DE-MRI predicts changes in breast tumour metabolic activity after chemotherapy.

S. I. Semple[1], R. T. Staff[2], F. J. Gilbert[1], T. W. Redpath[2], A. E. Welch[2], T. S. Ahearn[2], S. D. Heys[3], A. W. Hutcheon[4], E. H. Smyth[5], S. Chaturvedi[5]

[1]Radiology, University of Aberdeen, Aberdeen, Grampian, United Kingdom, [2]Bio-Medical Physics and Bioengineering, University of Aberdeen, Aberdeen, Grampian, United Kingdom, [3]Surgery, University of Aberdeen, Aberdeen, Grampian, United Kingdom, [4]Clinical Oncology, Grampian University Hospitals NHS Trust, Aberdeen, Grampian, United Kingdom, [5]Surgery and Pathology, Grampian University Hospitals NHS Trust, Aberdeen, Grampian, United Kingdom

INTRODUCTION

Chemotherapy is used in the management of large or locally advanced breast cancer (LABC). The primary aim of this therapy is to downstage the cancer prior to surgery in order to permit breast conservation. Conventional treatment monitoring used to assess clinical response, such as palpation, ultrasound and mammography, suffers from low sensitivity and high user-dependence such that only large changes in tumour size are detectable by the mid-way point of therapy, whilst histological response is only obtained after completion of therapy. A reduction in metabolic activity as measured using ^{18}F-FDG PET after a single dose of chemotherapy has previously been shown to correlate with a positive response to therapy[1]. A relationship between uptake of contrast in dynamic enhanced MRI (DE-MRI) and FDG uptake in PET has previously been established[2,3]. Uptake of contrast agent during DE-MRI may be thought of as an analogue for drug delivery. We hypothesise that response to chemotherapy is at least in part determined by the vascular characteristics of the tumour. We therefore investigate whether pharmacokinetic modelling of pre-therapy MRI contrast uptake in tumours may be used to predict a reduction in metabolism after one dose of therapy as measured using ^{18}F-FDG PET.

MATERIALS AND METHODS

DE-MRI and ^{18}F-FDG PET were performed on 18 women (mean age 49, range 30-63 years) with LABC, receiving 6 cycles of cytotoxic therapy (Epirubicin/Docetaxel or Doxorubicin/Cyclophosphamide). PET scans were performed prior to commencement of therapy, and prior to the second cycle of therapy. MRI scans were performed prior to therapy using a 1.5 T NVi/CVi scanner (GE, USA) with a dedicated open breast coil (MRI Devices, USA). After high resolution localisation of the tumour, dynamic enhancement data was obtained using a 9 slice 2D FSPGR[2] with 10 seconds temporal resolution, a 0.2 mmol/kg injection of Magnevist (Schering Healthcare, UK) administered on the fifth temporal frame using an automated pump injector (MEDRAD, USA). Robust pharmacokinetic modelling was applied (using a multiple initial estimates approach to ensure accurate model fitting[4]) according to the two compartment Brix model[5]. This model describes uptake in terms of three parameters, an amplitude A reflecting the degree of MR signal enhancement, an exchange rate constant k_{21} (min^{-1}) characterising the initial increase of the signal-time curves, and an elimination rate k_{el} (min^{-1}) for assessment of the late postcontrast "wash-out" phase. An automated analysis program calculated a tumour 'hot-spot' with the highest mean k_{21} value over a 3×3×3 pixel volume[2]. PET scans were performed using a CTI ECAT Exact scanner (Siemens, Germany) with a 10 minute transmission/attenuation scan and then a 10 minute emission scan acquired 60 minutes after a 5mCi injection of ^{18}F-FDG. Mean differential uptake ratios (DUR) were calculated for the tumour, comprising voxels within the tumour volume that exhibited a DUR greater than 80% of the tumour maximum DUR[1,2].

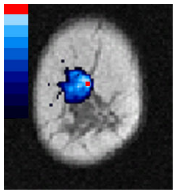

Fig 1 Typical post-contrast coronal MR image with k_{21} map overlay in blue scale. Hot-spot shown in red.

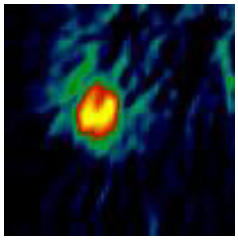

Fig 2 Typical axial PET emission image.

Absolute change in measured tumour DUR (ΔDUR) was calculated between first and second PET scans and any association in this change with pre-therapy MRI pharmacokinetic parameters tested by general linear modelling after a Kolmogorov-Smirnov test demonstrated that none of the variables differed significantly from a normal distribution (SPSS Inc. USA).

RESULTS

The group as a whole exhibited a significant reduction in DUR after administration of one dose of chemotherapy (p=0.016). The pre-therapy DCE-MRI model parameter k_{el} exhibited significant association with change in DUR (see table 1, figure 3).

MRI parameter	p-value	η^2 value	r - value
A	0.084	0.198	0.44
k_{21}	0.047 *	0.254	0.50
k_{el}	0.992	0.0	0.0

Table 1. Association of pre-therapy MRI pharmacokinetic parameters with change in PET DUR after one dose of therapy. * denotes a significant association.

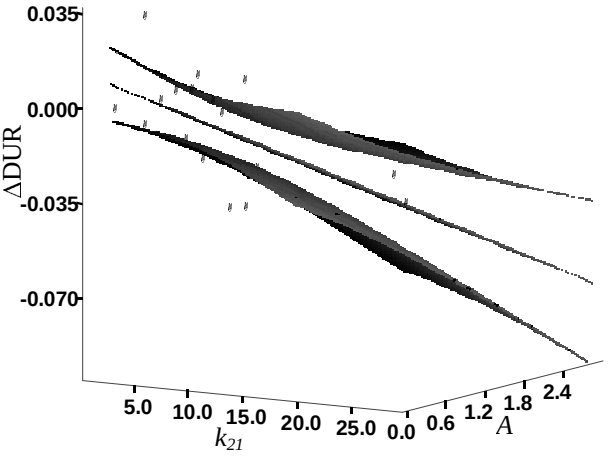

Fig 3 Relationship of pre-therapy$A$ and k_{21} with ΔDUR.

DISCUSSION

After a single dose of chemotherapy, a significant reduction in DUR in the entire population was observed, as expected. The pre-therapy DCE-MRI model results showed significant association with the change in DUR. General linear modelling showed that 45% of the variance of the change in DUR could be explained by the two compartment pharmacokinetic model.

CONCLUSION

PET imaging has previously been shown to be useful in detecting early responses of breast cancers to chemotherapy. Malignant cells have an elevated glycolytic rate which has been shown to fall significantly in response to therapy[1]. A precise level of DUR reduction to differentiate positive from negative response is still under debate. We have observed that pharmacokinetic modelling of pre-therapy MRI contrast uptake is significantly associated with a subsequent reduction in PET metabolism (DUR). A relationship has been previously established linking MR contrast uptake and PET metabolic activity. Although based on entirely different physiological mechanisms, the two processes are linked by a basic dependence on delivery of contrast and radioisotopes[6].

If MRI contrast uptake can be thought of as an analogue for drug delivery, then the pharmacokinetic parameters of the MR model (notably k_{21} and A) which are dependent on delivery, give an indication of chemotherapy delivery. The reduction in DUR depends at least in part on chemotherapy delivery as the drugs will not be effective if they cannot reach the cancer cells. Our results show that pre-therapy modelling of contrast uptake in primary breast cancers has prognostic value in determining which patients will respond to neo-adjuvant chemotherapy.

REFERENCES

1. Smith et al. *J Clin Oncol* **18:** 1676-1688, 2000.
2. Semple et al. *Euro Radiol.* **14(11):** 2038-2045, 2004.
3. Semple et al. *Lancet Onc* **4(12):** 759,2003.
4. Ahearn *PhD Thesis* University of Aberdeen 2003.
5. Tofts et al. *J. Magn. Reson. Imag* **10:** 223-232, 1999.
6. Brix et al. *Euro Radiol* **11:** 2058-2070, 2001.