FOLLOW-UP CARE
FOR EARLY-STAGE BREAST CANCER

Effective Date: May 2013

The recommendations contained in this guideline are a consensus of the Alberta Provincial Breast Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

The goals of follow-up care for patients with early-stage breast cancer are to detect recurrent or new breast cancer, to provide patient support (i.e., patient education, reassurance, and psychosocial support), and to monitor the efficacy and side effects of any adjuvant therapy. In order to meet these goals, an evidence-based strategy for follow-up should be included in the patient's care plan. Tertiary cancer care centres are currently unable to accommodate all breast cancer patients; however, it is known that follow-up care provided by general practitioners is equivalent, in terms of time to diagnosis, anxiety, and quality of life, to that provided at cancer care centres. [1] Moreover, patient satisfaction is higher with follow-up care provided in general practice than in hospital outpatient departments [2] and there are no significant increases in the workload of general practitioners. [3]

Assuming that a shared approach is appropriate for the follow-up care of patients who were treated for early-stage breast cancer, the purpose of this guideline is to provide evidence-based strategies for the care of patients who have been discharged to their referring physician. As such, this guideline should enable physicians to provide follow-up care to their patients and ensure that essential elements are communicated to the patient in a practical format.

GUIDELINE QUESTIONS

1. What investigations (i.e., tests and exams) constitute follow-up care for patients who have completed active medical or radiation oncology treatment for early-stage breast cancer? How often should these investigations be performed?
2. What are the responsibilities of the physician and cancer care centre, regarding follow-up care for patients with early-stage breast cancer?
3. Are there any complications, from treatment with surgery, chemotherapy, radiotherapy, endocrine therapy, and/or biologic therapy, of which the physician should be aware? What are the symptoms of these complications and how are they managed?
4. What are the signs and symptoms to look for regarding a breast cancer recurrence?
5. What are the more common survivorship concerns and challenges of patients who have been treated for early-stage breast cancer? How can survivorship be improved for these patients? What commendable supports are available in the community or on the internet?

DEVELOPMENT

This guideline was reviewed and endorsed by the Alberta Provincial Breast Tumour Team. Members of the Alberta Provincial Breast Tumour Team include medical oncologists, radiation oncologists, surgeons, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Breast Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

The guideline development panel, including medical oncologists, radiation oncologists, and breast surgeons, originally developed a patient discharge letter to be sent to patients' referring physicians regarding aspects of follow-up care. Recommendations contained in the physician letter were based largely on the 2005 Canadian Medical Association guidelines on follow-up after treatment for breast cancer, [4] as well as other available guidelines. Subsequently, the Alberta Provincial Breast Tumour Team

agreed to develop a formal consensus guideline, with updated recommendations based on more recent evidence from the literature. After a review of existing guidelines, consensus recommendations were agreed upon.

SEARCH STRATEGY AND REVISION HISTORY

A systematic search for relevant literature related to breast cancer follow-up was conducted of: MEDLINE and EMBASE. The search included the terms “follow-up” or “surveillance” or “discharge” or “investigation” or clinical examination” AND “breast neoplasm.” The MEDLINE and EMBASE search was limited to clinical trials and meta-analyses published in the English language during the previous ten years only (e.g., 2001 to September 2011); a total of 3,812 citations were returned, of which 29 were deemed relevant (i.e., presented data on delivery of follow-up or investigations for follow-up).

A second search was conducted of specific concerns related to follow-up. The MEDLINE and EMBASE databases were searched using the following terms: “lymphedema” or “weight management” or “bone pain” or “sexual functioning” or “psychosocial health” or “fatigue” AND “breast cancer follow-up” and limited to clinical trials and meta-analyses published in the English language during the previous ten years only (e.g., 2001 to September 2011).

The search strategies were repeated just prior to publication of the guideline and covered the period of time from September 2011 through April 2013. An additional 778 studies were identified; of these, 12 were deemed relevant and included in the full literature review.

In addition, the Cochrane Library, Cancerviewcanada, and the National Guidelines Clearinghouse were searched for guidelines and systematic reviews related to breast cancer follow-up. A total of six clinical practice guidelines and two systematic reviews were deemed relevant. A summary of the clinical practice guidelines is included in the Appendix.

TARGET POPULATION

The recommendations contained in this guideline apply to patients who have completed active medical or radiation oncology treatment for early-stage breast cancer and have been discharged by the cancer care centre for care by the referring physician.

RECOMMENDATIONS

1. Responsibilities of the physician and cancer care centre, regarding follow-up care.

- Cancer surveillance is a shared responsibility. Following completion of active medical or radiation oncology treatment, patients may be discharged from the tertiary cancer center back to their primary health care provider for ongoing breast cancer surveillance.
- Guidance on follow-up care and mechanisms for referral back to tertiary cancer care center should be made available, if required.
- A written care plan recorded by a named health professional with copies sent to the healthcare provider and the patient should be encouraged.
- Ideally a health practitioner (i.e. family physician, nurse practitioner, specialist from a breast or genetic clinic, etc.) with experience in clinical breast exam should provide follow-up care to patients who have been treated for early stage breast cancer.

2. Investigations and surveillance for the follow-up of all patients who have completed active medical or radiation oncology treatment for early-stage breast cancer.

- Self examination
  - o Patients may perform self-examination of their breasts and armpits every month.
- Clinical examination
  - o Components: at minimum, history and physical examination of the breast(s), chest wall, and supraclavicular and axillary nodes, auscultation of the chest, and palpation of the liver
  - o Frequency: every 6 months for 2 years, then annually
- Imaging tests (for patients with intact breasts*)
  - o Diagnostic mammography: annually, performed at an accredited mammography facility
  - o Other routine investigations (e.g. bone scan, ultrasound of the abdomen, chest x-ray, breast MRI, tumour markers, and laboratory tests, etc.) are generally not recommended for asymptomatic patients.

3. Signs and symptoms to look for regarding a breast cancer recurrence.

- Patients should be counseled on symptoms of potential recurrence (i.e., new lumps, bone pain, chest pain, persistent headaches, dyspnea, or abdominal pain).
- Patients should be informed on the use/limitations of monthly breast self-exam.
- Table 1 describes signs and symptoms that may suggest recurrence. Patients presenting with any of these symptoms should undergo the appropriate investigations, as described, with a copy of the results to be forwarded to the cancer centre.

Table 1. Symptoms and appropriate investigations for a local recurrence or metastatic disease.

Symptom	Action/Investigation
new mass in breast	mammography +/- ultrasound (+/- biopsy)
new suspicious rash or nodule on chest wall	refer to surgeon or interventional radiology for biopsy
new palpable lymphadenopathy	refer to surgeon or interventional radiology for biopsy
new persistent bone pain	plain x-ray of affected site(s) and bone scan
new persistent cough or dyspnea	chest x-ray and/or CT chest
new hepatomegaly or RUQ abdominal pain	ultrasound and/or CT scan of abdomen and liver enzymes
new onset seizures	seizure management (as required) and CT/MRI brain
back pain with limb weakness, change in sensation, change in reflexes, or loss of bowel/bladder control	MRI spine
new persistent headache or new concerning neurologic deficits	**CT/MRI brain**
altered level of consciousness, nausea, vomiting, and/or pain with symptomatic hypercalcemia	**IV hydration and bisphosphonate therapy**

- If at any time the physician has concerns regarding possible local or metastatic recurrence and requires an **urgent referral**, the **appointment booking office** should be contacted to arrange to see the patient. Should the physician have any specific questions, one of the oncologists in radiation oncology or medical oncology will be available to discuss the patient.

* Reconstructed breasts (autologous tissue or implants) do not require any form of imaging surveillance.

4. Potential complications from treatment.

General considerations for all patients

- For any patient with a history of previous breast cancer, the use of exogenous estrogens (such as oral contraceptives or hormone replacement therapy) is generally contraindicated.
- Raloxifene is not recommended for treatment of osteoporosis in patients with a previous breast cancer diagnosis while on adjuvant endocrine therapy (e.g. tamoxifen or aromatase inhibitors).

Endocrine therapy

- Adherence to adjuvant endocrine therapy should be assessed and encouraged.
  The referring physician may write the prescription for the patient, to be dispensed by the cancer centre pharmacy or fax the prescription the cancer center for it to be mailed to the patient.
- Patients receiving tamoxifen are at a slightly increased risk of deep vein thrombosis, strokes, and cataracts; investigations should be performed, as per signs and symptoms (e.g., sudden swelling or pain in an arm or leg, shortness of breath, visual changes, etc.).
  - o More common side effects of tamoxifen include hot flashes and vaginal discharge.
  - o In patients with an intact uterus, monitoring for endometrial cancer should include a gynecologic assessment, in addition to clinical examination.
  - o Patients experiencing abnormal vaginal bleeding should be referred to a gynecologist.
- Patients receiving aromatase inhibitors (i.e., anastrozole, exemestane, letrozole) may be at increased risk of joint pain and joint stiffness (especially among those with history of taxane use), bone pain, hot flashes, feeling tired, muscle pain, and insomnia.
  - o Patients at risk for developing osteopenia and/or osteoporosis should have a baseline and annual bone density assessment (DEXA scan) performed.
  - o Osteoporosis should be treated according to the 2010 Canadian Osteoporosis Guidelines. [5]
  - o Patients at risk of fracture are recommended to:
    - Perform regular weight-bearing, balance and strengthening exercises
    - Practice smoking cessation
    - Optimize total calcium (dietary and supplements): 1000-1200 mg per day if postmenopausal (preferably from dietary/food sources)
    - Optimize total vitamin D (supplements): Vitamin D: 1000 - 2000 IU per day [6]
  - o Raloxifene (Evista®) should not be prescribed for osteoporosis treatment in patients with a previous breast cancer diagnosis. In cases where osteopenia/osteoporosis treatment is indicated, consideration for an alternate bone targeted agent (e.g. bisphosphonate or RANK-ligand inhibitor) should be used instead.

Fatigue

- Long-term follow-up care is important for patients after cancer therapy. Fatigue may be caused by anemia, depression, anxiety, pain, dehydration, nutritional deficiencies, sedating medications, and therapies that may have poorly tolerated side effects. [7] A history of symptoms should be taken to rule out physical causes.
- Psychostimulant drugs, treatment for anemia, exercise, cognitive behavior therapy, activity and rest, or patient education may help patients alleviate the symptoms of fatigue.

Peripheral Neuropathy

- Chemotherapy may cause damage to nerves, resulting in neuropathy. Symptoms vary depending on the type of chemotherapy and whether sensory or motor nerves are involved, but can include paresthesias, numbness, imbalance, pain, and weakness of muscles in the hands and feet. [8,9]

- Work-up should include history and physical exam, as well as neurological exam (e.g., reflexes, muscle strength and tone, sensations, posture, and coordination). Electromyography, nerve biopsy, and CT or MRI imaging may be indicated. [10]
- Treatments may include pain relievers (i.e., acetaminophen, ibuprofen, opiates), anti-seizure drugs (i.e., gabapentin, topiramate, pregabalin, carbamazepine, phenytoin), lidocaine (patch), antidepressants (i.e., amitriptyline, nortriptyline) or transcutaneous electrical nerve stimulation. [10]
- Alternative techniques, such as acupuncture, capsaicin cream, alpha-lipoic acid, and biofeedback have been used to manage the symptoms of peripheral neuropathy; however, these methods have not been tested rigorously.

Lymphedema

- Lymphedema or swelling of the arm is a possible complication of breast cancer treatment. It occurs more frequently with mastectomy, axillary lymph node dissection, and radiation therapy.
- Treatments may include the following:
    - o Manual lymphatic drainage therapy: a technique that uses massage to move lymph fluid out of the affected limb to functioning lymph nodes for drainage; this technique may be contraindicated in individuals with a skin infection, active cancer, blood clots, and congestive heart failure, as well as on areas of the body that have received radiotherapy. [5]
    - o Physical therapy or exercise: a technique that uses light muscle contractions of the affected limb to facilitate the drainage of lymph fluid; strenuous exercises should be avoided.**Error! Bookmark not defined.**
    - o Compression therapy: a technique that uses garments, bandages, or gradient pumps to compress the affected limb and move lymph fluid towards the torso. [5] Compression therapy may be combined with manual lymphatic drainage and/or physical therapy.
    - o Surgery: several procedures, such as lymphatic venous anastomosis, vascularized lymph node transfer, and lymphatic liposuction can be performed to reconstruct the lymphatic vessels or remove lymphedematous tissue.
    - o Low level laser therapy (LLLT): infra-red light is used to displace nitric oxide from the cells and restore the production of cellular energy (ATP), allowing tissue to repair; LLLT has been approved by Health Canada, but is still considered experimental.
- Programs and services are available in Calgary and Edmonton:
    - o Calgary: www.albertahealthservices.ca/services.asp?pid=service&rid=1026510
    - o Edmonton: www.lymphovenous-canada.ca/lymphedemaclinics.htm

Cardiac dysfunction

- Cardiac dysfunction can occur in some patients undergoing treatment with anthracycline-based chemotherapy or trastuzumab.
- If patient is symptomatic or has clinical signs, evaluate further with ECG and MUGA or echocardiogram and refer to cardiology if significant abnormalities are noted.

Acute Leukemia/Myelodysplasia

- In some patients undergoing treatment with chemotherapy, perform CBC + differential (peripheral blood smear); refer to hematology if significant persistent cytopenias or blast cells are noted.

Support Resources & Recommendations

- Patients may experience fear of recurrence, stress over financial, family, or work issues, depression and anxiety, anger over their experience with cancer, or loneliness after support from caregivers is no longer needed. Patients should be assessed for emotional health issues. [11] Patients often struggle with emotional and psychological concerns post-treatment. Post-treatment adjustment should therefore be assessed, and if problems are identified, treatment and/or referral to an appropriately trained professional should be ensured.
- General Support Resources:
  - o CancerBridges – www.cancerbridges.ca
  - o Canadian Cancer Society – http://www.cancer.ca or 1-888-939-3333
  - o Wellspring – www.wellspring.ca
  - o Alberta Health Services – http://www.albertahealthservices.ca
    Click: *Health Information > Diseases & Conditions > Cancer*
  - o American Society for Clinical Oncology (patient site): http://www.cancer.net
- Counseling and Support:
  Psychosocial support should be encouraged and facilitated, as needed. Some patients may benefit by participating in educational, support, or counseling programs, available through the cancer centres and in the community:
  - o Calgary: call 403-355-3207; or visit
    www.albertahealthservices.ca/services.asp?pid=service&rid=1047804
  - o Edmonton: call 78-643-4303; 780-643-4304 or visit
    www.albertahealthservices.ca/services.asp?pid=service&rid=1053260
    www.albertahealthservices.ca/services.asp?pid=service&rid=1003332
  - o Peer Support via Telephone: www.cancer.ca/Alberta-NWT/Support%20Services/AB-Peer%20support%20programs/AB-CancerConnection.aspx

Healthy lifestyle

According to the American Institute for Cancer Research, once treatment for cancer has been completed, and unless otherwise advised, the patient should aim to follow cancer prevention recommendations for diet, physical activity, and healthy weight maintenance. [12]

Lfestyle factor	Recommendations
Body weight [13,14]	Body mass index (BMI): 18.5-25 kg/m^2 Waist circumference: less than 80 cm for women and less than 94 cm for men
Physical activity [15-18]	Be active 2.5 hours/week, focusing on moderate-vigorous activity spread throughout week
Diet [19]	Follow cancer prevention recommendations from the *American Institute for Cancer Research* • Avoid sugary drinks. Limit consumption of energy-dense foods. • Eat more of a variety of vegetables, fruits, whole grains and legumes such as beans. • Limit consumption of red meats (beef, pork and lamb) and avoid processed meats. • Limit consumption of salty foods and foods processed with salt.
Dietary supplements/ Bone Health [20-22]	Vitamin D: 1000 - 2000 IU per day Calcium: 1000-1200 mg per day if postmenopausal (preferably from dietary/food sources).
Alcohol [23,24]	Ideally none or limit consumption (<3 drinks/week)
Smoking	Practice smoking cessation. For help contact Alberta Quits 1-877-710-QUIT(7848) or www.albertaquits.ca

Sexual functioning/relationships

- **Sexual Health:**
  Common issues for patients include intimacy concerns, painful intercourse or loss of sensation, symptoms of menopause and loss of desire to have sex. [25,26] Sexual functioning should be discussed with the patient at follow-up visits.
  - **Menopause Symptoms:** Endocrine therapies commonly cause menopausal symptoms and chemotherapy may lead to early menopause. Hot flashes which interfere with sleep and daily function can be managed with non-hormone therapies (e.g. venlafaxine or gabapentin). Vaginal dryness can be managed with a dual purpose vaginal moisturizer and lubricant (eg. Replens®). If non-hormonal therapies do not help, vaginal estrogen (Estring®, Vagifem®) can be considered. Exogenous hormonal therapy is generally contraindicated. For refractory vaginal symptoms, referral to gynecology should be considered.
  - **Self-Image:** For some women, breasts are an important part of their self-image. If they are concerned about how a lumpectomy or mastectomy has changed their body, they may be interested in more information regarding a breast prosthesis or breast reconstruction. Psychological counseling can also be helpful for improving body image satisfaction, addressing relationship concerns and reducing sexual dysfunction.
- **Family planning**: Pregnancy while on endocrine therapy is contraindicated. The absence of regular menses does not equate to menopause in all cases. Non-hormonal contraception is generally recommended. There is an increased risk of sub-fertility/infertility and premature menopause in women who have had previous chemotherapy. There is no evidence that future pregnancy adversely affects recurrence or survival; there is no medical reason to terminate a pregnancy in absence of evidence of relapse.

DISCUSSION

Responsibility of follow-up

Cancer surveillance is a shared responsibility between the specialist, the family physician (if one is available) or specialty clinic, and the patient. Better coordination between specialists and physicians may be required to ensure that non-oncology services (i.e., influenza vaccination, cholesterol screening, colorectal cancer screening, and bone densitometry) are provided consistently. [27] Following completion of active medical or radiation oncology treatment, patients may be discharged from the tertiary cancer center back to their primary health care provider for ongoing breast cancer surveillance. This is based on evidence that family physician-led follow-up is equivalent to specialist-led follow-up, in terms of patient satisfaction and recurrence outcomes. [28]

Ideally a health practitioner (i.e. family physician, nurse practitioner, specialist from a breast or genetic clinic, etc.) with experience in clinical breast exam should provide follow-up care to patients who have been treated for early stage breast cancer. Due to the increasing burden of breast cancer on hospital clinics, means other than specialists or physicians have been investigated for delivering follow-up care. Data comparing nurse-led telephone follow-up with hospital-based follow-up has been shown to be equivalent in terms of patient satisfaction [29] and detection of recurrences, [30] with reduced hospital clinic burden. [31] Moreover, as compared to physician-led follow-up, nurse-led follow-up has demonstrated high patient satisfaction, no differences in terms of time to recurrence or death, and greater cost-effectiveness. [32,33]

According to the New Zealand Guidelines Group, guidance on follow-up care and mechanisms for referral back to the tertiary cancer care center should be made available, if required. [34] In Alberta, the Appointment Booking Offices at the Tom Baker Cancer Centre (Calgary) or Cross Cancer Institute (Edmonton) may be utilized if an urgent referral is necessary. Reasons for an urgent referral are discussed below. A written care plan recorded by a named health professional with copies sent to the healthcare provider and the patient may be useful. [35,36]

Follow-up investigations

Clinical examination for breast cancer outpatients should include, at minimum, patient history and physical examination of the breast(s), chest wall, and lymph nodes, auscultation of the chest, and palpation of the liver. The frequency of clinical examination should be every four to six months for five years, then annually. Similar recommendations have been developed elsewhere. [4,37-39] A randomized controlled trial comparing specialist-led versus family physician-led follow-up utilized a similar strategy that included examination of the breasts, chest, lymph nodes, and liver with similar frequency (e.g., three to six months for three years, then every six months for two years, then annually), but with the addition of assessment for bone pain/tenderness and neurological abnormalities; regardless of the way follow-up was delivered, the rate of death (all causes) was just six percent. [40] A cost analysis that included 472 breast cancer patients without distant metastasis after primary treatment and compared four strategies (e.g., three versus six months and routine versus clinical examinations) showed, after a mean follow-up of 4.2 years, that there was no difference in disease-free or overall survival, regardless of strategy. Cost, however, was more than two times greater for more frequent routine follow-up. [41]

Regarding imaging, only mammography is routinely recommended (i.e., annually). The sensitivity of annual mammography in patients with metachronous contralateral breast cancer was shown to be 70.8% (95% CI: 61.7-80.0) and was associated with better survival rates than detection by other means (HR: 3.18; 95% CI: 1.59-6.34). [42] Other investigations, such as bone scan, ultrasound of the abdomen, chest x-ray, and breast MRI are not recommended for asymptomatic patients. Furthermore, tumour markers and laboratory tests are also not recommended for asymptomatic patients. Although these recommendations are largely supported elsewhere, [4,38,39] there is some variation in the recommendations for mammography. The European Society for Medical Oncology (2010) [39] recommends ipsilateral (after breast conservation surgery) and contralateral mammograms yearly for premenopausal patients and every one to two years for postmenopausal patients. The National Institute for Health and Clinical Excellence (2009 guidelines) recommends that, after five years, patients be stratified and screened according to risk category. [35] Nevertheless, the recommendations on other imaging and blood work are in favor of signs and symptoms-based investigation only. This is based on lack of evidence from randomized controlled trial data and retrospective data that these tests lead to earlier detection of recurrences or survival differences. [28,43-47]

Special discussion topic: lymphedema

Lymphedema (e.g., swelling of the arm) is a possible complication of breast cancer treatment. The prevalence of lymphedema among female breast cancer patients with no sign of disease four or more years after surgery (n=355) was 17.5% in a cross-section study. [48] This study, as well as a meta-analysis published a year earlier, [49] both showed that lymphedema was more common among patients who had undergone mastectomy (versus breast conserving surgery). The meta-analysis also showed that lymphedema increased among patients who had undergone axillary lymph node dissection and patients who had received radiotherapy. [50,51] Several treatments exist for lymphedema, and have been used as

monotherapy or in combination. These include manual lymphatic drainage therapy, compression therapy, physical therapy, surgery, and low level laser therapy; each is discussed below.

Manual lymphatic drainage (MLD), or massage therapy, may represent a minimally invasive technique for relieving swelling of the arm. A randomized controlled trial (Martin, et al. 2011) among 58 women with post-mastectomy lymphedema is underway and will compare four weeks of daily standard treatment (e.g., skin care, exercise, and compression) with four weeks of daily standard treatment plus manual lymphatic drainage, at one, three, and six months. Results are pending. [51] Earlier research by Williams et al. (2002) showed that MLD reduces excess limb volume and dermal thickness in the upper arm and improves quality of life (e.g., emotional function, dyspnea, and sleep disturbance) and pain and heaviness. [52] The addition of compression therapy to MLD was shown, among a prospective cohort of 537 patients with breast cancer-related lymphedema, to reduce the mean volume by more than 400 ml; by one year, approximately half of patients experienced an increase above 10% of their value at the end of intensive therapy. [53] Overall, there appears to be some evidence of benefit for MLD, with or without compression therapy; however, given the relative paucity of literature, more data on this technique is required. The results of the pending randomized controlled trial by Martin, et al. should add to the body of evidence on MLD.

Compression therapy involves the use of garments, bandaging or wrapping, or a gradient pump to relieve lymphedema. Among 23 patients who had not previously been treated for lymphedema, the addition of intermittent pneumatic compression to decongestive therapy (DT) further reduced the mean volume by nearly 20% as compared to DT alone (45.3% vs. 26%; $p<.05$). [54] However, a larger study by Haghighat, et al. (2010), among 112 patients with mastectomy-related lymphedema, compared intermittent pneumatic compression plus DT with DT alone demonstrated better results with single modality therapy, in terms of volume reduction following treatment (43.1% vs. 37.5%; $p=.036$) and after three months (16.9% vs. 7.5%). [55] The efficacy of compression therapy was shown *not* to be related to the pressure of the bandage: low pressure (20-30 mm Hg) and high pressure (44-58 mm Hg) bandages resulted in equivalent reductions in edema after 24 hours (9.2% vs. 4.8%, respectively; not significant) in patients with breast cancer-related lymphedema resistant to other treatments. [56]

Physical therapy and exercise has been researched more extensively in the setting of breast cancer-related lymphedema. Complex decongestive physiotherapy (CDP) generally consists of a combination of modalities including lymph drainage, multi-layer compression bandage, elevation, remedial exercises, and skin care. Laio, et al. (2004) found that daily CDP reduced the limb circumference, calculated volume, and edema ratio ($p<.000$) versus pretreatment values, with a mean reduction of excess volume of 67.8 +/- 33.2%, among patients (n=30) with unilateral upper or lower limb chronic lymphedema after breast or pelvic cancer therapy. [57] Kim, et al. (2007) demonstrated reductions in volume along with increases in quality of life at six months, among breast cancer with lymphedema patients who underwent CDP. [58]

Exercise was previously thought to contribute to additional lymphedema in patients who had undergone treatment for breast cancer. However, a systematic review showed that exercise does not increase the risk of lymphedema and, in fact, appears to be beneficial for those with upper-limb dysfunction. [59] Twice-weekly progressive weight lifting has been shown, in a randomized controlled trial setting, to reduce the incidence of lymphedema in those at high breast cancer-related risk by 6% ($p=.04$); among those with five or more lymph nodes removed, the incidence was reduced by 15% ($p=.003$). [60] The authors also showed that this weight lifting regimen improved self-reported severity of lymphedema symptoms ($p=.03$) and lowered the incidence of lymphedema exacerbations (14% vs. 29%; $p=.04$), among breast-cancer survivors with stable lymphedema of the arm. [61] Despite these findings of a positive effect of exercise on

lymphedema, there is also data to the contrary. A randomized controlled trial comparing moderate resistance exercise plus no activity restrictions with usual care plus activity restrictions showed no differences in the development of lymphedema after two years, among patients treated with breast cancer surgery with axillary node dissection. [62] Furthermore, another randomized controlled trial comparing supervised, group, aerobic, and resistance exercise sessions (20 over 12 weeks) with habitual activities showed change among the intervention group at three-month follow-up (volume change: 2 +/- 71 mL). [63] Clearly additional data is required to determine the most effective exercise regimen, in this setting. The Physical Activity and Lymphedema (PAL) Trial is designed to measure the efficacy of a program of slowly progressive strength training with no upper limit on the amount of weight, among 295 breast cancer survivors (141 with lymphedema; 154 at risk for lymphedema). Between 22 and 52% of women were considered to have lymphedema at baseline according to the four diagnostic criteria used. No between-group differences were noted in the proportion of women who had a change in interlimb volume, interlimb size, interlimb ratio, or survey score of ≥5, ≥5, ≥10%, and 1 unit, respectively (cumulative incidence ratio at study end for each measure ranged between 0.6 and 0.8, with confidence intervals spanning 1.0).; results are pending. [64,65]

There is limited evidence regarding the efficacy of surgical interventions for the treatment of breast cancer-related lymphedema. A small prospective study among ten patients who were unresponsive to 12-weeks of non-operative treatment and were treated with lympho-venous anastomosis demonstrated a 4.8% reduction of lymphedema at three months and a 2% reduction after one year. Improvement in reported quality of life was minimal. [66] The LYMPHA technique (lymphatic-venous anastomoses at the time of axillary dissection) was prospectively compared to axillary dissection alone in 46 women with breast cancer. At 6 months, lymphedema occurred in one patient in the treatment group (4.34%) versus seven patients (30.43%) in the control group; no statistically significant differences in the arm volume were observed in the treatment group during follow-up, while the arm volume in the control group showed a significant increase after 1, 3, and 6 months from operation. There was significant difference between the 2 groups in the volume changes with respect to baseline after 1, 3, 6, 12, and 18 months after surgery (every timing P value < 0.01). [67] Despite these promising results, prospective randomized controlled trial data is lacking and there is a large variation in the selection of patients, classification of lymphedema, and indications and types of anastomosis procedures described in retrospective studies, [64] additional research is needed to better understand the efficacy of surgery as a treatment modality for breast cancer survivors with lymphedema.

Low level laser therapy (LLLT) is used for the management of several conditions, including joint pain, tendinopathy, and back pain. The use of LLLT for the management of lymphedema is still considered experimental, as the optimal wavelengths, durations, and doses are yet to be defined. Nevertheless, it has shown some promise. Carati et al. (2003) conducted a double-blind randomized controlled trial comparing LLLT (one cycle or two cycles to the axillary region) with placebo, which showed a reduction in the mean affected limb volume at three months of follow-up after two cycles of active laser treatment; approximately 31% of subjects had a clinically significant reduction in the volume (>200 mL). [68] More recently, Lau, et al. (2009) demonstrated, among 21 patients with breast cancer-related lymphedema in a randomized controlled trial setting, that LLLT (12 sessions over four weeks) reduced arm volume by 28% and increased tissue softening by 33% at four weeks post-treatment. [69] Although these results are promising, more prospective data on efficacy and safety is needed before this modality can become an accepted approach.

Special discussion topic: complications from endocrine therapy

Aromatase Inhibitors. In brief, short-term use of aromatase inhibitors appears to be safe; however, there is currently no long term data for cardiovascular, musculoskeletal, and central nervous system side effects. Switching from tamoxifen to exemestane may be associated with unfavorable changes in lipid profiles; [70] however, these changes may be due to the removal of tamoxifen rather than the aromatase inhibitor. Regarding musculoskeletal toxicity, some patients have reported non-inflammatory musculoskeletal symptoms or local inflammation in the tenosynovial structures. [71] Cognition, however, does not appear to be affected, at least in the short term. [72,73] Other side effects of aromatase inhibitors may include joint pain and joint stiffness (especially among those with history of taxane use), bone pain, hot flashes, feeling tired, muscle pain, and insomnia. [74-77] The continued use of endocrine therapy should be encouraged and side effects managed, as possible. Regarding drug-drug interactions, there is some concern with the concurrent use of CYP2D6 inhibitors, which can disrupt tamoxifen metabolism. Strong CYP2D6 inhibitors to be aware of include Bupropion (Wellbutrin), Fluoxetine (Prozac), Paroxetine (Paxil), and Quinidine (Quinidex). [78-80] Patients should discuss any concerns about interactions between prescription drugs with their cancer pharmacist. Guidance on the use of aromatase inhibitors, including side effects, can be found in the CancerControl Alberta guideline, *Aromatase Inhibitors as Adjuvant Therapy in Postmenopausal Women with Early-Stage Hormone Receptor-Positive Breast Cancer.* [81]

Tamoxifen. Patients receiving tamoxifen may be at a slightly increased risk of deep vein thrombosis, strokes, and visual disturbances; [82-84] investigations should be performed, as per signs and symptoms (e.g., sudden swelling or pain in an arm or leg, shortness of breath, visual changes, etc.). More common side effects of tamoxifen include hot flashes and vaginal discharge. In patients with an intact uterus, monitoring for endometrial cancer should include a gynecologic assessment, in addition to clinical examination. Patients experiencing abnormal vaginal bleeding should be referred to a gynecologist. As compared the aromatase inhibitor anastrozole, tamoxifen resulted in more treatment-related adverse events (61% vs. 68%; p<.0001) and treatment-related serious adverse events (5% vs. 9%; p<.0001), among postmenopausal women in the ATAC trial. Among these adverse events were gynaecological events (3% vs. 10%; p<.0001) and muscle cramps (4% vs. 8%; p<.0001); however, patients in the anastrozole group reported more frequent osteopenia or osteoporosis (11% vs. 7%; p<.0001), carpal-tunnel syndrome (3% vs. 1%; p<.0001), and hypercholesterolemia (9% vs. 3%; p<.0001). [85] The continued use of endocrine therapy should be encouraged and side effects managed, as possible.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
CDP	complex decongestive physiotherapy
CT	computed tomography
DEXA	dual-energy x-ray absorptiometry
DT	decongestive therapy
IU	international units
LLLT	low level laser therapy
MLD	manual lymphatic drainage
MRI	magnetic resonance imaging
U/S	ultrasound

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2016. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Breast Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Breast Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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APPENDIX

Table. Existing guidelines on surveillance and follow-up for breast cancer (BCa), published in the past five years.

Topic	Canadian Medical Association, 2005 [1]	American Society of Clinical Oncology, 2006 [2]	National Comprehensive Cancer Network, 2011 [3]	European Society for Medical Oncology, 2010 [4]	New Zealand Guidelines Group, 2010 [5]	National Institute for Health and Clinical Excellence, 2009 [6]
Responsibility for follow-up	A single physician.	A physician with experience in cancer surveillance & breast exam, including irradiated breasts.	Not addressed.	Not addressed.	A clinician (e.g., breast specialist, breast physician, nurse practitioner) with experience in BCa surveillance & breast exam, including irradiated breasts.	Discuss with patients where they would like to be followed up.
Involvement of general practitioner	Ensure all members of the team are in communication to avoid duplication of visits and tests.	The physician and patient should be informed of the long-term options regarding adjuvant hormonal therapy.	Not addressed.	Not addressed.	Care may be shared as appropriate (i.e., access to specialist support); in this case, guidance on management and referral back to secondary care to be provided.	Patients should have an agreed, written care plan recorded by a named health professional with copies sent to the GP and the patient.
Self-exam	Teach women who wish to carry out breast self-exam the proper procedure. Encourage patients to report new, persistent symptoms promptly, without waiting for the next appointment.	Counsel patients on symptoms of recurrence: new lumps, bone pain, chest pain, persistent headaches, dyspnea, or abdominal pain; provide helpful patient websites. All women should be counseled to perform monthly breast exam.	Not addressed.	Not addressed.	Not addressed.	Not addressed.
Psychosocial support	Psychosocial support encouraged and facilitated.	Not addressed.	Not addressed.	Not addressed.	Not addressed.	Not addressed.

Topic	Canadian Medical Association, 2005 [1]	American Society of Clinical Oncology, 2006 [2]	National Comprehensive Cancer Network, 2011 [3]	European Society for Medical Oncology, 2010 [4]	New Zealand Guidelines Group, 2010 [5]	National Institute for Health and Clinical Excellence, 2009 [6]
Laboratory and imaging investigations	Annual visits to include mammogram. *Not recommended:* Routine lab and radiographic investigations for the purpose of detecting distant mets.	Post-treatment mammogram at 1 year after diagnostic mammogram (or 6+ months post-definitive radiotherapy); subsequent mammograms as indicated for surveillance of abnormalities. *Not recommended:* Routine CBC, liver function tests, chest x-ray, DEXA scan, liver ultra-sound, computed tomography, FDG-PET scan, breast MRI, tumour markers (CA 15-3, CA 27.29, carcino-embryonic antigen).	Annual mammography.	Ipsilateral (after BCS) and contralateral clinical mammogram yearly for premenopausal and every 1–2 years for postmenopausal women. *Not recommended:* Other lab or imaging tests (e.g. CBC, routine chemistry tests, chest x-rays, bone scans, liver ultrasound, CT scans or tumour markers (CA 15-3 or CEA) if asymptomatic.	Regular mammography to detect recurrence or new breast cancers at an early stage in BCA patients. Post-treatment mammogram at 1 year after first diagnostic mammogram (or 6+ months after radiotherapy); annually thereafter. For high risk of contralateral BCa (e.g., BRCA 1/2) mammogram of contralateral breast should be done by 12 months after the post-diagnostic mammogram; other imaging can also be considered.	Annual mammogram for all patients with early BCa, including DCIS, for 5 years. After 5 years, stratify screening frequency in line with patient risk category. *Not recommended:* Mammography of the ipsilateral soft tissues after mastectomy. Ultrasound or MRI for routine post-treatment surveillance in patients who have been treated for early invasive breast cancer or DCIS.
Clinic visits/ physical exam	Regular follow-up surveillance adjusted according to the patient's needs. *To be included:* 1. History (all visits) 2. If tamoxifen: history of vaginal bleeding. 3. Physical exam: breasts, chest wall, lungs, regional lymph nodes, abdomen, arms (lymphedema).	Every 3-6 months for years 0 to 3 after primary therapy; every 6-12 months for years 4 to 5; then annually. *To be included:* 1. Regular pelvic exam for all women. 2. If tamoxifen: advise to report any vaginal bleeding to physician.	Every 4-6 months for 5 years, then every 12 months. *To be included:* 1. History 2. Physical exam 3. Assess/encourage adherence to adjuvant endocrine therapy. 4. Women on tamoxifen: annual gynecologic assessment if uterus present.	No standard established. *To be included:* 1. History taking, eliciting of symptoms 2. Physical exam	Not addressed.	Not addressed. *To be included:* Ensure that all patients with early BCa who develop lymphoedema have rapid access to a lymphoedema specialty service.

Topic	Canadian Medical Association, 2005 [1]	American Society of Clinical Oncology, 2006 [2]	National Comprehensive Cancer Network, 2011 [3]	European Society for Medical Oncology, 2010 [4]	New Zealand Guidelines Group, 2010 [5]	National Institute for Health and Clinical Excellence, 2009 [6]
Bone health	DEXA scan given if: 1. Postmenopausal 2. Premenopausal with risk factors for osteoporosis 3. Taking aromatase inhibitors *Counseling:* Exercise Calcium & vitamin D *Medical Therapy:* Osteoporosis treatment to include a bisphosphonate.	Not addressed.	DEXA san given if: Taking aromatase inhibitors or if experience ovarian failure secondary to treatment (baseline and periodically thereafter).	Not addressed.	DEXA scan given if: 1. Premature meno-pause due to chemo-therapy, ovarian function suppression or oophorectomy 2. Postmenopausal and receiving an aromatase inhibitor (at least every 2 yrs after a baseline DEXA of spine & hip). *Counseling:* Advice for good bone health: healthy diet, healthy weight, smoking cessation/abstinence, regular exercise, calcium, vitamin D.	DEXA scan given if: 1. Starting an adjuvant aromatase inhibitor 2. Treatment-induced menopause 3. Starting ovarian ablation/suppression therapy. DEXA not recommended for patients receiving tamoxifen alone, regardless of pretreatment menopausal status.
Cognitive functioning	No correlation between subjective impairment and objective measures; prospective longitu-dinal controlled studies encouraged.	Not addressed.	Not addressed.	Not addressed.	Not addressed.	
Pregnancy and sexual functioning	No evidence that future pregnancy adversely affects survival. Discuss sexual functioning at follow-up visits.	Not addressed.	Not addressed.	Not addressed.	No evidence that pregnancy increases relapse risk; no medical reason to terminate a pregnancy in absence of evidence of relapse.	
Clinical trial	Participation in clinical encouraged and facilitated.	Not addressed.	Not addressed.	Not addressed.	Not addressed.	Not addressed.

Topic	Canadian Medical Association, 2005 [1]	American Society of Clinical Oncology, 2006 [2]	National Comprehensive Cancer Network, 2011 [3]	European Society for Medical Oncology, 2010 [4]	New Zealand Guidelines Group, 2010 [5]	National Institute for Health and Clinical Excellence, 2009 [6]
Fatigue	History of symptoms; physical causes to be ruled out; depression & pain are potentially treatable factors; prospective longitu-dinal controlled studies encouraged.	Not addressed.	Not addressed.	Not addressed.	Not addressed.	Not addressed.
Weight management	Discuss with patients; if overweight, encourage to partake in evidence-based weight-management programs.	Not addressed.	Active lifestyle, achieving and maintaining an ideal body weight (20-25 BMI) may lead to optimal breast cancer outcomes.	Weight gain affects prognosis and should be discouraged; nutrition counseling if necessary. Regular long-term moderate/strenuous activity is associated with a favourable prognosis; aerobic & weight training do not cause lymphoedema.	Not addressed.	Not addressed.
Genetic counseling	Not addressed.	Offer counseling if: 1. Ashkenazi Jewish 2. Ovarian cancer in patient (any age) or 1st /2nd degree relative 3. BCa in a 1st degree relative before age 50 4. BCa in two or more 1st - or 2nd degree relatives at any age 5. BCa (bilateral) in patient or relative 6. Male BCa relative.	Not addressed.	Not addressed.	Not addressed.	Not addressed.