Draft PMB definition guidelines for early and locally advanced breast cancer

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DISCLAIMER

The breast cancer benefit definition has been developed for the majority of standard patients. These benefits may not be sufficient for outlier patients. Therefore regulation 15(h) and 15(I) may be applied for patients who are inadequately managed by the stated benefits. The benefit definition does not describe specific in-hospital management such as theatre, anaesthetists, anaesthetics, or supportive medication and nursing care. However, these interventions form part of care and are recognised prescribed minimum benefits.

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ABBREVIATIONS

ALT	-	Alanine transaminase
AST	-	Aspartate transaminase
ALP	-	Alkaline phosphatase
CMS	-	Council for Medical Schemes
CNB	-	Core needle biopsy
DPT	-	Digital breast tomosynthesis
DTP	-	Diagnosis and treatment pair
ER+	-	Estrogen receptor-positive breast cancer
FNA	-	Fine needle aspiration
GGT		Gamma-glutamyl transferase
HDI	-	Human development index
HER2+	-	HER2-positive breast cancer
IHC	-	Immunohistochemistry
ISH	-	In situ hybridisation
LDH	-	Lactate dehydrogenase
MRI	-	Magnetic resonance imaging
PET-CT	-	Positron emission tomography / computerised tomography (PET-CT)
PMB	-	Prescribed minimum benefit
PR+	-	Progesterone receptor-positive breast cancer
3D-CRT	-	Three-dimensional conformal radiotherapy

1. INTRODUCTION

1.1. Legislation governing the provision of prescribed minimum benefits (PMBs) is contained in the regulations enacted by the Medical Schemes Act 131 of 1998 (hereafter called 'the Act'). Medical scheme beneficiaries sometimes find it difficult to establish their entitlements beforehand in respect of some of the diagnosis treatment pairs (DTPs). Additionally, medical schemes interpret these benefits differently – resulting in a lack of uniformity regarding benefit entitlements.

1.2. The benefit definition project is undertaken by the Council for Medical Schemes (CMS) with the aim of defining the PMB package and guiding the interpretation of the PMB provisions by relevant stakeholders.

2. SCOPE AND PURPOSE

2.1. The guidelines are intended as a recommendation for the diagnosis, treatment, and care of individuals with early or locally advanced breast cancer in any clinically appropriate setting as outlined in the Act.

2.2. In this document, early breast cancer is defined as disease confined to the breast with or without regional lymph node involvement, and the absence of distant metastatic disease (WHO, 2014).

2.3. The purpose of these guidelines is to provide a detailed clarification in respect of benefits and entitlements to members and beneficiaries of medical schemes.

Table 1: Possible ICD-10 codes for identifying breast cancer

ICD10 code	WHO description
Z12.3	Special screening examination for neoplasm of breast.
C50.0	Malignant neoplasm, nipple and areola.
C50.1	Malignant neoplasm, central portion of breast.
C50.2	Malignant neoplasm, upper-inner quadrant of breast.
C50.3	Malignant neoplasm, lower-inner quadrant of breast.
C50.4	Malignant neoplasm, upper-outer quadrant of breast.
C50.5	Malignant neoplasm, lower-outer quadrant of breast.
C50.6	Malignant neoplasm, axillary tail of breast.
C50.8	Malignant neoplasm, overlapping lesion of breast.
C50.9	Malignant neoplasm of breast, unspecified.
D05.0	Carcinoma in situ, lobular carcinoma in situ
D05.1	Carcinoma in situ, intraductal carcinoma in situ
D05.7	Carcinoma in situ, other carcinoma in situ of breast.

3. EPIDEMIOLOGY

3.1. Breast cancer is both the most common cancer and the leading cause of cancer deaths among women worldwide. (NDOH, 2017)

3.2. Based on the 2015 Global Burden of Disease (GBS) study, of the 17.5 million cancer cases globally, breast cancer accounted for 2.4 million new cases and 523 000 deaths in 2015 (NDOH, 2017).

3.3. Breast cancer is the most common form of cancer to affect women in South Africa and in 2013 was accountable for 20.8 per cent of female cancers and more than 10 per cent of the entire cancer burden (NDOH, 2017)

3.4. Without significant advances in screening and treatment efforts in the near future, the number of women dying from breast cancer annually is predicted to increase (Lince-Deroche et al., 2017).

3.5. Based on current trends, it is estimated that by 2030 the number of women diagnosed globally with breast cancer will increase to almost 3.2 million per year, nearly double the incidence in 2012 (Lince-Deroche et al., 2017).

3.6. The incidence of breast cancer appears to be low among black South Africans when compared to other demographics, this has been attributed to certain epidemiological factors peculiar to breast cancer such as early age of first birth, multi-parity, universal and prolonged lactation, low use of hormone replacement therapy and a diet low in fat/ high in fibre (NDOH, 2017).

4. SCREENING

4.1. Screening is the systematic mass application of a simple screening test in a presumably asymptomatic population at regular intervals in order to identify individuals with an abnormality suggestive of specific cancers, who then receive further investigation.

4.2. Clinical breast examination (CBE) for breast cancer screening among average-risk women at any age (Oeffinger et al., 2015) is a very low-cost test that could advance the detection of breast cancer and could prompt breast ultrasonography in the case of a negative mammogram (Provencher et al., 2016). CBE is recommended as PMB level of care

4.3. Lack of resources and infrastructure in the South African public healthcare system renders screening mammography as unsustainable, hence mammography should be performed on symptomatic and identifiable high-risk patients at specialist breast units (NDOH, 2017). In line with the recommendation by NDoH, mammography is not PMB level of care for screening.

4.4. Breast self-examination (BSE) is associated with considerably more women seeking medical advice and having biopsies. However, regular breast self-examination is not an effective method of reducing breast cancer mortality.

5. DIAGNOSIS OF EARLY AND LOCALLY ADVANCED BREAST CANCER

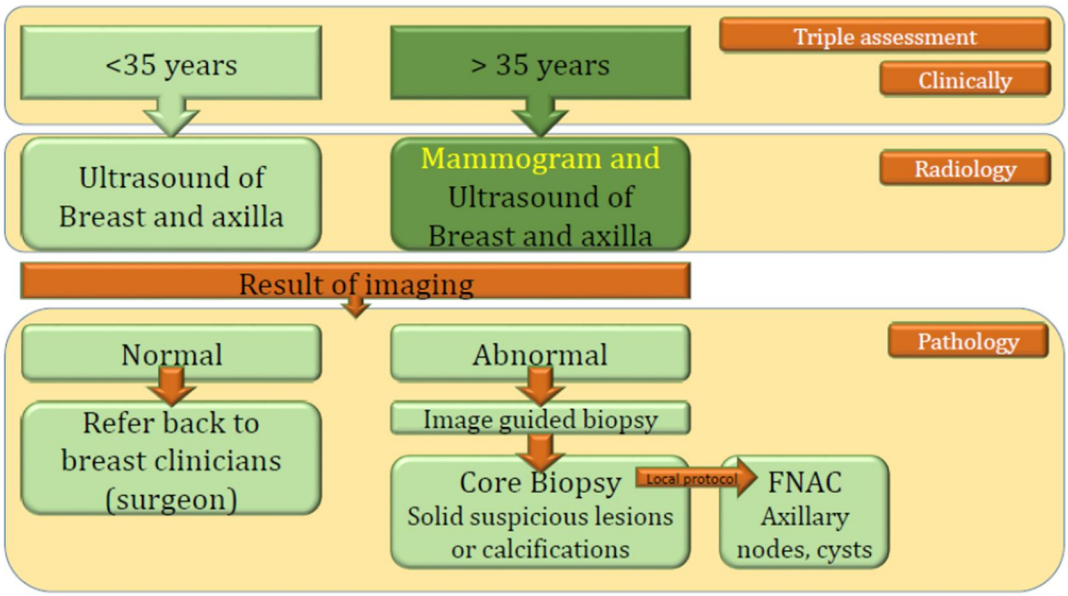
5.1. Consultations

5.1.1. All eligible patients should be diagnosed using a triple assessment.

5.1.2. The triple assessment is a diagnostic procedure that combines a clinical examination, imaging and histological confirmation. All three are a gold standard for the assessment of all patients presenting with symptomatic breast disease (NDOH,2017).

5.1.3. The figure below illustrates the triple assessment approach

Figure 1: Algorithm showing approach to diagnosis of early breast cancer (NDOH, 2017)



5.1.4. A multi-disciplinary team (MDT) is a mandatory part of breast cancer care in a number of countries. Ninety per cent of the respondents from Europe stated their MDTs met weekly to coordinate care for breast cancer patients (Saini et al., 2011).

5.1.5. The main perceived benefit of an MDT is that it provides consistent, continuous, coordinated, and cost-effective care to patients (Fleissig et al., 2006).

5.1.6. Medical professionals to be considered as part of the MDT includes GPs, surgeons, oncologist, radiologist, pathologists and allied health professionals as referred by the primary treating provider .

5.1.7. The role of general practitioners and family physicians in the early diagnosis and follow up care needs to be encouraged. This is evidenced by increased utilisation of primary health care service by breast cancer patients (Roorda, 2013).

5.1.8. Medical schemes are encouraged to establish funding models for MDTs in the management of breast cancer.

5.1.9. CMS recommends the below providers for the diagnosis of breast cancer:

Table 2: Recommended providers for diagnosis of early breast cancer

Discipline	Frequency of visit/consult
Registered nurse	1 – prompts referral after CBE
GP primary care	1
Surgeons	4
Oncologist	

5.2. Clinical examination

5.2.1. Every history taking in a patient complaining of breast lump should look at the age of the patient and take into great consideration the personal history of breast cancer as a risk factor for recurrence or a contralateral new primary tumour (Brennan & Houssami, 2012).

5.2.2. Family history of breast cancer in a first degree relative should also be sought in assessing risk.

5.2.3. A past history of a breast biopsy showing atypical hyperplasia, a family history of breast cancer, and other risk factors for breast cancer should be sought (Buccimazza, 2011).

5.2.4. Clinical examination includes bimanual palpation of the breasts and complete examination of tall systems (bones, liver, brain and lungs) to assess distant metastases.

5.3. Diagnostic workup and baseline investigations for early and locally advanced breast cancer

5.3.1. Laboratory investigation

Blood tests including liver function tests and renal function tests are PMB level of care for diagnostic workup of breast cancer as shown in table 3 below.

Table 3: Laboratory investigations for diagnostic workup

Description	Comment
Full blood count (FBC)	
Liver function tests · Total Bilirubin · Albumin · Alanine transminase (ALT) · Aspartate transminase (AST) Alkaline Phosphatase (ALP) Gamma-glutamyl transferase (GGT) Lactate dehydrogenase(LDH)	Baseline tests to assess possible liver involvement
Renal function tests · Urea	Assessment of possible obstructive renal symptoms

· Creatinine · Electrolytes · Calcium · Phosphates	
Follicle stimulating hormone	Only for peri-menopausal women
Oestradiol	
Luteinising hormone	

5.3.2. Diagnostic imaging

5.3.2.1. All patients with symptomatic disease should undergo imaging as part of triple assessment.

5.3.2.2. Imaging plays a crucial role for classifying and sampling both palpable and non-palpable breast abnormalities, as well as for defining the extent of breast tumours, both locally, loco-regionally, and at distant sites.

5.3.2.3. Diagnostic mammogram is indicated for most women with positive screening (Senkus et al., 2013).

5.3.2.4. Ultrasound is the appropriate first modality of imaging in women under 35 years, due to the increased breast density and absence of radiation in the modality (NDOH, 2017).

5.3.2.5. 2-D digital tomosynthesis where available can be an alternative to a diagnostic mammogram.

5.3.2.6. Ultrasound with mammogram has a better diagnostic value as compared to either test alone in symptomatic women above 35 years.

5.3.2.7. An MRI is recommended as PMB level of care if there is a chance that the surgical management may be changed (NDOH, 2017). The following should be considered:

- invasive lobular cancers
- suspicion of multi-centricity
- genetic high risk: BRCA1 or BRCA 2
- patients with breast implants
- diagnosis of recurrence post-BCS
- assessment after neo-adjuvant treatment
- extent of DCIS
- occult primary breast cancer

5.3.2.8. Positron Emission Tomography - Computed Tomography (PET-CT) scan, three dimensional mammographic ultrasound and computed tomography scan are not PMB level of care for diagnosis.

Table 4: Recommended imaging radiology for diagnosis of early and locally advanced breast cancer

Description	Comment
Diagnostic mammogram	Diagnostic mammogram is a gold standard.
2D- Digital breast tomosynthesis	As an alternative to diagnostic mammogram
Ultrasound	For women under 35 years due to breast density

Ultrasound with mammogram	Better diagnostic value as compared to either test alone in symptomatic women above 35 years, especially to assess the axillary nodes involvement which a mammogram will not do.
Magnetic resonance Imaging (MRI) of the breast	On motivation. Based on specific criteria
Exclusions	
Positron Emission Tomography - Computed Tomography (PET-CT) scan	
Three-dimensional mammographic ultrasound	
Computed tomography scan	

5.3.3. Diagnostic procedures

5.3.3.1. Fine needle aspiration cytology (FNAC) should be considered when an urgent diagnosis is required. FNAC are useful in the context of triple assessment of lesions and may support the benign clinical and radiologic appearances of a lesion. Difficulties encountered in FNAC comprise of sampling errors which may depend on the skill of the clinician, available real-time imaging modalities (e.g. ultrasound versus free-hand guidance) and access to rapid on-site screening. Although there are limitations, FNAC is still recommended as PMB level of care as it still has a role in the diagnostic workup of breast cancer (NDOH, 2017).

5.3.3.2. Core needle biopsy is recommended as the gold standard of diagnosis (NDOH, 2017). Core needle biopsy has been shown to reliably distinguish between in-situ and invasive cancers, allow evaluation of more histological, prognostic and predictive factors in breast cancer [17, 18].

5.3.3.3. Inflammatory breast cancer usually does not begin as a distinct lump, but instead as changes to the skin. A punch biopsy is often used to make the diagnosis in these circumstances.

5.3.3.4. Excision biopsy is considered a reference standard method of evaluating a suspicious breast lesion in specific situations. However, the availability of core needle biopsy has limited the role of open surgical biopsy, increasing patient risk of experiencing morbidities. Excision biopsy would be indicated in the following scenarios ((McLaughlin, Neal and Helvie, 2014):

- Atypical hyperplasia on core biopsy: approximately 20-30% will be upgraded to DCIS or invasive carcinoma with excision biopsy.
- When core biopsy results do not correlate with the clinical or radiological results
- If a new fibroadenoma is diagnosed in a woman over 40: (this doesn't include women having their first screening mammogram)

Table 5: Imaging radiology recommended as PMB level of care for early breast cancer

Description	Comment
Image guided core needle biopsy	Gold standard
Punch biopsy	For Pagets, inflammatory breast cancer and T4 lesion
Fine needle aspiration (FNA)	Not primary modality Will be followed up by core biopsy irrespective of the result for palpable breast lesions
Sentinel lymph biopsy	For women with operable breast cancer or ductal carcinoma in situ (DCIS) who will undergo mastectomy
Excision biopsy	Only in specific indications

5.3.4. Histological assessment

5.3.4.1. Tumour histological type and grading is PMB level of care.

5.3.4.2. Oestrogen receptor (ER), Progesterone receptor (PR), Ki67 index and human epidermal growth factor receptor 2 (HER2) status is determined on all breast cancers and breast cancer recurrences (Onitilo et al., 2009; Wolff et al., 2013).

5.3.4.3. Immunohistochemical staining can be performed on the core needle or excision biopsy.

5.3.4.4. Core biopsy specimens allow for assessment of hormone receptor and human epidermal growth factor receptor 2 (HER2) status to support decisions on adjuvant systemic treatment (Morrow et al., 2011).

5.3.4.5. Breast cancer is no longer viewed as a single disease, but rather as a series of diseases defined by biologic characteristics based on hormone receptor status and HER2 status. Tumours positive for either oestrogen or progesterone receptor can be considered hormone receptor (HR) positive. Breast cancer can be viewed as four sub-types, as follows: 1) HR positive/HER2 negative, 2) HR positive/HER2 positive, 3) HR negative/HER2 positive, 4) HR negative/HER2 negative

Table 6: Recommended histopathology for early and locally advanced breast cancer

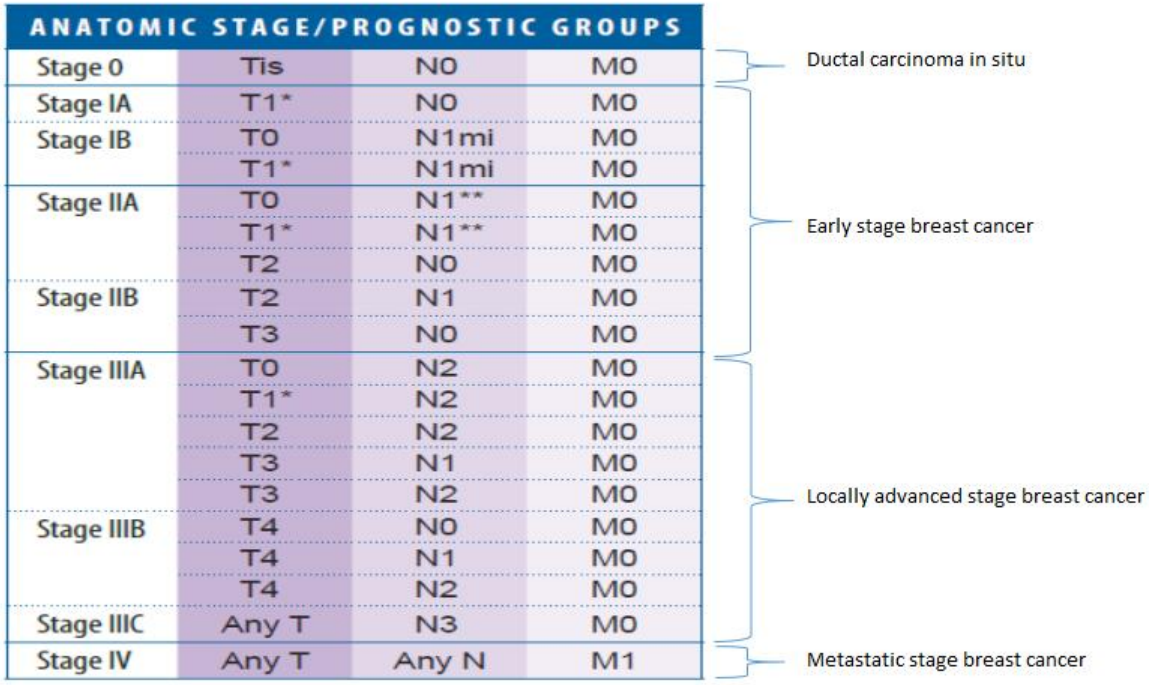
Description	Comment
Immunohistochemical staining.	ER, PR, HER2, Ki67
In situ hybridisation (ISH)	Only for HER2 2+

6. STAGING AND RISK ASSESSMENT OF EARLY AND LOCALLY ADVANCED BREAST CANCER

The TNM classification is a universally accepted system that is used to stage breast cancer. T refers to tumour size. For breast tumours bigger than 2cm, the T category changes. N refers to node' status, which changes as the tumour spreads into lymph nodes. M refers to metastasis, which indicates that the cancer has spread to places beyond the breast.

All breast cancer patients should adequately be assessed for metastatic disease at diagnosis. However, in early breast cancer, distant metastatic disease is uncommon. Early breast cancer is clinically defined as stage I disease or II or IIIA. Ductal carcinoma in situ (DCIS), is stage 0. The interventions described below are for patients who are asymptomatic. When patients are symptomatic, the interventions will be based on symptoms.

Figure 2: Anatomic staging of breast cancer, adapted from NDOH guidelines



ANATOMIC STAGE/PROGNOSTIC GROUPS				
Stage 0	Tis	N0	M0	Ductal carcinoma in situ
Stage IA	T1*	N0	M0	Early stage breast cancer
Stage IB	T0	N1mi	M0	
	T1*	N1mi	M0	
Stage IIA	T0	N1**	M0	
	T1*	N1**	M0	
	T2	N0	M0	
Stage IIB	T2	N1	M0	
	T3	N0	M0	
Stage IIIA	T0	N2	M0	Locally advanced stage breast cancer
	T1*	N2	M0	
	T2	N2	M0	
	T3	N1	M0	
	T3	N2	M0	
Stage IIIB	T4	N0	M0	
	T4	N1	M0	
	T4	N2	M0	
Stage IIIC	Any T	N3	M0	
Stage IV	Any T	Any N	M1	Metastatic stage breast cancer

6.1. Imaging radiology for staging and risk assessment of early and locally advanced breast cancer

6.1.1. Chest x-ray is recommended as PMB level of care.

6.1.2. Computed tomography (CT scan) chest and abdomen is recommended as the radiological tool of choice for staging and risk assessment in early breast cancer (NDOH, 2017).

6.1.3. CT scan is also considered for patients with clinically positive axillary nodes, large tumours, and clinical signs laboratory values suggesting metastases to determine metastatic regions.

6.1.4. Recommendations using advanced imaging technology, such as positron-emission tomography (PET), CT, and radionuclide bone scans, for patients with early-stage breast cancer is not a PMB.

Table 7: Recommended imaging for staging and risk assessment

Description	Indication
Chest x-ray	
Liver ultrasound	For locally advanced disease
Magnetic Resonance Imaging (MRI)	Only in specific instances. MRI may be considered in: (a) invasive lobular cancers (b) suspicion of multi-centricity (c) genetic high risk: BRCA1or BRCA 2 (d) patients with breast implants

	(e) diagnosis of recurrence post-BCS (f) assessment after neo-adjuvant treatment (g) extent of DCIS (h) occult primary breast cancer
Computed tomography (CT scan) chest and abdomen	Gold standard Positive axillary nodes, large tumors, and clinical signs laboratory values suggesting metastases to determine metastatic regions
Exclusions	
Bone scan	Not for early breast cancer. Only appropriate for locally recurrent and advanced disease
Positron emission tomography–computed tomography (FDG-PET/CT)	Only when conventional methods are not conclusive in determining metastases

7. TREATMENT OF BREAST CANCER

7.1. Surgery to the breast for early breast cancer

7.1.1. Breast conservation surgery (BCS) otherwise known as: lumpectomy, wide local excision, quadrantectomy or partial mastectomy for DCIS or invasive ductal carcinoma is the standard procedure for early breast cancer, unless contraindicated.

7.1.2. Mastectomy is required if there are absolute contraindications to BCS. Contraindications to BCS are:

(a) poor ratio of tumour size to the size of the breast

(b) location of the tumour would result in unacceptable cosmesis

(c) collagen vascular disease (scleroderma and systemic lupus erythematosis)

(d) conditions where local radiotherapy is contraindicated (such as previous radiotherapy at the site or connective tissue disease)

(e) multi-centric disease, clinically or radiologically

(f) persistent positive margins post-breast conserving surgery

(g)radiotherapy not available or acceptable to patient

(h)pregnancy, although such surgery may be done during the third trimester with irradiation following delivery (NDOH, 2017).

7.1.3. BCS is generally given with post-operative radiotherapy (Giordano, 2003; NDOH, 2017).

7.1.4. Tumour size, axillary node involvement, histological grade and type are no longer considered valid reasons for not performing breast-conserving surgery. These, and other poor prognostic factors, predict the risk of distant failure, not local recurrence, and may indicate the need for systemic therapy, but are not indications for mastectomy (NDOH, 2017).

7.1.5. The indications for surgery of the breast are independent from the indications for axillary surgery.

7.2. Indications for a mastectomy

A mastectomy can be indicated for oncological, personal and/ or cosmetic reasons as detailed in the table that follows.

<table>
<tr><th colspan="2">Oncological reasons</th></tr>
<tr><td>Absolute indications:
· Locally advanced breast cancer
· Muticentricity of either the invasive carcinoma or DCIS
· Wide spread DCIS around the index lesion
· Strong family history or known carrier of BRCA gene</td><td>Relative indications
· Tumours >5cm
· Cancers that are not detected radiologically</td></tr>
<tr><th colspan="2">Patient reasons</th></tr>
<tr><td colspan="2">· Personal preference
· If a patient is not able to have radiotherapy</td></tr>
<tr><th colspan="2">Cosmetic reasons</th></tr>
<tr><td colspan="2">· If more that 20% of the breast will be removed
· If the NAC (nipple areolar complex) has to be removed, the patient may request a mastectomy</td></tr>
</table>

7.3. Indications for contralateral prophylactic mastectomy (CPM)

CPM is the removal of a healthy breast in a patient undergoing mastectomy. This may also be due to oncological and/ or cosmetic reasons.

Oncological reasons
· Patient with a BRCA mutation · A very strong family history with no known mutation · A lifelong risk of developing breast cancer in the contralateral breast >25%
Cosmetic reasons
Women with large pendulous breasts may have problems wearing an external prosthesis: this should be judged on an individual basis with supplementary photographs supplied
Patient reasons
Symmetrisation

7.4. Breast reconstruction

7.4.1. Breast reconstruction post mastectomy is recommended as PMB level of care.

7.4.2. Breast reconstruction done immediately after mastectomy improves well-being and quality of life (QoL) for women undergoing mastectomy for breast cancer. Although many factors may influence

QoL, patients with immediate reconstruction after breast cancer surgery reported the same emotional wellbeing and physical role functioning as that of the normal population at one year (NDOH, 2017).

7.4.3. Reconstruction may be done as an immediate or delayed procedure. Alternatively, it may be done as a two-stage procedure with placement of an expander.

7.4.4. Reconstruction may be done using a prosthesis or the patient's own tissue (Latissimus Dorsi muscle). The abdominal fat may be used as part of a TRAM procedure or DIEP flap (microsurgery).

7.4.5. Nipple-areola complex (NAC) reconstruction should be considered as part of the reconstruction

7.5. Sentinel lymph node biopsy (SLNB)

Axillary lymph nodal status remains an important prognostic factor because treatment of breast cancer is influenced by the presence of and number of axillary lymph nodes involved. Most women with ductal carcinoma in situ (DCIS) do not require assessment of the axillary nodes, particularly if they are undergoing breast-conserving therapy (NDOH, 2017). However, women with DCIS may be candidates for SLN mapping if they are undergoing mastectomy, because the performance of SLNB will be impossible at a later time if invasive disease is found (NDOH, 2017).

7.5.1. Indications for a SLNB for invasive carcinoma (Miyake et al., 2011):

- Patients with no evidence of axillary disease clinically or radiologically
- Patients with a suspicious lymph node radiologically that has been tested for malignancy and found to be reactive

7.5.2. Indications for a SLNB in patients with DCIS (Giordano, 2003; NDOH, 2017):

- Patients with no evidence of axillary disease, clinically or radiologically
- Any patient having a mastectomy
- Any patient having breast conservation surgery (BCS) with one of the following:
- Palpable mass
- High grade DCIS
- Comedo necrosis
- An area of DCIS>4 cm

7.5.3. SLNB can be performed using radioactive dye (Tc99m) or iron oxide. Additional isosulfan blue dye should be used for selective cases:

- After neo-adjuvant chemotherapy
- If a SLNB is performed for a second primary on the ipsilateral side

7.5.4. Intraoperative assessment of SLN is standard of care for patients undergoing a mastectomy and may also be clinically indicated for patients undergoing BCS.

8. SYSTEMIC THERAPY IN EARLY STAGE BREAST CANCER

In early stage breast cancer, long term survival is governed by the control of micro-metastatic disease; which may occur very early in the evolution of the malignancy (McArthur & Hudis, 2007; Sukel et al., 2008). Multiple randomised controlled trials have demonstrated both a local control and overall survival benefit from the use of systemic therapy (given either before, or shortly after, definitive surgery for breast cancer) (McArthur & Hudis, 2007; Francis et al., 2015; NDOH, 2017). The indications for, and type of, adjuvant systemic therapy is based on the biological subtype of the primary tumour; the risk of recurrence; patient comorbidities and patient preferences. Adjuvant systemic therapy may involve one, or a combination of, the following options: endocrine therapy, chemotherapy and biological therapies.

8.1.1. Current recommendations on the duration of hormonal therapy depend on the type of blockade used and the risk of recurrence. Extended adjuvant therapy (i.e. beyond five years) is generally restricted to those patients with high risk disease. Acceptable options include (NDOH, 2017):

- AI for 5yrs (ATAC and BIG-19-8 studies)
- Tamoxifen for two to three years followed by AI for two to three years or vice versa (TEAM and IES study)
- Tamoxifen for 10 years (ATLAS study)

8.1.2. Gonadotropin-releasing hormone (GnrH) agonist are recommended for patients who are intolerant to Tamoxifen.

Table 8: Adjuvant endocrine therapy recommended as PMB level of care

Adjuvant endocrine options for post-menopausal women	Adjuvant endocrine options for premenopausal women include:
(a) Selective Oestrogen-Receptor Modulators (SERMs), e.g. Tamoxifen (b) Aromatase Inhibitors (steroidal and non-steroidal) (are PMBs) e.g. letrozole, anastrozole, exemestane (c) Tamoxifen followed by an Aromatase Inhibitor or Aromatase Inhibitor followed by Tamoxifen (so called "switching" strategy) (NDOH, 2017)	(a) SERMs – Tamoxifen

8.2. Adjuvant endocrine therapy

8.2.1. If adjuvant chemotherapy is considered, a multidrug regimen should be used. Anthracycline and taxane based regimens have shown superiority to older chemotherapy regimens especially in high-risk patients and are recommended as PMB level of care (Bedard et al., 2010; Hudis & Gianni, 2011).

8.2.2. Anthracycline and taxane based regimen may not be appropriate for low-risk patients and patients with cardiac and other comorbidities in which case, older chemotherapy such as Methotrexate, 5FU, Cyclophosphamide may play a role and also recommended as PMB level of care (NDOH, 2017).

8.2.3. In BRCA1 mutated patients, the inclusion of a platinum agent may be considered, but this is not currently recommended for all triple negative breast cancers (Irmejs et al., 2017; NDOH, 2017).

8.3. Adjuvant biological therapy

8.3.1. Due to the high risk of micro-metastatic disease associated with HER2+ tumours (even small, node negative tumours), adjuvant trastuzumab based therapy should be considered in all HER2+ tumours (NDOH, 2017).

8.3.2. Adjuvant trastuzumab is not recommended in either low-risk, negative patients or patients who have not received adjuvant chemotherapy.

8.3.3. Due to overlapping cardiotoxicities of anthracyclines and trastuzumab, the benefit of trastuzumab is greater if given concurrently with adjuvant chemotherapy (as opposed to sequentially).

8.3.4. In line with NDoH recommendations, the CMS recommends the use of trastuzumab (given every three weeks) for one year in the adjuvant treatment of HER-2 positive early stage breast cancer. The exclusions are:

- Patients with locally advanced or metastatic breast cancer
- T1N0M0
- Patients with clinically significant comorbid diseases
- Cardiac ejection fraction < 55%
- Significant hepatic or renal dysfunction
- ECOG Performance Status > 1
- Patients who have only received adjuvant hormonal therapy with no adjuvant chemotherapy
- Patients who are above 65 years
- Pregnancy or lactation

Table 9: Summary of adjuvant systemic therapy recommended as PMB level of care

Description	Comment
Taxanes	
Methotrexate	
5FU	
Anthracyclines	

Cyclophosphamide	
Platinum	
Trastuzumab	

8.4. Neo-adjuvant systemic therapy

8.4.1. Potential advantages of neo-adjuvant systemic therapy include:

- down-staging of locally advanced tumours, thereby rendering them amenable to surgical resection
- down-staging tumours to facilitate breast conserving surgery
- evaluation of in vivo chemo-sensitivity of the tumour

8.4.2. Chemotherapy is preferred over hormonal therapy in the neo-adjuvant setting except patients who are strongly ER positive and in which chemotherapy is contraindicated, then hormonal therapy may be considered.

8.4.3. Chemotherapy regimens (Anthracycline, Platinum, Taxane, Methotrexate, 5FU, Cyclophosphamide) used in the adjuvant setting can be used in the neo-adjuvant setting and as such are PMB level of care.

9. RADIOTHERAPY

9.1. Three-Dimensional Conformal Radiotherapy (3D - CRT) is recommended as PMB level of care.

9.2. For patients requiring whole breast irradiation, the dose should be either hypofractionated, 40 - 42.5Gy in 15 - 16# or conventionally fractionated, 45 - 50Gy in 25 - 28 #. The hypofractionated schedule is preferred

9.3. For patients requiring post-mastectomy- or/and regional nodal irradiation, the recommended dose is conventionally fractionated, 45 - 50Gy in 25 – 28

9.4. A boost to the tumour bed is recommended to those patients at higher risk of recurrence and this is typically in the range of 10 - 16Gy in 4 - 8#.

9.5. IMRT (Intensity-Modulated Radiotherapy) is recommended as PMB level of care in selected patients.

10. MANAGEMENT OF LOCALLY ADVANCED DISEASE

Locally advanced breast cancer (LABC) is a heterogeneous group of invasive cancers, from slow growing to rapidly proliferating and aggressive tumours, characterised clinically by size, features suggesting infiltration of chest wall or skin by tumour, and/ or nodal status. This is a common stage of presentation in breast cancer patients in South Africa. LABC includes cancer with:

- large size (> 5 cm) TNM stage IIIA: T3 with any N
- fixed or matted axillary: TNM stage IIIA: N2 with any T1-3

- skin ulceration or satellite nodules, peau d'orange or chest wall involvement
- inflammatory breast cancer
- supra-clavicular nodes (N3)
- these patients do not have distant metastatic disease

The prognostic factors for locally advanced tumours are similar to the prognostic factors for early stage breast cancer, with lymph node status and tumour size having the strongest effects on survival (Singletary, 2002).

The treatment of locally advanced breast cancer includes a combination of systemic chemotherapy, surgery, hormonal therapy and radiotherapy to optimise the chance of cure (Giordano, 2003; NDOH, 2017).

10.1. Neo-adjuvant chemotherapy

10.1.1. The main goal of neo-adjuvant chemotherapy is to enhance surgical options and breast conservation in women with stage 2 or 3 breast cancer who have inoperable breast cancer on presentation (Giordano, 2003. NDOH, 2017).

10.1.2. The use of systemic chemotherapy has become standard and has substantially improved the prognosis of locally advanced breast cancer (Giordano, 2003).

10.1.3. The Early Breast Cancer Trialists' Group established the superiority of anthracycline-based chemotherapy regimens (Baum, 1998). For patients with node-positive breast cancer, the addition of a taxane to an anthracycline-based regimen improves overall survival (Henderson, et al 2001).

10.1.4. Therefore, Taxanes, Methotrexate, 5FU, Anthracyclines, Cyclophosphamide, Platinum based are all recommended as PMB level of care in the neo-adjuvant setting for locally advanced breast cancer.

10.2. Hormonal therapy

10.2.1. Tamoxifen is not recommended as PMB level care in the neo-adjuvant setting

10.2.2. The following are the accepted hormonal therapy for locally advanced breast cancer in the neo-adjuvant setting and are accepted PMB level of care.

Table 10: Endocrine therapy in locally advanced breast cancer

Description	Comment
Aromatase inhibitors - Anastrozole - Letrozole - Exemestane	Postmenopausal women with ER-positive early invasive breast cancer
LHRH Agonist + Aromatase Inhibitors	Premenopausal patient where aromatase inhibitors is indicated

11. FOLLOW UP CARE

11.1.1. The purpose of long term follow up is to monitor disease progression, to assess and encourage adherence to adjuvant endocrine therapy, to encourage active lifestyle and maintenance of ideal body weight (20-25 BMI) and to manage chemotherapeutic adverse events.

11.1.2. Follow-up of patients with early and locally advanced disease includes interval history and physical examinations every three (3) to four (4) months for the first two (2) to three (3) years. This is imperative to monitor tolerance and compliance of hormonal therapy. This is extended to six (6) to twelve (12) months, up to five (5) years and then annually thereafter.

11.1.3. Mammography every 12 months is PMB level of care.

11.1.4. Annual gynaecologic assessment every 12 months if uterus present is PMB level of care for women on Tamoxifen for the duration of Tamoxifen use.

11.1.5. Women on an aromatase inhibitor or who experience ovarian failure secondary to treatment are monitored for bone health with a bone mineral density determination at baseline and periodically thereafter.

11.1.6. Bisphosphonates are PMB level of care for patients with reduced bone mineral density.

12. BEST SUPPORTIVE CARE

CMS developed a PMB definition document on best supportive care for gastrointestinal oncology conditions (available at https://www.medicalschemes.com/files/PMB%20Definition%20Project/BestSupportivCare%20GIT3103docx.pdf). The document contains some guidance for the management of side effects of chemotherapy, which can be applied across all oncology conditions, i.e. management of nausea and vomiting, management of diarrhea and pain management. Other rehabilitation interventions specific to early and locally advanced breast cancer should be considered for funding when referred by the primary treating provider.

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