30

Breast Cancer

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INTRODUCTION

Cancer in developing countries was not considered a priority until recently. Since 'non-communicable diseases' were the major topic at the general assembly of the United Nations (UN) in September 2011 this opinion has definitely changed within the international community. The four main non-communicable diseases – cardiovascular disease, chronic lung diseases, diabetes and cancer – kill three in five people worldwide causing great socio-economic harm particularly in developing nations.

Cancer of the breast is the most common cancer in women worldwide. Every year 1.6 million women are newly diagnosed with breast cancer globally and around 425,000 die of the disease. Breast cancer accounts for 23% of all female cancers globally and shows a geographic variation in incidence and death rates. Age-standardized incidence rates are 39 per 100,000 worldwide – 27 in less and 66 per 100,000 in the more developed regions. Out of the 425,000 global annual deaths from breast cancer, however, 68,000 are young women from developing countries[1]. Survival is highly dependent on resources available – there is a strong association between gross domestic product and survival[2].

As you can see, breast cancer is a public health problem; it attacks women in their most productive years of life. Breast cancer can be cured with limited resources if detected early, but treating advanced-stage disease is expensive and outcome is often poor. Early detection can improve survival and thus can save costs and lives. It is obvious that an early detection program for low-resource settings is needed but implementation and planning need financial and human resource allocation which might be difficult to assure.

International organizations such as the Breast Health Global Initiative (BHGI) together with the World Health Organization (WHO) are working on evidence-based guidelines for early detection, diagnosis and treatment of breast cancer in different settings (http://www.portal.bhgi.org). Activities are recommended for four different levels of resources: basic, limited, enhanced and maximal level of resource (Box 1). It is recommended that each health facility or program, passes from level to level once all the activities of one level are in place, functioning and evaluated[3].

Box 1 Levels according to the BHGI. These are defined and quoted throughout the chapter[4]

Basic level (1): Core resources/fundamental level – necessary for any breast health service, usually applied in single-center institutions

Limited level (2): Services intended to produce major improvements with limited financial means and modest infrastructure – single or multiple-center structure

Enhanced level (3): Optional important services improving outcome, increasing the number of therapeutic options and patient's choice

Maximal level (4): Used in some high-resource countries at extreme cost for additional improvement – usually not appropriate for a broad use in resource-limited environment, all lower level resources should be implemented first

Throughout the chapter we refer to the levels as BHGI level 1, 2, 3 or 4

EPIDEMIOLOGY IN DIFFERENT SETTINGS

Many cases of breast cancer have occurred in industrialized countries in the past but recently incidences in low- and middle-income countries rose significantly. China and India are presently affected by the greatest increase[5]. First, the demographic change with increasing numbers of older women account for higher incidence rates. Case–control studies show evidence of an increase in risk factors for breast cancer due to westernized lifestyle. Women with breast cancer are taller and heavier, have fewer children, shorter periods of breastfeeding and an older age at first parity[6,7]. Comparison between different birth cohorts confirms this trend[8]. However, epidemiological data from Afro-American breast cancer patients and from patients in Africa suggest that there are more factors to consider. Affected patients from Africa are often younger and lack risk factors common in Caucasian patients[9]. Therefore aspects of epidemiology, screening, early detection, treatment and survival may not be directly applied from standards validated for a caucasian population[10]!

HISTOLOGIC PRESENTATION

All different cell types in the breast may develop abnormal growth. This may eventually lead to malignancy: invasive, unregulated growth tendency and the ability to metastasize (grow in distant tissue). The most common histologic appearance is the ductal carcinoma of the breast (Figure 1). The cells derive from the milk ducts (or more seldom from the lobule – lobular cancer). Pre-invasive lesions such as ductal carcinoma *in situ* may also be present – these are confined within the margin of the basal membranes. Other forms such mucinous,

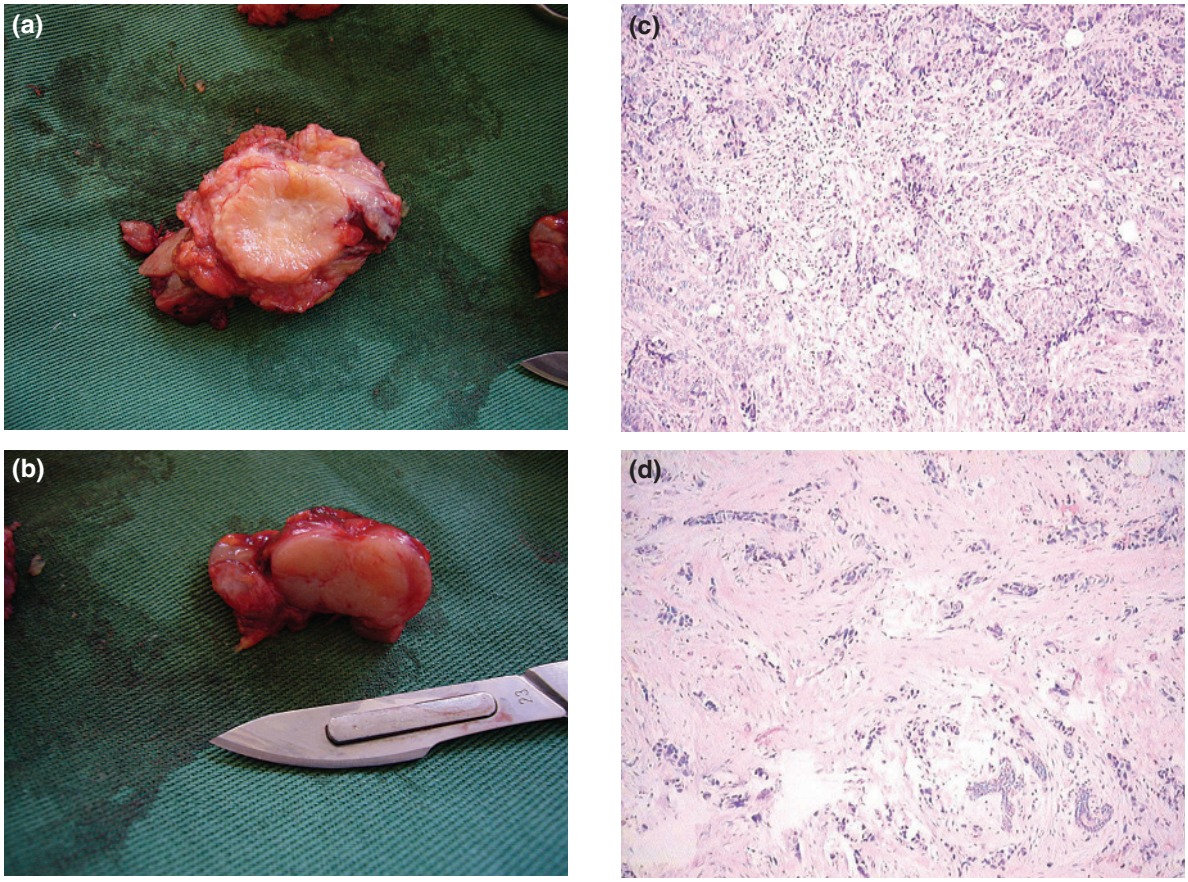

Figure 1 (a–d) Histology of a ductal carcinoma of the breast. (a) Macroscopic carcinoma of the breast; (b) axillary lymph node infiltrated by the carcinoma; (c) histologic findings of ductal adenocarcinoma on hematoxylin and eosin staining: predominantly solid trabecular formation of tumor cells with polymorphic, hyperchromatic and enlarged nuclei; (d) as in (c) with greater stromal component. (a, b) Courtesy of Eva Kantelhardt, Germany; (c, d) courtesy of Joerg Buchmann, Germany

serous, tubular, medullary and others types are rather rare. Grade of differentiation is referred to as 'grading' of the tumor[11]. Grade 1 tumors are rather slow growing, grade 3 tumors are more aggressive.

RARE ENTITIES

Phyllodes tumor (benign form described in Chapter 25) is a very fast growing entity derived from the stromal cells. A *sarcoma* is an aggressive tumor that develops from muscular cells. Beware that also malignant *non-Hodgkin lymphomas* may occur in the breast. *Mammary Paget disease* of the breast consists of malignant cells confined to the nipple and areola. An underlying breast cancer may be present!

MAGNITUDE OF THE PROBLEM IN LOW-RESOURCE SETTINGS

As many regions of the world don't have national cancer registries incidences are difficult to assess. Available data show that rates of newly diagnosed breast cancer cases are rising globally[5]. Figures from India show a rise in incidences for many regions. Rates have been doubling in the past 40 years in Japan, Korea and Singapore. In China incidences rose 20–30% in the past 10 years and are rising 2% per year in India. It is notable that almost 50% of the cases occur in pre-menopausal women. The same accounts for Pakistan and the Arab world. In Lebanon, 49% of the patients are less than 50 years of age[10]. Figures from Africa suggest a doubling of incidences but due to the lack of registries (5 out of 54 states have a functioning, population-based cancer registry entering data into 'Cancer incidence in 5 continents' vol. IX from IARC/WHO), these trends are difficult to evaluate for their correctness and underlying causes.

Breast cancer in low-resource settings has a much higher mortality (7 out of 10 newly diagnosed with breast cancer die) as compared with high-resource settings (2 out of 10 die)[2]. High mortality might have two reasons: first, many patients in those countries present with advanced-stage disease due to lack of awareness, barriers to seeking care early and unskilled healthcare workers. For these women prognosis is poor and disease-free survival short. Second, in those regions resources for healthcare are limited and are mostly put in the fight against other priority diseases such as infectious diseases, e.g. malaria and HIV/AIDS. But nevertheless women with breast cancer will finally present at the health system albeit with late-stage disease and need to be treated, maybe even outside your region in specialized centers which in turn will incur high costs for their families and the health system.

As you can see correct epidemiological data is important for making a case for breast cancer treatment as a priority in health resource planning.

CLINICAL PRESENTATION AND COURSE OF DISEASE

To estimate the extent of the disease the tumor has to be staged at diagnosis. The most recent 6th TNM classification provides the world standard for clinical and pathological staging[12].

The invasive tumor itself is documented as cT (clinically) or pT (pathologically) or ypT (through histology after neoadjuvant chemotherapy) – similar notation is used for nodal staging (cN, pN and ypN) (Box 2).

Box 2 TNM classification

T for tumor size (add a small c, p or yp before the T depending on method of assessment):

T0	no tumor detectable
Tis	carcinoma *in situ*, non-invasive
T1mic	microinvasion up to 0.1 cm
T1	up to 2 cm
T1a	≤ 0.5 cm
T1b	> 0.5 cm up to 1 cm
T1c	>1 cm up to 2 cm
T2	>2 cm up to 5 cm
T3	>5 cm
T4	any size including invasion of chest wall or skin or both

N for lymph node involvement:

N0	none
N1	1–3 in the axilla
N2	4–9 in the axilla
N3	10 or more in the axilla or below/above clavicle

M for metastasis:

M0	none (this will always be a clinical diagnosis cM0 – do not write pM0)
M1	distant metastasis present (may be cM1, e.g. lung metastasis on X-ray or pM1 if confirmed by histology)

The classification is needed for documentation and statistics but even more to assess the patient, decide on therapy and estimate prognosis!

HISTORY TAKING (BHGI LEVEL 1)

Make sure to find out more about the family history of a breast cancer patient. Also endometrial, ovarian and colorectal cancer may be associated with breast cancer. On the other hand, patients with a genetic mutation for breast cancer have a higher risk of developing ovarian cancer.

The social circumstances are important as the disease will surely affect all aspects of the woman's life. Social and psychological support may be needed. It is good to know which facilities are available around your setting (church, self-help groups, home-based care groups)! Please refer to Chapters 1 and 16 for details of history taking in breast disease.

INVESTIGATIONS

To improve your detection rates and avoid false-negative or -positive diagnosis you should always correlate your results from history taking, clinical examination, imaging findings and cytology/histology for the likelihood of the results (this is called triangulation) (Figure 2). Your investigations will help in making the diagnosis of breast cancer and assessing the stage of disease which will influence therapy options for your patient. Thus you have to evaluate the patient's breast for local disease and if necessary look for generalized disease (metastasis) (Table 1).

Clinical breast examination (BHGI level 1)

Clinical breast examination (CBE) can be used in a patient with symptoms of breast disease or suspicion of breast cancer or in a symptom-free client coming to your clinic for other problems. The CBE of the latter is called opportunistic. You should offer CBE to all your at-risk clients once yearly or at any visit according to BHGI, as it is a cost-effective method for screening in order to detect early stage breast cancer[13,14]. Please refer to Chapter 1 for the description on how to do CBE. It is important to remember that you should always check both breasts and arm pits as some patients with breast cancer have bilateral disease!

Most breastfeeding mothers who come with an ulcer will have a normal abscess after a puerperal mastitis but bear in mind that the average patient with breast cancer in low-resource settings is younger and that an ulcerated stage III breast cancer can mimic a breast abscess.

Inspection (patient seated) In a symptom-free patient look for differences in size and form of both breasts and nipples (Figure 3). Look for areas with swollen skin resembling the skin of an orange. This may be a sign for tumor invasion of the lymphatic vessels of the skin (orange skin phenomenon) – or otherwise it may indicate inflammation (see Figure 1 in Chapter 25). Look for bulging tumors, skin rashes of the breast or the nipples and for induration or retraction of the skin (plateau phenomenon).

In patients coming for a breast problem ask them to locate their findings in case they discovered a

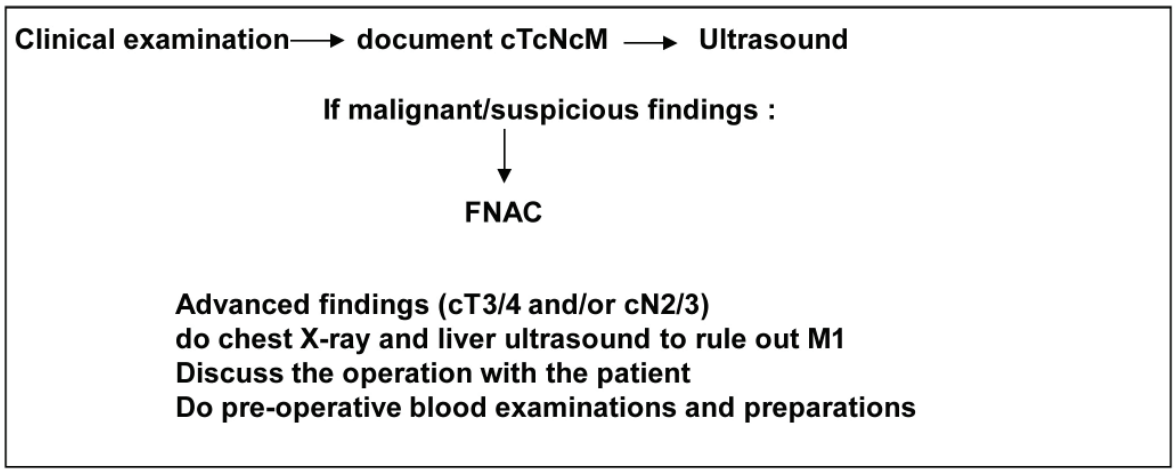

Figure 2 Decision-tree of investigations

Table 1 Diagnosis resource table for breast cancer

Level	*Clinical*	*Imaging and lab tests*	*Pathology*
Basic	History, physical examination, CBE Tissue sampling for cancer diagnosis (cytologic or histologic) prior to initiation of treatment	*	Pathology diagnosis obtained for every breast lesion by any available sampling procedure Pathology report containing appropriate diagnostic and prognostic/predictive information to include tumor size, lymph node status, histologic type and tumor grade Process to establish hormone receptor status possibly including empiric assessment of response to therapy† Determination and reporting of TNM stage
Limited	US-guided FNAB of sonographically axillary suspicious lymph nodes SLN biopsy with blue dye‡	Diagnostic breast US Plain chest and skeletal radiography Liver US Blood chemistry profile* CBC*	Determination of ER status by IHC† Determination of margin status, DCIS content, presence of LVI Frozen section or touch prep for SLN analysis §
Enhanced	Image-guided sampling Preoperative needle localization under mammo and/or US guidance SLN biopsy using radiotracer†	Diagnostic mammography Specimen radiography Bone scan, CT scan Cardiac function monitoring	Measurement of HER-2/neu overexpression or gene amplification§ Determination of PR status by IHC
Maximal		PET scan, MIBI scan, breast MRI, BRCA1/2 testing Mammographic double reading	IHC staining of sentinel nodes for cytokeratin to detect micrometastases Pathology double reading Gene profiling tests

CBE, breast examination; TNM, classification of malignant tumor system; US, ultrasound; FNAB, fine-needle aspiration biopsy; SLN, sentinel lymph node; CBC, complete blood count; ER, estrogen receptor; IHC, immunohistochemistry; DCIS, ductal carcinoma *in situ*; LVI, lymphovascular invasion; mammo, mammography; CT, computed tomography; HER-2, human epidermal growth factor receptor 2; PR, progesterone receptor; PET, positron-emission tomography; MIBI, methoxy-isobutyl-isonitrile; BRCA1/2, breast cancer genes 1 and 2. *Systemic chemotherapy requires blood chemistry profile and CBC testing for safety. When chemotherapy is available at the basic level, these tests should also be provided. †ER testing by IHC is preferred for establishing hormone receptor status and is cost-effective when tamoxifen is available. When tamoxifen is available at the basic level, IHC testing of ER status should also be provided. ‡The use of SLN biopsy requires clinical and laboratory validation of the SLN technique. §If the costs associated with trastuzumab were substantially lower, trastuzumab would be used as a limited-level resource. In this case, measurement of HER-2/neu overexpression and/or gene amplification would also need to be available at the limited level in order to properly select patients for this highly effective but expensive HER-2/neu-targeted biological therapy. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited and enhanced levels. Maximal resources level should not be targeted for implementation in low- and middle-income countries, even though they may be used in some higher income settings. (Adapted from Anderson BO, Yip CH, Smith A, *et al*. Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. *Cancer* 2008;113(8 Suppl.):2221-43. The American Cancer Society. This material is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

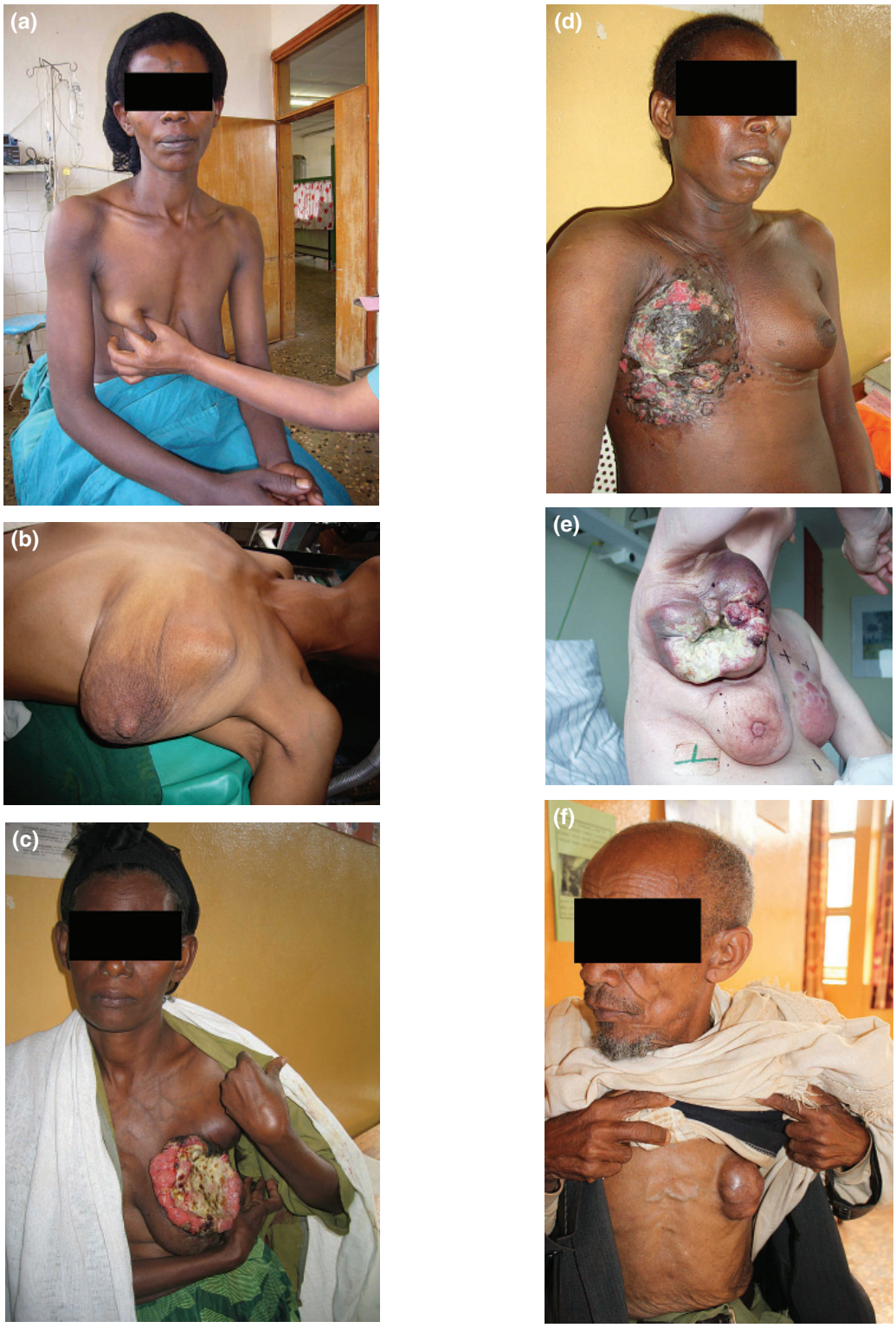

Figure 3 Examples of breast cancer on examination. (a) Patient with breast cancer; b) patient lying down; c) exulcerated-mobile mass; (d) exulcerated spread to thorax; (e) axillary lymph nodes exulcerated for radiotherapy; (f) male patient. (c, d, f) Courtesy of Erik Erichsen, Ethiopia; (e) courtesy of Regina Grosse, Germany

tumor themselves and inspect the site first for the above-mentioned signs.

Then look for swollen lymph nodes in axilla, around the neck and the clavicles. Inspect the margins of the ulcer if the patient comes with an ulcerated tumor. You may take a swab for cytology and for Ziehl–Neelsen stain to rule out tuberculosis. Tuberculosis or lymphoma of the breast can be seen in patients with advanced HIV disease (see Figure 7 in Chapter 25).

Examination (patient seated) Check the patient's axillae for swollen lymph nodes as described in Chapter 1. Then palpate the neck region for swollen lymph nodes on both sides. After location assess if the tumor is fixed to the skin or the underlying pectoral muscle. A mobile mass may be operated on much more easily, a fixed mass may not be operable at all (Figure 3c). Squeeze both nipples to see if there is any kind of discharge (milky fluid, clear fluid or blood) (see Figure 3 in Chapter 25). Take a swab for cytology and microbiology. Milky discharge is quite common in women who have breastfed.

Self-examination of the breast (BHGI level 1)

There is no evidence that self-examination of the breast (SEB) leads to a reduced mortality from breast cancer. The large 'Shanghai trial' did not find differences in breast cancer mortality between the groups who were taught SEB in comparison to the population without the intervention[15] (level of evidence 1b). But it is a common opinion among experts that SEB will raise women's awareness of their breasts and therefore promote breast health!

You should offer all your clients from age-risk groups CBE (opportunistic screening) on a yearly basis. At the same time you can teach your clients how to examine their breasts themselves once a month on a fixed day in order not to forget it. A pre-menopausal woman should do the examination on a specific day in the first week after her period started; let's say on day 4 or 5. This is important as hormonal changes after or around ovulation make the breast difficult to assess. This is why it is important to ask about her period as well when you do a CBE. You might need to call her back to re-check your findings after her period if in doubt.

A postmenopausal woman has no hormonal changes influencing her breasts anymore and no period to remember SEB. So you should recommend her to choose a date from the calendar for her SEB, let's say every first day of the month. Old women can get breast cancer as well so it is very important to explain this to your old clients, offer them CBE and teach them how to do SEB as well. Make sure the woman understands why to do SEB. After doing the examination regularly she should be able to note the following changes:

1. A breast lump that feels different from the surrounding tissue
2. Bloody discharge from the nipple
3. Change in the size or shape of a breast
4. Changes to the skin over the breast, such as dimpling
5. Inverted nipple (a nipple turned inward into the breast)
6. Peeling or flaking/swelling of the nipple or areola skin
7. Redness or pitting of the skin of breast, like the skin of an orange
8. A lump or thickening in the arm pit.

The idea of the examination is that the women will investigate *all* areas of both breasts.

Inspection is convenient in front of a mirror – with arms hanging down, on the waist and up in the air. Any skin or nipple changes, any change in shape, redness or suspicion of a lump may be noted. Palpation may be done in a concentric or 'up and down' manner – making sure to reach all areas. Especially the nipple should be inspected and also squeezed. Use three fingers – not only the finger tips. The procedure may take 20 min while comfortably lying on the back. It is essential to cover the area from sternum to lateral axillary line, from below the lower breast fold up to the clavicle and towards the axilla including the upper outer quadrant. The procedure should include deeper and more superficial palpation of the breast tissue. Palpating in different positions (on the side, standing and sitting) may add information. After a while the women will know about her breasts and notice even small changes. The website of the International Agency for Research on Cancer (IARC) gives good instructions on how to do SBE (http://screening.iarc.fr/breastselfexamination.php).

General physical examination (BHGI level 1)

In a patient with early breast cancer a general examination will usually provide no important

findings as the likelihood for metastasis is small. But you can still find signs for other diseases such as HIV/AIDS, tuberculosis or general malnutrition. This will have an impact on her survival or how well she will tolerate therapy, especially chemotherapy as this will influence her immune system.

It is nevertheless especially important to do general examination for patients with advanced disease as they are more likely to have metastasis. A woman with metastasizing breast cancer cannot be cured – palliative care is needed. Thus it is very important to look thoroughly for metastasis as this will influence her therapeutic options. Breast cancer most frequently spreads to the lymph nodes, lungs, the liver and the bones and to the brain. Always start to examine your patient from the head downwards.

Head, neck and arms (patient standing) During your breast examination you have already palpated the neck region and the axillae for swollen lymph nodes. Check her arms and hands for swelling and difference in circumference as this can indicate lymphedema from tumor cells blocking the lymph vessels.

Chest wall, vertebral spine, lungs and pelvic bones (patient standing) Look for skin metastasis. In early appearance they may be lentil-sized nodules, often a bit darker than the skin, most often on the thoracic skin. Auscultate and percuss both lungs and assess fremitus and bronchophony. Lung metastasis can lead to pleural effusions or atelectasis. In both you will hear reduced breathing sounds and decreased percussion. Gently percuss the patient's cervical and thoracic spine and the os sacrum with your fist. Be careful doing this as vertebrae with big osteolytic metastasis (a metastasis that destroys the bone) may break if you are too rough. A tender area may indicate bone metastasis. Put your hands on the patient's rib cage and gently compress it. Also, tenderness may indicate metastasis. Put your hands on the patient's pelvic brim and compress it gently, also looking for tenderness. In case of any bone pain an X-ray of the respective area may reveal the metastasis.

Abdomen and legs (patient supine) Percuss the whole abdomen for air or fluid. Late-stage breast cancer can spread to the liver, ovaries and the peritoneum and cause ascites! Palpate the whole abdomen for masses (ovarian metastasis). Percuss and palpate the liver to assess hepatomegaly and tenderness. Check for swollen inguinal lymph nodes and swollen legs. In case of abnormal findings, an abdominal ultrasound should be done.

Ultrasound (BHGI level 2)

Mammography is the gold standard for screening and assessment for breast cancer in developed countries. Often it is not available in a low-resource setting. Using ultrasound has several advantages for the following reasons. Many breast cancer patients in low-resource settings are pre-menopausal. Their breast tissue is often very dense and thus suspicious lesions may be better evaluated with ultrasound than with mammography[16]. As you can use ultrasound for many indications other than breast cancer, many hospitals in low-resource settings already have a machine or are more willing to buy one as it will be more cost-effective. With the same machine you can assess a patient's breast and look for metastasis in the liver, abdominal lymph nodes or other abdominal sites using different probes. Ultrasound is especially valuable to assess a palpable tumor for signs of malignancy and to guide fine-needle aspiration cytology (FNAC) or minimally invasive breast biopsy for cytology or core biopsy. In addition you can perform an ultrasound examination of the axillae for enlarged or suspicious lymph nodes. This is impossible with mammography.

Breast ultrasound (BHGI level 2)

See Chapter 1 on how to perform breast ultrasound. You should always scan both breasts and axillae. Start with the right axilla, proceed to the right breast, then the left axilla and the left breast (Figure 4).

Document your findings thoroughly as described in Chapter 1 including, size, location, the Breast Imaging-Reporting and Data System (BI-RADS) classification, distance to skin and areola and signs suggestive of malignancy. Your description is very important for relocating the suspicious area during tissue sampling or surgery. Always circle the area of the tumor with a permanent marker after ultrasound on the evening before the operation to locate it for the surgeon. This will make the operation easier and reassure the patient.

In cases where you give neoadjuvant chemotherapy to shrink a stage III tumor before the operation you will do repeated ultrasound to assess

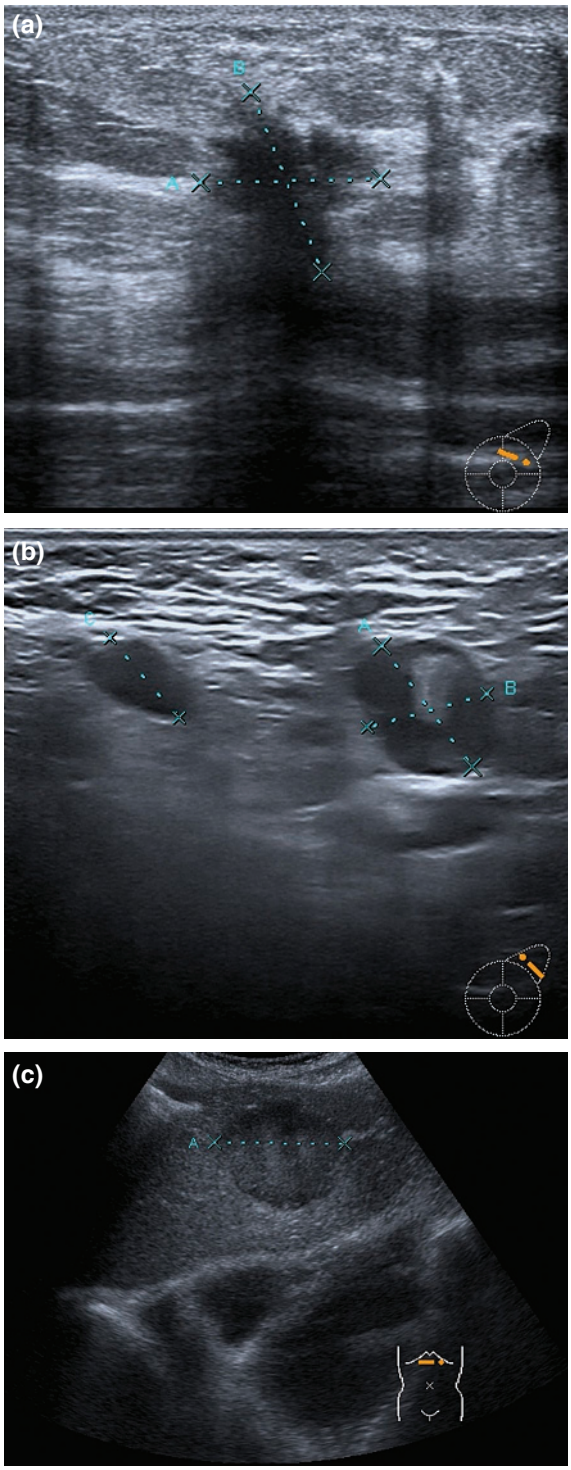

Figure 4 An ultrasound with (a) breast cancer finding and (b) suspicious lymph nodes. (c) An ultrasound of a liver metastasis – make sure to note down the diameter for the purpose of repeated control. (a, b) Courtesy of Regina Grosse; (c) courtesy of Hans-Georg Strauss, Germany

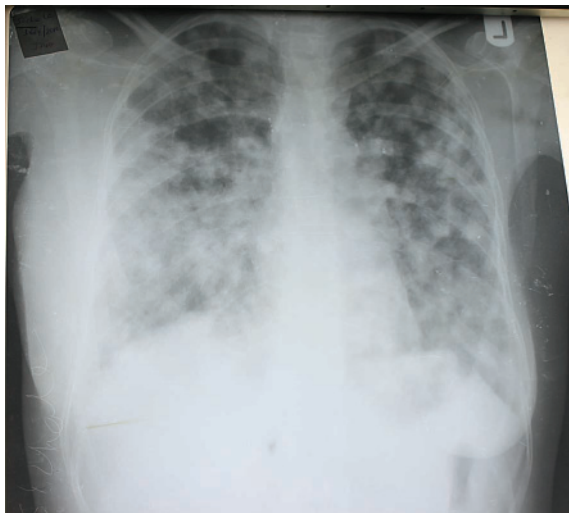

Figure 5 Multiple pulmonary metastasis due to breast cancer. Courtesy of Erik Erichsen, Ethiopia

the size of the tumor and thus the success of your therapy.

Chest X-ray (BHGI level 2)

A chest X-ray is the standard procedure to investigate pulmonary or pleural metastasis. Pulmonary metastases appear as radio-dense lesions, rather round in shape, single or multiple. Look for pleural effusion. Sometimes bone metastasis may be seen on the ribs or spine as osteolytic lesions (often round in shape and less dense than the surrounding bone) (Figure 5).

Laboratory investigations/pathology service (BHGI level 2)

A full blood count is needed to rule out anemia or pancytopenia from bone-marrow metastasis. Also, signs of infections should be evaluated, e.g. from a superinfected ulcerated tumor. In addition the standard investigations of your hospital for pre-surgery patients should be done. Grouping and cross-matching is reasonable for advanced-stage disease.

Pathology service should cover appropriate information: tumor size, lymph node status, histological type, tumor grade (BHGI level 1). Estrogen receptor determination (BHGI limited level) should be performed by immunohistochemistry (IHC) – this is cost-effective when tamoxifen tablets are available to avoid treatment of patients with unknown status (for treatment with tamoxifen see

below). Tamoxifen should be given if IHC is not available.

Mammography (BHGI level 3)

The use of mammography is to gain information on palpable lesions, suspicious previous mammograms and for monitoring of patients with a positive family history for breast cancer. When only limited resources are available, these indications are relative: patients with palpable lesions need histological confirmation even without mammography and patients with previous mammograms are extremely rare. Patients with a positive family history (breast cancer in sister, mother or male relative) and no current lesion should be advised to consult a specialized center and receive a mammogram and monitoring there.

Magnetic resonance imaging (BHGI level 4)

Magnetic resonance imaging (MRI) is not easily available in a low-resource setting. In case there are options to receive a breast MRI, make sure that a radiologist is available to read the images. Interpreting a breast MRI needs a substantial amount of experience! This very expensive method is used additionally to ultrasound for early detection in young patients with a family history of breast cancer. Also in patients with breast cancer after breast-conserving therapy an MRI may be needed for scarified tissue areas to rule out a local recurrence.

Cytology (BHGI level 1)

Assessment of cells from the lesion under the microscope may give valuable hints to the diagnosis. Doing a fine-needle aspiration is relatively easy. Usually no anesthesia is needed. Consider the following:

1. Make sure to have a normal hollow needle (21 or 23G), several 10 ml syringes, disinfection, strapping, assistant.
2. Identify the lesion by ultrasound or palpation (if palpable).
3. Avoid the ribs, axillary nerves or vessels.
4. Give the ultrasound probe to an assistant.
5. Position the needle exactly in the direction along the probe (see Figure 6).
6. The needle should reach the tumor in a horizontal manner (see Figure 6).
7. Hold the tumor (it may be firm!) with one hand and push in the needle with the other hand towards the tumor.
8. Assess correct position of the needle inside the tumor in all dimensions (rotating the ultrasound probe 90°).
9. Apply suction drawing the punch of the syringe to the 10-ml mark and aspirate cells if possible into the needle but not into the syringe. Push

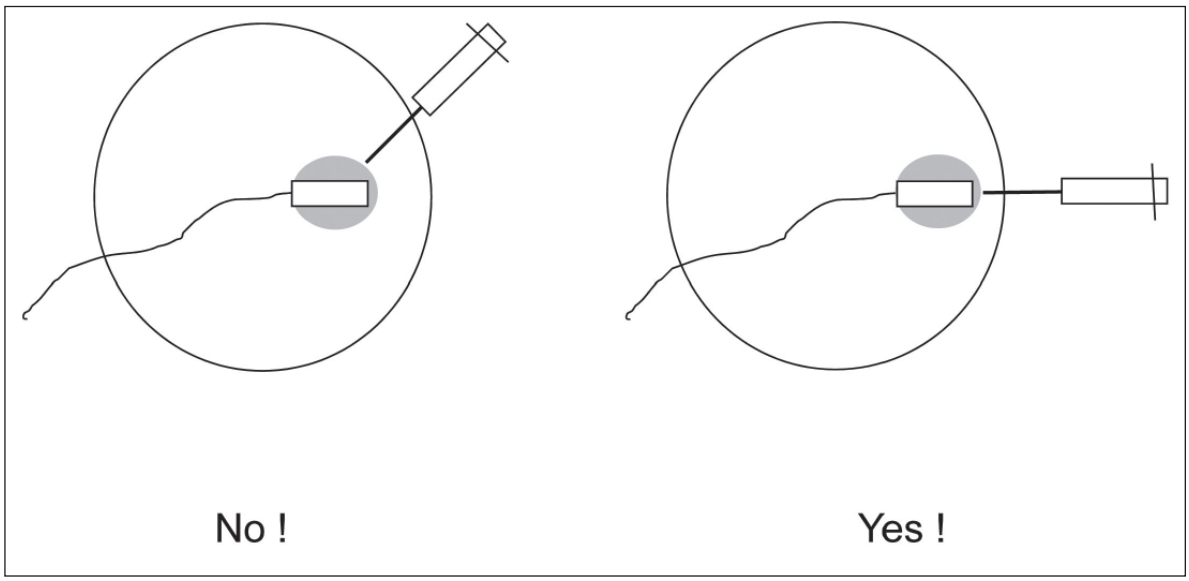

Figure 6 FNAC: position of the needle to the ultrasound probe (square) and the tumor (grey)

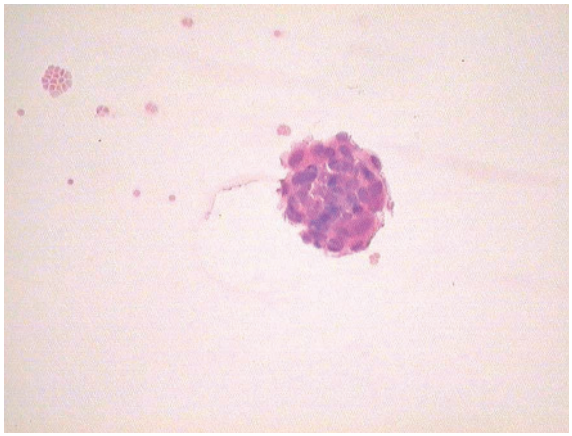

Figure 7 Example of breast cancer cytology. Courtesy of Joerg Buchmann, Germany

the needle back and forward three to four times (always inside the breast!) – then remove it and put the aspirated cells on a glass slide (avoid the aspirate coming into the syringe as it is not easy to get the few cells out again).

10. With this technique it will often, but not always be possible to obtain a sufficient number of cells – the aspirate is expressed on a clean dry glass slide.

Cytology is done with relatively little equipment (Figure 7) – e.g. Giemsa staining may be learned by a laboratory technician. Material may also be gained from secretion of the nipple, or with a wet swab from an incisional biopsy. Remember to look for bacteria under the microscope as well!

Giemsa staining

- Fix the slides in alcohol (methanol) for 5 min
- Stain in Giemsa working solution for 1 h
- Differentiate in 0.5% acetic acid and rinse with tap water
- Fix a cover slip with a mounting medium.

For quality assurance or if no pathologist is available pictures may be taken with a digital camera or a cell phone through the microscope and then sent by e-mail to a pathology center (telepathology)[17].

Minimally invasive breast biopsy (BHGI level 1 if available)

Core needle biopsy needs specific equipment and is not available in every setting. It may be taken from palpable lesions preferably guided by ultrasound. You should not attempt to biopsy axillary or neck lymph nodes or thoracal lesions as you might injure big vessels or cause a pneumothorax.

Inject 10–20 ml of local anesthesia around the lesion and position the needle as illustrated for FNAC. Make sure you are familiar on how to use the biopsy equipment before using it on the patient for the first time! Make sure you collect more than one tissue cylinder. Four are adequate according to international standards. The tissue cylinder should be put into buffered formaldehyde 4.5% and sent for pathology. Put a pressure bandage all around the breast and thorax. Have the patient rest for 2 h and check for bleeding. Apply ice-packs if a hematoma is developing. Be ready for surgical evacuation of a hematoma if needed – this occasionally happens!

Diagnostic surgical biopsy (BHGI level 1)

As the breast is easily accessible to surgery, excisional biopsies are a straightforward procedure. In cases where the lesion is suspicious but not confirmed breast cancer a two-step approach should be followed: diagnostic biopsy and then mastectomy/axillary dissection if malignant.

The diagnostic biopsy may be done in local anesthesia with lignocaine for small, superficial lesions, general anesthesia is needed for a deeper localization (Figure 8). Always perform the incision directly over the tumor and excise the lesion *in toto*. Make sure to coagulate/ligate all vessels since a large amount of blood may easily accumulate in the breast quickly and before being noticed. Compression (bandage around the chest) may be applied for 24 h.

In case of histologically confirmed breast cancer, definite surgery (mastectomy and axillary lymphadenectomy) is needed!

TREATMENT

Treatment of breast cancer involves surgery, radiotherapy and systemic therapy. The decision about individual therapy depends highly on the tumor stage as well as the condition of the patient.

Stage I (patients with disease confined to the breast – no lymph nodes clinically involved)

In a low-resource setting you will rarely see patients coming with early breast cancer without lymph node involvement (Table 2). In case you do see a

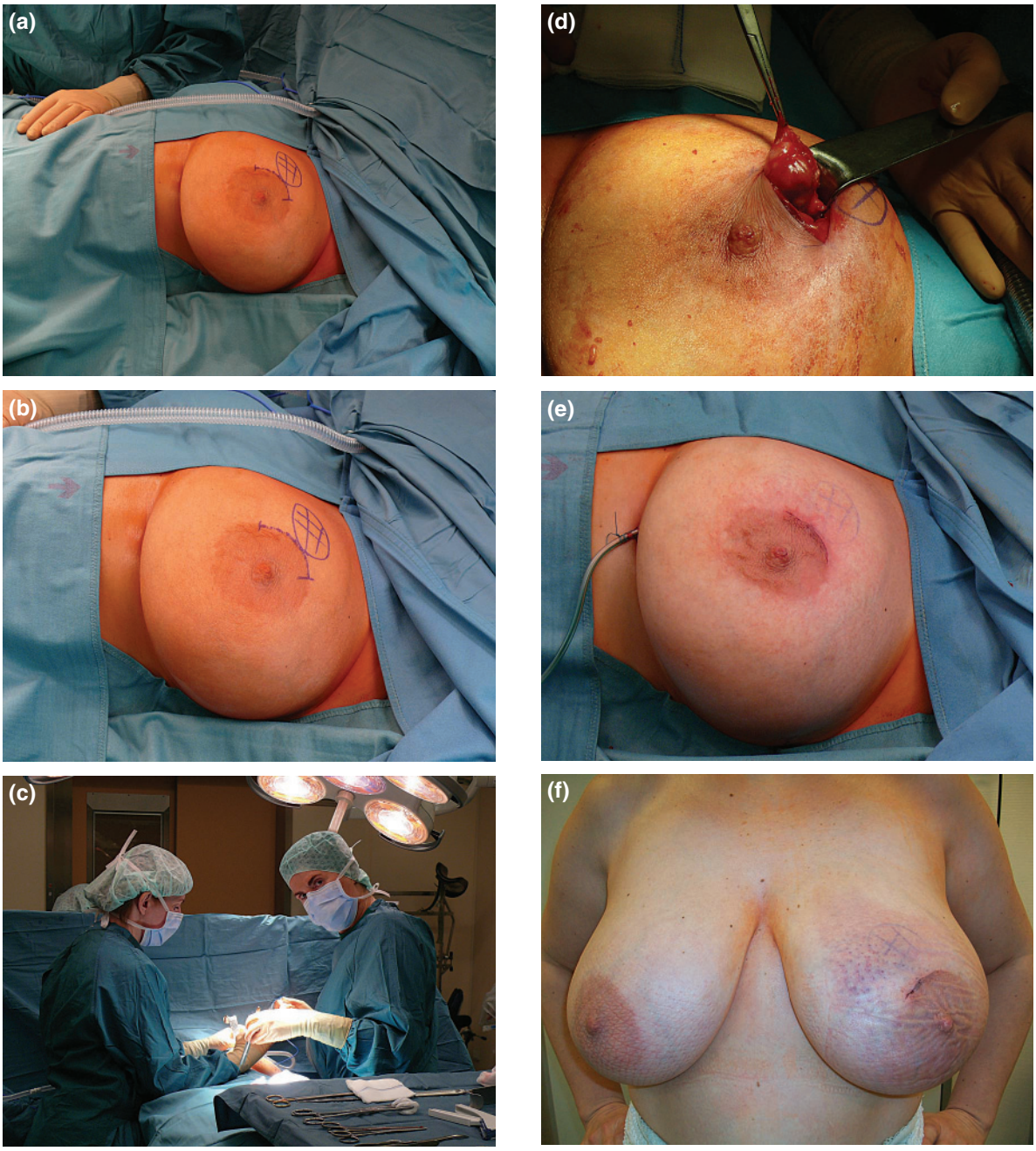

Figure 8 (a) Patient in supine position, arms 90° abducted, the tumor is outlined before surgery. (b) Palpable tumor close to the areola, small diagnostic incision close to the areola (if malignancy is strongly suspected, choose an incision directly above the lesion!). (c) Two surgeons left and right giving optimum exposure. (d) The tumor is extracted with careful bleeding control. (e) A drain is inserted securing downward flow of secretions. (f) Postoperative result after drain removal still showing some edema. (g) Standard incision above the tumor. (a–f) Courtesy of Regina Grosse

Table 2 Treatment resource allocation table for stage I breast cancer

Level	*Surgery*	*Radiation*	*Chemo*	*Endocrine*	*Biological*
Basic	Modified radical mastectomy			Oophorectomy in premenopausal women Tamoxifen*	
Limited	Breast-conserving surgery† SLN biopsy with blue dye‡		Classical CMF§, AC, EC or FAC§		¶
Enhanced	SLN biopsy using radiotracer‡ Breast reconstruction surgery	Breast-conserving whole-breast irradiation as part of breast-conserving therapy§	Taxanes	Aromatase inhibitors LHRH agonists	Trastuzumab for HER-2/neu positive disease¶
Maximal			Growth factors Dose-dense chemotherapy		

SLN, sentinel lymph node; CMF, cyclophosphamide, methotrexate and 5-fluorouracil; AC, doxorubicin and cyclophosphamide; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin and cyclophosphamide; LHRH, luteinizing hormone-releasing hormone; HER-2/neu, human epidermal growth factor receptor 2. *Estrogen receptor (ER) testing by immunohistochemistry (IHC) is preferred for establishing hormone receptor status and is cost-effective when tamoxifen is available. When tamoxifen is available at the basic level, then IHC testing of ER status should also be provided. †Breast-conserving surgery can be provided as a limited-level resource but requires breast-conserving radiation therapy. If breast-conserving radiation is unavailable, then patients should be transferred to a higher level facility for post-lumpectomy radiation. ‡The use of SLN biopsy requires clinical and laboratory validation of the SLN technique. §Systemic chemotherapy requires blood chemistry profile and complete blood count testing for safety. When chemotherapy is available at the basic level, these tests should also be provided. ¶If the costs associated with trastuzumab were substantially lower, trastuzumab would be used at a limited level. In this case, measurement of HER-2/neu overexpression and/or gene amplification would also need to be available at the limited level in order to properly select patients for this highly effective but expensive HER-2/neu-targeted biological therapy. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited and enhanced levels. An empty matrix box indicates that additional resource allocation is not mandated beyond those resources required at lower levels. Maximal level resources should not be targeted for implementation in low- and middle-income countries, even though they may be used in some higher income settings. (Adapted from Anderson BO, Yip CH, Smith A, *et al*. Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. *Cancer* 2008;113(8 Suppl.):2221–43. The American Cancer Society. This material is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

patient with early disease – aim for cure! This is an adjuvant (curable) situation. Operation is the most important treatment. Modified radical mastectomy is the standard of care for BHGI level 1 and 2. Breast-conserving therapy always includes whole-breast irradiation. Since the capacity of radiotherapy is usually limited on these levels, breast-conserving therapy will NOT be of high priority.

Endocrine therapy should be offered for hormone receptor (HR)-positive tumors. This should be done also in cases of unknown receptor status – even though not all patients will benefit.

Stage II (patients with disease confined to the regional area of the breast – lymph nodes involved and/or >2 cm tumor in the breast)

Again the operation is most important in this adjuvant setting (Table 3). Chemotherapy should be offered since the risk of future metastasis is high in lymph node-positive disease. Chemotherapy will reduce the number of patients who experience a distant relapse. Additional endocrine therapy will further improve the outcome of stage II patients. Radiation of the chest wall should be offered especially for patients with more than four lymph nodes involved. This will reduce local recurrence and also

Table 3 Treatment resource allocation table for stage II breast cancer

Level	*Surgery*	*Radiation*	*Chemotherapy*	*Endocrine*	*Biological*
Basic	Modified radical mastectomy	*	Classical CMF†, AC, EC or FAC†	Oophorectomy in premenopausal women Tamoxifen‡	
Limited	Breast-conserving surgery§ SLN biopsy with blue dye¶	Post-mastectomy irradiation of the chest wall and regional nodes for high-risk cases*			**
Enhanced	SLN biopsy using radiotracer¶ Breast reconstruction surgery	Breast-conserving whole-breast irradiation as part of breast-conserving therapy§	Taxanes	Aromatase inhibitors LHRH agonists	Trastuzumab for HER-2/neu-positive disease**
Maximal			Growth factors Dose-dense chemotherapy		

CMF, cyclophosphamide, methotrexate and 5-fluorouracil; AC, doxorubicin and cyclophosphamide; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; SLN, sentinel lymph node; LHRH, luteinizing hormone-releasing hormone; HER-2/neu, human epidermal growth factor receptor 2. *Chest wall and regional lymph node irradiation substantially decreases the risk of post-mastectomy local recurrence. If available, it should be used as a basic-level resource. †Systemic chemotherapy requires blood chemistry profile and complete blood count testing for safety. When chemotherapy is available at the basic level, these tests should also be provided. ‡Estrogen receptor (ER) testing by immunohistochemistry (IHC) is preferred for establishing hormone receptor status and is cost-effective when tamoxifen is available. When tamoxifen is available at the basic level, then IHC testing of ER status should also be provided. §Breast-conserving surgery can be provided as a limited-level resource but requires breast-conserving radiation therapy. If breast-conserving radiation is unavailable, then patients should be transferred to a higher level facility for post-lumpectomy radiation. ¶The use of SLN biopsy requires clinical and laboratory validation of the SLN technique. **If the costs associated with trastuzumab were substantially lower, trastuzumab would be used at a limited level. In this case, measurement of HER-2/neu overexpression and/or gene amplification would also need to be available at the limited level in order to properly select patients for this highly effective but expensive HER-2/neu-targeted biological therapy. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited and enhanced levels. An empty matrix box indicates that additional resource allocation is not mandated beyond those resources required at lower levels. Maximal level resources should not be targeted for implementation in low- and middle-income countries, even though they may be used in some higher income settings. (Adapted from Anderson BO, Yip CH, Smith A, *et al.* Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. *Cancer* 2008;113(8 Suppl.):2221–43. The American Cancer Society. This material is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

improve overall survival especially in the younger patients.

Locally advanced breast cancer

Often patients in low-resource settings come with locally advanced disease (60–80% of the cases) (Table 4). The number of patients presenting with advanced disease will gradually decrease when community sensitization is done, when healthcare workers perform CBE and people realize that good-quality treatment is available for breast cancer. Until then treatment for locally advanced breast cancer will always remain a continuous challenge. Especially as operative treatment is not easy! Always do staging in these patients first (chest X-ray, liver ultrasound). In case of metastasis, the palliative situation will require different care.

Table 4 Treatment resource allocation table for locally advanced breast cancer

Level	*Surgery*	*Radiation*	*Chemo*	*Endocrine*	*Biological*
Basic	Modified radical mastectomy	*	Preoperative chemotherapy with AC, EC, FAC or CMF†	Oophorectomy in premenopausal women Tamoxifen‡	
Limited		Post-mastectomy irradiation of the chest wall and regional nodes*			§
Enhanced	Breast-conserving surgery Breast reconstruction surgery	Breast-conserving whole-breast irradiation as part of breast-conserving therapy	Taxanes	Aromatase inhibitors LHRH agonists	Trastuzumab for HER-2/neu-positive disease§
Maximal			Growth factors Dose-dense chemotherapy		

AC, doxorubicin and cyclophosphamide; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; LHRH, luteinizing hormone-releasing hormone; HER-2/neu, human epidermal growth factor receptor 2. *Chest wall and regional lymph node irradiation substantially decreases the risk of post-mastectomy local recurrence. If available, it should be used as a basic-level resource. †Systemic chemotherapy requires blood chemistry profile and complete blood count testing for safety. When chemotherapy is available at the basic level, these tests should also be provided. ‡Estrogen receptor (ER) testing by immunohistochemistry (IHC) is preferred for establishing hormone receptor status and is cost-effective when tamoxifen is available. When tamoxifen is available at the basic level, then IHC testing of ER status should also be provided. §If the costs associated with trastuzumab were substantially lower, trastuzumab would be used at a limited level. In this case, measurement of HER-2/neu overexpression and/or gene amplification would also need to be available at the limited level in order to properly select patients for this highly effective but expensive HER-2/neu-targeted biological therapy. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. An empty matrix box indicates that additional resource allocation is not mandated beyond those resources required at lower levels. Maximal level resources should not be targeted for implementation in low- and middle-income countries, even though they may be used in some higher income settings. (Adapted from Anderson BO, Yip CH, Smith A, *et al*. Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. *Cancer* 2008;113(8 Suppl.):2221-43. The American Cancer Society. This material is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

A patient may still be cured if no distant metastases are present. Preoperative (neoadjuvant chemotherapy is an excellent option for assessing sensitivity to treatment as well as decreasing the tumor size to allow an operation after successful treatment. The tumor will shrink during chemotherapy if it works well – also the cancer cells that may have already spread to the body will be targeted and hopefully be eliminated. Mastectomy should be done immediately if no chemotherapy is available – removing the whole tumor may be a surgical challenge and not achieving this will reduce the chance of long-term cure. When performing the operation always make sure that there is enough skin left after tumor removal to cover the wound!

Standard pre-operative chemotherapy is an anthracycline-based regimen. CMF is less effective but may as well be used if anthracyclines are not available. Elderly women (with reduced general condition not allowing chemotherapy) may receive neoadjuvant endocrine treatment, e.g. for 3 months – the effect will occur rather slowly but will still be there.

Stage IV: metastatic and recurrent breast cancer

In many patients who come with locally advanced disease staging will reveal distant metastasis (Table 5). These patients cannot be cured. But palliative care will improve the quality of life tremendously! Local surgery will reduce the tumor load, prevent infection (and smell!), reduce pain and ease the patient's life. Systemic therapy will initially reduce the size of the metastasis (keep good records on your staging results to prevent giving therapy without effect). Always balance individual benefit concerning the disease and individual side-effects. The benefit should outweigh the side-effects – otherwise change the strategy. Psychological support is essential also for family members. Be aware that palliative care for those patients who are going to die will be very well noticed in the community! The families will be extremely grateful for all support given in such a situation. See Chapter 32 for more information about palliative care.

SURGERY

In a low-resource setting modified radical mastectomy is the standard of care. This involves a total mastectomy and level I/II axillary lymph node dissection. It is essential to be trained in this procedure to offer breast cancer care. A resection without tumor residuals and free margins (R0) and more than six dissected lymph nodes should be standard. The procedure doesn't take time and the patient may be cured if done correctly. In case radiotherapy options are available, breast-conserving therapy may be offered if indicated. Here the histological assessment of margins is needed as well as postoperative radiotherapy to the breast.

Table 5 Treatment resource allocation table for metastatic (stage IV) and recurrent breast cancer

Level	*Surgery*	*Radiation*	*Chemotherapy*	*Endocrine*	*Biological*
Basic	Total mastectomy for ipsilateral breast tumor recurrence after breast-conserving surgery			Oophorectomy in premenopausal women Tamoxifen*	Non-opioid and opioid analgesics and symptom management
Limited		Palliative radiation therapy	Classical CMF† Anthracycline monotherapy or in combination†		
Enhanced			Sequential single agent or combination chemotherapy Trastuzumab Lapatinib	Aromatase inhibitors	Bisphosphonates
Maximal			Bevacizumab	Fulvestrant	Growth factors

CMF, cyclophosphamide, methotrexate and 5-fluorouracil. *Estrogen receptor (ER) testing by immunohistochemistry (IHC) is preferred for establishing hormone receptor status and is cost-effective when tamoxifen is available. When tamoxifen is available at the basic level, then IHC testing of ER status should also be provided. †Systemic chemotherapy requires blood chemistry profile and complete blood count testing for safety. When chemotherapy is available at the basic level, these tests should also be provided. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. An empty matrix box indicates that additional resource allocation is not mandated beyond those resources required at lower levels. Maximal level resources should not be targeted for implementation in in low- and middle-income countries, even though they may be used in some higher income settings. (Adapted from Anderson BO, Yip CH, Smith A, *et al.* Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. *Cancer* 2008;113(8 Suppl.):2221–43. The American Cancer Society. This material is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

Modified radical mastectomy and axillary lymphadenectomy

This operation aims at removing the complete breast tissue and the lymph nodes from level I (brachial nodes and subscapular nodes) and II (central axillary, pectoral and interpectoral nodes) from the axilla. Unlike before, the pectoralis muscle is not removed and the axillary lymph nodes from level III (subclavian nodes) are left behind as well.

Mastectomy is a simple, straightforward procedure with a steep learning curve. Axillary lymph node dissection can be learned quickly as well. However, there are some important points to bear in mind for successful and uncomplicated surgery.

Hemostasis is very important in breast surgery. Breast tissue is very well vascularized, especially in premenopausal patients and expert breast surgeons are aware of the fact that postoperative hemorrhage can occur even when the operation went smoothly without major bleeding. Postoperative hemorrhage is rarely life-threatening but can be important in case of pre-existing anemia and if detected late. You should keep in mind that breast surgery is always cosmetic as well, and that conservative or surgical management of a significant hematoma increases the risk of infection and secondary healing. Don't forget that you cut off a woman's breast, the definite exterior sign of her femininity!

Knowledge of anatomy of the axilla is important in order not to injure major vessels and nerves, hampering the future functioning of the arm.

Important anatomy in breast surgery

See diagram in Figure 9.

Lymph nodes

The lymph nodes in the axilla that have to be removed are mentioned above for level I and II. They are usually embedded in axillary fatty tissue and only enlarged nodes can be identified visually or through palpation (you should palpate the axillary tissue during the operation and note your findings in your report). According to international standards for a complete axillary lymphadenectomy in advanced breast cancer at least six lymph nodes should be removed. You should examine your specimen digitally during the operation and count the lymph nodes you find. However, the exact number will be determined by pathology as some

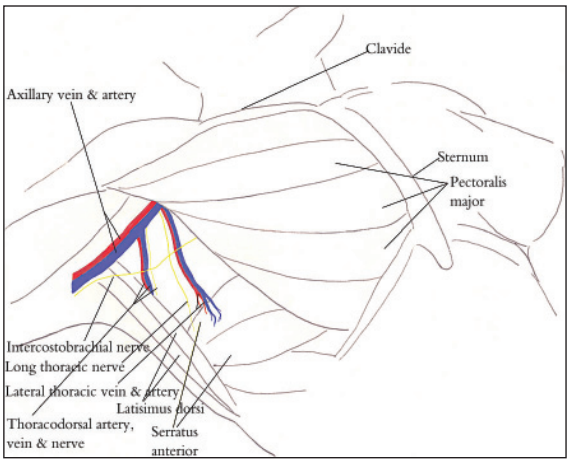

Figure 9 Breast anatomy

lymph nodes are too small to identify macroscopically. It is therefore important to remove the fatty tissue in the areas where you know the lymph nodes of level I and II can be found anatomically (see Figure 9):

Brachial lymph nodes are located in the lateral axilla beneath and inferior to the axillary vein and artery.

Subscapular lymph nodes are located alongside the thoracodorsal vessels and nerve on the floor of the axilla (posterior axilla).

Central axillary lymph nodes are located in the triangle between the medial part of the axillary vessels and the margin of the pectoralis minor muscle.

Pectoral lymph nodes are located in the medial parts of the axilla alongside the thoracic wall near the lateral thoracic vessels.

Interpectoral lymph nodes are located between the major and minor pectoralis muscles.

Blood vessels

The most important vessels for mastectomy are the perforating branches of the internal thoracic arteries and veins. They perforate the sternal part of the pectoralis major muscle and need to be suture-ligated meticulously during surgery as they will retract when injured and hemostasis will become very difficult. Important vessels of the axilla are described below (see Figure 9):

The axillary vein and artery are running in the superior part of the axilla from the chest to the arm

and indicate the upper margin of your lymph node dissection (see Figure 9). Make sure you do not injure these vessels as they are the size of a finger, will bleed heavily and are very difficult to repair!

The thoracodorsal vein and artery originate from the axillary vessels and run on the subscapularis muscle down to the floor of the axilla.

The lateral thoracic vein and artery originate as well from the axillary vessels and run along the chest wall on the serratus anterior muscle.

Nerves

The intercostobrachial nerve runs from below the pectoralis minor horizontally through the axilla until it joins the axillary vessels to continue towards the inner upper arm (see Figure 9).

The thoracodorsal nerve accompanies the thoracodorsal vessels on the floor of the axilla.

The long thoracic nerve runs along the lateral chest wall together with the lateral thoracic vein and artery.

Surgical technique

It is important for the breast surgeon to examine the patient before the operation in order to decide on the incision. To do that you need to talk to the patient and examine her in upright and supine position to see the shape of the breast, the mobility of the tumor and the patient's skin folds in different positions. A transverse incision gives the best results. Its position will depend on the site of the tumor. You should include the tumor and the nipple/areola-complex in your incision. It is a good habit to draw the shape of the incision on the patient's chest with a text marker once you have decided what to do. Make sure you are be able to close the skin after the breast is removed!

During the operation the patient should receive general anesthesia and be positioned in a supine position with the arm of the concerned side either elevated on a cross-bar or positioned at a 90° angle to the chest. We prefer the latter. She should receive an IV peri-operative antibiosis which includes staphylococci, such as cloxacillin or a cephalosporin. Wash and disinfect the patient's upper abdomen and chest of the concerned side up to the midline and the neck, and the complete arm including the arm pit and forearm, and drape appropriately.

Mastectomy

Incise the skin alongside your marked line. Place small non-toothed forceps such as Allis clamps in the subcutaneous tissue just below the skin and put traction on them (only grasp the specimen, not the remaining tissue). The aim of the operation is to remove all breast tissue but you still want to be able to close your incision. So you must prepare skin flaps and only remove the underlying breast tissue along the Cooper ligaments between breast and skin. The area should cover all tissue down to the submammary fold, upwards near the clavicle, medial near the xiphoid, lateral to the axilla and down to the fascia of the pectoralis major muscle. The fascia should be removed as well.

Take care that your skin flaps are thin enough to remove as much breast tissue as possible and thick enough to be well vascularized. Start by dissecting the subcutaneous fat tissue with small curved scissors, such as Metzenbaum scissors. In the beginning dissect more tangentially to reach the margins of the area described above, and then dissect downwards in the direction of the chest wall.

It is best to control for bleeding either by cauterization or by ligation (2–0 catgut or Vicryl) so you keep your field of operation clean and neat. Dissect the tissue until you reach the fascia and the pectoralis major muscle. Incise the fascia and remove it as well. This can sometimes be done bluntly by using your index finger. Keep in mind that the tumor might have invaded the fascia or even the muscle and take a good look at this area underneath the tumor. State your findings in your surgical report. If fascia or muscle are adherent to the tumor you might need to remove a piece of muscle to have clear margins.

Proceed to remove the breast from the medial side to the axilla on the lateral end. Watch out for the perforating branches of the internal thoracic arteries and veins in the sternal area. Identify them and ligate them before cutting them. Remember, they are very difficult to reach once they have retracted into the pectoral muscle. Once you are at the lateral margin of the pectoralis major muscle you will note a change in color of the fatty tissue of the axilla.

Remove the mastectomy specimen and position it on a flat surface, e.g. a tray in the direction it was located in your patient and put sutures of different length and record them on the pathology request

form: lateral, medial, superior and posterior suture. Like this the pathologist will be able to comment on tumor invasion of the different margins.

Axillary lymphadenectomy

Put a small retractor under the lateral margin of the pectoralis major muscle to incise the fascia covering the axillary fat. Identify the axillary vein under the fatty tissue in the upper part of the axilla. You can do this by using your index fingers or a non-toothed curved forceps. The axillary vein is your superior border of excision. The medial and inferior border is the chest wall, the lateral and posterior border is the latissimus dorsi muscle. The tissue within this triangle should be removed. Note that the intercostobrachial nerves are crossing the triangle rather superficially and take care not to cut them if ever possible as this will cause loss of sensation to the inner upper arm.

Identify the thoracodorsal blood vessels and nerve at the floor of the axilla and the long thoracic nerve along the chest wall and preserve them. Lastly, put traction on the retractor placed under the pectoralis major muscle to expose the lateral margin of the pectoralis minor muscle and remove some of the fatty tissue in between the two.

Control for hemostasis with either cauterization or 3–0 Vicryl or cat gut ligatures. Irrigate the axilla with normal saline to identify small bleeding vessels.

If available put drainages in the axilla and mastectomy wound. Close the axilla with several single subcutaneous stiches using 2–0 catgut or Vicryl. Ask your assistant to approximate the skin flaps of the mastectomy site and put single subcutaneous stiches with 2–0 Vicryl or catgut. These sutures are important as there will be quite some tension on them, so make sure you do this well. Start with a suture in the middle of the incision dividing the incision into two parts. Add a stitch in the middle of each part and so forth until you have approximated the skin flaps well without too much tension on one spot. Close the skin of axilla and mastectomy incision with 3–0 absorbable sutures either with single stitches or with an intracutaneous running suture.

Apply a wound dressing and a pressure dressing with a bandage around the chest wall for 24 h. The patient should receive postoperative antibiotic prophylaxis according to local standards. She can move, eat and drink as soon as she is fully awake.

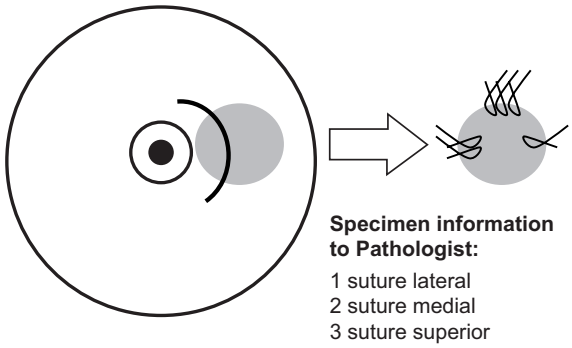

Figure 10 The former location of the specimen is clearly marked at medial, lateral and superior margins for the pathologist

Breast-conserving surgery

Breast-conserving surgery together with whole-breast irradiation yields the same rates of mortality as modified radical mastectomy, but in settings where radiotherapy cannot be ensured, it should be discouraged. Both surgical techniques are combined with axillary lymph node dissection. Breast-conserving surgery is done like an excisional biopsy (described above), but in contrast to a benign breast tumor, a malignancy should be excised with a macroscopic margin of healthy tissue of at least 1 cm. After removing your specimen from the breast mark the posterior, lateral, medial and superior surface with different numbers of sutures and write them down for the pathologist (Figure 10). This is extremely important to establish whether you left microscopic malignant tissue behind and if yes where.

CHEMOTHERAPY

Chemotherapy for breast cancer patients who are in good general condition may generally be done as an out-patient procedure. The general standard is anthracycline-based regimens as first choice. The patient will have an additional 5–10% survival-benefit when chemotherapy is added to the operation. The same holds true for endocrine treatment if indicated.

In patients presenting with stage II disease (tumor >2 cm or node-positive disease) chemotherapy is indicated even in basic levels. Giving chemotherapy requires laboratory facilities including full blood count and serum chemistry. Many healthcare institutions even in BHGI level 1 facilities have been equipped with advanced laboratory machines for

the provision of antiretroviral therapy (ART) for HIV/AIDS. These include hematology and biochemistry examinations. See Chapter 31 on more information about how to give chemotherapy and how to monitor and treat side-effects.

Chemotherapy is given on one day; then after a 3-week interval the next dose is given. The most important side-effect of chemotherapy used in breast cancer is neutropenia. This may lead to immunodeficiency during nadir (time-point of lowest blood counts) during one cycle, e.g. for CMF chemotherapy the nadir is between day 7 and day 14 of the cycle. The total number of cycles given is usually six. Make sure to see the patient weekly during each cycle to check full blood count and general condition. In case of signs of infection AND low blood counts broad-spectrum antibiotics have to be given immediately – specific antibiotic therapy should be added according to the results of a blood culture where this is available. Always document the toxicities experienced according to common toxicity criteria (CTC, see Chapter 31). There should not be more toxicities than CTC grade 1 when giving the next dose. Otherwise dose-delay or dose-reduction has to be considered (see Chapter 31). The general idea in the adjuvant situation is to cure the patient. Therefore giving the total dose in the appropriate time-schedule should be aimed at.

The palliative situation is completely different. A patient having metastasis will not be cured. Therefore give as much chemotherapy as needed to improve the situation and as little as possible to avoid side-effects. Preferably a single-agent regimen should be chosen to have less toxicities.

Polychemotherapy (basic level 1) may include the following agents (see Chapter 31 for detailed regimen):

- CMF (cyclophosphamide, methotrexate, 5-fluorouracil)
- AC (doxorubicin and cyclophosphamide)
- EC (epirubicin and cyclophosphamide)
- CAF (5-fluorouracil, doxorubicin and cyclophosphamide)

Single-agent therapy (enhanced level 3) includes the following: epirubicin/doxorubicin, capecitabine, vinorelbine, gemcitabine, carboplatin. These drugs are usually not available in a low-resource setting – sometimes patients may be able to access them personally through more capable relatives.

See Chapter 31 for details of the chemotherapy regimen.

ENDOCRINE THERAPY

Breast cancer cells may express receptors for estrogen and progesterone on their surface which, when reacting with those hormones, will induce cell and tumor growth. Endocrine therapy aims at either reducing the level of natural hormones or blocking those receptors so that they can no longer bind these hormones, like a keyhole where the key (estrogen or progesterone) doesn't fit anymore because another key (endocrine therapy) has been inserted.

Estrogen and progesterone production is reduced by interfering with the production of pituitary hormones which regulate the production of estrogens and progestins. This is either achieved through drugs or by performing a bilateral oophorectomy (see Chapter 11 on how to perform a bilateral oophorectomy). The patient will then be postmenopausal either temporarily (expensive! drugs) or for good (surgery).

The provision of endocrine therapy needs few resources – knowledge of the hormone-receptor status through pathology results is needed to assure a benefit. Patients with unknown receptor status should still be treated with the receptor-blocker tamoxifen (but a considerable overtreatment is to be expected especially in a setting with many receptor-negative tumors).

Tamoxifen 20 mg o.d. for 5 years is the gold-standard for patients with hormone receptor-positive tumors in the adjuvant setting. Patients with metastasis may receive tamoxifen as long as a response to the therapy is observed (stable disease or remission). Tamoxifen may cause thrombosis – take a careful history to find out about previous thrombosis, this is a contraindication.

In premenopausal women ovarian ablation is another option. Temporary castration may be achieved by luteinizing hormone-releasing hormone (LHRH) inhibitors as described above, but they are expensive, if available at all and have to be given intramuscularly monthly for 2 years. When considering surgical castration through bilateral oophorectomy be aware that very young patients will suffer from osteoporosis.

NOTE: endocrine therapy should always be given AFTER the completion of chemotherapy

(NOT concomitant)! Otherwise side-effects will occur but there is no therapeutic benefit.

RADIOTHERAPY

The usefulness of radiation is proven for breast-conserving therapy, chest-wall radiation after mastectomy (in case of positive lymph nodes or large tumor) and palliation of metastasis or locally advanced disease, especially bone metastasis. Any patient who opts for breast-conservative surgery in early-stage disease must know that she will have to have radiotherapy after her operation, otherwise her risk for recurrence will be high and she should be discouraged from breast-conserving surgery. The use of radiotherapy depends on the availability of the facility and the magnitude of the population to be served. There is a large demand in low-resource settings but only a few centers provide radiotherapy either by cobalt machine or linear accelerator.

PALLIATIVE CARE

Radiotherapy is an excellent option for pain relief of metastasis (especially bone metastasis). Additionally non-opioid and opioid medication must be available. This is usually mainly an administrative problem! Please refer to the WHO guidelines for pain medication (see Chapter 32).

EARLY DETECTION/PREVENTION

As we do not yet know what causes breast cancer, there is no way of preventing it. One of the main long-term goals in low-resource settings is to encourage patients to present earlier and thus with smaller tumors with higher chances for cure. Different options are recommended by BHGI (Table 6).

TREATMENT IN SPECIAL SITUATIONS

The *very young patient* <35 years has an unfavorable prognosis. She should nevertheless receive full adjuvant or neoadjuvant systemic treatment. In case of living children, bilateral oophorectomy must be thoroughly discussed with the patient. Doing oophorectomy in a nulliparous women does not seem adequate – tamoxifen for 5 years is a good alternative therapeutic option in this case. Many surgeons advise a young patient to wait for another pregnancy for 5 years as recurrence will then be less common. Especially in hormone receptor-positive breast cancer, a pregnancy with high hormonal levels could induce recurrence. Non-hormonal family planning must be used (e.g. intrauterine copper device, IUD). Counseling should be done to the family as inherited breast cancer is likely and close female relatives such as daughters, sisters or mothers should have regular examination of the breast.

Diagnosis of *breast cancer in pregnancy* is often delayed (even in high-resource countries). The operation is done just as in non-pregnant women. Staging is done similarly. Take a thorough history. Also do a chest X-ray covering the abdomen with a lead apron if advanced disease is present and there are pulmonary symptoms in the second or third trimester (avoid X-ray in first trimester). Since the information on metastasis will greatly affect the recommended therapy, exposure to radiation is justified and dosage is most likely unharmful to a second- and third-trimester fetus. Chemotherapy may be given in pregnancy. There are studies showing good results with anthracyclines. Do not give methotrexate (as in CMF)! Endocrine treatment is also contraindicated – start after delivery. Usually breast cancer in pregnancy is NOT a reason to terminate the pregnancy (it will NOT improve the maternal outcome!). When approaching delivery make sure that the chemotherapy is stopped >3 weeks before the expected date of delivery to avoid compromising the immune system due to neutropenia. Beware of potential contraindications of chemotherapy during times of breastfeeding (breastfeeding does not impair outcome of the mother).

Male breast cancer patients may also come to your center (up to 5% of the patients). The treatment is generally similar to that for female patients. The operative standard is modified radical mastectomy and axillary dissection. Radiotherapy and chemotherapy is similar. Tamoxifen will also improve outcome in hormone receptor-positive disease (aromatase inhibitors are contraindicated). Palliative therapy is similar.

Inflammatory breast cancer is a clinical diagnosis when localized redness and orange skin phenomenon on the breast is seen above a malignancy. Patients must be treated by neoadjuvant chemotherapy to allow surgery. Always do modified radical mastectomy; breast-conserving treatment is contraindicated.

Table 6 Resource allocation for early detection for breast cancer

Level	*Public education and awareness*	*Detection methods*	*Evaluation goal*
Basic	Development of culturally sensitive, linguistically appropriate local education programs for target population to teach early detection, breast cancer risk factors and breast health awareness (education + self-examination)	Clinical history and CBE	Breast health awareness regarding value of early detection in improving breast cancer outcome
Limited	Culturally and linguistically appropriate targeted outreach/education encouraging CBE for age groups at higher risk administered at district/provincial level using healthcare providers in the field	Diagnostic breast US ± diagnostic mammography in women with positive CBE Mammographic screening of target group*	Down-sizing of symptomatic disease
Enhanced	Regional awareness programs regarding breast health linked to general health and women's health programs	Mammographic screening every 2 years in women aged 50–69* Consider mammographic screening evert 12–18 months in women aged 40–49*	Down-sizing or down-staging of asymptomatic disease in women in highest yield target groups
Maximal	National awareness campaigns regarding breast health using media	Consider annual mammographic screening in women aged 40 and older Other imaging technologies as appropriate for high-risk groups†	Down-sizing and/or down-staging of asymptomatic disease in women especially in all risk groups

CBE, clinical breast examination; US, ultrasound. *Target group selection for mammographic screening should consider breast cancer demographics and resource constraints within the population. †It has been demonstrated that breast magnetic resonance imaging is more sensitive than mammography in detecting tumors in asymptomatic women who have an inherited susceptibility to breast cancer. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited and enhanced levels. Maximal level resources should not be targeted for implementation in low- and middle-income countries, even though they may be used in some higher income settings. (Adapted from Anderson BO, Yip CH, Smith A, *et al*. Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. *Cancer* 2008;113(8 Suppl.):2221-43. The American Cancer Society. This material is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

Mammary Paget disease is treated as other breast cancer. The nipple and areola have to be removed. This will usually involve a mastectomy unless reconstructive surgery with radiation is available. Adjuvant treatment is done as in other breast cancer forms.

Phyllodes tumors may rapidly reach a huge size without distant metastasis. A thorough surgical removal is indicated – a minimum of 1-cm margin has to be reached! Mostly a mastectomy will be done. Axillary clearance is not needed. Systemic therapy is NOT indicated!

Sarcoma or angiosarcoma of the breast is very aggressive and the prognosis is poor. It must be treated by radical surgery. Systemic therapy has little effect but may be indicated as for other sarcoma.

BREAST CARE PROGRAMS

Community sensitization (BHGI level 1)

This is very important especially in regions where patients do present late! Unless the women know about the disease, are aware of available treatment and see long-term survivors – early detection and down-staging cannot be achieved. In particular, primary healthcare workers at a grass-root level need to know about breast cancer. Who else should advise the women to seek care? Antenatal care is

one of the most successful healthcare programs worldwide – why not include a question and sensitization about breast lumps in your conversation with the pregnant women? The same accounts for pediatric services such as childhood vaccination clinics where mothers bring their children, which have an equally high coverage in many countries.

Do not forget to sensitize key players of the general population such as women's groups and religious leaders or other community leaders.

Since people are more and more educated, radio and TV are mass media easily accessible for campaigns. This includes advocacy at the ministries of health to put breast cancer awareness on the agenda.

Clinical breast examination (through field workers: BHGI level 2)

In two large clinical trials in India[18] and Malaysia CBE has been shown to down-stage the disease in a significant way[19]. However, so far, an effect on mortality has not been proven – but the final results of the trials are yet to come. Down-staging will definitely improve survival of the individual patient!

Breast cancer screening campaigns (BHGI level 3)

Breast cancer screening makes sense in countries with a high incidence of older people, widely available mammography sites and a good quality assurance program. It has been proven effective in Sweden from 40 years onwards[20]. It is not (cost-) effective in countries with a younger population and a low incidence of breast cancer. There would be too many false-positive findings due to dense breast tissue in mammography, and few cases found due to lower incidence. The human and financial resources needed for such a campaign are also too high to make it possible and effective in such a population. In addition there are by far too few functioning mammography units let alone qualified radiologists available for a large population in low-resource settings[21].

IMPLEMENTING A BREAST CANCER PROGRAM BY LEVEL OF RESOURCES

The BHGI gives well-developed, evidence-based guidelines for low- and middle-income countries to set up their specific breast care programs. It is essential to acquire basic data to assess the magnitude of the disease within the country (e.g. cancer registration at least in one town/area). A situational analysis of healthcare system and patient behavior is needed at baseline. Human resources available must be considered thoroughly. A multidisciplinary approach to implement a breast care program is essential. At basic resource level, a minimum of diagnostic/pathology services, nursing and oncology services, palliative and psychosocial services as well as primary care and surgical services have to be available. Drug delivery has to be established. Since the costs of systemic therapy are considerably high (even though tamoxifen, CMF and FAC are on the WHO essential drug list), partnership projects with pharmaceutical companies or non-governmental international organizations (e.g. pink ribbon) may be considered. Government involvement is needed, especially when it comes to the availability of essential opioid drugs for palliative care. Breast healthcare may well be integrated into existing healthcare infrastructures. At limited resource level, imaging services and radiation oncology services are added. Breast centers should be established. Public education should always be a major focus of a breast cancer program especially in settings where patients present at late stages. The service must include quality assurance and evaluation of cost-effectiveness[22].

Female breast cancer is the most prevalent neoplasm in the world[22]. It may be noted by the patient herself and can be treated with reasonable effort concerning man-power and costs. We therefore suggest a breast cancer program to be one of the first cancer programs in low-resource settings to address the issue of increasing numbers of cancer. Evaluations of sites which have implemented evidence-based guidelines according to resources available show encouraging results[23]! Patients present earlier, therapies become routine and the diagnosis of breast cancer is a challenge rather than a fatal diagnosis!

REFERENCES

1. Forouzanfar MH, Foreman KJ, Delossantos AM, *et al.* Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. *Lancet* 2011;378: 1461–84
2. Sankaranarayanan R, Swaminathan R, Brenner H, *et al.* Cancer survival in Africa, Asia, and Central America: a population-based study. *Lancet Oncol* 2010;11:165–73
3. Anderson BO, Cazap E, El Saghir NS, *et al.* Optimisation of breast cancer management in low-resource and

middle-resource countries: executive summary of the Breast Health Global Initiative consensus, 2010. *Lancet Oncol* 2011;12:387–98
4. Anderson BO, Yip C-H, Smith RA, *et al*. Guideline implementation for breast healthcare in low-income and middle-income countries. Overview of the Breast Health Global Initiative Global Summit 2007. *Cancer Suppl* 2008;113:2221–43
5. Ferlay J, Shin HR, Bray F, *et al*. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893–917
6. Adebamowo CA, Adekunle OO. Case-controlled study of the epidemiological risk factors for breast cancer in Nigeria. *Br J Surg* 1999;86:665–8
7. Akarolo-Anthony SN, Ogundiran TO, Adebamowo CA. Emerging breast cancer epidemic: evidence from Africa. *Breast Cancer Res* 2010;12 (Suppl. 4):S8
8. Ogundiran TO, Huo D, Adenipekun A, *et al*. Case-control study of body size and breast cancer risk in Nigerian women. *Am J Epidemiol* 2010;172:682–90
9. Huo D, Ikpatt F, Khramtsov A, *et al*. Population differences in breast cancer: survey in indigenous African women reveals over-representation of triple-negative breast cancer. *J Clin Oncol* 2009;27:4515–21
10. Tfayli A, Temraz S, Abou Mrad R, Shamseddine A. Breast cancer in low- and middle-income countries: an emerging and challenging epidemic. *J Oncol* 2010;2010: 490631
11. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology* 1991;19:403–10
12. Sobin LH, Wittekind C (eds). *TNM Classification of Malignant Tumors*, 6th edn. New York: Wiley-Liss, 2002.
13. Okonkwo QL, Draisma G, der Kinderen A, *et al*. Breast cancer screening policies in developing countries: a cost-effectiveness analysis for India. *J Natl Cancer Inst* 2008;100:1290–300
14. Torres Edejer TT, Baltussen R, Adam T, *et al*. Making choices in health: WHO guide to cost-effectiveness analysis. Geneva: World Health Organization, 2003
15. Thomas DB, Gao DL, Ray RM, *et al*. Randomized trial of breast self-examination in Shanghai: final results. *J Natl Cancer Inst* 2002;94:1445–57
16. Berg WA, Blume JD, Cormack JB, *et al*.; ACRIN 6666 Investigators. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. *JAMA* 2008;299:2151–63
17. Khurana KK, Swati I, Kasturi R, *et al*. Telecytopathology for rapid preliminary diagnosis of ultrasound-guided fine-needle aspiration of thyroid nodules. *Telemedicine and e-Health* 2011;17:763–7
18. Sankaranarayanan R, Ramadas K, Thara S, *et al*. Clinical breast examination: preliminary results from a cluster randomized controlled trial in India. *J Natl Cancer Inst* 2011;103:1476–80
19. Corbex M, Burton R, Sancho-Garnier H. Breast cancer early detection methods for low and middle income countries, a review of the evidence. *Breast* 2012;(in press)
20. Hellquist BN, Duffy SW, Abdsaleh S *et al*. Effectiveness of population-based service screening with mammography for women ages 40 to 49 years: evaluation of the Swedish Mammography Screening in Young Women (SCRY) cohort. *Cancer* 2011;117:714–22
21. Harford JB. Breast-cancer early detection in low-income and middle-income countries: do what you can do versus one size fits all. *Lancet Oncol* 2011;12):306–12
22. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer* 2012; (in press)
23. Harford JB, Otero IV, Anderson BO, *et al*. Problem solving for breast health care delivery in low and middle resource countries (LMCs): consensus statement from the Breast Health Global Initiative. *Breast* 2011;20 (Suppl. 2):S20–9