Scintimammography in conjunction with ultrasonography for local breast cancer recurrence in post-mastectomy breast

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ABSTRACT. The aim of this study was to compare the usefulness of ⁹⁹Tc^m-methoxy-isobutyl-isonitrile (MIBI) scintimammography and ultrasonography, alone and in combination, for the detection of chest wall recurrence in the post-mastectomy breast. A total of 41 consecutive post-mastectomy patients (mean age 46.6 years; median age 45 years) with clinical suspicion of breast cancer recurrence were evaluated. For scintimammography all patients received a 740–900 MBq iv injection of ⁹⁹Tc^m-MIBI; planar images were taken 5–10 min post-injection followed by supine single photon emission CT. Breast ultrasonography was performed in each patient using a 7.5 MHz transducer. Both MIBI uptake and ultrasound findings were documented using standard protocols. All patients had fine needle aspiration cytology biopsy (FNAC), core biopsy or excision biopsy for final tissue diagnosis. Of the 41 patients, 24 had true positive signs of local breast cancer recurrence upon ultrasonography, 10 were diagnosed as true negatives, a sensitivity of 86%, specificity 77%, positive predictive value (PPV) 89%, negative predictive value (NPV) 71% and accuracy 83% ($p=0.001$). By comparison, scintimammography findings were found to be true positive in 25 patients and true negative in 12 patients — sensitivity 89%, specificity 92%, PPV 96%, NPV 80% and accuracy 90% ($p=0.001$). Using a combination of these two modalities, the combined sensitivity was 100%, specificity 77%, PPV 90%, NPV 100% and accuracy 93%. The high NPV of the two studies in combination implies a potential use of this approach to exclude recurrent disease in patients with a low initial index of suspicion and/or when histology is indeterminate.

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The local recurrence rate in breast cancer is estimated to be approximately 1–2% per year [1]. After mastectomy, breast cancer recurs locally in 5–10% of patients, depending on the initial stage and grade of the tumour and the treatment administered [2, 3]. In patients who have undergone mastectomy with axillary node dissection followed by adjuvant chemotherapy, the most common site for local recurrence is the chest wall. In these patients, the usual presentation is of one or more asymptomatic nodules in or under the skin of the chest wall, typically located within or near the mastectomy scar [4]. Diagnosis of local recurrence carries a worse prognosis than the initial presentation owing to a significant number of patients, in whom there is local recurrence, having systemic metastases. The presence of local recurrence, therefore, mandates further investigation (*e.g.* by fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT).

Following modified radical mastectomy, the proportion of residual, subcutaneous tissue is greater than after radical mastectomy, rendering clinical examination alone relatively inaccurate in differentiating between benign and malignant lesions [5]. The role of

mammography in this situation is also limited because of technical considerations and the presence of scar tissue [6]. The sensitivity of ultrasonography for the detection of local recurrence is superior to that of palpation and mammography. In some patients, however, the possibility of local recurrence presents as a diagnostic dilemma for the referring physician and breast radiologist. Direct biopsy is most commonly used to categorise clinically suspicious lesions, an effective technique in the hands of a skilled operator. At times, however, histology can be indeterminate or misleading, and complications such as rib fracture or pneumothorax can rarely occur [7]. Some studies have suggested that the number of biopsies performed in these settings could be reduced using scintimammography (SMM) with ⁹⁹Tc^m-methoxy-isobutyl-isonitrile (MIBI) [8–10] to identify high-risk individuals. The aim of the current study was to evaluate the usefulness of a multimodality approach, and to assess whether this strategy is superior to either modality when used alone.

Materials and methods

A total of 41 consecutive patients (mean age 46.6 years, median age 45 years, age range 22–77 years) with clinical suspicion of chest wall recurrence of breast cancer

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Table 1. Patient characteristics

	Number of patients	%
Primary tumour type		
Infiltrating ductal carcinoma	38	93
Infiltrating lobular carcinoma	3	7
Post-operative radiotherapy	33	80
Post-operative chemotherapy	26	63
Supplementary hormonal treatment	23	56
Physical examination		
Nodule under and above the scar <3 cm	14	34
Nodule under and above the scar >3 cm	17	41
Cutaneous nodule	6	15
Diffuse swelling of skin	4	10

following modified radical mastectomy were included in this study (Table 1). The median time interval after primary treatment was 26 months (range 6–144 months).

Ultrasonography

Ultrasonography was performed by breast radiologists with more than 6 years experience in the sub-specialty, using a dedicated ultrasound machine equipped with a 7.5 MHz linear transducer. Ultrasound was targeted first to the index lesion and then to the surrounding tissue and insonated in clockwise radial and antiradial orientations around the lesion. During ultrasound, the size, border, acoustic impedance, relationship to surrounding structures and solid or cystic character of the mass were evaluated to determine the likelihood of malignancy. The examination included imaging of the axilla and the results were reported using a three-point scale: positive for probable malignancy, equivocal findings or negative for malignancy (either no visible abnormality or a probable benign lesion).

Scintimammography

All patients had scintimammography (SMM) using a double-headed gamma camera fitted with a low-energy high-resolution parallel-hole collimator. The energy peak was centred at 140 keV with a 20% window. All patients received a 740–900 MBq iv injection of $^{99}\text{Tc}^{\text{m}}$ -MIBI, preferably in a pedal vein so as to limit venous radioactivity in the field of view. At 5–10 min post-injection, planar images were obtained in the prone lateral and supine anterior positions. The detector was positioned below and as close as possible to the involved chest wall. The axilla was also included in the field of view; and a lead shield was positioned in the midline to minimise capture of counts originating from the contralateral breast.

After planar imaging, supine single photon emission CT was performed with a 64×64 matrix over a 360° arc (180° per head) in the supine position, using a 6° “step-and-shoot” technique and an acquisition time of 30 s per frame. MIBI uptake was scored as follows: (1) normal uptake (compared with the contralateral side); (2) focal low intensity uptake (equivocal); and (3) focal high

intensity uptake. Only high focal uptake was graded as positive. Two experienced nuclear physicians, who were blind to the patient’s clinical information, analysed the scintimammograms. Interobserver variability was extremely low; disagreement was observed in only one case and was resolved by consensus.

Histopathology and cytology

All patients with findings that led to suspicion of recurrence had fine needle aspiration cytology (FNAC), core biopsy or definitive wide local excision to ascertain the final tissue diagnosis. Of the 41 patients, 14 underwent FNAC, 10 had core biopsy and 17 had local excision. Of the 17 patients who underwent wide local excisions, 5 had prior FNAC and 3 had prior core biopsies that had been inconclusive. In remainder of these cases, wide local excisions were performed as the method of choice for superficial tumours.

Statistical analysis

The results of SMM and ultrasound were both analysed using an equivalent three-point grading system: Grade 1 as normal, Grade 2 as equivocal and Grade 3 as probable cancer. For combination imaging, ultrasound preceded SMM and the combined result was determined by the highest score obtained by either modality in each individual patient.

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated for ultrasound, SMM and a combination of both modalities. The χ^2 test was applied to compare the level of significance of any difference in findings between the imaging modalities and the histopathological results. A difference was considered statistically significant when p -values were <0.05 . McNemar’s test was used to assess the statistical differences in sensitivity, specificity, accuracy, PPV and NPV between SMM and ultrasound.

Results

Of the 41 patients, 28 had histopathological evidence of chest wall recurrence. Ultrasound produced true positive findings in 24 patients and true negative

Table 2. Scintimammography (SMM) and ultrasonography findings

	True positive	False positive	True negative	False negative	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
SMM	25	1	12	3	89	92	96	80	90
Ultrasound	24	3	10	4	86	77	89	71	83
SMM + ultrasound	28	3	10	0	100 ^a	77	90	100 ^b	93

^a $p=0.0301$, ^b $p=0.0031$ compared with the SMM and ultrasound value (McNemar's test results).

findings in 10 patients (Table 2). The sensitivity of ultrasound was 86%, specificity 77%, PPV 89%, NPV 71% and overall accuracy was 83% ($p = 0.001$).

SMM produced true positive findings in 25 out of 41 patients. It was a true negative in 12 patients and a false negative in 3 patients. The overall sensitivity of SMM in detecting chest wall recurrence of breast cancer was 89%, specificity 92%, PPV 96%, NPV 80%, and overall accuracy 90% ($p = 0.001$) (Table 2; Figure 1). No statistical difference was found between the sensitivities of ultrasound and SMM ($p = 0.321$ using McNemar's test).

In our study, ultrasound has a specificity of 77%. The results were true negative in 10 cases and false positive in 3 patients. The specificity of ultrasound was considerably lower than that of SMM (92%) ($p=0.321$ using McNemar's test).

The combined sensitivity of the two modalities was 100%, specificity 77%, PPV 90%, NPV 100% and accuracy 93% ($p=0.001$). The combination of two tests has significantly higher negative predictive value than either modality alone ($p=0.0031$ using McNemar's test). 12 patients with negative SMM and negative histopathology are under close follow-up with no evidence of loco-regional recurrence after 1 year.

Discussion

The treated breast is a complex structure and various post-treatment findings such as fluid collection, architectural distortion, scarring, oedema, skin thickening and calcification may mimic or mask local recurrence of cancer [11]. The results of a physical examination are frequently non-specific [12]. SMM has better diagnostic accuracy for chest wall recurrence than physical examination, but its sensitivity is low for small cutaneous lesions and occasionally there is diffuse uptake of radiotracer without any delineated focus (Figure 2). In such situations ultrasound can be effective, particularly in detecting and characterising small lesions in the near field, close to the skin surface. This improved sensitivity of ultrasound is, however, operator-dependent and is directly related to the subjective nature of image assessment, which in turn relies on identifying certain patterns of abnormality associated with malignancy. With SMM, operator skills are less crucial because the presence or absence of focal radiotracer uptake equates to a positive or negative result (Figure 3). The accuracy of ultrasound, unlike that of SMM, may also be affected by post-surgical and post-radiation changes. Ultrasound does, however, possess the advantage of facilitating

Figure 1. A 55-year-old woman with a 14-month history of left-sided breast cancer treated by mastectomy, chemotherapy and radiotherapy. She presented with a swelling under and above the scar. Scintimammography single photon emission CT shows a focal area of increased tracer uptake on (a) transverse, (b) sagittal and (c) coronal slices (arrows). (d) Ultrasonography was highly suspicious for malignancy. Biopsy revealed an invasive ductal carcinoma.

Figure 2. A 65-year-old woman with a 36-month history of right-sided breast cancer treated by mastectomy, chemotherapy and radiotherapy. She presented with a swelling under and above the scar. SMM planar images show diffuse increase in tracer uptake in the right anterior chest wall. SPECT images show a focal area of increased tracer uptake on transverse, sagittal and coronal slices. Ultrasonography was highly suspicious for malignancy and biopsy revealed an invasive ductal carcinoma.

targeted tissue sampling, and it is recognised that the management of patients with suspected recurrence is dependent on obtaining accurate histology, either by stereotactic or ultrasound-guided biopsy, using FNAC or core biopsy needles. In the post-operative patient, however, this process can sometimes be painful and technically difficult, requiring a high level of patient compliance and occasionally leading to indeterminate or non-representative histological results. Complications are rare, but can be distressing.

In our study, results indicate that ultrasound has a sensitivity of 86%, specificity of 77%, accuracy of 83%, PPV of 89% and NPV of 71% for the detection of local recurrence. In a previous study, Rissanen et al [4] reported a sensitivity of 91% for ultrasound in the post-mastectomy breast, whereas the sensitivities of clinical examination and mammography were only 79% and 45%, respectively. These results are comparable to those of our study. Kim and Park [13] suggest that evaluation of the mastectomy site by ultrasound is more effective than evaluation with either mammography or chest CT because abnormalities are usually small and situated close to the skin surface. Ultrasound is a reasonably reliable technique for assessing the extent of scarring in the tumour bed and interval studies can identify

progression [14]. Most recurrent cancers appear on ultrasound as hypoechoic lesions; but they occasionally manifest as areas of increased echogenicity [15] and, in these cases, discriminating tumours from fibrous tissue is more problematic.

In our study, the specificity of ultrasound was 77%. Three hypoechoic lesions detected with ultrasound were found to be false positive. One of these lesions had smooth borders, whereas the others had irregular borders. The lesion with smooth borders was found to be an oil cyst on histological analysis and the lesions with irregular borders were found to be caused by localised fat necrosis. Despite the sensitivity of ultrasound, findings at ultrasound are frequently non-specific because of the considerable overlap that exists between the appearance of benign and malignant disease. Thus, unless the appearance is unequivocally benign, all suspect or indeterminate lesions warrant tissue sampling. More recently, the use of Doppler imaging, with the addition of intravascular contrast agent to assist in identifying tumour neovascularisation, is gaining ground as a promising technique for conferring greater specificity on ultrasound appearance [16].

In this study, SMM yielded a sensitivity of 89%. It produced true positive findings in 25 patients and false

Figure 3. A 38-year-old woman with 24 month history of right-sided breast cancer treated by mastectomy and chemotherapy. She presented with a lump in the right upper chest. (a) Ultrasonography was suspicious for malignancy. (b) Scintimammography revealed no abnormality. Scar tissue was found at biopsy.

negative findings in 3 patients. These results are similar to those reported by Kolasinska et al [17]. In our study, false-negative scans were obtained from lesions that were <2 cm in size, in line with the finding that SMM has low sensitivity for detecting small lesions below 1 ± 1.5 cm in size [18]. The specificity of SMM in this study was 92%. A false-positive result was noted in one patient, in whom cytology revealed localised inflammation. Local inflammation, fibroadenomas and fibrocystic changes represent the major source of false-positive images on SMM.

Large series of data have shown equivalence between ultrasound and SMM in the detection of primary breast tumours before surgery [19–21]. These studies showed no convincing difference between the sensitivities of SMM and ultrasound, and suggest that, in palpable malignant tumours larger than 1 cm, SMM has high sensitivity and performs slightly better than ultrasound. There may be, however, a subset of patients for whom SMM could be of additional benefit. This includes patients in whom mammography and ultrasound are inconclusive, particularly patients with dense breasts, those with architectural distortion and those with breast implants [22].

In our study, there was no statistically significant difference between the sensitivities of SMM (89%) and ultrasound (86%). In the setting of breast cancer recurrence, Klaus et al [23] reported a statistically significant better specificity of SMM compared with that of ultrasound ($p < 0.01$), whereas Wang et al [24] reported significantly greater specificity of SMM compared with US ($p < 0.05$). Given the fact that the accuracy of ultrasound might be affected by post-surgical and post-radiation changes, one would expect a further decline in its specificity following cancer treatment. In our study, the specificity of ultrasound (77%) is considerably lower than that of SMM (92%)

($p = 0.0321$ using McNemar's test). Of the three lesions that appeared hypoechoic on ultrasound and were later confirmed as negative on histology, two were correctly identified as negative upon SMM.

When SMM and ultrasound were combined, the sensitivity was 100%, specificity 77%, PPV 90%, NPV 100% and accuracy 93%. The high NPV for a combination strategy highlights the strength of the multimodality approach. In any case, although SMM has greater specificity than ultrasound, it is unlikely to replace ultrasound as the primary tool for evaluation of breast cancer recurrence because of the inherent advantage of performing percutaneous biopsy under ultrasound guidance. If our results are born out by a more extended series, however, it would appear that the benefit afforded by the high NPV of multimodality imaging could be exploited in certain patient subsets: for example, those who decline biopsy or for whom the results are less than optimal owing to reduced compliance. Multimodality imaging could also be employed in patients with low pre-test likelihood of recurrent disease, or where histology may be uninformative or non-representative, particularly in the face of strong clinical suspicion. If both ultrasound and SMM are negative in patients from these groups, a "wait and watch" policy may be reasonably adopted. In addition, as a number of patients with suspected, but non-proven, recurrence are subjected to alternative diagnostic scrutiny when scanning for associated systemic disease, a multimodality imaging strategy could also prevent unnecessary exposure to high doses of ionising radiation.

Conclusions

Scintimammography is a simple, non-invasive and reliable tool for the diagnosis of chest wall recurrence of breast carcinoma. This study suggests that SMM is as

accurate as ultrasound and can be used to discriminate post-surgical changes, post-irradiation changes and scar tissue from tumour recurrence. Furthermore, a combination of SMM and ultrasound is significantly more accurate than either of these tests alone and has a high NPV. Although the currently accepted management of breast cancer recurrence relies on gaining histological confirmation, the strength of this combination strategy can be utilised in patients with a low index of clinical suspicion of recurrence and/or for patients in whom, for any reason, histological confirmation is not forthcoming.

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