UNIVERSITY OF CAPE TOWN AND GROOTE SCHUUR HOSPITAL

Breast Cancer Treatment Protocol

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Assessment and diagnosis

Referral guidelines

In most cases, the definitive diagnosis will not be known at the time of referral, and many patients who are referred will be found not to have cancer. Primary healthcare professionals should convey optimism about the effectiveness of treatment and survival because a patient being referred with a breast lump will naturally be concerned. The primary healthcare professional should discuss these needs with the patient and respond sensitively to them. Primary healthcare professionals should encourage all patients to be 'breast aware' in order to minimise delay in the presentation of symptoms.

A woman's first suspicion that she may have breast cancer is often when she finds a lump in her breast. The primary healthcare professional should examine the lump with the patient's consent. The features of a lump that should make the primary healthcare professional strongly suspect cancer are a discrete, hard lump with fixation, with or without skin tethering. In patients presenting in this way an urgent referral should be made, irrespective of the patient's age.

A patient who presents with symptoms suggestive of breast cancer should be referred to the diagnostic breast clinic. Patients who attend a breast clinic should have a consultation and physical examination by a suitably trained member of the team.

Referral to a breast clinic should be considered for female patients with:

i. Lumps, lumpiness and change in texture

- Discrete lump in any woman over the age of 30 years that persists after their next period, or presents after the menopause
- At any age
    - Discrete, hard lump with fixation, with or without skin tethering
    - A lump that enlarges
    - Persistent focal area of lumpiness or change in breast texture
    - Progressive change in breast size with oedema
    - Skin distortion
    - In whom there are other reasons for concern, such as family history
    - With previous breast cancer, who present with a further lump or suspicious symptoms

ii. Nipple symptoms

- Spontaneous unilateral bloody nipple discharge
- Unilateral eczematous skin or nipple change that does not respond to topical treatment (steroids)
- Nipple retraction or distortion of recent onset
- Bilateral nipple discharge sufficient to stain clothes
- Blood-stained discharge in patients of any age

iii. Male patients

- Aged 50 years and older with a unilateral, firm subareolar mass with or without nipple distortion or associated skin changes

iv. Other symptoms

- Asymmetrical nodularity that persists at review after menstruation
- Intractable, focal / unilateral pain which does not respond to simple measures (analgesia, right bra size)
- Persistent unexplained axillary swelling

Referral pathway to a diagnostic breast clinic

There are 2 diagnostic breast clinics in the Western Metro

- Groote Schuur Hospital (Wednesday and Friday morning)
- Mitchells Plain Hospital (Monday morning)

Referrals to the breast clinic can be made via www.gshbreastendocrine.co.za

Patients are generally seen within 2 weeks, but during busier times patients will be prioritised according to the following criteria

- Patients to be seen within 2 weeks:
    - aged 30 and over and have an **unexplained** breast lump with or without pain **or** aged 50 and over with any of the following symptoms in one nipple only:
        - Nipple discharge
        - Retraction
        - other changes of concern
    - with skin changes that suggest breast cancer **or**
    - aged 30 and over with an unexplained lump in the axilla.
- Patients to be seen within 6 weeks
    - aged under 30 with an unexplained breast lump with or without pain.

Clinical examination

History

This should include the following elements:

1. Presenting symptoms:
    - Breast mass
    - Breast pain
    - Nipple discharge
    - Nipple or skin retraction
    - Axillary mass or pain
    - Arm swelling
    - Symptoms of possible metastatic spread
    - Suspicious findings on routine mammography.
2. Past medical history of breast disease in detail.
3. Family history of breast and other cancers with emphasis on gynaecological cancers.
4. Reproductive history:
    - Age at menarche

- age at first delivery
- number of pregnancies, children and miscarriages
- age at onset of menopause
- history of hormonal use including:
    - contraceptive pills (type and duration)
    - hormonal replacement therapy (type and duration).

5. Past medical history

Physical examination

Careful physical examination should cover the following:

1. Performance status
2. Weight, height and surface area.
3. General examination of other systems.
4. Local examination:
    - Breast mass
        - size
        - location (specified by clock position and distance from the edge of the areola)
        - shape
        - consistency
        - fixation to skin, pectoral muscle and chest wall
        - multiplicity
    - Skin changes
        - erythema (location and extent)
        - oedema (location and extent)
        - dimpling
        - infiltration
        - ulceration
        - satellite nodules
    - Nipple changes
        - Retraction
        - erythema
        - erosion and ulceration
        - discharge(specify)
    - Nodal status
        - axillary nodes on both sides (number, size, location and fixation to other nodes or underlying structures)
        - supraclavicular nodes
    - Local examination of possible metastatic sites.

Laboratory investigations and Imaging

These include the following:

- Full blood count (FBC), and renal and hepatic profile.
  HIV test / Hep B / C
- Chest X-Ray
-

Clinical staging and risk assessment

Tumour, nodes, metastasis (TNM) staging system

The tumour staging system provides information about extent of disease that can be used to guide treatment recommendations and to provide estimates of patient prognosis. In addition, it provides a framework for reporting treatment outcomes allowing the efficacy of new treatment to be assessed. The TNM staging system classification criteria are summarized below.

a) American Joint Committee on Cancer Definition of Primary Tumor (T)—Clinical (cT) and Pathological (pT)

Primary tumour (T)	Regional lymph nodes (N)	Distant metastasis (M)
TX: Primary tumor cannot be assessed T0: No evidence of primary tumor Tis (DCIS): Ductal carcinoma in situ (DCIS) Tis (Paget): Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted. T1: Tumor ≤ 20 mm in greatest dimension T1mi: Tumor ≤ 1 mm in greatest dimension T1a: Tumor > 1 mm but ≤ 5 mm in greatest dimension (round any measurement from >1.0-1.9 mm to 2 mm) T1b: Tumor > 5 mm but ≤ 10 mm in greatest dimension T1c: Tumor > 10 mm but ≤ 20 mm in greatest dimension T2: Tumor > 20 mm but ≤ 50 mm in greatest dimension T3: Tumor > 50 mm in greatest dimension T4: Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4 T4a: Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4 T4b: Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma T4c: Both T4a and T4b are present T4d: Inflammatory carcinoma	cNX: Regional lymph nodes cannot be assessed (eg, previously removed) cN0: No regional lymph node metastases (by imaging or clinical examination) cN1: Metastases to movable ipsilateral level I and II axillary lymph node(s) cN1mic: Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm) cN2: Metastases in ipsilateral level I and II axillary lymph nodes that are clinically fixed or matted; or in ipsilateral internal mammary lymph nodes in the absence of axillary lymph node metastases cN2a: Metastases in ipsilateral level I and II axillary lymph nodes fixed to one another (matted) or to other structures cN2b: Metastases only in ipsilateral internal mammary lymph nodes in the absence of axillary lymph node metastases cN3: Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I and II axillary lymph node involvement; or in ipsilateral internal mammary lymph node(s) with level I and II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement cN3a: Metastases in ipsilateral infraclavicular lymph node(s) cN3b: Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s) cN3c: Metastases in ipsilateral supraclavicular lymph node(s)NX: Regional lymph nodes cannot be assessed (e.g., previously removed) **Pathologic classification (pN)** pNX: Regional lymph nodes cannot be assessed (eg, not removed for pathological study or previously removed) pN0: No regional lymph node metastasis identified or ITCs only	M0: No clinical or radiographic evidence of distant metastasesa cM0(i+): No clinical or radiographic evidence of distant metastases in the presence of tumor cells or and no deposits no greater than 0.2 mm detected microscopically or by using molecular techniques in circulating blood, bone marrow, or other nonregional lymph node tissue in a patient without symptoms or signs of metastases M1: Distant metastases detected by clinical and radiographic means (cM) and/or histologically proven metastases larger than 0.2 mm (pM)

	pN0(i+): ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s) pN0(mol+): Positive molecular findings by reverse transcriptase-polymerase chain reaction (RT-PCR); no ITCs detected pN1: Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or clinically negative internal mammary lymph nodes with micrometastases or macrometastases by sentinel lymph node biopsy pN1mi: Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm) pN1a: Metastases in 1-3 axillary lymph nodes, at least one metastasis larger than 2.0 mm pN1b: Metastases in ipsilateral internal mammary sentinel lymph nodes, excluding ITCs pN1c: pN1a and pN1b combined pN2: Metastases in 4-9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases pN2a: Metastases in 4-9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm) pN2b: Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary lymph nodes pN3: Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive level I and II axillary lymph nodes; or in more than 3 axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes pN3a: Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes pN3b: pN1a or pN2a in the presence of cN2b (positive internal mammary lymph nodes by imaging); or pN2a in the presence of pN1b pN3c: Metastases in ipsilateral supraclavicular lymph nodes	
(Refer http://onlinelibrary.wiley.com/doi/10.3322/caac.21393/full for more information)		

b) American Joint Commission on Cancer TNM Anatomic Stage Groups

T	N	M	STAGE
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

c) Molecular Profiling

	ER	PR	HER2	Ki67
Luminal A	>5/8	>5/8	Neg	low (<20%) Grade 1/2
Luminal B (HER2-)	Pos	Pos or neg	Neg	high (>20%) Grade 3
Luminal B (HER2+)	Pos	Any	Pos	Any
HER2 Enriched	Neg	-	Pos	-
Basal like/TNBC*	Neg	-	Neg	-
	* There is ~80% overlap between 'triple-negative' and intrinsic 'basal-like' subtype, but 'triple-negative' also includes some special histological types such as (typical) medullary and adenoid cystic carcinoma with low risks of distant recurrence.			

IHC score	% cases	% cases with amplification by b-DISH
0 / 1+ (negative)	~60%	5%
2+ (equivocal)	~20%	~20-30%
3+ (positive)	~20%	95%

Please Note

- ER 1/8 or 2/8: is most likely negative. Discuss with pathologist at CBC path meeting
- ER- and PR+ needs to repeat ER staining on a separate section of the histology specimen

Investigations to determine Molecular Profile

- ER: immunohistochemistry (IHC) - ALL patients
- PR IHC – ALL patients
- HER 2: IHC - ALL patients < 75 years
- Ki 67 - To be done on all ER positive patients
- B-DISH – On specific patient request only

Diagnosis

Patients are seen by practitioners with a special interest in breast disease. Wherever possible, a non-operative breast cancer diagnosis should be achieved by triple assessment. This include clinical assessment and biopsy followed by and radiological assessment. Core biopsy is preferable due to the additional information it can provide. However, it is recognised that there may be circumstances where only an FNA is possible. If multiple benign lesions are seen and they all have the same morphological features, needle biopsy of one lesion is usually sufficient. In multifocal malignancy, it may be necessary to sample more than one lesion to identify the extent of the disease and advice on appropriate surgical management, but usually a biopsy of the largest lesion would guide treatment.

Breast cancer is uncommon under the age of 30 years. In women under the age of 25 years, core biopsy should only be performed where there is clinical or radiological suspicion that a lesion is not benign.

The false negative rate of triple assessment in women who present with symptoms and are subsequently shown to have breast cancer is approximately 0.2%. Patients in whom the triple assessment is negative should be advised to seek further advice if they remain concerned or new symptoms or signs develop.

A non-operative diagnosis should be possible in the majority of invasive breast cancers with a minimum standard of achieving this in at least 90% of cases with a target of more than 95%. The majority of non-invasive cancers will be screen-detected and impalpable. The minimum standard for non-operative diagnosis for screen-detected cancer is at least 85% with a target of more than 90%.

Diagnostic excision biopsies should rarely be required. However, some breast lesions may still require diagnostic excision if the core biopsy not benign (e.g. B3/4 lesions). The presence of atypia in a core biopsy is recognised as a marker of increased risk of cancer being present and consideration should be given to excision of all B3 lesions with atypia. When a radial scar, sclerosing lesion or papilloma is present in a specimen without atypia, and the lesion is small enough, vacuum-assisted excision may be offered to the patient as the excisional technique. However, if the presence of atypia is then reported in the specimen, further excision is indicated and the patient should be advised to proceed to surgical excision of the cavity. Following vacuum excision, the cavity should always be marked using a mammographically-visible clip to facilitate future localisation prior to surgical excision.

Hypercellular fibroepithelial lesions, which are possible phyllodes tumours, should preferably be excised intact in order to facilitate histopathological reporting. This will usually require surgical excision. Columnar cell change is part of the continuum of precursor lesions and is usually classified as benign. Where atypia is also present, it is usually described as Flat Epithelial Atypia. These lesions should be sampled by multiple specimens being taken under vacuum assistance. This should be regarded as a diagnostic rather than a therapeutic surgical procedure.

The cause of axillary lymphadenopathy in the absence of breast pathology often presents a diagnostic challenge. FNA or core biopsy of an axillary node may provide useful information.

However, when there is diagnostic uncertainty or there is suspicion of lympho-proliferative disease, then formal excision biopsy of the node should be considered

Imaging

Breast imaging

Breast imaging is performed as part of a triple assessment. Digital mammography should be considered for all cases, especially if patients have breast implants, in the dense breast and in younger women.

Women who do not need imaging include:

- Bilateral breast pain only.
- Bilateral pain and symmetrical nodularity.
- Symmetrical nodularity alone.

In women under 40 years of age, ultrasound is the initial imaging modality of choice. Mammography is only indicated in strongly suspicious cases and in all cases found to be malignant on biopsy, to exclude other incidental lesions. In women over 40 years of age, mammography should be performed followed by ultrasound if indicated.

In advanced breast cancer in the elderly, it is only necessary to undertake investigations which will directly affect management. This may in many cases be limited to a clinical core biopsy to confirm the diagnosis and to test for ER status. If the size of a lesion needs to be monitored because of primary endocrine therapy, an individual decision should be made on each patient as to whether clinical examination, mammographic or ultrasound measurement is most appropriate.

It may be appropriate to insert a marker in the breast to mark the site of the tumour, if the intent of neo-adjuvant therapy is breast conservation. This is best introduced after two cycles of chemotherapy, and is only necessary if the tumour is responding to treatment. It is particularly useful if there is a possibility that there will be no detectable tumour to localise at the time of surgery.

In men with breast lumps, the vast majority of these cases are due to gynaecomastia. Symmetrical bilateral gynaecomastia does not require imaging. Asymmetrical gynaecomastia in men over the age of 50 years may require breast imaging. Focal lumps in the male breast are usually amenable to clinical core biopsy.

Axillary ultrasound

Pre-treatment ultrasound evaluation of the axilla should be performed for all patients being investigated for early invasive breast cancer. If morphologically abnormal lymph nodes are identified, especially with a cortex of more than 3.5 mm, then ultrasound-guided needle sampling (core biopsy or FNA) should be performed in patients in whom we foresee neoadjuvant chemotherapy being used. This include all patients under 70 years with triple negative, HER2 positive and locally advanced (T3N1, any T4, N2/3) breast cancers.

Metastatic screening

Metastatic disease at presentation occurs in only 4–6% of patients; whole-body staging is not required in the vast majority of cases. At present, there is no evidence base for carrying out staging prior to neoadjuvant chemotherapy in ≤T2 tumours with <N1 disease.

Formal staging investigations should only be considered if they are likely to affect the primary treatment of the disease. Not all patients shown to have axillary nodal metastases on pre-operative axillary ultrasound and FNA need to be screened. Screening of asymptomatic patients for metastatic disease should be avoided as far as possible. Metastatic screening should not be allowed to delay the first therapeutic intervention. CT of the thorax, abdomen and pelvis should be considered in cases where there may be involvement of the supraclavicular nodes, where it is known or likely that more than four axillary lymph nodes are involved or in patients at high risk of metastatic disease based on the size and grade of the primary tumour.

If there is clinical suspicion of metastatic disease, the type of imaging will depend on the presentation. In patients with bone pain, plain radiographs, isotope bone scan and MRI are indicated. MRI is particularly useful when there is diagnostic uncertainty on plain radiographs or bone scan and / or clinical suspicion of cord compression. In patients with neurological symptoms, contrast-enhanced head CT is the imaging modality of choice. MRI with contrast should be considered if there are cerebellar signs or signs of meningeal involvement. In patients with respiratory or abdominal symptoms, plain chest x-ray, liver ultrasound or thoraco-abdominal CT may be appropriate dependent on the degree of clinical suspicion. In patients where there is concern about axillary recurrence, axillary ultrasound and MRI of the axilla should be considered. PET scan is not generally required in the assessment of breast cancer patients and is reserved for patients with breast cancer recurrence.

Staging Protocol at GSH

At GSH the follow would be considered indications for staging

1. Any Symptoms raising suspicion of metastatic disease e.g. new onset bone pain, abdominal / chest pain or shortness of breath

2. Node positive (Large palpable axillary nodes or multiple impalpable solid nodes on ultrasound ≥4):
   - CT chest abdomen and pelvis
   - Consider adding bone scan in patients with lobular histology

3. Locally advanced (T3 (>5cm) with palpable nodes, T4, N2/3):
   - CT chest and abdomen
   - Bone scan

4. Loco-regional recurrence
   - PET/CT
     - Infiltrating ductal carcinoma (HIV negative)
     - Ductal carcinoma in HIV positive group that has sufficient viral suppression / adequate CD4 counts and on ARV's
     - PET/CT is often not so sensitive in the group with lobular or mucinous histology
     - If patient does not meet inclusion criteria, then do bone scan with CT chest and abdomen

5. Tumour biology
    - Consider staging in all triple negative breast cancers and tumours with a very high proliferation index (Ki 67 > 70%)

6. Whole body MRI
    - Equivocal results on other imaging modalities
    - Pregnant patients with locally advanced tumours

Magnetic resonance imaging

The routine use of MRI of the breast is not recommended in the pre-operative assessment of patients with biopsy-proven invasive breast cancer or ductal carcinoma in situ (DCIS). MRI of the breast should be considered in patients with invasive breast cancer in the following circumstances:

- If there is a discrepancy regarding the extent of disease between clinical examination, mammography and ultrasound assessment and accurate assessment of tumour size will assist in treatment planning.
- If breast density precludes accurate mammographic assessment
- To assess the tumour size if breast conserving surgery is being considered for invasive lobular cancer. MRI more accurately assesses the size and extent of lobular carcinoma and may detect cancer in the opposite breast. MRI can change the treatment plan in about one-third of cases of invasive lobular cancer.
- In patients with axillary node metastasis suggestive of breast cancer but no obvious primary lesion seen on mammogram or ultrasound. (TxN1)
- In some patients with inadequate margins after breast conserving surgery. In cases where there is suspicion of extensive residual disease and there is debate as to whether further excision or mastectomy is required, MRI should be considered to assess the extent of residual disease.

Where possible, the investigation should be carried out in the mid-portion of menstrual cycle.

Family history screening and surveillance protocols

Women with a significant family history of breast cancer should be referred to the clinical genetics service.

Surveillance for women with no personal history of breast cancer but a significant family history of breast cancer

Offer annual **MRI** surveillance to women:

- aged 25–30 years who have not had genetic testing but have a greater than 30% probability of being a *BRCA* carrier
- aged 25–30 years with a known *BRCA1* or *BRCA2* mutation aged 20–30 years who have not had genetic testing but have a greater than 30% probability of being a *TP53* carrier
- aged 20–30 years with a known *TP53* mutation.

Offer annual **mammographic** surveillance to women:

- aged 30–69 years at high risk of breast cancer (IBIS lifetime risk of > 25% or 10 year risk of > 5%)
- aged 30–69 years with a known *BRCA1 and BRCA2* mutation.
- Annual MRI should continue in patients with dense breasts at 30

Surveillance for women with a personal and family history of breast cancer

- Offer annual **mammographic** surveillance after the diagnosis of breast cancer up to age 69 years in patients with a personal history of breast cancer who: remain at high risk of breast cancer (first cancer under 50 and those who have a *BRCA1 and BRCA2* mutation who did not have a bilateral mastectomy)
- Offer annual **MRI** surveillance to all women aged 30–69 years with a personal history of breast cancer and very dense breast tissue who remain at high risk of breast cancer.

Chemoprevention for women with no personal history of breast cancer

5 years of tamoxifen can be offered for to women after the age of 40 with a uterus at high risk of breast cancer unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer. Bilateral salphingo-oophorectomy should be considered in patients over 40 who have completed their family in patients with a *BRCA1, BRCA2 and TP53* mutation.

Treatment planning and communication

Following confirmation of a breast cancer diagnosis and appropriate MDT discussion to plan management, the results should be discussed with the patient. The person conducting the consultation should be a member of the breast MDT. The consultation should take place in an appropriate environment with adequate privacy.

Breast MDT Process at GSH

I. Diagnosis and first treatment decision

- Diagnostic breast clinic
    - All new patients with suspected or already diagnosed breast cancer will be seen at the Groote Schuur Hospital diagnostic breast clinic on a Wednesday and Friday.
    - New patients will be seen by someone from the surgical department where a clinical history will be taken and the patient examined.
    - Patients with a diagnosis of breast cancer already known (mostly patients who had a biopsy in private or other hospital) will be referred directly to the oncologist / oncology registrar at the breast clinic after they have been seen by the surgical department.

- Oncology new patient clinic

- Patients with a new or recurrent diagnosis of breast cancer will be seen 1-2 weeks after the diagnosis by the oncology registrar in breast clinic.
- Staging investigations are booked by the oncology team based on indications discussed above.
- The patient is then booked for CBC (Combined Breast Clinic) follow up in LE33 in 1-2 weeks.
- Mammogram is booked on the same day as CBC to be done in the morning.

- Wednesday LE33 Combined Breast Clinic
  - Pathology and mammogram from every patient is reviewed
  - Patients will then be seen by an oncologist and surgeon together where a final treatment decision is made.

II. Genetics referral of affected individuals:

The following patients diagnosed with breast cancer should be referred to genetics:

- All patients < 40 years
- Age < 50 years with a family history of with breast or ovarian cancer
- Bilateral breast cancer or new primary in patients under 50 years
- Male patients with breast cancer
- Breast and ovarian cancer in the same patient

III. Psychology / Psychiatry referrals

- All patients who need any counselling relating to their cancer diagnosis can be referred to the LE psychiatrist / psychologist.
- Referrals are made at LE32 secretary office with a standard referral form.

IV. Social work referral

Counselling

- Patients are seen as individuals or as a group for supportive counselling.
- We also provide palliative care services as well as death and dying counselling as we deal with terminally ill patients.

Emotional support

- The newly diagnosed patients become confused, anxious and scared. There is lot of uncertainty as far as taking treatment is concerned. The social worker looks at patients fears and addresses those fears with patients with the hope of easing patient's fears.
- The oncology unit runs support groups where patients get the platform to discuss their fear and motivate each other. The group is on Tuesdays and Wednesdays at G7 at 09h00 - 10h00 am and we are assisted by volunteers in running them.
- The social worker also is involved with look good feel better workshop where 20 patients who are on treatment are pampered.

Education

- The social worker assesses patient's insight about her/his illness. Most patients have very poor insight about their illness except that it is fatal illness.
- The social worker educates the patients and their families about their illness and treatment it entails.

- The oncology unit host patient empowerment week to educate patients and their families about resources that are available in their communities.

Financial

- All illness affects patient's financial status. The social worker provides guidance by informing patients about illness benefits if patients are employed (UIF-LABOR DEP).
- The unemployed patients are assisted by temporal disability grant application (SASSA).
- The patients who need to attend the clinic on regular basis i.e. radiation treatment are assisted with bus fare.

Community Resources

- Patients are referred for community service i.e. Hospices, home-based care, Cansa association, Booth memorial, Life Esidimeni, frail care centres, shelters and social development.
- We work close with Eikenhof care home (CANSA) and that is where we refer patients who are from out of Cape Town for accommodation.

Surgery

Surgical treatment of patients with breast cancer should be carried out by surgeons with a special interest and training in breast disease. The need for breast reconstruction should not lead to unnecessary delay in surgery.

Surgery for invasive breast cancer

Surgery, with or without radiotherapy, remains the mainstay of early breast cancer treatment. Surgical treatment for breast cancer may consist of an excision of the tumour with surrounding normal breast tissue (breast conserving surgery) or mastectomy. Long-term follow up of randomised clinical trials have reported similar survival rates for women treated by mastectomy or breast conserving surgery.

Accurate pre-operative assessment of the size and extent of the tumour is essential for deciding whether breast conserving surgery is an alternative option to mastectomy. This can often be achieved with clinical examination and standard breast imaging. In difficult cases, particularly lobular cancers, MRI should be used in planning surgical treatment. The decision to offer MRI should be discussed at the MDT.

Breast conserving surgery

There is no exact size limit for conservation surgery. It is a balance between tumour size (as assessed by imaging) and breast volume that determines whether a patient is suitable for breast conserving surgery. However, excision of lesions over 4cm in an average sized breast tends to give a poor cosmetic result and have a higher rate of local recurrence and is not recommended. Patients of any age should be considered for breast conserving surgery but consideration must also be given to co-morbidities associated with age, the potential need for further surgery and their suitability for subsequent radiotherapy. Radiotherapy has been shown to reduce the risk of local recurrence and improve overall survival.

Indications for breast conserving surgery

- Patient choice
- Operable tumours up to 4cm in diameter in an average-sized breast
- Operable multi-focal tumour restricted to a single breast quadrant
- Two or more small tumours in different quadrants in a large sized breast
- No contraindications to radiotherapy
- Larger tumours may be treated by breast-conserving surgery when combined with oncoplastic procedures.
- Following neoadjuvant chemotherapy or hormonal therapy specifically aimed at reducing tumour size

At CBC the following should be checked before patients are offered BCT:

- **Oncological safety**: Clinical examination, ultrasound and mammogram should be checked to confirm that there is a single lesion or close multifocal lesions which are amenable to surgical excision. Mammogram should be reviewed to exclude widespread DCIS. Patients with T4 disease do not qualify for BCT.

- **Technical feasibility**: The following should be reviewed: the size of the tumour in relation to the size of the breast and the location of the tumour, particularly in relation to the nipple and skin

- **Delivery of Radiotherapy**: The patient should be assessed for contraindications to radiotherapy (previous radiotherapy at this site, connective tissue disorders, pacemaker on the side of treatment), if their weight exceeds the radiotherapy weight limit (150KG), whether they are physically able to undergo the treatment in the supine position, can attend 15 sessions of RT and have enough shoulder mobility.

If the following are all confirmed, women should be offered BCT as their first choice but also informed of the risk of re excision (10–15%) and the need for radiotherapy.

In cases where it is oncologically safe (see above) but not technically feasible to perform BCT, neoadjuvant chemotherapy to down size the tumour is an option. This decision must take place BEFORE neoadjuvant chemotherapy is given and should not be offered to a patient where the indication is for neoadjuvant chemotherapy is for locally advanced disease. The complete checklist for BCT should be reviewed in these cases with the following additional steps:

- A radio opaque marker (Magseed, Savi-Scout, Titanium marker) should be placed in the tumour prior to chemotherapy or at a date close to the commencement of chemotherapy

Margins of excision

The major surgical factor influencing local recurrence following breast conserving surgery is completeness of excision, and clear radial margins must be obtained. Close margins at the chest wall or near the skin may be less important. Controversy exists in the published literature about what constitutes an adequate margin, but agreement suggests a margin of at least 5 mm for invasive disease and at least 10 mm for DCIS **when radiotherapy will not be given**, should be aimed for. A margin of no ink at the margin in case of invasive disease and 2 mm in pure DCIS is acceptable with the addition of radiotherapy. In case of an invasive cancer and DCIS in the same lesion, the margin status will be determined by the pathology which represents the largest diameter. If there is an involved margin the pathologist should report on

the extent of involvement. Patients with a single focally involved margin (< 4 mm) must be discussed at the MDT. Selected patients with focally involved margins might be offered a radiotherapy boost rather than re-excision surgery.

Intra-operative specimen radiography is mandatory for impalpable lesions requiring radiological localisation. The specimen should be orientated and marked prior to delivery to the pathologist. Standard orientation will be used as follow:

- Long suture and 3 clips lateral
- Short suture and 2 clips superior
- Loop suture anterior if no skin removed

All specimen radiographs should be available to the pathologist.

Marking of the tumour bed with metal clips should be considered to allow accurate planning and delivery of radiotherapy. This is especially important when oncoplastic techniques are used to improve cosmetic outcome.

Skin marking of impalpable lesions

The use of a skin mark as means of localising an impalpable lesion may be appropriate if the lesion is close to the skin (less than 1cm). The method of localisation should be agreed by the MDT. The mark should be applied with the patient in the surgical position. An ultrasound should be performed in two orthogonal planes and the position of the centre of lesion confirmed. The position should be marked with ‘X’ in indelible black ink. A further scan should be performed to confirm that the mark is in the correct position. The depth of lesion below the skin should be measure using minimal compression. A gauze dressing should be applied to avoid the mark being rubbed off.

Therapeutic mammoplasty

Patients with large tumours, who on the traditional criteria are regarded as only being suitable for wide local excision, but have large breasts should be considered for therapeutic mammoplasty.

Mastectomy

Indication for mastectomy

- Patient choice
- Operable tumours more than 4cm in diameter in an average sized breast
- Operable multi-focal disease in more than one quadrant of the breast
- Contraindication to radiotherapy
- Failed breast conservation surgery (e.g. local recurrence or positive margins after wide local excision where further wide local excision is not feasible)
- Where breast conservation is unlikely to result in an acceptable cosmetic outcome (e.g. larger tumour in a small breast)
- Central breast cancer. It is generally accepted that adequate margins are more difficult to achieve with central breast tumours and that central wide local excision may be associated with a relatively poor cosmetic outcome. However, in many cases an adequate excision and good cosmesis can be achieved by a central wide local excision and oncoplastic techniques
- Local recurrence after previous BCS

Contralateral Risk Reducing Mastectomy

The following Stage 1 and 2 (early breast cancer) patients should be offered a contralateral risk reducing mastectomy:

- Known genetic mutation in BRCA1/2 or P53
- Patients who are not candidates for BCS and is due to receive a mastectomy on the effected side a contralateral mastectomy can be offered in:
    - Patients under 35 years
    - Patients under 40 with two first or second degree relatives with breast cancer
    - Patients under 50 with three or more first or second degree relatives with breast cancer.
    - Biopsy proven high risk pathology: LCIS / Atypical Ductal Hyperplasia /Papillomatosis in the contralateral breast
    - Assessment of the contralateral breast made difficult due to high breast density on mammogram or difficult clinical examination (relative indication)

- Low risk patients who request a contralateral mastectomy should be counselled sympathetically and informed of the following:
    - The risk of contralateral breast cancer, while higher than the baseline population, is approximately 0.5% per annum. The number of breast cancer patients developing contralateral breast cancer at 20 years is about 5%
    - Survival from breast cancer is directly related to the outcome from the treatment of the first cancer and not affected by cancer which may be detected in the other breast
    - After cancer treatment, close clinical and radiological follow up is offered for the contralateral breast.

Axillary surgery

Axillary surgery should be performed in all patients with invasive breast cancer in order to stage the axilla and eradicate metastatic disease within the nodes. Axillary lymph node status is the single most important prognostic factor in early breast cancer and has a role in deciding the use of adjuvant therapy. If an axillary staging procedure is not to be carried out, the reason for this should be discussed in the MDT and documented in the patient's notes.

Sentinel lymph node biopsy (SLNB)

Minimal surgery, rather than lymph node clearance, should be performed to stage the axilla for all patients with early invasive breast cancer and no evidence of lymph node involvement clinically, on ultrasound or who have a negative ultrasound-guided needle biopsy. Sentinel lymph node biopsy (SLNB) is the axillary staging procedure of choice. If node sampling is performed, at least 4 nodes should be obtained.

- It is recommended that SLN procedures should be performed by surgeons with training in this procedure. The surgeon should try and identify at least 3 nodes if possible. The sensitivity of the procedure does not increase much when taking more than 4 nodes

- Indications for SLNB in patients with invasive cancer:

- Patients with T1/T2 tumours and selected T3 tumours with a *clinically node negative axilla* (clinical axillary exam and axillary ultrasound)
- Ideally all patients without overtly pathologic axillary nodes should have an ultrasound of their axilla to exclude radiological suspicious nodes preferably before 1st CBC visit)
- Small soft nodes, especially if bilateral, should be considered reactive unless they have features on ultrasound to suggest otherwise.

The features on ultrasound of a pathological lymph node are:

- Asymmetrical cortical thickening
- Cortical thickening of > 3,5 mm
- Loss of fatty hilum

- Contra indications for SLNB:
  - Previous SLNB in BCT patients (If a repeat SLNB is considered, it has to be done with a nuclear tracer and include scintigraphy to document aberrant drainage)
  - Histologically or cytology-proven metastasis
  - Clinically overtly palpable pathological nodes
  - T4 cancers

- Patients where axillary surgery may be omitted (all criteria should be met):
  - >70 years of age
  - ER positive
  - HER2 negative
  - Grade 1/2
  - Node negative
  - T1 / 2

- Intra operative frozen section
  - Intraoperative frozen section is no longer routine practice when doing a sentinel lymph node biopsy and is only done in patients who received neoadjuvant chemotherapy.
  - Frozen section may be used intra-operatively in selective cases where the patient did not receive neoadjuvant chemotherapy at the discretion of the operating surgeon.

Sentinel lymph node biopsy technique

The preferred SLNB technique at Groote Schuur Hospital is the using super paramagnetic iron oxide (SPIO) with SentiMag. SPIO is injected into the breast behind the NAC up to 3 weeks before surgery. 0.25 ml of Magtrace has been found to be sufficient to allow for accurate identification of sentinel nodes.

Nuclear medicine tracers will be used when SPIO is not available or in circumstances where scintigraphy is needed. The main indication for scintigraphy is repeat SLNB.

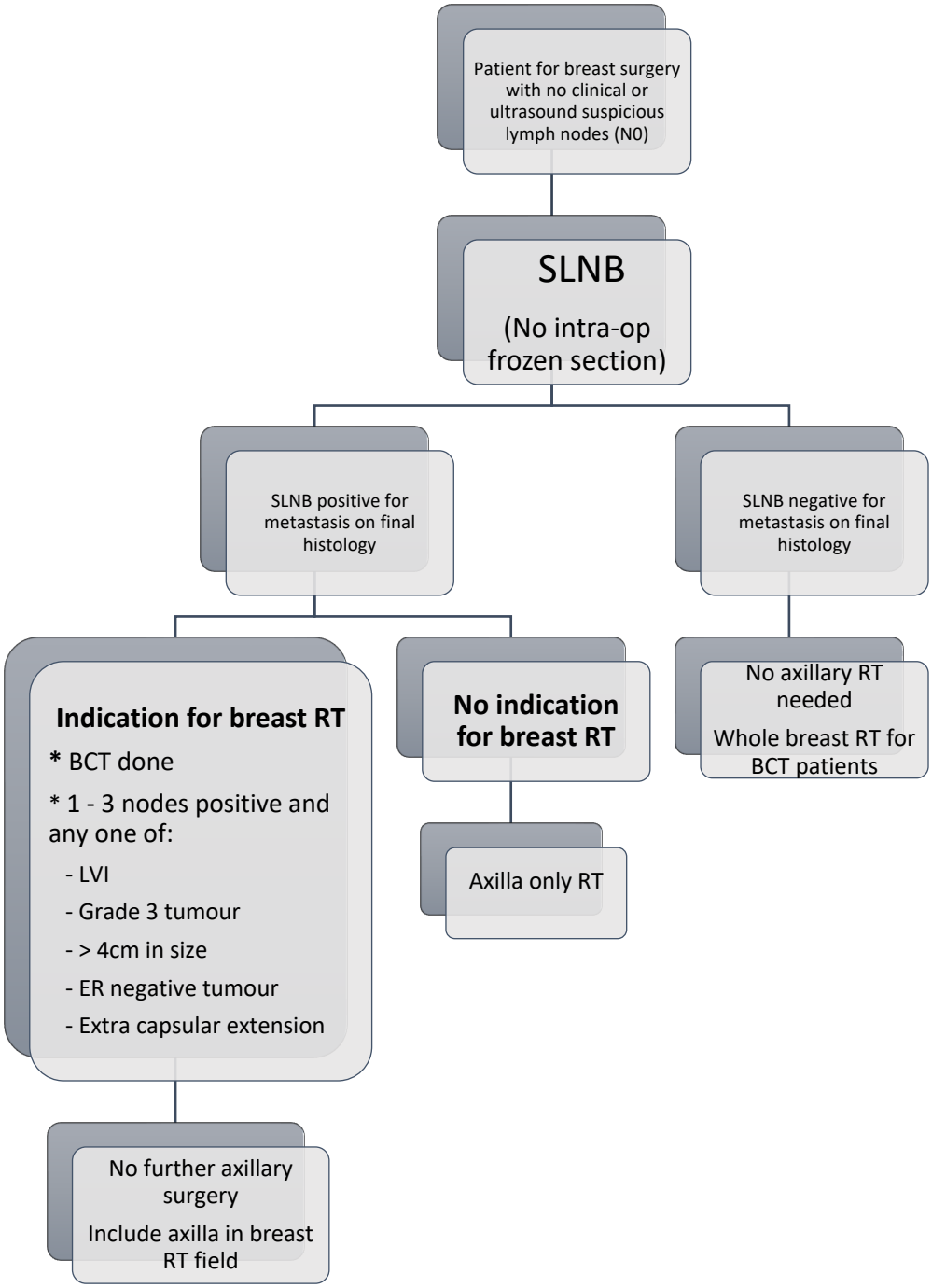
Axillary node clearance (ANC)

Patients shown to have axillary node metastases on preoperative axillary ultrasound and FNA should proceed directly to an axillary node clearance. The anatomical level of dissection should be specified in the operation notes and the apical extend marked with a Liga clip.

- Indications for axillary node clearance (ANC)

- Proven positive lymph node biopsy preoperatively
- Patients with clinically overtly pathological lymph nodes
- Contraindication to SLNB (see SLNB)
- Failed SLNB procedure (it is acceptable to do axillary sampling if SLNB failed, (remove at least four nodes)
- Lack of access to SLNB technique in the treating institution
- Inadequate prior ANC (less than six nodes) with residual suspicious nodes on examination
- Patients after neoadjuvant chemotherapy who had a SLNB with any residual disease on frozen section of the nodes (Isolated Tumor Cells and micro-metastasis included)

In a post-mastectomy patient with a positive sentinel lymph node, where the criteria for PMRT (see section 10) are not met, further management of the axilla, whether with RT or surgery, should be discussed at MDT and individualised.


Patient for breast surgery with no clinical or ultrasound suspicious lymph nodes (N0)
SLNB
(No intra-op frozen section)
SLNB positive for metastasis on final histology
SLNB negative for metastasis on final histology
Indication for breast RT
* BCT done
* 1 - 3 nodes positive and any one of:
- LVI
- Grade 3 tumour
- > 4cm in size
- ER negative tumour
- Extra capsular extension
No indication for breast RT
No axillary RT needed
Whole breast RT for BCT patients
Axilla only RT
No further axillary surgery
Include axilla in breast RT field

Axillary surgery post NACT

- Most patients who are clinically node-positive prior to NACT will proceed to ANC regardless of their clinical response
- Selected patients who are clinically node positive and achieve a complete clinical and radiological response to NACT, can be offered a SLNB. If this is done a dual technique (Tracer and Blue dye) should be used and a minimum of 3 nodes should be harvested
- Patients who are clinically node negative prior to NACT should have a SLNB after NACT
- Patients who are T4N0 and receive NACT, can be offered a SLNB on the discretion of the MDT

Surgery for Ductal carcinoma *in situ*

Retrospective studies of cases of low grade DCIS misdiagnosed as benign, found that 20 years after local excision, approximately 33% developed invasive carcinoma. DCIS should be regarded as a precursor of invasive disease. The aim of surgery for DCIS is to achieve complete excision and to minimise local recurrence. Approximately 50% of local relapses after treatment for DCIS are invasive cancer.

Pathology

DCIS is defined as a proliferation of malignant epithelial cells within ducts and lobules of the breast, without microscopic stromal invasion beyond the basement membrane. Benign myoepithelial cells are demonstrable microscopically around the ducts and lobules containing malignant epithelial cells. Immunohistochemical markers such as p63 or calponin may be used to highlight myoepithelial cells.

Macroscopically, DCIS with associated necrosis may be visible as small dilated ducts filled with “cheese-like” material on cut section. Small, mammographically detected foci of DCIS may, however, be invisible to the naked eye and not palpable clinically.

Architectural patterns

DCIS may show different architectural patterns which is mainly helpful in microscopic identification of disease, but this is less important for clinical outcome and management than grading and the presence or absence of necrosis. Calcification may be noted in association with necrosis or inspissated secretions.

- Solid: This was previously known as comedo-type DCIS. Malignant cells fill and expand ducts. Central necrosis may be present.
- Cribriform: Punched-out or “cookie cutter”-like spaces are seen within ducts harbouring DCIS.
- Papillary: Finger-like projections with central fibrovascular cores are seen lined by malignant epithelial cells within ducts.
- Micropapillary: Small, finger-like projections or tufts consisting of malignant epithelial cells and lacking fibrovascular cores are seen within ducts.
- Flat/clinging DCIS: A single layer or a few layers of malignant epithelial cells are seen lining ducts.

Other rare types of DCIS such as neuroendocrine DCIS, spindle cell DCIS, apocrine DCIS or signet ring cell DCIS may be seen.

Grading

A three-tiered grading system based on the nuclear size is most widely used.

- Low grade: The cells are usually evenly spaced and nuclei are monotonous in appearance. The nuclei are less than 2x a red blood cell in size. Necrosis is uncommon.

- Intermediate grade: Features intermediate between low grade and high grade DCIS are seen. Necrosis may be present and cells are usually less uniform than low grade DCIS. Nuclei are 2x to 2.5x the size of a red blood cell.

- High grade: Cells are clearly malignant with large, pleomorphic nuclei. Nucleoli are frequently seen. The nuclear size is greater than 2.5x to 3x the size of a red blood cell. Necrosis is often present.

Management

Diagnosis of DCIS: Isolated DCIS is often a screen detected lesion that presents as calcification on a mammogram. The best diagnostic test is a stereotactic vacuum assisted biopsy. It is mandatory for a radio-opaque marker to be left in the breast post biopsy.

Surgery

i. Surgery to the breast – Current evidence would suggest that the majority of DCIS is unicentric in origin and breast conserving surgery is the treatment of choice. This usually requires a localization technique and x-ray of the surgical specimen should be performed to ensure complete removal of all microcalcification.
    - Contraindications for breast conserving surgery in DCIS:
        - Widespread DCIS and excision would leave unacceptable cosmetic result
        - Multicentric DCIS (More than 1 quadrant in the breast)
        - Patient choice to have mastectomy
        - Contraindications to RT and intermediate / high grade DCIS
    - All patients that have a mastectomy should be offered breast reconstruction unless contraindicated (see section on breast reconstruction)

ii. Surgery to the axilla – Axillary surgery should be avoided in patients with DCIS. Axillary node clearance is contraindicated in patients with a non-operative diagnosis of DCIS alone. Sentinel lymph node biopsy is indicated in selected patients with DCIS otherwise no axillary surgery is done.
    - Indications for SLNB in patients with DCIS on biopsy specimen
        - Mastectomy / (Therapeutic Mammaplasty)
        - Lump on examination / Solid component suspicious of invasion on mammogram
        - Large area of DCIS (> 4 cm)
        - High grade DCIS
        - Surgery in axillary tail of breast (relative)

The USC / Van Nuys Prognostic Index scoring system

The van Nuys Prognostic Index system is a **post-operative** scoring system that guides treatment to try and prevent local recurrence of DCIS. The rate of DCIS recurrence in patients who had a lumpectomy and RT is similar to early stage invasive breast cancer. The VNPI has very limited use in clinical practice. It is mainly used in patients with a low score as a guide to omit RT. It is not used much to guide surgery decisions.

One to three points are awarded for each of four different predictors of local breast recurrence (size, margin width, pathologic classification, and age). Scores for each of the predictors are totalled to yield a VNPI score ranging from a low of 4 to a high of 12.

Score	1	2	3
Size (mm)	≤ 15	16-40	> 41
Margin width (mm)	≥ 10	1-9	<1
Pathologic classification	Low grade	Intermediate grade	high grade
Age (yr)	> 60	40-60	<40

Treatment guidelines by USC/Van Nuys Prognostic Index Score

VNPI Score	Treatment plan
4 to 6	Wide Local Excision alone
7 to 9	Wide Local Excision + radiation
10 to 12	Mastectomy

Margin status in DCIS

As in invasive disease, adequate margins are essential to reduce the risk of local recurrence and patients should be offered re-excision if the margins are close or involved. For all patients treated with breast conserving surgery for DCIS, a minimum of 2 mm radial margin of excision is essential. A 10 mm margin is preferable in patients not proceeding to radiotherapy. Re-excision should be considered if the margin is less than 2 mm, after discussion of the risks and benefits with the patient.

Important factors that should be considered before a decision on re-excision of margins is made are:

- Age of the patient
- Extend of DCIS excised
- Grade of DCIS
- Extend of DCIS at the margin (Extensive vs focally involved margin)

Radiotherapy for DCIS

Three large trials have found a reduction in ipsilateral local recurrence following radiotherapy. It is recommended that adjuvant radiotherapy be discussed with all patients following breast conserving surgery for high grade DCIS and those with DCIS showing comedo necrosis.

After Breast Conserving Treatment

- Whole breast RT (WBRT) was become the standard of care for BCT in DCIS.
- The NSABP-17 trial showed an absolute benefit of 9% (16% vs 7%) for invasive breast cancer.
- However, omission of RT is considered acceptable in low risk patients
  - Low risk VNPI

- Advanced age
- Co-morbidities
- Patient preference
- RT is not a substitute for positive margins in DCIS
- In patients receiving RT, margins of 2mm are regarded as adequate

After Mastectomy

- There is no role for PMRT in patients who have no invasive cancer on histology.
- A Positive margin is not an indication for PMRT.

Endocrine Therapy for DCIS

The NSABP-24 showed an absolute benefit of 3% for tamoxifen (16% vs 13%) – for all breast cancer recurrence, both DCIS and invasive

- There is no OS benefit
- There is no regional LN or distant DFS
  - NNT =15
  - Non-significant increase in endometrial cancer and T-E events

At Groote Schuur Hospital well informed woman may be offered 5y of tamoxifen to reduce the incidence of invasive breast cancer and DCIS.

Surgery for Paget's disease

Breast conserving surgery with removal of the nipple-areolar complex should be offered as an alternative to mastectomy for patients with Paget's disease of the nipple that has been assessed as localised. In patients in who BCS is considered with dense breasts where it is difficult to interpret the mammogram, to exclude underlying disease, MRI would be indicated due to the high rate (up to 90%) of associated disease elsewhere in the breast in patients with Paget's disease. Oncoplastic dermo-parenchymal flaps should be considered to maximise cosmesis.

Surgery for lobular *in situ* neoplasia

Lobular *in situ* neoplasia (LISN) is often an incidental finding and is usually occult. Low or intermediate grade LISN is not a locally malignant precursor lesion, but it does confer an increased future risk of invasive cancer in both breasts. The risk of developing breast cancer is about 1% per year.

The limited data available on LISN suggests that clear resection margins are not required following surgery for low or intermediate grade LISN alone. A policy of close clinical and mammographic surveillance after excision biopsy is appropriate. There is however evidence that high grade or pleomorphic LCIS behaves in as an established carcinoma *in situ* and consideration should be given to formal excision with clear margins

Ambulatory Breast Care / Day surgery for breast cancer

Exclusion Criteria

Anticipated length of surgery should be less than one hour in duration. Where intra-operative sentinel lymph node assay is undertaken, clinical judgement is required as to the actual length of time the patient is being operated on, rather than the time they may be anaesthetised and in theatre. The procedure should be associated with minimal post- operative pain or bleeding. Patients should have ASA Grade 1 or 2 and a BMI < 35. There is no upper age limit. Patients should have no previous anaesthetic or airway problems. Co-morbidities excluding day surgery include:

- Uncontrolled hypertension
- Valvular Heart Disease
- Cardiac failure
- MI or Stroke within previous 6 months
- Severe Asthma / COPD
- Poorly controlled IDDM
- Clotting disorders
- Sickle cell disease
- Epilepsy ~ if had a fit in the last 12 months

Drains and Dressings Policy

The use of drain can increase the risk of infection. It is acknowledged that there may be long term cosmetic disadvantages associated with not using drains. Low suction drains should be used when required. The use of drains is to be decided by the surgeon at time of surgery.

- Breast Conserving Surgery + Sentinel Lymph Node Biopsy ~ No drain
- Breast Conserving Surgery + Axillary Node Clearance ~ Patient may go home with drain *in situ*.
- Mastectomy + Sentinel Lymph Node Biopsy ~ Patient may go home with drain *in situ*.
- Mastectomy + Axillary Node Clearance ~ Patient may go home with drain *in situ*.

All wounds should be closed with absorbable sutures. An occlusive dressing suitable to remain in situ for 7 days should be used.

Discharge

All patients should be discharged with appropriate take home medication and information regarding dressings and drains.

Breast reconstruction

Approximately 70% of women at GSH undergo mastectomy for treatment of their breast cancer. Breast reconstruction can be performed immediately at the time of mastectomy or delayed to sometime in the future. Women should be advised of this possibility at the time of their initial surgical diagnosis and treatment.

Concerns that immediate reconstruction may compromise oncological safety or hide cancer recurrence are unfounded. It has not been shown to significantly delay adjuvant therapy. Radiotherapy has been reported to have a detrimental effects on the cosmetic outcome of

some types of breast reconstruction, especially if an implant is present. The risks of radiotherapy on outcome of breast reconstruction should be discussed and these women may be advised to consider a delayed rather than immediate reconstruction. Patients should have access to information about the various types of reconstruction available and the associated risks and complications.

Patients who have had a wide local excision for invasive disease who need adjuvant chemotherapy, but require completion mastectomy to gain adequate margins may be offered chemotherapy prior to completion mastectomy and immediate reconstruction. This enables patients to receive systemic treatment without delay, and allows more time for planning of further surgery.

Breast Reconstruction at GSH

Patients with large node positive cancer, extensive co-morbidity, obesity (BMI >35) or heavy smokers may not be appropriate for reconstruction and reconstruction will not be offered for patients with more than 2 risk factors.

Risk factors in breast reconstruction
- Smoking
- BMI >35
- Uncontrolled diabetes HbA1C >7
- Connective tissue disorders

Indications for breast reconstruction at GSH

- BMI < 30
- Early stage disease in breast and axilla (Tis, T1, T2 and N0, N1)
- Non smokers or evidence of having stopped

Immediate implant reconstruction

Skin sparing mastectomy with direct to implant (DTI) reconstruction should be considered for the following patients:

- Risk reducing surgery – nipple sparing mastectomy indicated here
- Isolated DCIS
- DTI should not be offered to patients with any risk factors and ideally the patients BMI should be < 30

Skin sparing mastectomy with the immediate insertion of expander should be considered for the following patients:
- Any risk factors
- Likely postoperative radiotherapy

Delayed Reconstruction

All patients who have had a mastectomy without a reconstruction should have the option of delayed reconstruction and this should be discussed at follow-up visits.

Contralateral breast reduction / Mastectomy for symmetry

Patients may require contralateral breast reduction or reshaping after any of the above procedures, including simple mastectomy and BCS. It is most often done in patients with gigantomastia who has a unilateral mastectomy and needs reduction of the opposite breast to prevent severe asymmetry. This is at the discretion of the operating surgical team.

Pathology

All breast cancer cases should be reviewed by a breast pathologist.

Post neo-adjuvant chemotherapy specimens

Thorough sampling is essential and more blocks are often required than from an equivalent specimen from a patient who has not received neo-adjuvant treatment. Identification of residual disease may be facilitated by identification of a marker inserted previously by the radiologist. Large blocks may be helpful in determining the distribution of residual tumour foci if residual disease is no longer contiguous. Specimen x-rays assist the identification of subtle alterations in tissue architecture in patients who have had a good response to treatment.

Ductal carcinoma in situ (DCIS)

In both wide local excision and mastectomy specimens, specimen slice x-ray permits identification of the targeted lesion and appropriate sampling. Particular attention should be given to excision at the margin nearest the nipple and this margin should be separately identified by the surgeon.

Sentinel lymph nodes

Each sentinel node should be sliced along the short axis at 1-2mm intervals and processed in its entirety. Very small nodes can be bisected. At least one H&E section should be examined. Pathologists may choose to examine additional sections or perform immunohistochemistry for epithelial markers to improve the accuracy of identifying metastatic cells and to measure the largest size of a metastasis, micrometastasis or isolated tumour cells (ITC) identified on initial examination. Classification of single node involvement should be done using the TNM classification.

Use of ancillary techniques

Invasive carcinomas should have their hormone receptor status assessed. Oestrogen receptor (ER) status should be determined on all cases. If scored, this should be using the Quickscore method (scores 0-8). HER2 status should be assessed on all newly diagnosed breast cancers less than 75 years of age.

Immunohistochemistry assessment should follow current national guidance with scores of 0 and 1+ considered negative, 3+ as positive for amplification and 2+ cases requiring FISH.

A wide range of immunohistochemical markers are available. Those which are most relevant to breast cancer include CK5, CK8, CK18, CK20, EMA, CEA, e-cadherin, Smooth muscle actin, S100 protein, high molecular weight cytokeratin (34bE12), laminin, GATA3 and CD45.

Surgical pathology report of breast cancer specimens

The final pathology report should include certain information of prognostic importance required for therapy.

Diagnostic specimens

For all breast core biopsy specimens

- Diagnostic category code (B1-5)
- For B3 lesions the presence or absence of atypia should be reported
- For malignant core and diagnostic breast biopsy specimens
    - Presence of invasion, microinvasion and / or DCIS
    - Invasive tumour type*
    - Invasive tumour grade*
    - Lymphovascular invasion*
    - Hormone receptor status
    - HER2 status (all patients less than 75 years old)

    *as far as can be judged in the material present

For breast fine needle aspiration specimens

- Diagnostic category code (C1-5)

Therapeutic specimens

Invasive carcinoma

- Laterality of the breast and procedure.
- Histological type:
    - ductal (usual, no special type)
    - lobular (specify type: classic or other)
    - tubular
    - medullary
    - mucinous
    - papillary
    - secretory
    - adenoidcystic
    - metaplastic
    - other(specify)
- Histological grade. All invasive carcinomas with the exception of medullary carcinoma should be graded. The Elston and Ellis modification of Scarff-Bloom-Richardson grading system is recommended. It evaluates the following three parameters:
    - tubule formation:
        - score 1. ≥ 75% of the tumour is composed of tubules.
        - score 2. 10%–75% of the tumour is composed of tubules.
        - score 3. < 10% of the tumour is composed of tubules.
    - nuclear pleomorphism:
        - score 1. small and regular nucleus
        - score 2. moderate variability in size and shape.
        - score 3. marked increase in size and marked irregularity.
    - Mitotic index
        - score 1. ≤ 10 mf/10 hpf
        - score 2. 11–20 mf/10 hpf
        - score 3. > 20/10 hpf

The histological grade is determined by summing the points of these parameters:

grade I = total score 3–5 grade II = total score 6–7 grade III = total score 8–9

- Margins of resection. There is no standard definition of what constitutes a positive or negative margin. However, when reporting margins state:
    - if tumour is at the margin (grossly or microscopically)
    - if tumour is not at the margin, the distance from the margin should be specified e.g. within 5 mm of the nearest margin or more than 5 mm.
    - If the margin is involved the extend of involvement should be recorded
        - < 4mm = focally involved
        - > 4mm = more than focally involved

- Lymph node status. The number of nodes involved and the total number of nodes removed should be mentioned. The presence or absence of perinodal extension of the carcinoma cells into axillary fat should be recorded. If metastases size is ≤ 2 mm, this should be recorded.

- Lymphovascular invasion. Peritumoural vessel invasion is assessed; if the lymphovascular spaces in the skin are involved, this should be mentioned separately.

- Size of the carcinoma. It is preferred to mention this in the diagnosis, even though this is recorded in the gross description (maximum diameter).

- Extent of in situ carcinoma. The presence or absence of in situ component should be recorded. If it is present, its extent should be approximated. If it is more than 25% of the tumour mass or the tumour is primarily intraductal with only focal microscopic invasion, the in situ component is considered to be “extensive”. If only focal microscopic invasion is present, the size of this focus/foci should be measured on the slide and recorded, in addition to the maximum diameter of the DCIS.

- Microcalcifications. If seen on the mammogram their presence or absence and location should be stated, to be sure a calcified lesion was not missed.

- Other significant disease such as papillomas, Paget’s disease of the nipple, etc.

- If information required for therapy or prognosis is not available or cannot be adequately assessed (e.g. no nodes submitted with a mastectomy specimen, margins not assessable because specimen was cut before inking, etc.) this should be stated specifically in the report.

- Prognostic factors, if available, should be included in the report (e.g. ER/PR receptor studies, HER2, etc.). Hormone receptor (estrogen and progesterone) investigation is now almost exclusively performed by immunohistochemical means, performed on paraffin embedded material. It should be performed on all cases of invasive carcinoma. Only nuclear staining is considered to indicate a positive result. An estimate of the percentage of nuclei stained should be included in the report. There is no consensus on the lower cut-off point for a positive assay, but a practical cut-off point is greater than 10% of nuclei staining.

Axillary and lymph node procedures

- Status of nodal excision
- Number of nodes excised
- Number of nodes involved
- Extra capsular spread

- Size of largest nodal metastasis

Ductal carcinoma in situ

- Laterality of the breast and procedure.
- Nuclear grade. Should be reported as low, intermediate, or high grade (grade 1, 2,3) using the same criteria advocated for invasive carcinoma.
- Necrosis:
    - present (central duct necrosis i.e. comedo necrosis)
    - absent or minimal (no central duct necrosis, but focal)
- Architecture type (many tumours show more than one type):
    - cribriform
    - micropapillary
    - solid
    - comedo (high nuclear grade; necrosis usually present)
    - papillary (includes intracystic)
    - mixed
- Margins of resection. Distance of DCIS from the closest margin should be recorded in millimetres. If DCIS is present at the margin, this should be specified.
- Size. If a mass is present, state the size from the gross. If not, then an estimate of the extent of the tumour may be attempted:
    - estimate the percent of the breast units affected by DCIS or
    - estimate the size of the lesion based on the sections by counting the number of specimen slices in which the lesion occurs and multiplying by the average slice thickness (3mm–4mm) or
    - if the lesion is small, measurement of the size of the tumour should be obtained directly from the slide.
- Presence and location of microcalcification.
- Other significant disease (atypical hyperplasia or papilloma, etc.)

The following should be reported on

Invasive tumour size	mm
DCIS tumour size	mm
Combined tumour size	mm
Histological invasive cancer grade	1 / 2 / 3 / Unknown / not assessable
Highest DCIS grade	Low / Intermediate / High
DCIS architecture	Cribriform / Flat / Micropapillary / Papillary / Solid / Solid papillary / Encapsulated papillary carcinoma in situ / Other (specify)
DCIS necrosis	None / minimal / Present / Unknown
DCIS only microinvasion <1 mm	No / Yes
Lymphovascular invasion	Present / Absent

Morphology of invasive carcinoma	Ductal / Lobular / Other
Non-epithelial tumour type	Phyllodes (benign) / Phyllodes (borderline=intermediate) / Phyllodes (malignant=high grade) / Sarcoma / Other (specifiy)
Non-epithelial tumour size	mm
Resection margin invasive & in situ	Negative / Positive
Invasive closest margin	mm
Invasive positive margin (extend of involvement)	mm
Invasive closest margin type	Lateral / Medial / Superior / Inferior / Anterior, superficial / Posterior, deep / Clear of margins
DCIS closest circumferential margin	mm
DCIS positive margin (extend of involvement)	mm
DCIS closest margin type	Lateral / Medial / Superior / Inferior / Anterior, superficial / Posterior, deep / Clear of margins
Atypical lobular hyperplasia	No / Yes
Lobular carcinoma in situ (classical)	No / Yes
Pleomorphic LCIS (PLCIS)	No / Yes
Extent of lobular neoplasia	Focal / Extensive
Pleomorphic / variant LCIS at margin	No / Yes
Pleomorphic / variant LCIS closest margin	mm
Flat epithelial atypia	No / Yes
Axillary nodes	SLNB / ALND / No axillary nodes
Total number of nodes removed	
Number of nodes involved by tumour	
Nodal metastasis based on the largest deposit	Isolated tumour cells / Micrometastasis / Macrometastasis

Extra capsular / nodal spread	No / Yes
Residual invasive carcinoma in further re-excisions	No / Yes
Residual DCIS in further re-excisions	No / Yes
Neo-adjuvant treatment	No / Yes / Unknown
Neo-adjuvant treatment effect	No response / Partial response / Complete response
Residual cancer burden	RCB-0 / RCB-1 / RCB-2 / RCB-3
Neo-adjuvant treatment effect in lymph nodes	Nodes negative, no treatment effect / Nodes negative, with treatment effect / Nodes positive, with treatment effect / Nodes positive, no treatment effect / Unknown
Pathological T stage based on primary tumour	
Pathological N stage	
Pathological M stage	

Adjuvant therapy

The oestrogen receptor (ER) status of all invasive breast cancers should be assessed, using immunohistochemistry with a standardised and qualitatively assured methodology and the result reported quantitatively. The human epidermal growth receptor 2 (HER2) status of all invasive breast cancers should be assessed, using a standardised and qualitatively assured methodology, in all patients under 75 years of age. It should be ensured that the results of ER (+/-PR) and HER2 assessments be available and recorded at the MDT meeting when decisions about systemic treatment are made.

Adjuvant therapy planning

Adjuvant therapy should be considered at the MDT meeting for all patients and the decisions recorded in the patient's notes. Decisions should be made based on assessment of the prognostic and predictive factors and the potential benefits and side effects of the treatment. Decisions should be made following discussion of these factors with the patient.

Consideration should be given to using Adjuvant Online for patients with early invasive breast cancer to support estimations of individual prognosis and the absolute benefit of any proposed adjuvant treatment. Adjuvant chemotherapy or radiotherapy should be started as soon as clinically possible.

Radiotherapy

Radiotherapy after breast conserving surgery

Patients with early invasive breast cancer who have had breast conserving surgery with clear margins should have breast radiotherapy. Adjuvant radiotherapy should be discussed with patients with high-grade DCIS following adequate breast conserving surgery and the potential benefits and risks explained.

Following breast conserving surgery, postoperative radiotherapy to the intact breast should be delivered via a tangential pair. Standard dose will be 40 Gy in 15 fractions.

An external beam boost to the site of local excision should be considered in patients with early invasive breast cancer who are at high risk of local recurrence, following breast conserving surgery with clear margins and whole breast radiotherapy. If an external beam boost to the site of local excision is being considered, the patient should be informed of the side effects associated with this intervention, including poor cosmesis, particularly in women with larger breasts. This is given 10.68Gy/4# or else 10Gy/5#

Radical Radiotherapy after BCS at GSH

Unless contra-indicated, all women <70y (see "Elderly patients" below) are to receive post-op RT to the whole breast. WBRT reduces overall mortality by 5% at 15y.

Doses and fractionation:

Hypofractionation schedules have shown similar effectiveness and side effect profile.
Chest Wall (CW): 2.67 Gy x 15 = 40.05 Gy
Supra clavicular (SC):2.67 Gy x 15 = 40.05 Gy

Boost to surgical bed:

A 10-16Gy RT boost gives all women a relative 50% decrease in local failure but have no effect on OS. The absolute gains for low-risk women do warrant boost RT.

ESMO classification of high risk:
- <50 year
- Grade 3
- Lymphovascular invasion (LVI)
- Focal positive margin (< 4mm involved margin)

At GSH a boost is given to women <50y or + margin in whom repeat surgery is not feasible.
Dose: 2.67Gy x 4 # (START B used 2 Gy x 5#)

Technique

3DCRT
Include high tans if SLNB+ (1-2 LNs) with no completion ALND (Z0011)
Include supaclav if:
- ≥4LN+ (post ALND)
- ≥3LN+ (SLNB)
- 1-3LN+ and Extra Capsular Extension (ECS)
- Additional risk factors to be taken into account include <10LN sampled, G3, LVI, young age and non-luminal disease

Elderly patients

Based on CALGB 9343 trial and PRIME II, women who fulfil all of the below criteria can forego adjuvant RT following WLE:

- >70y age
  - < T2N0
  - ER+ (who will receive 5 years of adjuvant Endocrine Treatment)
  - Clear margins

- >65y age
  - <T2 (<3cm) N0
  - ER+ (who will receive 5 years of adjuvant Endocrine Treatment)
  - Clear margins
  - Not G3 or LVI
  -

Due to resource limited setting in regards to systemic therapy , we can offer EBRT in older patients if the benefit outweight the risk ,
To improve local control without adding much toxicity

Radiotherapy after mastectomy

Adjuvant chest wall radiotherapy should be given to patients with early invasive breast cancer who have had a mastectomy and are at a high risk of local recurrence. Patients at a high risk of local recurrence include those with tumours more than 4 cm in diameter, four or more positive axillary lymph nodes or involved resection margins.

Patients at an intermediate risk of local recurrence include those with less than 3 nodes involved, lymphovascular invasion, histological grade 3 tumours, ER-negative tumours, and those aged under 40.

Radiotherapy should not be given following mastectomy to patients with early invasive breast cancer who are at low risk of local recurrence

Radiotherapy doses of 40 Gy in 15 fractions via tangential pair to chest wall should be given

Post Mastectomy (PMRT) at GSH

Chest Wall only:

- T3/T4, N0
- Involved margin
- 1-3 LN + and no additional risk factors (see below):

  If patient >50 years and N0 disease we can now offer FAST FORWARD regime 26Gy / 5#

Chest Wall + Supra Clavicular

- ≥4LN +
- NACT for irresectable disease
- 1-3 LN+ (see below)

1-3LN+

All these patients should receive PMRT. The decision as to whether it is CW only vs CW+sclav is dependant on the following prognostic factors:

- G3
- LVI
- Age < 40 years
- Tumour > 4cm
- ECS
- <10 Lymph Nodes sampled
- Non-luminal disease

Doses and fractionation:

CW: 2.67 Gy x 15 = 40.05Gy (5 x week)
SC: 2.67 Gy x 15 = 40.05Gy (5 x week)

Bolus

All patients with cT4 disease should be treated with PMRT. Alternate fractions are given with 0.5cm bolus to the CW, starting with bolus on. Bolus is not applied to supraclavicular fossa

Technique

3DCRT (VIRT SIM)
All patients to be CT scanned.
Target volume do not need to be contoured.
OAR must be contoured by registrar.

Breast cancer chest wall recurrence

Discuss with consultant.
NB: must document previous RT.
Patients who have received previous ipsilateral RT are not candidates for re-treatment.
Factors favouring Chest Wall only:

- Luminal disease
- Isolated CW recurrence
- resected with R0
- No LVI
- No fixation to chest wall
- LN negative

All others: CW + SC

Radiotherapy for DCIS

Patients with low or intermediate grade disease with adequate surgical margins may avoid radiotherapy. The potential benefits and risks of radiotherapy should be discussed with all patients with high grade disease. Following mastectomy, there is no established role for postoperative radiotherapy in patients with DCIS only.

Endocrine therapy

Women with ER positive tumours (ER > 3/8) will benefit from at least 5 years of anti-oestrogen therapy. All patients with ER positive invasive breast cancer should, therefore, receive endocrine therapy. Following results of the ATLAS , ASCO guidelines published June 2014 recommend extended adjuvant endocrine therapy for women with early breast cancer either with tamoxifen alone or using sequential treatment with tamoxifen and aromatase inhibitors, with the exception being those women treated with aromatase inhibitors for 5 years as there is currently a paucity of data to support the use of aromatase inhibitors beyond 5 years.

Patients with hormone receptor negative disease should not receive endocrine therapy. If the patient is receiving adjuvant chemotherapy, endocrine therapy should be deferred until chemotherapy has finished. Any vaginal bleeding whilst on tamoxifen should be investigated by a gynaecologist.

Pre-menopausal patients

There is good evidence that adjuvant tamoxifen works in pre-menopausal women. All pre-menopausal women should receive at least 5 years of tamoxifen 20 mg once a day. Treatment beyond 5 years can be with either tamoxifen or an aromatase inhibitor dependent on menopausal status. There is little evidence that ovarian ablation should be used in addition to tamoxifen but in a small high risk group of < 40yrs with other high risk factors , there may be a 2-5% added benefit for doublet blockage

Endocrine treatment in pre-menopausal patients at GSH

High risk patients are defined as ≥4LN+I

- Tamoxifen 20mg daily x 5yr

- Ovarian Function Suppression (OFS)
    - Consider in high-risk pts and age <35 years (SOFT/TEXT)
    - Patients offered chemotherapy but have chosen not to have it
    - Considered in premenopausal women who are unable to tolerate tamoxifen
    - Only if patient remains premenopausal after chemotherapy
    - The gains in DFS must be balanced against the risks and side effects of OFS
    - OFS: EBRT 15Gy in 5# + Tamoxifen

- Extended use
    - Offer to high-risk woman
    - After completion of 5 years of tamoxifen, an additional 5 years can be considered if patient is tolerating Rx well (ATLAS/ATTOM) ?data now only showing benefit up to 7-8 years

- A baseline dual energy X-ray absorptiometry (DEXA) scan can be done for all patients started on hormonal suppression

Post-menopausal patients

Standard of care

Postmenopausal women with ER positive should be offered an aromatase inhibitor, as their initial adjuvant therapy. Tamoxifen should be offered to women if an aromatase inhibitor is not tolerated or contraindicated. The choice of treatment should be made after discussion between the responsible clinician and the patient about the risks and benefits of each option. The aromatase inhibitor anastrozole, within their licensed indications, are recommended as options for the adjuvant treatment of early ER-positive invasive breast cancer in postmenopausal women. Therapy should be continued for at least 5 years. (in some high risk patients up to 7-8 years) Factors to consider when making the choice include whether the woman has received tamoxifen before, the licensed indications and side-effect profiles of the individual drugs and the assessed risk of recurrence.

All aromatase inhibitors increase the risk of osteoporosis and its complications. Therefore, all patients who receive an aromatase inhibitor should be advised regarding the implications for osteoporosis. Concerns regarding bone density should not prevent the prescription of aromatase inhibitors. All women who have finished chemotherapy and who are commencing treatment with an aromatase inhibitor should have a baseline dual energy X-ray absorptiometry (DEXA) scan. Lifestyle advice should be given to help reduce the risk of osteoporosis such as regular weight bearing exercise, cessation of smoking and a high calcium diet.

- Woman receiving an AI should be given Vit D 5000IU weekly PO and Calcium 1200mg daily PO to prevent osteoporosis

Male breast cancer

Male breast cancer patients who are ER positive should be offered adjuvant tamoxifen 20mg daily for 5 years.

Chemotherapy

Neoadjuvant chemotherapy (NACT)

Indications

1. Triple negative breast cancer
2. HER2 enriched breast cancer
3. Downsizing to achieve breast conserving treatment
4. Locally advanced (unresectable)
5. Inflammatory breast cancer

The data available from randomised trials shows that breast conserving surgery after neo-adjuvant chemotherapy is associated with an increased risk of local recurrence. When neo-adjuvant chemotherapy is being considered with a view to breast conserving surgery, the increased risk of local recurrence should be discussed with the patient.

Regimens

- AC4 x P4
- TC x 4 (>70y, anthracycline contraindicated)
- AC x 4
- FEC x 6
- Tamoxifen alone (luminal A, poor chemo candidate)

Pre-chemo workup

In patients who are deemed to be potential BCT candidates, surgical clips should be placed prior to or early during chemo.

- Staging of the axilla (Ultrasound axilla) is important to guide post chemotherapy treatment.
- ERNA prior to first cycle.

Re-assessment

All patients must be seen by a Doctor at cycle 3 to assess chemo response. Patients found to have progressive disease must be re-discussed at CBC for a decision regarding surgery, 2nd line chemo or 2nd line Tamoxifen alone.

Patients must be seen at CBC at / or after cycle 6 to assess surgical options and get date for surgery

Adjuvant chemotherapy

Systemic treatment must start within 12 weeks of surgery (ideally <6 weeks).

The benefit of chemotherapy is directly related to the molecular subtype of breast cancer. Thus, were relevant, Ki-67 and b-DISH should be requested to distinguish between subtypes.

- *Luminal A*

  These cancers are less responsive to chemotherapy and are endocrine responsive.

Chemotherapy is indicated for ≥4LN+.

- *Luminal B*

  This subgroup constitutes the most uncertainty regarding chemo.
  Relative indications favoring chemo are:
  - Grade 3
  - Low ER score
  - Lack of PR
  - High Ki 67
  - Age <35y
  - Node positivity
  - LVI+

PREDICT and Adjuvant online can help with assessing chemo benefit.

If available, Oncotype Dx and Mammaprint have been validated to determine chemo benefit.

Use 2nd generation chemo when calculating chemo benefit on PREDICT.

Consider chemo if benefit >5% at 10y or 3% at 5 years

Regimens
- AC4 x P4
- TC x 4 (>70y)
- AC x 4
- FEC x 6

- *HER2 enriched / LumB HER2+ / TNBC*

  If no chemo was received in the neo-adjuvant setting, then all patients should receive chemo in the adjuvant setting. The one exception is stage 1 LumB HER2+. Discuss with consultant.

Regimen
- AC4 x P4

Radiotherapy
- If indicated, patients should be booked for RT at cycle 6 (AC-P) or cycle 2 (TC).

Cardiotoxicity
There is a 5% risk of cardiotoxicity with cumulative dose of Doxorubicin 450 mg/m2 and Epirubicin 900 mg/m2.

Baseline:
- If clinical CCF, unstable angina: not for anthracycline
- If LVEF< 50% not for Adriamycin, use Epirubicin (60mg/m2) if anthracycline indicated.
- If LVEF< 40% not for Epirubicin

Repeat ERNA/MUGA:
- At cycle 2 or 3 (depending on availability)

- If LVEF has reduced by 10% or has dropped below 50% then switch to Epirubicin 60mg/m2.
- If significant drop >15% or cardiac symptoms – discuss with consultant.

Chemotherapy in Pregnant patients

- Chemotherapy is contraindicated in trimester 1
- Adriamycin, cyclophosphamide and taxanes can be used in Trimester 2 and 3
- Notify the GSH high risk antenatal clinic for patient assessment
- Discuss with cardiology for ECHO, because ERNA contraindicated
- If in 3rd trimester: preferable to have upfront surgery followed by adjuvant chemo after delivery.

Biological therapy

When applicable (HER2 Positive disease (Confirmed with B-Dish), trastuzumab (Herceptin) should be given at 3-week intervals for one year or until disease recurrence (whichever is the shorter period), as an adjuvant treatment to women with HER2-positive early invasive breast cancer following surgery, chemotherapy, and radiotherapy.

An assessment of cardiac function should be made before starting treatment with trastuzumab and it should not be offered to women who have any of the following:

- left ventricular ejection fraction (LVEF) of 55% or less
- history of documented congestive heart failure
- high-risk uncontrolled arrhythmias
- angina pectoris requiring medication
- clinically significant valvular disease
- evidence of transmural infarction on electrocardiograph (ECG)
- poorly controlled hypertension

Repeat cardiac functional assessments should be made every three months during trastuzumab treatment. If the LVEF drops by 10 % (ejection) or more from baseline and to below 50%, then trastuzumab treatment should be suspended. Trastuzumab therapy should only be restarted after further cardiac assessment and a fully informed discussion of the risks and benefits with the woman. The standard protocol is a loading dose of 8mg/kg followed by 6mg/kg repeated three weekly to a total of 17 doses.

Currently Trastuzumab is not available in public hospitals in the Western Cape and there have been no official national guidelines as to which patients will qualify for treatment, the duration of such treatment and what budgeting will be provided.

Below are current international recommendations.

- *Adjuvant*
  - T1a: no role for Trastuzumab (herceptin)
  - T1b, T1c: Pacli + Herceptin
  - Node negative: 9 weeks of Herceptin is non inferior to 1y (ASCO 2017 – SHORT-HER trial)
  - Node positive: ACx4+Pacli Herceptin x 4 + 1y Herceptin

- *Dual blockage*
  - Neoadjuvant: NeoSphere trial: improved pCR for trastuzumab + pertuzumab + docetaxel
  - Adjuvant: Aphinity trial (ASCO2017) reported as positive trial for pertuzumab and trastuzumab, however the benefit in DFS is +- 2%

Metastatic disease

If not previously documented, ER and HER 2 status should be determined at time of first relapse either from the original tumour specimen or biopsy from a recurrent or metastatic lesion.

General principles

- Early referral to palliative care is essential
- Patients and family must be counseled about prognosis, treatment options, aims of treatment and side effects of treatments
- Assess local and systemic complications of the metastatic disease to guide initial treatment

Prognostic factors

The most important prognostic factors in metastatic breast cancer are

- Performance Status
- Visceral vs non-visceral disease
- Molecular subtype
- Number of metastases
- LDH
- Young age

Palliative Endocrine Treatment

Luminal disease only

- *ET therapy is the preferred option (*even in the presence of visceral metastasis)
- Only patients with rapidly progressing disease or a visceral crisis should proceed with upfront chemotherapy
- It is NB that ET is not switched before at least a trial of 3months on Rx has been used to assess treatment response
- Rx options:
  - Pre-menopausal: Tamoxifen + OFS
  - Post-menopausal: AI
  - ET will be influenced by type of ET received in the adjuvant setting
- Treatment is continued until clinical progression. Stopping ET in metastatic breast cancer is not recommended. At progression, patients may well be offered chemotherapy, after which they should be switched to 2nd/3rd line ET.

ET available

- Tamoxifen 20mg dly
- Anastrazole 1mg dly (or else Letrozole)
- Provera 400mg dly
- Fulvestrant 500mg IMI after loading dose of 500mg IMI

Palliative chemotherapy

Indications

- Visceral crisis
- Rapidly progressing disease
- Patients in whom a rapid response is desirable
- Non-luminal disease
- PS≤2

First Line

- AC (if chemo naïve)
- Paclitaxel (if received more than 12 months ago in the adjuvant setting)

Second Line

- Capecitabine
- Gemcitibine + Cisplatin (TNBC previously exposed to both anthracycline and taxane)
- Navelbine
- CMF regime

Targeted therapy

Targeted Rx is not available at GSH

HER2+

- 1st L: Herceptin is commonly given with either paclitaxel or docetaxel – continued till progression
- 2nd L: Herceptin commonly given with Navelbine or Xeloda – continued to progression
- Dual blockage: trastuzumab + Pertuzumab + Docetaxel (Cleopatra trial) is considered gold standard if resources are unlimited as FIRST LINE METASTATIC

ER+, HER2 negative

- Everolimus + Exemestane (mTOR inhibitor)
  - 2nd L progressing after AI *(Bolero-2)*
- Palbociclib + exemestane (CDK4/6 inhibitor)
  - 2nd L progressing on AI *(Paloma-3)*
- Palbociclib + letrozole
  - 1st L *(Paloma-2)*
- Ribociclib + letrozole (CDK4/6 inhibitor)
  - 1st L *(Monalessa-2)*

Palliative RT

Breast

36Gy in 5# over 5 weeks (1/week)

Can add bolus if T4 /or even treat with dressing to achieve better dosage in skin

20Gy/5 or 30Gy/10#
8Gy/1 poor PS

Bone metastasis

Single 8Gy (SIM): if limited disease
20Gy in 5# (VIRT-SIM): extensive ds

Spinal cord compression

Single 8Gy
20Gy in 5# if significant soft tissue component

Brain metastasis

SRS: discuss with Dr Naiker if oligometastatic disease, ER+, lesion<5cm
WBRT: 20Gy in 5# if PS≤3 or else 30Gy/10#
BSC: PS=-4

Radionuclide Therapy of Bone Metastases

Radionuclide treatment is available to selected patients meeting the following criteria:

- If 3 or more lesions
- Failed EBRT
- Normal FBC and renal function

(Please discuss possible patients with the clinical oncology consultant in LE33 and nuclear medicine)

Assessment of response

Treatment response can be assessed with repeat CT scan (for visceral metastases) or bone scan (for bone metastases) after 6 cycles of treatment or after 6 months if endocrine treatment was used

Palliative Surgery

Palliative surgery is seldom done at GSH due to surgical complications. Any patients considered for palliative mastectomy MUST be discussed at CBC.

Patients with locally advanced (M0) breast cancer should undergo neoadjuvant chemotherapy, and be considered for surgery thereafter. In Luminal A patients, neoadjuvant

Endocrine treatment is a viable option. Response should be evaluated at 3 months and if change in tumour size is observed treatment can be continued up to 9 months for full effect.

Radical mastectomy with complex skin flap reconstruction for locally advanced disease (T4) is to be considered only after MDT review.

Patients with metastatic disease should not undergo mastectomy, unless motivated for by clinician for urgent local control palliation, or if metastases are isolated and stable. These cases must be discussed at CBC with consultant. In general, these patients are treated with palliative RT for local control.

Patients with isolated metastasis that may benefit from surgery to the primary breast lesion are the following:

- Patients < 55 years
- ER positive
- Solitary bone metastasis
- Her 2 negative patients

Local recurrence may be amenable to Wide Local Excision, even in the context of metastases. This is best decided at MDC recommendation

Fertility issues

Issues surrounding ovarian function and fertility should be discussed with patients prior to starting adjuvant therapy.

Assessment of bone loss

Patients with early invasive breast cancer should have a baseline dual energy X-ray absorptiometry (DEXA) scan to assess bone mineral density if they:

- Are starting adjuvant aromatase inhibitor treatment
- Have treatment-induced menopause
- Are starting ovarian ablation / suppression therapy

A DEXA scan should not be offered to patients with early invasive breast cancer who are receiving tamoxifen alone, regardless of pre-treatment menopausal status.

Complications of local treatment and menopausal symptoms

Lymphoedema

All patients with early breast cancer should be given information about the risk of developing lymphoedema and should receive relevant written information before treatment with surgery and radiotherapy. Advice should also be given on how to prevent infection or trauma that may cause or exacerbate lymphoedema. It should be ensured that all patients with early breast cancer who develop lymphoedema have rapid access to a specialist lymphoedema service.

Arm mobility

Breast cancer patients with pre-existing shoulder conditions should be identified preoperatively as this may inform further decisions on treatment. Instructions should be given to all breast cancer patients undergoing axillary surgery on functional exercises, which should start the day after surgery. This should include relevant written information from a member of the breast or physiotherapy team. Patients should be referred to the physiotherapy department if they report a persistent reduction in arm and shoulder mobility.

Menopausal symptoms

Hormone replacement therapy (HRT) should be discontinued in women who are diagnosed with ER positive breast cancer. HRT (including oestrogen/progestogen combination) should not be routinely offered to women with menopausal symptoms and a history of breast cancer. HRT may, in exceptional cases, be offered to women with severe menopausal symptoms and with whom the associated risks have been discussed.

Information and counselling should be offered to all women about the possibility of early menopause and menopausal symptoms associated with breast cancer treatment. Tibolone or progestogens are not recommended for women with menopausal symptoms who have breast cancer. The selective serotonin re-uptake inhibitor antidepressants paroxetine and fluoxetine may be offered to women with breast cancer for relieving menopausal symptoms, particularly hot flushes, but not to those taking tamoxifen. Clonidine, venlafaxine and gabapentin should only be offered to treat hot flushes in women with breast cancer after they have been fully informed of the significant side effects. Soy (isoflavone), red clover, black cohosh, vitamin E and magnetic devices are not recommended for the treatment of menopausal symptoms in women with breast cancer.

Follow Up

Clinical follow up

Due to resource constraints, the follow up policy at GSH has been developed to cope with excessive patient numbers.

Patients who attend their local Day Hospital for a 6 monthly follow up should have a “Day Hospital Follow up letter”.

Patients who are discharged from GSH at 5y should receive a “Discharge letter”
Palliative patients not eligible for further cancer treatment should receive a “Palliative Care Plan” letter.

Patients treated with curative intent

- After completion of surgery +-chemo +- RT, all patients are to be seen 6 monthly in the 1st year then yearly at GSH.
- All patients are advised to attend their local DH for a 6 monthly visit. Ensure the appropriate letter with the treatment plan is given to the patient.
- F/U mammography is done at the yearly GSH visit.
- After 5y, discharge all patients in remission. Give the appropriate letter.

WE have now shortened the follow-up period in LE 33 due to limited resources
And will discharge patients earlier with a letter to their local day hospitals

Palliative patients

- Patients with a PS 0-2 are seen 3-6 monthly at GSH. Interval between visits is decided by; symptom control, treatment options remaining and the need to assess treatment response.

All other patients should be discharged with a "Palliative Care Plan". This must include what further treatment options are available (Endocrine options/RT etc), HBC/hospice arrangements, and how the patient can access LE33 if needed.

Follow up mammography

Breast-conserving treatment initially

i. Mammogram yearly for 5 years in all patients
   - Stop after 5 years if there is no family history of breast cancer, or the patient is older than 70.
   - Continue 2 yearly if there is a first-degree (mother, sister, daughter) family member with breast cancer
   - In young patients, especially if they had their first cancer before 40 years, continue with 2 yearly mammograms until 70, even if there is no family history.

Mastectomy initially

ii. A Mammogram of the contralateral breast is not indicated unless the following is present.
   - The patient has first-degree (mother, sister, daughter) family members with breast cancer, then 2 yearly mammograms need to be done up to the age of 70.
   - The patient is young, especially if she had her first cancer before 40 years old, continue with 2 yearly mammograms until 70, even if there is no family history.