Baseline MRI delivery characteristics predict change in invasive ductal breast carcinoma PET metabolism as a result of primary chemotherapy administration

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Background: The aim of the study was to investigate whether pre-therapy vascular delivery assessment [using dynamic contrast enhanced magnetic resonance imaging (DCE-MRI)] can predict reduction in breast cancer metabolism [detected using 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG-PET)] after a single cycle of chemotherapy. Reduction in 18F-FDG PET metabolism has previously been shown to correlate with histological response to primary chemotherapy.

Patients and methods: Seventeen patients with large or locally advanced invasive ductal carcinomas of the breast were imaged using DCE-MRI and 18F-FDG-PET prior to therapy and 20 days after the first cycle of chemotherapy. MRI data were analysed using a multi-compartment model. PET data were analysed using standardised uptake value (SUV) analysis.

Results: A significant association (P <0.05) was observed between pre-therapy DCE-MRI vascular parameters and the reduction in PET metabolism resulting from administration of one cycle of chemotherapy.

Conclusions: A relationship was demonstrated between pre-therapy DCE-MRI vascular parameters and the reduction in PET metabolism after a single cycle of chemotherapy. This suggests that reduction in PET metabolism as a result of chemotherapy may be dependent, at least in part, on pre-therapy vascular delivery. These pre-therapy vascular characteristics may be suitable for use as a surrogate measure for initial chemotherapy delivery, a key factor in chemotherapeutic efficacy.

Key words: breast cancer, dynamic MRI, 18F-FDG PET, chemotherapy, efficacy, delivery

introduction

Management of patients with large or locally advanced cancer involves determination of the best therapy regimen for maximum antitumour efficacy together with minimisation of morbidity and mortality. Approximately 10% of patients with breast cancer present with large or locally advanced breast cancer (LABC) with primary chemotherapy routinely used with the aim of downstaging the primary tumour prior to facilitating breast conservation surgery and to attempt to eliminate micrometastatic disease and improve overall survival [1, 2]. Unfortunately, 20%–25% of patients treated in this way will not exhibit a clinical response (partial or complete) to primary chemotherapy, experiencing breast tumour stasis or progression during treatment [1–4].

Conventional monitoring of patients with LABC during chemotherapy is achieved with clinical examination, ultrasonography and mammography. These techniques suffer from low sensitivity to changes in tumour size [3–7] such that a reduction in tumour size may not be evident until administration of multiple cycles of chemotherapy [1, 7]. An assessment of patient response to chemotherapy is made at the mid-way point of the chemotherapy regimen after three cycles of primary chemotherapy. This means that patients who will not ultimately respond to chemotherapy may experience repeated cycles of an ineffective treatment with its associated morbidity, mortality and financial costs.

The most accurate method of assessing tumour response to primary chemotherapy is histological examination of residual tumour after the full course of chemotherapy has been completed [1, 2], but can only be determined at the end of treatment when the residual tumour is removed for pathological examination. It is clear that there is a clinical need for a reliable technique that will predict tumour response to primary
chemotherapy in patients with LABC, and in particular to identify those patients who will not respond to chemotherapy. This would offer the potential to optimise clinical management and lead to ‘customised’ treatment strategies for individual patients.

Our group has previously demonstrated a delivery-limited relationship between the pre-chemotherapy vascular and metabolic characteristics of LABC in patients using dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) and PET imaging using the glucose analogue 2-[18F]fluoro-2-deoxy-D-glucose (18F-FDG) [4, 8]. We hypothesise that this relationship may also be indicative of drug delivery limitation and therefore drug efficacy.

DCE-MRI allows assessment of the passage of an injected contrast agent into the extravascular–extracellular leakage space over several minutes [4, 9]. This agent preferentially accumulates in the tumour as a result of the increased amount of ‘leaky’ immature blood vessels within cancer tissues allowing assessment of tumour vascular characteristics. These vascular characteristics have been shown to be an important factor in the initial diagnosis of breast cancer and in assessing chemotherapeutic response to chemotherapy [9–12]. Change in MRI signal intensity during and immediately after the injection can be modelled using multi-compartment models and characteristics of tumour vascular structure expressed as a series of pharmacokinetic parameters which may be used in the assessment of chemotherapeutic response in breast cancer [4, 13–18].

It is difficult to investigate predictors of eventual response over a complete course of chemotherapy since those patients not exhibiting a clinical response at the mid-point of the primary chemotherapy regimen are moved to other treatment options rather than completing a full chemotherapy regimen. Hence, comparison of traditional gold standard therapy end-point outcomes, such as histological examination of excision of residual breast tumour at the time of surgery, are of limited value in this case since a significant proportion of patients will be subjected to different treatment regimens prior to surgery. An ideal outcome measure, therefore, correlates with response to chemotherapy and is measurable in all patients before treatment divergence occurs.

Cancers have an elevated glycolytic rate that can be imaged using 18F-FDG PET [3, 19, 20]. A reduction in metabolic activity as measured using 18F-FDG PET after a single cycle of chemotherapy has been shown to correlate with a significant histological response of a breast cancer to primary chemotherapy [3, 19–23]. We therefore propose that a measure of reduction in uptake of 18F-FDG in PET after a single cycle of primary chemotherapy is a suitable measure of initial response to primary chemotherapy to assess the predictive value of DCE-MRI vascular modelling in this study.

In this study we measured vascular characteristics using DCE-MRI and glycolytic metabolic activity using 18F-FDG PET in a group of patients with large or locally advanced invasive ductal carcinomas (IDC) of the breast. These examinations were performed prior to chemotherapy and then repeated after the first cycle of chemotherapy. We investigated the ability of the pre-therapy vascular characteristics of these tumours to predict the observed reduction in metabolic activity that occurs after administration of a single cycle of chemotherapy.

patients and methods
patients and study protocol

Patients presenting to the Breast Unit at Aberdeen Royal Infirmary were diagnosed as having breast cancer using standard triple assessment [clinical examination, imaging (mammography and ultrasonography) and fine needle aspiration cytology]. Histological confirmation and grading of breast cancer was obtained by core biopsy. Patients with large T2 or T3 cancers (defined as >3 cm as measured by clinical examination) or locally advanced (T4 with any N status, or N2 status with any T size) breast cancers were invited to take part in this study. Contraindications for inclusion were patient claustrophobia or presence of metal implant for MRI, and diabetes mellitus for PET. No potential patients for the study were found to exhibit any of these contraindications. Two patients were excluded due to difficulty of scheduling imaging before the start of therapy. Two patients were excluded due to technical problems. Four patients declined to take part due to personal commitments during the required imaging times.

The population examined in this study comprised 17 women with confirmed breast IDC (mean age 49, range 30–63 years), five with grade 1, three with grade 2 and nine with grade 3 tumours. Patients received a DCE-MRI scan and 18F-FDG PET scan prior to the start of any cancer therapy within 4 days of one another. The DCE-MRI and 18F-FDG PET scans were then repeated 20 days after administration of the first cycle of primary chemotherapy (before the second cycle of primary chemotherapy). Each patient received a maximum of six cycles of primary chemotherapy. Ten patients received a combination of epirubicin and docetaxel and seven patients received a combination of doxorubicin and cyclophosphamide according to standard protocols in use at the time.

Fully informed written consent was obtained from each patient prior to entry into the study (approved by the Joint Ethical Committee of the University of Aberdeen and Grampian Health Board).

The imaging protocol for the DCE-MRI and PET examinations has been described in detail elsewhere [4] but is outlined below.

MRI protocol

Patients were imaged prone using a 1.5 T NVi/CVi scanner (GE, Waukesha WI, USA) and a four-channel phased array receive only open breast array coil (MRI Devices, Waukesha WI, USA). Following three-plane localisation, a coronal 3D fast spoiled gradient echo (FSPGR) covering both breasts was obtained for localisation of tumour. Next, a 2D FSPGR (nine slices) was acquired ensuring complete coverage of the lesion. This sequence was acquired with flip angles of 6°, 10° and 35° to calculate accurate pre-contrast T1 values using a Levenberg–Marquardt best fit algorithm for each voxel [4, 24]. The 35° sequence was then repeated over 40 time points (10 s temporal resolution) with an intravenous injection of 0.2 mmol/kg gadopentetate dimeglumine (Magnevist, Schering Health Care Ltd., Burgess Hill, UK) administered on the fifth temporal frame. Injection was performed using a SPECTRIS MR compatible pump injector (MEDRAD, Pittsburgh, PA, USA) at a rate of 3 ml/s, immediately followed by a 20 ml saline flush administered at the same rate.

PET protocol

Patients were imaged using a CTI ECAT Exact scanner (Siemens, Erlangen, Germany) with a spatial resolution of 6–8 mm in the axial and both transaxial directions. Patients were required to fast for at least 4 h before PET imaging and were imaged prone on a purpose built couch in a similar orientation to that achieved with MRI. The PET protocol consisted of a
10-min transmission/attenuation scan acquired 60 min after a 185 MBq injection of 18F-FDG (synthesised on site) followed by a 10-min static emission scan. Patient blood glucose was ascertained via a blood sample obtained immediately after the examination. The emission data were acquired in the 2D mode and reconstructed by filtered back-projection with a Nyquist-frequency cut-off Hanning window.

**MRI analysis**

MR images were analysed using purpose written software in the programming language IDL (Research Systems Inc., Boulder, CO, USA) [4]. An experienced radiologist defined a region of interest (ROI) for each slice within the 2D acquisition. Pharmacokinetic analysis was performed according to the Brix two compartment model [13, 14]. This model describes contrast enhancement using three parameters, an amplitude $A$ reflecting the degree of MR signal enhancement, an exchange rate constant $k_{ep}$ (per min) characterising the initial increase of the signal-time curves, and an elimination rate $k_e$ (per min) for assessment of the late postcontrast (‘wash-out’) phase. A Levenberg–Marquardt algorithm was used to perform a least-squares fit of the observed signal curves to both models. Fitting was performed using a range of starting values for each model, with automatic selection of the best fit as assessed by resultant $R^2$ values [4].

For this analysis, pharmacokinetic parameters were fitted on a voxel-by-voxel basis within the tumour and a hot-spot region of highest exchange rate constant $k_{ep}$ automatically selected [4, 16].

**PET analysis**

Standardised uptake values (SUV) were calculated to evaluate tumour metabolism for the PET images according to

\[
\text{SUV} = \frac{C}{r \cdot BSA}
\]

where $C$ = concentration in image voxel × body surface area/injected activity

SUV values were generated for each voxel, then a ROI was selected around the tumour area on the slice that bisected the centre of the tumour and applied to the central tumour slice and two slices on either side of the central slice to calculate mean tumour SUV [3, 4].

Example pre-therapy DCE-MRI vascular maps and the corresponding pre-therapy and post-one-chemotherapy cycle PET SUV metabolism maps are presented in Figure 1.

**Statistical analysis**

All statistical analysis was performed using SPSS for Windows version 13.0 (SPSS Inc., Chicago, IL, USA). A Kolmogorov–Smirnov test was used to test the data for normal distribution. Absolute change in calculated DCE-MRI and PET parameters between first and second scans was tested using a paired $t$-test. General linear modelling was used to test the association of each of the pre-therapy DCE-MRI parameters ($A_{1(1)}$, $k_{ep(1)}$, $k_{el(1)}$) with ΔSUV, generating partial $R^2$ values, which are an estimate of the effect size, i.e. the proportion of the variance in ΔSUV that can be attributed to each MRI parameter. These values are equivalent to the square of a correlation type measure. The modelling was repeated four times using $A_{1(1)}$, $k_{el(1)}$, $k_{el(1)}$ alone (model 1), with pre-therapy tumour histological grade as an additional co-variate (model 2), with choice of chemotherapy agent as a fixed factor (model 3) and with both tumour grade and choice of chemotherapy included (model 4).

**Results**

The MR pharmacokinetic parameters and PET SUV values did not differ significantly from a normal distribution ($P > 0.12$). The absolute change in parameters is presented in Table 1. A significant reduction in SUV of approximately 17% after administration of one cycle of primary chemotherapy was noted for the population ($t = 2.58$, $P < 0.05$).

The pre-therapy DCE-MRI model vascular parameters $A_{1(1)}$ and $k_{ep(1)}$ exhibited significant association with ΔSUV. These results are shown in Table 2. Table 2 demonstrates that the type of chemotherapy and tumour grade had no significant effect on ΔSUV. The addition of these factors into the general linear model reduced the association of $k_{ep(1)}$ with ΔSUV to an

**Figure 1.** Sample MRI and PET functional parameter maps (each shown with corresponding colour scale). (a) Patient 1 pre-therapy MRI $A_{1(1)}$, (b) patient 1 pre-therapy MRI $k_{ep(1)}$, (c) patient 1 pre-therapy PET SUV, (d) patient 1 post-therapy PET SUV, (e) patient 1 pre-therapy MRI $A_{1(1)}$, (f) patient 2 pre-therapy MRI $k_{ep(1)}$, (g) patient 2 pre-therapy PET SUV, (h) patient 2 post-therapy PET SUV. Both patients presented with >3 cm (clinically determined) diameter IDC. Patient 1 exhibited low pre-therapy MRI $k_{ep(1)}$ and $A_{1(1)}$ values (a, b), no subsequent significant change in SUV after one cycle of chemotherapy (c, d) and minimal histological end point response to therapy. Patient 2 exhibited higher pre-therapy MRI $k_{ep(1)}$ and $A_{1(1)}$ values (e, f), a significant reduction in SUV after one cycle of chemotherapy (g, h) and partial histological end point response to therapy.
insignificant level \((P = 0.54)\), however, \(A_{1(1)}\) remained significantly associated with \(\Delta S U V\).

As our group has previously demonstrated that pre-therapy vascular delivery characteristics measured by DCE-MRI are associated with pre-therapy \(^{18}\)F-FDG uptake in locally advanced breast cancers [4] it might be argued that the observed reduction in SUV after one cycle of primary chemotherapy is simply due to a reduction in tumour delivery characteristics. In order to test this hypothesis we tested the association between \(\Delta S U V\) uptake and both the pre-therapy and post-one-cycle primary chemotherapy DCE-MRI parameters (model 5). These results are shown in Table 3. The results demonstrate that the post-therapy MRI parameters are not significantly associated with \(\Delta S U V\). However, \(\Delta S U V\) remains strongly dependent on pre-therapy \(A_{1(1)}\).

discussion

We have demonstrated that the pretreatment vascular characteristics of large or locally advanced breast cancers calculated using DCE-MRI data predicted a significant proportion of the change in metabolism of these tumours (measured using \(^{18}\)F-FDG PET) after a single cycle of primary chemotherapy. This was demonstrated in a group of 17 women with invasive ductal carcinomas of the breast. Although uptake of MRI contrast media and PET radiopharmaceuticals are based on entirely different physiological mechanisms, the two processes are linked by a basic dependence on delivery of contrast and radiopharmaceutical to the tumour [4, 14]. Similarly, one would expect that to an extent, delivery would also influence the efficacy of any chemotherapy agent.

Table 1. DCE-MRI pharmacokinetic and PET SUV parameter values for patient population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Scan 1 (mean ± SD)</th>
<th>Scan 2 (mean ± SD)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A)</td>
<td>1.08 ± 1.08</td>
<td>0.865 ± 0.465</td>
<td>0.476</td>
</tr>
<tr>
<td>(k_{ep}) (1/min)</td>
<td>7.80 ± 8.33</td>
<td>5.76 ± 2.74</td>
<td>0.054</td>
</tr>
<tr>
<td>(k_{el}) (1/min) × 10^{-6}</td>
<td>-0.618 ± 1.73</td>
<td>0.0939 ± 2.51</td>
<td>0.359</td>
</tr>
<tr>
<td>SUV</td>
<td>0.0621 ± 0.0365</td>
<td>0.0470 ± 0.0310</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Scan 1 data obtained pre-therapy, scan 2 data obtained 20 days after first cycle of primary chemotherapy (prior to second cycle). Change in parameters between scans was test using a paired \(t\)-test (significance indicated in bold).

Table 2. Relationship between change in SUV after one course of therapy \((\Delta S U V)\) and pre-therapy DCE-MRI pharmacokinetic parameters \((A_{1(1)}, k_{ep}, k_{el})\)

<table>
<thead>
<tr>
<th>Model 1</th>
<th>(P) value ((\eta^2))</th>
<th>Model 2</th>
<th>(P) value ((\eta^2))</th>
<th>Model 3</th>
<th>(P) value ((\eta^2))</th>
<th>Model 4</th>
<th>(P) value ((\eta^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A_{1(1)})</td>
<td>0.001 (0.580)</td>
<td>(A_{1(1)})</td>
<td>0.000 (0.557)</td>
<td>(A_{1(1)})</td>
<td>0.002 (0.574)</td>
<td>(A_{1(1)})</td>
<td>0.004 (0.553)</td>
</tr>
<tr>
<td>(k_{ep})</td>
<td>0.016 (0.370)</td>
<td>(k_{ep})</td>
<td>0.045 (0.294)</td>
<td>(k_{ep})</td>
<td>0.024 (0.356)</td>
<td>(k_{ep})</td>
<td>0.058 (0.289)</td>
</tr>
<tr>
<td>(k_{el})</td>
<td>0.256 (0.098)</td>
<td>(k_{el})</td>
<td>0.297 (0.090)</td>
<td>(k_{el})</td>
<td>0.293 (0.091)</td>
<td>(k_{el})</td>
<td>0.340 (0.083)</td>
</tr>
<tr>
<td>grade</td>
<td>0.944 (0.000)</td>
<td>chemo type</td>
<td>0.970 (0.000)</td>
<td>grade</td>
<td>0.950 (0.000)</td>
<td>chemo type</td>
<td>0.977 (0.000)</td>
</tr>
</tbody>
</table>

\(P\) values and \(\eta^2\) values are results of general linear modelling. The effects of including tumour grade as a co-variant in the model and chemotherapy type as a fixed factor are shown. Significance indicated in bold.
demonstrate that no significant change in vascular parameters was observed reduction in SUV. However, the results in Table 1 show that this reduction could be explained, at least in part, by a change in the vascular architectural characteristics of the tumour as a result of primary chemotherapy, i.e. the delivery of \(^{18}\)FDG would be compromised leading to an observed reduction in SUV. This is consistent with the findings of a larger group. As shown in Table 3, when we tested for changes in SUV and included the \(A_{(2)}\) and \(kp_{(2)}\) values generated for the second DCE-MRI scan in our model, only the strong association between \(A_{(1)}\) and change in metabolism remained. Hence we hypothesise that observed initial reduction in SUV is due to a reduction in metabolism that predates any change in vascular architectural characteristics.

It has been demonstrated using PET imaging that a low ratio of metabolic activity to blood flow correlates well with macroscopic complete response to chemotherapy although blood flow and metabolic rate are highly variable. Several groups have demonstrated the usefulness of a combination of MRI and PET to assess breast cancer before therapy. Our preliminary study of 17 patients requires confirmation in a larger study but is, to the best of our knowledge, the first demonstration that measurable in vivo vascular imaging parameters can be used to predict early changes in tumour metabolism as a result of primary chemotherapy in patients with large or locally advanced breast cancer, using a combination of MRI and PET. An accurate prediction of response to chemotherapy will allow a targeted and rational use of chemotherapy in locally advanced cancer patients, tailoring treatment to best meet the requirements of individual patients. These results also suggest that the modulation of delivery characteristics using vascular therapeutic agents may significantly modify sensitivity of locally advanced cancers to primary chemotherapy. Preventing patients receiving ineffective and highly toxic treatment would significantly improve patient quality of life. However, it remains to be seen whether any cost reduction caused by cessation of ineffective expensive chemotherapy treatment in this patient group would offset the increase in scan costs associated with MRI and PET if implemented on a larger scale. This should be considered as a direction for future work.

Here we have investigated the initial phase of the primary chemotherapy regimen and demonstrate that the pre-therapy vascular characteristics are an important factor in tumour metabolism reduction after one cycle of primary chemotherapy. If the chemotherapy agent is initially effective in this manner it may be that in the later stages of therapy the delivery characteristics of the tumour significantly alter. A reduction in blood supply would have a limiting factor on the delivery and therefore influence the efficacy of subsequent cycles of primary chemotherapy. It would therefore be of interest to assess the impact of primary chemotherapy on vascular delivery and metabolism at subsequent points throughout the chemotherapy regimen in order to tailor chemotherapy administration according to an individual’s changing vascular and metabolic characteristics.

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