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Angiogenic response of locally advanced breast cancer to neoadjuvant chemotherapy evaluated with parametric histogram from dynamic contrast-enhanced MRI

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Abstract

The aim of this study was to evaluate angiogenic compositions and tumour response in the course of neoadjuvant chemotherapy in patients with locally advanced breast cancer (LABC) using dynamic contrast-enhanced (DCE) MRI. Thirteen patients with LABC underwent serial DCE MRI during the course of chemotherapy. DCE MRI was quantified using a two-compartment model on a pixel-by-pixel basis. Analysis of parametric histograms of amplitude, exchange rate k_{out} and peak enhancement over the whole tumour was performed. The distribution patterns of histograms were correlated with the tumour response. Initial kurtosis and standard deviation of amplitude before chemotherapy correlated with tumour response, $r = 0.63$ and $r = 0.61$, respectively. Comparing the initial values with the values after the first course of chemotherapy, tumour response was associated with a decrease in standard deviation of amplitude ($r = 0.79$), and an increase in kurtosis and a decrease in standard deviation of k_{out} ($r = 0.57$ and 0.57 , respectively). Comparing the initial values with the values after completing the chemotherapy, tumours with better response were associated with an increase in kurtosis ($r = 0.62$), a decrease in mean ($r = 0.84$) and standard deviation ($r = 0.77$) of amplitude, and a decrease in mean of peak enhancement ($r = 0.71$). Our results suggested that tumours with better response tended to alter their internal compositions

from heterogeneous to homogeneous distributions and a decrease in peak enhancement after chemotherapy. Serial analyses of parametric histograms of DCE MRI-derived angiogenic parameters are potentially useful to monitor the response of angiogenic compositions of a tumour throughout the course of chemotherapy, and might predict tumour response early in the course.

1. Introduction

Breast cancer is a leading cause of mortality in women (Tabar *et al* 2003, Chie *et al* 2002). Patients with locally advanced breast cancer (LABC) have poor prognosis and require multimodality therapy to increase the survival (Heys *et al* 1994). To date, neoadjuvant chemotherapy is a standard treatment for LABC because of more effective control of local disease and better long-term survival (Weidner *et al* 1991, Koning and Hart 1998). However, the rate of local control varies significantly between series, depending on factors such as the choice of chemotherapeutic agents, number of cycles in a treatment course, response to treatment selection and clinical status of patients. To tailor the choice of chemotherapy for individuals, objective assessment is desirable to monitor the local tumour response in the course of treatment.

Conventional evaluation of tumour response relies on physical examination and mammography (Pierce *et al* 1996, Vinnicombe *et al* 1996). Physical examination depends heavily on examiners' experience and is prone to subjectivity. Mammography is limited by uncertain significance of residual microcalcifications and residual masses on post-induction chemotherapy (Pierce *et al* 1996). Recently, magnetic resonance imaging (MRI) has shown to be more accurate than other imaging techniques in determining the size and extent of most breast tumours, whether the assessment is made prior to or following therapeutic intervention (Mumtaz *et al* 1997, Rodenko *et al* 1996, Boetes *et al* 1995, Gilles *et al* 1994, Weatherall *et al* 2001). Particularly, dynamic contrast-enhanced (DCE) MRI is found useful in differentiating benign from malignant tumours (Kuhl *et al* 1999) and in detecting residual tumours after chemotherapy (Gilles *et al* 1994).

DCE MRI is a method of imaging the physiology of microcirculation based on the measurement of enhancement modulation before and after the injection of a contrast agent such as gadolinium chelate. Evidence is mounting that DCE MRI-based measurements correlate well with tumour angiogenesis (Tofts *et al* 1995, Knopp *et al* 1999, Taylor *et al* 1999). These measurements are sensitive to physiology and to the pharmacokinetics of the contrast agent in individual tumours. Moreover, they can present anatomical images of tumour microcirculation at excellent spatial resolution. Sequential assessment of tumour mass and tumour angiogenesis during neoadjuvant chemotherapy provides an opportunity to understand molecular mechanism associated with pathologic response and to study the possibility of guiding appropriate choices for induction treatment.

Most analysis of DCE MRI is restricted to assessing the region of interest on a single slice (Mussurakis *et al* 1997, Fischer *et al* 1999, Buadu *et al* 1996). This approach does not address the heterogeneity of angiogenic compositions within the tumours and is subjected to sampling bias. In this study, a new approach was proposed to assess angiogenic compositions of the whole tumour with the use of DCE MRI-derived parametric histograms. The purposes of our study were: (1) to study whether initial histograms of tumour angiogenic compositions can predict tumour response, (2) to determine the relationships between the tumour response

and the change in histograms after the whole course of chemotherapy and (3) to study whether changes in histograms early in the course of chemotherapy can predict tumour response.

2. Materials and methods

2.1. Patient recruitment

Thirteen patients (50.92 ± 7.95 years of age) of LABC who fulfilled the criterion of tumour staging as T3 or T4 according to the American Joint Committee on Cancer (AJCC) were enrolled in our study. None of these patients had distant metastasis before initiating neoadjuvant chemotherapy. Written informed consent was obtained from all patients by the Institutional Review Board of the Hospital. All patients received at least three serial breast MR studies at the following time points: before receiving incision biopsy and initiating chemotherapy, following the completion of the first course of chemotherapy and before final surgical tumour resection ($n = 8$) or core biopsy ($n = 5$). All the 13 cases received incision biopsy after completing the first MR study of breasts. Twelve cases were invasive ductal carcinoma and one case was invasive lobular carcinoma. The chemotherapy regimens included CEF (cyclophosphamide, epirubicin, fluorouracil) in three patients; paclitaxel plus cisplatin in three patients; weekly docetaxel plus oral UFUR (tegafur/uracil) in six patients, in which three of them received AC (doxorubicin, cyclophosphamide) later due to unsatisfied response of docetaxel treatment; and vinorelbin plus weekly high dose 5-fluorouracil/leucovorin 24 h infusion in one patient. Patients were followed for 15 ± 6.9 months (median 13 months) after completing their final MRI scan.

2.2. MR technique and protocol of dynamic enhancement

The dynamic enhancement of MRI for bilateral breasts was performed in a 1.5 T superconductive MR scanner (Sonata, Siemens, Erlangen, Germany) with dedicated breast coils. Patients were prone in position with anterior chest wall abutting on the coil. To avoid motion artefact, regular and shallow breathing were instructed and mild compression of the breasts was applied. All patients received intravenous bolus injection of the contrast medium (Gadonilium-diethyltriaminepentaacetic acid, Gd-DTPA, with the dose of $0.2 \text{ mmole kg}^{-1}$) at the rate of 4 ml per second via automatic injector (Optistar MR injector, Mallinckrodt, MO, USA). A rapid scanning with 3D fast low angle shot (FLASH) pulse sequence coupled with elliptical scanning technique and partial Fourier acquisition were performed. Scan parameters were TE/TR = 3.1/12 ms, flip angle = 25° , field of view = $110 \text{ mm} \times 320$ to 360 mm , image matrix = 176×512 , slice thickness = 4–5 mm, no gap, 30 slices, 14 s per acquisition, and total 46–50 acquisitions. The parameter setting resulted in a pixel resolution of approximately 625–700 μm . Both breasts were covered in the dynamic study for the possibility of detecting multifocal or bilateral breast cancers in our patients. Bolus injection was started at the fourth acquisition in order to achieve a steady state of magnetization and to avoid flow-related enhancement. Patients who could not tolerate scanning for approximately 45–50 min of the whole examination or presented with severe motion artefact in the images were excluded from our study.

2.3. Analysis of dynamic MR data and evaluation of tumour response

Time–intensity curves obtained from DCE MRI were analysed on a pixel-by-pixel basis with a two-compartmental model proposed by Brix *et al* (1991). Two angiogenic parameters,

namely, amplitude and redistribution rate constant (k_{out}), were determined by fitting the time–intensity curves (Buckley *et al* 1994). Amplitude represents the initial slope of enhancement and redistribution rate constant (k_{out}) represents the exchange rate of the contrast agent between the intravascular and extravascular extracellular space (Buckley *et al* 1994, Knopp *et al* 1999). Colour maps of amplitude and k_{out} were generated for all imaging slices.

We defined the tumour margin by manually tracing the subtraction images of dynamic enhancement showing the best margin of the tumour. Total tumour volume was determined by summing the traced tumour volumes over all slices. Tumour response was defined as the ratio of the tumour volume at the final MRI scan to the tumour volume at the first scan. For comparison, bidimensional measurement according to the World Health Organization (WHO) criteria of tumour response was also performed in each mass at the largest diameter in the axial subtraction dynamic contrast enhancement images. The tumour response assessed by tumour volume was correlated with that assessed by bidimensional measurement. The responders were defined as the patients who showed greater than 50% reduction in tumour volume whereas non-responders were those showing less than 50% reduction. The definition of region of interest (ROI) or tumour margin and the largest tumour dimension were performed by one author (Chang) who had 4 years of experience in breast MRI. Data analysis was performed with Matlab 6.1 (MathWorks Inc., Natick, MA, USA) and Mathematica 4.1 (Wolfram Media, Inc., Champaign, IL, USA).

Histograms of DCE MRI-derived angiogenic parameters of the whole tumour, including amplitude, k_{out} and peak enhancement were also obtained. To describe distribution patterns of tumour compositions, we calculated statistical indices including mean, standard deviation, skewness (degree of asymmetry of a distribution) and kurtosis (degree of peakedness of a distribution) from the histograms of each angiogenic parameter. Images of different patients were considered to be independent measurements.

To determine the predictive value of the statistical indices, we analysed the association between tumour response and initial values of statistical indices. We also analysed the association between tumour response and the ratio of statistical indices after the first cycle of chemotherapy to the same indices before chemotherapy. To characterize the change of statistical indices over the whole course of chemotherapy, we analysed the association between tumour response and the ratio of statistical indices after completing the whole course of chemotherapy to the same indices before chemotherapy. The test of correlation between statistical indices and tumour response was performed with the linear regression model, and the p value of less than 0.05 was considered significant.

3. Results

There were 61 MR studies in total with a minimum of three studies for each case. The interval between the first and final MR studies was 4.88 ± 2.87 months (median 4.2 months). Excellent correlation was found between tumour response assessed by tumour volume and that by bidimensional measurement ($r = 0.93$). The numbers of responders and non-responders were, respectively, 8 and 5 by volume measurement, and 7 and 6 by WHO criteria. The tumour size was 188.88 ± 140.54 ml before chemotherapy and was 70.27 ± 73.90 ml after completing the course of chemotherapy.

Colour maps of amplitude showed that better tumour response was marked by a change from heterogeneous to homogeneous tumour compositions and a decrease in peak enhancement (figure 1(a)). In contrast, there was little perceptible change of internal tumour compositions in the non-responders (figure 2(b)). In the responders the histograms of amplitude showed a progressive decrease and left shift of the peak, and narrowing of the base (figure 1(b)).

Figure 1. An example of a responder. (a) A large left breast cancer containing heterogeneous compositions before chemotherapy (as shown in the amplitude map in the upper row, the first on the left) becomes more homogeneous following serial courses of chemotherapy (upper row, from left to right). In contrast, there is no significant change of the tumour compositions based on k_{out} map during serial courses of chemotherapy (lower row, from left to right). The final tumour response is 16% in this case. (b) Serial tumour volume change (left panel) and normalized histograms of amplitude of the whole tumour (right panel). There is a marked decrease of tumour size (left panel, red dot followed by yellow, green and blue dot). Correspondingly, the initial histogram of amplitude appears flat and wide (right panel, red curve). Serial follow-up during the course of chemotherapy reveals gradual left shift of the peak of the histograms and more uniform distribution in the final MR study (right panel, blue curve).

Such change was not observed in the histograms of k_{out} or histograms of both amplitude (figure 2(b)) and k_{out} in the non-responders.

As listed in table 1, kurtosis and standard deviation of amplitude before chemotherapy correlated with tumour response ($r = 0.63$ and $r = 0.61$, respectively). After the first course of chemotherapy the changes in standard deviation of amplitude, and in kurtosis and standard deviation of k_{out} correlated with tumour response ($r = 0.79$, 0.57 and 0.57 , respectively). In comparing the final preoperative MRI study with the initial study, better tumour response was indicated by a significant change in amplitude, showing an increase in kurtosis ($r = 0.62$), and a decrease in mean ($r = 0.84$) and standard deviation ($r = 0.77$), and in peak enhancement showing a decrease in mean ($r = 0.71$).

4. Discussion

In this study, we analysed signal time curves on a pixel-by-pixel basis over bilateral whole breasts. This approach allowed complete mapping of tumour angiogenic compositions and

Figure 2. An example of a non-responder. (a) Serial colour mapping of both amplitude (upper row) and k_{out} (lower row) shows rather homogeneous compositions before chemotherapy (the first on the left, upper and lower rows). No significant perceptible change of internal tumour compositions is found during serial courses of chemotherapy on amplitude maps (upper row, from left to right) and k_{out} maps (lower row, from left to right). The final tumour response is 84% in this case. (b) Serial volume change of tumour (left panel) and normalized histograms of amplitude of the whole tumour (right panel). The histograms of amplitude during the course of chemotherapy show little change in distribution over the whole course of chemotherapy.

Table 1. Correlation between different MRI-derived angiogenic parameters and tumour response at different time points.

	Before C/T				After first C/T				After final C/T			
	Mean	SD	Kurtosis	Skewness	Mean	SD	Kurtosis	Skewness	Mean	SD	Kurtosis	Skewness
Amplitude versus tumour response												
r	0.42	0.61*	0.63*	0.45	0.24	0.79*	0.41	0.46	0.84*	0.77*	0.62*	0.49
p	0.14	0.03*	0.02*	0.12	0.43	0.001*	0.16	0.11	0.0003*	0.002*	0.02*	0.09
k_{out} versus tumour response												
r	0.1	0.1	0.41	0.46	0.26	0.57*	0.57*	0.33	0.24	0.41	0.5	0.35
p	0.70	0.76	0.16	0.11	0.38	0.04*	0.04*	0.26	0.43	0.16	0.08	0.25
Peak enhancement versus tumour response												
r	0.32	0.00	0.37	0.26	0.1	0.22	0.00	0.24	0.71*	0.37	0.54	0.2
p	0.28	0.93	0.22	0.38	0.74	0.44	0.84	0.40	0.01*	0.21	0.06	0.51

SD: standard deviation, C/T: chemotherapy, r : correlation coefficient; * $p < 0.05$.

facilitated visual perception of tumour response to chemotherapy. We further characterized tumour heterogeneity in terms of histograms of angiogenic parameters. Using this metric we

found that tumour heterogeneity in LABC was associated with tumour response to neoadjuvant chemotherapy.

Neoadjuvant chemotherapy of LABC can result in satisfactory local control, and even increased overall survival, especially in patients with a complete clinical or histopathological response (Eltahir *et al* 1998). Mammography has been widely accepted as an important tool to detect breast cancer but plays a limited role in assessing the response of breast cancer to neoadjuvant chemotherapy. Its efficacy is even inferior to physical palpation in patients with dense breasts (Vinnicombe *et al* 1996, Weatherall *et al* 2001). Although serial biopsy during neoadjuvant chemotherapy provides a window to observe tumour response over time, a small amount of tissue specimen is subjected to sampling bias in the context of heterogeneous internal compositions. DCE MRI has been extensively studied in patients with breast tumours, and is found valuable in monitoring tumour residua, finding unsuspected or multifocal tumours, differentiating benign from malignant lesions, and characterizing tumour angiogenesis (Gilles *et al* 1994, Mussurakis *et al* 1997, Tofts *et al* 1995, Knopp *et al* 1999, Taylor *et al* 1999, Fischer *et al* 1999, Kuhl *et al* 1999, Carriero *et al* 2002, Hulka *et al* 1997). Recent studies also showed that DCE MRI is potentially useful in assessing tumour response to neoadjuvant chemotherapy (Abraham *et al* 1996, Rieber *et al* 1997, 2002, Wasser *et al* 2003, Delille *et al* 2003). It has been demonstrated that the kinetics of Gd-DTPA uptake is contributed from microvessel density (MVD), vessel size and permeability (Buadu *et al* 1996, Carriero *et al* 2002, Hulka *et al* 1997). To better explain the kinetics of Gd-DTPA uptake, a pharmacokinetic two-compartment model was proposed to characterize time–intensity curves in terms of amplitude, redistribution rate constant (k_{out}) (Knopp *et al* 1999, Brix *et al* 1991, Buckley *et al* 1994). In this model, the amplitude was related to MVD, and exchange rate k_{out} was related to vascular permeability that was proportional to vascular endothelial growth factor (VEGF) (Knopp *et al* 1999). Using these MRI-derived angiogenic parameters Knopp *et al* (1999) were able to subclassify malignant breast tumours. The pixel-by-pixel analysis of Gd-DTPA uptake time curves not only improves the specificity of diagnosis, it can produce parametric images that provide information about tumour heterogeneity, permeability and vascularity (Mussurakis *et al* 1997). Therefore, DCE MRI is a useful tool to monitor the response of tumour angiogenesis and tailor the choice of therapeutic regimens for patients with LABC.

Most of the DCE MRI studies analysed averaged signal time curves from a tumour region in a single slice. However, this approach cannot indicate the heterogeneity of tumour compositions that may be a key factor affecting tumour response to chemotherapy. In our study, we compared the tumour response with the dynamics of angiogenic compositions during serial neoadjuvant chemotherapy. Better tumour response was associated with a larger change of tumour compositions from heterogeneous to homogeneous distributions, and larger decrement of peak enhancement over the whole tumour. Before chemotherapy, lower kurtosis and higher standard deviation of amplitude correlated with better tumour response ($r = 0.63$ and $r = 0.61$, respectively). After the first course of chemotherapy, better responders showed larger decrease of standard deviation of amplitude ($r = 0.79$), larger increase of kurtosis and decrease of standard deviation of k_{out} ($r = 0.57$ and 0.57 , respectively). In the final MR study, better responders showed larger increase of kurtosis ($r = 0.62$), decrease of mean ($r = 0.84$) and standard deviation ($r = 0.77$) of amplitude and decrease of mean of peak enhancement ($r = 0.71$). These results suggest that the change in internal compositions may arise from different susceptibility of individual compositions to chemotherapy. Particularly, compositions with higher amplitude may be more susceptible to chemotherapy.

Ellis *et al* (1997) found that during neoadjuvant treatment a measurable increase in apoptosis occurred in breast tumours within 24 h after the start of chemotherapy; this increase

was associated with concomitant decrease in proliferation of tumour cells (Cleator *et al* 2002). Gilles *et al* (1994) showed that tumour response to primary chemotherapy was related to the replacement of tumour cells with loose fibrosis and that the proportion of tumour cells and fibrotic change correlated well with the pattern of enhancement of residual tumour. These studies also indicate that there are substantial alterations of internal compositions in the breast cancer undertaking chemotherapy. Relationships between histological changes and MRI-derived tumour angiogenic parameters are currently under active investigation in our lab.

A recent study by Wasser *et al* (2003) revealed the potential capability of DCE MRI to assess therapeutic effects of neoadjuvant chemotherapy in breast cancer. On the basis of the two-compartment model, they showed good correlation between tumour diameter measured by histopathology and MRI ($r = 0.7$, $p < 0.003$). Furthermore, a reduction of tumour size after chemotherapy was associated with a decrease of both k_{ep} (equivalent to k_{out}) (Padhani and Husband 2001) and amplitude, where k_{ep} was a more sensitive indicator that began to drop right after the first cycle of chemotherapy. On the other hand, the reduction of contrast enhancement was not a sign of tumour responsiveness (Wasser *et al* 2003). In our study, tumours with better response were more heterogeneous in the histograms of amplitude before chemotherapy (table 1). Histograms of k_{out} showed increased kurtosis and decreased standard deviation after the first course of chemotherapy. These findings suggest that compositions of tumour angiogenesis might become more homogeneous under effective chemotherapy. However, we did not find significant decrease in the mean values of k_{out} or amplitude. The disparity might arise from variable chemotherapy regimens employed in our study. Further investigation with randomized controlled study will be needed to draw a more conclusive result. Comparing with amplitude, we found that the response of k_{out} was rather inconsistent, suggesting that k_{out} might respond differently to different chemotherapy regimens. Delille *et al* (2003) reported that DCE breast MRI using extraction flow product (EFP) could provide important functional information regarding changes in tumour angiogenesis due to neoadjuvant chemotherapy. Similar to the behaviour of k_{out} , changes of EFP appeared to be dependent on the chemotherapeutic regimens.

Motion artefact with consequent pixel shift may cause error in data fitting of signal intensity–time curve. Minor motion artefact during dynamic study with free breathing is inevitable (Gilles *et al* 1994, Tofts *et al* 1995, Knopp *et al* 1999, Taylor *et al* 1999, Fischer *et al* 1999, Kuhl *et al* 1999). Manual tumour definition may also cause interobserver and intraobserver variation. These errors, however, may not cause significant change in statistical indices because LABC allows large numbers of pixels to be sampled for analysis. Although our results revealed the possibility of using internal MR parametric composition to predict tumour response to neoadjuvant chemotherapy, large number series with histopathologic correlation is warranted for further validation.

In conclusion, we demonstrated the potential usefulness of parametric histograms derived from DCE MRI to characterize the heterogeneity of tumour compositions and to study the response of tumour angiogenesis to neoadjuvant chemotherapy. Using this method, *in vivo* angiogenic compositions of the whole breast tumour mass can be monitored by serial MRI studies during the whole course of neoadjuvant chemotherapy. This method might be clinically useful in understanding pathophysiologic changes, predicting tumour response and guiding therapeutic approach.

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References

- Abraham D C, Jones R C, Jones S E, Cheek J H, Peter G N, Knox S M, Grant M D, Hampe D W, Savino D A and Harms S E 1996 Evaluation of neoadjuvant chemotherapeutic response of locally advanced breast cancer by magnetic resonance imaging *Cancer* **78** 91–100
- Boetes C, Mus R, Holland R, Barentsz J O, Strijk S P, Wobbes T, Hendriks J H and Ruys S H 1995 Breast tumors: comparative accuracy of MR imaging relative to mammography and US for demonstrating extent *Radiology* **197** 743–7
- Brix G, Semmler W, Port R, Schad L R, Layer G and Lorenz W J 1991 Pharmacokinetic parameters in CNS Gd-DTPA enhanced MR imaging *J. Comput. Assist. Tomogr.* **15** 621–8
- Buadu L D, Murakami J, Murayama S, Hashiguchi N, Sakai S, Masuda M, Toyoshima S, Kuroki S and Ohno S 1996 Breast lesions: correlation of contrast medium enhancement patterns on MR images with histopathologic findings and tumor angiogenesis *Radiology* **200** 639–47
- Buckley D L, Kerslake R W, Blackband S J and Horsman A 1994 Quantitative analysis of multi-slice Gd-DTPA enhanced dynamic MR imaging using an automated simplex minimization procedure *Magn. Reson. Med.* **32** 646–51
- Carriero A, Ambrossini R, Mattei P A, Angelucci D and Bonoma L 2002 Magnetic resonance of the breast: correlation between enhancement patterns and microvessel density in malignant tumors *J. Exp. Clin. Cancer Res.* **21** 83–7
- Chie W C, Chang S H, Huang C S, Tzeng S J, Chen J H, Fan B Y and Chang K J 2002 Prognostic factors for the survival of Taiwanese breast cancer patients *J. Formos. Med. Assoc.* **101** 98–103
- Cleator S, Parton M and Dowsett M 2002 The biology of neoadjuvant chemotherapy for breast cancer *Endocr. Relat. Cancer* **9** 183–95
- Delille J P, Slanetz P J, Yeh E D, Halpern E F, Kopans D B and Garrido L 2003 Invasive ductal breast carcinoma response to neoadjuvant chemotherapy: noninvasive monitoring with functional MR imaging—pilot study *Radiology* **228** 63–9
- Ellis P A, Smith I E, McCarthy K, Detre S, Salter J and Dowsett M 1997 Preoperative chemotherapy induces apoptosis in early breast cancer *Lancet* **349** 849
- Eltahir A, Heys S D, Hutcheon A W, Starkar T K, Smith I, Walker L G, Ah-See A K and Eremin O 1998 Treatment of large and locally advanced breast cancer using neoadjuvant chemotherapy *Am. J. Surg.* **175** 127–32
- Fischer U, Kopla L and Grabbe E 1999 Breast carcinoma: effect of preoperative contrast-enhanced MR imaging on the therapeutic approach *Radiology* **213** 881–8
- Gilles R, Guinebretière J M, Toussaint C, Spielman M, Rietjens M, Petit J Y, Contesso G, Masselot J and Vanel D 1994 Locally advanced breast cancer: contrast-enhanced subtraction MR imaging of response to preoperative chemotherapy *Radiology* **191** 633–8
- Heys S D, Eremin J M, Sarkar T K, Hutcheon A W, Ah-See A and Eremin O 1994 Role of multimodality therapy in the management of locally advanced carcinoma of the breast *J. Am. Coll. Surg.* **179** 493–504
- Hulka C A, Edmister W B, Smith B L, Tan L, Sgroi D C, Campbell T, Kopans D B and Weisskoff R M 1997 Dynamic echo-planar imaging of the breast: experience in diagnosing breast carcinoma and correlation with tumor angiogenesis *Radiology* **205** 837–42
- Knopp M V *et al* 1999 Pathophysiologic basis of contrast enhancement in breast tumors *J. Magn. Reson. Imaging* **10** 260–6
- Koning C and Hart G 1998 Long-term follow-up of a randomized trial on adjuvant chemotherapy and hormonal therapy in locally advanced breast cancer *Int. J. Radiat. Oncol. Biol. Phys.* **41** 397–400
- Kuhl C K, Mielcareck P, Klaschik S, Leutner C, Wardelmann E, Gieseke J and Schild H H 1999 Dynamic breast MR imaging: are signal intensity time course data useful for differential diagnosis of enhancing lesions? *Radiology* **211** 101–10
- Mumtaz H, Hall-Craggs M, Davidson T, Walmsley K, Thurell W, Kissin M W and Taylor I 1997 Staging of symptomatic primary breast cancer with MR imaging *Am. J. Roentgenol.* **169** 417–24
- Mussurakis S, Buckley D L, Drew P J, Fox J N, Carleton P J, Turnbull L W and Horsman A 1997 Dynamic MR imaging of the breast combined with analysis of contrast agent kinetics in the differentiation of primary breast tumors *Clin. Radiol.* **52** 516–26
- Padhani A R and Husband J E 2001 Dynamic contrast-enhanced MRI studies in oncology with an emphasis on quantification, validation and human studies *Clin. Radiol.* **56** 607–20
- Pierce L, Adler D, Helvie M, Lichter A and Merajver S 1996 The use of mammography in breast preservation in locally advanced breast cancer *Int. J. Radiat. Oncol. Biol. Phys.* **34** 571–7
- Rieber A, Brambs H J, Gabelmann A, Heilmann V, Kreienberg R and Kühn T 2002 Breast MRI for monitoring response of primary breast cancer to neo-adjuvant chemotherapy *Eur. Radiol.* **12** 1711–9

- Rieber A, Zeitler H, Rosenthal H, Görlich J, Kreienberg R, Brambs H J and Tomczak R 1997 MRI of breast cancer: influence of chemotherapy on sensitivity *Br. J. Radiol.* **70** 452–8
- Rodenko G N, Harms S E, Pruneda J M, Farrell R S Jr, Evans W P, Copit D S, Krakos P A and Flamig D P 1996 MR imaging in the management before surgery of lobular carcinoma of the breast: correlation with pathology *Am. J. Roentgenol.* **167** 1415–9
- Tabar L, Yen M F, Vitak B, Chen H H, Smith R A and Duffy S W 2003 Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening *Lancet* **361** 1405–10
- Taylor J S, Tofts P S, Phil D, Port R, Evelhoch J L, Knopp M, Reddick W E, Runge V M and Mayr N 1999 MR imaging of tumor microcirculation: promise for the new millennium *J. Magn. Reson. Imaging* **10** 903–7
- Tofts P S, Berkowitz B and Schnall M 1995 Quantitative analysis of dynamic Gd-DTPA enhancement in breast tumors using a permeability model *Magn. Reson. Med.* **33** 564–8
- Vinnicombe S, MarVocar A D, Guy R L, Sloane J P, Powles T J, Knee G and Husband J E 1996 Primary breast cancer: mammographic changes after neoadjuvant chemotherapy with pathologic correlation *Radiology* **198** 333–40
- Wasser K, Klein S K, Fink C, Junkermann H, Sinn H P, Zuna I, Knopp M V and Delorme S 2003 Evaluation of neoadjuvant chemotherapeutic response of breast cancer using dynamic MR with high spatial temporal resolution *Eur. Radiol.* **13** 80–7
- Weatherall P T, Evans G F, Metzger G J, Saborrian M H and Leitch A M 2001 MRI vs. histologic measurement of breast cancer following chemotherapy: comparison with x-ray mammography and palpation *J. Magn. Reson. Imaging* **13** 868–75
- Weidner N, Semple J P, Welch W R and Folkman J 1991 Tumor angiogenesis and metastasis—correlation in invasive breast cancer *N. Engl. J. Med.* **324** 1–8