Diagnosis and staging of breast cancer

Breast cancer is a very common cancer among women world-wide.

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Women have an average lifetime risk of 1 in 8 of being diagnosed with breast cancer, making it the most common non-skin cancer in women in the Western world. While the incidence has increased, the overall breast cancer death rate has shown a steady decrease since the early 1990s,[1] most likely as a result of improved detection techniques, increased sensitivity of investigations, and better treatment protocols. In developing countries such as South Africa, statistics are less reliable, but breast cancer remains a major health problem, affecting women of all population groups and of all ages, and causing significant morbidity and mortality.

Invasive ductal carcinoma is the most common histological type, accounting for 70 - 80% of cases, while invasive lobular carcinoma is the second most common, accounting for 5 - 10% of cases. Less common epithelial cancers include tubular, medullary, mucinous and papillary carcinomas. Phylloides tumour, angiosarcoma and lymphoma are non-epithelial cancers that occur infrequently.

The suspicion of breast cancer is raised either during investigation of a complaint, routine examination, or screening mammography. The diagnosis of breast cancer is based on the triple assessment[2] and comprises:

- physical examination
- imaging – mammography and/or ultrasonography
- biopsy – fine-needle aspiration biopsy (FNAB) and/or core-needle biopsy.

The three modalities are complementary, enabling the diagnosis of most cases of breast cancer.

Physical examination [2-5]

Breast cancer may present as a lump or increased tissue thickening in the breast, with skin or nipple changes, nipple discharge or may be incidentally discovered by radiological imaging.

The examination of the breast should proceed with the patient in the upright sitting position with inspection for obvious masses, asymmetry, skin or nipple retraction and skin changes. Raising the arms above the head or tensing the pectoralis muscles may accentuate asymmetry or skin dimpling. Then, with the patient supine, and the hands placed above the head, the breasts should be gently palpated against the chest wall, feeling for any masses or thickening. Next, the axillae are palpated for any nodal involvement while supporting the patient's arm. Lastly, the supraclavicular areas are palpated for the presence of lymph nodes.

A non-tender breast lump is the most common finding in women with breast cancer. The stronger the risk factors for developing breast cancer (Table I), the more likely it is that a lump is cancerous. It is important to remember that most breast cancers occur in women without any overt risk factors at all.

Table I. Major risk factors for breast cancer

Increasing age
Postmenopausal
BRCA gene positive or strong family history
Multiple 1st- and 2nd-degree relatives with breast and ovarian cancer
1st-degree relative diagnosed with breast cancer before 50 years
Male relatives diagnosed with breast cancer
Jewish ancestry with family history
Previous breast cancer or DCIS or LCIS or atypia
Longstanding exposure to unopposed oestrogens
Chest wall irradiation

Differential diagnosis of a breast lump

Common causes of benign breast lumps are fibroadenomas, cysts and fat necrosis (Table II). The differential diagnosis is strongly influenced by the patient's age (Fig. 1). Breast lumps should be characterised according to their size, consistency and location. Carcinomas are typically firm and less well circumscribed, and their movement produces a drag of the adjacent tissue. Cysts and fibroadenomas are typically firm, but well-circumscribed and mobile.

Some carcinomas may not necessarily present with a well-defined discrete lump on examination, but rather an area of focal breast thickening, with or without overlying skin dimpling. In the majority of cases, these clinical findings reflect fibrocystic changes,

Table II. Differential diagnosis of a breast lump

Benign	Malignant
Fibroadenoma	Non-invasive
Cysts	Lobular carcinoma *in situ* (LCIS)
Breast abscess	Ductal carcinoma *in situ* (DCIS)
Fat necrosis	Invasive epithelial
Papilloma	Ductal carcinoma
Hamartoma/adenoma	Lobular carcinoma
Other sclerosing lesions	Medullary/mucinous/papillary carcinoma
Radial scar	Other non-epithelial neoplasms
Sclerosing adenosis	Phylloides tumour
	Angiosarcoma
	Lymphoma
	Metastasis to the breast

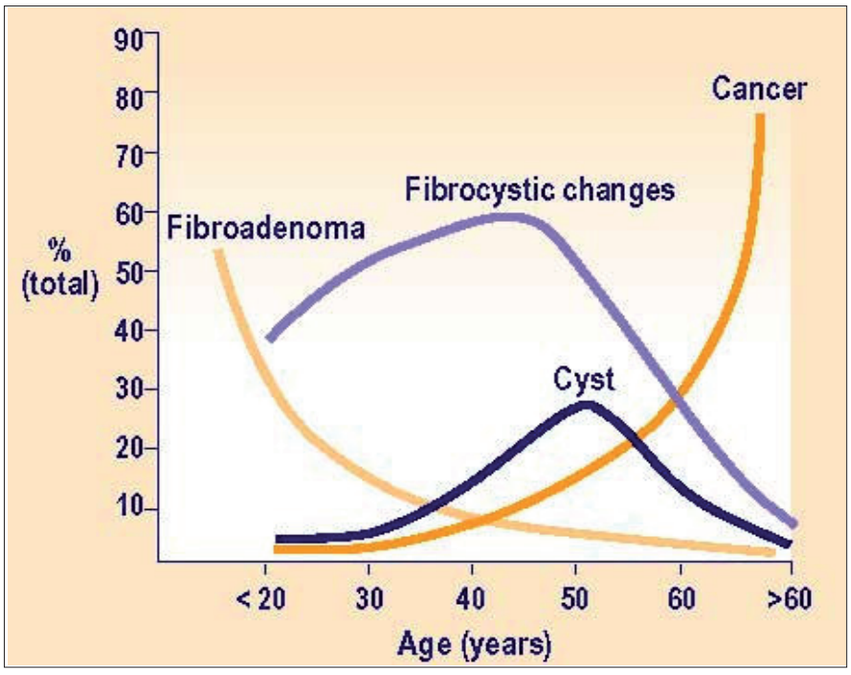


Fig. 1. Age distribution of benign and malignant breast lesions in patients presenting with a palpable breast lump.

but it is important to consider that some carcinomas, particularly lobular in type, may present with similar subtle clinical findings. An area of focal breast thickening should be evaluated thoroughly with breast imaging and directed needle biopsy.

Oedema of the skin produces a clinical sign known as peau d'orange (skin of the orange) and, when associated with breast cancer, is a sign of locally advanced disease. When combined with erythema, warmth and tenderness, these signs are the hallmark of inflammatory carcinoma, and may be mistaken for mastitis or breast abscess.

Nipple discharge is common and rarely associated with an underlying breast cancer. Common causes include physiological discharge, intraductal papilloma, duct ectasia and periductal mastitis. A spontaneous unilateral non-milky discharge from a single duct orifice is significant and warrants further investigation, although in the absence of a palpable mass or suspicious mammogram, this symptom is usually not associated with cancer. This clinical scenario is best investigated with a microdochectomy (excision of breast duct).

An eczematous nipple reaction is highly suggestive of Paget's disease. Histologically, this condition is produced by intraductal carcinoma occurring in the large lactiferous sinuses just under the nipple. Carcinoma cells invade into the epidermal layer of skin of the nipple, and may then spread radially onto the areola. By contrast, benign skin conditions such as eczema usually originate on the areola. Paget's disease may or may not be associated with an underlying mass. A punch biopsy of the affected skin is diagnostic.

Breast imaging[7]

Mammography

Mammography is the traditional first-line radiological test for breast cancer, and can be used for diagnostic and screening purposes. Standard mammography comprises a craniocaudal and oblique view of each breast, but this can be augmented with a coned compression (paddle) view and magnification of a suspicious lesion. The classic appearance of invasive ductal carcinoma is a hyperdense, spiculate mass, although architectural distortion, asymmetry, stellate lesions and calcification may also indicate carcinoma (Fig. 2a). The development of digital mammography has further increased the quality of this technique, particularly in patients with dense breast parenchyma. It is important to remember that mammography has a false negative rate of approximately 15%. A normal mammogram, therefore, does not exclude breast cancer, and clinical signs should not be ignored.

Ductal carcinoma *in situ* (DCIS) is diagnosed on mammography and by core biopsy, and consists of malignant cells contained within the basement membrane of the breast ducts. It is usually asymptomatic and not clinically palpable, being detected on mammography as multiple pleomorphic microcalcifications arranged in clusters or linear formations.

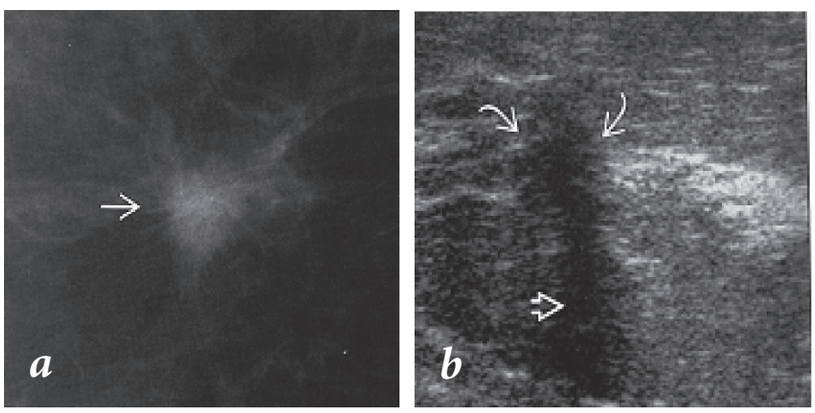


Fig. 2. Images of infiltrating ductal carcinoma: mammogram (a) and ultrasound (b).

Less commonly, it presents as a mass, nipple discharge or Paget`s disease of the breast. Approximately 30 - 50% of patients with DCIS will develop invasive ductal carcinoma over a 10-year period. In contrast, lobular carcinoma *in situ* arises from the terminal duct lobules and is considered a marker of increased risk of breast cancer rather than a precursor of cancer.

A suspicious lesion detected by mammogram should be referred to a specialist centre, regardless of whether it is palpable or not.

Ultrasound

Ultrasound has a sensitivity of about 75% for the diagnosis of breast cancer. It is seldom used in isolation, but it is useful in assessing a breast mass where mammography is nonspecific, particularly in young women with dense breasts. Benign lumps appear as iso- or hypoechoic, well-circumscribed masses, and lack hypoechoic shadows. Malignant tumours appear as mixed echogenic, irregular masses, and cast hypoechoic shadows (Fig. 2b).

Magnetic resonance imaging

The use of MRI has exponentially increased in the last decade. The best documented role for MRI is as a screening modality in young women carriers of BRCA1 or 2 mutation, and in the evaluation of patients who may have a local recurrence after previous breast-conserving surgery and irradiation.

Tissue diagnosis

Fine-needle aspiration[6]

If a mass is palpable, fine-needle aspiration biopsy (FNAB) should be performed *after* mammography. In the case of a sonographically detected mass, FNA may be done under ultrasound guidance. It is carried out using a 22 G needle on a 10 ml syringe. Leaving 2 ml of air in the syringe, negative pressure is applied while making multiple passes through the lump (Fig. 3). Thin smears of aspirate are prepared on slides which are either air dried or sprayed with a fixative, depending on the unit protocol.

After specialised staining the slides are examined by a breast cytopathologist. The findings fall into one of five categories: inadequate, benign, atypical, suspicious and malignant. The presence of carcinoma cells on FNAB may not differentiate between *in situ* and *invasive* carcinoma and most units do not recommend definitive treatment based on cytological assessment. False-positive diagnoses are rare (<0.5%), but well documented. Benign cells on a breast aspirate tend to show cohesion, and regularity of nuclear detail. Malignant cells are discohesive and depending on the size and arrangement of the cells suggest malignancy of either the ductal or lobular components of the breast epithelium. As can be seen from Fig. 4, the size of the cells of a lobular carcinoma is smaller, and therefore can cause more problems in false-negative diagnosis.

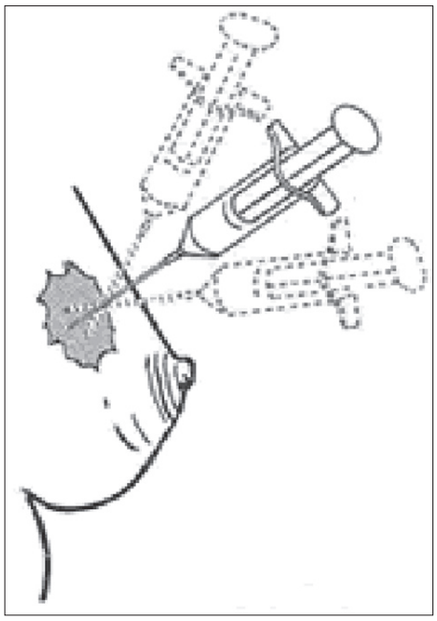


Fig. 3. Fine-needle aspiration biopsy.

Core biopsy

Core biopsy establishes a histological diagnosis. Using a cutting needle device (e.g. Trucut), it is carried out immediately after FNAB. A core biopsy can establish cell type, differentiate between *in situ* and *invasive* cancer, and will often establish receptor status and tumour grade. Core biopsy is more technically difficult than FNAB but, when positive, establishes an *unequivocal diagnosis* of carcinoma.

Both needle techniques have a false-negative rate, mostly as a result of technical error or geographic mis-sampling.

Excision biopsy

In most breast units the diagnosis of carcinoma is made without resorting to excision biopsy. However, approximately 5% of cases of breast cancer are not confidently diagnosed with a triple assessment, and require formal excision (Table III). For small lesions, radiologically guided biopsies may greatly simplify the diagnostic process. Some breast tumours are particularly difficult to characterise with needle biopsy only, particularly low-grade phylloides tumours, and solid-cystic papillary carcinomas in the elderly.

Impalpable breast cancer

With the use of imaging modalities an increasing number of breast cancers are identified before they present with any clinical signs. In this context the diagnosis may be made by using stereotactic (Fig. 5) or US-guided core biopsies, or by guided excision biopsy, either using hookwire or radio-guided tracers (radio-guided occult lesion localisation (ROLL)). The narrow diameter of the biopsies can represent a special challenge to the pathologist as the 'whole' lesion is seldom sampled. Close liaison between radiologist, clinician and pathologist is essential when selecting patients for these procedures.

Staging breast cancer[9]

The tumour, node, metastases (TNM) classification system is used worldwide to stage breast cancer (Tables IV and V). There are two parts to this classification: a clinical staging relating to the clinical assessment of tumour size (T), node status (N) and presence of metastases (M), and a final pathological T and N staging of the resected breast and axillary specimen.

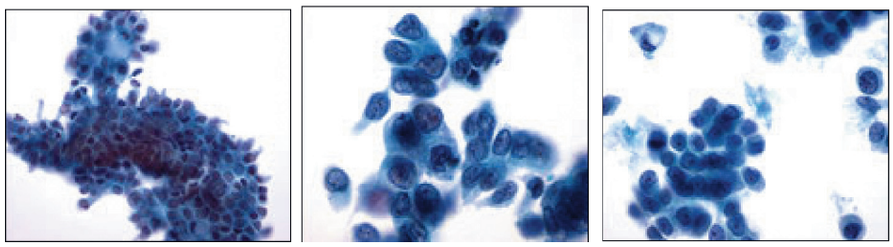


Fig. 4. Benign and malignant breast aspirates. Left: sheet of benign cells; middle: malignant ductal cells; right: malignant lobular cells.

Table III. Indications for excision biopsy

Discordant results of needle biopsy or mammography

- Cytology report suspicious or malignant but mammogram and core biopsy inconclusive / benign
- Mammogram suspicious / malignant, cytology and core biopsy inconclusive / benign

Patient request

Symptomatic discrete mass in patient older than 35 years

Table IV. TNM staging

TNM clinical classification		TNM pathological classification
T – primary tumour		Same as clinical stage
Tx	Can't be assessed	
T0	No evidence of primary tumor in the breast	
Tis	Carcinoma *in situ*	
T1	<2 cm	
T2	2 - 5 cm	
T3	>5 cm	
T4	Any size, with direct extension onto skin or chest wall, or inflammatory carcinoma	
N – regional lymph nodes		
Nx	Can't be assessed	Can't be assessed
N0	No regional nodes	No regional nodes
N1	Mobile ipsilateral axillary nodes	1 - 3 axillary nodes, and/or non-clinically apparent internal mammary node involvement
N2	Fixed or matted axillary nodes, or palpable internal mammary nodes	4 - 9 axillary nodes, or clinically apparent internal mammary node involvement
N3	Palpable infra- or supraclavicular nodes, or palpable axillary and internal mammary nodes	10 or more axillary nodes, or infraclavicular or supraclavicular node involvement, or axillary *and* internal mammary node involvement
M – distant metastases		Same as clinical stage
Mx	Can't be assessed	
M0	No distant metastases	
M1	Distant metastases	
M	Distant metastases	

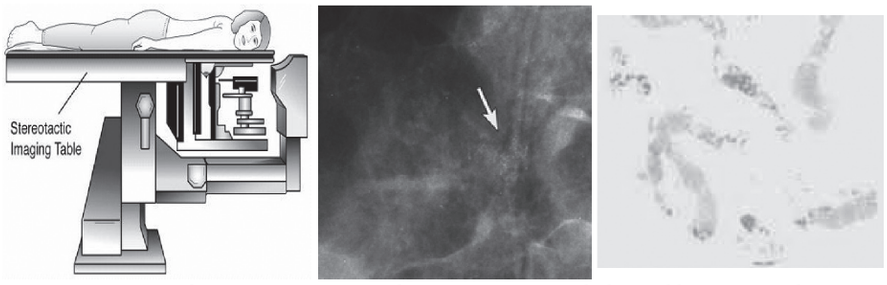


Fig. 5. A stereotactic biopsy requires a special imaging system, with directed biopsy towards particularly abnormal areas of calcification.

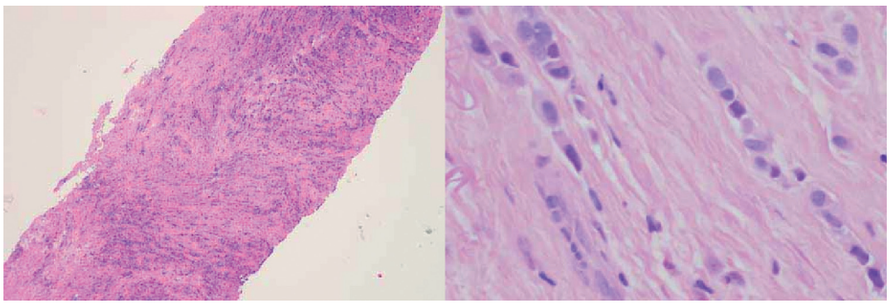


Fig. 6. The diffuse nature of lobular carcinoma on core biopsy which can sometimes be mistaken for lymphocytes. The 'Indian file' configuration of the small discohesive cells which is typical of lobular carcinoma (right).

The metastatic screen (M) should include a full blood count, serum urea and electrolytes and calcium, liver function test, chest X-ray, bone scan and liver ultrasound. Investigations such as PET imaging or bone marrow biopsy are not routinely used for staging purposes. The combining of the T, N and M is used for the final determination of the stage of the disease, which has prognostic and therapeutic implications.

Pathological considerations

- Ductal carcinoma – not otherwise specified (NOS) – accounts for 70 - 75% of all malignancies. It shows some similarity to the breast duct, therefore a degree of tubule differentiation is often seen.
- Invasive lobular carcinoma constitutes 10% of all invasive cancers. It grows in a typically 'Indian file' pattern and has a tendency toward multi-focality and bilaterality (Fig. 6).
- Other types of breast cancer include tubular carcinoma, mucinous carcinoma, cribriform carcinoma, medullary-like carcinoma and papillary carcinoma.
- Ductal carcinoma *in situ* (DCIS) is diagnosed on mammography and core biopsy, and consists of malignant cells contained within the basement membrane of the breast ducts. It is usually asymptomatic and not clinically palpable, being detected on mammography as multiple pleomorphic microcalcifications arranged in clusters or linear formations. Less commonly, it presents as a mass, nipple discharge or Paget's disease of the breast. Approximately 30 - 50 % of patients with DCIS will develop invasive ductal carcinoma over a 10-year period.
- Lobular carcinoma *in situ* (LCIS), on the other hand, arises from the terminal duct lobules and is considered a marker of increased risk of breast cancer rather than precursor of cancer.

Prognostic factors

The most important prognostic factor is stage. However, grade, lymphovascular invasion, hormonal and Her2 status also have significance:

- Histological grade (Fig. 7) provides important prognostic and management information.The internationally accepted system is that defined by Elston and Ellis.[1] Assessment is made by evaluating acinar formation, nuclear size/pleomorphism and mitotic activity. Each element evaluated is given a score of 1 - 3.
- Angiolymphatic invasion is best assessed around the periphery of tumour. It is an independent prognostic factor.

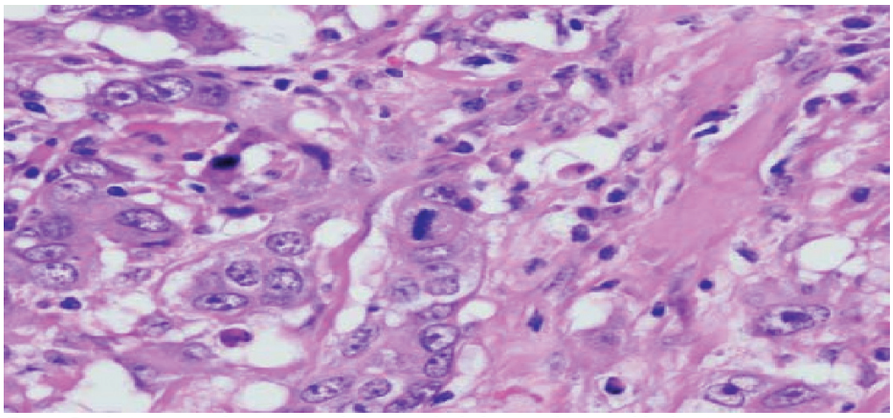


Fig. 7. Grade 3 tumour showing no tubules, marked pleomorphism and high mitotic rate.

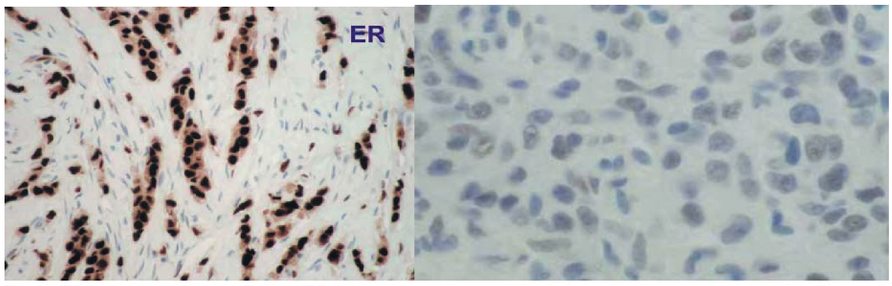
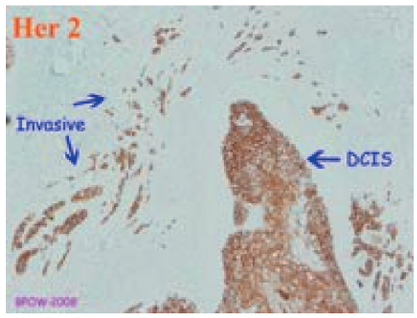


Fig. 8. Hormone receptor studies. ER is strong positive on the left and negative on the right. The intensity of staining is scored by the pathologist.

Table V. Staging and clinical outcome

Stage	Tumour (T)	Node (N)	Metastasis (M)
Stage 0	Tis	N0	M0
Stage 1	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Stage	5-year relative survival rate
0	100%
I	100%
IIA	92%
IIB	81%
IIIA	67%
IIIB	54%
IV	20%



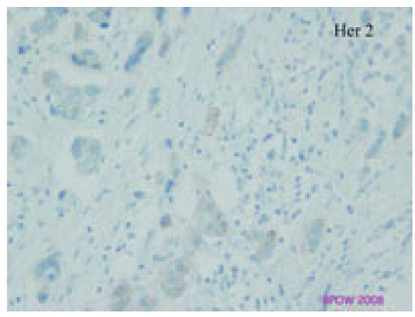


Fig. 9. Her2 receptor testing. Strong 3+ staining (above) and negative staining (below) for the Her2 Neu oncogene.

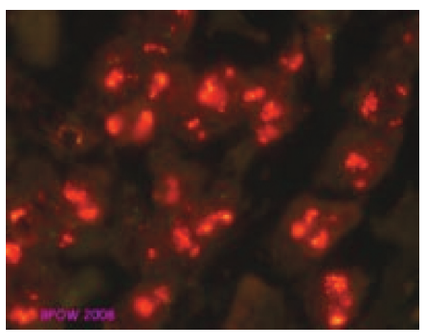


Fig. 10. FISH/red marker for the Her2 gene.

- Hormone receptor (Fig. 8) analyses are made in almost all invasive breast cancers. Oestrogen receptor (ER) is positive in 80% of cancers. Progesterone (PGR) receptors are rarely positive if ER is negative. There is some evidence that ER-positive/PGR-negative tumours behave differently.
- Her2 Neu testing (Fig. 9) is now carried out on all newly diagnosed breast cancers, and approximately 20% are positive. Fluorescence *in situ* hybridisation (FISH) is used to evaluate Her2 gene copy numbers when immunohistochemistry produces equivocal results (Fig. 10).

Conclusion

Diagnosing breast cancer is simple and rapid in the majority of cases. It relies on clinical acumen, the liberal use of breast imaging, usually mammography, together with fine-needle cytology and core-needle biopsy. In cases of discordant information arising from the above triple assessment, an excision biopsy is indicated.

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In a nutshell

- Invasive duct carcinoma accounts for 70 - 80% of breast carcinomas.
- Breast lumps should be evaluated using the triple assessment, enabling the diagnosis of breast cancer in the majority of cases.
- The stronger the risk factors for developing breast cancer, the more likely it is that a lump is cancerous.
- The subtle mammographic features of DCIS are important to recognise, as up to half of these lesions will progress to invasive duct carcinoma within 10 years.
- Diagnostic doubt, despite triple assessment, of a lump or mammographic lesion should be referred for excision biopsy.
- Mammography is the first-line radiological investigation for breast cancer, with ultrasound and MRI being used in selected cases.
- There are 2 parts to the TNM classification of breast cancer: clinical staging and a final pathological staging.

Single Suture

Roman occupation of Europe may have destroyed resistance to HIV

Those living within countries that were conquered by the Romans are more susceptible to HIV because of variations in a gene that confers resistance to the virus. The gene in question codes for a protein receptor called CCR5, which is the receptor that HIV binds to before entering cells. One gene variant, *CCR5-Delta32*, has 32 DNA base pairs missing and produces a receptor that HIV cannot bind to – and so prevents the virus from entering cells. People with this gene variant have some resistance to HIV infection and take longer to develop AIDS.

In general, only people in Europe and western Asia carry the variant, which becomes less frequent the further south a population is. More than 15% of people in some areas of northern Europe carry *CCR5-Delta32* compared with less than 4% of Greeks. The HIV pandemic itself occurred too recently to have influenced the distribution of the variant. However, the changing frequency of the variant reflects the changing boundaries of the Roman Empire from 500 BC to AD 500, according to Eric Faure and Manuela Royer-Carenzi from the University of Provence. They looked at the links between Roman colonisation and the frequency of the *CCR5-Delta32* variant in nearly 19 000 DNA samples from across Europe. They found that the gene variant was less common in regions conquered by the Romans.

Faure thinks that the Romans introduced a disease to which people carrying the *CCR5-Delta32* gene were particularly susceptible, and as the Romans moved north the disease killed off people with this variant.

New Scientist 2008; 6 September: p. 10.