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Newly diagnosed early breast cancer

An update on pre-operative assessment and staging

Background

Most breast cancer seen in developed nations is diagnosed at an early stage and surgery is the recommended first line treatment in most cases.

Objective

This article reviews the current approach and related evidence on pre-operative assessment of women with newly diagnosed breast cancer. It discusses the use of conventional assessment tools (mammography, ultrasound and needle biopsy) for staging the breast and axilla, the evidence relating to breast magnetic resonance imaging and the indications for staging investigations for distant metastatic disease. It highlights recent changes in practice, including areas of nonconsensus, and informs general practitioners on evolving issues in the pre-operative care of the newly diagnosed breast cancer patient.

Discussion

Once a breast cancer diagnosis has been established, appropriate pre-operative evaluation to assess the extent of disease (locally and sometimes systemically) helps guide surgical management and decisions on adjuvant therapy.

Keywords

breast cancer, pre-operative, staging; breast MRI; general practice; family medicine

highlights changes in practice, including areas of nonconsensus, to inform general practitioners on evolving issues in pre-operative care of the newly diagnosed breast cancer patient.

Conventional breast assessment and imaging

Standard assessment of the breast over the past few decades has followed the triple testing strategy of:

- clinical examination
- breast imaging (mammography and ultrasound)
- needle biopsy (fine needle or core needle).⁴

Once a cancer diagnosis is established, these conventional tests provide information critical to planning treatment: for example, mammography and ultrasound help guide selection to breast conservation,⁵ and core needle biopsy allows tissue testing for hormone receptor and human epidermal growth factor receptor 2 (HER2) status⁶ to support decisions on adjuvant systemic treatment. The more recent evolution of imaging and image-guided biopsy methods has allowed opportunity to further refine pre-operative testing, including extension of breast ultrasound scanning to cover the axilla in women with invasive breast cancer.⁷

Pre-operative axillary lymph node assessment

The presence or absence of metastatic cancer in the axillary lymph nodes (commonly termed 'node-positive' cancer) remains a key prognostic feature and determinant of adjuvant treatments. The majority of women with early stage breast cancer will be clinically lymph node-negative at diagnosis (ie. no clinically palpable malignant nodes) and will be managed with sentinel lymph node biopsy. These women will undergo full axillary lymph node dissection (ALND) only if there is proven malignancy in the sentinel

Each year around 1.4 million women worldwide are diagnosed with breast cancer. Breast cancer represents approximately 10% of all new cancers and nearly a quarter (23%) of all female cancer cases.¹ With increased breast awareness and the widespread implementation of population screening programs, the majority of breast cancer in developed nations is diagnosed at an early stage.^{2,3}

Surgery remains the recommended first line treatment for most early breast cancers. Once a breast cancer diagnosis has been established, appropriate pre-operative evaluation to assess the extent of disease and for staging purposes can guide surgical management and decisions on adjuvant therapy. This article reviews the current approach and related evidence on pre-operative assessment of women with newly diagnosed breast cancer. It

node(s) identified with intra-operative lymph node assessment (cytology or frozen section) or on final histological assessment. Women presenting with positive lymph nodes at diagnosis will usually be recommended to undergo planned up-front ALND (at the time of primary tumour excision).

Pre-operative ultrasound examination of the axilla is part of the routine assessment of women with invasive breast cancer. Guidelines from the National Institute for Health and Clinical Excellence recommend axillary ultrasound in all cases.⁷ While the sensitivity of ultrasound for detecting lymph node metastases is modest (61.4% in a meta-analysis of 30 studies), it has relatively high specificity (82%).⁸ Of importance, ultrasound-guided needle biopsy can be performed on lymph nodes with an abnormal appearance. This has moderate to high sensitivity (79.6%) but very high specificity (98.3%) and positive predictive value (97.1%).⁸ The high specificity and implications of a positive ultrasound-guided needle biopsy for changing surgical management have made it an acceptable strategy to triage patients to sentinel node based management versus ALND. When used in this way, ultrasound and biopsy will correctly triage 55.2% of histologically node-positive newly diagnosed invasive cancer cases directly to ALND, avoiding unnecessary sentinel node biopsy and allowing planning of adjuvant therapy at an early stage.⁸

The use of sentinel node based management in women with larger or multifocal/multicentric tumours is debated. Based on limited evidence, accuracy may be similar to that for smaller/unifocal tumours, but the node positivity rates are high (for the sentinel node(s) as well as the nonsentinel axillary nodes) so only a minority of these patients will avoid ALND.⁹ Clinical trials are ongoing. These women may also benefit from pre-operative ultrasound assessment of the axilla (with needle biopsy of abnormal nodes) and the literature suggests that these tests may have a higher accuracy in this situation when there is a higher underlying risk of lymph node metastases.⁸

Breast magnetic resonance imaging

The use of breast magnetic resonance imaging (MRI) has increased dramatically over recent

years. Initial evidence supported the use of breast MRI as a screening test (in conjunction with mammography) in asymptomatic young women at high hereditary risk of breast cancer, as MRI is able to detect additional cancers compared to mammography alone.¹⁰ Breast MRI in high risk screening should be distinguished from the use of MRI pre-operatively in newly diagnosed breast cancer to 'map out' the extent of disease within the affected breast and to screen the contralateral breast at the time of diagnosis. The indications for breast MRI in newly diagnosed cancer are controversial and there is no consensus on the best use of this test.

Breast MRI detects additional cancer in the breast (compared to mammography) in around 16% of new breast cancers.¹¹ It may show the index lesion to be larger than on conventional imaging, or may show separate smaller foci not seen on conventional imaging. The sensitivity of MRI for detecting additional cancer in this setting has led to some investigators recommending the routine use of pre-operative breast MRI where breast conservation is planned, with the intention of adapting the surgical plan to include a larger excision or mastectomy if additional disease is seen on MRI. However, there is evidence that this approach leads to additional surgery (conversion from wide local excision to mastectomy in 8.1% and wider excision in 11.3% of cases),¹¹ without proof that the additional surgery has clinical or prognostic benefit.^{5,12} It is argued that most of these additional small foci of disease would have been adequately treated with adjuvant whole-breast radiotherapy that is part of routine treatment following breast conserving surgery.^{5,12} There has been a worldwide increase in mastectomy rates in recent years and some authors have implicated the introduction of breast MRI as a possible factor contributing to this trend.^{13,14}

A potential benefit of pre-operative breast MRI may be a reduced rate of re-excision. A cancer that is shown to be larger on breast MRI than estimated using conventional imaging may be treated with wider excision; in theory, the need for a second operation to obtain clear margins could be reduced by the use of pre-operative MRI. The available evidence (two randomised trials) however does not support this theory.^{15,16}

Breast MRI finds lesions suspicious of malignancy in the contralateral breast in 9.3% of cases; around half of these will be false positive tests and among the true malignant lesions detected, the majority are small lesions or ductal carcinoma in situ (DCIS).¹⁷ Use of MRI to screen the contralateral breast is limited by its poor specificity and the fact that the lesions it detects tend to be lesions that may not be of clinical significance and/or may be treated adequately by adjuvant systemic treatments given for the index cancer. There is some evidence that women who are found to have suspicious contralateral breast lesions will choose to undergo bilateral mastectomy without a biopsy to assess the additional MRI detected lesion.¹⁷

The role of breast MRI in the context of newly diagnosed breast cancer, therefore, has been rigorously debated.^{12,18-21} National Institute for Health and Clinical Excellence guidelines recommend against the routine use of MRI and suggest it be considered selectively where there is a discrepancy in other pre-operative tests, where the breast tissue is extremely dense and in some cases of invasive lobular carcinoma.⁷ It is also reasonable to consider the use of breast MRI for screening the contralateral breast in pre-menopausal women with a strong family history of breast cancer or a proven BRCA1 or BRCA2 gene mutation when they are diagnosed with breast cancer.

A pre-operative diagnosis of ductal carcinoma in-situ

The incidence of ductal carcinoma in-situ (DCIS, noninvasive disease) has increased since the introduction of breast screening. It now represents around 25% of breast malignancy and 20% of cases detected in the United Kingdom screening program.² While the local treatment for DCIS is similar to that for invasive breast cancer, there are differences. As DCIS is a local rather than a systemic disease, assessment of the axillary lymph nodes and the use of chemotherapy are not part of the usual management.

One of the main challenges in the management of DCIS is making an accurate pre-operative diagnosis. As most DCIS presents as asymptomatic mammographic microcalcification, core needle biopsy (CNB),

usually under stereotactic guidance, is often required for diagnosis. Where stereotactic biopsy is unavailable or the lesion is not accessible, open surgical biopsy may be necessary to make the diagnosis. When DCIS presents as a palpable mass or is visible on ultrasound, biopsy may be performed under clinical or ultrasound guidance.

A challenge in the management of DCIS is 'underestimation', where CNB shows DCIS but subsequent excision histology shows invasive breast cancer. This occurs in 25% of all CNB diagnoses of DCIS.²² Understaged 'DCIS' cases have a higher chance of needing a second operation compared to patients who have concordant CNB and excision histology findings.²³ In addition, these women undergo considerable emotional upset as their diagnosis changes from in situ disease to potentially life-threatening invasive disease. In this respect, an understanding of the complexity of a CNB diagnosis of DCIS and the risk of underestimated cancer is helpful to allow discussion about the potential change in diagnosis following excision.

Underestimation is more likely when a lesion presents with a breast symptom, is palpable, is larger than 20 mm in diameter on imaging or shows a mass lesion on mammography (rather than microcalcification alone).²² Ductal carcinoma in-situ assessed with CNB under ultrasound or clinical guidance is more likely to represent understaged invasive disease than that biopsied under stereotactic guidance. An awareness of factors associated with underestimation allows treatment planning. This includes considering the use of sentinel lymph node biopsy at the time of lesion excision, even if invasive disease has not been confirmed pre-operatively.²²

Screening for distant metastases as part of initial staging

Current guidelines for the management of women with early breast cancer generally recommend against the routine use of staging imaging studies to detect asymptomatic distant metastases at the time of diagnosis.^{24–27}

These recommendations are based on early studies that showed the incidence of

detectable metastatic disease in women at breast cancer diagnosis is extremely small using chest X-ray, bone scan and ultrasound of the liver.^{28,29} A recent review of this area, incorporating newer technology such as positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) showed similar findings and further supports the view that routine 'screening' for distant metastases in newly diagnosed women is not warranted. In this review, the median prevalence of metastatic disease on conventional imaging in Stage I breast cancer was 0.2%, Stage II breast cancer 1.2%, and Stage III breast cancer 8.0%.³⁰ The incidence was highest in inflammatory breast cancer (30.5% and 48.8%). Studies using PET or integrated PET/CT had a higher accuracy than CT, X-ray, bone scan and ultrasound. The review concluded that the routine use of staging scans in cases of early breast cancer could not be justified, however, it may be considered in more advanced presentations such as inflammatory cancer and more advanced Stage III cases (with a large number of axillary lymph nodes involved by cancer at presentation).³⁰

Conclusion

The appropriate use of pre-operative staging investigations can guide surgical management and adjuvant therapy decisions. Assessment with triple testing using conventional modalities is essential. Ultrasound assessment of the axilla is recommended for women with invasive breast cancer (with biopsy of abnormal looking lymph nodes) as this can select patients for sentinel node based management. Breast MRI may have a role in the pre-operative assessment of disease in selected cases but is not recommended for the majority of cases. The management of DCIS is complicated by the common situation of 'underestimation' where invasive breast cancer is present but is not detected on pre-operative core biopsy. The routine use of imaging studies to look for distant metastases is not indicated in the vast majority of breast cancer presentations. General practitioners are well placed to discuss these issues with the newly diagnosed breast cancer patient.

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