ORIGINAL ARTICLE

Guidelines on Management of the Patient with Breast Cancer

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ABSTRACT

Breast cancer is the leading cause of cancer death in women and the second most common cancer in the Jamaican population. Additionally, Jamaican women have a significant incidence of locally advanced cancer that has been shown to be associated with significant morbidity and inferior treatment outcomes. Delays in presentation and diagnosis further contribute to this treatment dilemma. On this background, a consensus group of healthcare practitioners involved in breast cancer care was convened by a joint initiative of the University of the West Indies and the Association of Surgeons in Jamaica. The objective of this body was to outline management guidelines to assist Jamaican physicians with management of patients with breast cancer. These guidelines are published below and are divided into four main headings: Screening, Making the diagnosis, Treatment and Aftercare. This document is aimed at both specialist and non-specialist physicians and includes an easy-to-follow algorithm as a brief summary of the treatment recommendations.

Keywords: Locally advanced, neoadjuvant chemotherapy, prophylactic mastectomy, screening mammography

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Preamble

This guideline was prepared under the mandate of the Department of Surgery, University of the West Indies (UWI)/University Hospital of the West Indies (UHWI), and the Association of Surgeons in Jamaica (ASJ). The panel that formulated this document comprised a diverse group of healthcare practitioners involved in various aspects of breast cancer management and who are engaged in government and private practice across both urban and semi-urban settings.

The process of development followed the Guidelines International Network's 2012 recommendations on international standards for guideline development (1). A deliberate effort was made to provide information on breast cancer care for the non-specialist physician practising in Jamaica utilizing locally available infrastructure. However, the panel would like to emphasize that care for the patient with breast cancer needs to be individualized and it is absolutely crucial that patients are provided with enough information for them to give informed consent about treatment decisions. Techniques that are not routinely available are also mentioned in the guideline if the consensus position is that where these resources can be accessed, it can significantly impact further management.

Additionally, the panel would like to highlight that two of the major hurdles to optimum care of the patient with breast cancer in Jamaica are delayed presentation and refusal of adjuvant therapy. Socio-cultural misconceptions about breast cancer as well as treatment options and objectives help to reinforce and perpetuate this situation. For these guidelines to be effective, there needs to be a coordinated effort, perhaps by the government with the aid of certain non-governmental organizations to promote early presentation for care and to debunk myths about breast cancer and its treatment.

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The care of the breast cancer patient was divided into different stages. Management goals for individual stages were decided by consensus with members providing evidence for their individual positions. Where differences of opinion remained as to the best evidence on particular points, a consensus position was arrived at by majority decision in an open ballot of members participating in that meeting.

Intended use

This document aims to provide clarity on appropriate management of the patient with suspected or proven breast cancer living in Jamaica but does not aim to provide guidance on the management of all patients with breast lumps. It is intended to guide treatment decisions that will ultimately decrease the morbidity and mortality associated with breast cancer, particularly as it relates to the presentation of patients with advanced disease.

Preparation of this document has generated some important research questions about the disease in our local population. These will be addressed in the medium term.

Breast cancer in Jamaica

Breast cancer is the second most common cancer in the Jamaican population and the most common in women (2). The age-standardized incidence rate of breast cancer in Jamaica was documented as 40/100 000 in 2002 but by 2007 had increased to 43/100 000(3). Internationally, breast cancer is the leading cause of cancer-related death in women (4) and while there are no reported data on death rates from breast cancer, our local data documents a very high-incidence of locally advanced breast cancer in Jamaican women of approximately 20% (5). This is significantly greater than in developed countries like the United States of America (USA), which has an incidence of approximately 6% (5). This therefore, exposes our Jamaican cohort to significant morbidity and mortality and makes the publishing of these guidelines for breast cancer care very timely.

1. Pre-diagnosis/ screening

1.1. *Mammography*

1.1a. Women aged 50–70 years
Mammographic screening recommended and should be implemented as a national policy for screening mammograms every two years.

1.1b. Women aged 40–49 years
National screening not recommended but opportunistic/ individualized screening may take place as per patient request or physician recommendation.

1.1c. Women aged < 40 years
Mammographic screening not recommended.

1.1d. Women aged > 70 years
Screening recommended only if life expectancy >10 years

1.1e. Digital Mammography *vs* Film-screen Mammography
Film-screen Mammography remains the imaging standard for mammographic imaging. Digital mammography where available may increase sensitivity especially in patients with dense breasts and reduce patient callback for follow-up imaging.

1.1f. Digital breast tomosynthesis *vs* Mammography
Film screen Mammography remains the imaging standard for mammographic imaging.

Rationale

Screening women for breast cancer is currently one of the most contentious topics in breast cancer care. Breast cancer is known to have an asymptomatic phase that can be identified with mammography when it could be more effectively treated than after clinical symptoms occur (6).

Regular mammographic screening is done to decrease the morbidity and mortality from breast cancer (7–10). On average, cancers detected by mammography are smaller than those detected by other means and therefore, confer a better prognosis (7). A United Kingdom review of randomized controlled trials of screening mammography has shown a decrease in disease-specific mortality risk of approximately 20% in women aged 50–70 years that undergo screening compared to the general population (10, 11). An International Agency for Research on Cancer (IARC) review identified an average risk reduction of death from breast cancer of 23% among women 50–69 years invited to screen (effectiveness analysis) and 40% among those who attended for screening (efficacy analysis); this review only included studies adjusted for lead time, treatment effects and over-diagnosis (9).

However, regular screening mammography carries risks including over-diagnosis, false-negative and false-positive results as well as radiation-induced breast cancer (9, 11). Over-diagnosis refers to the possibility that a screen-detected cancer may not have become apparent in a patient's lifetime (7). Estimates of the effect of over-diagnosis vary depending on the programme. The Euroscreen working group calculated a summary estimate of over-diagnosis as 6.5% using data from European trials (9) while estimates from the Canadian National Breast Screening study were reported as 22% (7). In the USA, the incidence of breast cancer increased by 50% with the addition of mammographic screening (6). The Cancer Intervention and Surveillance Modelling Network (CISNET) estimates, using various assumptions that approximately 12.5% of breast cancers diagnosed with screening are over-diagnosed (6).

False-positive results are obtained when imaging identifies a suspicious lesion in what is normal or benign breast tissue. These patients may then require additional imaging or a biopsy, which may have significant negative psychological impact on the patient. False-negative results are obtained when the mammogram fails to identify a tumour present in the breast which later presents as a clinical lump in an interval fashion. False-negative results give women and their physicians a false sense of security and may contribute to delayed treatment when symptoms arise (12). The radiation dosage to the breast from a single two-view mammogram is very small (13). However, patients who start mammogram at a very early age and have more frequent screening interval (*eg* annual) as well as patients who have very large breasts may be at an increased risk for radiation-induced cancer (14). In addition, certain techniques like digital breast tomosynthesis (DBT) may expose patients to a higher radiation dose (15).

The benefits of screening in women less than 50 years is significantly less than in older women (10). A meta-analysis of randomized controlled trials (RCTs) looking at the risk reduction in women 39–49 years who underwent screening compared to non-screening showed an absolute mortality risk reduction of four per 10 000 women per ten years (16). Additionally, starting screening at age 40 years instead of 50 would expose women to more of the harms of mammography. Therefore, in this patient population, women who may have particular risk factors such as a parent, child or sibling with breast cancer may choose to begin at age 40 years (opportunistic screening) but this cannot be routinely recommended (17).

It becomes more obvious then that mammographic screening is not a one size fits all and certainly in resource-constrained countries, may need to be applied selectively. Our panel chose to make recommendations for mammographic screening that could be applied to a National Screening Programme for Jamaica and not for individual or opportunistic screening. However, we are cognizant of the high-incidence of advanced breast cancer and relatively low-incidence of early breast cancer in our local population. It is therefore, imperative that we are robust in investigating the factors that govern our local disease characteristics.

1.2. *Ultrasound*

Ultrasound may be used as an adjunct to mammogram particularly in women with dense breasts and other risk factors for breast cancer.

Rationale

Ultrasound as an adjunct to mammography may increase the detection rate of breast cancer but it also increases the number of false-positive results that lead to repeated exams or biopsies (9). Most studies looking at ultrasound for screening have been observational and include cohorts that make the results not generalizable to a general screening population (18).

1.3. *Magnetic resonance imaging*

Magnetic resonance imaging (MRI) is recommended as an adjunct to mammography in patients with a known hereditary risk for breast cancer *eg* BReast CAncer genes 1 and 2 (BRCA1 or BRCA2) mutation as well as those with a parent, child or sibling with breast cancer. Magnetic resonance imaging screening should begin ten years prior to

the youngest affected family member but not before age 25 years.

Rationale

Contrast-enhanced MRI has been shown in multiple studies to increase the sensitivity of screening when used as an adjunct to mammography (9, 10, 19). Magnetic resonance imaging has also been shown to shift stage at diagnosis to more curable stages and decrease the incidence of advanced disease. Several factors prevent more liberal application of MRI to all women including cost, availability, claustrophobia, metallic implants and pacemakers (19). One study found that as many as one in four eligible women were unable to undergo MRI because of claustrophobia (20). An abbreviated examination that takes only three minutes has been developed and is to be validated (21).

1.4. *Clinical breast examination*

Clinical breast examination is an option for screening particularly in women who may not have access to routine mammography.

Rationale

Clinical breast examination (CBE) is a simple, readily available and inexpensive technique. There is some controversy in the literature about the clinical utility of CBE. The American Cancer Society in their updated guideline on breast cancer screening changed their recommendations on CBE and no longer recommended it as a screening tool for women of all ages (22). However, as pointed out by several authors, this assumes that women were undergoing screening mammography. Several other studies have shown clinical utility for CBE, particularly in populations without mammography screening, to decrease the risk of advanced disease at presentation (23, 9). This would be important in our population. The International Agency for Research on Cancer (IARC) working group has agreed with the position that it may shift the stage distribution at diagnosis toward lower stage disease (9) and we therefore, include CBE in our local recommendations.

1.5. *Breast self-examination*

Breast self-examination (BSE) is not recommended as a screening tool for breast cancer for women of all ages.

Rationale

Even though a substantial proportion of breast cancers are self-detected (22), data from both observational and randomized controlled trials have failed to show a benefit on mortality for BSE as a screening tool (9). In addition, it has been shown to increase patient anxiety as well as investigation for non-malignant disease (24).

2. Making the diagnosis

Public education programmes need to be designed to target socio-cultural beliefs and attitudes that lead to delayed presentation. Determining the precise nature of these factors requires local qualitative research. Until the results of such research become available, we believe it is necessary to emphasize the benefits of early presentation and treatment, debunking myths about chemotherapy in particular, through education campaigns. The evaluation of women who present with symptoms of breast cancer should include an urgent clinical assessment by a physician, imaging of the breasts as well as pathological assessment of the lesion [triple assessment] (11). Patients who are diagnosed with breast cancer should be referred to a surgeon for further care.

2.1. Common symptoms of breast cancer include a painless lump in the breast, a change in the appearance of the breast or nipple, as well as a bloody nipple discharge (25). Pain in the breast is a very unreliable symptom for cancer (26). Clinical breast examination includes bimanual palpation of both breasts as well as regional lymph nodes (11). Adjuncts to the clinical examination include the complete blood count and assessment of the kidney and liver function including alkaline phosphatase and calcium levels (11).

2.2. Breast imaging in symptomatic patients should include bilateral mammography (patients > 30 years) and ultrasound. Magnetic resonance imaging is not routinely recommended but may be useful in younger patients (< 30 years), lobular cancer (multifocal/multicentric tumours), patients with breast implants and where there is a discrepancy between clinical examination and mammography/ultrasound results. Imaging findings should be reported by a radiologist and should utilize the Breast Imaging Reporting And Data System

(BI-RADS) classification with an explanation and recommendation.

Rationale

Diagnostic mammography has been shown to have an accuracy of 86–91% in evaluating palpable lesions in the breast (27). It may also assist in identifying occult lesions in the contralateral breast. Ultrasound may decrease the false-negative rate of mammography particularly in younger patients with dense breasts. Soo *et al* showed the negative predictive value of sono-mammography as 99.8% in the presence of a palpable lump, which is significantly improved over mammography alone (28). In addition; ultrasound may facilitate image-guided biopsy of suspicious areas in the clinical lesion (29), because of its excellent soft-tissue resolution, magnetic resonance imaging may detect lesions that are missed by mammography and ultrasound and should be utilized in difficult or ambiguous cases (11). The Breast Imaging Reporting and Data System (BIRADS) was developed in 1986 by the American College of Radiology to standardize reporting on mammography. Since that time, the descriptive terminology has broadened to include ultrasound and MRI. The value of BIRADS is the ability to express risk of malignancy and therefore, need for biopsy based on imaging features (30).

2.3. Clinically suspicious breast lesions should undergo image-guided core needle biopsy (CNB) in preference to non-image guided CNB or fine needle aspiration cytology (FNAC) to decrease the risk of inconclusive results.

Rationale

Both FNAC and CNB are able to adequately diagnose breast cancer in the majority of patients (11, 31, 32). However, CNB has a higher sensitivity and specificity than FNAC [87%: 74% and 98%: 96%, respectively] (28). More significantly, FNAC cannot distinguish *in-situ* from invasive carcinomas and while some studies have reported receptor evaluation of FNAC specimens, the general consensus is that these stains should be performed on tissue specimens (27). Image-guided Biopsy has been shown to be at least as accurate as open biopsy with decreased complication rates so should be used where available (33).

2.4. Open surgical biopsy is recommended where image guided core needle biopsy is inconclusive; where excisional biopsy is performed, consideration should be given to leaving markers as a guide to any subsequent cavity excision that might be required to achieve satisfactory margins.

Rationale

Failure of image-guided biopsy is usually due to areas of the lesion that are not sampled. Surgical biopsy by removing the entire lesion would therefore, eliminate this potential source of error (34).

2.5. Hook-wire localization (HWL) biopsy should be utilized for non-palpable lesions that are suspicious for breast cancer and are not visible to ultrasonography. Specimen radiography, where available, is recommended for all HWL biopsy specimens using mammography or a dedicated cabinet specimen radiographic machine.

Rationale

The National Comprehensive Cancer Network (NCCN) has recommended percutaneous breast biopsy for lesions with a BIRADS classification of four or five (35). However, the diagnostic accuracy of core biopsy increases with the number of biopsies taken (36). Particularly in patients with micro-calcifications and very small specimens, hook-wire localization has been shown to decrease the false-negative rate (37) and offers the opportunity to provide a diagnosis with very low miss rate and false-negative results (29, 32, 33).

2.6. Patients may undergo either FNAC or core biopsy for clinically suspicious axillary node pre-operatively; this may be helpful in selecting patients for intra-operative axillary lymph node dissection (ALND) *versus* sentinel lymph node biopsy (SLNB).

Rationale

The axilla is the principal site for metastases from the breast and confirmation of metastases in the axilla significantly affects patient management. Both FNAC and core biopsy are acceptable techniques for confirming lymph node status (11). Preoperative diagnosis of

lymph node metastatic status does not substitute for the need to assess lymph nodes intra-operatively, either by ALND or SLNB as indicated.

2.7. Pathological reporting of the histological type of breast cancer and the status of the axilla should be in accordance with the World Health Organization (WHO) classification guideline. The report should also include the histological grade using the Nottingham modification of the Scarff-Bloom-Richardson system.

Rationale

The 4th update of the WHO classification of tumours has updated the clinical knowledge related to breast disease. It addresses not only invasive breast tumours but also non-invasive and pre-malignant lesions (38). It is therefore, the essential reference for healthcare workers involved in care of patients with breast disease. The Nottingham Grading System is a strong predictor of outcome in patients with invasive breast cancer and should be incorporated in prognostic systems (39).

2.8. Patients diagnosed with early breast cancer (Stages I and II) and no systemic symptoms should complete clinical staging with haematological investigations (complete blood count, liver and kidney function) only. Patients with advanced disease (Stage III) should also have contrast Computed tomography (CT) scan of the chest, abdomen and pelvis as well as bone scan if there are any symptoms suggesting bone involvement. Positron emission tomography/ computed tomography (PET/ CT) scan may be considered where conventional imaging tests are inconclusive.

Rationale

Staging investigations are used to identify asymptomatic or occult metastases that may impact the patient's care and prognosis. The prevalence of radiologically evident metastases is only 0.2% and 1.2% in Stage I and II disease, respectively (40). Routine staging scans in asymptomatic patients with Stages I and II disease have low detection rate and high false-positives and are therefore, not recommended (41). Computed tomography scans are recommended for patients with more advanced stage disease. Positron emission tomography/ computed tomography scanning, which assesses both anatomical and functional information, may be useful where CT scan results are inconclusive (11).

2.9. Immuno-Histochemical assessment for oestrogen (ER) and progesterone receptor (PR) status as well as human epidermal growth factor 2 receptor (HER 2) over-expression must be requested for all patients with pathology confirmed breast cancer; the pathologist may omit HER-2 assessment in cases of DCIS without invasion. Where available the proliferation rate (Ki-67 level) should also be assessed.

Rationale

The presence of ER, PR and HER2 over-expression are important prognostic and predictive factors in invasive breast carcinoma (42). For non-invasive breast cancer, studies have shown that HER2 status does not affect outcome and need not be assessed by the pathologist. Oestrogen and PR status may however, be useful in the management of non-invasive breast cancer. Receptor studies are now routinely available in the government health service at no cost to patients and therefore should be part of the routine reporting of pathology specimens, Ki-67 levels are also useful but are not routinely available locally and remain conditionally recommended (42).

3. Treatment of breast cancer

Care should be individualized and patient-directed after patient education. A multidisciplinary team involving surgical oncology, medical oncology and radiation oncology, is recommended because this has been associated with a reduction in breast cancer mortality (43).

3.1. *Ductal carcinoma in-situ*

3.1.1. *Breast surgery*

Simple mastectomy or Wide Local Excision plus Radiation Therapy (WLERT) are recommended options. Wide Local Excision plus radiation therapy should only be attempted if a cosmetically acceptable excision to achieve clear margins can be obtained.

Rationale

The goal of primary therapy for Ductal carcinoma *in-situ* (DCIS) is to prevent progression to invasive

cancer (44). Treatment is therefore, aimed at local control. The choice of treatment does not affect survival (45) but local recurrence is greater after WLE than after mastectomy but this risk can be reduced by the use of adjuvant radiotherapy (46, 47).

3.1.1a. Reconstruction:
Immediate breast reconstruction should be discussed with all patients who are considering mastectomy and it should be offered at centers where available unless contra-indicated due to patient co-morbidities. The option of delayed reconstruction should also be discussed.
Rationale
Multiple studies have shown that breast reconstruction has a positive effect on psychological health, self-esteem, body image, sexuality and reduced concerns of cancer recurrence after mastectomy (48).

3.1.2. *Axillary surgery*
Women who are to have mastectomy for DCIS or breast conservation that may affect the lymphatic drainage of the axilla (WLE in the axillary region) should undergo an SLNB at the time of initial surgery (49, 45). Axillary dissection is not recommended for DCIS.
Rationale
The lymphatic drainage pattern of the breast will be permanently altered after mastectomy or WLE in the axillary region and therefore, sentinel node biopsy will no longer be an option for women who have either procedure if the final pathology is upgraded to invasive cancer (45).

3.1.3. *Chemotherapy*
This not recommended for DCIS.
Rationale
Chemotherapy has not been shown to affect survival in DCIS (11).

3.1.4. *Hormonal therapy*
Tamoxifen/aromatase inhibitors may be recommended for ER-positive DCIS to reduce risk of contralateral breast cancer.
Rationale
Patients with ER-positive DCIS have lower-incidence of contralateral DCIS as well as ipsilateral recurrence post resection of DCIS after adjuvant endocrine therapy with tamoxifen (pre-and post-menopausal women) and aromatase inhibitors [post-menopausal women] (45, 1).

3.1.5. *Radiotherapy*
This should be given after wide local excision to reduce local recurrence.
Rationale
For patients treated with breast conservation, the risk of recurrence is significantly greater without radiation even for low-risk subsets and therefore, radiotherapy is recommended for all women who undergo breast conservation regardless of other prognosticators (45).

3.2. *Early disease* (Stages I and II)
Surgery to the breast (local) and axilla (regional) is recommended as first line definitive treatment for early stage breast cancer (4).

3.2.1. *Breast surgery*
The curative options for definitive local treatment are mastectomy or breast conserving surgery (BCS), which consists of Wide Local Excision to negative margins (no ink on tumour) plus Radiation Therapy (WLERT). The pros and cons of both should be discussed with the patient including the equivalent effect on survival, increased risk of local recurrence with WLERT and the increased risk of complications with mastectomy.
Rationale
Several well-performed studies have documented that breast conservation is equivalent to mastectomy in terms of survival after local treatment of invasive breast cancer (4). Breast conservation has advantages, which include shorter operating times, less post-operative pain, decreased wound complications such as haematoma or seroma as well as psychological benefits (1).

3.2.1a. *Reconstruction*

All patients who chose mastectomy should have a discussion about breast reconstruction. This can be offered immediately (preferred where available) if not contra-indicated due to patient co-morbidities or need for adjuvant radiotherapy. Delayed reconstruction is also an acceptable option in women who undergo mastectomy.

Rationale

As discussed earlier regarding mastectomy for DCIS, the benefits of reconstruction after mastectomy indicate that this should be offered to all patients (48). In patients who require adjuvant therapy or have had previous radiation to the area, there is an increased risk of complications particularly with the use of implants. The use of autologous tissue for reconstruction may still be offered to these patients (4).

3.2.2. *Axillary surgery*

Sentinel lymph node biopsy (is recommended for histological appraisal of the axilla when axillary nodes are assessed as normal by clinical or ultrasonographic examination; that is, when there is high likelihood of negative axillary nodes. Intra-operative assessment of SLNB by touch imprint cytology or frozen section is preferable but the procedure may still be offered where this is not possible as long as the patient understands the implications of a positive SLN, including delayed Axillary Lymph Node Dissection (ALND) or axillary radiation.

Axillary Lymph Node Dissection is recommended when axillary nodes are assessed as likely to be positive by clinical or ultrasonographic examination or known to be positive from prior cytological/histological assessment.

Rationale

The status of the regional lymph nodes is one of the strongest long-term predictors of outcome in breast cancer (11). Patients with no evidence of metastases in the axilla do not benefit from axillary surgery and are at increased risk of complications from ALND. In patients with clinically node-negative early breast cancer, SLNB is a method of staging the axilla with less morbidity than ALND (4) enabling avoidance of unnecessary ALND in patients with histologically negative sentinel nodes.

3.2.3. *Contralateral breast*

Prophylactic mastectomy (with/without immediate reconstruction) may be considered if high-risk can be demonstrated by genetic testing.

Rationale

Women with a deleterious BRCA1/BRCA2 or other pathogenic mutation have a lifetime risk of breast cancer of up to 90% with the ten-year risk of a contralateral cancer being 5–30%. Prophylactic mastectomy decreases that risk by 90–95% (4).

3.2.4. *Systemic therapy*

Systemic therapy should be undertaken under the supervision/guidance of a medical oncologist. Patients should see the oncologist prior to local treatment or within one-month of such treatment. All applicable systemic therapies including chemotherapy, hormonal therapy and biologic therapy should be discussed with the patient by the oncologist.

3.2.4a. Chemotherapy and/or Trastuzumab should be commenced within three months of surgery if indicated.

3.2.4b. Hormonal (anti-estrogen) therapy is recommended for patients with ER-positive breast cancer. Tamoxifen is recommended for pre- and post-menopausal women while aromatase inhibitors are recommended only for post-menopausal women. Ovarian suppression therapy may be considered as a component of management in premenopausal women at high-risk for recurrence.

Rationale

In early-stage breast cancer, the benefits from systemic therapy using endocrine therapy, chemotherapy, and/or biologic therapy are largely dependent on tumour characteristics and patient status (11). Patients with hormone receptor-positive cancer benefit from the use of endocrine therapy and patients with HER2-positive cancers benefit from treatment directed against HER2 [Trastuzumab] (52). New genomic and biomarker assessment may transform the management of breast cancer in the future (11).

3.2.5. *Radiation therapy*

Radiotherapy post-BCS is mandatory. Post mastectomy radiation therapy (RT) to chest wall and regional nodes is recommended for patients with high-risk for local recurrence, such as deep margins ≤ 3 mm, four or more pathologically involved axillary nodes and one to three nodes if chemotherapy is not being given. Radiation therapy to the axilla is recommended for node positive early breast cancer if ALND is not done.

Rationale

Radiation therapy decreases the incidence of first recurrence after breast conservation therapy and also the 10- and 20-year risk of recurrence in node-positive patients after mastectomy and patients at high-risk of local recurrence (4). Radiation therapy after mastectomy has been shown to decrease loco-regional recurrence, and increase long-term breast cancer-specific survival (53). Radiation therapy to the supraclavicular/infraclavicular fields has low-rate of lymphedaema, in contrast to RT to axilla that is associated with higher rates of lymphedaema after ALND (11). Radiation therapy to the left-chest wall is associated with increased risk of coronary artery disease although this risk is decreasing as newer more efficient techniques of delivering radiotherapy decrease the radiation exposure to the heart (54).

3.3. *Locally advanced breast cancer (Stage III)*

3.3.1. *Neo-adjuvant therapy*

Neo-adjuvant therapy is recommended, if available, for locally advanced breast cancer. This should begin as soon as necessary investigations and consultations are completed but definitely within eight weeks of confirming the diagnosis. If this timeline is not feasible, then primary local therapy (surgery or radiotherapy) should be initiated as the initial treatment modality, if surgically feasible to obtain clear margins and closure. If neo-adjuvant treatment is considered, marking clips, if available, should be placed for tumour marking as the tumour may become non-palpable with chemotherapy. The initial choice of systemic neo-adjuvant therapy will be directed by the treating oncologist, and will depend on patient factors, as well as breast cancer receptor profile. Re-assessment for clinical response after each cycle of chemotherapy is recommended, and will direct any changes in therapeutic regimen. Radiological re-assessment may be done at intervals, if clinically indicated.

Rationale

Tumours in patients with locally advanced breast cancer are often not amenable to primary resection. Neo-adjuvant therapy decreases the size of the primary tumour and incidence of lymph node metastases in > 80% of cases. It also allows *in-vivo* assessment of treatment efficacy therefore, permitting early cross-over therapy in cases of poor tumour response (55). Primary systemic therapy may also decrease the extent of final surgical therapy (11). Sanford *et al* recommended against treatment delays in their retrospective review of women receiving neo-adjuvant therapy at MD Anderson Cancer Center. In

that paper, initiation of neo-adjuvant treatment after 56 days was associated with an increased rate of death as opposed to those who commenced treatment before 56 days (56). If the tumour completely disappears, then breast-conservation therapies become extremely challenging and require original mammogram images to localize the margins for conservation (55).

3.3.2. *Breast surgery after neo-adjuvant therapy*

We recommend that all patients should undergo surgery following neo-adjuvant systemic therapy, even if they have a complete clinical and/or radiological response. This should ideally be performed within four to six weeks of completing systemic therapy, once any treatment-related cytopenias have resolved.

3.3.2a. Both mastectomy and BCS are options after neo-adjuvant therapy with the most appropriate choice dependent on the extent of disease (*eg* multifocality) treatment response and patient characteristics. The choice of procedure should be an informed decision made by the patient and dependent on similar factors as guide primary surgery.

3.3.2b. Patients who have no response or experience progression while on neo-adjuvant systemic therapy should be re-evaluated and consideration given to changing regimen *vs* starting local therapy (surgery/radiotherapy).

Rationale

Avoidance of surgery after neo-adjuvant therapy, even in patients with a complete clinical/ radiological response, has been shown to be associated with a significant increase in local recurrence and surgery after primary systemic therapy is current standard of care (57). The oncologic surgeon should assess the patient before and after neo-adjuvant therapy and the final decision re-type of surgery based primarily on the post-treatment tumour volume (55). Worse outcomes have been documented with delayed local treatment after systemic therapy and delays more than eight weeks have been associated with lower disease-free survival (56).

3.3.3. *Axillary surgery*

We recommend ALND in preference to SLNB except in patients who have clinical and ultrasound negative axillary lymph nodes post neo-adjuvant therapy.

Rationale

Sentinel node identification rates have been shown to be lower after neo-adjuvant therapy and

ALND is therefore, recommended (56).

3.3.4. *Systemic therapy*

Patients should be assessed after neo-adjuvant systemic therapy and surgery, to see if they are candidates for further systemic therapy. Adjuvant systemic therapy may be offered, after assessment of the pathological response to pre-operative chemotherapy and breast cancer immunohistochemistry receptor profile. Adjuvant chemotherapy, endocrine therapy, and/or anti-HER2 therapy may be recommended for patients with locally advanced breast cancer.

Rationale

Tumour subtypes and patient status determine the type of systemic therapeutic agent to be administered but systemic treatment has been shown to decrease patient relapse after treatment as well as overall mortality (11).

3.3.5. *Radiation therapy*

Radiation therapy is recommended post-surgery and is based on the pre-treatment stage and type of surgery done. Treatment decisions should be based on original tumour volume. If patients are still irresectable after systemic treatment, RT should be delivered to the residual tumour sites. The surgeon should monitor patients during this treatment in case the tumour becomes resectable; in

which case surgery should be offered after RT. Axillary radiation is recommended if there are more than three pathologically involved axillary lymph nodes on ALND.

Rationale

The benefits of RT have been documented previously in this guideline (Section 3.2.5). The NCCN guidelines recommend radiotherapy to the chest wall and regional nodes in patients who have > 3 positive axillary lymph nodes. The regional nodes to be targeted include the supra- and infraclavicular regions, internal mammary nodes as well as the axillary bed (58).

3.4. *Metastatic breast cancer*

Medical management is recommended for patients with metastatic breast cancer, and may include palliative systemic therapy, or best supportive care only. These patients should be referred to an oncologist, with palliative care as part of their management. Chemotherapy, endocrine therapy and/or biologic therapies, supportive care as well as palliative salvage mastectomy and in some cases radiotherapy should be recommended as appropriate and discussed with the patient.

Rationale

Metastatic breast cancer is unlikely to be cured but meaningful improvements in quality of life (QOL) and survival have been seen, especially with newer systemic therapies (59, 60). The selection of a therapeutic strategy is complex and depends upon both tumour biology and clinical factors and requires a tailored approach. The oncologist is the best-suited specialist to discuss and guide this treatment strategy. Many patients with metastatic breast cancer benefit from systemic medical therapy consisting of chemotherapy, endocrine therapy, and/or biologic therapies and supportive care measures (61, 62).

4. Breast cancer support and special situations

4.1. *Surveillance after breast cancer*

Appropriate cancer care involves a combination of treatment modalities, including surgery, radiation therapy and chemotherapy. Adjuvant endocrine therapy for women with ER/PR positive breast cancers, and/or adjuvant trastuzumab therapy for women with HER-2 positive breast cancers would extend the treatment period even further. After completion of this therapy, patients are at varying risk for breast cancer recurrence, whether local or systemic, and are also at risk for late and delayed adverse effects due to previous cancer treatment. A cancer care survivorship plan involves guiding the patient through this time with appropriate evidence-based, compassionate care.

4.1.1 *Clinical surveillance for breast cancer recurrences*

Patients should undergo regular surveillance for breast cancer recurrence. This may be undertaken by the treating surgeon, medical oncologist and/or radiation oncologist and for some patients may be undertaken by their primary care physician.

Clinical evaluation should include:

4.1.1a. Cancer-related history for any symptoms suggestive of local or distant disease recurrence.

4.1.1b. Physical examination of the breast cancer surgical site (and remaining breast if patient had breast-conserving therapy) and ipsilateral axilla for signs of loco-regional recurrences; examination of the contralateral breast and axilla; as well as general examination for signs of distant recurrences.

4.1.1c. Clinical surveillance visits are recommended every three to six months for the first three years after surgery, every 6 to 12 months for the next two years and annually thereafter.

4.1.1d. Imaging tests are not recommended in asymptomatic patients to evaluate for breast cancer recurrence.

4.1.1e. Serum tumour markers are not recommended to evaluate for breast cancer recurrence.

Rationale

Long-term survival after breast cancer is common (63). Issues affecting survivors include side effects of their cancer treatments as well as continued care for their pre-existing co-morbidities (64). This is in addition to the fear

of cancer recurrence. Survivorship care plans have been shown to decrease patient anxiety and improve patient's perception of care received. By avoiding unnecessary testing, they may also decrease the long-term cost of care (65). Future studies will detect if these plans increase patient survival. Patients and their primary care physicians should be educated about the risk of recurrence (66, 67). Existing data do not support performing routine laboratory tests or imaging tests in asymptomatic patients to evaluate for breast cancer recurrence (62).

4.1.2. *Treatment during surveillance*

Modern therapeutic management of breast cancer will see many patients undergo prolonged systemic therapies such as anti-HER2 therapy (recommended for 1 year), and/or adjuvant endocrine therapy (recommended for at least 5 years) after they have completed surgery, chemotherapy and radiation therapy. These patients will need to be monitored for adverse effects of these on-going therapies, such as cardiotoxicity of anthracyclines and anti-HER2 therapy and genitourinary adverse effects of anti-estrogen therapies. Patients should also be monitored for compliance with endocrine therapy. Either their primary care physician (PCP) or an oncologist may do this monitoring.

Rationale

Women with endocrine-sensitive tumours will receive endocrine therapy for five to ten years to decrease the risk of recurrence and/or second primary breast cancer and improve overall survival (62). Adherence to endocrine therapies has however, been reported to be variable, and assessing women for adverse effects that may cause non-compliance is an important aspect of care. Survivors will also need screening for other physical and psychosocial impacts of breast cancer treatment (62). Most cancer survivors, who do not die of their disease, die from conditions that are modifiable or can be managed by an appropriate intervention (68). Either an oncologist or PCP can do monitoring for these conditions appropriately (62, 69).

4.1.3 *Surveillance for new primary breast cancer*

The contralateral breast (if the patient has not had a risk-reducing prophylactic mastectomy) should be assessed for a new primary breast cancer. The appropriate techniques include regular clinical examination and annual screening mammography at intervals outlined above (*Section 1.1*). Breast MRI is only recommended for specific situations of a known hereditary predisposition to breast cancer, such as BRCA1/2.

Rationale

Patients who have had a breast cancer diagnosis are at increased risk of developing contralateral breast cancer, and as such risk-appropriate breast cancer screening is recommended (11).

4.2. *Reducing morbidity after treatment*

The morbidity of breast cancer treatment can be significant and include physical, social and psychological issues such as lymphoedema (from axillary surgery/ radiation) and chemotherapy-associated adverse effects such as anthracycline-related cardiotoxicity as well as cognitive impairment, body image concerns and chronic pain. Patients may remain at risk for complications of their previous cancer treatment for a long-time. As we improve treatment outcomes and survival, it is imperative that physicians caring for patients with a diagnosis of breast cancer pay attention to long-term treatment effects.

Recommendations

4.2.1. Patients should be counseled about the risks of long-term complications of therapy and measures to reduce treatment-related toxicity should be instituted at diagnosis.

4.2.1a. Hypertensive patients should have their blood pressure optimized to reduce cardiac complications.

4.2.1b. Cardiology consultation is recommended for patients with significant cardiac risk factors.

4.2.1c. Patients who manifest symptoms or signs of lymphedaema should be referred to a physiotherapist.

4.2.1d. Patients should be counseled about the importance of maintaining a healthy lifestyle and monitor for other post-treatment symptoms that can adversely affect quality of life such as fatigue, cognitive impairment and other psycho-social factors such as anxiety, body image impairment *etc*.

Rationale

While survival rates from breast cancer continue to increase, survivors continue to experience physical as well as psychosocial issues following treatment (70). Studies have shown that after initial treatment of breast cancer, approximately 80% of women will experience at least one bothersome symptom in the next five years (71). In addition, women who have completed their breast cancer treatment have more established cardiac risk factors such as diabetes, hypertension *etc* than the general population (72) and this along with the effects of medications such as anthracyclines and/or radiation therapy increase the risk of morbidity. Active management of these risk factors is therefore, recommended at diagnosis and continuing after completion of standard treatment (73).

4.3. *Risk evaluation and genetic counseling*

4.3.1. The patient's personal and family cancer history should be evaluated for potential hereditary risk factors preferably by the treating oncologist. Patients at higher than average risk include patients with bilateral breast cancer, first-degree relatives diagnosed with cancer (breast, ovarian, colon, endometrial), or patients aged 60 years or younger and patients with triple negative breast cancer.

4.3.1a. At-risk patients should be referred to an oncologist who is able to provide genetic testing.

4.3.1b. Women with a high lifetime risk for second primary cancer should be managed according to standard risk-reduction guidelines for the particular tumour.

Rationale

Evaluation for genetic risk should be performed in all patients diagnosed with breast cancer. Risk evaluation begins with the clinical assessment to highlight risk factors such as age of onset of the cancer, family history of breast or other malignancies as well as specific biomarkers in the tumour (74). This information is useful for decision-making not only for the patient but also family members in situations where a hereditary genetic mutation is identified. A Cochrane review in 2012 showed favourable outcome in women who had genetic testing done (73). Testing for high-risk genes like BRCA1 and BRCA 2 have been around for over 20 years but new technology has made testing for a panel of genes including moderate risk and limited evidence genes (such as PTEN and TP53) available at much lower costs (75). Established organizations like the United States Preventive Services Task Force have established risk-reduction guidelines that incorporate results of the most common genetic tests (17).

4.4. *Breast cancer and pregnancy*

Pregnancy-Associated Breast Cancer refers to women who are diagnosed with breast cancer during pregnancy as well as the first year after delivery (17). While still uncommon, this is an increasing problem as North American data show that since the turn of the century, women have been delaying the age of first pregnancy from approximately 25 to 27 years (17, 76). This combined with an increase in the number of pre-menopausal women diagnosed with breast cancer has resulted in an overlap of both diagnoses. As a result, 0.4% of cases of breast cancer are diagnosed during pregnancy and breast cancer in pregnancy occurs in 15–35/100 000 deliveries (17).

Additionally, a significant number of pre-menopausal women who have completed treatment for breast cancer may still be desirous of having children – some reports suggest as much as 50% (77). Management of these patients needs to be individualized and should involve a multidisciplinary team.

4.4.1. *Diagnosis*

4.4.1a. Ultrasound plus U/S-guided biopsy should be performed for pregnant patients who present with suspicious symptoms (as described previously).

4.4.1b. Diagnostic Mammography (with appropriate shielding of the fetus) may be performed. This should include the affected breast as well as the contralateral breast.

4.4.1c. Magnetic resonance imaging is not recommended for patients who are still pregnant because of potential fetal toxicity of contrast. Magnetic resonance imaging may be considered in women who are in the immediate post-partum period or breast-feeding.

Rationale

There is a very low-incidence of screen-detected cancers in pregnant patients as these women are often not at the age to begin routine screening. Additionally for older patients who become pregnant, the sensitivity and density of breast tissue increases making screening more painful and less accurate (17). Most women diagnosed with breast cancer during pregnancy usually present with a palpable mass and ultrasound has been shown to have a very high sensitivity and specificity in this patient population (17). Mammography may be helpful to determine the extent of the disease as well as to assist in evaluation of the contra-lateral breast albeit with a lower sensitivity than ultrasound (17). Magnetic resonance imaging may be useful in post-partum patients, as this modality has been shown to more accurately evaluate tumour size in some patients than mammogram or ultrasound (77). However, MRI with contrast should not be used in pregnant patients as Gadolinium crossed the blood-placental barrier and is considered a potential teratogen. Negligible amounts of gadolinium have been reported in breast milk but side effects have not been reported (17).

4.4.2. *Treatment*

Treatment decisions are generally similar to those of non-pregnant women stage for stage. However, some modalities are limited to the later stages of pregnancy and some (endocrine therapy, biologic therapy and radiation) are not appropriate at all until after delivery. Termination of pregnancy or delayed treatment until after delivery is not routinely recommended as it has been demonstrated that timely treatment can be administered without worsening maternal outcome or excessive risk to the fetus (78).

4.4.2.1. *First trimester*

4.4.2.1a. Breast surgery – Mastectomy or breast conservation with RT to the remaining breast are appropriate options - provided that the woman who opts for breast conservation will be receiving adjuvant chemotherapy after surgery with RT after delivery so initiation of adjuvant treatment is not delayed.

4.4.2.1b. Axillary surgery – ALND should be performed in the patient with positive axillary nodes. For women with a negative axilla, SLNB is an option providing this is done with 99 m-Tc Sulfur Colloid (17). Isosulfan blue is a Category C drug in pregnancy and should not be used. Methylene blue is not an option either as this is a Category D drug in pregnancy.

4.4.2.1c. Adjuvant therapy – Chemotherapy is contraindicated during the first trimester because of the risk of fetal loss or significant fetal abnormalities.

4.4.2.2. *Second trimester*

4.4.4.2. Breast surgery – Surgery should be done as per treatment guidelines outlined previously.

4.4.4.2b. Axillary surgery – Axillary lymph node dissection (ALND) or sentinel lymph node biopsy.

4.4.4.2c. Chemotherapy – Chemotherapy may be given either before or after surgery as per stage appropriate treatment guidelines.

4.4.2.3. *Third trimester*

4.4.2.3a. Breast surgery – Consider delivery before initiation of surgical treatment where possible. If surgery is done before delivery, this should be done with the patient in 15° left lateral tilt (to avoid aorto-caval compression) and fetal monitoring.

4.4.2.3b. Chemotherapy – Chemotherapy can be administered but should be discontinued four weeks before the expected date of delivery. Chemotherapy can be restarted after delivery.

Rationale

Tamoxifen and Trastuzumab are classified as category D drugs by the FDA. Radiation therapy is a potential carcinogen having teratogenic and potentially lethal effects on the fetus (17). Surgery, including breast conservation and mastectomy, are both safe during pregnancy and carry minimal risk to the fetus (80). Overall, the safest time to perform surgery is during the second trimester (76). If surgery is performed during the third trimester, there is a risk of premature labor and delivery and surgery should be performed with intra-operative fetal monitoring and obstetric services available (17).

4.4.3. *Fertility after breast cancer*

Young female patients may still have reproductive aspirations post breast cancer treatment. However, the use of cytotoxic chemotherapeutic agents and hormonal agents result in a decrease in women's reproductive function (79). Fertility in this group of patients is usually significantly less than in the general population (76). There is no evidence to suggest that getting pregnant after breast cancer treatment worsens prognosis for breast cancer (76). The best time to discuss fertility management is during the discussion of treatment options. There is inconsistent evidence regarding the impact of ovarian stimulating drugs for sub-fertile women and risk of breast cancer (80).

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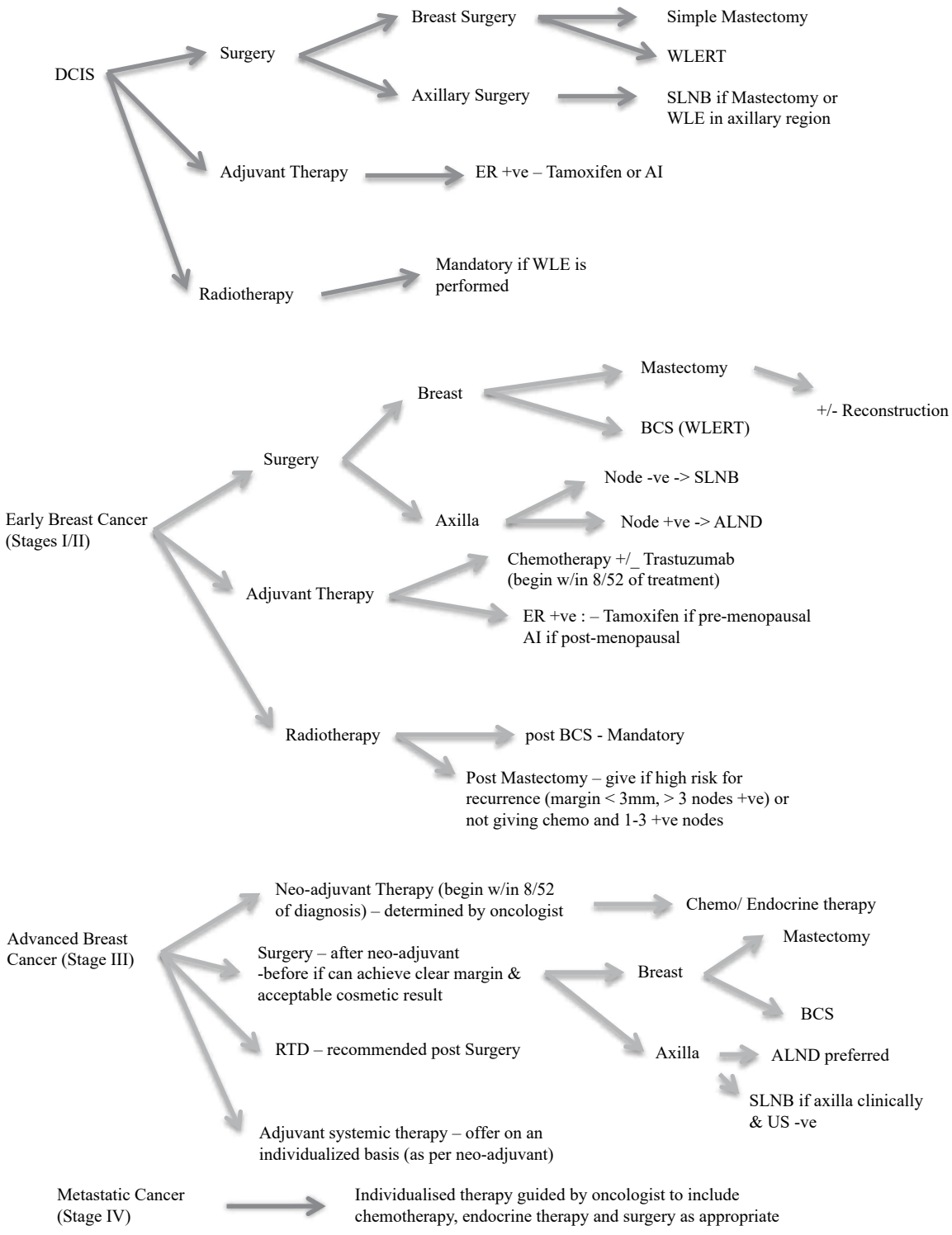
Breast Cancer Treatment Algorithm



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