Management of breast cancer: basic principles

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Abstract

Breast cancer is the most common cancer in the UK predominately affecting women. The majority of breast cancer patients present with symptoms, but approximately 40% are diagnosed in asymptomatic women through the NHS Breast Screening Programme. Most breast cancers are now diagnosed non-operatively by triple assessment (the combination of clinical, radiological and pathological assessment) in specialist breast clinics. Breast cancer management is provided by a multidisciplinary team of breast specialists, including surgeons, radiologists, pathologists, breast care nurses and clinical/medical oncologists. Breast cancer patients now receive individualized treatment plans that may include surgery to both the breast and axilla (including breast reconstruction when appropriate), radiotherapy, endocrine treatment, chemotherapy and targeted treatments such as trastuzumab.

Keywords Breast cancer; diagnosis; risk factors; treatment

Breast cancer incidence and survival

Breast cancer is the most common cancer in the UK with over 55,000 new cases in 2015, accounting for 15% of new cancer diagnoses. It predominantly affects women, of whom 1 in 8 will be diagnosed with breast cancer in their lifetime. Since the 1990s the incidence of breast cancer in the UK in women has increased by approximately 20%, with a further 2% rise projected between 2014 and 2035. Male breast cancer is uncommon with approximately 370 cases (<1%) per year in the UK and the incidence of this is stable. Breast cancer incidence increases with age, with 80% of cases diagnosed in the over 50s and around a quarter diagnosed in women aged 75 and over. Just under 8000 breast cancers diagnosed are in situ cancers, 60% of which are detected by the NHS Breast Screening Programme.

In the UK, 11,600 women died from breast cancer in 2016, and it is the second most common cause of death from cancer in women after lung cancer. However, breast cancer mortality in the UK has decreased by more than 20% in the last decade. Breast cancer survival rates have been steadily improving for 40 years and 78% of women diagnosed with breast cancer now survive their disease for at least 10 years.[1]

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Risk factors for breast cancer

Female gender and increasing age are the biggest risk factors for the development of breast cancer.

Increased oestrogen exposure is known to increase breast cancer risk. Endogenous causes include nulliparity, later age at first pregnancy (first full-term pregnancy 35 years or over), not breastfeeding, early menarche and late menopause. Exogenous causes include longer term use of hormone replacement therapy (in particular combined oestrogen–progestogen preparations) in post-menopausal women and current or recent use of the combined oral contraceptive pill. Plant phytoestrogens have not been shown to increase breast cancer risk. Increased breast density is associated with raised breast cancer risk but not thought to be hormonally related.

Lifestyle-related risk factors include increased alcohol intake, post-menopausal obesity and reduced physical activity. Supradiaphragmatic radiotherapy (predominantly as treatment for Hodgkin's lymphoma) in young women is associated with a high latent breast cancer risk. In approximately 5% of breast cancer cases, there is a strong inherited familial risk. Mutations in two autosomal dominant genes, *BRCA1* and *BRCA2*, account for most of the cases of familial breast cancer. Other gene mutations associated with a high risk of developing breast cancer include TP53, PALB2, PTEN, STK11 and CDH1(E-Cadherin).

Breast cancer diagnosis

Mode of presentation

A significant proportion of breast cancers are detected through breast screening. In the UK, mammographic screening is offered to women aged 50–70 years every 3 years (and also as part of a randomized trial in the 47–49 and 71–73 year age groups in England). The NHS Breast Screening Programme in England screened over 2.2 million women and detected over 18,000 cancers in 2016–2017.[2]

The majority of breast cancers are diagnosed when patients with breast symptoms are referred by their general practitioners to specialist breast clinics. Best practice diagnostic guidelines for patients presenting with breast symptoms were published in 2010[3] and describe those symptoms that require specialist referral as shown in Box 1. In England, patients referred urgently (U) with symptoms of suspected breast cancer and those with non-urgent (NU) symptoms are all required to be seen within 2 weeks of referral.

Triple assessment

The diagnostic assessment of patients with breast symptoms is initially based on multidisciplinary triple assessment:

- clinical assessment – history and examination
- radiological assessment – mammography and/or ultrasound scan
- pathological assessment – core biopsy or fine needle aspiration cytology.

For each component of triple assessment a scoring system is used:

1 Normal
2 Benign
3 Equivocal/indeterminate
4 Suspicious of malignancy
5 Malignant.

Best practice diagnostic guidelines 2010: referral of patients with breast symptoms

Lump, lumpiness, change in texture

Discrete lump in any woman 30 years and older that persists after next period or presents after menopause (U)

At any age

Discrete hard lump with fixation ± skin tethering/dimpling/altered contour (U)

- A lump that enlarges (U)
- A persistent focal area of lumpiness or focal change in breast texture (U)
- Progressive change in breast size with signs of oedema (U)
- Skin distortion (U)
- Previous history of breast cancer with new lump or suspicious symptoms (U)

Under 30 years

- A lump that does not meet above criteria (NU)

Male patients

- Over 50 years with unilateral firm subareolar mass ± nipple discharge or associated skin changes (U)

Nipple symptoms

- Spontaneous unilateral blood stained nipple discharge (U)
- Unilateral nipple eczema or nipple change that does not respond to topical treatment (U)
- Recent nipple retraction or distortion (U)

Breast pain

- Patient with minor/moderate degree of breast pain with no discrete palpable abnormality, when initial treatment fails and/or with unexplained persistent symptoms (NU)

Axillary lump (in absence of clinical breast abnormality)

- Persistent unexplained axillary swelling (U)

Box1

A prefix is given for each component: clinical assessment, P (for palpation); radiological assessment, R, which can be sub-divided into M for mammography and U for ultrasound scan; core biopsy is B (for biopsy) and fine needle aspiration is C (for cytology).

Clinical assessment: a thorough history and full examination of both breasts and regional lymph nodes (axillae and supraclavicular fossae), including inspection and palpation, should be carried out. This has traditionally been carried out by a breast surgeon but increasingly nurse practitioners and breast physicians fulfil this role.

The most common clinical sign of breast cancer is the finding of a discrete lump or asymmetric thickening. Other signs of breast cancer include skin dimpling or inflammation, nipple retraction, swelling or oedema (peau d'orange), bloody or serous nipple discharge and nipple eczema (Paget's disease) (Figure 1). Some breast cancers will present as an axillary lymph node mass alone.

Radiological assessment: in the diagnostic breast clinic mammography and ultrasound are the main imaging modalities used. The sensitivity of mammography is reduced in younger women due to increased breast density and is therefore only used routinely in women over 40 years old. It is used selectively in younger women but is required in all women with proven malignancy. Two-view mammography, with craniocaudal and oblique views is usually carried out. Breast tomosynthesis or digital breast tomosynthesis is increasingly used as an adjunct to conventional mammography. Like CT scans it takes a series of images of the breast which are then computer reconstructed to give a 3D image of the breast. It can be particularly helpful in women with dense breast tissue.

Figure 1 Paget's disease of the nipple.

Ultrasound is suitable for patients of all ages. It is useful in determining if there is a focal breast abnormality and whether a lesion is cystic or solid, as well as assessing the nature of any solid abnormality. If a suspicious or malignant breast lesion is seen, ultrasound of the ipsilateral axillary lymph nodes should be carried out.

Pathological assessment: those patients found to have an abnormality either on clinical or radiological assessment require a needle biopsy. Needle biopsies are carried out under image guidance for greater accuracy in the majority of cases unless there is only a clinical abnormality.

Needle core biopsy performed under local anaesthetic is preferred to fine needle aspiration (FNA) for biopsy of most solid lesions due to the higher sensitivity and specificity achieved in most centres. For proven breast cancers it also provides important useful additional information such as invasive status, tumour type, grade, oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status which can be useful in preoperative treatment planning. Vacuum-assisted biopsy may be used to provide more tissue for histological assessment if initial core biopsy is insufficient.

FNA is generally only used to sample very small breast lesions and those in difficult locations (e.g. immediately adjacent to a breast implant).

A punch biopsy of the skin performed under local anaesthetic may be used to assess skin lesions that are suspicious of Paget's disease or local recurrence.

If an abnormal axillary lymph node is seen in cases suspicious of malignancy then an ultrasound guided FNA or core biopsy of the lymph node is usually carried out.

The aims of triple assessment are:

- the non-operative diagnosis of benign breast disorders aiming to avoid the need for open surgical diagnostic biopsy

- the preoperative diagnosis of breast cancer to allow treatment planning.

Not all patients seen in the diagnostic clinic will undergo full triple assessment. Those with normal clinical and radiological findings may be reassured without biopsy.

Multidisciplinary care

Breast care should be provided by a team of breast specialists including surgeons, radiologists, pathologists, breast care nurses and clinical/medical oncologists together with a dedicated multidisciplinary team (MDT) coordinator. Breast cancer patients are likely to be discussed at MDT meetings at multiple points during their care, including at diagnosis, following surgery to plan adjuvant treatments and if they develop recurrent or metastatic disease.

Those patients undergoing full triple assessment with biopsy should be discussed at an MDT meeting. The outcome for most cases will either be a definitive diagnosis of cancer or a benign breast disorder. The discussion should confirm that the findings for each of the three parts of triple assessment are concordant and, where necessary, additional diagnostic investigations may be required to achieve a clear diagnosis.

Using triple assessment, a non-operative diagnosis can be achieved for the majority of breast cancers. Breast screening programme standards[4] state that for invasive cancers an acceptable rate of non-operative diagnosis is at least 90%, with an achievable rate of more than 95%. Non-invasive breast cancers are invariably impalpable, making a non-operative diagnosis potentially more difficult. The acceptable rate of non-operative diagnosis is at least 85% for non-invasive cancers with an achievable rate of more than 90%.

With modern image-guided techniques, including vacuum-assisted biopsy only a small minority of patients should require an open surgical biopsy to achieve a definitive diagnosis of breast cancer. Frozen sections with immediate pathological reporting at surgical breast biopsy should not be performed except in exceptional circumstances and the reasons documented. A non-operative diagnosis allows the MDT to develop an individual plan of the potential treatment options to discuss with each breast cancer patient prior to the commencement of treatment.

Additional investigations

Breast magnetic resonance imaging (MRI): is not used in the initial imaging assessment of patients in the symptomatic or screening assessment clinic. However, it can be a useful problem-solving tool in the diagnostic setting for certain clinical scenarios such as equivocal mammographic findings, mammographically occult lesions, evaluation of patients with metastatic axillary lymphadenopathy but an unknown primary malignancy, patients with Paget's disease and determination of silicone breast implant integrity.

Dynamic contrast-enhanced breast MRI may also be used in the further evaluation of patients with confirmed breast cancer. MRI is more accurate for assessing the size of invasive tumours, for detecting the presence of multiple invasive foci in the ipsilateral breast and concurrent contralateral breast cancer, particularly for proven invasive lobular carcinomas. However, MRI identifies a significant number of false-positive abnormalities that then require further investigation that can lead to additional biopsies, add to patient anxiety and may delay cancer treatment.

MRI is being increasingly used in the evaluation of breast cancer patients treated with neoadjuvant chemotherapy to assess initial tumour size and subsequently the response to chemotherapy. It may also be used to look for multiple tumours in breast cancer patients at high genetic risk (*BRCA* gene mutation carriers).

It is used to aid decision making regarding local disease extent and suitability for breast conserving surgery where there may be disparity between the size of lesion as seen on ultrasound and mammogram. A significant proportion of patients, however, still require re-excision for positive or close margins following breast conserving surgery. The UK COMICE study[5] randomized over 1600 women to conventional imaging plus MRI or conventional imaging alone for preoperative evaluation, and reported no significant difference in re-excision rate for positive margins (19% in both arms).

Preoperative staging investigations: aimed at detection of occult metastases, such as CT scanning, liver ultrasound or isotope bone scans, are not generally helpful and should not normally be routinely carried out. Staging investigations should be reserved for patients who have symptoms suspicious of metastatic disease or are found to be at very high risk due to extensive node-positive axillary disease.

Discussion of breast cancer results

Results should be given by an appropriately trained senior clinician who has both experience and training in communicating a cancer diagnosis to patients. The patient should be given their results in the presence of a breast care nurse and any relative/carer/friend of the patient that they wish to have at the consultation. The breast care nurse (BCN) plays an important role in improving the experience for patients with breast cancer throughout all stages of the patient journey starting from the referral from the GP. As well as a coordination role they can provide appropriate information, give emotional support to the patient and their family and provide continuity of care throughout the patient pathway.

Treatment of breast cancer

Carcinoma in situ or non-invasive breast cancer

Breast cancers arise from epithelial cells lining the terminal duct lobular unit. If the cancer cells have not passed through the basement membrane they are in situ or non-invasive breast cancers. An invasive cancer is one where cancer cells have passed through the basement membrane of the ducts and lobules invading the surrounding adjacent normal breast tissue and thus have the potential to metastasise.

There are two types of breast carcinoma in situ.

Lobular carcinoma in situ (LCIS): lobular neoplasia represents a spectrum of changes that can occur within breast lobules ranging from atypical lobular hyperplasia to lobular carcinoma in situ (LCIS). It is associated with an increased risk of developing subsequent invasive breast carcinoma.

LCIS is usually mammographically occult and is most often diagnosed as an incidental finding in breast biopsies. When LCIS was first described, it was assumed to be premalignant because it was found in association with invasive carcinoma and was

therefore believed to be best managed by surgical excision. However, it is now considered to be a risk factor for the subsequent development of invasive cancer in either breast (conveying an eight to ten times relative rather than absolute risk), rather than a direct precursor to invasive cancer.

Increased surveillance is the usual strategy adopted for the management of LCIS, rather than surgery. Rarely, a woman with LCIS may undergo risk-reducing bilateral mastectomies, but this would usually be in association with a strong family history of breast cancer or proven *BRCA* gene mutation. There is one subtype, pleomorphic LCIS, that may exhibit more aggressive biological behaviour than classical type LCIS and this is usually managed as for DCIS by surgical excision.

Ductal carcinoma in situ (DCIS): of the breast constitutes a heterogeneous group of lesions with variable malignant potential. It is the precursor lesion for most invasive breast cancers, but not all DCIS lesions appear to have the time or genetic potential to progress to invasive cancer. As a result, estimates of the likelihood of developing subsequent invasive breast cancer vary widely.

DCIS may occasionally present with symptoms such as blood-stained nipple discharge, Paget's disease or a palpable mass, but the majority is detected by mammography in asymptomatic women. The widespread introduction of mammographic breast screening has resulted in a dramatic increase in the diagnosis of DCIS and this will further increase with the introduction of digital mammography.

Approximately 20% of cancers detected by the NHS Breast Screening Programme are DCIS. The large rise in DCIS diagnoses has not been accompanied by a fall in incidence of invasive cancers, as would be expected if DCIS inevitably leads to invasive cancer. There is undoubtedly a degree of 'overdiagnosis' where healthy women are diagnosed with a malignancy that would never otherwise have presented as a symptomatic breast cancer in their lifetime. An inevitable consequence of 'overdiagnosis' is 'overtreatment' which is currently the subject of considerable debate.

Surgery to the breast – at present all DCIS is treated by surgery, because it cannot be predicted which cases would progress to a life-threatening invasive tumour in the woman's lifetime. The aim of surgery is to achieve complete excision of the in situ tumour and to minimize local recurrence. Before the widespread introduction of mammographic screening and resultant increase in incidence of DCIS, the customary treatment was mastectomy. Mastectomy remains the most effective treatment for DCIS in terms of preventing local recurrence. Most series report local recurrence rates of approximately 1% and breast cancer mortality rates close to zero after mastectomy. Mastectomy is indicated in cases of multicentricity (disease in multiple quadrants), where a unicentric DCIS lesion is too large to excise with clear excision margins and an acceptable cosmetic result, where there has been previous irradiation to the breast or mediastinum or if it is the patient's choice. Postoperative chest wall radiotherapy is not required after a mastectomy for DCIS and these patients are therefore ideal candidates to consider immediate breast reconstruction.

Mastectomy, however, is clearly overtreatment for the majority, and in view of the success of breast conserving surgery and radiotherapy for invasive cancer, this conservative approach has been extended to DCIS. Clinical trials have shown that local excision with clear excision margins followed by radiotherapy can provide excellent rates of local control.[6] Radiotherapy decreased local recurrence by 60% in these trials, but had no significant effect on overall survival. Approximately 50% of local relapses after treatment for DCIS are invasive and not in situ.

The majority of patients diagnosed with DCIS are now offered a choice of breast conserving surgery or mastectomy. The introduction of modern oncoplastic techniques, such as therapeutic mammoplasty (Figure 2), has also increased the proportion of patients potentially suitable for breast conserving surgery. The majority of DCIS lesions will be impalpable and will require preoperative radiological localization to facilitate breast conserving surgery. This will usually be achieved by placement of a marker wire under stereotactic (X-ray) or ultrasound guidance. The placement of multiple wires may be required to localize the extent of larger lesions. Alternative options include the use of a small amount of radioactive tracer to facilitate this, a technique known as radio-guided occult lesion localization (ROLL), or the insertion of radioactive or magnetic seeds.

At the time of surgery a specimen X-ray should be taken to ensure adequate excision of the mammographic abnormality (Figure 3). The surgical specimen should be orientated with either sutures or clips to allow accurate determination of margin status by the pathologist. The patient should be warned preoperatively that further surgery may be required (either re-excision of margins or conversion to mastectomy) if adequate excision margins are not achieved. The repeat breast operation rate following breast conserving surgery for DCIS in the UK breast screening programme was 25% in 2016–17.[7]

DCIS represents a spectrum of disease that requires individualized treatment. The Van Nuys Prognostic Index has been developed to provide a clinical algorithm for the management of DCIS taking into account the size and grade of the lesion, the excision margin status and the age of the patient.[8] While there is evidence that positive excision margins are associated with a significant increase in local recurrence, there is no clear consensus regarding the optimum excision margin width for DCIS. Radiotherapy is thought not to be necessary for smaller, low grade DCIS lesions that are adequately excised and trials are ongoing investigating the safety of an observation only policy for

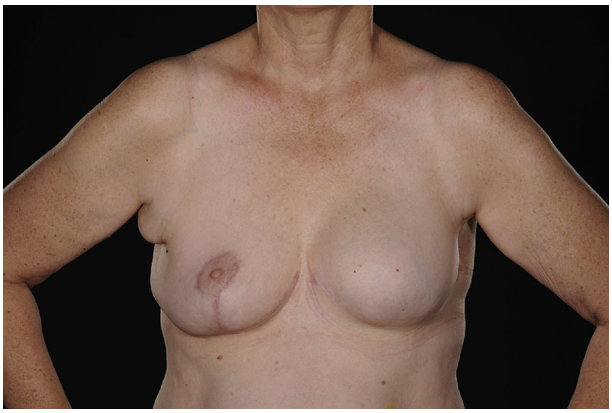

Figure 2 Bilateral breast cancer surgery: right therapeutic mammoplasty and left mastectomy and implant reconstruction.

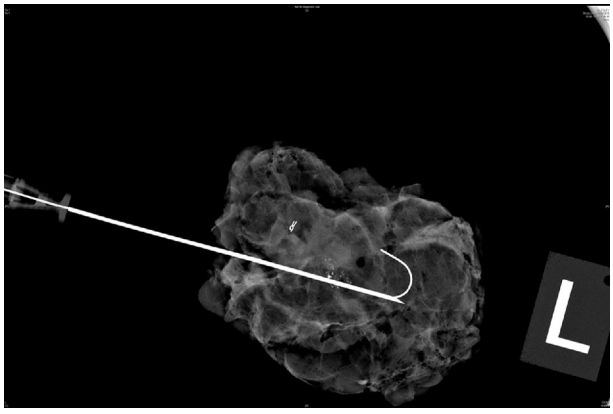

Figure 3 Specimen X-ray showing removal of malignant microcalcifications (DCIS) following wire localization.

low and intermediate grade lesions. The benefits of adjuvant endocrine therapy following adequate local treatment of DCIS are not currently thought to be sufficient to justify treatment.

Surgery to the axilla – axillary nodal status is not required to estimate prognosis or for treatment planning in cases of DCIS. However, a small but variable proportion of patients with a DCIS diagnosis on preoperative core biopsy will subsequently be upgraded to invasive cancer on final histology which would then necessitate a sentinel node biopsy. It is therefore possible to justify carrying out a sentinel node biopsy procedure when there is a preoperative core biopsy diagnosis of DCIS and a mastectomy is being carried out for an extensive area of microcalcifications as there is a significant possibility of upgrade to invasive cancer which would then require axillary lymph node sampling as a second procedure. Unless there is a very high degree of suspicion of invasive disease, sentinel node biopsy is best avoided when carrying out breast conserving surgery for DCIS to avoid overtreatment and potential axillary morbidity.

Invasive breast cancer

Patients with primary operable invasive breast cancers will usually undergo surgery to both the breast and axillary lymph nodes, with over 80% of patients having surgery as their first treatment. The postoperative requirement for adjuvant treatments is determined by the final histology report, including tumour grade, the presence of lymphovascular invasion, the axillary nodal status and determination of ER and HER2 status.

Surgery to the breast: long-term follow-up of randomized clinical trials have reported similar survival rates for women treated by mastectomy or breast conservation surgery and postoperative whole breast radiotherapy.[9,10] Wherever possible, patients should be offered an informed choice between breast conserving treatment and mastectomy.

In modern practice the majority of patients will undergo breast conservation surgery. The tumour is removed with clear excision margins followed by postoperative whole breast radiotherapy aiming to minimize local recurrence without adversely affecting the cosmetic outcome. With current techniques and improved adjuvant treatments, local recurrence rates are generally low and should be less than 3% at 5 years.

Contraindications to breast conserving surgery are discussed in the article on pages 164-175 of this issue but male breast cancer patients invariably require treatment by mastectomy due to the smaller breast size.

As previously described for DCIS, impalpable invasive cancers require radiological localization. Intraoperative specimen X-rays should be taken and the specimen orientated for pathological assessment of margins. There is evidence that positive excision margins are associated with a significant increase in local recurrence, but there is no clear consensus regarding the optimum excision margin width for invasive cancer. The repeat breast operation rate following breast conserving surgery for invasive cancer in the UK breast screening programme in 2016–2017 was 13%[7] and the patient should be warned of this possibility preoperatively.

Postoperative whole breast radiotherapy has been established as the standard of care in patients treated with breast conserving treatment. Recent developments include hypofractionation where radiotherapy is given in 15 fractions over 3 weeks rather than 25 fractions over 5 weeks. There are a number of ongoing trials looking at partial breast and targeted intraoperative radiotherapy techniques that are likely to be introduced for lower risk subgroups of patients in the near future.

Patients choosing or advised to have mastectomy for invasive breast cancer should have the opportunity to discuss whether breast reconstruction is feasible and its timing (immediate or delayed). The likelihood of requiring postoperative chest wall radiotherapy is often a key factor in this decision making.

Surgery to the axilla: the presence of axillary node metastases is the most powerful prognostic determinant in primary operable breast cancer and a significant factor in adjuvant treatment decision making. All patients undergoing surgery for invasive breast cancer should undergo an axillary nodal procedure either for staging purposes or as treatment of the node-positive axilla.

A proportion of patients with invasive breast cancer will be diagnosed with axillary disease prior to surgery as a result of the routine use of preoperative axillary assessment with ultrasound scan and where appropriate percutaneous needle biopsy. If a positive preoperative diagnosis of axillary nodal metastasis is made then an axillary lymph node dissection is normally carried out at the same time as definitive breast surgery. This may in future be regarded as overtreatment for some patients, but is currently the standard of care.

Axillary lymph node dissection (ALND) can be defined as clearing the axillary contents bounded by the axillary skin laterally, the latissimus dorsi muscle posteriorly, the lower border of the axillary vein superiorly, the pectoralis muscles anteriorly, and the chest wall medially. Essential structures are identified and preserved at the time of surgery, in particular the long thoracic nerve and the thoracodorsal neurovascular bundle to latissimus dorsi. Axillary nodes may be divided into three levels according to their relationship with the pectoralis minor muscle: level 1, inferolateral; level 2, posterior; level 3, superomedial. All patients undergoing axillary surgery should be warned of the potential sequelae including lymphoedema, shoulder stiffness, pain and sensory nerve damage leading to paraesthesia and numbness. It is usual to carry out a level 2 or 3 ALND as surgical treatment of the node-positive axilla, with some surgeons opting not to remove level 3 nodes unless there is

gross macroscopic disease present in an attempt to reduce morbidity from lymphoedema.

Those patients with invasive breast cancer that do not have proven preoperative axillary node involvement should undergo an axillary node staging procedure. Historically, ALND was carried out to achieve this, but that is clearly overtreatment for the majority of patients who will have node-negative disease. Sentinel lymph node biopsy (SLNB) using the combined radio-isotope/blue dye localization technique is now the gold standard surgical axillary staging procedure. This was widely introduced following the results of a number of randomized trials comparing SLNB to ALND. These included the UK ALMANAC Trial which demonstrated that SLNB provides accurate assessment of the axilla, with few false negatives and a significant reduction in surgical morbidity, especially lymphoedema.[11]

The sentinel lymph node (SLN) is defined as the first draining lymph node to which cancer cells are most likely to spread from a primary tumour. Sometimes, there can be more than one SLN. If the SLN shows no evidence of metastatic spread then in theory the remaining lymph nodes should also be tumour free and no further action is required. The technique is less invasive than the ALND or axillary node sampling procedures that were previously used as staging techniques.

In advance of surgery a superficial periareolar injection of technetium-labelled nanocolloid (20 MBq on the day, or 40 MBq the day before) is required. When the patient is anaesthetized 2 ml of patent V blue dye is injected at the same site. A gamma probe is used to locate radiologically 'hot' nodes intraoperatively. A SLN is one that is blue, hot, or hot and blue (Figure 4). A hot node is one with ten times the background radioactivity count and more than 10% of the activity of the hottest node if there are multiple hot nodes. The latter criteria aims to limit the number of SLNs harvested to minimize morbidity and the median number of SLNs removed in the majority of studies is two.

Should the blue dye and radio-isotope fail to localize a SLN, then a four- node axillary sample should be carried out to provide the required nodal information. In modern practice, ALND should not be used as a staging procedure for primary operable breast cancer. Preoperative lymphoscintigrams are useful when training to carry out SLNB and for the initial introduction of the technique at an institution, but are generally not required once the procedure is established. The patient should be warned that the dye may stain the breast tissues, including the skin, blue for a number of months postoperatively and can cause an allergic reaction that can be serious. As a result many surgeons are now omitting the use of blue dye and use radio-isotope alone. They should be able to demonstrate equivalent rates of sentinel node identification (96% +).

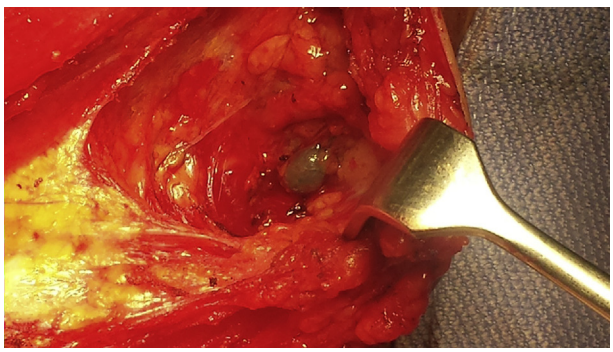

Figure 4 Intraoperative photograph of blue staining of a sentinel lymph node.

As SLNB yields a smaller number of axillary lymph nodes it allows more extensive histological sectioning with nodes routinely sliced at 2 mm intervals. This has resulted in the increased detection of smaller, low volume metastases such as isolated tumour cells (<0.2 mm) and micrometastases (<2 mm). Their clinical significance is yet to be completely established but no further axillary treatment is currently recommended when they are detected. For this reason conventional H&E staining alone is recommended in the routine analysis of axillary nodes, with selective use of immunohistochemistry in difficult cases to avoid their over detection.

The management of macrometastases (2 mm or greater) remains controversial due to the recent publication of the results of two key clinical trials of positive SLN management.

The EORTC-AMAROS randomized trial[12] compared ALND with axillary radiotherapy after a positive SLN. It showed that both treatments provided excellent and comparable axillary control for patients with T1–2 invasive breast cancer and no palpable lymphadenopathy, but that axillary radiotherapy resulted in significantly less morbidity.

The ACOSOG Z11 randomized trial[13] aimed to determine whether ALND is beneficial for survival or locoregional control in breast conserving surgery with whole-breast radiotherapy and systemic therapy in patients with SLN metastases. It included women with clinically T1-2 invasive breast cancer, no palpable lymphadenopathy and one or two SLNs containing metastases. Patients with SLN metastases on SLNB were randomized either to ALND or to no further axillary treatment. The trial closed early due to slow accrual and a lower than anticipated event rate. It was concluded that no significant difference was observed between the two groups and that SLNB when compared to ALND did not result in inferior survival. The trial methodology remains controversial, but it has opened up a debate regarding the identification of a subgroup of patients with lower risk disease who may not require further axillary treatment after the removal of 1–2 positive SLNs. This approach is currently being considered in patients who are undergoing breast conservation surgery with whole breast radiotherapy, that are post menopausal and have T1, grade 1 or 2, ER-positive and HER2-negative tumours.

Both of these trials predominantly included patients with low volume axillary nodal disease. For patients with more than three positive axillary lymph nodes ALND remains the standard of care. Decisions regarding the management options for a positive SLN require careful discussion at the postoperative MDT meeting with subsequent discussion of the options with the patient. The POSNOC randomized trial[14] is further evaluating the need for further axillary treatment following the finding of 1–2 positive SLNs.

There are a number of intraoperative methods of SLN analysis available such as imprint cytology, frozen section and one-step nucleic acid (OSNA) amplification. Their aim is to detect SLN metastases at the time of surgery, and if found to then proceed to

ALND at the same operation. Given the current controversies relating to positive SLN management their current place in axillary management is not clearly established and while the OSNA technique is used in a number of centres it is not in general use.

Neoadjuvant treatment: neoadjuvant chemotherapy (chemotherapy as the first treatment) has traditionally been used in the treatment of locally advanced and inflammatory breast cancers. Such cancers are often inoperable at presentation and the chemotherapy aims to downstage the tumour such that it becomes operable. In HER2-positive patients the addition of trastuzumab (Herceptin) and pertuzumab (Perjeta) has resulted in improved responses to neoadjuvant treatments.

More recently this approach has also been applied to larger operable tumours that would require a mastectomy as surgical treatment at the time of presentation. In this situation the aim of the neoadjuvant treatment is to reduce the size of the tumour such that breast conserving surgery becomes feasible. This requires a multidisciplinary approach to treatment including careful patient selection, careful assessment and monitoring of tumour size by MRI and/or ultrasound scanning and placement of marker clips prior to treatment to mark the initial tumour position to facilitate tumour marking if a good response is achieved. A similar approach may also be considered in selected patients with ER-positive tumours using neoadjuvant endocrine treatment, usually an aromatase inhibitor.

Primary endocrine treatment: some patients with ER-positive tumours that are either unfit for surgery due to comorbidity or refuse surgery may be considered for primary treatment with endocrine agents such as tamoxifen or aromatase inhibitors (anastrozole, exemestane or letrozole). These patients require regular surveillance to ensure compliance with and response to treatment. If a tumour progresses on treatment an alternative endocrine agent may be introduced.

In patients deemed unfit for a general anaesthetic, who either do not respond to endocrine treatment or have ER-negative tumours, breast cancer surgery (either wide excision or mastectomy) may be considered under local or regional anaesthetic to achieve local control.

Adjuvant treatments: the postoperative MDT meeting should discuss the final histology report to determine the need for adjuvant treatments. Discussion should include radiotherapy, endocrine treatment, chemotherapy and trastuzumab. The development of genomic testing has influenced decision making regarding adjuvant chemotherapy. An individual's risk of disease recurrence can now be assessed using a multi-gene assay which can inform the decision to give or withhold chemotherapy. In current clinical practice the use of such tests is confined to patients with node-negative, ER-positive, HER2-negative disease. ◆

REFERENCES

1 Cancer Research UK. Breast cancer statistics, 2018.
2 Breast Screening Programme. England 2016-17. NHS Digital, 2018.
3 Best practice diagnostic guidelines for patients presenting with breast symptoms. Breakthrough Breast Cancer, 2010.
4 NHS Breast Screening Programme Consolidated Standards. Public health England, 2017.
5 Turnbull L, Brown S, Harvey I, et al. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. *Lancet* 2010 Feb 13; **375:** 563–71.
6 Viani GA, Stefano EJ, Afonso SL, et al. Breast-conserving surgery with or without radiotherapy in women with ductal carcinoma in situ: a meta-analysis of randomised trials. *Radiat Oncol* 2007; **2:** 28–39.
7 NHS Breast Screening Programme and Association of Breast Surgery. An audit of screen-detected breast cancers for the year of screening April 2016 to March 2017. Public Heath England, 2018.
8 Silverstein MJ, Buchanan C. Ductal carcinoma in situ: USC/Van Nuys prognostic index and the impact of margin status. *Breast* 2003; **12:** 457–71.
9 Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; **347:** 1233–41.
10 Veronesi U, Saccozzi R, Vecchio Del, et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *N Engl J Med* 1981; **305:** 6–11.
11 Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. *J Natl Cancer Inst* 2006; **98:** 599–609.
12 Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS):a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lacet Oncol* 2014; **15:** 1303–10.
13 Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with and without axillary dissection in patients with sentinel lymph node metastases. The American College of Surgeons Oncology Group Z0011 Randomized Trial. *Ann Surg* 2010; **252:** 426–32.
14 POSNOC - POsitive Sentinel NOde-adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy. 2014, https://www.thelancet.com/protocol-reviews/14PRT-0519.