

Multidisciplinary Symposium — Breast Cancer

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Contemporary problems in the surgical management of breast cancer: the surgical/radiological interface

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Problems with breast-conserving surgery for invasive disease

The morbidity of axillary dissection

The immediate complications of axillary node surgery are relatively insignificant. It is very uncommon for any patient to sustain serious injuries such as brachial plexus nerve or axillary vein injury, and although seroma formation is a very frequent occurrence it is well tolerated and is rarely prolonged. Delayed complications and long-term morbidity are by contrast commonplace and impact on the lives of many individuals. The principle symptoms that may be encountered after axillary surgery are arm swelling, susceptibility to upper limb infections, shoulder stiffness, pain and altered sensation or numbness. Quality of life studies show that lymphoedema is the most troublesome complaint^[9].

Lymphoedema

Incidence: depends on degree of swelling that is used to define the condition.

Serious swelling that interferes with limb function = 2–8%^[1,9]

Significant swelling that is well tolerated = 15–20%^[1–4]

Objective arm swelling without symptoms = 40%

Transient early lymphoedema that resolved = 7.5%^[1]

Risk factors:

Degree of axillary surgery (sample, level I, II or III)^[5]

Obesity predisposes^[1,6]

Incidence increases with time^[1]

More common in older patients and possibly after wound infection^[7]

Chronic pain

Incidence = 2.5%^[6]–25%^[3,4]

Numbness/paresthesia

Early post-op incidence = 70–77%^[3,4,6,8]

Resolves in 20%, improves in 60–100%, remains in 20%^[6,8]

Shoulder stiffness

Abduction reduced by >15 degrees in 9% at 1 year, other movements unaffected^[3].

Local recurrence

Rate

Local recurrence following mastectomy approx. = 1%/year (incl. Regional)

Local recurrence following breast-conserving surgery approx. = 2%/year (incl. Regional)

Table 1 *Loco-regional recurrence rates in the larger trials of breast-conserving surgery*

Authors	<i>n</i>	F/U years (median)	% Local recurrence	% Local recurrence/year
M. D. Anderson	525	5	10.3	2.15
Institut Curie	518	13	18	1.3
Yale ^[15]	278	7.5	17	2.3
Marseilles	1593	11	12.9	1.2
Harvard	733	6	13.3	2.2
Univ. Pennsylvania	1030	3	9.3	3.1
Marsden	211	10	22	2.2
NSABP ^[6]	629	6.5	14.5	2.2
Westminster	356	5	13.5	2.7

Effects of local recurrence on survival

Most studies show no impact on survival in patients with isolated local recurrence^[10,17,19]

Local recurrence (intra-breast) is associated with a relative increase in the risk of metastatic disease (and therefore death) of 2.0–4.5 times^[11,12,16]

Increased risk of metastatic disease is principally confined to early recurrences (<5 years, and especially in recurrences <2 years after primary surgery)^[10,12,13,19]

Overall survival following local recurrence = 50% @ 5 years^[12,15,19]

Local recurrence is controllable by mastectomy in 70–95%^[12,20]

Overall survival following local recurrence in breast-conserving surgery is no worse than local recurrence following modified radical mastectomy^[18]

Risk factors for local recurrence

Ninety per cent of local recurrences occur in the same quadrant of the breast suggesting that most represent residual disease.

Approx. 10% of patients undergoing breast-conserving surgery can be shown to have adjacent residual areas of multifocal disease^[24]

General: local recurrence is more frequent in younger patients^[21] and those with larger tumours

Surgical: moderately or extensively involved surgical margins are associated with increased rate of local recurrence^[22], close or focally involved margins are probably not^[23]

Pathological: local recurrence increased with extensive in-situ component, tumour grade^[17] and lymphatic/vascular invasion. Nodal status is a possible risk factor.

Problems with breast-conserving surgery for DCIS

DCIS is often extensive in one area of the breast and may be multi-centric. The mainstay of treatment is complete surgical excision. The successful elimination of DCIS represents a chance to avoid potentially fatal invasive disease, but just as with invasive disease the earlier fashion of simple mastectomy has given way to breast-conserving surgery in many patients. A recurrence rate of approximately 1% @ 10 years can be expected after mastectomy compared with 12–20% for breast-conserving surgery. The factors associated with recurrence are the surgical margin, the presence of multifocal or multicentric disease, lesion size and the degree of differentiation of the in-situ change. DCIS is usually not palpable and the pre-operative assessment of extent and multicentricity are problematic given current imaging techniques.

Background

Prevalence

PM studies=8.9%

15–20% of detected breast malignancy

Distribution in the breast

Holland studied 82 mastectomy specimens in patients with DCIS and correlated the pathology with specimen radiology^[25]

DCIS associated with microcalcification in 94% of comedo necrosis and in 53% of micropapillary/cribiform

Histological grade not related to size

Microcalcification underestimates lesion size by >20mm

12% of comedo necrosis DCIS

44% of micropapillary/cribiform

50% of mixed micropapillary/cribiform+comedo necrosis

True multicentric disease is uncommon — 1/82 breasts (1.2%)

Extensive disease is frequently found

23% DCIS extends through >1 quadrant (90° sector)

33% DCIS measured >40 mm in diameter

i.e. complete surgical clearance difficult in >50%

A focus of DCIS was closely associated with the nipple in 52%

in comedo DCIS there was a nipple area focus in 64%

in micropapillary/cribiform DCIS nipple area disease in 34%

DCIS involved the nipple itself in half of these cases

70% of disease close to the nipple is mammographically occult

In patients with clear excision margins (>1mm) 43% have residual DCIS^[33].

Relative recurrence rates

Recurrence at 5 years following mastectomy = 1–2% @ 10 years^[29,35]

Recurrence at 5 years following breast-conserving surgery = 12–22% @ 5–10 years^[26]

Approximately 50% of all recurrences following any treatment modality are invasive and 50% represent further DCIS. Invasive recurrences occur later (2 vs. 5 years)^[27]

Cause-specific mortality of those treated by breast conservation = 0–2% @ 10 years^[27]

Recurrence rates after breast conservation are approximately halved by radiotherapy^[34]

NSABP-24 investigated the recurrence rates following surgery plus tamoxifen. The recurrence rate is reduced but the follow-up is too short to tell whether recurrence is being prevented or just delayed^[32].

Risk factors

The following are recognized as being associated with recurrence following surgical excision of DCIS

Close margins — most studies define ‘close’ as 1 or 2 mm. Risk is particularly high when the margin is <2 mm but decreases progressively with widening margins. By a margin of 10 mm the risk is down to 4% @ 7.5 years^[31,34]

Large lesion diameter. As with the measurement of margins this may be very difficult for the pathologist to assess accurately. Areas of DCIS >4–5 cm are associated with high recurrence rates^[30]

High histological grade/poor cytological differentiation. Assessment is somewhat subjective. The intermediate grade is particularly inconsistent^[35]

Histological evidence of necrosis. This is related to higher histological grade^[34]

Atypical ductal hyperplasia or cancerization of lobules adjacent to lesion^[28].

Predicting recurrence

The Van Nuys Prognostic Index (VNPI)^[36]

Has the advantage of being from a ‘single’ institution
Combines the three most significant variables by multivariate analysis

Log rank test to find cut off values that would divide the variable into three separate groups:

Score	1	2	3
Lesion size	<16 mm	16–40 mm	>40 mm
Histopathology	Not high grade, no necrosis	Not high grade, necrosis present	High grade, necrosis present
Margin	>10 mm	1–9 mm	<1 mm

Identifies three risk groups

VNPI=3 or 4 — low risk of Local recurrence, 3% recurrence @ 8 years

VNPI=5,6 or 7 — intermediate risk of LR, 23% recurrence @ 8 years

VNPI=8 or 9 — high risk of LR, 80% recurrence @ 8 years.

Sentinel node biopsy^[38]

Definition

There is some argument as to how the sentinel node is defined^[37]. Theoretically the sentinel node is the node or nodes in each of the sometimes multiple lymph node basins that receives the direct lymph drainage from the site of the lesion. Practically, the sentinel node is the node or nodes in each lymph node basin that receive a blue-stained lymphatic and/or accumulate sufficient tracer to be clearly discernable at surgery. In the case of radioisotope tracers local definitions involving the count ratio of the node and the nodal bed are often used. The ratio has been defined as anywhere between 2 and 10.

Sentinel node biopsy aims to predict the status of the regional lymph node basin draining a carcinoma by analysis of the sentinel node(s) only. There is strong evidence that if the sentinel node is free from metastasis then the rest of the lymph nodes in that nodal basin will also be tumour-free. These sentinel node-negative patients can then safely omit nodal clearance and the morbidity that is associated with it.

In breast cancer approximately two thirds of sentinel node-positive cases have metastases confined only to the sentinel node(s) with all non-sentinel nodes being tumour-free. At the present time patients with a sentinel node containing tumour all undergo further axillary treatment (clearance or radiotherapy).

Methods

Tracer

Blue dye^[39], 99-m technetium labelled colloid^[40] (particles 50–500 nm diameter) or both^[41]

Site of injection

This varies. The most common is around the tumour. Also popular is sub- or intra-dermal. Occasionally reported into the tumour

Pre-operative lymphoscintigram

This is not an essential part of sentinel node biopsy but it does have two advantages:

- (1) alerts the surgeon to drainage outside the axilla;
- (2) often shows the presence of multiple sentinel nodes.

Results

Accuracy

Population accuracy=% of cases where the sentinel node biopsy correctly predicts the status of the nodal basin as a whole. (In series with 50–70% node-negative cases the population accuracy can never be worse than 50–70%)

Underlying accuracy=% of node-positive cases that were accurately predicted.

Author	Method	ID rate	Population accuracy	Underlying accuracy
Early (1996–1998) results				
Giuliano ^[42]	Dye	93%	99%	98%
Albertini ^[41]	Dye & isotope	92%	100%	100%
Veronesi ^[43]	Isotope	98%	97.5%	95%
Recent (1999–2000) results				
Guenther	Dye	71%	97%	90%
Roumen	Isotope	69%	98%	96%
Morgan	Dye	73%	94%	80%
Institut Curie	Dye	87%	97%	92%
Imoto	Dye	74%	94%	86%

The figures for the underlying accuracy do not appear in the published results but can be extracted from them. The underlying accuracy represents the number of patients who would benefit most from adjuvant chemotherapy but may miss out on it due to incorrect staging.

Benefits

Reduced morbidity

Can avoid axillary dissection and the associated arm morbidity in approx. 50–60% of patients with primary breast cancer.

Facilitates the detection of micrometastases

Allows intense histological examination to be concentrated on the sentinel node(s) rather than spread between a large number of non-sentinel nodes. Nodes can be subjected to serial sectioning, immunohistochemistry and reverse transcriptase PCR

Extra axillary nodes

Lymphoscintigraphy has demonstrated drainage to the internal mammary chain in approx. 10% of cases of primary breast cancer^[45]

Improved axillary sampling

Sentinel node biopsy can be used in conjunction with axillary node sampling. This ensures that the sample is representative of the rest of the axilla.

Problems

False negatives

There are probably a small number of unavoidable false-negative results. Even when the sentinel node is clearly identified false-negative results seem to arise in approximately 5% of cases. This may be due to an inherent flaw in the convenient sentinel node theory. Current results (see above) indicate a 5–20% false-negative rate in node-positive patients. A small number of node-positive patients may undergo less intensive treatments in error, with potentially fatal results

Upstaging

The more rigorous histological examination of the sentinel node is resulting in 'up-staging'. This means that there is a larger percentage of node-positive patients in any series (e.g. 29% node positivity increased to 42% when the sentinel node was subjected to more sophisticated analysis)^[44]. The increase is largely due to the increased detection of micrometastases. The prognostic implications of these small micrometastases is unclear and optimal management will take many years of clinical trials to evaluate

2-stage procedure

Attempts to analyse the sentinel node by frozen section during surgery have resulted in unacceptable inaccuracy^[43]. Presently, the sentinel node biopsy has to be done first and if axillary surgery is required a second operation is necessary

Radiation exposure

The absorbed dose to the patient is 0.1 mSv

Absorbed dose to surgeon = 2–5 μSv per case (maximum dose = 1 mSv/year)

Absorbed dose to surgeon's fingers = 100 μSv per case, (maximum dose = 500 mSv/year).

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Is imaging mandatory for staging?

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Mammography is the primary imaging modality in the detection of breast cancer. However, the limited sensitivity and specificity of mammography in the radiographically dense or treated breast and in assessing response to chemotherapy has led to the development of adjunctive imaging techniques including Magnetic Resonance Imaging (MRI), Positron Emission Tomography

(PET) and Scintimammography (SMM). The role of each of these specialized investigations is yet to be defined, but it has been established that they should not replace the use of conventional mammography and ultrasound, but be reserved as complementary techniques for resolving specific defined problems. One of their main benefits appears to be improved loco-regional

staging. In the current era of breast-conserving surgery accurate staging is mandatory so that inappropriate conservative surgery is not performed. Adjuvant imaging will help define the local extent of disease pre-operatively and thereby reduce local recurrence rates.

Loco-regional staging

In the current era of conservative surgery for early breast cancer it is critical for accurate loco-regional staging to be carried out so that appropriate treatment can be selected. Breast cancer may have a multicentric, multifocal origin; in a radiographic-histologic evaluation of mastectomy specimens, Hollands *et al.* showed 41% of cases had remote cancer foci most of which were occult at mammography^[1]. Tumour size, multifocality, retroareolar tumours and in situ component need to be accurately detected so that optimal local tumour control is made and mastectomy performed as a one-stage procedure if indicated. Flanagan *et al.* claim mammography to be almost exact in assessing tumour size^[2], but ultrasound tends to be more accurate^[3].

MRI has recently been advocated as the most accurate method of assessing tumour size and extent and detecting extensive ductal carcinoma in situ due to its extreme sensitivity^[4-10]. MRI of the breast using a surface coil and rapid dynamic contrast-enhanced gradient echo imaging shows almost all malignant lesions enhance rapidly, concomitant with early vascular enhancement^[11] and relative to normal breast parenchyma, and also have characteristic morphological appearances. Clinically and mammographically occult multifocal tumours are readily detected by MRI^[5-9,12] as shown in Table 1. Orel^[13] and Morris^[14] showed MRI is very sensitive in patients with malignant axillary lymphadenopathy and unknown primary tumour for the detection of clinically and mammographically occult breast cancer. The main limitation with MRI is the poor specificity; Gilles showed that early contrast enhancement in 37 of 79 patients with benign lesions giving a specificity of 53%^[15]. Boetes found that assessing morphological appearance as well as the rate of enhancement increased specificity to 86%^[16].

MR mammography as an adjunct to mammography and ultrasound reveals breast cancer with a higher confidence and sensitivity^[10], but with lower specificity. MR imaging-guided needle localization and biopsy systems have been developed to evaluate lesions

Table 2 Differentiation of benign and malignant breast lesions: MR vs Tc-99m sestamamigraphy^[17]

	MR	Planar mibi	SPECT mibi
Sensitivity	96%	62%	83%
Specificity	82%	88%	80%

identified by MR that are clinically and mammographically occult^[6]. Cost, lengthy imaging time and poor availability may restrict access to MRI.

Scintimammography (SMM) using technetium-99m sestamibi has recently been evaluated as an adjunctive technique to mammography. ^{99m}Tc-MIBI accumulates in tumour cells and has been reported to be accurate in detecting breast cancer and can help differentiate benign from malignant lesions^[17-20]. SMM can be especially useful in the mammographically dense breast and, therefore, the young. Khalkhali *et al.* first reported the usefulness of Tc-99m sestamibi imaging in the detection of breast cancer^[21]. Palmedo detected tumours as small as 9mm and detected 100% of palpable tumours and, including impalpable lesions, the overall specificity was 83% and sensitivity was 88%. Helbich compared MR to ^{99m}Tc-sestamibi in differentiating benign from malignant breast lesions^[17] (see Table 2).

Whilst both MR imaging and scintimammography are useful in the evaluation of breast cancer, MR was found to be more sensitive and just as specific. MR is a shorter examination time to scintimammography, but claustrophobia in the magnet can often lead to early termination of the procedure. In this instance scintimammography is a good alternative and can also give important information about the axilla. Scintimammography has limited spatial resolution and therefore the size of the tumour affects detection that may account for the low sensitivity. The main problem with scintimammography currently is limited availability as a special prone coil that improves imaging is required. The suggested use of scintimammography is as an adjunct to conventional imaging in failed triple assessment, breast prosthesis and with axillary metastasis and unknown primary^[22].

Indications for scintimammography:

- Failed triple assessment
- Previous surgery
- Breast prosthesis

Table 1 Detection of multifocal tumours and assessment of tumour size by MRI: comparison with conventional imaging

Author	Conrad ^[5]	Kerslake ^[8]	Mumtaz ^[7]	Orel ^[6]	Boetes ^[9]
No of patients in study	40	50	90	64	60
Multifocal tumour detected by MRI but not BM	9	14	6+5	22	9
MR/histology tumour size correlation	Good	Good	Good	Good	Good

BM=bilateral mammogram.

Negative biopsy of suspicious mass
Axillary nodes with occult primary

Several studies have addressed the imaging of breast cancer with PET. PET produces images that reflect the physiological and biochemical processes of tissues. The most widely used PET pharmaceutical is fluorine-18-fluorodeoxyglucose (FDG) which evaluates the glucose metabolic rates of tissues. Malignancies have exceptionally high rates of glycolysis compared with benign tissues. FDG-PET is suitable for detecting breast cancer and evaluating response to treatment. FDG is taken up by all malignant tissues and therefore whole body scanning can be undertaken with assessment of lymph node involvement and distant metastases. Wahl reported visualization of all 10 primary breast cancers using FDG-PET^[23] and Adler showed 96% sensitivity and 100% specificity for the detection of malignancy^[24]. A limited number of benign lesions were studied, but these had a lower uptake than malignant lesions. Given the high cost of PET and limited availability, this technique is unlikely to serve as a screening modality for breast cancer. As an adjunct to conventional imaging it can be used in the indeterminate mammogram, prior to biopsy, with axillary metastasis of an unknown primary to search the breast^[25] and to evaluate the axilla prior to axillary surgery.

FDG-PET may be used in circumstances where mammography is technically difficult.

This includes:

- Dense breasts
- Breast implants
- Lumpy breasts/ multifocal disease
- Post-operative breast
- Equivocal biopsy

Assessment of tumour response to chemo-endocrine therapy prior to surgery

Adjuvant systemic therapy following surgery for primary breast cancer with Tamoxifen or chemotherapy can reduce the risk of relapse and mortality. Neo-adjuvant chemo-endocrine therapy is also used as primary treatment prior to surgery. Assessment of response to treatment is an important role of imaging in the multidisciplinary approach to treatment of breast cancer.

Changes seen on mammography associated with tumour response include a decrease in size and density of the lesion, calcifications becoming more tightly packed and complete resolution of the lesion^[26]. The remaining mammographic lesion may not necessarily contain tumour cells. Ultrasound can be useful in monitoring tumour size and recording changes in Doppler signal. However, even in the presence of no detectable lesion on ultrasound the presence of a viable tumour cannot be eliminated^[27].

MR has recently been reported in the evaluation of response to neo-adjuvant chemotherapy. Gilles assessed residual active disease using dynamic contrast-enhanced MR, and the presence or absence of early contrast enhancement appeared to be a reliable diagnostic criterion for the presence of residual tumour^[28]. Abrahams, using rotating delivery of excitation off resonance (RODEO) with gadolinium enhancement, reported that changes in vascularity early in the course of chemotherapy help to predict response^[29]. They accurately evaluated residual disease and suggest MR is superior to conventional imaging in the assessment of response to chemotherapy. Conversely Rieber *et al.* found that post-neo-adjuvant chemotherapy MR led to some false-negatives and an underestimation of residual tumour volume in some, although MR could provide evidence of response after the first two cycles with a high degree of probability^[30].

FDG-PET is valuable for monitoring the effects of pre-operative chemotherapy in patients with locally advanced breast cancer, with better sensitivity for tumour and specificity for nodal metastasis than ultrasound^[31].

Local recurrence

Radiation therapy is increasingly being utilized following breast conservation. Post-treatment follow-up is difficult as surgical and radiation changes can mimic recurrence. Mammographic radiation changes are well known and the late phase usually stabilizes by 12 months after completion of radiotherapy. If diagnosed early, recurrences are treated with mastectomy and do not impair survival of these patients. Previously, biopsy was performed to determine whether changes were radiation-induced or a recurrence. Several studies have shown promising results with MRI^[32]. FDG-PET and SSM may also have a role in diagnosing local recurrence. Hathaway reported the combined use of MR and FDG-PET^[25] and their complementary role: PET identified all cases of metastatic tumour, whereas MR was useful in determining the relationship of the tumour to the axillary and supraclavicular neurovascular structures. Orel reports a high positive predictive value for MR predicting residual tumour after excisional biopsy, which would complement traditional methods of margin evaluation^[33]. Patients underwent MR imaging 6–40 days after excision biopsy and results suggest that those with positive margins following surgery should undergo MR to assess for residual disease prior to re-excision.

Conclusion

Imaging plays an important role in loco-regional staging in the current era of breast-conserving surgery otherwise local recurrence rates may be unacceptably high. MR, PET and SSM are being increasingly utilized as adjuvant imaging in loco-regional breast disease and the choice may depend on local availability. PET and SSM are not

widely available and, due to increasing access to MR, this may be the favoured technique. MR, PET and SSM should only be used in specific problem-solving areas discussed by the multidisciplinary team. Further studies comparing all three imaging modalities are required.

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