Breast Cancer

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According to the CANSA statistics, breast cancer is the most common cancer affecting South African women.

Unfortunately, the national registry has been fraught with challenges, and this has hindered accurate assessment of the burden of disease. This is currently in the process of being updated with NHLS and the Department of Health.

South Africa is among the most unequal societies in the world. This is apparent in the disparate care of patients in the private sector compared to those in the public sector. Breast cancer is unfortunately no different, with the majority of women in the private sector presenting with early stage breast cancer, where the treatment intent is usually curative, compared to the public sector, where women present with advanced stage disease, with subsequent poorer outcomes, against the backdrop of limited resources.

The most common presentation of breast cancer is the finding of a breast lump, or axillary lymphadenopathy. Other symptoms may include thickened skin with an orange-peel appearance (*peau d'orange*), an enlarged node at the base of the neck, a bloody nipple discharge, or ulceration of the breast and surrounding tissues.

The risk of breast cancer increases with age. However, increasingly younger patients are being diagnosed. Only 10-15% of breast cancers are as a result of a genetic aberration, meaning that the majority of breast cancers are sporadic.[1]

The diagnosis is made on a mammogram combined with a breast ultrasound. A core biopsy of the breast mass, rather than a fine-needle aspiration (FNA) is preferred. Core biopsy allows for more accurate assessment of the biology of the cancer, which is important in determining the treatment approach.

STAGING

Breast cancer is staged according to the TNM criteria, which takes into account tumour size, locoregional nodal involvement, and the presence or absence of distant metastasis (see Table 1).

By definition, early breast cancer is cancer that is limited to the breast and/or axilla. However, a tumour in excess of 5 cm, involvement of multiple locoregional lymph nodes, skin changes and/or invasion of the chest wall imply the diagnosis of locally advanced breast cancer.

TUMOUR BIOLOGY

In broad terms, breast cancer biology is divided into *favourable vs unfavourable biology*. The surrogate for this is the IHC 4 test, which includes assessment of oestrogen receptors (ER), progesterone receptors (PR), HER2 neu expression, and Ki67.

HER2 neu overexpression is found in 20-30% of all breast cancers, and portends a poorer prognosis with a propensity for distant spread.

The diagnosis is made on immunohistochemistry, and an equivocal result is confirmed by SISH and reported according the College of American Pathologists (CAP).

Immunohistochemistry is a surrogate for profiling of tumour biology which is best characterised by tumour micro-arrays, which are not readily available.

Tumour biology is divided into luminal A-like, luminal B-like, HER2-enriched, and basal-like.

Luminal A cancers tend to be ER/PR-positive, HER2-negative, with a low Ki 67 of less than or equal to 14%.

Luminal B-like cancers are ER-positive, PR-negative, HER2-negative, with a high Ki 67 of >14%.

HER2-enriched are HER2-overexpressing, and the basal-like cancers include, but are not limited to, triple-negative breast

Table 1. Breast carcinomas TNM staging

Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
Tis (DCIS)	Ductal carcinoma *in situ*
Tis (LCIS)	Lobular carcinoma *in situ*
Tis (Paget's)	Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorised based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted.
T1	Tumour ≤20 mm in greatest dimension
T1mi	Tumour ≤1 mm in greatest dimension
T1a	Tumour >1 mm but ≤5 mm in greatest dimension
T1b	Tumour >5 mm but ≤10 mm in greatest dimension
T1c	Tumour >10 mm but ≤20 mm in greatest dimension
T2	Tumour >20 mm but ≤50 mm in greatest dimension
T3	Tumour >50 mm in greatest dimension
T4	Tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or oedema (including *peau d'orange*) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph-node metastases
N1	Metastases to moveable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph-node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph-node metastases

Regional lymph nodes (N) (cont.)	
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph-node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph-node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph-node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)
pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0	No regional lymph-node metastasis identified histologically
pN0(i-)	No regional lymph-node metastases histologically, negative immunohistochemistry (IHC)
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2mm (detected by H&E or IHC including isolated tumour-cell clusters (ITC))
pN0mol-)	No regional lymph-node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PCR), but no regional lymph-node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph-node biopsy, but not clinically detected
pN1mi	Micrometastases (greater that 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1-3 axillary lymph nodes, at least one metastasis greater than 2 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph-node biopsy, but not clinically detected
pN1c	Metastases in 1-3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph-node biopsy, but not clinically detected
pN2	Metastases in 4-9 axillary lymph nodes; or in clinically detected internal mammary lymph nodes in the *absence* of axillary lymph-node metastases
pN2a	Metastases in 4-9 axillary lymph nodes (at least one tumour deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes in the *absence* of axillary lymph-node metastases

Regional lymph nodes (N) (cont.)	
pN3	Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph-node biopsy, but not clinically detected, or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumour deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph-node biopsy, but not clinically detected
pN3c	Metastases in ipsilateral supraclavicular lymph nodes
Distant metastasis (M)	
MO	No clinical or radiologic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly- or microscopically-detected tumour cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Anatomic stage/Prognostic groups			
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0
	T1	N1mi	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0

cancer, a particularly aggressive type of breast cancer.

INITIAL WORK-UP AFTER A BREAST-CANCER DIAGNOSIS

Staging tests that should be performed after a breast-cancer diagnosis are a chest x-ray, abdominal ultrasound, blood tests (which must include a liver function test and a calcium level). Tumour markers are not standard tests, but may aid in the overall assessment and monitoring of a patient following diagnosis.

INDICATIONS FOR AN MRI BREAST

An MRI of the breast is not a standard imaging technique in all breast-cancer patients. Doing an MRI pre-operatively increased mastectomy rates and was not shown to reduce re-excision rates.[2] Furthermore, there was no difference in eight-year local recurrence rates (97% *vs* 95%) or disease-free survival rates (89 *vs* 93%)[3] in patients in whom preoperative MRI had been utilised, compared to those who did not undergo preoperative MRI, based on a meta-analysis of in excess of 3 000 patients with newly diagnosed breast cancer.

Indications for an MRI of the breast include lobular cancer, BRCA-positive patients, or patients harbouring other high-risk mutations and multifocal/multicentric breast cancer. Ongoing clinical trials are evaluating the use of breast MRI to assess response to neoadjuvant chemotherapy.

TREATMENT MODALITIES FOR NON-METASTATIC BREAST CANCER

Treatment of non-metastatic breast cancer is best managed in a multidisciplinary team comprising radiologists, breast surgeons, plastic surgeons, medical and radiation oncologists, as well as allied services that include lymphoedema therapists, psychologists and dieticians.

The treatment consists of surgery, which could be a lumpectomy, mastectomy or bilateral mastectomy, chemotherapy with or without HER2-blockade in appropriate patients (HER2-positive), radiation treatment and hormonal blockade in patients whose tumours are endocrine-responsive.

Treatment for breast cancer is personalised, based on patient factors including comorbidities, tumour factors (biology), staging, and so on. A "one-size-fits-all" approach is not appropriate, and each case needs to be evaluated looking at the factors mentioned above.

SURGERY

The choice of surgery is influenced by the size of the tumour, the location within the breast, the presence or absence of deleterious mutations, and patient preferences.

The timing of surgery is determined by the initial stage of the cancer, tumour size, and the use of neoadjuvant chemotherapy.

The trend towards bilateral mastectomies has been increasing across the globe, fuelled by media awareness and celebrities who have undergone this procedure. Contralateral prophylactic mastectomy does not confer a survival benefit, except in patients with a hereditary breast cancer.[4]

CHEMOTHERAPY

Not all patients with breast cancer require chemotherapy. This is based largely on disease biology and chemotherapy sensitivity of a particular type of breast cancer, the intensity of oestrogen receptor and progesterone receptor expression, and HER2 neu status.

Indications for neoadjuvant chemotherapy

Locally advanced breast cancer – Stage IIB-IIIC tumours (see Table 1) must be considered for neoadjuvant chemotherapy, as they are often too large for upfront resection. In addition, smaller tumours with an unfavourable tumour-to-breast ratio are considered for neoadjuvant therapy, as this may improve the likelihood of breast conservation.

Smaller tumours with an unfavourable biology (triple-negative breast cancer, HER2-overexpressors) are often treated with neoadjuvant chemotherapy, as these tumours are chemotherapy-sensitive, and the patients will be candidates

for chemotherapy at some stage in their treatment course.

A large meta-analysis by the Early Breast Trialist Collaborative Group, which included 4 756 patients from 10 clinical trials, found an increased rate of breast conservation among patients treated with neoadjuvant chemotherapy (65% *vs* 49%). There was no difference in the risk of breast-cancer recurrence between the neoadjuvant group and the adjuvant chemotherapy group (15-year rate of 38.2% *vs* 38%) and breast-cancer mortality (34.4% *versus* 33.7%)[5].

The choice of chemotherapy depends on patient factors and physician preferences. The chemotherapy regimens used in this setting are the same as those used in the adjuvant setting.

These largely comprise anthracycline-containing *vs* non-anthracycline-containing regimens.

The most common neoadjuvant chemotherapy schedule in HER2-negative breast cancer is adriamycin, cyclophosphamide 3-weekly x 4, followed by weekly paclitaxel x 12 weeks, or 3-weekly docetaxel x 4.

In patients who cannot tolerate an anthracycline, TC (docetaxel, cyclophosphamide) administered 3-weekly x 4 is a good alternative.

20-30% of cancers overexpress HER2 neu protein. This makes the cancers more aggressive, with a higher propensity for distant spread.

The addition of trastuzumab to neoadjuvant and subsequently adjuvant therapy increases complete pathological response rates, which in turn have been linked to a survival benefit in breast cancer.[6] The duration of trastuzumab is a total of one year.

In 2013, the FDA approved pertuzumab, an anti-HER2 monoclonal antibody that binds HER2/HER3 heterodimers, which is believed to be an important mechanism that is responsible for trastuzumab resistance. The combination of pertuzumab to trastuzumab and chemotherapy improves complete pathological response rates compared to trastuzumab and chemotherapy alone.[7]

ADJUVANT CHEMOTHERAPY

Adjuvant chemotherapy is chemotherapy administered following definitive surgery for breast cancer, with the aim of reducing the risk of local and distant breast-cancer recurrence.

The indications for adjuvant chemotherapy have shifted from the use of clinicpathological factors to genomic profiling of an individual cancer.[8]

The traditional indications for chemotherapy were tumour size of more than 2 cm, positive axillary nodes, triple-negative breast cancer, HER2-positive breast cancer, the presence of lymphovascular invasion, and young age.

Recently, however, a number of genomic profiling tests have received FDA approval, and these quantify the risk of breast-cancer recurrence with or without chemotherapy. In South Africa, two tests, namely the Oncotype DX test and the Mammaprint tests, are in use. The tests are reported as a risk group (low-risk, intermediate-risk or high-risk for Oncotype DX, or low-risk *vs* high-risk for Mammaprint.)

The low-risk group patients do not attain a benefit from chemotherapy, and the high-risk group are managed with chemotherapy. An ongoing clinical trial is underway to assess the benefit of chemotherapy in the intermediate-risk group where Oncotype Dx test is used. (TailoR$_x$)

The tests are indicated in endocrine-responsive, HER2-negative breast cancer, including patients with 1-3 positive axillary nodes, and assist the clinician with decision-making pertaining to the additional benefit of chemotherapy in addition to hormone blockade in patients who have undergone definitive surgery for breast cancer.

This has challenged the traditional indications for chemotherapy, sparing patients from the short- and long-term effects of chemotherapy. Clinical trials have indicated that the use of genomic profiling changes clinician opinion in approximately 25%-30% of cases.

HORMONAL BLOCKADE

Patients whose cancers are hormone-responsive are candidates for adjuvant

hormonal blockade with tamoxifen or aromatase inhibitors. Tamoxifen is used in premenopausal patients with or without luteinising hormone-releasing hormone agonists (LHRH), and aromatase inhibitors are mainly indicated for postmenopausal women. Aromatase inhibitors can also be used in high-risk premenopausal women combined with an LHRH agonist.[9]

In this instance, high-risk disease includes node-positive patients, those who were deemed to require adjuvant chemotherapy, high grade and presence of lymphovascular invasion.

Clinical trials have also supported consideration for 10 years compared to five years of hormonal blockade. This is on the basis of an increased risk of recurrence up to 15 years following completion of five years of adjuvant endocrine therapy.[10] Two large trials have demonstrated the superiority of 10 years *vs* five years of hormonal blockade with tamoxifen.[11] There have been conflicting data on 10 years of aromatase inhibition.

RADIATION

The indications for postoperative radiation are a tumour size of 5 cm or more, positive axillary nodes (including patients with 1-3 positive nodes), and patients who have undergone a lumpectomy.

Radiation can be omitted in elderly women (over 70) following a lumpectomy for a small luminal A-like cancer.

TREATMENT OF METASTATIC BREAST CANCER

The median survival for metastatic breast cancer is two to three years, with 25% of patients being alive at five years. The intention of treatment is to increase survival with a good quality of life. The choice of treatment depends on disease biology, patient factors, tumour burden (including the presence or absence of a visceral crisis), previous treatment, and the rate of disease progression (see Table 2). Patients with a visceral crisis should be treated with combination chemotherapy, provided that their performance status permits.

Table 2. Factors determining choice of treatment in ABC

Disease characteristics	Patient characteristics
Prior adjuvant chemotherapy	Patient preferences (e.g., oral *vs* IV treatment)
Disease burden	Socio-economic and psychological factors (e.g., distance between home and hospital; costs)
Prior therapies and response	Age, PS, comorbidities
Aggressiveness of disease	Menopausal status
ER/PgR, HER2 receptor status	
Disease-free interval	

According to the ABC3 guidelines, visceral crisis is defined as "severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases, but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible."

The first-line treatment for endocrine-responsive metastatic breast cancer is therefore hormonal blockade, and chemotherapy should be considered only once the hormonal-blockade treatment options have been exhausted. It is important to emphasise that the presence of metastatic disease is not an indication for systemic chemotherapy.

A new class of drugs, CDK 4/6 inhibitors, has received regulatory approval in combination with aromatase inhibitors in first-line metastatic breast cancer, or with fulvestrant, an anti-oestrogen that downregulates

the oestrogen receptor (ER) in previously treated patients.

CDK pathway is overactive in a number of cancers, including breast cancer. CDK inhibition leads to activation of the tumour-suppressor gene, Rb, leading to cell-cycle arrest.

For patients in whom chemotherapy is deemed appropriate, single-agent chemotherapy is preferred over combination chemotherapy (in the absence of a visceral crisis), as there is no prospective evidence to demonstrate the survival benefit of combination chemotherapy over single-agent sequential chemotherapy.

Chemotherapy options to be considered for this indication include anthracyclines, taxanes, capecitabine, vinorelbine, gemcitabine, eribulin and cisplatin, among others. The final choice of drug depends on toxicities, previous therapies, and patient preferences.

MALE BREAST CANCER

Male breast cancer is a rare disease, and accounts for 0.5-1% of all breast cancers diagnosed in the US.

The treatment recommendations for male breast cancer are adapted from the guidelines for the management of female breast cancers, as there is a paucity of clinical trials in this patient population.

Male breast cancers are higher in patients who harbour a genetic mutation of BRCA 2 more than BRCA 1. BRCA 2-positive men have a 6% absolute lifetime risk of developing breast cancer, significantly higher than the average man. Other non-BRCA mutations, such as PTEN, PALB2, P53, may also be implicated.

In addition, conditions that increase the oestrogen ratio, e.g., obesity, gynaecomastia, alcohol, marijuana use, and Klinefelter syndrome may increase the risk of male breast cancer.

Patients with non-metastatic breast cancer are managed with surgery, radiation therapy, and adjuvant hormonal blockade with tamoxifen, if indicated. The majority of male breast cancers are endocrine-responsive. There are insufficient data for the use of aromatase inhibitors in male breast cancer, and those patients treated with aromatase inhibitors must either have undergone an orchidectomy, or be treated with an LHRH agonist.

The approach to treatment of metastatic breast cancer in males is similar to the treatment in females.

Overall, the prognosis of males with breast cancer is comparable to females.

WHEN TO REFER

Any patient who presents with a breast lump must be referred for investigation with a mammogram, and at least a breast ultrasound, regardless of age.

A core biopsy, rather than a fine-needle aspiration (FNA), must be performed on the breast mass, and any axillary glands must be cytologically evaluated.

The histology must contain the following:

- The diagnosis
- Grade of the tumour
- Subtype (lobular vs ductal)
- The immnunohistochemistry, that includes oestrogen receptor, progesterone receptor expression, HER2 neu expression and Ki 67

Once the diagnosis is made, the patient should be referred to a breast surgeon, preferably within a multidisciplinary team for further management.

REFERENCES

1. Couch FJ, Nathanson KL, Offit K. Two decades after BRCA: setting paradigms in personalized cancer care and prevention. *Science*. 2014;343(6178):1466. .
2. Houssami N, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: meta-analysis of surgical outcomes. *Ann Surg*. 2013 Feb;257(2):249-55. Doi: 10.1097/SLA.0b013e31827a8d17.
3. Houssami N, Turner R, *et al*. An individual person data meta-analysis of preoperative magnetic resonance imaging and breast cancer recurrence. *J Clin Oncol*. 2014 Feb;32(5):392-401.
4. Fayanju OM, Stoll CR, *et al*. Contralateral prophylactic mastectomy after unilateral breast cancer: a systematic review and meta-analysis. *Ann Surg*. 2014;260(6):1000.
5. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for

neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol*. 2018;19(1):27. Epub 2017 Dec 11.

6. Cortazar P, Zhang L, *et al*. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014 Jul;384(9938):164-72.
7. Gianni L, Pienkowski T, *et al*. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2012;13(1):25.
8. Geffen S, Abu-Ghanem N, *et al*. The impact of the 21-gene recurrence score assay on decision making about adjuvant chemotherapy in early-stage estrogen-receptor-positive breast cancer in an oncology practice with a unified treatment policy. *Annals of Oncology*. 2011 Nov;22 (11):2381-2386.
9. Pagani O, Regan MM, *et al*. International Breast Cancer Study Group. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. TEXT and SOFT Investigators. *N Engl J Med*. 2014;371(2):107.
10. Pan H, Gray R, *et al*. 20-Year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. EBCTCG *N Engl J Med*. 2017;377(19):1836.
11. Davies C, Pan H, *et al*. Adjuvant tamoxifen: longer against shorter (ATLAS). *Lancet*. 2013;381(9869):805.