

Breast cancer guidelines for Uganda (2nd Edition 2007)

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Clinical specialties: General surgery, oncology, radiation oncology, internal medicine, palliation medicine, obstetrics and gynaecology, family practice, radiologist, pathologist.

Intended users: Doctors, nurses, clinical officers, allied health personnel, students, and patients.

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Introduction

Breast cancer in Uganda is the third commonest cancer in women coming only next to cancer of the cervix and Kaposi's sarcoma. The incidence of breast cancer in Uganda has doubled from 11: 100,000 in 1961 to 22:100,000 in 1995^{1,2}. Many patients are often seen in late stages thus the outcome of treatment is mostly unsatisfactory. The present day knowledge of this disease does not have any effective primary prevention. It is thus imperative that efforts should be made to detect the disease in its early stages. Mammography has been found to be useful but it is not feasible for mass screening in Uganda, as there is a limited number of units accessible to the general public.

Public education towards Breast Self Examination (BSE) should be propagated because it is practical and affordable³.

These guidelines were compiled by the Uganda Breast Cancer working group whose objectives are to improve the quality of life of the breast cancer patients and their families by working towards encouraging early detection; harmonize treatment, referral of patients and to create a reference document for health workers dealing with breast cancer. In addition it aims at creating awareness about breast cancer to health workers and the community and to be part of the National Cancer Society creating a breast cancer registry and cancer control program.

This edition is an updated version of the one published in 2003⁴. This version highlights the importance of Breast Self Examination (BSE), which is still practical and affordable though it is discouraged in other resource rich settings. It includes a section on

pathological specimen reporting in an effort to information sharing and therefore decision making. It includes a section on prognostication. It presents a relaxed view on and recommends Breast conserving surgery a different stand from the previous edition and lastly it presents a one-page reader friendly, at a glance overview of Breast cancer treatment for easy reference by the user.

Objectives of these guidelines:

- To assist women and their doctors to make decisions on managing breast cancer
- To provide information for physicians handling breast specimen.
- To present the many treatment options open to patients with breast cancer

Methods:

This is a consensus document, a result of a team of mostly Uganda experts reviewing the past guidelines, incorporating new ideas accruing from accumulated experience through a multidisciplinary clinic that runs weekly over a seven year period dealing with Ugandans Cancer patients.

Breast self- examination (BSE) detection of breast cancer^{5,6}

The woman stands in front of a mirror, puts up her arms and observes her breasts; she may note wrinkling of skin, elevation of the nipple, and a mass may also be seen. Then the woman lies flat on her back, puts one hand behind her head and uses the opposite hand to palpate the opposite breast.

If she notices any abnormality she should seek attention of health care provider immediately. In premenopausal women BSE should be done on every 10th day of the menstrual cycle.

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Triple assessment of symptomatic cases

This is essential before treatment is undertaken and includes clinical evaluation, breast imaging and histopathological examination, it is done for any patient suspected to have breast cancer.

i. Clinical assessment:

History of a mostly painless breast mass, nipple discharge especially if from one duct, nipple or skin retraction, axillary mass, arm swelling, hair loss and development of other symptoms with reference to possible metastatic disease. A past medical history of breast disease and family history of breast cancer should be sought.

The reproductive history is also important. This should include age at menarche, menstrual history, age at first pregnancy, and age at onset of menopause, number of pregnancies and abortions, breast-feeding duration and history of contraceptive pill use. Physical examination should include weight, height and surface area (BMI). The local examination should be done with the patient both in sitting and in supine positions. One should look for breast masses, skin and nipple changes, axillary and supraclavicular lymph nodes as well as arm swelling.

ii. Breast imaging:

Patients are divided into 3 categories:

- Symptomatic patients
- Patients for testing including those with a family history of breast cancer, benign disease, follow up after surgery or those more than 45 years of age.
- Patients for image guided interventional procedures.

Imaging procedures offered include: mammography, breast ultrasound, galactography and pneumocystography. Mammography is the imaging technique of first choice in symptomatic patients. The ages at which mammography should be done were adopted depending on our clinical experience and may be reviewed. Mammography is done for the symptomatic group for those over 25 years, and testing is done for those over 30 years. The BISM system of reporting a mammogram is recommended.

Normal -1. Benign lesion- 2. Indeterminate- 3. Suspicious- 4. Malignant- 5.

iii. Pathological examination:

- Fine needle aspiration cytology Biopsy has a high degree of accuracy^{7,8} and with minimal discomfort⁹ when malignant cells are noted and definitive surgery may go ahead based on this provided the results are in agreement with the clinical and/or mammography assessment. For impalpable lesions, ultrasound or

mammography guided fine needle aspiration (FNA) is advocated.

- Core biopsy
- Open biopsy Frozen section histology can be used during biopsy but this is not practiced in Uganda at the moment.

Staging

Staging investigations include bilateral mammography to exclude multifocal or bilateral disease, breast ultrasound for accurate tumor size assessment and other tests. Full blood count, urea & electrolytes, liver function tests and baseline chest X-ray. The routine uses of liver ultrasound, skeletal survey and skeletal scintigraphy in asymptomatic women has very low yield and does not improve survival or quality of life. The TNM classification of breast cancer is recommended^{10, 11}.

Treatment

Like in all cancers the diagnosis of breast cancer is frightening and exposes the patient and her family to psychosocial trauma. Adequate counseling, pain and other symptom control should be part and parcel of the entire management strategy. Good counseling enables the patient and her family to cope with the stress that is part and parcel of cancer. It enables them to adjust their life styles. For example if she was the breadwinner some one else may have to take up that role as she undergoes treatment. Counseling should continue during treatment and follow up.

Management of early breast cancer

Ductal carcinoma-in-situ (DCIS)

We recommend wide excision (Breast Conserving Surgery) and adjuvant radiotherapy as effective methods of treating DCIS^{12, 13, 14} unless in presence of multicentric tumors in more than one quadrant, or diffuse malignant looking micro calcifications through out the breast¹⁵. The other relative contraindication to breast conserving surgery is pregnancy, previous radiotherapy to breast area and collagen vascular disease of BCS is not possible or feasible a mastectomy is done.

Mammography detected ductal CIS or palpable ductal CIS with no multicentric or diffuse micro calcifications qualifies for breast conserving surgery and axillary dissection^{16,17}

The likelihood of axillary involvement in DCIS is about 2-3% and axillary dissection is therefore not recommended^{12, 16, 17}.

Role of sentinel node biopsy is unresolved in literature and not yet available in Uganda. Routine use

of tumor matters, imaging for metastases and LFT tests in DCIS is not useful and discouraged¹⁸.

Post operative Clinical reviews

We recommend 3-6 monthly follow up for first year then annually for life, unless concerns or complications arise¹⁷. Postoperative mammography may be done after 1 year when surgery and postoperative treatment changes resolve after that 2 yearly if possible

Lobular carcinoma in situ (LCIS)

Lobular carcinoma in situ is generally considered a pre cancerous condition. It is lobular because the cancer is confined to the lobules (the glands that secrete milk). Lobular carcinoma in situ is an unusual histological pattern of non-invasive neoplastic disease of the breast¹⁸.

Lobular carcinoma in situ is frequently multicentric and bilateral and there is evidence that it is associated with an elevated familial risk of breast cancer¹⁹. We offer a wide excision and give tamoxifen for a 2 to 5 year period. Prophylactic mastectomy is an option.

Paget's disease^{20,21}

Paget's disease of the breast is a rare malignancy of the nipple-areola complex^{22, 23}; it is manifested by progressive eczematoid changes of the areola with persistent soreness or itching²⁴. It is mostly associated with an underlying ductal carcinoma in-situ or invasive carcinoma even when there is no palpable mass or mammography findings^{25,26}.

Simple mastectomy and adjuvant radiotherapy are given as well as tamoxifen. If breast-conserving therapy is a choice it must be carefully indicated²⁴.

Invasive breast cancer

Surgery

Surgery with or without radiotherapy remains the mainstay of treatment for early breast cancer. Surgical treatment may consist of tumor excision with surrounding margins or mastectomy (removal of the entire breast tissue and the fascia overlying pectoralis major muscle). Breast conserving surgery should be followed by radiotherapy as it has been shown that local recurrence is minimized^{12,14}.

T₁N₀M₀ and T₂N₀M₀ tumors (T < 3cm) may be considered for breast conserving surgery plus radiotherapy. The tumor-free margin should not be less than 10mm at surgery. If the tumors are central, breast-conserving surgery could be done if other factors allow like tumor breast size ratio.

Patients should have mastectomy if these cancers are multifocal or central or larger than 3 cm^{16,17}.

The mastectomy incision should be short and transverse to ease execution of radiotherapy. Physiotherapy of the ipsi-lateral shoulder joint should start on the first postoperative day to ease radiotherapy planning.

Adjuvant radiotherapy

A number of patients may fail to get radiotherapy because of socio-economic constraints and the long distances they may have to travel. However, health workers throughout the county should know that most of the patients would need radiotherapy after surgery. Adjuvant radiotherapy is required to reduce the risk of local recurrence^{18,25}. There is evidence it improves survival²⁶. In circumstances where the clinical and histopathological information is not sufficient we recommended that radiotherapy to the chest wall and supra-clavicular region be given in all patients that have had mastectomy.

To reduce the risk of shoulder joint fixation and arm oedema, the axilla should not be irradiated in patients that have had proper axillary clearance, With proper planning, radiotherapy to the chest wall should avoid irradiating the heart and more than 3 cm of lung tissue. Adjuvant radiotherapy is also indicated in localized non-invasive breast cancer where wide local excision has been done. Adjuvant radiotherapy to the chest wall following mastectomy with axillary clearance is given in many centers when the primary tumour is more than 5cm or is T₄, or when the surgical margins are unclear, or if four or more axillary lymph nodes have tumour in them.

Adjuvant systemic therapy

Adjuvant systemic treatment is recommended in almost all patients in Uganda except ductal carcinoma in situ, lobular carcinoma in-situ, Paget's disease and patients for which it may be contraindicated for medical reasons. All patients with lobular carcinoma in situ should have tamoxifen after wide local excision or mastectomy. Cytotoxic chemotherapy and hormonal therapy are recommended in all other patients. The chemotherapy should start immediately after surgery and be augmented by radiotherapy.

Neoadjuvant chemotherapy can be given to down-stage the tumour before local treatment (radiotherapy or surgery) can be offered. The dose of tamoxifen is 20 mg once daily for as long as 2 - 5 years. Active drugs include: methotrexate, 5-fluoro-uracil, anthracycline antibiotics and cyclophosphamide.

Adjuvant therapy with tamoxifen, cytotoxic drugs and ovarian suppression all reduce the risk of recurrence, risk of cancer in the other breast and death in women under 50 years of age, with node positive and node negative breast cancers.

Tamoxifen alone reduces recurrence and improves overall survival in all age groups. Elderly patients and those patients in poor performance status should ideally not be given cytotoxic chemotherapy, but they may benefit from hormonal treatment.

Tamoxifen is withheld while patients are receiving tamoxifen.

Follow up after treatment for early breast cancer

The aim of follow-up is to detect recurrence at an early stage, and thus improve chances of salvage treatment, to screen for a new primary in the opposite breast, to detect and manage treatment related toxicity, and to provide psychological support.

It is recommended that palliative care team such as Hospice Uganda get involved with breast cancer patients as early as possible. Hospice is able to offer psychosocial support, drugs for pain and other symptom control. It is also recommended that more health workers (doctors and nurses) be trained in palliative care delivery to be able to offer the necessary support quite early during the patient's illness.

Patients who have had mastectomy should have mammography of the opposite breast every 2 years. For those that have had breast-conserving surgery, mammography of both breasts should be done every year. The incidence of local recurrence in a conserved breast is 10- 15% in Europe.

Patients should be seen at 3 and 6 months following radiotherapy and then once every year for life or at any time that they develop symptoms.

Special groups or circumstances:

- Patients with locally advanced breast cancer where surgery is not possible, systemic treatment or radiotherapy or both should be considered.
- Local recurrence after breast conserving surgery; salvage mastectomy and systemic chemotherapy should be given; if recurrence is small and the breast is large a second breast conserving surgery can be considered.
- Local recurrence after mastectomy – local excision, radiotherapy if not previously delivered and chemotherapy.

- In Metastatic breast cancer the main aim is to alleviate symptoms and maintain the highest possible quality of life. Biphosphonates significantly reduce skeletal related events. They are recommended for use whenever possible²⁸. Clodronate reduces risk of new bony and visceral metastases^{23,29}

Visceral brain metastases are treated with radiotherapy and corticosteroids³⁰.

- Breast cancer during pregnancy requires a multi-disciplinary approach involving surgeons, oncologists and obstetricians. Termination of pregnancy is not necessary, as it does not improve survival. Radiotherapy and chemotherapy should be avoided during pregnancy.

After 32 weeks, induced delivery followed by conventional treatment is recommended.

Prognostic factors and Pathology reporting

It is clear that most important prognostic factors in breast cancer remain the traditional histopathological features of tumor size, lymph node stage and histological grade.

30, 31, 32, 33

Standardized Pathology reports to include the following information:

Gross description

1. Nature of specimen – core biopsy, excisional biopsy (lumpectomy), re-excision, quadrantectomy, simple mastectomy, modified radical mastectomy.
2. Condition – fresh/ in formalin, intact/cut.
3. Dimensions – overall
4. Tumour description: Mass/masses/no mass, size (3 dimensions), contour, texture, location and distance from nearest margin
5. Previous biopsy site – if present
6. Remainder of breast tissue, nipple, skin if present
7. Lymph nodes – number and appearance
8. Frozen section diagnosis – if one was done

Diagnosis

1. Laterality of breast and procedure
2. Histological type
3. Histological grade
4. Margins of resection
5. Lymph node status

Comments

1. Tumour size
2. Mitotic score
3. Extensive intraductal component – **if present** in a specimen that is less than a total mastectomy
4. Lympho-vascular invasion – peri-tumoral and/or dermal, **if present**

5. Other significant disease – **if present** (e.g. a typical ductal hyperplasia, Paget's disease of the nipple, biopsy site changes, papillomatosis)
6. Hormone receptors
7. Other tumor markers ancillary studies
8. If information required for prognosis is not available or cannot be adequately assessed (e.g. No nodes submitted, margins not assessable), this should be stated specifically in the report.

Summary of Treatment Guidelines for Breast Cancer

TNM Stage	Treatment Surgery	Options			Remarks
		Radiotherapy	Chemotherapy (CAF/CMF)	Hormonal (Tamoxifen)	
1. DCIS tumor	Wide excision (1)	√(2) 50/25/5	X	√ Routine use (1b)	If multiple or >3cm do mastectomy
2. LCIS	Wide excision (1)	X	X	If ER+ PgR + 2-5 (2) fails.	Anastrozole if Tamoxifen years Prophylactic mastectomy is an option
3. Pagets disease	Simple Mastectomy (1)	√(3) 50/25/5	X	(2) ER+ PgR+	Anastrozole if Tamoxifen fails
4. ToN ₁ Mo	Excise nodes (1)	X	√ (2)	X	Chemotherapy if nodes positive 5FU, adriamycin & Cisplatin
5. T ₁₋₂ NoMo <3cm >3cm	Wide excision plus Nodal sampling (1) Simple mastectomy plus Axillary clearance (1)	(3) 50/25/5 √(3) Minus axilla	√(2) If Nodes positive √(2) Nodal positive	√ (3) ER+ PgR+ √ (3) ER + PgR+	Anastrozole if Tamoxifen fails Anastrozole if Tamoxifen fails
6. T ₁₋₂ N ₁ Mo> 3cm	Simple Mastectomy and Axillary clearance (1)	√(3) 50/25/5	√(2)	√ ER+ PgR+	Anastrozole if Tamoxifen fails
7. T ₃₋₄ No ₃ Mo (1 or 2)	± Toilet Mastectomy (1 or 2)	± Neoadjuvant	√(1 or 2 or 3)	√ ER+ PgR+(4)	Downstage first if it flaps inadequate
8. Any T&N M ₁	Surgery mostly not indicated	√(2) Local control Breast and distant sites	√(1) 50/25/5	√ ER+ PgR+(3)	For visceral metastases use chemo, for bone & brain metastases give radiotherapy

Key:

Numbers in (1) signify sequence of events, what comes first, 2nd and 3rd

ER+ estrogen receptor – positive

PGR+ Progesterone Receptors – positive

- Rationale for Surgery – Eliminate source and local control of tumor, hemorrhage and discharge
 - Rationale for Radiotherapy – Local control, control of pain and destruction at distant sites
 - Rationale for Chemotherapy – Systemic and local control of disease
 - Rationale for Hormonal – Systemic, local control of disease and preventive as well.
 - Tamoxifen failure is when a recurrence occurs while on treatment
 - Tamoxifen for 2-3 yrs followed by Anastrozole is an option as is Anastrozole straight way if can be afforded
 - A sandwich arrangement of 3 cycles of chemo then radiotherapy followed by the last 3 cycles of chemotherapy
 - CAF is used for the young (<50yr) and or with poor tumor grades, CMF is for the elderly and or those with favorable tumor grades
- Recent Advances: Trails for use of Anastrozole instead of Tamoxifen, Molecularly targeted therapies e.g. HER

1 Inhibition – gefitinib, Lapatinib, HER 2 Inhibition – trastuzumab and Anti-angiogenic agents – bevacizumab and taxanes for metastatic disease.

Conclusion

This guidelines document is a consensus document a result of work by a team of mostly Ugandan experts with hands on experience over the past seven years involved in the management of Breast Cancer patients. The first edition published in 2003 was deemed to be useful to the target audience; it has been referred to by students in training among others and cited in other publications. This updated version is enriched to capture changing view and much easier to reference.

This shared work underpins our continued commitment to do the best we can with what we have for the good of our patients in a resource-limited environment like Uganda.

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