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Review

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Surveillance of breast cancer patients following primary therapy

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Abstract

Objective: To offer a summary of evidence-based recommendations for the surveillance of breast cancer patients after primary treatment. **Quality of evidence:** A literature search was conducted in Pubmed/MEDLINE using the terms: *breast cancer, follow-up, surveillance, survivorship, guidelines and survivorship care plans*, with focus on review of recent guidelines published by major cancer organizations. **Main message:** Four key tasks of survivorship care have been described: surveillance, management of treatment related complications, lifestyle modifications and care coordination. According to current guidelines, surveillance for breast cancer recurrence involves mainly physical examination and yearly mammography. Screening for other cancers should be done according to general health maintenance guidelines. Survivorship care involves management of common consequences of cancer and cancer treatment such as pain, lymphedema, fatigue, medication side effects as well as long-term concerns about cardiovascular and bone health. All major organizations recommend an active lifestyle and maintenance of ideal body weight. Survivorship care involves various health care professionals. Continuous communication and cooperation between the attending physician and the oncology team is crucial to ensure that follow-up is evidence based. **Conclusions:** Evidence based follow-up strategy has a large economic impact given the fact that there is a large number of women alive with a history of breast cancer. A number of major organizations have evaluated the evidence relating to surveillance and issued recommendations for evidence-based follow-up. Recommendations are consistent among organizations. But recent data evaluating the progress in imaging technologies and in the treatment of metastatic disease are insufficient and further research for the optimal breast cancer follow-up is needed.

Key words: endometrial cancer; sonohysterography; transvaginal ultrasound; endometrial cytology

Introduction

The efficiency of modern breast cancer therapy results in an increasing number of breast cancer survivors being monitored for recurrence of disease. It is estimated that in 2017 252,710 new breast cancer cases will be diagnosed and that there are approximately 3 million breast cancer survivors in the United States alone [1]. Breast cancer is the most common diagnosed cancer in women, representing 4 in 10 female cancer survivors in the United States [2]. Five-year survival after breast cancer treatment is higher than 90% in women with up to stage II disease [3]; thus, follow-up of this large group of patients requires efficient, timely and cost effective monitoring.

In addition, there is a trend to shift the surveillance of breast cancer survivors from oncologists to general practitioners (GP). Randomized trials have shown the efficacy of general practitioner's follow-up [4,5] and the need of tertiary centers to focus on primary treatment, complex treatment related side effects or on those who have metastatic disease [6,7]. There is no standardized surveillance plan for patients with early stage breast cancer who have completed primary therapy. There are few evidence-based guidelines for breast cancer survivorship follow-up care. Most of these women will require endocrine therapy for 5 to 10 years, have a possibility for local or systemic recurrence of their breast cancer and also have indefinite risk of treatment related complications. Furthermore, it is important to manage the physical, psychosocial and practical long-term effects of breast cancer treatment in order to improve quality of life (QoL) of breast cancer survivor. In this context, this article provides a summary of evidence-based recommendations for surveillance of breast cancer patients after primary therapy.

Quality of evidence

A literature search was conducted in Pubmed/MEDLINE using the terms breast cancer, follow-up, surveillance, survivorship, guidelines and survivorship care plans. Recent guidelines published by major cancer organizations were also reviewed. An additional search of selected articles from reference lists of guidelines was also performed.

Key tasks of survivorship care

Four key tasks of survivorship care have been described [8].

- Surveillance in order to detect earlier local or systemic recurrence of disease or contralateral breast cancer.
- Assessment and management of therapy-related complications such as osteoporosis, cardiac failure, fatigue, lymphedema.
- Lifestyle modifications.
- Care coordination

1) Task 1: surveillance (Table 1).

Fear of cancer recurrence is one of the most common concerns of cancer survivors [9]. The goal of surveillance is to detect recurrence at a time that allows initiation of therapy to improve survival and to maintain a high QoL. There is scarce high level evidence that these goals are achieved by any surveillance program. A number of professional organizations have evaluated the evidence relating to surveillance and issued recommendations for evidence-based follow-up. Recommendations from representative major organizations are outlined (Table1).

According to NCCN [10] optimal surveillance for breast cancer recurrence involves routine follow-up history updates and physical examination every 4 to 6 months for the first 5 years after primary therapy and annually thereafter. According to ASCO [11] the follow-up visits should occur every 3 to 6 months for the first 3 years after primary therapy,

Table 1. Comparison of guidelines recommendations for surveillance of women following primary therapy of breast cancer

	NCCN [10]	ACS/ASCO [11, 14]	ESMO [8]	Canadian Breast Cancer Initiative [12]	German Cancer Society and German Society for Gynecology and Obstetrics 13
history and physical examination	1–4 times/year as clinically appropriate for 5 y, then annually	every 3-6 mo for the first 3 y every 6-12 mo for the next 2 y, and annually thereafter	every 3–4 mo in the first 2 years, every 6 mo from years 3–5 and annually thereafter	according to individual patient's needs	every 3 moin the first 3 years, every 6 mo in years 4 and 5, and annually thereafter
mammography	annual mammography	annual mammography	Annual ipsilateral and/or contralateral mammography with ultrasound is recommended	annually	Annual mammography with ultrasound is recommended
breast self exam	- -	monthly	-	if a woman wishes	-
gynecologic assessment	Every 12 mo for women on tamoxifen if uterus present	regular gynecologic follow up	For patients on tamoxifen, an annual gynaecological examination possibly with a gynaecological, ultrasound, by an experienced gynaecologist is recommended	for women on tamoxifen, important to ask about vaginal bleeding	-
bone health assessment	ongoing monitoring of bone health	-	Regular bone density evaluation is recommended for patients on AIs	Bone mineral density testing for postmenopausal or premenopausal with risk factors for osteoporosis, or on aromatase inhibitors	-
encourage active life style and ideal BMI	ongoing	ongoing	ongoing	ongoing	ongoing
encourage adherence to endocrine therapy	ongoing	ongoing	ongoing	ongoing	ongoing
Blood counts Blood chemistrie Tumor markers Routinei maging of chest abdo-men or bone Breast MRI	Not recommended in asymptomatic patient	Not recommended in asymptomatic patient	Not recommended in asymptomatic patient	Not recommended in asymptomatic patient	Not recommended in asymptomatic patient

every 6 to 12 months for the next 2 years, and annually thereafter. The ASCO panel notes that women should be educated of signs and symptoms of disease recurrence and should be instructed to seek medical attention if any of these occur between scheduled follow-up visits. ESMO [8] recommends regular visits every 3 to 4 months in the first 2 years, every 6 months for the next 3 years and annually thereafter, but notes that no randomized data exist to support any particular follow-up protocol.

All major organizations (NCCN[10], ASCO[11], ESMO [8], Canadian Breast Cancer Initiative[12], German Cancer Society[13]) recommend that mammography of any retained breast should be performed every 12 months. ESMO[8] recommends that mammography can be accompanied by ultrasound every year. The first mammogram after primary therapy must be performed 6-12 months after the completion of radiation therapy. Suspicious findings on physical examination or surveillance imaging might warrant a shorter interval between mammograms.

The guidelines are very consistent in not recommending surveillance radiographs, blood counts, blood chemistries, tumor markers, radionuclide scans, CT/MRI/PET scans or ultrasound examinations in an otherwise asymptomatic patient with no findings in clinical examination. The use of all these examinations in the asymptomatic patient provide no advantage in survival or QoL and are not recommended[10,14]

All randomized controlled trials (RCTs) assessing the effectiveness of different strategies of follow-up after primary treatment are included in a recent systemic review[15].This review includes five RCTs involving 4023 women with breast cancer (clinical stage I-III). Two RCTs involving 2563 women were included in this review, comparing surveillance based on clinical visits and mammography versus more intensive follow-up, including laboratory and radiological tests. After pooling the data there were no significant differences in overall survival (hazard ratio (HR) 0.98, 95% confidence interval (CI) 0.84 to 1.15) or disease-free survival (HR 0.84, 95% CI 0.71 to 1.00). This review also includes 2 RCTs involving 1264 women [16] comparing follow-up by a hospital based specialist versus follow-up by a general practitioner. No difference was observed for time to diagnosis of recurrence (HR 1.06, 95% CI 0.76 to 1.47), overall survival (HR 1.07, 95% CI 0.64 to 1.78) and QoL. One RCT of 196 women with breast cancer, compared regular follow-up visits versus annual visits at the time of mammography[17]. Most participants found the visits reassuring, however, 25% of the regular follow-up group and 35% of the annual follow-up group preferred less frequent visits in the future. No differences were noted in interim use of telephone and general practitioner's services. Finally the authors concluded that the surveillance based on regular physical examination and annual mammography alone is effective and more intensive care using regular laboratory and imaging examinations is not necessary. Moreover GP's follow-up is as effective as hospital-based specialist's follow-up in terms of overall survival, recurrence detection and quality of life.

For patients on endocrine therapy, blood tests are indicated due to the potential side effects of these medications, such us in the lipid profile[8]. Chest x-rays and advanced body imaging (eg, CT, MRI, positron emission tomography-CT, bone scan) should be ordered only if disease recurrence is suspected[18].

The role of magnetic resonance imaging (MRI) of the breast in the surveillance of breast cancer patients is undefined. No RCTs of breast MRI as follow-up are available in any clinical setting. It is noted that this is not routine screening imaging[19] and it may be considered as an option in women with high lifetime risk (greater than 20% based on models largely dependent on family history) of de-

veloping a second primary breast cancer or in young survivors with dense breast tissue[8,10].

Postmenopausal women on adjuvant tamoxifen, if uterus is present, should undergo yearly gynecologic assessment and rapid evaluation of any vaginal spotting that might occur because of the risk of tamoxifen-associated endometrial carcinoma[20]. The performance of routine endometrial biopsy or ultrasonography in asymptomatic women is not recommended[20]. Despite that, ESMO is the only organization that recommends an annual gynecological examination, possibly with a transvaginal ultrasound, by an experienced gynecologist for patients on tamoxifen[8].

It is important for patients to be informed about signs and symptoms of locoregional recurrence, such as skin changes, new lumps, changes in the shape or size of the breast and swelling of the breast or arm [14], in order to seek immediate medical attention.

These international guidelines that recommend minimal follow-up procedures after breast cancer primary treatment are based on trials conducted in an era of, more or less, outdated technology and limited therapeutic options[21]. There are studies showing that in every-day clinical practice, medical oncologists or primary care physicians routinely recommend both blood tests and non-mammographic imaging studies in asymptomatic patients[22,23]. Considering the progress in imaging technologies and in treatment of metastatic disease, patients could have a real benefit in survival and QoL from the earlier detection of disease recurrence. Thus, there is a need for further research in optimal breast cancer follow-up, in order to investigate this hypothesis.

Genetic Counseling

Follow-up also includes assessment of patient's cancer family history. The physician should refer breast cancer survivor to a genetic counselor for consideration of gene testing, if one of the criteria provided in Table 2 exist[24]. Physician must review these issues periodically with the patient because new cancer cases may have occurred in the family after the initial diagnosis[11].

Endocrine Treatment adherence

It is important during each visit to assess adherence to endocrine therapy (ET) (tamoxifen, aromatase inhibitors or ovarian suppression therapy) for 10 years. The physician must give simple explanation of the benefits of such therapy to the patient: It reduces the risk of recurrence, of subsequent second primary breast cancer and improves overall survival. Side effects of ET and failure to understand the benefits of this therapy are predictors of discontinuation. Reported rates of adherence to adjuvant hormone therapy range from 50% to 92%[10,25].

2) Task 2: therapy-related complications

Second non-breast cancers

Breast cancer survivors have a risk of developing second non-breast cancers such as secondary malignancies related to radiation therapy, chemotherapy and endocrine therapy; other potential causes including malignancy predisposing genetic mutations (BRCA1 and BRCA 2) .

Individuals with breast cancer treated with radiation therapy have an increased risk of second malignancies including lung cancer, esophageal cancer and sarcomas, although the absolute risk is small [26]. In patients treated with chemotherapy there is no excess second cancer risk[26], but patients on tamoxifen documented an increased risk of cancer of the uterus[26]. The increased risk of endometrial cancer associated with tamoxifen is limited to postmenopausal women and no additional monitoring beyond routine gynecologic care is recommended[20]. The vast majority of tamoxifen associated endometrial cancers are associated with symptoms of vaginal bleeding, bloody vaginal discharge, staining, or

spotting. In the absence of these symptoms, routine gynecologic care is appropriate. In the presence of these symptoms, gynecologic evaluation to exclude the presence of benign or malignant endometrial pathology is appropriate.

There is no evidence that breast cancer patients should be screened for other cancers differently than the general population (such as routine screening colonoscopy according to published guidelines). It is recommended that postmenopausal women on selective estrogen receptor modulator therapies (SERMs) have an annual gynecologic assessment[11].

Cardiovascular health

Breast cancer survivors must be considered as high risk population for cardiovascular disease. Endogenous estrogens have cardioprotective effect[27]. Breast cancer patients that experience treatment related premature menopause and patients on aromatase inhibitors are at increased risk of heart disease. Aromatase inhibitors can cause dyslipidemia. Radiation therapy of breast cancer has been associated with an increased risk of cardiovascular disease[28]. Anthracyclines (doxorubicin, epirubicin) and trastuzumab are associated with an increased risk of cardiac dysfunction / cardiomyopathy[29,30]. Significant weight gain may lead to hypertension and insulin resistance, which further elevate the risk of cardiovascular events.

Therefore, the physician responsible for the surveillance of breast cancer survivors should request routine blood tests to monitor lipidemic profile for patients on ET, should inform on potential cardiac risk factors and counsel on healthy lifestyle modifications (balanced diet, exercise and smoking cessation).

Bone health

Bone loss is accelerated by cancer therapy[31]. Chemotherapy induces premature menopause, GnRH analogues suppress gonadal function and reduce estrogen levels, anti-estrogen therapies (tamoxifen, aromatase inhibitors) and glucocorticoids are risk factors for osteoporosis[32]. Moreover, this group of patients may have other lifestyle-related factors including smoking, excess alcohol intake, inadequate exercise, low calcium levels, vitamin D deficiency, increasing the risk for osteoporosis[32]. Up to 80% of breast cancer patients experience bone loss[33].

Postmenopausal breast cancer survivors should have a baseline dual-energy x-ray absorptiometry (DEXA) scan; thereafter DEXA scan should be performed every 2 years in patients on aromatase inhibitors, in premenopausal women on tamoxifen or on gonadotropin-releasing hormone agonist (GnRH) and in women who have chemotherapy-induced premature menopause. If major risk factors change, then it is reasonable to consider repeat DEXA scan every 1 year[11]. Physicians should counsel patients to avoid smoking, to limit alcohol consumption, to have a physically active lifestyle, to have regular weight-bearing exercise. A total daily calcium intake of 1200 mg and vitamin D of 800-1000 IU to all adults aged 50 years or older is recommended[32,34]. Bisphosphonates or denosumab are the preferred medications to improve bone mineral density, always balancing adverse effects versus benefit before starting therapy[32,35,36].

Musculoskeletal Health

Breast cancer survivors experience musculoskeletal problems after breast surgery and as side effects of systemic therapy. They report limited range of shoulder motion, upper limb weakness and numbness, musculoskeletal pain. These symptoms negatively affect daily living activities and QoL. Aromatase inhibitors (AIs) may cause arthralgias and myalgias and these side effects are the main cause of therapy discontinuation[37]. Helping patients cope with these symptoms is crucial for ET adherence[38]. Nonsteroidal anti-inflammatory drugs or acetamin-

ophen are the first intervention, but often are not effective in breast cancer survivors on ET. Another option is to switch from one type of endocrine therapy to another. Approximately 60% of those who discontinue AIs generally tolerate tamoxifen and the rest may tolerate a different aromatase inhibitor[39]. Physical therapy is an effective intervention for managing postsurgical musculoskeletal symptoms[40]. There are studies that demonstrate improvement in aromatase inhibitor-related symptoms with acupuncture[41] and exercise[42].

Pain and Neuropathy

One to two thirds of breast cancer survivors experience chronic pain, often leading to poor QoL. The chronic pain may be the result of surgery, chemotherapy, radiation therapy or endocrine therapy[43,44].

Secondary causes of pain must be evaluated, such as lymphedema or skin tightness and patients should be referred to the appropriate specialist, depending on the cause of the pain (eg lymphedema specialist). If secondary causes of pain are excluded, first intervention for chronic pain after breast surgery is acetaminophen and nonsteroidal anti-inflammatory drugs[11]. Multiple RCTs and meta-analyses have shown the efficacy of acupuncture and physical activity for the treatment of pain in breast cancer survivors. Acupuncture is effective in decreasing aromatase inhibitor-associated joint symptoms in women with breast cancer[41,45]. However there is no data demonstrating efficacy of acupuncture in chemotherapy-induced peripheral neuropathy (CIPN)[11]. On the other hand, exercise can improve pain in breast cancer survivors and that is shown in multiple studies[46].

Lymphedema

Lymphedema is a complication following breast cancer treatment[47], and is a chronic process that cannot be predicted. Accumulation of interstitial fluid due to impaired lymphatic transport is called lymphedema and is presented as swelling of the arm, breast, or chest wall. Common risk factors for lymphedema include ALND, axillary radiation, obesity and injury or infection in the ipsilateral arm after surgery. Primary care physicians should counsel the patient how to reduce the risk of lymphedema; weight loss if obese or overweight patient, skin care, avoiding injuries or infections of the ipsilateral arm[11]. Historically, patients with axillary lymphadenectomies / radiation have been advised to avoid overuse and weight lifting. However, one study has shown that supervised, slowly progressive resistance training is safe and effective for breast cancer survivors regarding lymphedema development. Furthermore, this type of physical activity may reduce the likelihood of arm swelling among high risk patients for lymphedema; these who have five or more lymph nodes removed. It may also improve the symptoms when already present[48] While the results of this study suggest a promising intervention for lymphedema, additional research is warranted. Therefore, clinicians should assess for lymphedema in every visit, should identify lymphedema at an early stage and refer to a lymphedema specialist when symptoms exist[11].

Body Image Concerns

Women after breast surgery have concerns about their body image, causing them anxiety and distress. Problems about body image and their self-esteem are greater after mastectomy, chemotherapy-related hair loss, post-surgery scarring with or without lymphedema, therapy-related premature menopause, sexual dysfunction, radiation fibrosis and weight gain[49]. These problems affect 31-67% of breast cancer survivors, impact negatively QoL[50] and are a major area of concern especially for young breast cancer patients[51].

The options for women who do not feel comfortable with their appearance after breast cancer therapy are adaptive devices such as breast prostheses, bras or wigs, and breast reconstructive surgery when appropriate. If the above options do not correct the body image concerns, physician should refer the patient for psychosocial care[11].

Distress, Depression, and Anxiety

Fear of recurrence is a main concern of breast cancer survivors[9], affecting negatively their return to "normal" life. Many cancer survivors experience mental heath problems such as anxiety, distress and depression. The risk of depression is higher in younger patients, in patients with personal or familial history of mental disorder and in patients with low socioeconomic status[52]. A health care provider who monitors such patients must be familiar with these problems, constantly assessing patients and be knowledgeable of the screening tools for mental health issues. NCCN proposes some screening questions for anxiety and depression to be asked at regular intervals[53]. A tool for initial screening is the distress thermometer, with scores from 0 (no distress) to 10 (extreme distress). A score of 4 or higher suggests a clinical significant level of distress. There are other tools, as well, available online such as Patient Health Questionnaire-9 and the Generalized Anxiety Disorder 7-item scale. If the score in any of the abovementioned tools is of clinical significance, then the clinician should refer the patient to a mental health professional[11,53].

Infertility

Ten percent of breast cancer patients are younger than 45 years old[3]. This group of cancer survivors has fertility issues. Chemotherapeutic agents are gonadotoxic and result in decreased fertility or premature menopause[54]. The age of a breast cancer patient is associated positively with the incidence of chemotherapy-related amenorrhea. Thus, cancer survivors who experience infertility problems should be referred to a multidisciplinary team formed by the breast surgeon, a specialist in reproductive endocrinology and infertility and an oncologist, as soon as possible[54].

3) Task 3: Lifestyle modifications

Existing data suggests that several modifiable lifestyle factors may play a role in improved prognosis among breast cancer survivors of all ages [55]. A population based study showed that obesity, smoking, and alcohol consumption increase contralateral breast cancer risk among women with estrogen receptor-positive breast cancer [56]. In the Women's Intervention Nutrition Study 2,437 women with early-stage breast cancer were randomized to an intervention and a control group. The intervention consisted of eight visits with a registered dietitian implementing a previously developed low-fat eating plan with subsequent every 3 month dietician contact. The relapse-free survival was higher in the intervention group, but there was no statistically significant difference in the overall survival between the two groups. Subgroup analyses suggested a greater dietary effect on women with hormone receptor negative cancers[57]. A prospective study of 1490 women diagnosed with early stage breast cancer showed a significant survival advantage with high fruit and vegetable consumption and physical activity, regardless of obesity[58]. ASCO recommends that breast cancer survivors should have a diet high in fruits, vegetables, whole grains and legumes, low in saturated fats. They should limit alcohol consumption and avoid smoking[11].

All major organizations recommend an active lifestyle. Specifically ACS recommends 150 minutes of moderate or 75 minutes of vigorous aerobic exercise per week and strength training exercises at

Table 2: Criteria for referral for genetic counseling[24]

Age of diagnosis ≤50 years
History of ovarian cancer at any age or in any first or second-degree relative
A first-degree relative who had breast cancer diagnosed ≤50 years
Two or more first or second-degree relatives diagnosed with breast cancer at any age
Those with at least one grandparent of Ashkenazi Jewish origin
Diagnosis of bilateral breast cancer
History of breast cancer in a male relative
Any survivor diagnosed at age ≤60 years with triple-negative breast cancer

least 2 days per week[11]. Observational data suggests a potential survival benefit of physical activity and numerous systematic reviews have shown health benefits from exercise, including mitigating treatment-related side effects and QoL improvement.

Breast cancer survivors should maintain ideal body weight (BMI 20–25) for optimal overall health and breast cancer outcome. Sixty percent of breast cancer survivors are overweight or obese (have a body mass index of at least 25). Weight loss improves QoL and mitigates treatment-related symptoms[11].

4) Task 4: Care coordination

As mentioned before, several RCTs show that follow-up delivered by primary care physicians is as effective as specialist's follow-up[16,59]. It is recommended that the primary care physician should communicate with the oncology team and obtain a treatment summary and survivorship care plan[59]. Continuous communication and cooperation between primary care physician and the oncology team is crucial to ensure that follow-up is evidence based. Coordination of the treatment protocol (ET switches or duration of ET) is the responsibility of the oncology team.

Conclusions

There is a large number of women alive with a history of breast cancer. Given that, evidence based follow-up strategy has a large economic impact. A number of major organizations have evaluated the evidence relating to surveillance and issued recommendations for evidence-based follow-up. Recommendations, as can be seen in Table 1, are consistent among organizations.

Current guidelines for the optimal surveillance for breast cancer recurrence involve routine follow-up history taking and physical examination, yearly mammography of any retained breast and monitoring for treatment related complications. Patients on tamoxifen should have yearly gynecologic assessment, possibly with a gynecological ultrasound. Patients on aromatase inhibitors or treatment related menopause should have regular bone mineral density evaluation. The guidelines are very consistent in not recommending surveillance radiographs, CT-MRI scans, ultrasounds, blood counts, blood chemistries, tumor markers, radionuclide scans for asymptomatic patients. Patients who have symptoms or physical findings concerning recurrence should have a focused evaluation appropriate for the organs of concern. Recommendations are consistent among organizations. But recent data evaluating the progress in imaging technologies and in treatment of metastatic disease is lacking and constant updated research for the optimal breast cancer follow-up is encouraged.

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