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Original

The role of scintimammography and mammography in recurrent breast cancer. Evaluation of their accuracy using ROC curves

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Abstract

BACKGROUND: With the increasing demand for breast conservation surgery, the probability of recurrent tumour within the breast increases. Traditionally x-ray mammography (XMM) was used to assess the post-surgical breast, but post-surgery and radiotherapy changes have reduced the accuracy of this method. Scintimammography (SMM) has also been proposed and appears to be more accurate than XMM.

MATERIAL AND METHODS: A total of 101 women received Tc-99m MIBI SMM and 88 had a subsequent XMM. There were 142 sites suspected of loco-regional recurrence breast cancer. During the study the patients did not receive any treatment other then hormonotherapy. SMM was performed by the standard Diggles-Khalkhali method and XMM was performed using standard 2 views. Analysis was performed and the results of each type of imaging compared with histology. In the ROC curve analysis 5 points of certainty were used: from 1 being definitely normal to 5 being definitely cancer; grades 4 and 5 were counted as positive.

RESULTS: The overall sensitivity value of SMM was 84% and specificity was 85%, compared with a sensitivity of 52% for XMM and a specificity of 84%. Analysis of areas under ROC curves provides statistically significant difference between SMM and XMM ($p < 0.05$). Combining the two tests did not significantly improve the diagnostic accuracy of sequence imaging over SMM.

CONCLUSION: ROC curve analysis demonstrates that scintimammography should be the primary investigation in suspected local recurrence following breast conservation surgery.

Key words: scintimmamography, breast cancer, ROC curves

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Introduction

Conservative treatment of breast cancer is well accepted as an alternative to mastectomy for patient with early stage disease. Also it has been demonstrated that breast-conserving local therapies and mastectomy vield similar overall and disease-free survival [1]. However women undergoing more conserving breast surgery have a higher risk of loco-regional recurrence, which is estimated as approximately 25% at 5 years compared with 10% at 5 years after mastectomy [1, 2].

Traditionally X-ray mammography and ultrasound were used to assess the post-surgery and post-radiated breast. The anatomical imaging is impaired due to previous treatment and the sensitivity of XMM in this group of patient ranges from 55% to 68% in different papers [3–6]. Scintimammography using Tc-99m sestaMIBI is a well-established method as a second-line diagnostic test in finding primary breast cancer [7, 8]. Also it has been proposed in diagnosis of recurrent breast cancer [9]. This imaging seems to be more accurate then XMM because it is independent of any anatomical changes [7, 10]. However combinations of tests may improve finding recurrent cancer than a single test alone. SMM was used as the primary test with XMM as a secondary test in the receiver operator curve (ROC) analysis.

Receiver operating characteristic (ROC) curves have become increasingly popular over the past few years as the imaging community has become concerned with the measure-

ment of the information content of a variety of imaging modalities [10–12].

It is also the statistical method of choice to combine various clues for predictive purposes. As previously noted, the area under the ROC curve [11, 13] corresponds to the probability of correctly identifying which of the two stimuli is noise and which is signal plus noise. In medical imaging studies, the more economical rating method or sequence of methods is generally used. Images from diseased and non-diseased subjects are thoroughly mixed, then presented in random order to a reader.

Therefore the aim of this study was to compare the diagnostic accuracy of Tc-99m sestaMIBI SMM and XMM and also sequence examination scintimammography as a first test and then mammography in the diagnosis of recurrent breast cancer using ROC curves in patients after breast conservative therapy.

Material and methods

Patients

101 female patients were enrolled in this study, with 142 lesions suggestive of breast cancer. The mean age of the patients was 57 years (SD 10; range 28–85). The mean time from initial diagnosis of breast cancer was 8 years (SD 6; range 1–24 years). Each patient had physical examination by a surgeon in supine and upright positions and 78 had XMM.

Mammography

Patients with suspected recurrent breast cancer were imaged using a standard 2-view XMM before SMM. Imaging was performed in standard projections, using a dedicated mammography unit (DMR International General Electric, Paris, France). A standard two-view protocol, caudal-cranial and lateral oblique, was used with 28 keV and automatic exposure control. The images were interpreted by trained specialist radiologists, with knowledge of the patient's history, clinical presentation and the results of any previous mammograms. Cancer was described when there was a spiculated or irregular dense lesion, suspicious microcalcifications, or other architectural distortion, compared to previous examination and indicating recurrent tumour. The clinical reports of all patients were reviewed and graded using a simple 5 point grading system as follows: grade 1: definitely normal or benign; grade 2: probably normal or benign; grade 3: equivocal; grade 4: probably cancer; grade 5: definitely cancer.

Scintimammography

Scintimammography imaging was performed 5–10 minutes after intravenous injection of 740 MBq Tc-99m sestaMIBI (DuPont, Billerica, MA, USA) in a foot vein. All patients were imaged using prone dependent lateral, and anterior supine planar imaging (7,14).

This method was used to provide maximum separation of the breast from underlying thoracic activity. Planar images were performed with 256 × 256 matrix, imaging with 10% windows around a 140 keV photopeak and with an acquisition time of 10 min in both lateral and anterior views, using a two-head gamma camera (Picker Prism 2000 XP, Picker, Cleveland, OH, USA). A high-resolution, low-energy collimator was used in each case. After 10 minutes imaging of each breast a repeat image was performed with cobalt markers placed on the nipple.

The anterior view was obtained with the patient supine and both arms held above the head. Studies were reported by a specialist in Nuclear Medicine using the same 5 grades as were used in the reporting of the XMM. All Tc-99m sestaMIBI images were interpreted blinded to the clinical presentation and mammographic result. Focal or abnormal diffuse uptake in at least one planar image of the breast, chest wall or axilla was the criterion for evaluating a picture as suspicious or malignant. Diffuse uptake without focal accumulation was scored as equivocal. Homogeneous uptake of tracer in both breasts was classified as normal.

Confirmation of pathology

All patients with suspected recurrent breast lesions had limited incisional biopsy, fine needle aspiration biopsy (FNAB), or definitive wide local excision or minimum 6 months clinical follow-up to confirmed final diagnosis. Axillary node dissection was performed in 16 patients with confirmed malignancy of the breast. All histology and cytology slides were read by a specialist with an interest in breast cancer. If the results of FNAB indicated a benign lesion, follow-up physical examination and mammography were done periodically.

Data analysis

Images were interpreted as true-positive when cancer was confirmed by the histological examination, and the images had been scored as probably or definitely cancer (grade 4 and 5). False negative result was when cancer was present but the images had been reported definitely or probably benign or normal or as equivocal (grades 1–3). The examination was interpreted as true negative when cancer was excluded by histopathology or minimum 6 months clinical follow-up and the images were scored as definitely or probably normal or benign (grades 1 and 2). A false positive result was defined when the images were reported as probably or definitely cancer or equivocal (grades 3–5) but there were no malignant tumours.

The ROC curve for SMM, XMM and sequence imaging were composed using the same grading score for detection of recurrent cancer. Each point of the curve was evaluated to assess false positive rate and true positive rate for grade 5, grades 5 + 4 and also grades 5 + 4 + 3. To compare all three techniques the area under the curve was calculated for each modality [15].

The area under the curve corresponds to the probability of correctly identifying which of the two stimuli is noise and which is signal plus noise. Using the trapezoidal rule of calculating ROC curve area, Willcoxon statistics was performed and evaluated properties of the area under each ROC curve [11, 13].

Results

The histological examination confirmed loco-regional recurrent breast cancer in 45 of 142 lesions (32%). There were 29 of recurrent breast cancer within the breast, 23 of them at the site of surgical procedure, 6 within the breast at the opposite side. Additionally there were 16 cases of lymph node involvement which were confirmed as a recurrence. There were 13 at the ipsilateral side: 10 in the axilla, 2 in subclavicular fossa, 1 as lymph node of the neck. Three cases of lymph nodes of the axilla involvement were localised at the opposite side.

Table 1. Histopathological type distribution rate in recurrent breast carcinoma, considered mean age of patients and mean size of the recurrent tumour (including SD)

Histology	Number	Age	SD	Size	SD
IDC	36	60	10	28	20
Lobular	5	45	5	43	28
Dcis (ductal ca in situ)	1	61	–	32	–
Medullare	2	65	2	47.5	11
Papillar	1	59	–	20	–
All	45	52	12	26.7	19

Table 2. Distribution rate of invasive ductal carcinoma considered Bloom-Richardson's scale of malignancy

Histology	Number	Bloom-Richardson	Age	SD	Time	SD
IDC	2	1	51	6	5.5	5
IDC	18	2	61	9	8	3
IDC	16	3	60	11	7	2.5
IDC all	36		60	10	9	3

Histopathological type distribution rate in recurrent breast carcinoma is presented in Table 1. Additionally in Table 2 there is histological type distribution rate for IDC according to the Bloom Richardson scale of malignancy. All histological types of recurrent breast cancer were in similar pathology with the primary lesions.

Tc99m sestaMIBI SMM correctly diagnosed 38 of 45 (84%) recurrent breast cancers (Fig. 1, 2), compared to the XMM, which correctly diagnosed 17 of 33 (52%) cases. There were 7 malignant lesions which were false negative in SMM, 1 of them evaluated as equivocal results.

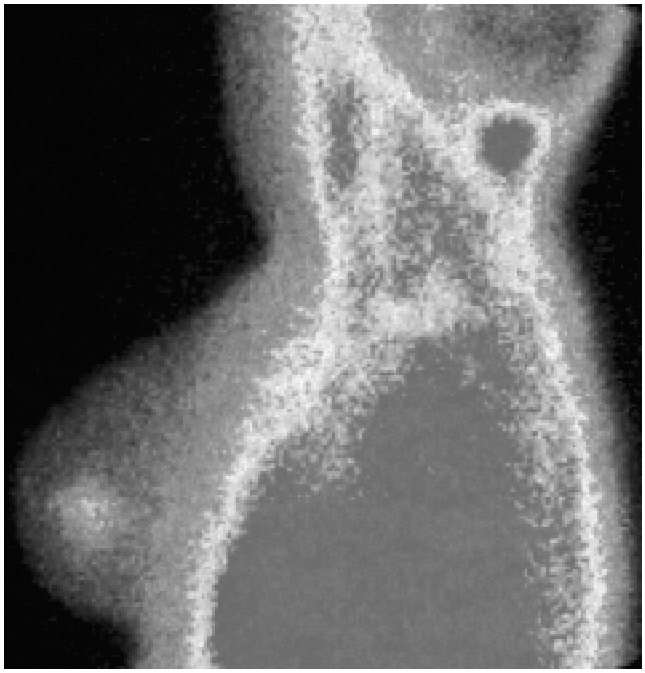

Figure 1. True positive study, 48 year old lady with previous history of BCT left breast 2 years ago due to IDC Bloom-Richardson grade II. Tc-99m sestaMIBI SMM with high focal uptake of tracer [5] within left breast confirmed as local recurrent breast carcinoma.

Figure 2. True positive study, 54 year old woman with previous BCT of her right breast 5 years ago due to IDC Bloom-Richardson grade II and DCIS commedo type. Tc-99m sestaMIBI SMM with uptake of radiotracer evaluated as probably cancer [4] within left breast confirmed as local recurrent breast carcinoma.

False positive uptake of Tc-99m sestaMIBI was seen in 15 sites suspected of recurrent breast cancer (5 equivocal results) with no cancer detectable in histology or FNAB. Therefore the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of SMM came to 84, 85, 72 and 92%, respectively.

XMM was able to identify 17 of 33 (52%) recurrent breast tumours, 16 recurrent cancers were reported as benign lesion or equivocal results (Fig. 3). There were 62 true negative studies. The sensitivity, specificity, PPV and NPV of XMM for detection of recurrent breast carcinoma in patient after breast conservation therapy came to 52, 84, 84 and 80%, respectively.

However, if a combination of the two methods was used, SMM followed by XMM, there was a much better result than each modality separately, providing finally sensitivity for identifying cancer of 87%, specificity 87%, PPV 75% and NPV 93%. Additional ROC curve composed as a sequence of SMM and XMM was with high specificity 99%, if grade 5 only is used for diagnosis of recurrent cancer, with sensitivity of 64%. The sensitivity went up to 89% if grades 3-5 were called positive for cancer, specificity dropped to 87%.

Only 6 cancers could not be seen with either modality. Three of the 6 were IDC (2 of 3 with DCIS component), 1 of them was DCIS (cribriform and solid) and 2 of them were lobular cancers (1 with DCIS pattern). All these patients were treated with chemotherapy before operation on primary breast cancer. Sensitivity, specificity PPV and NPV for XMM, SMM and sequence imaging are presented in Table 3.

An evaluation of the index area under ROC curve in XMM, SMM and additional sequence imaging provides results as fol-

Figure 3. False negative study, 58 year old patient with previous history of IDC Bloom-Richardson II right breast and BCT. X-ray mammography evaluated as equivocal result [3], confirmed as recurrent breast carcinoma.

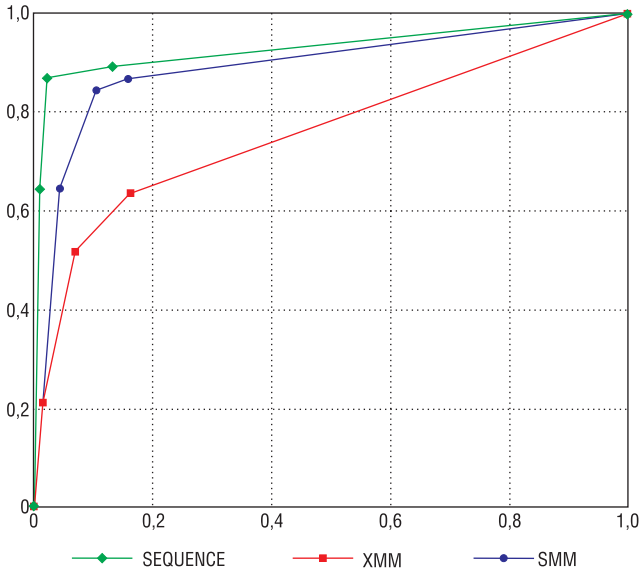

Figure 4. ROC curves for XMM, SMM and sequence imaging.

lows: SMM — 0.895, XMM — 0.764 and sequence imaging — 0.93 (Fig. 4). Analysis of areas under ROC curves provides statistically significant difference between SMM and XMM ($p < 0.05$). There was no significant difference between SMM and sequence imaging. There was significant difference between sequence imaging and XMM ($p < 0.05$).

Discussion

Our results confirmed higher accuracy of scintimammography than X-ray mammography in detecting loco-regional recurrent breast cancer. Also the sensitivity and specificity in finding loco-regional recurrence are similar to those seen in patients with primary breast cancer [8, 14, 16, 17]. The higher accuracy of scintimmamography is related to greater specificity of the agent, which makes this imaging independent on the anatomical changes [8–10, 14, 16, 17]. The low sensitivity of XMM in this study is consistent with other studies evaluating the role of mammography in the early detection of recurrent breast cancer [5, 6, 18].

Although XMM images rely on changes caused by postoperative scarring to stabilise or decrease with time, the differentiation of recurrent breast cancer from benign changes has been a problem for radiologists [19].

It has also been suggested that XMM detection of local recurrence manifesting as a mass may be more difficult then that manifesting as microcalcification [20].

Table 3. Overall diagnostic accuracy (sensitivity, specificity, PPV and NPV) for SMM, XMM and sequence imaging for detecting recurrent breast cancer in patient post BCT

Modality	Sensitivity	Specificity	PPV	NPV
XMM	52%	84%	84%	80%
SMM	84%	85%	72%	92%
Sequence	87%	87%	75%	93%

However these are not in themselves diagnostic, due to scar formation and deformity and a radiation-induced inflammatory pattern and breast calcification [5, 21].

Although it seems that in the first 6 years after treatment, the majority of the recurrent cancers are found at the lumpectomy site, with increasing time tumours are found with increasing frequency at other locations [22].

This has the implication that XMM has its limitations in finding regional recurrent tumours. In our study 49% (16 cases) recurred in regional lymph nodes. XMM was able to detect only 4 of 16 recurrences (Fig. 5).

In addition, XMM evaluation of the irradiated breast is frequently compromised by difficulty in compressing the fibrosed breast or architectural distortion or retraction [19–21]. In contrary to XMM

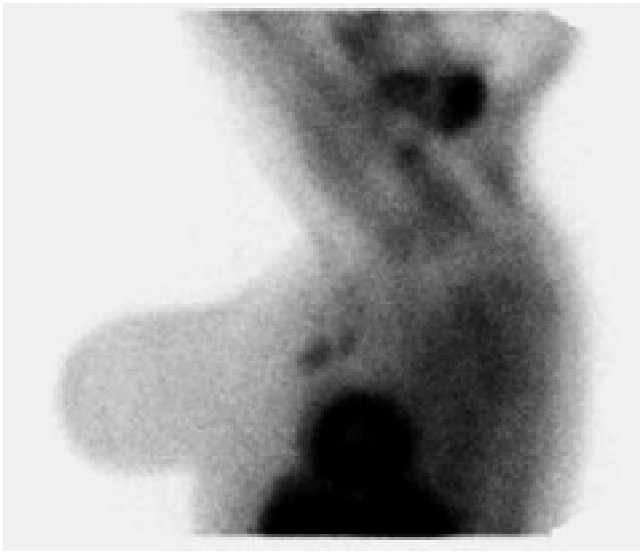

Figure 5. True positive study 62 year old woman with previous history of right breast IDC and BCT 5 years ago, with high Tc-99m sestaMIBI uptake within right axilla, confirmed as axillary node involvement IDC Bloom-Richardson grade III.

scintimammography showed increase uptake of Tc-99m sesta-MIBI in 13 of 16 true positive cases of lymph nodes involvement. Also this technique enables breasts to be evaluated without painful compressing. In addition, recurrent tumour in regional lymph nodes and other tissues, e.g. in the chest wall, can be seen on the scintimammography but not on mammography [23, 24].

However there were 7 false negative cases. The reason of missreporting of those patients are present not clear but it can be related to changes in intracellular pH and transmembrane potential, which might disturb ABC transporters membrane protein [25–27].

There were also 15 false positive examinations. The uptake of any radiopharmaceutical into breast tissue is dependent on the vascularity of the tissue, a specific or non-specific uptake mechanism and retention of the radiopharmaceutical within the tumour [25–27]. It is known that histological changes in the breast after irradiation consist of replacement of normal parenchyma and adipose tissue with fibrosis [28]. Also, flow-through and resultant distension of lymphatic and small vessels are increased [29].

Radiation therapy itself may cause cytologic atypia [30] and this potentially could explain why there were some false positive uptakes of Tc-99m sestaMIBI in these sites. Additional factors influencing the uptake of Tc-99m sestaMIBI into breast tissue are specific or non-specific uptake mechanisms and retention of the radiopharmaceutical within the tumour on the cellular and molecular level mentioned above [25–27]. A paradigm in cancer pharmacology has been that ABC transporters (MDR protein is one of this group) confer drug resistance by acting as an adenosine 5'-triphosphate (ATP)-coupled active drug efflux pump with broad specificity. Currently there is a suggestion that MDR protein acts to indirectly mediate decreased drug retention in tumour cells via modulating pH_i and/or the electrical membrane potential that exists across cell plasma membranes which might also play an important role in resistance [27]. This phenomenon may explain the lack of uptake of Tc-99m sestaMIBI in our study. All patients with false negative results of SMM scan were treated with chemotherapy. In contrast, in the true positive group there were only 4 patients post-chemotherapy.

Conclusion

In conclusion we have found that in the diagnosis of recurrent breast cancer, SMM should be the first choice test in detecting recurrent breast cancer.

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