E16. Staging the breast and axilla

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Abstract

Staging of breast cancer should determine the extent of disease as a prerequisite to planning surgical and non-surgical therapy and predicting overall survival. Sentinel lymph node biopsy is widely accepted practice in tumours 2–3 cm in diameter or smaller. Further axillary dissection has been omitted in negative cases with no evidence of metastasis. Clinical examination, X-ray mammography and ultrasound are the first-line and most cost-effective methods to stage the breast pre-operatively. Mammography is superior to ultrasound in ductal carcinoma *in situ* (DCIS) with calcifications. Ultrasound is superior to mammography in the radiodense breast and in lobular carcinoma. Doppler techniques are an adjunct to greyscale ultrasound, showing only limited value in breast staging. Nuclear medicine techniques are helpful in staging the axilla, but have no proven benefit in local staging of the breast. Magnetic resonance imaging (MRI) of the breast is the most sensitive technique in the pre-operative assessment of multifocal and multicentric cancer foci. General use of MRI is restricted by high costs. It is, however, probably a more effective approach to diagnose pre-operatively and successfully treat multifocal and multicentric or contralateral tumour foci than to diagnose and treat postoperative recurrences due to residual tumour burden, at least in patients presenting with radiodense breasts in mammography, or with severe fibrocystic disease or scarring in ultrasound.

Background to oncological principles

The most detailed current staging system is the tumour-node-metastasis (TNM) system according to the Union Internationale Contre le Cancer (UICC; International Union Against Cancer) or the American Joint Committee on Cancer (AJCC). Staging of the breast should provide detailed information about local in-breast extent and spread of the tumour and histology. Site, size, the tumour-to-breast relationship and special cases such as skin or mamillary involvement, multifocality, extended ductal carcinoma *in situ* (DCIS) or familiar cancer influence the surgical tactics. Breast-conserving therapy should be performed whenever local resection with tumour-free margins can be achieved. Modified radical mastectomy is indicated in diffuse, extended carcinoma, associated intraductal carcinoma >4–5 cm in diameter (extensive or predominant intraductal component), multicentricity (multiple quadrants, <4 cm distance of foci), incomplete secondary tumour resection and inflammatory carcinoma. Other reasons include various situations that prevent radiotherapy, or the decision of patients not to undergo breast conservation.

Pathological staging is based on biopsies taken from sentinel lymph node or complete axillary lymph node dissections. Sentinel lymph node biopsy is generally accepted in tumours 2–3 cm in diameter or smaller. Further axillary dissection will be omitted in negative cases with no evidence of metastasis. Single tumour cells or micrometastatic deposits 0.2 mm or smaller are also considered negative in the revised TNM system. Axillary dissection is not mandatory in old patients suffering from small tubular carcinoma <1 cm diameter and localized small amounts of DCIS. In all other cases axillary dissection is requested.

Pre-operative staging of the breast

Clinical examination, X-ray mammography and ultrasound are the first-line and most cost-effective methods of staging the breast pre-operatively. The reported sensitivity of X-ray mammography ranges from 55% to 95% depending on pre-selection of collectives, age, size of breast cancer and prevalence of DCIS. False negative diagnoses of between 5% and 50% have been reported. Mammography tends to overestimate the tumour size compared with histological measurements [1]. Size measurements are less accurate in lobular than in ductal invasive carcinomas [2]. Extension of low and intermediate DCIS associated with calcifications is better determined by mammography compared with other methods.

Sensitivity of greyscale ultrasound ranges from 57% to 90% and specificity from 65% to 90% depending on study population, equipment and diagnostic criteria. To date, high-frequency breast ultrasound (13 MHz) has been proven to achieve a higher diagnostic accuracy than standard breast ultrasound (7.5 MHz), especially in small invasive tumours [3]. Tumour detection of masses by ultrasound is superior to mammography in radiodense breasts grade 3 and 4 [4].

To date, duplex, colour Doppler and power Doppler have been regularly used in high-end ultrasound technology. Sensitivity of colour Doppler instruments ranges from 64% to 100% and specificity from 50% to 96%. Tumour vascularisation detected by colour Doppler ultrasound reflecting neoangiogenesis appears to be an independent predictor of overall survival in women with early breast cancer [5]. Doppler techniques are an adjunct to greyscale ultrasound, they are of limited help in pre-operative assessment. Data concerning various echo signal enhancement media are promising, though still equivocal.

The combination of clinical examination, mammography and ultrasound yields a higher diagnostic accuracy compared with these single methods. Our results for 540 patients with histologically or cytologically proven malignant ($n=279$: 52% carcinoma in situ or T_1 stage) or benign ($n=261$) findings showed similar receiver operating characteristic (ROC)-curves for both methods. Microcalcifications without a solid soft tissue component in DCIS and stage T1a carcinomas are not reliably detected by ultrasound (false-negative findings are seen). However, ultrasound-guided biopsy or needle marking is possible in the vast majority of solid lesions and architectural distortions of 5 mm in diameter or more. Furthermore, combined ROC curves of palpation, mammography and ultrasound have a similar diagnostic performance compared with pre-operative magnetic resonance (MR) mammography.

In previous studies sensitivity of MR mammography ranged from 80% to 100%, and specificity ranged from 29% to 95%, respectively. Fischer and colleagues performed pre-operative contrast-enhanced MR imagingof the breast in 463 patients with probably benignlesions ($n=63$), suspicious lesions ($n=230$), or lesions highlysuggestive of malignancy ($n=170$) per established clinical,mammographic, and/or ultrasonographic criteria. Histopathological analysis revealed 143 benign and 405malignant lesions. The sensitivity, specificity and accuracywere 58%, 76% and 62% for clinical examination; 86%, 32% and72% for conventional mammography; 75%, 80% and 76% for ultrasound;and 93%, 65% and 85% for contrast-enhanced MR imaging. Multifocalityin 30 of 42 patients, multicentricity in 24 of 50 patients,and additional contralateral carcinomas in 15 of 19 patientswere detected with MR imaging alone. Due to the MR imaging findings,therapy was changed correctly in 66 patients (14.3%); unnecessaryopen biopsy was performed in 16 patients (3.5%) [6].

Van Goethem and colleagues determined the extent of breast cancer in 65 patients with dense breasts planned for breast-conserving surgery [7]. Sensitivity for detection of index lesions was 83% for mammography, 70.8% for ultrasound, and 98% for MR mammography. Mammography underestimated tumour extent in 37%, ultrasound in 40% and MR in 12.5%.

Schelfout and colleagues [8] examined 170 patients with breast cancer. MRI detected 96% of multifocal disease and 95% of multicentric disease, whereas mammography detected 37% and 18%, and ultrasound 41% and 9%, respectively. MRI changed the therapeutic approach correctly in 30.6% of breast cancer patients. In another comparative study more than 90% of all patients gained no advantage from MR. Positive MR findings with a corresponding lesion in ultrasound have a higher probability of malignancy (43%) than those without a corresponding ultrasound finding (14% carcinoma) [9].

In line with these data, a change is now increasingly recommended to the use of pre-operative rather than post-operative MRI, at least in patients with mammographically radiodense breasts (ACR grade 3 and 4) or ultrasound criteria of extended fibrocystic disease or multiple scar formations that impair tissue interpretation.

Scintimammography, radioimmunoscintigraphy and positron emission tomography (PET) (with fluoro-oxyglucose or with oestrogen analogue) are functional image techniques that promise new opportunities in the characterization of breast lesions, although reduced spatial resolution is a major problem of these modalities to date. These techniques present reasonable sensitivities from 60% to 96% and specificities from 78% to 100% in pre-selected collectives only if the diameter of lesions is greater than 10 mm. Therefore they are of limited value to solve pre-operative in-breast problems.

Pre-operative staging of the axilla

Only minor scientific interest was focused on axillary imaging before the concept of sentinel lymph node emerged. In the past, every patient presenting with an invasive cancer experienced standard care for complete axillary dissection. This includes both level 1 and 2 lymph nodes, with harvesting of at least 10 lymph nodes. Pre-operative suggestion of a suspicious lymph node within level 3 has the consequence of level 3 dissection, i.e. medial to the minor pectoralis muscle. Currently, axillary lymph node dissection is increasingly being replaced by the sentinel node procedure, which is associated with less patient complications and morbidity compared with complete axillary dissection. A number of large single- and multi-institutional trials have demonstrated the accurate predictability of axillary metastatic disease based on the histology of the sentinel node. These studies show that in approximately 90% (62–94%) of cases the sentinel node is localized in the lower axilla, and in less than 10% within the marginal area of the breast (Sorgius lymph node). Accuracy rates range from 96% to 100% and false negative rate is approximately 2% [10].

Table 1. Sensitivity and specificity in axillary metastatic lymph node disease. Summarized data of literature are dependant on diagnostic threshold, prevalence, size of lymph nodes, and other factors

Imaging method	Sensitivity (%)	Specificity (%)
Ultrasound	68–92	49–100
Colour Doppler	71–96	53–75
MRI	79–90	78–93
CT	60–94	60–90
PET	40–94	96–100

MRI, magnetic resonance imaging; CT, computed tomography; PET, positron emission tomography.

Accurate definition of axillary involvement by imaging and imaging-guided fine needle aspiration or large-core needle biopsy saves a significant number of sentinel lymph node dissections by selecting those patients who need a complete axillary lymph node dissection at primary surgery [11]. Sensitivity and specificity of axillary imaging methods are given in Table 1. Abnormal rounding, enlarged size, focal or diffuse parenchymal thickening and pathological changes of echogenicity, radiodensity or MR signal intensity, hypervascularity, and an increased unilateral number of nodes are the morphological mainstays of diagnosis. Reading of minimal signs of abnormal sonographic lymph node appearance will enhance sensitivity in a pre-operative high-prevalence collective, though at the cost of lower specificity.

Future expectations

Future staging systems will probably add new technologies, including in-depth molecular analysis using gene or protein expression profiles [9]. Trends for the future include further spread of the sentinel lymph node concept and, last but not least, intensified impact of economic and political issues on medical advice in a united Europe.

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