Keynote Lecture

Tuesday 16 October 2001, 09.40–10.10

Recent advances in imaging breast cancer

S C Rankin

Department of Radiology, Guy's Hospital, Guy's and St Thomas' Trust, St Thomas Street, London SE1 9RT, UK

Mammography remains the main investigation for the diagnosis of breast cancer, supplemented by ultrasound for the rapid assessment of palpable masses. However, even in the best of hands the sensitivity and specificity of mammography is limited and full staging of invasive carcinoma requires axillary node dissection. MRI and nuclear medicine techniques may be helpful in some circumstances. These methods will be discussed in this review.

Staging of breast cancer

Mastectomy or breast-conserving surgery and radiotherapy can treat breast cancer. Recurrence following breast-conserving surgery ranges from 3% to 19% compared with local recurrence after primary mastectomy of 2% to 9%. Whether a patient is suitable for breast-conserving surgery depends on the size of the mass, the presence of multifocal or multicentric disease and involvement of the nipple. Accurate staging of invasive breast cancer includes the histology of the axillary lymph nodes. Axillary dissection has a significant morbidity including lymphoedema, infection and anxiety. The cost is considerable, with 70% of the patients being node-negative and therefore unable to benefit from dissection.

Mammography

The detection of breast cancer by mammography, even when performed optimally has a sensitivity between 69 and 90%. Tumours may be missed because of poor technique (6–17%), observer error or the size and nature of the lesion relative to the surrounding breast tissue, which obscures it. This is a particular problem in the dense breast, following surgery or radiotherapy, where tumour is adjacent to implants or in the younger population. Specificity of mammography (10–40%) is sacrificed to improve sensitivity, leading to increased numbers of biopsies for indeterminate lesions, 75% of which will be benign.

Ultrasound (US) is an excellent method for the assessment of palpable abnormalities, differentiation of cystic and solid lesions and guiding biopsies. Improved spatial resolution means lesions less than 1 cm will be identified, however, microcalcification is not and the reported false-negative rate ranges from 0.3 to 47%[1,2].

Sentinel node biopsy

Axillary node dissection is combined with mastectomy or lumpectomy in invasive ductal cancer for staging and local control. The extent of the dissection is based on the level of nodes removed. A low axillary dissection removes level 1 nodes, and all three levels are dissected in a full clearance. This extensive surgery could be avoided if the status of the axilla could be predicted by sentinel node status.

Sentinel node techniques include the use of blue dye or Tc labelled sulphur colloid. Both are carried by the lymphatics to the first node draining the tumour.
(1) Blue dye (3–5 ml) injected 5 min before surgery. Technical success ranges between 65–93%. False-negative rate = 5%.
(2) Tc sulphur colloid (1 mCi in 4–5 ml saline) injected 1–9 h prior to surgery and a hand-held counter is used to identify the nodes. Technical failure = 10–15%.
(3) Combination of both techniques: Tc sulphur colloid (0.4 mCi) is injected 2–4 h before surgery and 10–15 min before surgery the dye is injected. Nodes are localized by the probe and after the cut-down the blue dye is followed. The technical success for this method is 96%.

In many series the false-negative rate is 1–2%. The gold standard is axillary dissection, however, this may not be appropriate as up to 25% of patients go on to develop loco-regional disease, so presumably some nodes are missed at axillary dissection.

Technetium 99m sestamibi

Technetium 99m methoxy-isobutyl isonitrile (sestamibi) can be used in the diagnosis of breast cancer. Tc 99m sestamibi is a cationic lipophilic agent that transfers across cell membranes and is taken up into the mitochondria of malignant cells. The technique involves the

injection of 20–25 mCi of Tc sestamibi into the contra-lateral arm and the patient is imaged 5 min and 1 h later in the prone position. If bilateral tumours are suspected, a pedal injection should be used. Focal areas of uptake in the breast are considered positive.

The results in selected groups of patients undergoing biopsy are good with recent reports suggesting sensitivity of 84–98%, specificity of 89–95% with a negative predicted value of 61–98%. However, Tc sestamibi is of more limited value in small lesions or in DCIS and the results for non-palpable lesions are poorer with sensitivity of 62%, specificity 91%[3]. Tc 99m sestamibi cannot be used for screening but may be of use in young women with dense breasts or following surgery. It should be remembered that Tc sestamibi is used to improve specificity to decrease the number of unnecessary biopsies. Tc sestamibi and MRI appear to have similar accuracy in the diagnosis of breast cancer in the mammographically indeterminate lesion[4]. However, biopsy, especially with ultrasound guidance, is cheap, accurate and safe. Tc sestimibi and MRI are expensive and the cost is not justified in most cases.

Tc 99m sestamibi can be used for assessing the lymph nodes as well as the primary tumour and in patients with suspected recurrent disease. Taillerfer *et al.*[5] assessed 65 patients with breast cancer and identified 43 of 47 primary tumours and 16 of 19 positive axillary nodes giving a sensitivity of 84% and specificity of 90%. Cwikla *et al.*[6] found Tc sestamibi identified recurrent disease in 78% of cases compared with the 42% identified on mammography.

for false-positive results on MRI, will be negative on FDG-PET.

In patients with known breast cancer, FDG-PET may be helpful in identifying involved axillary nodes with reported sensitivity of 94%[8] although other authors report sensitivity as low as 50%[9], in assessing brachial plexus pathology and detecting distant metastases. Primary chemotherapy is now used in patients with locally advanced disease and FDG-PET is useful for predicting the response based on glucose metabolism. Schelling *et al.*[10] studied a small group of patients with locally advanced disease and, based on the final histology, divided them into those with minimal residual disease, who have a significantly improved survival, and those with gross residual disease. These authors found a reduction in the standardized uptake value (SUV) of FDG-PET of 55% of baseline predicted which patients would respond. After the first course the sensitivity for assessment was 100%, with specificity of 85%, and accuracy 88% and after the second course the sensitivity was 83%, specificity 94% and an overall accuracy of 91%. In this small series the only patient with minimal residual disease that did not show a significant reduction in SUV had a large *in situ* component, which is known to be chemoresistant.

Similarly, Tc sestamibi may be of value in assessing response with a decrease in uptake of more than 40% identifying macroscopic complete response (sensitivity 100%, specificity 89%)[11] and using contrast-enhanced MRI, changes in the uptake curves can predict response with a flattening of the uptake curve in responders[12].

Positron emission tomography

Positron emission tomography (PET) utilizing the glucose analogue 2-^{18}fluoro-2-deoxy D-glucose (^{18}FDG) yields physiological information with the majority of malignant tumours having an increased glycolytic rate compared with normal tissues. ^{18}FDG PET has been used successfully in a large number of tumours to diagnose malignancy in regions difficult to biopsy, to stage tumours before therapy and to follow up the effects of treatment.

Breast cancer can be identified but detection depends on the method of interpretation, the size and the histology of the tumour. Avril *et al.*[7] studied 144 patients with palpable masses and used a conventional and sensitive image reading. The overall sensitivity was 64% and 80%, with 35% and 19% false-negative rates, respectively. The specificity dropped from 94% to 75% using the sensitivity reading. The limitations were: poor detection rate for small (<1 cm) tumours; inability to detect non-invasive tumours (sensitivity 25–41%) and lobular carcinomas (65% false-negatives). FDG-PET also detected only 50% of multicentric tumours. Indeterminate lesions will still require biopsy but FDG-PET is not affected by breast density, previous surgery or radiotherapy and benign breast disease, which accounts

Magnetic resonance imaging

Using contrast-enhanced 3D FLASH or MP-RAGE sequences the sensitivity for the detection of tumours is reported between 90 and 100%, but specificity is variable between 37 and 85%. Combining morphological with dynamic sequences will increase the specificity.

MRI is sensitive in the detection of multicentric disease. Orel *et al.*[13] found 34% of patients had additional foci of tumour not seen on mammography and in 20% there was multifocal disease which altered the surgical approach.

MRI is very sensitive for the detection of invasive cancer, however, the reported sensitivity for MRI in the detection of DCIS ranges between 40 and 100%[13]. Invasive tumours tend to enhance more than non-invasive tumours but there is no correlation between the degree of enhancement and the histological type, grading, nodal status or immunohistochemistry[14].

In suspected recurrence MRI is a sensitive test, particularly in the dense distorted breast and is better than palpation or mammography. The only limitation is the false positives that may occur if the MRI is performed less than 9 months after radiotherapy. This problem can be overcome by using Tc-sestamibi or FDG-PET in this group.

Conclusions

(1) Mammography combined with ultrasound will continue to be the main investigation for breast cancer.

(2) Sentinel node biopsy may allow more limited and appropriate axillary node dissection.

(3) In patients with dense breasts or following surgery or radiotherapy both MRI and Tc sestamibi have a role.

(4) FDG-PET can be used both for staging and early assessment of response to chemotherapy.

References

[1] Kacl GM, Liu P, Debatin JF, Garzoli E, Caduff RF, Krestin GP. Detection of breast cancer with conventional mammography and contrast-enhanced MR imaging. Eur Radiol 1998; 8: 194–200.

[2] Stavros AT, Thickman D, Rapp CL, Dennis MA, Parker SH, Sisney GA. Solid breast nodules: use of sonography to distinguish between benign and malignant lesions. Radiology 1995; 196: 123–34.

[3] Piasano ED, Parham CA. Digital mammography, sestamibi breast scintigraphy, and positrin emission tomography breast imaging. Radiol Clin N Am 2000; 38: 861–9.

[4] Imbriaco M, Del Vecchio S, Riccardi A et al. Scintimammography with 99m-Tc-MIBI versus dynamic MRI for non-invasive characterization of breast masses. Eur J Nucl Med 2001; 28: 56–63.

[5] Taillefer R, Robidoux A, Lambert R et al. Technetium-99m-sestamibi prone scintimammography to detect primary breast cancer and axillary lymph node involvement. J Nucl Med 1995; 36: 1758.

[6] Cwikla JB, Kolasinska A, Buscombe JR, Hilson AJ. Tc-99m MIBI in suspected recurrent breastcancer. Cancer Biother Radiopharmaceuticals 2000; 15 (4): 367–72.

[7] Avril N, Rose CA, Schelling M et al. Breast imaging with positron emission tomography and fluorine-18 fluorodeoxy-glucose: use and limitations. J Clin Oncol 2000; 18: 3495–502.

[8] Greco M, Crippa F, Agresti R et al. Axillary lymph node staging in breast cancer by 2-fluoro-2-deoxy-D-glucose-positron emission tomography: clinical evaluation and alternative management. J Natl Cancer Inst 2001; 93: 630–5.

[9] Yutani K, Shiba E, Kusuoka H et al. Comparison of FDG-PET with MIBI-SPECT in the detection of breast cancer and axillary lymph node metastasis. J Comput Assist Tomogr 2000; 24: 274–80.

[10] Schelling M, Avril N, Nahrig J et al. Positron emission tomography using [^{18}F] fluorodeoxyglucose for monitoring primary chemotherapy in breast cancer. J Clin Oncol 2000; 18: 1689–95.

[11] Mankoff DA, Dunnwald LK, Gralow JR, Ellis GK, Drucker MJ, Livingston RB. Monitoring the response of patients with locally advanced breast carcinoma to neoadjuvant chemotherapy using [technetium 99m]-sestamibi scintimammography. Cancer 1999; 85: 2410–23.

[12] Rieber A, Zeitler H, Rosenthal H et al. MRI of breast cancer: influence of chemotherapy on sensitivity. Br J Radiol 1997; 70: 452–8.

[13] Orel SG, Schnall MD, Powell CM et al. Staging of suspected breast cancer: effect of MR imaging and MR-guided biopsy. Radiology 1995; 196: 115–22.

[14] Fischer U, Kopka L, Brinck U, Korabiowska M, Schauer A, Grabbe E. Prognostic value of contrast-enhanced MR mammography in patients with breast cancer. Eur Radiol 1997; 7: 1002–5.