A NOVEL APPROACH FOR LOCAL TREATMENT OF BREAST CANCER

DISSERTATION FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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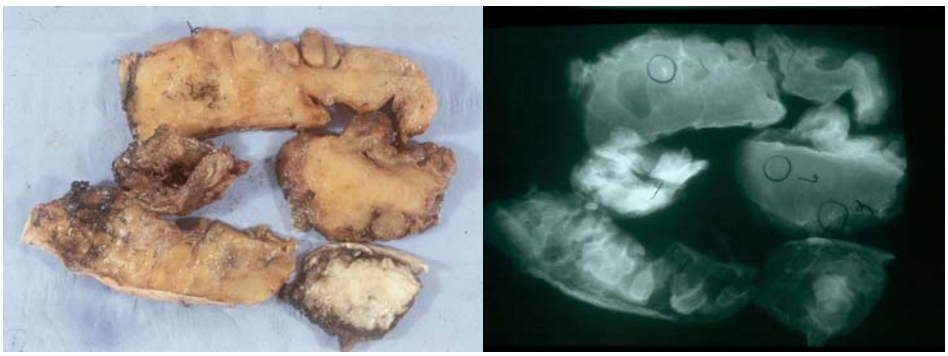
Introduction

We have shown that when mastectomy specimens are examined by detailed radiological-histological correlational methods, small additional invasive or in-situ cancer foci are found in over 60% of patients; 80% of these lie remote from the index quadrant [Vaidya et al., 1996]. Since 90% of local recurrences occur in the index quadrant, we have questioned the clinical relevance of these small cancer foci that remain dormant for a very long time.[Baum et al., 1997]. Since most of these small cancers may not cause clinical cancers and endanger the patient's life we wished to investigate whether there is any non-invasive and pre-operative test that might reveal which of these dormant cancers are clinically relevant.

Angiogenesis is a prerequisite for tumour growth beyond 1–2 mm in diameter and is directly correlated with poor prognosis. [Weidner et al., 1991]. Unlike radiography that relies on tissue density for detecting cancers, magnetic resonance imaging (MRI) relies on tumour vascularity and vascular permeability [Buadu et al., 1996], as demonstrated by contrast enhancement. MRI is highly sensitive for breast cancer detection but its specificity is relatively low [Heywang-Kobrunner et al., 1997]. We hypothesised that if any of these occult tumours were detectable by MRI, then these would be the ones that were potentially more dangerous. In that case, we would be able to geographically map these "more dangerous" tiny tumours and tailor treatment accordingly. We therefore tested how many of the occult tumours that are detected by the detailed radiological-histological method were detected by MRI.

Method

We evaluated prospectively whether small enhancing foci, seen separately from the main tumour on contrast-enhanced MRI, were indeed cancer foci and whether MRI could detect all cancer foci identified by radiological-histological correlation. We studied ten patients. All patients underwent preoperative contrast-enhanced breast MRI. High resolution transverse T1-weighted 3D FLASH images (TR=18 ms, TE=7 ms, FA=40°, TA=4 m 56 s, FOV=410 mm) before and after an intravenous bolus hand injection of dimeglumine gadopentetate (Magnevist, 0·2 mL/kg) were acquired at 1·0 T (Siemens Magnetom Scanner 42 SP with dedicated breast coil). The 3D volume was 64 mm thick with 32 partitions giving an effective slice thickness of 2 mm and this was sufficient to cover the entire breast in all cases. All patients underwent surgery for the breast cancer. Modified radical mastectomy was performed in four patients and wide local excision in six patients.



Specimen slices and mammograms of slices

The surgical specimens were fixed and sliced at 5 mm intervals in the same plane as the MRI. An experienced breast pathologist performed routine histopathological examination and the remaining material was radiographed. Two observers (Jayant Vaidya and Michael Douek) identified radiological abnormalities (calcifications, densities, or spiculations) and all lesions that were deemed suspicious by either observer were mapped on to the specimen, sampled and examined histologically. A specialist radiologist (Margaret Hall-Craags) reviewed MRI images independently and findings were compared with histopathology results.

Results

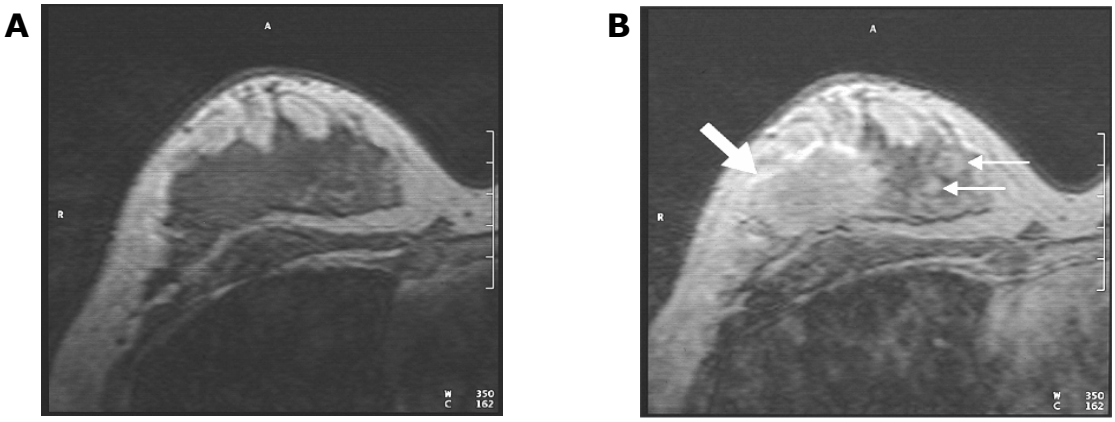
On MRI, 19 enhancing foci separate from the main tumour were identified in seven out of ten patients (figure). On radiography of specimen slices, 71 suspicious areas were sampled and histological examination revealed 15 areas of 'occult' cancers in five patients. Of these 9 were in-situ and 6 were invasive cancers. All five patients with cancer foci on histopathology were amongst the seven patients who had enhancing foci on MRI. In two of these five patients, the tumour was surrounded by widespread enhancement on MRI and all 11 (four+seven) areas sampled showed cancer foci. In all wide local excision specimens, the enhancing foci on MRI were within 11 mm of the tumour edge and therefore within the resected specimen.

MRI		Number of patients	Number of foci
Separate MRI foci absent (3)	No enhancement	3	0
Separate MRI foci present (7)	Focal enhancement	5	8
	Multiple enhancing foci	2	11*
Total		**10**	**19***

*In the 2 patients with multiple enhancing foci, all 11 histological samples were found to harbour invasive or in-situ cancer and a count of 11 was awarded to MRI for comparison with histology.

Histology		Number of patients	Number of foci
Separate histological foci absent (5)		5	0
Separate histological foci present (5)	DCIS only	2	5
	IDC only	1	1
	IDC + DCIS	2	5 IDC + 4 DCIS
Total		**10**	**15**

N.B. Thus 5 specimens showed separate foci on histology- all these were had shown enhancement on MRI.



T1-weighted breast MRI before (A) and after (B) contrast-enhanced MRI - Two separate enhancing foci (small arrows) are visible away from the primary tumour (large arrow) after contrast enhancement.

Discussion

Our data suggest that enhancing foci on MRI represent cancer foci and that MRI detected 14 out of 15 cancer foci (sensitivity 93%). Of course, this is based on the assumption that the radiological-histological correlational method is indeed the gold standard. If that is so, the specificity of MRI for tumour detection would be 79% (15/19). However, bearing in mind that the spatial resolution of MRI is of the order of 1–2 mm, it may yet transpire that MRI could have even greater sensitivity and specificity that may become apparent with an even more obsessive sampling of the specimen.

Our findings provide strong circumstantial evidence that small enhancing foci on MRI represent cancer foci and that MRI is highly sensitive for the detection of invasive or in-situ cancer foci.

This was contrary to our hypothesis that MRI might detect only a subset of the occult cancers in the breast-mainly those that might have stimulated local angiogenesis and are therefore more vascular. We thus realised that MRI might not be able to identify a subset of occult tumours that are clinically relevant allowing us to selectively treat patients. We found that MRI on the other hand is highly sensitive in detecting multicentric foci. Finding these enhancing foci on pre-operative MRI may prompt many a surgeons to advise their patients to undergo a mastectomy. The number of MRI machines is increasing worldwide and the additional cost of a breast coil is insignificant compared to the cost of the MRI. So we fear that when MRI is used for pre-operative evaluation in breast cancer, many unsuspecting women will be found to have these 'enhancing foci' in their breasts. The surgeon will be in a dilemma and to be on the safe side might advice a mastectomy to a woman who might otherwise safely have had a breast conserving therapy, reversing the trend of the last 30 years.

On the other hand, the high sensitivity of MRI could be used more constructively. Our results suggest that MRI could be used to investigate prospectively the clinical significance of unresected cancer foci in order to convincingly determine their natural history in the context of breast conserving surgery. A study in which women found to have enhancing foci on MRI but have no other evidence of multicentric tumours on clinical or radiological grounds are prospectively followed up, would be deemed ethical because breast MRI is still considered experimental for preoperative planning of surgery. In a few years we might be able to ascertain whether any of these latent occult tumours progress to an actively progressive phenotype.