Breast Cancer

Breast Practice Guideline

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Breast Disease Site Team

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This guideline is a statement of consensus of the Breast Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgment of the physician in the context of individual clinical circumstances to determine any patient’s care or treatment.
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Breast Oncology Practice Guidelines

BREAST DISEASE SITE MEDICAL TEAM

CHAIR: Dr. M. Brackstone (Surgical Oncology)

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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 1996 (May)
Updated 1998 (March)
Updated 1998 (November)
Updated 1999 (January)
MANAGEMENT GUIDELINES - Breast Interdisciplinary Team

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.

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
Appendix 6: Chemotherapy
Appendix 7: Hormone Therapy
Appendix 8: Guidelines for Referral for Genetic Counseling
Appendix 9: Long Term Follow-up Issues

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, this drug should be discontinued and functional assessment measured by FSH/LH at least two months later. 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 which 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, node positive or high risk node negative disease or at the request of an oncologist.
Tis NON-INVASIVE CARCINOMA

This includes ductal carcinoma in-situ (DCIS), lobular carcinoma-in-situ, 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 intraduct tumor at or close to (0.2 cm) the margins of the lumpectomy should have surgical revision.

Radiotherapy
(a) Breast irradiation
Patients with completely resected DCIS should be offered breast radiation. There may be patients with small (less than 1 cm), low grade DCIS excised with adequate margins (1-2 cm), who may not need radiation. Patients with less than 2.5 cm DCIS, intermediate or low grade and with resection margins greater than 3 mm should be considered for RTOG 9804 protocol (observation versus radiation).

(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 non-invasive cancer. For intraductal cancer there are data from several retrospective studies, as well as a subset of patients in the NSABP-06 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 (i.e. 4-5 cm or more) high grade (comedo) DCIS especially with close or with pathologic positive margins.

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 i.e. careful clinical and mammographic follow-up. 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 draft 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). No guidelines were given on which subsets of women with DCIS may stand to benefit more from tamoxifen. Recent publications on risk-benefit /cost-benefit of tamoxifen have addressed this topic only for breast cancer prevention (J Clin Oncol 2002; 20(1): 9-16, Br J Cancer 2001; 85(9): 1280-1288, JNCI 1999; 91(21): 1829-1845). In this setting, high risk women younger than 50 years stand to benefit most, especially since the absolute risks of endometrial cancer, stroke, and thrombosis increase with age.

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. The RTOG has started a 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.

There is currently no information on the role of AIs for the treatment of DCIS. Trials are underway to address this question.

Interpretative Summary:

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 should be discussed with each woman, weighing the risks and the benefits. The UKCCCR trial (Lancet 2003; 362(9738):95-102) in the tamoxifen analysis showed a difference in ipsilateral or contralateral DCIS but no difference in invasive carcinoma. 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 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 FOLLOW-UP

Time interval
Year 1, 2: 4-6 months
Year 3, 4, 5: 6 months

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

FOLLOW-UP INVESTIGATIONS

CBC + SMA-9 only for patients in clinical trial.
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 (low risk at investigator discretion) (see Surgery Appendix 4)

Assessment: history and physical, complete blood count, biochemical profile, bilateral mammography (before surgery if possible), chest radiograph, bone scan (optional). Liver imaging is not required unless alkaline phosphatase, or AST and/or ALT are greater than 1.5 times upper normal limit.

LOCAL THERAPY

Surgery

Types of surgery
(1) Partial mastectomy (or lumpectomy) and axillary node dissection
(2) Simple mastectomy and sentinel node biopsy
(3) Modified radical mastectomy.

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 versus total mastectomy and axillary node dissection
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 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 intraduct carcinoma component with margin involvement, are usually indications for mastectomy. All resected margins should be histologically free of tumor. A minimum margin of 1 cm is preferred (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. Axillary node dissection is recommended for all patients with early stage breast cancer if SLNB cannot be done. A full dissection of level 1 & 2 nodes is indicated, even if the first node identified is positive. Axillary irradiation is not usually given after a full axillary dissection, as this may increase morbidity, particularly arm edema. This may also occur after partial dissection and irradiation, and therefore a single procedure is preferred. 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).
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: 1\textsuperscript{st}/2\textsuperscript{nd} trimester of pregnancy, history of prior radiation to the breast region (e.g., 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).

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 (ASTRO 2001, Plenary 4 update 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
There is no indication for routine regional nodal radiation in this group.

(d) Partial breast radiation (including Brachytherapy)
May be considered 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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<td>Low Risk</td>
<td>- Tumour size less than 1cm.</td>
<td>Pre and postmenopausal</td>
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<td></td>
<td>- Tumour size 1-2 cm and all prognostic factors favourable (Grade 1, no LVI).</td>
<td><strong>No systemic treatment</strong></td>
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<tr>
<td>High Risk</td>
<td>- Tumour size greater than 3 cm irrespective of other factors.</td>
<td>All premenopausal, or ER and PR -ve less than 70 postmenopausal Chemotherapy</td>
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<tr>
<td></td>
<td>- Tumour size 1-3 cm and Grade 3 or LVI +ve.</td>
<td>Postmenopausal ER or PR +ve Tamoxifen or AI or MA.27. Chemotherapy may be added after discussion of risks/ benefits</td>
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<td>Intermediate Risk</td>
<td>- T greater than 1 cm and other combinations of risk factors than above.</td>
<td>Premenopausal ER or PR +ve <strong>Tamoxifen</strong></td>
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<td>ER / PR -ve <strong>Chemotherapy</strong></td>
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<tr>
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<td></td>
<td>Postmenopausal ER or PR +ve Tamoxifen or AI or MA.27. ER / PR -ve <strong>No systemic treatment</strong></td>
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*As an alternative, Adjuvant! Online [http://www.adjuvantonline.com](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 recently 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. Patients eligible for clinical trials should also be encouraged to enter studies assessing the impact of micro arrays to evaluate the role of chemotherapy such as the PACCT/TAILORx trial or other similar trials.

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. Eligible patients should be encouraged to participate in the SOFT or TEXT trials evaluating the impact of ovarian function suppression or ablation. Premenopausal patients for whom an AI is being considered, and who are not candidates for the SOFT or TEXT trial require ovarian ablation either through surgery or LHRH agonist. Those going on an LHRH agonist should wait for at least four weeks after the initial injection prior to starting on an AI.

Hot flashes may be an indicator of improved response to adjuvant tamoxifen, Therefore it may be 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.

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 (St. Gallen’s, 2005-unpublished (New Engl J Med 2005; 353: 2747-57) showed a HR of 0.83 for DFS with 68 months median follow up.
- 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.

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.

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, recommend discuss entry into MA.27 bone and breast density extension trial (see below) 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 after the AI data have matured and more reports from other trials are available.

NCIC MA.27 Trial
Any postmenopausal woman with receptor positive early breast cancer is eligible for a randomized phase III bone and breast density trial of exemestane versus anastrozole.
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.

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 \( F_{500} \cdot E_{100} \cdot C_{600} \times 3 \rightarrow \text{Docetaxel} \times 3 \) over \( F_{500} \cdot E_{100} \cdot C_{600} \times 6 \). 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. Docetaxel at 100 mg/m2 is associated with a high (>20%) risk of toxicity. Prophylactic G-CSF should be considered in any situation where the risk of febrile neutropenia is 20% or more (ASCO Guidelines, 2006 http://jco.ascopubs.org/cgi/reprint/JCO.2006.06.4451v2.pdf ). 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 herceptin therapy. Intermediate and low risk node negative breast cancers will be tested at the discretion of the consulting oncologist.

Adjuvant chemotherapy may be discussed with healthy women greater than or equal to 70 years old, but should be considered with caution because of the paucity of data concerning benefits, and the greater potential for co-morbidity and greater toxicity.

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/index_chemoRegimensbyDisease.htm

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 randomized 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 follow-up.

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.
T1T2 N1M0 AXILLARY NODE POSITIVE BUT NOT LOCALLY ADVANCED

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, and 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.

Routine liver scan and ultrasound are not recommended, as they have a significant false positive rate and a low true positive incidence. These studies may be used to investigate abnormal biochemical liver function tests such as alkaline phosphatase, or AST and/or ALT greater than 1.5 times upper normal limit (however abnormal liver function tests may occur after a recent anesthetic). The value of carcinoembryonic antigen (CEA) is controversial. Levels are rarely elevated when screening patients with apparent stage II breast cancer, and raised levels are not specific for breast cancer.

Patients with 4 or more positive axillary nodes should have a baseline CXR, bone scan and ultrasound or CT abdomen as they are at higher risk of metastatic disease.

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 localization (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 other adverse features (see below). Patients
enrolled on MA.20 may be randomized to regional node radiation. 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 other adverse features (see below). However, such patients may be enrolled in RTOG 9915 and will be randomized to observation or locoregional radiation. Chest wall radiation is indicated for patients who have extension to the chest wall, or less than 2 mm of positive resection margins after mastectomy. 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. 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 START Trial in the U.K. and the 2005 Oxford meta-analysis confirm evidence of locoregional recurrence and overall survival benefit. 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) 4 or more positive axillary nodes
4) 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 (e.g. less than 10 nodes removed), the addition of a posterior axillary field may be appropriate (see Radiotherapy Appendix 5 for details).

**SYSTEMIC THERAPY**


**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 node positive hormone receptor positive postmenopausal and 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. Three trials (EORTC 10901 [EBCC/04] and IBCSG IX [ASCO/04] and NCIC MA.12 [ASCO/07, Abs 547]) have been reported and show a DFS benefit of 72% versus 64% at 5 years (p=0.005) and 67% versus 63% at 6.5 years (p=sign for ER+ subgroup) and 78% v 71% at 5 years (p=0.09). 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 have now been reported for INT 0100 (MA.9), showing superiority for sequential over concurrent CAF and tamoxifen at ten years (60% versus 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 (unpublished) 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 premenopausal women and selected postmenopausal women who cannot tolerate or who have contraindications to aromatase inhibitors. 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.
Hot flashes may be an indicator of improved response to adjuvant tamoxifen. Therefore it may be 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 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 should be considered the SSRI 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 (St. Gallen’s, 2005-unpublished (New Engl J Med 2005; 353: 2747-57) showed a HR of 0.83 for DFS with 68 months median follow up.
- The International Exemestane (IES) trial (N Engl J Med 2004; 351: 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 (ASCO/06) 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.

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.

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, recommend discuss entry into MA.27 bone and breast density extension trial (see below) 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. Those women who elect to start on tamoxifen should be reassessed after 2-3 years after the AI data have matured and more reports from other trials are available.

NCIC MA.27 Trial
Any postmenopausal woman with receptor positive early breast cancer is eligible for a randomized phase III bone and breast density trial of exemestane versus anastrozole.

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 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.

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, but so far no survival benefit. 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). Dose dense chemotherapy is 
not currently funded through the new drug program.
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_x 3→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.

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 are also reasonable options.

Adjuvant chemotherapy may be discussed with healthy women greater than or equal to 70 
years old, but should be considered with caution because of the paucity of data concerning 
benefits, and the greater potential for co-morbidity and greater toxicity.

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 down staging 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 long term 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, or AC. FEC100 could also be considered if approved for funding
- FAC, or AC followed by four cycles of docetaxel (100 mg/m²) every three weeks*. FEC100 could also be considered if approved for funding.

*Only FAC or AC followed by docetaxel is approved for funding as of June, 2005.

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/access](http://www.cancercare.on.ca/access)

**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). The four absolute survival benefit is 3.2%.
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.

SUGGESTED FOLLOW-UP

Time interval

During chemotherapy
3-4 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 randomized 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 follow-up.

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

CBC + SMA-9 each visit
CXR yearly
Mammogram yearly

{ Only if on clinical trial
(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 T4 and/or N3 and inflammatory carcinomas. Patients presenting with concurrent positive ipsilateral supraclavicular node(s) may be managed in a similar way although recognized to be N3.

Recommendation: Patients should be seen by a medical oncologist within one week of pathological and clinical confirmation of T4 malignancy. Chemotherapy should start within a week of assessment by a medical oncologist.

INVESTIGATIONS

Biopsy: tru-cut or incisional (see Surgery Appendix 4)

Assessment: as for stage II disease
bone scan and liver scan/ultrasound should be done in these high risk patients
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. Assuming response is less than pathologically complete, simple or modified radical mastectomy should be performed, if technically feasible.

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, 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. Patients achieving complete remission by clinical and mammographic criteria may be considered for breast conservation with breast irradiation.

SYSTEMIC THERAPY (possible regimens include CEF, CAF-po, FAC or FEC)

Chemotherapy

Patients with ER- T4 or inflammatory carcinomas should be treated with anthracycline based primary chemotherapy (see Chemotherapy Appendix 6). 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 considered as a part of neoadjuvant chemotherapy for non-metastatic 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 or AC. FEC100 could also be considered if approved for funding.
• *FAC or AC followed by four cycles of docetaxel (100 mg/m²) every three weeks. FEC100 could also be considered if approved for funding.

*Only FAC or AC followed by docetaxel is approved for funding as of June, 2005.

It is recommended that all women with T4 disease or with node positive or 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 herceptin therapy.

**Hormone therapy**

At the completion of primary chemotherapy, premenopausal patients with hormone receptor positive tumors should be given tamoxifen 20 mg/day for 5 years. Postmenopausal patients who are elderly or medically unfit for chemotherapy, with hormone receptor positive tumors, may be treated with anastrozole or letrozole. 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. Patients progressing on hormonal therapy should receive immediate radiotherapy.

**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.

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 (e.g. 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.

Combination chemotherapy with docetaxel and capecitabine should be considered front line if there are life-threatening metastases (J Clin Oncol 2002; 12: 2812-23).

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 selected patients unable to tolerate or failing 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.

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).

**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.
- Until further information is available, intravenous bisphosphonate treatments should be given for one year. 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.

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**
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. Although there is very little information on the use of AIs in male breast cancer, 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.
APPENDIX 1 - TNM STAGING
(J Clin Oncol 2002; 20: 3628-36)

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
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<tbody>
<tr>
<td>TX</td>
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<tr>
<td>T0</td>
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<tr>
<td>Tis</td>
</tr>
<tr>
<td>Tis (DCIS)</td>
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<tr>
<td>Tis (LCIS)</td>
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<tr>
<td>Tis (Paget)</td>
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<tr>
<td></td>
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<td>T1</td>
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<tr>
<td>T1mic</td>
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<td>T1a</td>
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<td>T1b</td>
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<td>T1c</td>
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<td>T2</td>
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<td>T3</td>
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<td>T4</td>
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<tr>
<td>T4a</td>
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<tr>
<td>T4b</td>
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<tr>
<td>T4c</td>
</tr>
<tr>
<td>T4d</td>
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</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
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<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
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<tr>
<td>N2</td>
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<tr>
<td>N2a</td>
</tr>
<tr>
<td>N2b</td>
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<tr>
<td>N3</td>
</tr>
<tr>
<td>N3a</td>
</tr>
<tr>
<td>N3b</td>
</tr>
<tr>
<td>N3c</td>
</tr>
</tbody>
</table>
Regional lymph nodes (pN)*

**pNX**  Regional lymph nodes cannot be assessed (e.g. 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 infraclavicular 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 infraclavicular 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” (e.g. 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 (e.g. 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
# APPENDIX 2 - PATHOLOGY CHECKLIST

## Pathology Checklist: In Situ Breast Cancer

<table>
<thead>
<tr>
<th>Name:</th>
<th>Surgical #:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Procedure:</th>
<th>Lumpectomy</th>
<th>Wire localization biopsy</th>
<th>Segmental excision</th>
<th>Re-excision</th>
<th>Mastectomy</th>
<th>Biopsy</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Site:</th>
<th>Right:</th>
<th>Left:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Histologic Type(s):</th>
<th>DCIS (only)</th>
<th>LCIS (only)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Distribution of Tumor:</th>
<th>Multifocal: Yes</th>
<th>No</th>
<th>Multicentric: Yes</th>
<th>No</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Means of Detection:</th>
<th>Palpable mass</th>
<th>______ x ______ x ______ cm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mammographic calcifications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mammographic mass</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mammographic architectural distortion</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DCIS Nuclear Grade:</th>
<th>I (low)</th>
<th>II (intermediate)</th>
<th>III (high)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>DCIS Necrosis:</th>
<th>Absent</th>
<th>Punctate (non zonal)</th>
<th>Zonal (comedo)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>DCIS Type (specify all that apply):</th>
<th>Cribriform</th>
<th>Solid</th>
<th>Micropapillary</th>
<th>Papillary</th>
<th>Comedo</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Extent of DCIS:</th>
<th>Size of largest focus: _________ mm</th>
</tr>
</thead>
<tbody>
<tr>
<td># of blocks involved: _______</td>
<td></td>
</tr>
<tr>
<td>Total # of blocks: _______</td>
<td></td>
</tr>
<tr>
<td>Extent of mammographic abnormality (if know): _____ cm</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Calcification:</th>
<th>Absent</th>
<th>Present</th>
<th>Intraluminal</th>
<th>Stromal</th>
<th>Benign breast tissue</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Resection Margins:</th>
<th>Positive (at margins)</th>
<th>Negative (not at margin)</th>
<th>Not evaluable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance to closest margin: ______ mm</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Microinvasion &lt; 1 mm:</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Comment:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Diagnosis:</th>
<th>Breast, left</th>
<th>/ right</th>
<th>______________________________ (procedure)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ductal carcinoma in situ, nuclear grade ________/ III</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference: Consensus Conference on the Classification of Ductal Carcinoma In Situ: Cancer 1997; 80: 1798-1802

---

Pathology Checklist: Invasive Breast Cancer Call @ 36368 to get update including HER2
<table>
<thead>
<tr>
<th>Name:</th>
<th>Surgical #:</th>
</tr>
</thead>
</table>

| Procedure: | Surgical Procedures:
| Lumpectomy | Wire localization biopsy | Segmental excision |
| Re-excision | Mastectomy | Biopsy |
| Axillary dissection: | Yes | No |

| Site: | Right:  | Left: |

| Histologic Type(s): | Histologic Types:
| Invasive mammary carcinoma (of no special type) | Invasive lobular |
| DCIS (only) | LCIS (only) | Other(s) [specify] |

| Distribution of Tumor: | Distribution of Tumor:
| Multifocal: | Yes | No |
| Multicentric: | Yes | No |

| Tumor Size: | Tumor Size:
| __________ x __________ x __________ cm |

| Combined Histologic Grade (SBR): | Combined Histologic Grade (SBR):
| I / III | II / III | III / III | Score _______/g |

| Nuclear Pleomorphism: | Nuclear Pleomorphism:
| Tubule Formation: | Tubule Formation: |
| Mitotic Score: | Mitotic Score: |

| Lymphatic/Vascular Invasion: | Lymphatic/Vascular Invasion: |
| Present | Not identified |

| In Situ Component: | In Situ Component:
| Not present | LCIS | DCIS |

| Nuclear Grade of DCIS: | Nuclear Grade of DCIS: |
| I / III | II / III | III / III |

| EIC Status*: | EIC Status: |
| EIC negative | EIC positive | EIC indeterminate |

| Calcification: | Calcification: |
| Not present | Benign breast tissue | DCIS | invasive tumor |

| Resection Margins: | Resection Margins: |

| Invasive Cancer: | Invasive Cancer: |
| Negative | Positive | Not evaluable |
| - closest distance to margin: | Macroscopic involvement | Microscopic only |
| _________ mm |

| Ductal Carcinoma In Situ: | Ductal Carcinoma In Situ: |
| Negative | Positive | Not evaluable |
| - closest distance to margin: | Macroscopic involvement |
| _________ mm |

| Invasive Tumor Necrosis: | Invasive Tumor Necrosis: |
| Present | Absent |

| Nipple Involvement: | Nipple Involvement: |
| Absent | Tissue not present | DCIS | Invasive | Paget’s |
| Dermal lymphatics |

| Skin Involvement: | Skin Involvement: |
| Absent | Tissue not present | Dermis | Epidermis |
| Dermal lymphatics |

| Chest Wall Involvement: | Chest Wall Involvement: |
| Absent | Present | Tissue not present |

| Abnormalities in Non-Neoplastic Breast Tissue: | Abnormalities in Non-Neoplastic Breast Tissue: |
| Absent | Present |

| Hormone Receptors Ordered: | Hormone Receptors Ordered: |
| Yes | No | Biochemical Method |
IHC Method (antibody) □

<table>
<thead>
<tr>
<th>Estrogen Receptor:</th>
<th>Positive □</th>
<th>Negative □</th>
<th>Pending □</th>
</tr>
</thead>
<tbody>
<tr>
<td>% cells positive: ______; staining intensity: ______</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progesterone Receptor:</th>
<th>Positive □</th>
<th>Negative □</th>
<th>Pending □</th>
</tr>
</thead>
<tbody>
<tr>
<td>% cells positive: ______; staining intensity: ______</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymph Nodes:</th>
<th>Number resected: _______</th>
<th>Number involved: ______</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Nodal Mets greater than or equal to 2 mm # ______</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Micromets less than 2 mm # ______</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Nodes fixed to one another or to other structures</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Extranodal extension: Present □ Absent □

Comment:

Diagnosis:
- Breast, left □ / right □, [procedure] ___________________________
- Invasive mammary carcinoma of no specific type, Grade ______/III
- Invasive special type carcinoma [specify: tubular, mucinous, etc]
- Axillary node dissection, right □ / left □:
  - Metastatic adenocarcinoma in ______ / ______ lymph nodes
  - ______ / ______ lymph nodes negative for malignancy

* Extensive Intraductal Component (EIC) Status – Note: If a tumor is primarily DCIS with focal invasion or has a moderate or marked amount of DCIS (greater than25%) within infiltrating tumor and in the adjacent tissue, it is EIC positive

### Reference:

**Elston’s Modified Bloom Richardson Grade**

| Grade 1 (well differentiated, score 3-5) |
| Grade 2 (moderately differentiated, score 6-7) |
| Grade 3 (poorly differentiated, score 8-9) |

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*Field diameter – 0.59 mm
APPENDIX 3 - BREAST IMAGING

Mammography
Mammography has been proven to be the “GOLD STANDARD” for imaging breast disease, in particular, occult breast carcinoma. Film/screen mammography is considered to be the breast imaging system of choice and has replaced xeromammography. When performed on state-of-the-art equipment by well trained technologists and interpreted by experienced radiologists, mammography will detect between 85% and 90% of breast cancers. There is a false/negative rate of approximately 10% and, because of this, mammography must always be interpreted in conjunction with clinical breast physical examination, history and ancillary diagnostic imaging modalities, such as breast sonography, galactography and pneumocystography. Despite the high accuracy of mammography, adjunctive therapy should never be instituted without tissue diagnosis.

Breast Ultrasound
Breast ultrasound has matured with the availability of high frequency hand-held transducers. It is no longer ancillary to mammography, but rather is an integral part of the diagnostic workup of symptomatic patients. For palpable breast masses, it has been demonstrated that the accuracy of the combined use of ultrasound and mammography is greater than that of either used alone. Its inability to demonstrate microcalcifications and small masses prevents its use as a screening modality.

Aspirations of Cysts
The diagnosis of a simple breast cyst can be made with almost 100% accuracy using ultrasound. Sonographic accuracy exceeds clinical accuracy when both palpable and non-palpable cysts are considered. However when the cyst is palpable, clinical accuracy, if it includes aspiration, is as good as sonographic accuracy.

Cyst aspiration may be warranted when a breast cyst is large, painful, or shows some irregularity on ultrasound. A pneumocystogram can be performed following the cyst aspiration by injecting an equal amount of air into the cyst. Two mammographic views are obtained which allow for assessment of the inner wall of the cyst, specifically to exclude an intracystic tumor mass. The instillation of air, not only speeds resolution of the cyst, but is therapeutic in that it prevents recurrence in a high percentage of cases.

Surgical excision is recommended when the aspirate shows atypical or clearly malignant cells, if the aspirate is bloody and, in some instances, if the cyst is recurrent.

Fine Needle Aspiration Biopsy (FNAB)
Stereotactic computer guided mammographic equipment is now available to assist in needle placement for aspiration cytology of non-palpable lesions. Results from the cytology must be correlated with mammographic, sonographic and clinical information. A false/negative biopsy should not preclude open surgical biopsy in the face of changes in the mammogram and/or sonogram that suggest malignancy.

Preoperative Needle Localization of Non-palpable Lesions
Preoperative needle localization employing a needle/hook-wire combination was developed to direct the surgeon to a non-palpable breast lesion. It serves to increase the accuracy of surgical excision, reduces operative time and, perhaps, minimizes the amount of tissue that needs to be excised. A hook-wire (there are many models on the market) is left in situ and the position is documented on two mammographic views. This is most often indicated for non-palpable lesions that are suspicious for very early cancer, such as microcalcifications (whether clustered or not),
tiny masses, areas of architectural distortion and asymmetric opacities. By far, the commonest indication for the procedure is microcalcifications and tiny stellate lesions.

Methylene Blue can be used to mark the suspicious area, in conjunction with the hook-wire/needle combination. Some surgeons do not like the use of Methylene Blue dye as it diffuses throughout the surrounding tissue and may obscure their view. The presence of the dye, however, does not interfere with pathologic interpretation of the specimen.

Following the localization procedure, the patient is then anesthetized and an ellipse of skin is removed. The suspicious area may be reached, either by dissecting along the course of the wire or by intercepting the tip of the wire in an orthogonal plane. A specimen radiograph, using magnification, is always recommended to document the presence of the suspicious area in the excised tissue. Frozen section is discouraged on most non-palpable lesions, particularly with microcalcifications and when a radical scar is suspected.
APPENDIX 4 - SURGERY

Core or trucut biopsy
When adequately performed this is of great value. It is a simple painless procedure that provides an accurate diagnosis in about 75% of those with cancer. 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.

Incisional biopsy
This is indicated, using local anesthesia, in those with T4 or inflammatory tumors. The diagnosis can be confirmed and a specimen obtained for receptor status.

Excisional biopsy
This is performed in those with small tumors, in which core biopsy is not possible. If there is a high likelihood of the condition being malignant, it should be performed using the wide local excision technique. Sentinel node or staging axillary dissection should be performed if diagnosis is confirmed.

Needle localization biopsy
See Appendix 3.

Partial mastectomy
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 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 systemic therapy (hormone or chemotherapy) with or without radiotherapy. Subsequently they are considered for partial or total mastectomy, depending upon amount of tumor regression.

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.

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). However there are a number of uncertainties that arise with the use of sentinel node sampling (SNS) and the treatment and management of breast cancer.

Patient Selection
Women appropriate for SNS 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
- clinically or radiologically identified multi-centric disease not amenable to a single lumpectomy
- 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 transitional 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). The ACOSOG Z00 10 study (closed) is looking at the correlation between bone marrow aspiration positivity and sentinel node biopsy to determine prognostic accuracy (AM Surg 2004; 70: 420-424).

**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).

The only exceptions to this would be enrollment in a clinical trial (such as ACOSOG Z0011 or NSABP B-32).
The axillary node dissection should be done prior to the initiation of adjuvant therapy (systemic therapy or radiotherapy).

**Total mastectomy**

**Indications for total mastectomy**

The number of total 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 total mastectomy or radiotherapy alone. The occasional patient with two infiltrating carcinomas or with multicentricity in the same breast should be treated by total 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**

Total 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 prosthesis (if used) should be inserted deep to the pectoralis muscle. Reconstruction should be discussed if it will not unduly delay adjuvant therapy performed at a later period.

**Indication for bilateral mastectomies**

This is a controversial subject and should only be performed after considerable discussion.

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 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.

**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 second rib.
   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 should be used to minimize cardiac volume within the field when radiating the left side.

   Boost: In cases where a boost is required, the light field will encompass the scar with a 2-3 cm margin, or encompass the surgical clips, if any, with a similar margin using an appositional beam at 100 cm SSD. U/S can be used to measure the depth to the chest wall. 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. A tangential, coaxial pair of beams at 100 cm SAD will be arranged to fulfill the volume requirements stated above. If lung shielding is to be used, the medial and lateral aspects of the breast should be identified on fluoroscopy/film to ensure shielding is appropriately drawn. Medial and lateral films should be taken. A contour will be taken of the intact breast or chest wall in selected mastectomy patients along the central rays to determine the dose distribution. The lung volume included may be estimated from the simulation films, or measured directly along the contour with ultrasound.

4. Dose Specification
The distribution, including lung correction, wedging, 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.

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.

In mastectomy patients, in whom a contour and distribution have not been done, dose will be specified at the isocentre.

For boosts, dose will be specified as a given (maximum) dose of electrons, with the energy chosen such that the 60% isodose line falls on the pleural surface. If cobalt is used, dose will be specified as given.

5. **Dose**

The optimal dose fractionation for breast radiation has not been determined. 5000 cGy/25 fractions have been used by the NSABP effectively. One OCOG study that has been presented in abstract form only has suggested similar local control rates and cosmetic results between 4250 cGy/16 and 5000 cGy/25 (ASCO 2000).

Currently used regimens include: 4250 cGy/16, 5000 cGy/25 (plus or minus boost) and 4000 cGy/16 plus 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 can be planned with CT simulation or by conventional means. 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 1\textsuperscript{st} to 3\textsuperscript{rd} intercostal space internal mammary nodes. It is recommended that a wire be placed at the lower border of the anterior 3\textsuperscript{rd} 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

**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 4 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 extra cranial 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. Generally mask mobilization will not be required for palliative treatment.

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 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

Adjuvant Chemotherapy – Nontrial Regimens

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 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 citalopram should be considered the SSRI of choice.

CHEMOTHERAPY

ADJUVANT CHEMOTHERAPY

Non-trial chemotherapy regimens

CMF-po (Bonadonna, Milan)

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<td>5-Fluorouracil</td>
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CEF

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

CAF-po

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<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>100 mg/m² po d 1 to 14</td>
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<tr>
<td>Doxorubicin</td>
<td>30 mg/m² IV d 1 and 8</td>
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</tr>
<tr>
<td>5-Fluorouracil</td>
<td>500 mg/m² IV d 1 and 8</td>
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FEC-100

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<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>5-Fluorouracil</td>
<td>500 mg/m² IV d 1</td>
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<td></td>
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<tr>
<td>Epirubicin</td>
<td>100 mg/m² IV d 1</td>
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<td></td>
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<tr>
<td>Cyclophosphamide</td>
<td>500 mg/m² IV d 1</td>
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FEC-D

<table>
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<th>Drug</th>
<th>Dose</th>
<th>Route</th>
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</thead>
<tbody>
<tr>
<td>5-Fluorouracil</td>
<td>500 mg/m² IV d 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epirubicin</td>
<td>100 mg/m² IV d 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>500 mg/m² IV d 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Docetaxel 100 mg/m² over 1 hour IV q 21 days x.6 cycles. Premedicate with dexamethasone

AC → T
Doxorubicin 60 mg/m² IV d 1
Cyclophosphamide 600 mg/m² IV d 1 q 21 days x 4 cycles

↓ 21 day interval from last cycle AC
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

LOCALLY ADVANCED
Intensive anthracycline based non-trial regimens as listed under adjuvant chemotherapy (CEF, CAF-po, FEC-100) or metastatic chemotherapy (FEC, FAC).

- Paclitaxel weekly x 12 weeks prior to a standard anthracycline containing regimen such as FAC or AC. FEC100 could also be considered if approved for funding.
- FAC or AC followed by four cycles of docetaxel (100 mg/m²) every three weeks. FEC100 could also be considered if approved for funding.

METASTATIC

CMF
Cyclophosphamide 600 mg/m²
Methotrexate 40 mg/m²
5-Fluorouracil 600 mg/m²
IV q 3 to 4 wk, max. 9 to 12 cycles

FAC
Cyclophosphamide 500 mg/m²
Doxorubicin 50 mg/m²
5-Fluorouracil 500 mg/m²
IV q 3 to 4 wks, max. 6 to 8 cycles

FEC
Cyclophosphamide 500 mg/m²
Epirubicin 50 mg/m²
5-Fluorouracil 500 mg/m²
IV q 3 to 4 wks, max. 9 to 12 cycles

EPI
Epirubicin 90 mg/m²
IV q 3 to 4 wks, max. 6 to 8 cycles

MITOX
Mitoxantrone 12 mg/m²
IV q 3 to 4 wks, max. 6 to 8 cycles

Vinorelbine 25 mg/m² IV days 1 and 8. No treatment day 15
Repeat cycle every three weeks

Paclitaxel 175 mg/m² or 135 mg/m² over 3 hours IV q 3 wks
Premedicate with dexamethasone 20 mg po at 12 and 6 hrs before, Ranitidine 50 mg or cimetidine 300 mg IV and diphenhydramine 50 mg IV 30 minutes before paclitaxel.

**Docetaxel**

100 mg/m² over 1 hour IV q 3 wks max. 6 cycles
Premedicate with dexamethasone
Low dose weekly docetaxel should be given at 35 mg/m² either three weeks in a row with one week off (3/1) or six weeks on and two weeks off (6/2). Premedicate with dexamethasone with treatment, and the evening of therapy. 6 cycles of low dose therapy are as defined six treatments of 3/1 or 3 treatments of 6/2.

**Capecitabine**

1000 mg/m² bid po for 14 days every 3 weeks in patients progressing on or unable to tolerate taxane therapy.

<table>
<thead>
<tr>
<th>Toxicity, NCIC Grade*</th>
<th>During a Course of Therapy</th>
<th>Dose Adjustment for Next Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>maintain dose level</td>
<td>maintain dose level</td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>♦ 1st appearance</td>
<td>interrupt until resolved to grade 0-1</td>
<td>100%</td>
</tr>
<tr>
<td>♦ 2nd appearance</td>
<td>interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td>♦ 3rd appearance</td>
<td>interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
<tr>
<td>♦ 4th appearance</td>
<td>discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>♦ 1st appearance</td>
<td>interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td>♦ 2nd appearance</td>
<td>interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
<tr>
<td>♦ 3rd appearance</td>
<td>discontinue treatment permanently</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>♦ 1st appearance</td>
<td>discontinue permanently OR if physician deems it to be in the patient’s best interest to continue, interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
</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 over expression by IHC or FISH. All samples should be sent to Dr. Alan Tuck, Pathology Department, London Health Sciences Centre.
- 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.
**RECOMMENDATIONS FOR MONITORING PATIENTS RECEIVING TRASTUZUMAB**

**SCHEDULING AND DOSING**: Loading dose 8 mg/kg IV, maintenance dose 6 mg/kg IV every 3 weeks for 1 year

**BASELINE MUGA SCAN** (prior to Trastuzumab and post-chemo)
- repeated every 3-4 months (15-16 weeks)

**HISTORY / PHYSICAL AND BLOOD WORK** (CBC, renal and LFTs)
- repeated every 9 weeks

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**ASYMPTOMATIC PATIENTS: RULES FOR TRASTUZUMAB CONTINUATION BASED ON SERIAL LVEFs**

<table>
<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

---

**Symptoms of CHF**
- Asymptomatic: Based on MUGA scan results

- Permanently discontinue Trastuzumab
- Repeat MUGA and CXR
- Consult Cardiology

- LVEF unchanged
- Continue Trastuzumab

- Decrease in LVEF
- Refer to table below

---

**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
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).
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. It is strongly recommended that these women have LH, FSH and serum estradiol determination (preferably at least two months after stopping tamoxifen) to determine menopausal status.

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 - GENETICS COUNSELLING

PREAMBLE

Most breast, ovarian and colorectal cancers occur sporadically in families and the cause is either unknown or associated with one or more risk factors. In a minority of cases (5-20% overall), cancer is associated with a strong hereditary factor, which greatly increases the risk of developing a malignancy.

The MOHLTC has defined clinical criteria for referral of patients at risk for inherited cancer syndromes. It is recognized that such a list 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 Familial Cancer Genetics Clinic or Genetics Clinic. Upon referral, services such as genetic counseling and assessment, education and surveillance recommendations are available to individuals and families. Referrals may be made both for individuals with cancer and those without cancer.

PLEASE NOTE THAT GENETIC TESTING MAY OR MAY NOT BE OFFERED IN THE COURSE OF A GENETICS CONSULTATION.

The following clues from an individual’s personal or family history may suggest an increased risk for hereditary cancer. A pertinent family history may be found either on the maternal or paternal sides of the family, but should be on the same side of the family. The family history will be assessed by the genetics clinic to evaluate whether a genetic counseling appointment is indicated. It is likely that this guide will be modified, as new scientific information arising from advances in the field of genetics becomes available. Referrals for other hereditary cancer syndromes not addressed by this document can be made to your local genetics centre.

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 other associated cancers or conditions suggestive of an inherited cancer syndrome.
APPENDIX 9 - LONG TERM FOLLOW-UP ISSUES

Increased evidence showing benefits of adjuvant 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.

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 as their effect on risk of recurrence is unknown (CMAJ 1992; 166: 1017-22). Black cohosh is not effective. Vitamin E is somewhat less effective.

  - 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 increased 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.

  - 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.

  - Genitourinary symptoms: These show significant improvement with HRT. Vaginal dryness and dysparenia can be treated with lubricating gels (Replens) as a first approach, or topical estrogen cream, which has minimal systemic absorption. However, some postmenopausal women with severe vaginal atrophy may have increased systemic absorption of even vaginal estrogen preparations. The e-string is an alternative approach. If HRT is considered, intermittent (less than 5 years) rather than continuous therapy is recommended.

  - 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.
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 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. Pap tests are not recommended until six months after completion of chemotherapy, unless there are symptoms, because of cytologic atypia induced by prior chemotherapy.

- Cardiac toxicity and acute leukemia are rare complications of anthracycline-based chemotherapy. There is no evidence that serial cardiac assessment or CBC’s in the asymptomatic person alter the outcomes of these events.
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This guideline is a statement of consensus of the Breast Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgment of the physician in the context of individual clinical circumstances to determine any patient’s care or treatment.