and are at increased risk of developing a second primary breast cancer (six times the lifetime risk). Recurrence is likely to show the same mammographic features as the primary lesion, so although interpretation may be hampered by post-operative scaring and radiation changes, mammography can detect 30-40% of clinically occult recurrence. It is considered reasonable practice that mammography should be performed annually.

2. Symptomatic breast imaging

The majority of women presenting with symptomatic breast disease first consult with their general practitioner. Frequent symptoms which indicates further assessment include:

1. Breast or axillary lump or thickening


3. Nipple discharge: if bloody, or clear nipple discharge
4. Change in skin contour or color

5. Changes in nipple appearance; distortion, eczema, inversion

* The recommended protocols for the use of breast imaging are age-dependent and mammography should be the initial imaging modality of choice in symptomatic patients over 30 years. It is recommended that the standard mammographic examination should normally include a mediolateral oblique and a craniocaudal projection of each breast. Supplementary projections may be performed as directed by the supervising radiologist. Mammography is not recommended for woman who had obtained mammogram within less than 6 months prior to her symptoms. Woman with new symptoms presented over 6 months but less than 12 months since her last routine mammogram, should obtained unilateral mammogram of the symptomatic side.

* Female patients younger than 30 years old, male patients younger than 20, pregnant and breast feeding patients: Ultrasound should be obtained first. Mammography will be applied if needed. Shielding should be used in a pregnant patient.

3. Imaging of women with breast implants

Mammography carried out on these women often presents significant technical and interpretational difficulties. The presence of implants is very likely to lower both the sensitivity and specificity of diagnostic or screening mammography. Women with a prosthesis who undergo mammography should be aware that the risk of prosthesis rupture as a result of compression during mammography is extremely small. The presence of any visible breast asymmetry should, however, be recorded before mammography is performed in case the examination is blamed for producing an existing abnormality. Routine plus displacement techniques described by Eklund are particularly valuable. Women with implant who are over the age of 50 cannot be screened through the OBSP and should be referred by their clinician.

**Implant integrity**

MRI is now the investigation of choice for the diagnosis of - or exclusion of - implant rupture. The ability of MRI to detect both intra- and extra-capsular rupture and the detection of migration of free silicone away from the implant site are reasons for its superior performance. Routine MRI for the assessment of implant integrity does not include contrast injection and cannot exclude malignancy.

**Ultrasound**

Ultrasound is an imaging method in which high-frequency sound waves are used to create images. Breast ultrasound is often used to evaluate breast abnormalities that are found during mammography or a clinical breast exam. The accuracy of breast ultrasound is highly dependent on the skill level and training of the ultrasound technician and radiologist. This creates an increased risk of false positives, requiring follow-up exams and biopsy -- which can be expensive and lead to unnecessary anxiety for the patient.

Appropriate indications for breast sonography include:

1. Evaluation of palpable masses and other breast related signs and/or symptoms. Initial imaging evaluation of palpable masses in women under 30 years of age and in lactating and pregnant women.
2. Evaluation of suspected or apparent abnormalities detected on other imaging studies, such as mammography or magnetic resonance imaging (MRI).

3. Evaluation of problems associated with breast implants.

4. Evaluation of breasts with microcalcifications and/or architectural distortion suspicious for malignancy or highly suggestive of malignancy in a setting of dense fibroglandular tissue, for detection of an underlying mass that may be obscured on the mammogram.

5. Guidance of breast biopsy and other interventional procedures.

6. Treatment planning for therapy.

7. Evaluation of the axilla for occult lymph node metastasis.

* The efficacy of ultrasound as a screening study for occult masses in dense fibroglandular breasts of high risk women or women with newly diagnosed or suspected breast cancer is an area of research. If it used, mammography should be obtained at the same time.

* Sonographic features are helpful in characterizing breast masses. Features and descriptors suggested to be based on ACR Breast Imaging Reporting and Data System lexicon. The BI-RADS sonographic categories include size, shape, orientation, margin, echogenicity, lesion boundary, attenuation (e.g., shadowing or enhancement), special cases, and surrounding tissue. **Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI) is a diagnostic procedure that uses a magnetic field to provide three-dimensional images of internal body structures, including the breast. MRI is expensive and requires the injection of intravenous contrast agent. The exact role of breast MRI in the investigation and management of breast cancer has yet to be fully established. Breast MRI has advantages in high sensitivity for invasive (but less so for in situ) disease and does not use ionising radiation. It may be useful in evaluating potential recurrence following conservation surgery, the detection of multifocal disease and the evaluation of patients undergoing neoadjuvant chemotherapy. Patients with breast implants can be assessed for implant integrity and the presence of suspected malignancy. The disadvantages of MRI are its expense, limited availability, a wide variation in reported specificity and the lack of biopsy facilities for lesions detected by MRI alone. There are no study data showing that MRI screening reduces the number of breast cancer deaths.

**Recommendations:**

1. Screening breast MRI is not recommended at the present time in the general population of asymptomatic, average-risk women.

2. Breast MRI may detect abnormalities that are not evident clinically, mammographically, or sonographically. They may or may not be clinically significant. As with mammography or any other diagnostic test, false positive results can be expected, and the literature shows a wide range of specificity for breast MRI. The additional abnormalities detected on MRI may result in a follow-up examination or recommendation for biopsy. Published biopsy rates for MRI are similar to those for mammography.

3. Information from the MRI examination may change the planned treatment management. Caution should be exercised in changing management based on MRI findings alone without
initial biopsy confirmation. Additional biopsies and/or correlation with other clinical and imaging information should be used together with clinical judgment.

4. MRI should not supplant careful problem-solving mammographic views or ultrasound in the diagnostic setting. Because MRI will miss some cancers that mammography will detect, it should not be used as a substitute for screening mammograms. MRI should not be used in lieu of biopsy of a mammographically, clinically, and/or sonographically suspicious finding.

* Interpreting physicians should have knowledge and expertise in breast disease and breast imaging diagnosis. Mammographic correlation, directed breast ultrasound, and MRI-guided intervention should be available.

* Patients should undergo standard mammography in addition to breast MRI, and the mammography study images and report should be available for review.

* Increased parenchymal enhancement has been observed normally during the secretory phase of the menstrual cycle. This normal enhancement can give rise to false positive MRI scans. It is therefore recommended that breast MRI scans be performed during the second week of the menstrual cycle whenever possible. Bilateral imaging is helpful to improve specificity, as enhancement characteristics vary from patient to patient and during the menstrual cycle, and enhancement of some benign conditions such as fibrocystic changes is often bilateral.

Galactography

1. Recommended for symptomatic patients presented with bloody or clear nipple discharge. Can only be performed if a discharging orifice is identified and cannulated.
2. Ultrasound of the retroareolar complex should be obtained prior to galctography in a search for intraductal masses.
2. Galactography is suggested even if an abnormality is detected by ultrasound, for the exclusion of multiple filling defects.
3. Ultrasound guided biopsy can be offered for indeterminate lesions but only after a galactography is performed
4. If an intraductal papilloma is highly suspected on ultrasound the patient is sent for surgical consultation. Ultrasound guided core biopsy may be performed if requested by surgeon.
5. Galactography can be used to localize lesion prior to surgery by injecting blue dye into the discharging orifice, in case that no sonographic abnormalities are detected.

Image-guided breast interventional procedures

* Percutaneous sampling of breast lesions is important to avoid unnecessary surgery for benign problems and provide pre-operative diagnosis of malignant lesions, allowing for treatment planning. Biopsy should be performed on all clinically or radiologically indeterminate, suspicious or malignant breast abnormalities. To ensure accurate sampling, image guidance may be the preferred technique for sampling palpable as well as impalpable lesions.

* The best results are likely to be achieved if 14-gauge needles are used with a spring-loaded biopsy device. Stereotactic biopsy is suggested for microcalcifications, and specimen radiography is required to confirm adequate sampling. Vacuum-assisted biopsy will yield greater amounts of tissue which should produce greater diagnostic accuracy however, the equipment is expensive and its exact role is still being established. Ultrasound guidance is recommended where lesions can be confidently seen on ultrasound.
* The imaging assessment and the cytopathologic or histopathologic interpretations should be correlated for concordance by the physician performing the biopsy, and records should be kept to document results and patient management recommendations.

**Indications for percutaneous ultrasound-guided breast interventional procedures**

1. Simple and complicated cysts when: They are symptomatic, documentation of evacuation is desirable, correlation with other imaging findings (mammography, MRI) is likely to provide important diagnostic information that will guide patient management. Abscesses or infected cysts are suspected, and diagnostic aspiration and therapeutic drainage are clinically indicated.

2. Complex cysts and solid masses when:
   a. Masses are assessed as highly suggestive of malignancy (BI-RADS Category 5)
   b. Masses are assessed as suspicious abnormalities (BI-RADS Category 4).

3. Biopsy of lymph nodes in the axilla/axillary tail in cases of known or suspected malignancy; when the suspicion of malignancy is high, and if abnormal lymph nodes are seen within the axilla or axillary tail, core biopsy sampling of the cortex of the abnormal lymph node(s) can be performed at the time of initial imaging-guided core biopsy of the suspicious breast mass, or at a later time. Care should be taken if core biopsy is performed in the axilla due to the presence of sensitive structures (the brachial plexus and axillary artery and vein).

* Following performance of core biopsy, and as appropriate following aspiration or FNA biopsy, placement of a localizing clip at the biopsy or aspiration site should be considered to facilitate surgical excision if necessary, especially for lesions that may be difficult to visualize on subsequent ultrasound examinations, for mammo-graphically occult lesions, for those that may undergo neoadjuvant chemotherapy, and for correlating with findings on other imaging modalities. When multiple lesions are present and biopsy of more than 1 suspicious lesion is performed to establish multicentricity, placement of markers of different shapes should be considered. When a clip has been placed, a post biopsy mammogram consisting of is recommended following the procedure to document clip location.

* The physician who performs the procedure is responsible for obtaining results of the cytopathologic or histopathologic sampling to determine if the lesion has been adequately biopsied and is concordant or discordant with the imaging findings. These results should be communicated to the referring physician and/or to the patient, as appropriate.

**Presurgical localization**

1. Ultrasound-guided localization may be performed when the lesion or an appropriately positioned marking device placed during a previous biopsy is identifiable with ultrasound.
2. Mammographic guidance is suggested for microcalcifications or lesions seen only on mammography or lesions marked with tissue marker and are not seen on ultrasound.
3. The tissue marker inserted for lesions that were biopsies using MRI guidance can be localized under mammography. Wider excision is required as there is an expected larger clip mobility given the use of vaccum assisted device.
4. Specimen radiography is required to confirm adequate sampling.
5. If there is doubt regarding adequate surgical excision, routine ipsilateral ultrasound and or mammography are required to be obtained within a month following the procedure to ensure that the lesion had completely excised.
The Breast Imaging Report

The location of breast abnormality can be indicated by using clock face notation and/or quadrant of the breast; and/or location within the anterior, middle, or posterior third of the breast; and/or distance from the nipple. The mammogram report should describe detected abnormalities and pertinent observations, establish levels of suspicion of malignancy based on the imaging findings, and provide recommendations for diagnosis, patient management, and follow-up. If additional, separate breast imaging studies or procedures are performed or are available, they may be correlated in the diagnostic mammography report.

The ACR BI-RADS lexicon provides a framework for reporting, lesion assessment, imaging-pathologic correlation, and quality improvement.
A description of detected abnormalities and recommendations for subsequent follow-up studies should be included in the report. Overall final assessment of findings may be based on all imaging studies performed that day. In addition, they must be classified according to the final assessment categories and should follow the categories defined in the ACR BI-RADS lexicon.

BI-RADS
Mammographic Assessment Category Description

BI-RADS 0: Incomplete assessment: Need additional imaging evaluation and/or prior mammograms for comparison.

BI-RADS 1: Negative.

BI-RADS 2: Benign finding(s).

BI-RADS 3: Probably benign finding – initial short-interval follow-up suggested.

BI-RADS 4: Suspicious abnormality – biopsy should be considered.

BI-RADS 5 Highly suggestive of malignancy – appropriate action should be taken.

BI-RADS 6 Known biopsy – proven malignancy – appropriate action should be taken.

BI-RADS Category 0 assessments are assigned to incomplete evaluations. Additional mammography views, ultrasound, or previous studies are necessary to assign a final assessment category.

A category 3, 4, or 5 assessment is not recommended for a screening mammogram, although in some instances a highly suspicious abnormality may be identified that will warrant a recommendation for biopsy. Patients with screening abnormalities will be given a BI-RADS category 0 and recalled for further diagnostic studies.

BI-RADS 3 follow-up: Usually offered for a period of 2 years at 6 months 12 months and 24 months using the modality where the abnormality is seen the best. Mammogram should always obtain at 12 months and 24 months unless the patient is younger than 30, pregnant or breast feeding. Follow-up intervals and period may be adjusted based on findings. The report during the period of follow-up should always included information regarding the next suggested appointment by mentioning the month, year and the modality (ies) to use.
In cases where the assessment is a BI-RADS category 4 or 5, reasonable attempt to communicate directly with the health care provider as soon as possible should be made. An attempt to arrange an urgent appointment and to deliver the patient with the information regarding the time and the date should be obtained if possible. The actual or attempted direct communication should be documented in the mammogram report. If the date and time of the appointment is known, this should be mentioned in the report.
APPENDIX 4

SURGERY

Core or trucut biopsy
When adequately performed this is of great value. It is a simple procedure that provides an accurate diagnosis in about 75% of those with cancer with much higher sensitivity when done under image guidance (mammogram or ultrasound). We have never had a false positive. A false negative is often appreciated at the time of the procedure when the needle cannot be made to penetrate the tumor due to its hardness and a negative biopsy must be interpreted with the radiologist to determine whether the findings are concordant with imaging results.

Incisional biopsy
This is indicated, using local anesthesia, in those with T4 or inflammatory tumors ONLY when image-guided biopsies have failed. In the case of inflammatory cancers, an MRI should be done prior to a skin punch biopsy in order to minimize a false interpretation of the MRI finding, as these tumours are often mammographically and sonographically occult. The diagnosis can be confirmed and a specimen obtained for receptor status (need to request ER/PR and Her2 status on the core biopsy of all Locally Advanced breast cancer specimens as they are typically treated with preoperative systemic therapy).

Excisional biopsy
This is not considered an appropriate standard approach, but may be considered in cases deemed indeterminate by imaging, discordant with the core needle biopsy specimen or based on patient preference, where the finding of malignancy was not expected at the time of excision. In these cases, the excision must include clear margins, and the patient needs to be referred back for a sentinel lymph node biopsy procedure (injecting radiocolloid and dye peri-lumpectomy cavity

Needle localization biopsy
See Appendix 3.

Partial mastectomy(otherwise known as lumpectomy or breast conserving surgery)
Partial mastectomy is indicated for those patients in whom an adequate procedure does not result in significant cosmetic impairment. The aim of partial mastectomy is to completely remove the lesion with a margin of normal breast tissue. Curvilinear incisions should be used along the skin lines. Suture approximation of breast parenchyma or subcutaneous tissues should be avoided. Surgical drains should not be used. Subcuticular skin closure is recommended. Surgical clips placed to mark the margins of the resection bed are helpful for radiotherapy planning.

The specimen should be oriented with sutures for the pathologist, and submitted intact for inking of the margins.

Patients with T4 tumors should be treated by incisional or core biopsy for diagnosis, to obtain the receptor status and then pre-operative systemic therapy (hormone or chemotherapy) with or without radiotherapy. Subsequently they are considered for partial or total mastectomy, depending upon amount of tumor regression. Locally advanced breast cancers are at high likelihood of being lymph node positive (>80%) therefore current standard continues to include an axillary dissection for these patients, particularly T4 and Inflammatory cancers.
Staging axillary nodal dissection
During the Halstedian era, it was felt that the axillary dissection was therapeutic and that an additional number of patients could be cured by widespread removal of the axillary nodes. It is now appreciated that if the axillary nodes contain metastases, there is a high risk of distant metastases. The operation is therefore mainly a staging procedure, although it may also have therapeutic benefit.

It was also thought that surgical excision of axillary nodes was the best way to control nodal metastases. It is now appreciated that they are as effectively controlled by chemotherapy, hormonal manipulation or radiotherapy or a combination and with less morbidity, than following an extensive axillary dissection. There has been considerable interest in the number of nodes that should be removed. The NSABP study found that no additional information was obtained by removing more than eight nodes. The other controversial issue is the level at which the nodes should be removed. Namely do skip metastases occur? The majority of metastases develop at Level I, lateral to the pectoralis minor muscle, however, perhaps as many as 10% may develop metastases at Level II, deep to pectoralis minor, without involvement of Level I. We feel that nodes at both levels should be excised. Radiotherapy to the axilla can be avoided after complete axillary dissection, reducing the incidence of arm edema which may result if both procedures are used.

A number of incisions have been used for the axillary dissection. We have found that a straight or curved incision, just behind the anterior pectoral fold or a “smiling” incision at the base of the axillary hair line gives adequate exposure and good cosmetic results. The clavipectoral fascia is then divided at the lateral border of the pectoralis minor and this permits medial retraction of the pectoralis minor muscle. The third part of the axillary vein is then exposed between the lateral margin of the pectoralis minor and the subscapular vessels. The axillary fat pad is then dissected downwards from the vein exposing the chest wall. The nerves to the latissimus dorsi and the serratus anterior are identified. The pad of fat is then removed and the axilla is drained.

The drain is left in position until drainage is less than 30 cc's per day. The patient is encouraged to move the arm freely. Full movement is possible in about one week and edema should occur in less than less than 10% of patients related to the surgery alone, and a doubling of lymphedema risk in patients who also receive radiation that overlaps the axilla.

The role of sentinel lymph node dissection (SLND) is now established. This approach will reduce morbidity and hospital stays. It is recommended that SLND be performed in a prospective standard fashion with input from surgery, pathology, radiology and nuclear medicine and that any results be audited and evaluated prior to a policy statement. SLND should not be performed in an ad hoc fashion.

Background
The publication of an initial study of sentinel node biopsy in 1998 in the New England Journal of Medicine described it as “technically challenging”, with the success rate varying according to the surgeon and patient characteristics (NEJM 1998; 339: 941-946). Much has changed over the past few years with its use having increased significantly in clinical practice (J Clin Oncol 2003; 21: 3357-3365). A recent randomized study stated “it is a safe and accurate method of screening the axillary nodes for metastasis in women with a small breast cancer”( NEJM 2003; 349: 546-553).

The sentinel lymph node technique has been validated as the appropriate technique for axillary staging in early breast cancer (George et al, 2010). The evidence for this is outlined on the Cancer Care Ontario PEBC website.

Patient Selection
Women appropriate for SLND should have the following characteristics:
- tissue diagnosis of invasive breast cancer or significant risk (ie: extensive high grade DCIS and planned mastectomy)
- less than 5 cm (T1 or T2)
- clinically negative nodes
- no evidence of metastatic disease

Patients are NOT considered suitable if they have any of the following factors:
- neoadjuvant radiation or systemic therapy has been given (chemotherapy or hormonal therapy)
- have a previously placed pre-pectoral breast implant (not a full contra-indication but may increase non-identification rate)
- clinically or radiologically identified multi-centric disease not amenable to a single lumpectomy
- Pregnancy, allergy to blue dye or radiocolloid
- prior axillary surgery

Health Care Team Requirements for Performing SNS
In order to successfully perform SNS, a standardized protocol should be in place (CMAJ 2001; 165: 166-173; Breast J 2004; 10: 85-88). Appropriate training and experience is required in order to implement this technique (Ann Surg Oncol 2004; 11: 211S-215S). Teams may include surgeon, nuclear medicine/radiology and surgical pathology.

Procedure
Methods include the use of radiocolloid and blue dye together or one technique exclusively. The combination of both has been shown to result in higher identification rates of the sentinel node and is preferable, but the use of one method may provide acceptable rates with enough expertise (CMAJ 2001; 165: 166-173; ANZ J Surg 2003; 73: 815-818; Eur J Surg Oncol 2004; 30: 913-917; 8th Annual Clinical Congress of the American College of Surgeons, 1999). Our recommendation is that the two methods be used together.

Surgical Skills
Previously published Canadian guidelines suggest the following (NEJM 2003; 349: 546-553):
1. Surgeons should thoroughly familiarize themselves with the literature on the topic and technique needed to perform successful SNS.
2. Surgeons should follow a defined protocol for the procedure.
3. Initially surgeons should always perform backup axillary dissection when doing SNS.

With regards to the third point, the American Society of Breast Surgeons policy (endorsed by the American College of Surgeons Oncology Group) suggests performance of 30 SNS followed by complete axillary dissection (American Society of Breast Surgeons. Revised consensus statement on guidelines for performance of sentinel lymphadenectomy for breast cancer, 2000). An 85% success rate in identifying the sentinel node and a less than or equal to 5% false-negative rate should be achieved. At least 10 cases should have metastatic disease in the axilla. Recent published guidelines have similar suggested numbers with a 95% identification rate of sentinel node(s) and false-negative rates of less than 5%. Until these rates can be achieved consistently, individual surgeons should not abandon traditional axillary dissection. In all cases, patients should be informed of the number of cases performed by the surgeon and his/her false-negative rate and explained the implications of a false-negative result.

Surgical Pathology
A standard protocol should be in place for analyzing sentinel nodes. This would include how the nodal tissue is sliced and sectioned and the methods used for analysis (frozen section, touch
prep, H&E). As per the sixth edition of the AJCC Staging Manual, micrometastatic (less than or equal to 0.2 mm) deposits are considered node-negative (AJCC Cancer Staging Manual, 6th Edition, 2002). Further surgery is not required if this represents the only evidence of disease. Immunohistochemistry may be performed and reported but should NOT alter the subsequent decision-making with regards to further surgery or adjuvant therapy (Ann Surg Oncol 2004; 11(12): 1056-1060; Eur J Surg Oncol 2004; 30: 807-816.12,13).

Indications for Complete Axillary Node Dissection
The standard of practice has been axillary node dissection that has a known diagnostic benefit and a possible therapeutic value. Even if SNS is being performed, an axillary node dissection should be done for ANY of the following reasons:
1. Inability to identify the sentinel node.
2. Presence of matted nodes or gross extranodal disease at the time of SNS.
3. Positive sentinel nodes by frozen section, touch prep or H&E staining on permanent section (a focus of disease less than or equal to 0.2 mm is NOT considered positive).

Mastectomy

Indications for mastectomy
The number of mastectomies being performed is rapidly decreasing. This procedure is indicated in those in whom partial mastectomy would result in significant cosmetic defect. Those with T4 tumors should initially be treated with systemic therapy plus radiotherapy, and those who have good response may be considered for partial mastectomy while those with poor response may be treated by mastectomy or radiotherapy alone. The occasional patient with two infiltrating carcinomas or with multicentricity in the same breast should be treated by mastectomy.

There is no place for toilet mastectomy as primary treatment in those with T4 tumors. These patients should initially be treated by hormonal manipulation, chemotherapy or radiotherapy or a combination of the three.

Technique
A mastectomy consists of removal of the areola and nipple and all the mammary lobular tissue. Reconstruction should be considered at the same time or later. A tissue expander or one-stage implant (if used) should be inserted deep to the pectoralis muscle by a plastic surgeon at the time of mastectomy ONLY IF adjuvant radiation is not expected. Patients eligible for autologous breast reconstruction can have breast reconstruction done at the same time as mastectomy in order to preserve skin and optimize cosmesis for appropriate patients and only if it will not unduly delay adjuvant therapy performed at a later period. Refer to Breast Reconstruction section for further details.

Indication for bilateral mastectomies
This is a controversial subject and should only be performed after considerable discussion. Patients should be advised that no overall survival benefit is derived from a prophylactic contralateral mastectomy. Additionally, if bilateral mastectomy is desired, the option for immediate reconstruction should be discussed with the patient.

About 5 to 10% of carcinomas of the breast develop on a genetic, compared with an environmental, basis. Relatives are described as first degree (mother and sister), and second degree (other relatives). The likelihood of a woman developing a carcinoma depends on the degree of the relative, age at diagnosis, unilaterally or bilaterally and the histology (namely lobular carcinoma). There are published tables which can be used to counsel the individual patient about her risks (Bryant et al, CMAJ 1994; 150(2): 211-216).
In those with insitu or invasive lobular carcinoma there is about 1 in 3 likelihood of developing a carcinoma in either breast in 10 years. Formerly bilateral mastectomies were often recommended. However there is now increasing support for treating those patients by partial mastectomy, examining the patient every three months and having a mammogram every six months. Currently, the option of close follow-up in the form of frequent physical examinations and annual imaging including MRI and mammogram versus prophylactic mastectomy with or without immediate reconstruction should be discussed and the patient can choose in accordance with their preference.
APPENDIX 5
RADIOThERAPY

Technical guidelines for irradiation of breast/chest wall and lymph node areas

BREAST/CHEST WALL

1. Timing
   Following lumpectomy or mastectomy, adjuvant radiation to the breast or chest wall should be started ideally within twelve weeks after surgery. Our own published experience has shown no adverse effect to radiation started up to sixteen weeks after surgery (IJROBP 1998; 40: 4). Exceptions would be:
   
i) stipulated otherwise by protocol
   ii) postoperative infection
   iii) adjuvant chemotherapy administration requiring deferral of radiation

2. Volume
   Target volume includes: ipsilateral breast (postlumpectomy), chest wall, and generally covers most of the Level I and II axillary nodes (IJROBP 2001; 51(3): 671-8).
   
The boundaries of the target volume should be set so the light field edges include the breast with a 1.5–2.0 cm margin. They are initially set up at:
   
   Medical: midsternal line
   Lateral: the midaxillary line. This may be adjusted slightly such that no more than 3.5 cm of lung is irradiated.
   Superior: The suprasternal notch, unless concurrent supraclavicular and axillary radiation is to be given, in which case the superior border should correspond to the level of the inferior aspect of the clavicle.
   Inferior: 1.5-2.0 cm below the inframammary sulcus or the lower part of the breast or in the case of a mastectomy patient estimated from the contralateral breast.
   
   Care should be taken to note the position of the surgical scar and it should be included over the breast/chest wall volume. The width of the lung should be less than 2 cm at the central axis of the field. Collimator rotation or shielding should be used to minimize cardiac volume within the field when radiating the left side.
   
   Boost: The boost can be planned using the data from the CT Simulation. The seroma cavity plus 1-1.5cm should be covered. The volume need not extend beyond the chest wall unless there is specific concern regarding involvement in that region. In certain cases an electron boost may be utilized, particularly in the post mastectomy setting. Additional information such as the pre-op mammogram and patient localization of the prior lump should be used when available.

3. Simulation
   The patient will be simulated, and treated supine, with the arm supported above the head with a breast board. CT simulation will be performed for planning purposes. A tangential,
coaxial pair of beams at 100 cm SAD will be arranged to fulfill the volume requirements stated above. In difficult cases Inverse planned Intensity Modulated Radiation may also be used to cover the volumes as outlined.

4. **Dose Specification**
The distribution, including lung correction, compensation and any bolus required shall be no more than plus or minus 7% in variation with areas less than 2 cm² in cross section being deemed insignificant as per ICRU 29. Forward IMRT will be utilized in order to obtain an optimal dose distribution.

Dose will be specified at a point two-thirds the distance from the skin towards the base of the tangential fields at mid-separation in patients with intact breasts.

5. **Dose**
The optimal dose fractionation for breast radiation has not been determined. 5000 cGy/25 fractions have been used by the NSABP effectively. An OCOG study has shown in ten year follow up similar local control rates and cosmetic results between 4250 cGy/16 and 5000 cGy/25 (NEJM 2010 May 13, 362(19)).

Currently used regimens include: 4250 cGy/16 or 5000 cGy/25 (plus or minus boost). Treatment is delivered using 6 or 10 MV photons, 100 cm SAD, 2 fields per day, 5 days per week.

A boost is given in 5-8 fractions for an additional dose of 1000-1600 cGy.

**SUPRACLAVICULAR, AXILLARY (plus or minus INTERNAL MAMMARY NODES)**

Treatment, concurrent with tangents

Patients will be planned with CT simulation. CT planning has several advantages such as providing DVH’s of lung and heart especially when anthracycline-based chemotherapy is used.

**Supraclavicular/Axillary Volume**
The boundaries of the target volume are set by placing light field edges at:

i) **Superior**: to include the supraclavicular fossa

ii) **Medial**: to the ipsilateral edge of the vertebral bodies (to exclude spinal cord)

iii) **Lateral**: to the coracoid process, unless a Level I and II dissection has left known disease in the lower axilla in which case the lateral border shall be increased to encompass the disease. A humeral head shield may be used.

iv) **Inferior**: to match the superior border of the tangent field, generally at the 2nd rib. Junction shifting is not required unless known disease is at the junction.

This field will be simulated and treated at 100 cm SSD. Dose will be prescribed at depth, usually 3 cm. In cases where less than 10 nodes were removed, greater than 3 nodes are positive or gross residual disease is left behind, an anterior parallel pair may be used. Dose is 4600-5000 cGy, in 23-25 fractions with 6 MV photons.

**Internal Mammary Volume**
In cases where a decision is made to treat the internal mammary nodes, it is useful to have the position of the nodes mapped by lymphscintigraphy (done in radiology). The boundaries of the target volume are set to cover the upper 1st to 3rd intercostal space internal mammary nodes. It is recommended that a wire be placed at the lower border of the anterior 3rd intercostal interspace.
The simplest (and preferred) technique is using modified wide tangents where all borders are the same as for the breast/chest wall except the medial:

**Medial:** 3 cm contralateral to the mid sternum

This volume can be difficult to adequately cover and may require IMRT in order to achieve an acceptable dose distribution.

**Technical guidelines for recurrent/metastatic breast cancer**

**LOCOREGIONAL RECURRENCE AFTER MASTECTOMY**

If possible, surgical excision of recurrent solitary chest wall lesions should be done unless the patient has metastatic disease elsewhere and this lesion is to be used as a marker for systemic treatment. Surgical removal of an axillary recurrence may be considered, especially if the patient has not had a previous lymph node dissection and, as above, the nodal recurrence is not required as a marker for systemic treatment.

In patients in whom locoregional recurrence (only) develops, 70-80% will eventually develop distant metastatic disease. Therefore, while aggressive treatment can apparently significantly reduce the relative risk of second recurrence in this area, the absolute effect is smaller than that because death from distant disease reduces the population at risk for locoregional recurrence. Furthermore, no effect on survival will result from locoregional treatment.

The patients selected for aggressive locoregional treatment should have both the chest wall and nodal areas irradiated simultaneously. See above sections for description of technique.

**BRAIN METASTASES**

All patients requiring brain treatment should be treated with a coaxial pair of photon beams, two fields per day using 10 or 6 MV may be used. A series of RTOG trials reported (IJROBP 1980; 6: 1) has not shown the superiority of one dose fractionation. Commonly used regimens are 3000 cGy/10 or 2000 cGy/15. Late complications of radiation are associated with larger fraction size, so patients with favourable prognostic features (absence of extracranial disease, young age, solitary metastasis (on MRI etc) should receive smaller daily fractions. Regimens include 3750 cGy/15 or 4000 cGy/20.

Simulation or clinical mark-up may be used. If the patient is marked-up clinically, the volume treated should be defined by a line running from the superior orbital ridge to the inferior edge of the ear lobe and anteriorly, superiorly and posteriorly by lines extending beyond the margins of the skull.

In cases with low lying metastatic disease, or leptomeningeal involvement, the inferior border may be placed lower and eye shields used.

In certain cases, retreatment may be considered. These patients should have had a response of at least six months duration to the initial treatment and have little co-morbidity.

**SPINAL METASTASES**

Prophylactic treatment of spinal metastases may be considered when the pedicle as viewed on plain films loses its definition. Otherwise asymptomatic spinal metastases do not generally require treatment.
In symptomatic cases of spinal metastases with neural root irritation, vertebral body collapse or electively after laminectomy for spinal cord compression, radiation to the spine is indicated.

Thoracic and lumbar areas should be treated with posterior photon beams except in very heavy patients in whom the lumbar spine may be treated with coaxial anterior and posterior opposed pair. The cervical spine may be treated with a lateral coaxial opposed pair or with a single posterior beam.

The volume should include the vertebral body affected. Traditionally two vertebral bodies above and below the affected area have been included but this is not necessary if precise information is available by MRI, myelogram, CT scan or surgical clips. The field width should include the vertebral body with 1½ -2 cm margins on either side depending on beam energy unless a paraspinal soft tissue mass is also to be included. Superior and inferior field edges should be at the intervertebral spaces. A tattoo is recommended.

Beam energies should be chosen to keep the given dose under 125% of the tumor dose. The dose shall be prescribed at the level of the spinal cord or 5 cm or at the isocentre of the coaxial pairs. The dose shall be 800 cGy in a single fraction or 2000 cGy in five fractions in one week.

Retreatment may be considered in patients with whom a response of several months duration was initially obtained. The risk of inducing radiation myelitis with retreatment must be weighed versus current symptoms and life expectancy. The retreatment dose should be chosen with these factors in mind.

**SPINAL CORD COMPRESSION**

If the patient had previous radiation therapy to the area in question, then a surgical opinion should be sought.

If radiation for the treatment of spinal cord compression is indicated, the volume treated should be determined by myelogram or MRI. In cases where a myelogram has not been performed, several vertebral bodies above the level of compression should also be treated. While single fractions have been sufficient for pain control in vertebral metastases, it is not clear whether such doses can control spinal cord compression and therefore a dose of 2000 cGy in five fractions should be considered as a minimum dose.

**OTHER BONY METASTASES**

Bony metastases should be treated only if symptomatic or in areas where progression may be catastrophic, in which case prophylactic treatment should be given. Such areas and circumstances indicating prophylactic treatment most commonly are those related to weight bearing. Involvement of the femoral shaft, neck or head with loss of cortex and the superior medial aspects of the acetabulum with loss of cortex would be the most common indications for prophylactic treatment.

Firm surgical indications are not established but a surgical opinion prior to radiation may be sought for femoral metastases greater than one-half of the bony diameter at that point, for metastases in the femur in which greater than one-half of the thickness of the cortex is eroded, or for metastases in which a length of the cortex greater than the bone’s diameter is affected, in patients in whom reasonable survival is otherwise expected.

In patients receiving internal fixation for pelvic, femoral, acetabular and perhaps humeral lesions, radiation should be given afterwards. The new scar should be excluded from the treatment volume but if this is not possible, radiation should be delayed for 10 or 14 days to allow healing and prevent dehiscence from the radiation. A strip of normal tissue should be left unirradiated in the extremity treated postoperatively. If a metallic prosthesis is in place, radiation
from at least two directions should be used to reduce shielding of the residual tumor by the prosthesis. In patients in whom allogenic bone is used, the auto-allo interface should not be irradiated but the remainder of the allograph may. Irradiation of the interface may inhibit bony union.

The ideal dose, fractionation and volume for the treatment of bony metastases is not known but a single dose of 800 cGy appears to be comparable in effect to 2000 cGy in five fractions and to 3000 cGy in ten fractions.

In lesions in long bones in the limb and lesions in the pelvis, a coaxial opposed pair should be used for treatment. For rib lesions, appositional beams may be used. In all cases, the volume should attempt to include adjacent soft tissue masses. It is not usually necessary to include the whole bone but only the areas affected.

Patients with multiple and/or poorly localized areas of pain may be referred for radio-isotope studies (strontium or samarium).

**OTHER METASTATIC SITES**
These should be treated as deemed appropriate with a palliative regimen aimed at improving quality of life.
APPENDIX 6

Hormone Therapy

Hot flashes may be an indicator of improved response to adjuvant tamoxifen. Therefore it is important to encourage women to stay on tamoxifen despite negative effects on quality of life. Although SSRIs reduce hot flashes, this may be occurring through the reduction pf endoxifen, the most important tamoxifen metabolite, via inhibition of CYP2D6. The NCCN 2007 Breast Cancer Guideline includes the cautionary note that some SSRIs decrease the formation of endoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. The clinical impact of these observations, however, is not known. Until further information is available, venlafaxine and citaloprim should be considered the SSRI of choice.

CHEMOTHERAPY

ADJUVANT/NEOADJUVANT CHEMOTHERAPY

Non-trial chemotherapy regimens

CMF-po (Bonadonna, Milan)

\[
\begin{align*}
\text{Cyclophosphamide} & \quad 100 \text{ mg/m}^2 \text{ po d 1 to 14} \\
\text{Methotrexate} & \quad 40 \text{ mg/m}^2 \text{ IV d 1 and 8} \\
\text{5-Fluorouracil} & \quad 600 \text{ mg/m}^2 \text{ IV d 1 and 8} \\
\end{align*}
\]

q 28 days x 6 cycles

CMF-IV

\[
\begin{align*}
\text{Cyclophosphamide} & \quad 600\text{mg/m}^2 \text{ IV d1} \\
\text{Methotrexate} & \quad 40\text{mg/m}^2 \text{ IV d1} \\
\text{Fluorouracil} & \quad 600\text{mg/m}^2 \text{ IV d1} \\
\end{align*}
\]

q 21 days x 6 cycles 5-

AC

\[
\begin{align*}
\text{Doxorubicin} & \quad 60 \text{ mg/m}^2 \text{ IV d 1} \\
\text{Cyclophosphamide} & \quad 600 \text{ mg/m}^2 \text{ IV d 1} \\
\end{align*}
\]

q 21 days x 4 cycles

TC (funded for adjuvant)

\[
\begin{align*}
\text{Cyclophosphamide} & \quad 600 \text{ mg/m}^2 \text{ IV d 1} \\
\text{Docetaxel} & \quad 75 \text{ mg/m}^2 \text{ IV d 1} \\
\end{align*}
\]

q 21 days x 4 cycles

Premedicate with dexamethasone 8mg po bid x 3 days (day before, day of, and day after)

CEF

\[
\begin{align*}
\text{Cyclophosphamide} & \quad 75 \text{ mg/m}^2 \text{ po d 1 to 14} \\
\text{Epirubicin} & \quad 60 \text{ mg/m}^2 \text{ IV d 1 and 8} \\
\text{5-Fluorouracil} & \quad 500 \text{ mg/m}^2 \text{ IV d 1 and 8} \\
\end{align*}
\]

q 28 days x 6 cycles

All patients should receive Septra 2 tabs bid x 6 months or Ciprofloxacin 500 mg bid x 6 months during CEF
FEC-100

5-Fluorouracil  500 mg/m² IV d 1
Epirubicin      100 mg/m² IV d 1
Cyclophosphamide 500 mg/m² IV d 1

FEC-D

5-Fluorouracil  500 mg/m² IV d 1
Epirubicin      100 mg/m² IV d 1
Cyclophosphamide 500 mg/m² IV d 1

Followed in 21 days by Docetaxel 100 mg/m² over 1 hour IV q 21 days x 3 cycles.
**Premedicate with dexamethasone 8mg bid for 3 days (the day before, day of, and day after)**

AC →T

Doxorubicin 60 mg/m² IV d 1
Cyclophosphamide 600 mg/m² IV d 1

Followed in 21 days by Paclitaxel 175 mg/m² 3 hr IV infusion q 21 days x 4 cycles
**Premedicate with dexamethasone 20 mg po at 12 and 6 hrs before, ranitidine 50mg IV prior and diphenhydramine 50mg IV prior**

AC →D

Doxorubicin 60mg/m²
Cyclophosphamide 600mg/m²

Followed in 21 days by Docetaxel 100mg/m² IV q21 days x 4 cycles. **Premedicate with dexamethasone 8mg bid for 3 days (the day before, day of, and day after)**

AC→T (DD)

Doxorubicin 60mg/m² IV d1
Cyclophosphamide 600mg/m² IV d1
Filgrastim 5µg/kg/day SC d3-10

Followed in 21 days by Paclitaxel 175mg/m² IV q14 days
Filgrastim 5µg/kg/day SC d3-10.
**Premedicate with dexamethasone 20mg po 12 and 6 hours before, ranitidine 50mg IV prior and diphenhydramine 50mg IV prior**

AC→T weekly (not funded)

Doxorubicin 60mg/m² IV d1
Cyclophosphamide 600mg/m² IV d1

Followed in 21 days by Paclitaxel 80mg/m² IV d1 x 12 weekly cycles.
**Premedicate with dexamethasone 10mg IV prior, ranitidine 50mg IV prior and diphenhydramine 50mg IV prior**
## METASTATIC

### CMF
- **Cyclophosphamide**: 600 mg/m² IV d1
- **Methotrexate**: 40 mg/m² IV d1
- **5-Fluorouracil**: 600 mg/m² IV d1

### FAC
- **Cyclophosphamide**: 500 mg/m² IV d1
- **Doxorubicin**: 50 mg/m² IV d1
- **5-Fluorouracil**: 500 mg/m² IV d1

### FEC
- **Cyclophosphamide**: 500 mg/m² IV d1
- **Epirubicin**: 50 mg/m² IV d1
- **5-Fluorouracil**: 500 mg/m² IV d1

### EPI
- **Epirubicin**: 90 mg/m² IV d1

### MITOX
- **Mitoxantrone**: 12 mg/m² IV d1

### Vinorelbine
- **25 mg/m² IV days 1 and 8**

### Paclitaxel
- **175 mg/m² or 135 mg/m² over 3 hours IV q 3 wks**
- **Premedicate with dexamethasone 20 mg po 12 and 6 hrs before, ranitidine 50mg IV prior and diphenhydramine 50mg IV prior**
- **80mg/m² IV d1 weekly**
- **Premedicate with dexamethasone 10mg IV prior, ranitidine 50mg IV prior and diphenhydramine 50mg IV prior**

### Docetaxel
- **100 mg/m² over 1 hour IV q 3 wks max. 6 cycles**
- **Premedicate with dexamethasone 8mg bid x 3 days (day before, day of and day after)**

Low dose weekly: docetaxel 35 mg/m² IV either three weeks in a row with one week off (3/4) or six weeks on and two weeks off (6/8). **Premedicate with dexamethasone 8mg x 3 doses (night before, right before and night of).**

### Nab-Paclitaxel (Abraxane)
- **260mg/m² IV d1**
No premedication required. Only funded where there is a documented previous reaction to paclitaxel or docetaxel.

**Capecitabine**
1000 mg/m² bid po for 14 days every 3 weeks in patients pretreated with or unable to tolerate anthracyclines and taxanes.

<table>
<thead>
<tr>
<th>Recommended Dose Modifications for Capecitabine Monotherapy</th>
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<tbody>
<tr>
<td><strong>Toxicity, NCIC Grade</strong></td>
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</tr>
<tr>
<td>Grade 1</td>
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<td>♦ 3rd appearance</td>
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<tr>
<td>Grade 4</td>
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<td>♦ 1st appearance</td>
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</tbody>
</table>

*National Cancer Institute of Canada Common Toxicity Criteria*

25% dose reduction also recommended in patients with poorer performance status or in elderly or with impaired renal function (see below). Serious interaction with warfarin reported. Alternative treatment is infusional 5-FU 225 mg/m²/day.

All patients will have a serum creatinine and the creatinine clearance will be calculated by the physician or pharmacist prior to the first course of capecitabine.

Mild Impairment (CrCl 51 to 80 mL/min) given standard dose and monitor
Moderate Impairment (CrCl 30 to 50 mL/min) reduce dose by 25%
Severe Impairment (CrCl less than 30 mL/min) withhold

**Trastuzumab Therapy**

*Eligibility:*
- Only patients whose cancers are positive for HER2/neu protein overexpression by IHC (3+) or FISH (≥ 2). All samples should be sent to Pathology Department, London Health Sciences Centre. Treatment of small node negative HER2 positive cancers is funded through the CCO Evidence Building Program (see page 14).
- As first line therapy with paclitaxel (175 mg/m²) or docetaxel (100 mg/m²) in a patient who will not be receiving subsequent anthracycline chemotherapy.
- As second line therapy with paclitaxel (175 mg/m²) or docetaxel (100 mg/m²) in a patient failing first line chemotherapy and is anthracycline resistant or cannot tolerate anthracyclines. This includes patients who have received near maximal doses of anthracyclines as adjuvant therapy.
- With vinorelbine after progression with anthracycline or taxane.
• CCO will not cover the cost of paclitaxel if patients previously funded for docetaxel or vinorelbine. Docetaxel or vinorelbine should not be administered with trastuzumab, but rather given as a single agent.
• As second or third line therapy for patients who have received at least two chemotherapy regimens for metastatic disease or an anthracycline as adjuvant therapy and one chemotherapy regimen for metastatic disease.
• ECOG performance status 0 to 2.
• Eligibility form must be filled out and a copy of the HER2/Neu report must be attached.
• Trastuzumab will not be reimbursed if given with chemotherapy other than docetaxel, paclitaxel, or vinorelbine. Trastuzumab will not be reimbursed if continued after disease progression while receiving trastuzumab.

**Trastuzumab Therapy**

• Weekly dosing schedule
  Initial loading dose 4 mg/kg IV over 90 minutes, week one, then 2 mg/kg over 30 minutes weekly.

• Q 3 week dosing schedule
  Initial loading dose 8mg/kg IV, then 6 mg/kg q 3 weekly.

For delays of more than one week, a repeat loading dose is required.
**ASYMPTOMATIC PATIENTS: RULES FOR TRASTUZUMAB CONTINUATION BASED ON SERIAL LVEFs**

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<thead>
<tr>
<th>Relationship of LVEF to LLN **</th>
<th>Absolute decrease of &lt; 10%</th>
<th>Absolute decrease of 10–15%</th>
<th>Absolute decrease of ≥ 16%</th>
</tr>
</thead>
<tbody>
<tr>
<td>within normal limits</td>
<td>continue</td>
<td>continue</td>
<td>hold *</td>
</tr>
<tr>
<td>1–5% below LLN</td>
<td>continue</td>
<td>hold *</td>
<td>hold *</td>
</tr>
<tr>
<td>≥ 6% below LLN</td>
<td>continue *</td>
<td>hold *</td>
<td>hold *</td>
</tr>
</tbody>
</table>

* If Trastuzumab is on hold, repeat LVEF assessment after 4 weeks:
  - if criteria for continuation met – resume Trastuzumab
  - if 2 consecutive holds, or total of 3 holds – permanently discontinue Trastuzumab
  - always reassess LVEF relative to baseline (pre-treatment) LVEF

If Trastuzumab on hold > 7 days, will require repeat loading dose (8mg/kg)
If delay due to any Grade III or IV toxicity, hold until toxicity reduced to Grade I

** LLN = lower limit of normal

[www.cancercare.on.ca/toolbox/drugs/drugformulary/drugregimens/breastreg/](http://www.cancercare.on.ca/toolbox/drugs/drugformulary/drugregimens/breastreg/)
APPENDIX 7
HORMONE THERAPY

Adjuvant Therapy

Axillary node negative ER+ and/or PR+

Non-trial standard hormone therapy:
Tamoxifen 20 mg daily po x 5 years, then review

Axillary node positive ER+ and/or PR+

Non-trial standard hormone therapy:
Tamoxifen 20 mg daily po x 2-5 years, then review or consider an aromatase inhibitor
Either initially, sequentially after 2-3 years of tamoxifen or after 5 years of tamoxifen (see node positive section above). Premenopausal patients must have oophorectomy prior to going on an adjuvant AI.
AIs should be used with caution in women who are within two years of their last period or who have had a prior hysterectomy and who are younger than 56. In the absence of clear guidelines, it is strongly recommended that these women have LH, FSH and serum estradiol determination to determine menopausal status at baseline and at three month intervals for two years after starting an aromatase inhibitor. After two years this can be done once every six months until treatment is stopped.

Locally advanced

Non-trial regimens as for stage II

Metastatic

Non-trial Standard Hormone Therapy:

1. Tamoxifen 20 mg daily po

2. Anastrozole 1 mg daily po
   OR Letrozole 2.5 mg daily po
   OR Exemestane 25 mg daily po

3. Megestrol acetate 160 mg daily po, if improved appetite/weight gain desired

4. Fulvestrant 250mg IM q 4 wks

4. Leuprolide (Leupron depot) 7.5 mg IM monthly
   Goserelin (Zoladex) 3.6 mg sc monthly or 10.8 mg sc q 3 months + Tamoxifen or anastrozole for premenopausal patients.
Hormone therapies are usually continued until relapse, unless toxicity necessitates their dose reduction or withdrawal.
APPENDIX 8

CANCER GENETIC COUNSELLING & GENETIC TESTING

PREAMBLE

Although most cancers occur by chance or are caused by known or unknown environmental factors, it is now well recognized that in a small number of families (5-20% overall), an inherited genetic factor is the primary cause. Families with an inherited predisposition to cancer usually have multiple individuals in their family with a certain type or pattern of cancer over several generations, whereas the cancers often occur at a younger age than expected and can sometimes involve multiple primary cancers in the same individual.

The Cancer Genetics clinic at the London Regional Cancer Program provides genetic counselling and risk assessment for persons from families with a strong history of cancer. Although most of the families seen involve families with breast, ovarian or colorectal cancer histories, referrals are accepted on any patient whose personal and/or family history of cancer is concerning or involves more cases than expected.

The MOHLTC has defined clinical criteria for referrals of patients at risk for the Hereditary Breast and Ovarian Cancer (HBOC) syndrome ($BRCA1/2$ genes). These criteria are listed below. It is recognized, however, that such defined criteria cannot adequately address all clinical situations. Therefore, health care providers should use clinical judgment when assessing situations that do not fit the criteria.

Individuals considered to be at increased risk for an inherited cancer can be referred to the Cancer Genetics clinic at the LRCP (fax 519-685-8005). Upon referral, providers are encouraged to provide as much personal and family cancer history information as possible to help facilitate the triage process. Patients are also required to complete a family history questionnaire prior to their genetic counselling appointment. Geneticists and Genetic Counsellors provide genetic counselling and risk assessment, and education regarding cancer surveillance recommendations based on a patient’s personal and family history of cancer. When indicated and appropriate, genetic testing may be offered. The first person in a patient’s family to give a blood sample for genetic testing is usually a family member who has already had cancer. If genetic testing is possible, it is discussed with the interested family members so that informed decisions can be made. For this reason, genetic counselling should always be a part of the genetic testing process.

It is important to note that genetic testing may or may not be offered in the course of a genetics consultation. As well, due to significant advances in molecular genetics technology, there are sometimes limitations in our ability to interpret a genetic test result. In such cases, an increased risk of cancer may not be ruled out, thus diligent cancer surveillance remains important and we encourage these families to keep in touch with us as our knowledge improves.

The following are criteria for when a referral should be made for genetic counselling and risk assessment, as defined by the MOHLTC. It should be noted that these criteria were established in 2001, and may well be revised as new research and evaluation prevails.

Risk Factors for Inherited Breast and/or Ovarian Cancer:
1. Multiple cases of breast cancer (particularly where diagnosis occurred less than 50 years) and/or ovarian cancer (any age) in the family, especially in closely related relatives in more than one generation.
2. Age at diagnosis of breast cancer less than 35 years.
3. A family member diagnosed with both breast and ovarian cancer.
4. Breast and/or ovarian cancer in Ashkenazi Jewish families.
5. Family member(s) with primary cancer occurring in both breasts, especially if one or both cancers were diagnosed before age 50.
6. A family member diagnosed with invasive serous ovarian cancer.
7. Presence of male breast cancer in the family.
8. Family member with an identified BRCA1 or BRCA2 mutation.
9. Presence of additional associated cancers or conditions suggestive of an inherited breast/ovarian cancer syndrome (i.e. prostate cancer, pancreatic cancer, melanoma).
APPENDIX 9

LONG TERM FOLLOW-UP ISSUES

Increased evidence showing benefits of systemic therapy and the trend to more widespread use of chemotherapy mean that more women are surviving for long periods of time after initial diagnosis. More of the follow-up is now done by local and family physicians.

Consider recommendations for diet/exercise in these patients given ongoing evidence that weight loss strategies may reduce recurrence and increase sensitivity to aromatase therapy in overweight patients (see J Clin Oncol 2007;25:2345-51 and accompanying editorial, 2335-37).

Some long term toxicities require special attention in this group:

- **Toxicities related to early menopause:**

  - Hot flushes: These tend to improve with time. For symptomatic individuals, especially if interfering with activities of daily living, consider clonidine 0.05 mg po bid or venlafaxine 37.5 mg po bid. Venlafaxine may be particularly useful if these symptoms are associated with depression or sleep disturbance. Other options include fluoxetine 20 mg/day. Progestational agents (medroxyprogesterone or megace) should be used with caution only in patients who do not benefit from these previously mentioned agents as their effect on risk of recurrence is unknown (CMAJ 1992; 166: 1017-22). A randomized trial suggests that a low 20mg dose of megestrol acetate is as good as a higher dose (J Clin Oncol 2008;26:1650-6). Black cohosh and phytoestrogens (evening primrose oil) are not significantly effective. Vitamin E is somewhat less effective and may interfere with tamoxifen (J Surg Res 2009 May 1: 153(1): 143-7).

  - Risk of reduced bone density: For women menstruating prior to chemotherapy and who are amenorrheic six months following chemotherapy and for those who are already amenorrheic, a bone density study should be considered. Bisphosphonate therapy should be considered in those with significant bone loss, depending on other medical factors after consultation with their family physician. Although there is evidence of benefit with hormone replacement therapy (HRT), the strength of evidence is greater with bisphosphonates. Until more data is available, it is better to avoid the use of selective estrogen response modulators (SERMs) such as raloxifene in women with breast cancer. The specific role of raloxifene in the prevention of breast cancer is still investigational and it is not approved in North America for this indication. Raloxifene also increases the frequency and severity of hot flushes. Women who have been placed on aromatase inhibitors (anastrozole, letrozole, exemestane) are at increase risk of osteoporosis and bone fractures. They should therefore have regular bone density testing and consider either vitamin D and calcium supplementation or bisphosphonate therapy after a discussion with their family physician. Bone density improves after stopping exemestane and anastrozole.

  - Cardiovascular and stroke risk: Regular exercise and good dietary habits (see Canada’s Food Guide at [http://www.hc-sc.gc.ca/hppb/nutrition/pube/foodguid/](http://www.hc-sc.gc.ca/hppb/nutrition/pube/foodguid/)) are recommended. Smoking cessation will be more effective than any other intervention in those who
smoke. The role of HRT in the primary prevention of cardiovascular disease is unclear and it may actually be detrimental immediately after a heart attack. Postmenopausal women should be monitored for hypercholesterolemia and hyperlipidemia. Similarly, there is no clear evidence that HRT reduces stroke risk and is expected to increase breast cancer recurrence risk, and therefore should be avoided, particularly in ER+ or PR+ patients.

- Genitourinary symptoms: These show significant improvement with HRT, however given the same concerns regarding breast cancer recurrence risk, should be avoided. Vaginal dryness and dysparenia can be treated with lubricating gels (Replens) as a first approach, or topical estrogen cream, which has minimal systemic absorption, particularly when prescribed as once weekly or at most twice weekly, rather than daily. This is expected to be sufficient for patients developing recurrent urinary tract infections as a result of vaginal dryness and atrophy as well. However, some postmenopausal women with severe vaginal atrophy may have transient increased systemic absorption of even vaginal estrogen preparations. The e-string is another alternative approach. If HRT is considered, intermittent (less than 5 years) rather than continuous therapy is recommended following a discussion of risk/benefit balance with the patient.

- Weight gain: This is usually related to postmenopausal status but can also be a result of fatigue after treatment. Regular exercise and diet (see above) are recommended.

- In general, HRT should be discouraged. There are definite increases in the risk of endometrial cancer and venous thromboembolism as well as probable increases in the risk of gall bladder disease and breast cancer with long term use (NEJM 2001; 345: 34-40). The HABITS trial, a non-blinded randomized trial employing HRT or best supportive care was terminated December 2003 after women on HRT were found to have a HR of 3.3 for new breast cancer (Lancet 2004; 363: 453-455).

- Screening for complications
  
  - Although tamoxifen is associated with an approximate 1% five year risk of endometrial carcinoma, transvaginal ultrasonography as a screening tool for asymptomatic patients is not recommended because of the high false positive rate of endometrial thickening. Women with a uterus should be appropriately investigated if they develop vaginal bleeding or pelvic discomfort. Premenopausal patients who continue to have or redevelop periods following their breast cancer treatment will be difficult to follow for abnormal bleeding and therefore transvaginal ultrasounds may be useful on a q6 monthly basis or in accordance with consultation with a gynecologist. Pap tests are not recommended until six months after completion of chemotherapy, unless there are symptoms, because of cytologic atypia induced by prior chemotherapy, but should be encouraged thereafter as part of routine recommended screening guidelines for cervical cancer.

- Arthralgias and Als:-

- For further discussion regarding hormonal therapy, refer to the hormonal therapy section.

- Cardiac toxicity and acute leukemia are rare complications of anthracycline-based chemotherapy. There is no evidence that serial cardiac assessment or CBCs in the asymptomatic person alter the outcomes of these events.
APPENDIX 10

FERTILITY

How to facilitate a referral to The Fertility Clinic at LHSC for breast cancer patients wishing to preserve fertility prior to chemotherapy

1) Patient and her partner must have an Infectious Disease Screening (IDS) which takes 4-6 weeks to complete. This should be done as soon as possible.

Female Partner:
- CBC
- Rubella,
- Hepatitis B Surface Antigen,
- Hepatitis C,
- Blood Type,
- VDRL,
- HIV1/HIV2,
- HTLV I /HTLV II

Male Partner:
- Hepatitis B Surface Antigen,
- Hepatitis C,
- Blood Type,
- VDRL,
- HIV1/HIV2,
- HTLV I /HTLV II

2) Refer to either of The Fertility Clinic physicians (www.londonfertility.ca) - let the receptionist know that this is a cancer patient and appointment has to be as soon as possible.

J Hollett-Caines 519-646-6103
V Feyles 519-663-3019
S G Power 519-685-8257
M Rebel 519-646-6103
BREAST RECONSTRUCTION OPTIONS

Breast reconstruction options offered by the plastic surgeon may include:

1. autologous (using tissue transferred from elsewhere in the patient’s body, usually from the abdomen). This is only an option if the patient has adequate tissue to recreate an acceptable new breast-like mound.

2. implant based reconstructions. This may be two stages – a tissue expander placement then a second surgery for placement of the final implant, or a single stage implant procedure. Implants are always placed beneath the pectoralis muscle.

Discussion with patients prior to the plastic surgery consultation should include risk of developing a contralateral breast cancer so the patient is well informed regarding the consideration of unilateral versus bilateral reconstruction, if the patient has an unaffected breast.

Immediate reconstruction – can be considered if there is a low risk of the patient requiring radiation. Cosmesis of a reconstructed breast is likely to be adversely affected by adjuvant radiation therapy, particularly with implant based reconstruction.

Delayed reconstruction – Following mastectomy, delayed reconstruction can be offered following adjuvant treatments, such as chemotherapy and radiation. If the patient has undergone chemotherapy alone, she could be a candidate for autologous or implant based reconstruction. If she has had radiation therapy, reconstruction may be delayed while the effects of radiation abate; however, a consult for reconstruction would be appropriate during this stage and would facilitate planning. Reconstruction with an implant alone is generally not recommended after radiotherapy but may be done in conjunction with a pedicled latissimus dorsi flap with good results.

Follow-up - Following mastectomy and reconstruction, breast imaging is NOT required or recommended. Twice yearly clinical examinations are recommended, as recurrences would be superficial.

Referrals- physicians are advised to refer directly to a plastic surgeon’s office (currently offered by Dr. B Evans at University Hospital, Dr. C. Scilley at Victoria Hospital and Dr.’s. D. Ross, R Richards and B. Gan at St. Joseph’s Hospital). Wait times for delayed reconstruction can vary, but may be as high as two years. Immediate reconstruction requests for cancer need to be communicated directly between physicians.

We are currently making efforts to develop a centralized referral process for London and area involving all breast cancer surgeons and reconstruction surgeons.

Specialization in surgical approaches may vary among the surgeons. To discuss further, contact Margo Bettger-Hahn CNS Breast Reconstruction, 519-646-6100 ext 64782