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BREAST CANCER ^{99m}Tc SM3 RADIOIMMUNOSCINTIGRAPHY

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^{99m}Tc SM3 radioimmunoscintigraphy is combined with kinetic analysis and probability mapping using a change detection algorithm to investigate axillary node involvement before primary surgery in patients with breast cancer. Whereas planar imaging was unsuccessful, axillary node involvement was correctly determined in 11 out of 13 patients 6 out of 7 true negatives and 5 out of 6 true positives down to 0.35 grams. A prospective study is underway.

In the UK more than 24 000 new cases of breast cancer per year are detected with 15 000 deaths (1). One in 14 women will contract breast cancer and one in 21 will die of the disease. The 5-year survival depends on staging, minimal disease having a 98% 5-year survival, those with negative nodes 85%. However, those whose axillary nodes are involved with cancer have only a 55% 5-year survival and those with distant metastases a 10% survival. The aim of the present study was to identify preoperatively whether or not there is malignant involvement of regional lymph nodes in patients with breast cancer using ^{99m}Tc SM3 radioimmunoscintigraphy. A successful outcome would help to tailor the extent of surgery to the individual needs of woman with breast cancer. The monoclonal antibody used, SM3, reacts with deglycosylated mucin core protein binding to the epitope sequence Pro.Asp.Thr.Agr.Pro. However, the conventional HMFG2 (human milk fat globule) monoclonal antibody against the fully glycosylated glycoprotein reacts with the epitope Asp.Thr.Arg (2).

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Patient protocol

^{99m}Tc SM3 radioimmunoscintigraphy is undertaken using an intravenous injection of 15–20 mCi (600–750 MBq) ^{99m}Tc labelled monoclonal antibody SM3 in an amount of 0.5 mg. The antibody SM3, a murine IgG1, is produced in the laboratory of Joyce Taylor-Papadimitrou of the ICRF and prepared to good manufacturing practice level by the laboratories at Clare Hall under Dr Tom Seddon. Imaging is performed at 10 min, 4–6 h and 22–24 h after injection with 800 000 counts per image using a single head gamma camera with a low energy parallel hole general purpose collimator, peaked for ^{99m}Tc with a 15% window. Images are taken serially of the anterior and lateral chest with markers on prominent bones. Typical examples are illustrated in the following case histories and figures which are black and white representations of color images where the color scale was set in standard deviations (SD), and where a change of 2SD is taken as significant.

Case 1

A 65-year-old woman presented with a non tender lump in the right breast. An immobile lump in the right lower medial quadrant of the breast, tethered to the skin was found. No axillary nodes were palpable and mammography was non-specific (R2 category). Planar images showed no definite uptake in the region of the breast but some possible uptake in the right axilla. The technique of probability mapping was applied using a change detection algorithm comparing the 10-min image with the 22 one. Significant uptake was shown in the right axilla and the right breast region, (Fig. 1), both on the anterior and the right lateral oblique view. Only focal sites of significant uptake below the line of the subclavian vessels are taken as positive. Artefacts are seen along the line of the subclavian vessels and above, due to head

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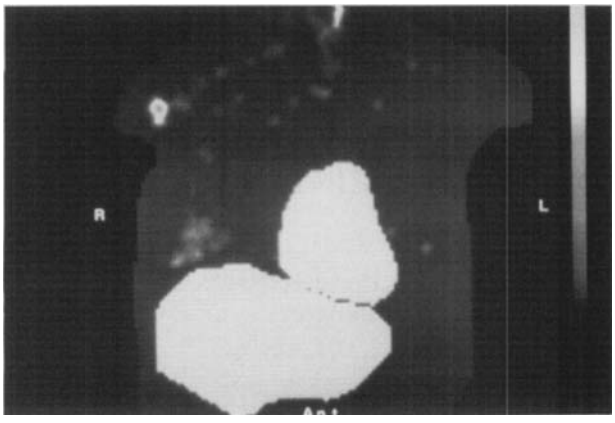

Fig. 1. Case 1. ^{99m}Tc radioimmunoscintigraphy of the breast. Anterior view change detection algorithm shows uptake in the right breast, light grey (+2SD), and focally increased uptake in the right axilla white, indicating involved axillary lymph node (+3SD). The liver and heart are masked out in white. Other spots are at one SD, see test.

and neck movement. The tumour histology was that of a well-differentiated, invasive, mixed ductal and lobular carcinoma of the breast, grade1, 2.1 cm in size with one out of 16 axillary lymph nodes involved with malignant disease. The weight of the involved gland was 0.35 g.

Case 2

A 36-year-old woman developed painful breasts after starting hormone replacement therapy. On examination a mass related to the left nipple was seen but no nodes were palpable in the axillae. Mammography was positive. Planar images showed some uptake in the left breast lesion but nothing in the axilla. The probability map showed positive uptake both in the left breast and in the axilla (Fig. 2). Uptake in the neck region was affected because of movement artefacts and not taken as positive as are changes above the level of the subclavian vessels. Histology showed a moderately differentiated invasive ductal carcinoma of the breast, grade 2, with vascular invasion. Five out of 15 lymph nodes were involved and the excision was considered incomplete by the pathologist.

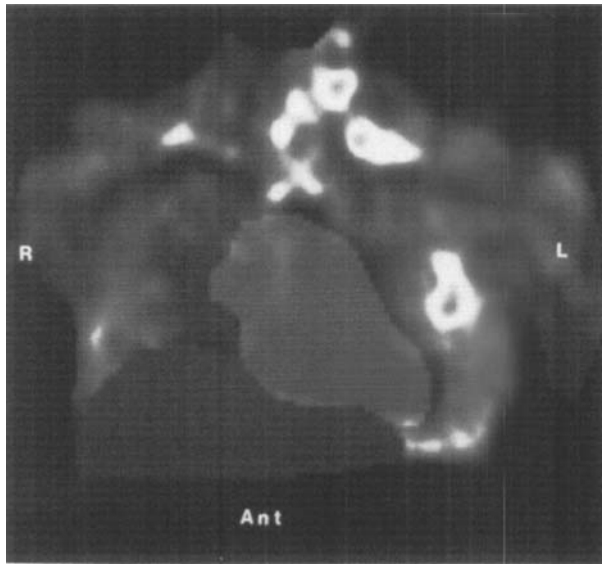

Fig. 2. Case 2. ^{99m}Tc radioimmunoscintigraphy of the breast. Anterior view change detection algorithm shows uptake in the left breast in white, (+3SD) and increased uptake in a deep axillary node close to the neck (+3SD). Other activity in the neck is related to blood vessels and movement artefacts above the thoracic inlet.

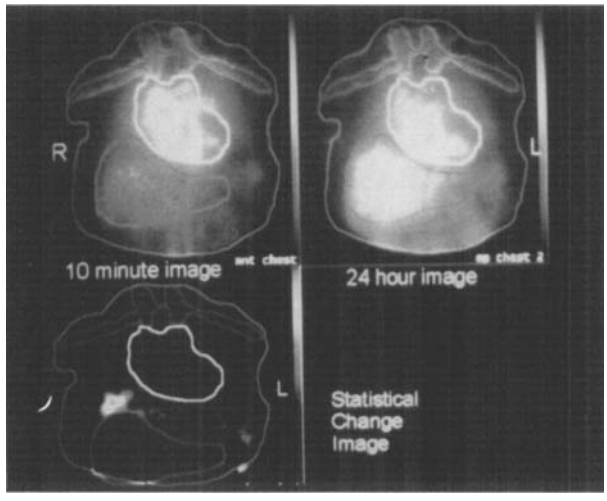

Fig. 3. Case 3. ^{99m}Tc SM3 radioimmunoscintigraphy. Top left 10 min image with liver heart and blood vessels outlined. Top right 24 h image with liver heart and blood vessel outlined. Bottom left statistical change image showing high uptake in the right breast in white (+3SD). The left breast uptake is at 1SD and not significant. There is no significant abnormality in the axilla. Axillary nodes were free of tumour on surgery and histology.

Case 3

An 83-year-old woman presented with right breast cancer and no palpable nodes. The breast cancer was shown on histology to have an infiltrating ductal, intraduct and globular carcinoma, grade 2. Examination of the excised axillary nodes showed that none of 7 sampled nodes were involved. Planar images and probability maps showed uptake in the right breast cancer but no sign of axillary node involvement (Fig. 3).

Kinetic analysis with probability mapping

Kinetic analysis with probability mapping (3) is required for detection of small metastases in lymph nodes for preoperative staging since nodal status is difficult to determine by conventional planar imaging even with ^{99m}Tc-labelled monoclonal antibodies. The basic observation is that specific uptake of a whole monoclonal antibody by tumour increases with time over 24 h whereas after the initial distribution non-specific uptake decreases with time. ^{99m}Tc SM3 has a half-life in blood of 24 h. In order to identify very small tumour sites in axillary lymph nodes, a change detection algorithm makes use of these kinetics to compare the 10-min image with virtually no specific uptake

and the 22-h images to determine whether specific uptake of ^{99m}Tc SM3 has occurred. The new images are recorded and registered. The images are superimposed using the anatomical markers for translation and rotation of the images. A change detection algorithm (probability mapping) is applied. Output images are set with different thresholds either as 1, 2 or 3 standard deviations of which two standard deviations or more are considered significant, or with p-value distributions where a p-value of less than 0.05 is considered significant (4).

The 6 anatomical markers are used on the anterior chest image: the sternal notch, Corocoid processes, xiphisternum and lower costal margins. Image processing sharpens up the marker images to points (single pixels) as they are Gaussian spread functions. A rigid or elastic transform is undertaken to superimpose the marker images and then the patient images by following the same transform. Marker-free image superimposition is a goal whereby the edges of obvious anatomical structures such as the liver, heart and blood vessels are used for image superimposition. This would avoid the need for marker images. Faulty image superimposition is detected by the appearance of 'negative shadows' beside each vessel or major structure.

Results

In 14 patients with primary breast cancer, one of whom with a suspect cancer also in the other breast, the sensitivity for clinical palpation was 86% and for mammography 71%, including two equivocal mammograms (R2 category) called negative. Planar imaging with ^{99m}TcSM3 and probability mapping had sensitivities of 10/12, 83%. The two negative image breast cancers out of 12 appeared to be overlapping the liver and the one false positive probability map was a mass considered to be histologically benign.

Axillary node involvement was clinically assessed and the one palpable node was histologically free of tumour. Of 12 impalpable nodes, 6 were involved and 6 were not. For planar imaging only 3 out of 6 involved nodes were detected in the axilla (sensitivity 50%) but all axillae free of nodes (7) were correctly indicated. Using probability mapping 5 out of 6 axillae with involved nodes were correctly identified, sensitivity 83%. In the patient with the missed node only one out of 20 axillary nodes was involved microscopically. Probability mapping correctly identified the absence of involved nodes in 6 out of 7 (specificity 86%), the one false positive was close to the breast tumour and was called an involved node but might well have represented an extension of the breast tumour.

Conclusion

Using ^{99m}Tc SM3 in breast cancer one can see that planar imaging is insufficient for nodal status. The change detection algorithm with image superimposition and probability mapping gives encouraging results. Prior determination of nodal status would allow the tailoring of the extent of primary surgery for breast cancer for each woman.

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