Breast Cancer Treatment Guidelines

(Approved at Provincial Breast Cancer Guideline Meeting from March 8 - 10, 2012)

Clinical practice guidelines have been developed after multi-disciplinary consensus based on best available literature. As the name suggests, these are to be used as a guide only. These guidelines do not replace Physician judgment which is based on multiple factors including, but not limited to, the clinical and social scenario, comorbidities, performance status, age, available resources and funding considerations.

Participating in clinical trials is encouraged when available.

Content:

Primary Breast Cancer

Screening: Breast cancer screening has shown substantial reduction in mortality related to breast cancer. For details, visit Saskatchewan breast cancer screening program at www.saskcancer.ca

Breast Cancer prevention by anti-estrogens: Data from placebo-controlled randomized trials and a meta-analysis demonstrate that treatment with the selective estrogen receptor modulators (SERMs) tamoxifen or raloxifene reduces the risk of breast cancer in women at high risk for the disease.
Raloxifene has a lower risk of thromboembolic events and uterine cancer, although it is slightly less effective for breast cancer prevention when directly compared to tamoxifen.
In the placebo-controlled NCIC CTG MAP.3 trial, exemestane reduced the risk of breast cancer in post-menopausal women at high risk for the disease.
Although breast cancer prevention using either a SERM or an AI can reduce the incidence of new primary breast cancers, **there is no data that this reduces breast cancer-related or overall mortality.** Therefore while this strategy cannot be considered as a standard of care, it can be discussed with individuals at high risk with discussion of the risks and benefits.

1. **Definition of High risk group:**
   - **a)** Age greater than 60.
   - **b)** A history of lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS), or atypical proliferative lesion of the breast (atypical ductal or lobular hyperplasia).
   - **c)** Women between 35 and 59 years of age with an estimated risk of breast cancer of 1.66 percent or higher over five years from the Gail model (www.cancer.gov/bcrisktool/).
   - **d)** Individuals with BRCA 1 and 2 mutations.

   References: 1 to 7.

Diagnosis:

1. **Clinical examination:** Bimanual palpation of breast and locoregional lymph nodes.
2. **Radiological Examination:** Bilateral mammography and ultrasound of breasts and regional lymph nodes. MRI of the breast is not needed as a routine procedure, but may be considered in cases with diagnostic challenges as:
   a) Dense Breast tissue especially in young women.
   b) Familial breast cancer associated with BRCA mutations.
   c) Silicone Gel implants.
   d) Positive axillary nodal status with occult primary tumor in the breast.
   e) Multiple tumor foci are suspected especially with lobular carcinoma.
3. **Pathological diagnosis:** A **core needle biopsy** is recommended before surgery. If preoperative chemotherapy is anticipated, a core needle biopsy with placement of surgical clips into the tumor to facilitate later surgical resection is encouraged.

Reference: 8.

Staging: Based on AJCC TNM classification. **(Appendix 1)**

1. **History and physical:** In addition to regular history and physical emphasis on family history, performance status and menstrual history.
2. **Radiological Investigations:** are not routinely recommended pre operatively. Patients with clinical or biochemical suspicion of metastatic disease or in patient with locally advanced disease and/or clinically positive lymph nodes, radiological investigations as clinically indicated are suggested. Post operatively radiological investigations are indicated in lymph node positive disease and large size tumors (>5cm).
3. **Blood test:** Pre-operative blood test should include complete blood count (CBC), Renal and liver function tests, alkaline phosphatase level, calcium. Follicle stimulating hormone level (FSH) and serum estradiol level if the menopausal status is in doubt.

   Patients with low risk disease do not benefit from comprehensive lab work including tumor markers and radiological staging.

Pathology: Breast tissue excised for invasive carcinoma or DCIS will be handled and reported according to the current College of American Pathologist protocols (www.cap.org). Estrogen and progesterone receptor testing will be performed on invasive breast cancers and on DCIS without invasive carcinoma. HER 2 testing will be performed on invasive breast carcinomas and reported according to ASCO/CAP guidelines.

References: **9-10**

Surgery for Invasive cancers:

1. **Breast conservation surgery (BCS):** BCS combined with radiotherapy has very low local recurrence rates and is equivalent to mastectomy in terms of local control and overall survival. Careful histological assessment of resection margins is essential and marking the tumor bed with clips will facilitate planning of radiation therapy.

2. **Mastectomy:** Is the procedure of choice if:
   a) Patient's choice.
   b) Multiple tumors in the breast.
   c) Large size or location of the tumor, removal of that could result in considerable distortion of the breast.
   d) Contraindication for radiotherapy.
   e) Extensive microcalcification on mammogram.
   f) Prior radiation to the chest wall or breast.

3. **Axillary Staging:** Sentinel lymph node biopsy rather than full axillary nodal dissection is considered standard of care, unless axillary node involvement is suspected clinically or by radiology. Surgeons qualified in performing the procedures have low false negative rates.
   On the basis of a randomized clinical trial, patients with T1 or T2 tumors who underwent breast conservation surgery (BCS) and found to have one or two positive lymph nodes on SLNB can be spared of full axillary lymph node dissection. Patients treated with this approach must agree to be treated post operatively with appropriate systemic and radiation therapy. All other patients with sentinel lymph node positive disease should undergo full axillary lymph node dissection.

   The optimal axillary management of micro metastatic spread and isolated tumor cells identified on sentinel lymph nodes are not clear. We would recommend no further axillary dissection in patients with isolated tumor cells (<0.2mm) and micrometastatic disease.

4. **Surgical Margins:** It is important to obtain negative resection margins at the time of surgery. An adequate margin is greater than or equal to 2mm from an inked margin. This is for both invasive cancer and DCIS.
   A positive margin is defined as tumor touching ink and/or transected tumor.
   A close margin is defined as tumor less than 2 mm.
   Patient with positive or close margin is recommended to have re-excision. If re-excision is declined or not possible, a radiation boost to the tumor bed is recommended.

5. **Risk reducing mastectomy:** Prophylactic bilateral mastectomy and reconstruction may be offered to women with BRCA 1 or 2 mutation. Surgery substantially reduces the risk of developing breast cancer but does not completely eliminate it.

For patients diagnosed with breast cancer where the risk of contralateral disease is high as multifocal lobular cancer or where invasive cancer is associated with widespread LCIS or hyperplasia with atypia in surrounding breast tissue, prophylactic mastectomy may be an option.

6. **Breast Reconstruction:** Immediate or delayed reconstruction should be offered to patients undergoing mastectomy. When post mastectomy radiation therapy is anticipated immediate reconstruction should be avoided.
   Surgical options include silicone gel implants and myocutaneous tissue flaps.
   There is no evidence that reconstruction makes detection of local recurrence difficult.

   References: 11 to 13.

Surgery for In situ disease:

1. **Paget's disease of the nipple:** Majority of patients require a mastectomy, partial mastectomy may be offered to selected patients if breast conservation will lead to adequate cosmetic results. Patient undergoing breast conservation therapy should be referred to radiation oncology.
   Since Paget's disease can be associated with an underlying breast mass, breast imaging with mammography and MRI should be considered.
2. **Ductal carcinoma in situ (DCIS):** BCS followed by adjuvant breast radiation would be considered standard of care. Mastectomy may be required for larger or mutifocal and muticenteric disease. Mastectomy is curative for DCIS and radiation therapy is not required.
   Axillary node sampling by sentinel lymph node biopsy is not required, however may be reasonable in the context of large tumor requiring mastectomy.
   There is no general consensus on margins however margins less than 2mm are considered inadequate.
   Patients with positive or close margin are recommended to have re-excision. If re-excision is declined or not possible, a radiation boost to the tumor bed is recommended.
3. **Lobular neoplasia (lobular carcinoma in situ and atypical lobular hyperplasia):** Is considered a non-obligate precursor of invasive carcinoma and is best regarded as risk factor for future development of invasive carcinoma in both breasts.
   Lobular neoplasia does not usually produce a clinically detectable change in the breast, and lobular neoplasia by itself is not usually detected on breast imaging studies.
   If an image-guided core biopsy of a breast lesion shows only lobular neoplasia, consideration needs to be given as to whether the core biopsy has actually sampled the target lesion seen on imaging.

When lobular neoplasia represents the targeted lesion and no other significant lesion is present (on atypical ductal hyperplasia, DCIS, or invasive carcinoma) the literature does not provide clear guidance whether surgical excision is always required. When lobular neoplasia is present at the margins of an excision done for any type of lesion, but no other significant lesion is present at or close to the resection margins, a margin revision is not required.

4. **Pleomorphic variant of lobular neoplasia:** It behaves similarly as DCIS and should be treated accordingly.

Reference: 14.

Radiation Therapy:

1. **Adjuvant Radiation for Invasive disease after Breast Conserving Surgery.**

   a) **Lymph node negative disease:** Whole breast radiotherapy is recommended for all patients following segmental resection. Tangential breast fields: 5000 cGy in 25 fractions or 4250 cGy in 16 fractions are standard, but other fractionation can also be used. Partial breast radiotherapy is considered investigational as part of a clinical trial, such as the OCOG12 study (for tumours <3 cm and node negative).
   b) **Lymph node positive disease:** If 1-3 nodes are positive, for both pre– and postmenopausal women, whole breast radiotherapy is recommended. Regional nodal radiation is individualised based on other features such as: age, grade, extranodal extension and size. If four or more nodes are positive, breast plus regional nodal radiotherapy is recommended. Inclusion of internal mammary lymph nodes as clinically indicated. 16 or 25 fractions are common, but other fractionation can also be used. If more than 10 nodes are resected, then radiation field may be limited to the supraclavicular nodes.
   c) **Patient with close or positive margins:** If breast conserving surgery was done and margins are <2 mm, then re-excision is recommended to clear the margins. Close margin at fascia is an exception. Radiotherapy boost is recommended in case surgical re-excision is not done.
   d) **Radiation Boost:** It is recommended in all women less than 40 years of age, regardless of margin. In women more than 40 years of age, boost is individualized based on risk assessment as for grade 3 disease, less than or equal to 2 mm margin. Usually 5 to 8 fractions are delivered.

2. **Adjuvant Radiation for invasive cancer after Mastectomy:**

   a) **Lymph node negative disease:** Radiation is recommended in patients with tumour more than 5 cm in size and patients with T4 disease. Radiation therapy can be considered in tumors less than five centimeter in size if there are additional high risks features. Adjuvant RT is recommended when margins are positive. Chest wall and or regional nodal radiotherapy is recommended. Inclusion of internal mammary nodes as clinically indicated. 16, 20, or 25

fractions are common, but other fractionation can also be used. Use of bolus on the chest wall is recommended

b) **Lymph node positive disease:** For patients with tumors less than 5cms in size and less than or equal to three nodes are involved, then RT to chest wall with regional nodal RT is individualized. For patients with more than three positive nodes, breast plus regional nodal radiotherapy is recommended. Inclusion of internal mammary nodes in the radiation field can be considered. 16 or 25 fractions are common, but other fractionation can also be used. Use of bolus on the chest wall is recommended as clinically indicated.

c) **Radiation therapy for patients with Ductal Carcinoma in-situ (DCIS):** After breast conserving surgery for DCIS, whole breast radiotherapy is recommended.
The risk of recurrence is relatively low for women whose DCIS has good prognostic pathological features, such as clear surgical margins, low-grade lesions without necrosis, and small extent (<10mm).Although radiotherapy offers a statistically significant benefit over breast conservation surgery alone, for these women, the absolute benefit may be small. In such cases, the small gain in local control should be weighed against the inconvenience and morbidity of radiotherapy in discussion with the woman.
Partial breast radiotherapy is considered investigational.

Margins greater $\geq$ 2 mm are recommended. If margins are <2 mm, then re-excision is recommended (close posterior margin at fascia is an exception) prior to adjuvant radiation. If re-excision is not possible, the role of RT boost is not well defined.

The commonest adjuvant radiotherapy fractionation schedule used post segmental resection is 5000 cGy in 25 fractions to the whole breast without a boost when excision margins are clear of disease. The role of boost irradiation to the primary site is unclear.
Women with DCIS treated with total mastectomy alone have recurrence rates of less than 1%. Adjuvant radiotherapy may be considered if margins are positive; however, the benefit of radiotherapy in this setting is not well defined.

Contraindications to breast irradiation: include pregnancy, previous breast irradiation (including mantle irradiation for Hodgkin's disease) and inability to lie flat or to abduct the arm. Scleroderma and systemic lupus erythematous are relative contraindications.

References: 69 to 77.

Adjuvant systemic therapy:

1. Risk Stratification: Decision to treat patient with systemic adjuvant therapy and the type of treatment to be offered depends on multiple clinical and pathological factors. Size of the tumor, involvement of axillary lymph nodes, grade of the tumor, presence of Estrogen and or progesterone receptor, over expression of HER 2 status are some of the factors on which treatment decisions are made.
Clinical parameters have been integrated into scoring systems that allow a relatively accurate estimation of the probability of recurrence and death from breast cancer. Nottingham prognostic index (NPI) or Adjuvant online (www.adjuvantonline.com).
Gene expression profile such as Mammaprint or Oncotype Dx recurrence score is used to complement pathology assessment.
In patients with T1 and T2 lesions, lymph node negative, ER and or PgR positive disease, use of Oncotype Dx recurrence score and Mammaprint gene profile can help in avoiding chemotherapy in low risk patients.
Patients with hormone receptor and HER 2 negative breast cancer (Triple negative disease) are considered to have high risk disease.
For each individual, the choice of adjuvant therapy must take into account the potential benefit, possible side effects and patient's preference.

2. Endocrine Therapy:

A) Premenopausal Women: Tamoxifen 20mg per day is the standard therapy in particular after chemotherapy.
Ovarian function suppression and tamoxifen is at least as effective as chemotherapy.
Ovarian function ablation can be achieved by bilateral oophorectomies, GnRHAs leads to reversible ovarian suppression. GnRHAs should be given for at least 2 years, although the optimal duration of the treatment has not been established.
Patient's with intact ovarian function after completion of chemotherapy may benefit from ovarian function suppression.
CYP2D6 (cytochrome p450 2D6) a microsomal enzyme, limits the synthesis of endoxifen, which is the active metabolite of tamoxifen. The activity of CYP2D6 is determined by genotype and by inhibitor drugs. Some retrospective studies point towards unfavorable prognosis of patients with low activity genotypes (poor metabolizer). Two retrospective analysis of randomized controlled trials failed to detect a differential effect of CYP2D6 poor metabolizer genotype on the efficacy of tamoxifen. Thus routine genotyping is not recommended. However moderate to potent inhibitor of CYP2D6 be avoided in patients on tamoxifen.

B) Postmenopausal Women: Aromatase inhibitor (AI's) is used upfront for 5 years.
For patients treated with tamoxifen, a switch to an AI after 2 to 3 years is recommended.
Five years of tamoxifen is still a viable option for certain patients at low risk of recurrence. For patients treated with five years of tamoxifen the addition of an AI for

further 2 to 5 years is recommended especially for patients with lymph node positive disease.

3. Chemotherapy: Decision to offer adjuvant chemotherapy is based on risk stratification showing benefit of adjuvant chemotherapy with acceptable risk of toxicities. Tumor related factors as size of tumor, axillary lymph node involvement, grade of the tumor, presence or absence of hormone receptors and over expression of HER 2 are combined with patients co-morbid conditions, patients preference and toxicity profile of different chemotherapy regimens.
Standard chemotherapy regimens are superior to less intensive regimens in elderly patients.
Anthracyline based chemotherapy is commonly used. However non anthracycline based therapies with similar or superior efficacy such as Docetaxel plus cyclophosphamide or classic cyclophosphamide, methotrexate, flurouracil (CMF) are also an option. Patients treated with anthracycline based chemotherapy are recommended to have base line cardiac function checked by either an echocardiogram or cardiac wall motion study.
Chemotherapy regimens combining anthracycline and taxanes have been investigated mainly in patients with high risk disease. Studies suggest sequential rather than concomitant use of anthracyclines and taxanes is better. Patients treated with paclitaxel as adjuvant therapy should use weekly regimen as three weekly regimens is noted to be inferior.
Dose dense schedule of chemotherapy with granulocyte colony stimulating factor (G-CSF) is an option for patients with high risk disease.
Adjuvant chemotherapy is associated with significant risk of immediate and long term toxicities and appropriate supportive care measures including use of appropriate anti emetics, use of primary or secondary prophylaxis with GCSF, and/or use of prophylactic antibiotics should be considered.
For list of available chemotherapy see **Appendix 2.**

4. Trastuzumab: overexpression of HER 2 is associated with poor prognosis in breast cancer patients. Overexpression of HER 2 protein is measured by immunohistochemistry. Equivocal result (HER 2+ on IHC) is subjected to gene amplification testing by in situ hybridization (FISH, CISH or SISH). Testing will be done as per ASCO/College of American Pathologist guidelines for HER2:CEP17 interpretation.
Adjuvant trastuzumab in patients with HER 2 overexpressed tumors (IHC 3+ or ISH positive) lowers the hazard of recurrence by about a quarter to a half and the hazard of death by about one sixth to one third.
While randomized trials have excluded patients with small primary cancers (<1cm), over expression of HER 2 confers a poor prognosis even in small tumors. Use of trastuzumab can be discussed with women having smaller than 1cm size tumor and lymph node negative disease.
Trastuzumab can be given as weekly schedule or three weekly schedules. At this stage one year of therapy is recommended.
Use of trastuzumab alone or with hormonal therapy is not tested yet in patients who cannot undergo chemotherapy.

Trastuzumab should NOT be given concurrently with anthracyclines due to the risk of severe cardiotoxicity.
Non anthracycline based chemotherapy as Docetaxel/carboplatin/trastuzumab (TCH) is replacing anthracycline based chemotherapy in the hope of avoiding cardiotoxicity.
Trastuzumab is associated with cardiotoxicity and it is important to avoid trastuzumab in patients with low left ventricular ejection fraction (LVEF<50). We would recommend every three month monitoring of cardiac functions in addition to a base line study with either an Echocardiogram or cardiac wall motion study till the completion of adjuvant trastuzumab.
Appropriate management algorithm of patients with asymptomatic decline in LVEF is available on **Appendix 3.**

Treatment for Invasive tubular and colloid cancer: patients with invasive tubular and colloid cancer have much better prognosis. Tumors are usually hormone receptor positive. For tumors less than 3cm in size with lymph node negative disease no adjuvant therapy is needed. In a patient with lymph node positive disease or tumor greater than 3 cm in size adjuvant hormonal therapy is recommended.

References: 15 to 43.

Systemic therapy for DCIS: Meta-analysis of two large randomized trials shows that five years of Tamoxifen reduces the risk of invasive and non-invasive recurrences after breast conservative surgery in ER positive patients with DCIS. However there was no impact of tamoxifen on overall survival at fifteen years. Tamoxifen is associated with significant toxicities as thromboembolic events and small risk of uterine cancer. Use of tamoxifen may be discussed on a case by case basis.
Use of aromatase inhibitor is being evaluated in this situation.

References: 44 and 7.

Neo adjuvant Therapy:

1. **Indications:**
   a) Locally advanced breast cancer and inflammatory breast cancer
   b) Operable tumor for reducing tumor size with the plan to perform BCS.
2. **Prior to Systemic therapy:** A **core needle biopsy** and complete pathological assessment of the tumor including hormone receptor and HER 2 status is required. An MRI prior to start of therapy is suggested. Staging work up to rule out metastatic disease is required.
   In case of suspicious axillary lymph node in the axilla, biopsy is recommended to prove lymph node positive disease. It is also recommended to mark the primary site using a marker clip under ultrasound guidance at the time of core biopsy.

For patients undergoing neo-adjuvant therapy to reduce tumor size, with the plan to perform BCS, sentinel lymph node biopsy is recommended prior to start of systemic therapy.

3. **Systemic Therapy:** Anthracycline followed by taxanes is considered standard neo-adjuvant therapy. Trastuzumab should be added to primary chemotherapy in patients with HER 2 positive tumors. Optimal duration of therapy is not known, however 18 to 24 weeks of therapy is suggested. **See Appendix 2.**
   It is preferable to complete all chemotherapy before surgery.
   ER-Positive, HER 2 negative carcinomas may be less responsive to primary chemotherapy; primary hormonal therapy is active, in particular with AIs, but the long term recurrence and survival results are not yet available. Patients with locally advanced disease who cannot tolerate chemotherapy can be treated with hormonal therapy.
4. **Surgery after primary therapy:** BCS is a possibility in this group of patients with adequate response, otherwise mastectomy is performed. If BCS is planned an MRI is recommended to see the size of residual disease and the presence of multifocal disease. Full axillary lymph node dissection is considered standard of care.
5. **Adjuvant Radiotherapy**: Pre-treatment biopsy of palpable node or sentinel node procedure for non-palpable node is recommended to assess role of nodal RT**.** Adjuvant radiotherapy is given after definitive surgery with same principle as discussed above.
6. **Systemic Therapy after surgery:** Hormone therapy would be indicated in hormone receptor positive disease as standard adjuvant hormonal therapy. Use of trastuzumab should continue for a total of one year from initial dose.

References: 45 to 48.

Follow Up after completion of therapy:

1. **Goals:** to detect early in-breast and local recurrence or contralateral breast cancer. To evaluate and treat therapy related complications such as menopausal symptoms, osteoporosis, and second cancers. To provide psychological support and information in order to enhance returning to normal life after breast cancer.
2. **Recommended follow-up:** There is no evidence from randomized trials supporting any particular follow up sequence or protocol. We would recommend.
   a) Physical examination every six months for the first five years and then annually. Examination should include the affected breast or mastectomy site, chest wall, regional lymph node areas (axillary and supraclavicular), contralateral breast, auscultation of the chest, palpation of the liver and a check for vertebral column tenderness.
   b) Annual bilateral mammogram, or in the case of unilateral mastectomy, annual mammogram of the contralateral breast.

c) If women wish to carry out breast self-exams, it is reasonable to educate them regarding the proper procedures.

d) For any patient with a history of breast cancer, the use of hormone replacement therapy should be reviewed with their health care provider as it is relatively contraindicated.

e) In the absence of clinical signs or positive physical findings, blood work including tumor marker, chest x-rays, bone scans or other special investigations are not recommended.

f) **Contraception:** If permanent contraception is desired by the patient and her husband, then tubal ligation should be considered. For patients who are not yet ready to contemplate sterilization, a non-hormonal procedure such as barrier techniques or an IUD should be recommended.

g) **Side effects of Hormonal therapy:** Women treated with AI are recommended to take Vitamin D and calcium as nutritional supplements. A dual energy X-ray absorption scan (DEXA) is recommended to allow early treatment of osteoporosis. Women experiencing premature menopause due to chemotherapy or ovarian suppression should also have DEXA scan. Bisphosphonates prevents bone lass in patients with iatrogenic premature menopause and in post-menopausal patients treated with AIs. Vasomotor symptoms should be managed without hormonal therapy; Venlafaxine, gabapentin and clonidine are used with limited success. SSRI's except venlafaxine should be avoided in patients on tamoxifen as these drugs are CYP2D6 inhibitors. Vaginal dryness and atrophy should be treated with non-hormonal lubricants. In refractory cases low dose vaginal estrogen therapy (eg, Estring or Vagifem vaginal tablet 10 microgram) can be used after discussing the risks with patients.
Patients on Tamoxifen are at higher risk of developing endometrial cancer and are recommended to have a yearly pelvic examination and close monitoring for signs and symptoms of endometrial cancer.

Visit www.saskcancer.ca for follow up guidelines.

Genetic testing: Familial susceptibility to breast cancer accounts for <25% of all breast cancer cases. *BRCA1* and *BRCA2* are high-penetrance breast cancer predisposition genes identified by genome-wide linkage analysis and positional cloning. Mutations in *BRCA1/2* explain ~20% of the familial clustering of breast cancer. Germline mutations in the other high-risk genes *TP53*, *PTEN* and *STK11* are identified in <1% of breast cancer families and are usually associated with rare cancer syndromes (Li–Fraumeni, Cowden and Peutz–Jeghers syndromes, respectively). Screening of genes functionally related to *BRCA1* and/or *BRCA2* has identified mutations in *CHEK2*, *ATM*, *BRIP1* and *PALB2*. Mutations in these genes are rare and confer an intermediate risk of breast cancer, and therefore explain only a small proportion of the remaining predisposition. More recently, *RAD51C* has been discovered as a potentially high-risk cancer predisposition gene in breast/ovarian cancer families. Association studies have further identified 18 common variants associated with low-penetrance breast cancer

predisposition. Despite these discoveries, the underlying cause of >70% of the familial breast cancer cases still remain unexplained.
Widely accepted clinical criteria for genetic testing referral include: three or more breast and/or ovarian cancer family cases, with at least one <50 years; two breast cancer cases <40 years; male breast cancer and ovarian cancer or early onset female breast cancer; Ashkenazi Jew with breast cancer of <60 years; young onset bilateral breast cancer; and breast and ovarian cancer in the same patient. The addition of pathological features of breast cancer such as medullary carcinoma and triple negative phenotype (estrogen receptor, progesterone receptor and no overexpression of HER2neu) in women younger than 50 has been evaluated as a cost-effectiveness strategy for mutation.
Since BRCA gene mutations are called actionable genetic mutations, genetic testing and offering further preventative methods as prophylactic surgery can save lives.
Patients are recommended to be referred to the genetic counseling clinic in Saskatoon.

Locally recurrent and Metastatic disease

1. **Need for biopsy:** efforts should be made to obtain a biopsy preferably from soft tissue or from a visceral lesion. Biological markers as hormone receptors and HER2 status should be evaluated in the metastatic lesion whenever possible. Biopsy may potentially be avoided
   a) In situations where the procedure is too risky.
   b) In cases where the time elapsed between the primary tumor and metastatic disease diagnosis is relatively short (<1-2 years).
   c) When the results of biopsy are unlikely to change the therapeutic decision, as in a patient where chemotherapy or anti HER 2 therapy is not possible.
2. **Staging:**
   a) **History and physical examination.**
   b) **Blood tests:** complete blood counts, liver and renal function tests, alkaline phosphatase and calcium levels. The clinical value of tumor markers has not been proven. However they may assist in response evaluation to treatment especially in patients with non-measurable disease.
   c) **Radiological investigations:** CT chest, abdomen and pelvis or MRI should be done to identify and measure visceral disease.
   Bone scintigraphy with confirmation of the lesions by x-ray or CT and MRI.
   Brain CT or MRI only if patients have symptoms related to CNS disease.
   PET/PET-CT may be useful when traditional methods to identify metastatic disease are equivocal or conflicting. It may also be helpful to identify or confirm the situation of an isolated loco regional relapse or metastatic lesion, since this subset of patients may benefit from a more aggressive

multidisciplinary approach. PET/PET CT may also be useful in response evaluation in patients with bone only disease.
In case of lesions inaccessible for biopsy, PET CT may be helpful to evaluate malignant characteristics.

3. **Pathology:** ER and PgR, HER2 receptors analysis of the metastatic lesion is recommended to be obtained if possible.
4. **Loco regional Recurrence:**
   a) **Surgery:** Isolated loco regional recurrence should be treated like a new primary with a curative intent. Complete removal of recurrent tumor is recommended. In patients with previous breast conserving surgery, a mastectomy is recommended. In patients with locally advanced disease but potential candidates for curative resection primary, systemic therapy should be considered.
   b) **Radiation Therapy:** In patients not exposed to post-operative irradiation, full dose radiotherapy to the chest wall and when indicated regional lymph node areas should be given.
   In patients previously treated with radiation therapy the value of re irradiation is not proven. Radiation therapy to limited area in the chest wall may be given after careful risk-benefit assessment, taking into account the duration of the radiation free period, intensity of post radiotherapy changes and the risk of additional loco regional relapse.
   Inoperable patients can if feasible undergo radical radiotherapy to the chest wall and regional lymph node areas with boost to macroscopic disease site. However in these patients upfront systemic therapy to decrease the size of the tumor and render it operable should be the first option.
   c) **Systemic therapy:** The value of systemic therapy (Pseudo adjuvant) is not well proven due to poor accrual on clinical trials designed to answer this question.
   Factors such as tumor aggressiveness, previous adjuvant systemic therapy, patient's co-morbid conditions and preferences should be taken into account before deciding on adjuvant chemotherapy.
   Similar principles of chemotherapy treatment are usually applied as in adjuvant chemotherapy including the use of trastuzumab in HER2 positive disease.
   Although unproven systemic (pseudo adjuvant) hormonal therapy is a common practice in hormone receptor positive disease in view of its predicted benefit and low toxicity.
   d) **Follow-up:** follow-up after treatment of loco regional recurrence may be carried out as for primary breast cancer.
5. **Metastatic disease:** is incurable in majority of cases. The goal of treatment is palliation, with the aim of maintaining and improving quality of life, and possible improvement in survival.
   a) **Factors affecting treatment decision in MBC:** Disease related factors include disease free interval, previous therapies and response, biological factors as hormone receptors, HER2 status, tumor burden as number and site of metastases, need for rapid response.

Patient related factors include patient's preference, biological age, menopausal status, performance status and comorbid conditions, socioeconomic and psychological factors.

b) Role of surgery in metastatic disease: For limited metastatic presentation surgery can be considered to remove metastatic lesions.
Although no randomized data is available, review of retrospective data suggests a significant survival benefit from removal of primary tumor (Breast) in patients with metastatic disease. This can be considered in select group of patients.

c) Role of radiation therapy in metastatic disease: The most common indications for palliative radiotherapy include painful bone metastases, bone metastases with risk of fracture and or neurological complications.
Patient's with brain metastases also benefit from radiation therapy.
Stereotactic radiosurgery is an option in a selected group of patients.
Use of radiation therapy is helpful in painful or fungating soft tissue masses.

d) Endocrine therapy: In ER and or PgR positive patients' endocrine therapy is the preferred option except in aggressive disease when rapid response is required.
The value of maintenance with hormonal therapy after chemotherapy has not been confirmed in clinical trials, but is considered a reasonable approach.
Addition of anti HER 2 therapies to hormonal therapy in patients with HER overexpression is beneficial.

i) Premenopausal patients: If no prior adjuvant tamoxifen was given or if it has been discontinued for >12 months, tamoxifen with ovarian ablation (by LHRH agonists or surgery) is the preferred option. Patients otherwise can be treated with an aromatase inhibitor with or after ovarian ablation. Drugs modulating the activity of CYP2D6 such as some SSRI's as paroxetine and fluoxetine should be avoided in patients on Tamoxifen.

ii) Postmenopausal patients: Aromatase inhibitor should be the first choice of therapy in patients if no prior adjuvant aromatase inhibitors were given or if they have been discontinued for >12 months. Upfront aromatase inhibitor therapy has shown higher response rate, time to progression and in case of Letrozole survival as well. Patients on aromatase inhibitors have accelerated bone loss; calcium and vitamin D supplementation is recommended.

iii) Further lines of hormonal therapy: if not previously used includes Tamoxifen or, aromatase inhibitors. Fulvestrant at a dose of 500 mg intramuscular injection with a loading schedule has shown improvement in progression free survival after failure of other anti-estrogen therapy. In a randomized phase III trial use of this drug has shown doubling of time to progression compared to anastrozole in the first line setting. While studies of Fulvestrant are in post-menopausal patients; this estrogen antagonist can be safely used in premenopausal patients as well.

iv) Reversal of hormone resistance with use of oral MTOR inhibitor: In a recently published trial patients with progression of disease on aromatase inhibitors showed significant improvement in progression free survival when treated with oral MTOR inhibitor everolimus in combination with exemestane. This treatment is awaiting approval from regulatory authorities.

e) Chemotherapy: palliative chemotherapy has shown to improve disease free and overall survival in breast cancer patients.
1st line chemotherapy options include use of anthracyclines (if not used in adjuvant setting) or taxanes.
The selection of best agents and regimens should be individualized and should take into the account the disease related and patients related factors as discussed in section "a", of the metastatic disease.
For available agents and regimens see **Appendix 4.**
Duration of each regimen, number of regimens and sequential vs. combination treatment should be tailored to each individual patient's need.

f) Anti HER 2 therapy: Trastuzumab should be offered to all patients with HER2 positive metastatic breast cancer patients, unless they have progressed while on adjuvant trastuzumab therapy. It can be used alone, with single or combination chemotherapy regimens. **See Appendix 4** for regimens utilizing anti HER 2 therapy.
A recent trial has shown that adding pertuzumab to trastuzumab based chemotherapy results in better progression free survival without significantly increasing toxicity. This treatment is not yet approved by the regulatory authorities.
Trastuzumab is associated with risk of cardio toxicity. Cardiac monitoring with echocardiography or by cardiac wall motion study is suggested to be done prior to start of therapy and during therapy if deterioration in cardiac functions is suspected.
A phase III randomized trial and retrospective data show that continuing trastuzumab with a different chemotherapy regimen after the disease progression is superior to the discontinuation of this agent. At this stage available evidence points to the continuity of anti HER 2 therapy for as long as possible.
Lapatinib has shown improved time to progression in combination with capecitabine in patients progressing after trastuzumab, anthracyclines and taxanes.
The question of continuing trastuzumab or changing to lapatinib at the time of first progression remains open. Herceptin can be continued beyond first line failure. Lapatinib can be used after failure of Herceptin in second line setting.
Trastuzumab in combination with Lapatinib has shown improved progression free survival compared to Lapatinib alone in patient who have failed trastuzumab. This treatment however is not currently funded.
Addition of both trastuzumab and lapatinib to endocrine therapy in hormone receptor positive disease allows improvement in progression free survival. It

is an option in patients who are evaluated as not needing or not being able to tolerate chemotherapy.
Brain metastases are increasingly reported as a site of first relapse in breast cancer, particularly among women receiving trastuzumab for HER2-positive metastatic breast cancer. The development of central nervous system metastases in a patient receiving trastuzumab should not necessarily prompt a change in chemotherapy as long as extra cerebral disease control is maintained. Preliminary results support the possibility that lapatinib, unlike trastuzumab, may penetrate the CNS and be effective against brain metastases. Nevertheless, brain metastases is recommended to be treated with radiation therapy +/- surgery.

g) Response Evaluation: It is routinely recommended after 2-3 months of endocrine therapy and after 2 to 3 cycles of chemotherapy. This is done by clinical evaluation, subjective symptoms, blood tests and repeating the initially abnormal radiological examination with comparative measures.
In case of clinical suspicion of progressive disease, appropriate investigations should be done irrespective of scheduled examination.
Bone scan should be used with extreme caution due to the potential for a flare response being confused with progression.
Tumor markers as CA 15-3 or CA27.29 and CEA may be helpful in monitoring response, especially in cases of not easily measurable disease, but should not be used as the only determinant for treatment decision.

h) **Bone modifying agents in metastatic breast cancer:** Potent inhibitors of osteoclast function, reduce the morbidity of metastatic bone disease, decrease the prevalence of skeletal-related events and improve control of bone pain. Bone-modifying agent therapy is only recommended for patients with breast cancer with evidence of bone metastases; denosumab 120 mg subcutaneously every 4 weeks, intravenous pamidronate 90 mg over no less than 2 hours, or zoledronic acid 4 mg over no less than 15 minutes every 3 to 4 weeks is recommended. **There is insufficient evidence to demonstrate greater efficacy of one bone-modifying agent over another.** Pamidronate is approed in Saskatchewan for this indication. Serum creatinine should be monitored before each dose. In patients with a calculated serum creatinine clearance of more than 60 mL/min, no change in dosage, infusion time, or interval of bisphosphonate administration is required. All patients should receive a dental examination and appropriate preventive dentistry before bone-modifying agent therapy and maintain optimal oral health.

References: 49 to 68

Axillary Nodal metastases with Occult primary Breast Cancer: Women who present with axillary lymph node metastases who have adenocarcinoma or poorly differentiated carcinoma histology, compatible immunohistochemical staining, no other distant metastases and no evidence of

a breast cancer primary on clinical examination, mammography, breast ultrasound, and breast MRI represent a potentially curable subset of individuals with carcinoma unknown primary. These women are treated according to guidelines for stage II breast cancer.
Optimal treatment for the ipsilateral breast is controversial. A standard approach is to perform a modified radical mastectomy at the time of ALND. For women who wish to preserve their breast, whole breast radiation therapy is an acceptable option.
Women with axillary lymph node metastases who have adenocarcinoma or poorly differentiated carcinoma, compatible immunohistochemical staining, and no evidence of a breast cancer primary but who have evidence of other distant metastases should be treated according to guidelines for metastatic breast cancer.

Breast Cancer during Pregnancy and lactation: In general breast cancer is treated in the same fashion with few modifications.
Mastectomy is typically preferred for most women with pregnancy-associated breast cancer. Breast conserving surgery is an option, but radiation therapy is delayed until after delivery to avoid fetal radiation exposure.
Sentinel lymph node biopsy is currently not recommended.
Adjuvant chemotherapy can be safely given to the patients in second or third trimester. Anthracycline based therapy is preferred.
Chemotherapy should be avoided if possible for three to four weeks before delivery to avoid transient neonatal myelosuppression and potential complication.
Trastuzumab should not be given to pregnant patients due to the risk of fetal death, pulmonary hypoplasia and other developmental abnormalities.
Similarly safety of Lapatinib is not established in pregnancy.
Patient with breast cancer should not breast feed while on chemotherapy, hormonal and anti Her 2 therapy.
It is unclear if pregnancy-associated breast cancer is associated with decreased survival when compared to breast cancer in non-pregnant women. In contrast, there is no evidence that subsequent pregnancy after the treatment of breast cancer worsens prognosis.

Male Breast Cancer: For male breast cancer simple mastectomy rather than more radical surgery is usually recommended.
More extensive surgery may be needed if invasion of the chest wall musculature is found at the time of surgery.
However, if locally advanced disease is suspected at the time of initial evaluation, neo adjuvant therapy should be considered.
An expert panel convened by the American Society of Clinical Oncology considered sentinel lymph node biopsy to be an acceptable alternative to full axillary node dissection for men with breast cancer and a clinically negative axilla.

Adjuvant and metastatic therapy guidelines are similar to female patients with breast cancer; however there is no data on aromatase inhibitors in male breast cancer; therefore, Tamoxifen is the preferred hormonal therapy. In patients with hormone receptors positive metastatic diseases who have failed tamoxifen, megesterol acetate is another option.

All patients with male breast cancer should have referral to genetic counseling clinic for detection of BRCA gene mutations.

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