PERGAMON

European Journal of Cancer 38 (2002) 375–379

European Journal of Cancer

www.ejconline.com

Evaluation of good clinical response to neoadjuvant chemotherapy in primary breast cancer using [^{18}F]-fluorodeoxyglucose positron emission tomography

R.J. Burcombe[a], A. Makris[a,*], M. Pittam[c], J. Lowe[b], J. Emmott[b], W.L. Wong[b]

[a]*Marie Curie Research Wing, Mount Vernon Hospital, Rickmansworth Road, Northwood, Middlesex HA6 2RN, UK*
[b]*The Paul Strickland Scanner Centre, Mount Vernon Hospital, Rickmansworth Road, Northwood, Middlesex HA6 2RN, UK*
[c]*Luton & Dunstable Hospital, Lewsey Road, Luton, Bedfordshire LU4 0DZ, UK*

Received 3 July 2001; received in revised form 31 August 2001; accepted 19 October 2001

Abstract

To determine whether [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) can predict complete pathological response (pCR) in patients achieving a good clinical response to neoadjuvant chemotherapy for primary breast cancer, 10 patients underwent FDG PET scanning prior to definitive breast surgery. Scan reports were compared with histopathological findings. No abnormal uptake at the primary tumour site was visualised in any patient. 9 of the 10 patients had residual invasive carcinoma at operation, ranging from 2 to 20 mm in maximum dimension. One patient achieved a complete pathological response. Of the 5 patients who underwent axillary surgery, no axillary FDG uptake was seen preoperatively although 3 of the 5 were histologically node-positive. FDG PET did not reliably identify residual disease in this series of good clinical responders to neoadjuvant chemotherapy, and its discriminatory power as a tool to predict complete pathological response therefore appears to be inadequate for clinical use in this setting.

Keywords: Breast neoplasms/radionuclide imaging; Breast neoplasms/pathology; Breast neoplasms/drug therapy; Fluorodeoxyglucose F 18/diagnostic use; Tomography, emission-computed/methods; Antineoplastic agents, combined/therapeutic use; Predictive value of tests

1. Introduction

Neoadjuvant chemotherapy is increasingly used in the treatment of large primary breast cancers. Objective response rates are high and large randomised trials show no survival disadvantage compared with conventional postoperative adjuvant chemotherapy [1,2]. In addition, the administration of preoperative chemotherapy results in a small, but significant, increase in breast conservation rates.

Complete pathological response (pCR) to neoadjuvant chemotherapy is an important prognostic indicator for prolonged disease-free and overall survival [1,3–6]. However, clinical assessment of response is a poor predictor of pathological tumour regression [1,3,7,8]. Indeed, in the largest randomised trial of neoadjuvant treatment to date, 75% of those achieving complete clinical response (cCR) at the primary site had viable tumour at pathological assessment (64% invasive carcinoma, 11% *in situ*) [1]. Conventional radiological assessment of response using ultrasound, mammography and magnetic resonance imaging (MRI) also often fails to identify residual invasive tumour [9].

Patients who achieve pCR may not require surgery for optimum local control. However, at present, surgical excision and histological examination of the resected specimen is the only way to reliably identify this small subgroup of patients. More effective imaging strategies that can non-invasively identify complete pathological responders could potentially distinguish a subgroup of patients who need not undergo surgery at all.

It is widely accepted that [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) can visualise primary breast tumours and metastatic axillary lymph nodes for the purposes of staging [10–12]. FDG PET has also been shown to be helpful for monitoring

* Corresponding author. Tel.: +44-1923-844964; fax: +44-1923-844462.
E-mail address: andreas.makris@whht.nhs.uk (A. Makris).

0959-8049/02/$ - see front matter
PII: S0959-8049(01)00379-3

clinical response to neoadjuvant chemotherapy by virtue of a rapid and significant reduction in *in vivo* cellular glycolysis induced by effective cytotoxic drugs [11,13–15]. Moreover, such functional changes in glucose metabolism predate conventional clinical and radiological methods of assessing tumour response. More recently, two studies have demonstrated that an early reduction in uptake on serial FDG PET scans taken before and during chemotherapy can identify pathological responders [16,17].

In this study, 10 patients who achieved a good clinical response to neoadjuvant chemotherapy underwent a single post-chemotherapy, preoperative FDG PET scan in an attempt to establish whether post-treatment FDG PET imaging can predict complete pathological response.

2. Patients and methods

2.1. Patients and treatment

All 10 patients had non-inflammatory biopsy-proven, large (T2 or greater) or locally advanced primary breast cancers. Six cycles of neoadjuvant FEC chemotherapy (5-fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) were delivered intravenously (i.v.) at 21-day intervals. One patient received four cycles of AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2).

Clinical assessment of response was graded according to standard Union Internationale Contre le Cancer (UICC) criteria [18] by calculating the bidimensional product of the two greatest perpendicular tumour measurements. On completion of chemotherapy, all patients had a good clinical response, defined as either cCR (complete resolution of a palpable mass within the breast) or minimal residual disease (MRD) (residual thickening with no palpable mass). Eight patients underwent radiological assessment of response using ultrasound and/or mammography at baseline and on completion.

Prior to surgery (breast conserving surgery or mastectomy with or without axillary dissection at the surgeon's discretion) patients underwent an FDG PET scan. Routine histological examination of the surgical specimen followed. The Mount Vernon and Watford Hospitals National Health Service (NHS) Trust Local Research and Ethics Committee approved the protocol.

2.2. FDG PET imaging protocol

FDG PET scans were performed at The Paul Strickland Scanner Centre after the final cycle of chemotherapy and before definitive surgery. Patients' weights and blood glucose levels were recorded before scanning, having fasted for at least 4 h previously. 250 MBq (range 213–258) of [^{18}F]-FDG was injected i.v. via an arm vein on the contralateral side to the breast lesion.

A Siemens Medical ECAT EXACT 47 scanner (Knoxville, TN, USA) was used, producing a 16 cm axial field view with intrinsic spatial resolution of 5 mm. Localised views of the chest and axilla were taken 1 h post-injection using a total scanning time of 30 min in one bed position. A baseline transmission scan was performed in each case to measure attenuation correction. Images were reconstructed by a standard filtered back projection algorithm onto a 128×128 matrix using a Hanning filter with a cut-off of 0.45. The final resolution in constructed images was approximately 8 mm. All FDG PET data was reviewed by one observer experienced with FDG PET imaging and blinded to all clinical information. Hypermetabolism otherwise unexplained in terms of physiological causes was considered positive for residual disease.

3. Results

3.1. Patient characteristics

The median age at diagnosis was 46 years (range 36–58 years). The mean weight and blood glucose level before FDG PET scan was 76 kg (range 64–91 kg) and 5.3 mmol/l (range 4.5–7.0, mmol/l), respectively. No patient had a history of diabetes mellitus. The median time difference between the final cycle of chemotherapy and the FDG PET scan was 21 days (range 9–31 days). The median delay between the FDG PET scan and surgery was 17 days (range 3–75 days). 3 patients achieved a cCR and 7 MRD on completion of chemotherapy.

The clinical TNM stage at diagnosis, clinical and radiological response, PET scan findings, surgery and histopathology are shown in Table 1.

3.2. FDG PET and histological findings

No FDG uptake was visualised at the primary tumour site on FDG PET scan in any patient. 9 of the 10 patients had residual invasive breast carcinoma at operation, ranging from 2 to 20 mm in maximum dimension. There was one complete pathological response. 5 patients underwent axillary surgery. No axillary FDG uptake was seen preoperatively although 3 of these 5 patients were histologically node-positive.

Increased uptake discrete from the primary site was seen in 2 cases. One patient was found to have an abnormal focus in the ipsilateral axillary tail, distant from the upper, inner quadrant primary tumour. In view of the clinically node-negative status at diagnosis, and in keeping with the patient's wishes to avoid unne-

cessary mastectomy or axillary surgery, no axillary procedure was performed. She remains clinically free of disease 16 months postoperatively. In a second patient, a tiny focus of increased uptake was noted in the contralateral chest wall, which, on radiological review was not felt to represent active disease. Isotope bone scan failed to demonstrate metastases. The patient remains well and asymptomatic nearly 18 months later.

3.3. Comparison between FDG PET and conventional imaging

2 of the 9 patients with residual invasive carcinoma had a complete radiological response on ultrasound and/or mammographic criteria. Both had residual thickening (MRD) clinically. The 6 individuals with a radiological partial response were found to have residual masses measuring 5–15 mm on repeat imaging. The only patient to achieve a complete pathological response underwent repeat ultrasound, mammogram and MRI preoperatively, revealing an equivocal focus of calcification measuring 7 mm. When localised and excised, no viable tumour was identified. FDG PET scans were negative in every case. 2 patients were not reassessed radiologically (Table 2).

4. Discussion

In this study, a single post-treatment FDG PET scan failed to predict complete pathological response amongst a group of good clinical responders to neoadjuvant chemotherapy.

Accurate and reliable identification of pathological complete responders before surgery offers the potential to avoid unnecessary operations in this subgroup of patients with an excellent prognosis, without jeopardising local control or long-term survival [19]. Currently, postoperative histological examination is required to confirm pCR. The ability to prospectively identify pCR using functional imaging techniques may allow surgery to be safely avoided.

Early monitoring of response using baseline and serial FDG PET scans is able to accurately differentiate pathological [16,17] and clinical [11,13–15] responders from non-responders, providing an opportunity to offer patients with non-responding tumours alternative therapies, and thereby spare them toxicity from ineffective chemotherapy. Using a threshold of 20% or more reduction in FDG uptake after a single cycle of chemotherapy, Smith and colleagues were able to accurately predict pathological responders with a sensitivity of 90% and specificity of 74% [16]. Schelling and colleagues, using a 55% decrease in standard FDG uptake below the baseline as a cut-off, correctly identified all pathological responders after the first cycle of chemotherapy with 88% accuracy, increasing to 91% after the second cycle [17]. Serial FDG PET scans must therefore be considered the current 'gold standard' imaging modality for early and accurate identification of pathological responders. However, amongst pathological 'responders' neither Smith and colleagues [16] nor Schelling and colleagues [17] were able to make the all-important distinction between those with scattered foci of residual carcinoma cells and those achieving a true pathological complete response.

The hypothesis of this study was to establish whether a single post-chemotherapy FDG PET scan in good clinical responders could reliably identify the subset of patients with complete histological regression of disease in whom surgery may be safely avoided. This important practical matter has not, to our knowledge, been previously addressed. In those patients in whom early clinical assessment shows a good response to therapy, the attractions of a single post-treatment scan are clear. Serial FDG PET studies are costly, time-consuming and involve significant radiation exposure.

Table 1
TNM stage, clinical and radiological response, PET scan findings, surgery and histopathology

Patient no.	TNM stage at diagnosis	Clinical response	Radiological response	PET scan findings	Surgery performed	Histopathology report
1	T3N0	MRD	PR	No uptake	WLE + ANC	G3T1(6 mm)N1(1/15)
2	T3N1	MRD	PR	No uptake	Mx + ANC	G1or2 T1(11 mm)N1 (3/23)
3	T2N0	CR	NIL	No uptake	Mx + ANC	G1T1(14 mm)N0 (0/12)
4	T2N0	MRD	CR	No uptake	WLE	GxT1(8 mm)Nx
5	T2N0	MRD	PR	No uptake	WLE	G2T1(20 mm)Nx
6	T2N0	CR	PR	Axillary focus; no breast uptake	WLE	GxT1(7 mm)Nx
7	T2N1	MRD	PR	Small focus R chest wall	WLE + ANC	G3T1(2 mm)N1(5/9)
8	T3N0	MRD	CR	No uptake	WLE + ANC	G2T1(15 mm)Nx + HG DCIS
9	T3N0	MRD	NIL	No uptake	WLE	G2T1(13 mm)N0 (0/16)
10	T2N0	CR	PR	No uptake	WLE	Pathological CR

TNM, tumour, node and metastases stage; R, chest wall, contralateral; MRD, minimal residual disease; CR, complete response; PR, partial response; WLE, wide local excision; Mx, mastectomy; ANC, axillary node clearance; Gx, grade not assessable; PET, positron emission tomography; DCIS, ductal carcinoma *in situ*; HG, high grade.

Table 2
Conventional radiology and FDG PET scan findings and histopathology

Patient no.	Radiological response	Post-chemo USS	Post-chemo mammo	PET scan findings	Histopathology report
1	PR	15 mm	Nil	No uptake	G3T1(6 mm)N1(1/15)
2	PR	Nil	6, 9, 10 mm	No uptake	G1or2 T1(11 mm)N1(3/23)
3	Nil	Nil	Nil	No uptake	G1T1(14 mm)N0(0/12)
4	CR	Nil	CR	No uptake	GxT1(8 mm)Nx
5	PR	14 mm	10 mm	No uptake	G2T1(20 mm)Nx
6	PR	5 mm	10 mm	Axillary focus; no breast uptake	GxT1(7 mm)Nx
7	PR	6 mm	Nil	Small focus R chest wall	G3T1(2 mm)N1(5/9)
8	CR	CR	CR	No uptake	G2T1(15 mm)Nx + HG DCIS
9	Nil	Nil	Nil	No uptake	G2T1(13 mm)N0(0/16)
10	PR[a]	7 mm	5 mm	No uptake	Pathological CR

USS, ultrasound; mammo, mammography; PR, partial response; CR, complete response; chemo, chemotherapy; FDG-PET, [^{18}F]-fluorodeoxyglucose positron emission tomography; HG DCIS, high grade ductal carcinoma *in situ*.

[a] Patient also underwent repeat post-chemotherapy magnetic resonance imaging (MRI) revealing a small focus <5 mm of indeterminate significance.

Despite the persistence of residual invasive carcinoma at the primary site on histological examination in 9 patients after chemotherapy, and the presence of metastatic axillary lymph nodes in 3 cases, FDG PET failed to detect disease at any of these sites in this study. The only pCR in this small group of clinical responders was also FDG negative. The failure of FDG PET to detect residual tumours measuring up to 20 mm in maximum dimension suggests its discriminatory power as a tool to predict pCR is inadequate for clinical use in this setting.

One explanation for the failure of FDG PET to detect residual tumour may be the sensitivity with which abnormal uptake can be reliably distinguished from background activity. A major limitation of FDG PET in breast cancer is its poor detection rate for small carcinomas. Avril and colleagues demonstrated that none of four pT1a and only one of eight pT1b tumours could be detected using FDG PET [20]. The current spatial resolution available on modern FDG PET scanners is usually 4–8 mm. In general, sensitivity is lower for lesions less than 1 cm diameter, although even very small tumour foci may be identified if their metabolic activity is sufficiently high. Consequently, FDG PET seems unable to differentiate between those with pathological MRD and pCR [17].

It is well documented that mammography is unable to differentiate viable metabolically active tumour from fibrotic scar tissue [21,22]. However, FDG PET can help distinguish viable tumour from the sequelae of treatment [23]. In this series, four of the nine tumours had microscopic foci of invasive cancer measuring 8 mm or less (smaller than the 8 mm resolution threshold of the scanner). It is not surprising, therefore, that these tumours could not be visualised, particularly if they had been rendered metabolically inactive by chemotherapy. However, the remaining five cancers ranged from 11 to 20 mm in size, exceeding the threshold of detection of the scanner, but did not produce abnormal foci of uptake. The precise explanation for this is unclear. The effects of chemotherapy on glucose metabolism are not fully understood and it may be that FDG avid cells are readily killed by chemotherapy, whilst residual clones of chemoresistant cells are less likely to take up FDG and are, therefore, not detectable after treatment. In addition, the relatively low dose (250 MBq) of FDG employed, which is strictly limited by UK regulations, may further reduce the sensitivity of the technique.

2 patients did have small, equivocal abnormal foci of uptake distant from the primary site that can not be satisfactorily explained. Limited restaging investigations failed to confirm the presence of metastases. Early and ongoing clinical follow-up, whilst clearly insufficient to exclude additional disease, has so far failed to offer any satisfactory interpretation for the abnormal uptake. The patients are aware of the uncertain clinical relevance of these PET scan findings.

Until the resolution of the scanners improves, or new functional imaging techniques or PET radiopharmaceuticals become available, postoperative histopathological examination will remain the only method able to accurately identify pCR. New imaging modalities for predicting pCR must therefore be validated against histopathological examination as the 'gold standard' for comparison.

The optimum role of FDG PET in predicting the response of breast cancers to neoadjuvant chemotherapy is still not clearly defined. There is strong, prospective validated evidence that an early reduction in uptake on FDG PET can identify pathological non-responders from and predict those unlikely to regress clinically. However, post-chemotherapy FDG PET images do not seem able to identify the small group of complete pathological responders in whom surgery may be safely avoided.

Acknowledgements

The Paul Strickland Scanner Centre kindly funded the FDG PET scans.

References

1. Fisher B, Brown A, Mamounas E, *et al*. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 1997, **15**, 2483–2493.
2. Powles TJ, Hickish TF, Makris A, *et al*. Randomized trial of chemoendocrine therapy started before or after surgery for treatment of primary breast cancer. *J Clin Oncol* 1995, **13**, 547–552.
3. Feldman LD, Hortobagyi GN, Buzdar AU, Ames FC, Blumenschein GR. Pathological assessment of response to induction chemotherapy in breast cancer. *Cancer Res* 1986, **46**, 2578–2581.
4. Honkoop AH, van Diest PJ, de Jong JS, *et al*. Prognostic role of clinical, pathological and biological characteristics in patients with locally advanced breast cancer. *Br J Cancer* 1998, **77**, 621–626.
5. Eltahir A, Heys SD, Hutcheon AW, *et al*. Treatment of large and locally advanced breast cancers using neoadjuvant chemotherapy. *Am J Surg* 1998, **175**, 127–132.
6. Machiavelli MR, Romero AO, Perez JE, *et al*. Prognostic significance of pathological response of primary tumor and metastatic axillary lymph nodes after neoadjuvant chemotherapy for locally advanced breast carcinoma. *Cancer J Sci Am* 1998, **4**, 125–131.
7. Fisher B, Bryant J, Wolmark N, *et al*. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 1998, **16**, 2672–2685.
8. Gazet JC, Coombes RC, Ford HT, *et al*. Assessment of the effect of pretreatment with neoadjuvant therapy on primary breast cancer. *Br J Cancer* 1996, **73**, 758–762.
9. Yang WT, Lam WW, Cheung H, Suen M, King WW, Metreweli C. Sonographic, magnetic resonance imaging, and mammographic assessments of preoperative size of breast cancer. *J Ultrasound Med* 1997, **16**, 791–797.
10. Smith IC, Welch AE, Chilcott F, Heys SD, Sharp P, Eremin O. Gamma emission imaging in the management of breast disorders. *Eur J Surg Oncol* 1998, **24**, 320–329.
11. Bassa P, Kim EE, Inoue T, *et al*. Evaluation of preoperative chemotherapy using PET with fluorine-18-fluorodeoxyglucose in breast cancer. *J Nucl Med* 1996, **37**, 931–938.
12. Wahl RL, Cody RL, Hutchins GD, Mudgett EE. Primary and metastatic breast carcinoma: initial clinical evaluation with PET with the radiolabeled glucose analogue 2-[F-18]-fluoro-2-deoxy-D-glucose. *Radiology* 1991, **179**, 765–770.
13. Wahl RL, Zasadny K, Helvie M, Hutchins GD, Weber B, Cody R. Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: initial evaluation. *J Clin Oncol* 1993, **11**, 2101–2111.
14. Bruce DM, Evans NT, Heys SD, *et al*. Positron emission tomography: 2-deoxy-2-[18F]-fluoro-D-glucose uptake in locally advanced breast cancers. *Eur J Surg Oncol* 1995, **21**, 280–283.
15. Jansson T, Westlin JE, Ahlstrom H, Lilja A, Langstrom B, Bergh J. Positron emission tomography studies in patients with locally advanced and/or metastatic breast cancer: a method for early therapy evaluation? *J Clin Oncol* 1995, **13**, 1470–1477.
16. Smith IC, Welch AE, Hutcheon AW, *et al*. Positron emission tomography using [(18)F]-fluorodeoxy-D-glucose to predict the pathologic response of breast cancer to primary chemotherapy. *J Clin Oncol* 2000, **18**, 1676–1688.
17. Schelling M, Avril N, Nahrig J, *et al*. Positron emission tomography using [(18)F] Fluorodeoxyglucose for monitoring primary chemotherapy in breast cancer. *J Clin Oncol* 2000, **18**, 1689–1695.
18. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
19. McMasters KM, Hunt KK. Neoadjuvant chemotherapy, locally advanced breast cancer, and quality of life [editorial; comment]. *J Clin Oncol* 1999, **17**, 441–444.
20. Avril N, Rose CA, Schelling M, *et al*. Breast imaging with positron emission tomography and fluorine-18 fluorodeoxyglucose: use and limitations [in process citation]. *J Clin Oncol* 2000, **18**, 3495–3502.
21. Vinnicombe SJ, MacVicar AD, Guy RL, *et al*. Primary breast cancer: mammographic changes after neoadjuvant chemotherapy, with pathologic correlation. *Radiology* 1996, **198**, 333–340.
22. Helvie MA, Joynt LK, Cody RL, Pierce LJ, Adler DD, Merajver SD. Locally advanced breast carcinoma: accuracy of mammography versus clinical examination in the prediction of residual disease after chemotherapy. *Radiology* 1996, **198**, 327–332.
23. Ahmad A, Barrington S, Maisey M, Rubens RD. Use of positron emission tomography in evaluation of brachial plexopathy in breast cancer patients. *Br J Cancer* 1999, **79**, 478–482.