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Jacobs Journal of Cancer Science and Research

Research Article

^{18}F-Fluorodeoxyglucose versus ^{18}F-Fluoromethylcholine Positron Emission Tomography in The Detection of Ductal Carcinoma *in situ* of The Breast

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Received: 07-30-2014

Accepted: 03-19-2015

Published: 03-26-2015

Abstract

Purpose: Poor sensitivity and accuracy have been reported using ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) in the detection of ductal carcinoma *in situ* (DCIS), yet no reference to the use of ^{18}F-fluoromethylcholine (FCH) PET can be identified in the *in situ* breast cancer literature. This study determined the tumour to background ratio for cases where both FDG and FCH-PET were used to detect DCIS.

Methods: Patients with newly diagnosed DCIS were recruited from the Breast Assessment Centre at a Western Australian teaching hospital. During the 16 month recruitment period, two patients consented to participate in the study. Each underwent a FDG-PET and a FCH-PET scan. The activity within the tumour was measured against the activity in the contralateral breast to obtain the tumour-to-background ratio.

Results: The DCIS lesions were visualised on the FDG and FCH-PET scans in both patients. The tumour to background ratios were 1.49:1 and 1.47:1 for the FDG-PET scan, compared to 1.49:1 and 1.20:1 for the FCH-PET scan. Both patients had comedo/solid unifocal DCIS, with intermediate and high nuclear grade.

Conclusions: FDG-PET gave a higher tumour to background ratio than FCH-PET in the detection of DCIS and hence appeared to be the preferred radiopharmaceutical for imaging and hand-held PET technology in *in situ* breast cancer management.

Keywords: ^{18}F-Fluorodeoxyglucose; ^{18}F-Fluoromethylcholine; Positron Emission Tomograph; Ductal Carcinoma in situ; Breast Cancer

Introduction

Ductal carcinoma *in situ* (DCIS) is defined as neoplastic cells confined to the mammary duct system of the breast. When these neoplastic cells spread outside the ducts into the tissue, the lesion becomes invasive ductal carcinoma. The reported sensitivity of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) in breast cancer varies from 25% to 96%, but is generally at the lower end for *in situ* and small size tumours [1,2]. Several other radiopharmaceuticals that target other tissue characteristics also demonstrate poor sensitivity and low accuracy [3,4]. However, the use of ^{18}F-fluoromethylcholine (FCH) for DCIS has never been investigated although its potential has been referenced in other literature and merited exploration [5]. This study aims to determine the tumour-to-background (TTB) ratio of FDG-PET and FCH-PET in detecting newly diagnosed DCIS.

Methods

Following ethics approval, patients with newly diagnosed DCIS referred to Royal Perth Hospital (RPH), Perth Western Australia, between September 2005 and December 2006, were invited to participate. Eligibility criteria were: (1) a newly diagnosed DCIS of the breast ≥10mm on mammogram; (2) planned to undergo surgical excision of DCIS in ≥7 days' time, with no neoadjuvent therapy prior to surgery; (3) aged 50-69 years; and (4) without a previous history of DCIS or invasive breast cancer. As per the clinical PET protocol, patients were excluded if they had uncontrolled diabetes mellitus, were pregnant at the time of PET scan or weighed ≥135kg.

The medical records of all patients were reviewed to assess their eligibility. Where consent was obtained, an appointment was made for the PET scans two weeks following biopsy, to allow sufficient time for any inflammatory response to the biopsy to subside, but scheduled before the planned surgical excision date. PET works by giving the patient an intravenous injection of a radiopharmaceutical labelled with a positron-emitting radionuclide that targets specific tissue characteristics, and scanning the patient using a PET scanner (camera). The camera is able to detect the high energy gamma emissions from the radiopharmaceutical caused by annihilation of the positrons in the tissues and generate a three-dimensional image of the region scanned. Areas which take up the radiopharmaceutical will show as a 'hot spot' on the image that can be measured to determine the TTB ratio. FDG is a positron-emitting analog of glucose, used because a higher metabolism of glucose is noted in tumour cells. FCH was selected because choline is a constituent of phosphatidylcholine, a major component of the phospholipid cell membrane. Malignant tumours have an increased intracellular choline pool and increased production and turn-over of cell membranes. The procedure for each is described in the results below. At the conclusion of each PET scan, visual analysis and semi-quantative reporting was performed. The activity in the lesion and in the normal contralateral breast was measured in order to calculate the TTB ratio. This is the measure of the radiopharmaceutical activity in the tumour compared to that in the contralateral breast (x:1). Each PET scan was independently read by two specialists credentialed for PET reporting. Findings were not released to the surgeon prior to surgery. The surgeon then removed the DCIS as planned. The pathologist documented the dimensions of the DCIS and other routine data were also collected.

Results

During the 16 month recruitment period 192 referred patients attending RPH were assessed. Only 8 patients (4.2%) satisfied the selection criteria and were invited to participate in the study. Six patients declined due to their perception of radiation dose (4) or family commitments (2). The following provides a case summary for the two consented patients.

Case 1

The first patient, aged 63 years, had a lesion measured mammographically as 25mm in the lower outer quadrant of the right breast. A stereotactic core biopsy showed high grade DCIS. The patient was not diabetic and had a body mass index of 29.9. On the day of the first PET scan, the patient was injected with 386MBq of FDG and rested supine for 43 minutes in a dimly lit stall. Both PET clinicians reported that the DCIS could be visualised on the PET images. The tumour activity ranged from 1095kBq (±332) to 1139 (±462) in the tumour and 705 (±233) to 794 (±128) in the contralateral breast, giving a TTB ratio of 1.49:1 (±0.08; 95% CI 0.74–2.25). The patient reported no adverse effect from the FDG-PET scan when she returned the following day for the FCH-PET scan. The patient was injected with 207MBq of FCH and imaged immediately. Whilst the DCIS could be visualised on the FCH-PET image, both PET clinicians reported that uptake was less intense than on the FDG-PET scan. The tumour activity ranged from 424 (±482) to 2590 (±123) in the tumour and 203 (±209) to 1150 (±132) in the contralateral breast, giving a TTB ratio of 1.49:1 (±0.70; 95% CI 0.24–3.21). The FDG and FCH-PET images are shown in Figure 1.

The patient underwent a wide local excision six days later. Histology confirmed a 15mm high grade DCIS with calcifications present. Cell type was classified as comedo/solid with comedo necrosis. The margin was 6mm from the superficial margin and greater than 10mm from all other margins. Tubal score was 3 and Nottingham category B. Table 1 provides a summary for this case. A subsequent review determined that no further excisions would be undertaken and that surgery was complete. As the peripheral margins were clear, mastectomy and chemotherapy were not recommended, while radiotherapy was

Characteristics		Case 1	Case 2
Age		63.6	56.3
Significant past history		Benign breast lesion, site unspecified	Nil
Breast		Lower outer quadrant of right	Lower outer quadrant of left
Surgery type		Wide local excision	Wide local excision
Margin identification		Inking	Inking
Histological type		Comedo/solid, pseudoangiomatous change	Comedo/solid, cribriform, with comedo necrosis present
Grade		High	Intermediate
Focality		Unifocal	Unifocal
Size mammography		25mm	30mm
Size excised specimen	Superior to inferior	85mm	45mm
	Medial to lateral	90mm	55mm
	Deep to superficial	20mm	15mm
Weight		121g	21g
Microscopic dimensions of tumour		15mm	35mm x 7mm x 5mm
Volume		~3375mm^3	1225mm^3
Invasive components		No	No
Tubular score		3	4
Nottingham category		B	A
Margins	Superficial	6mm	6mm
	Medial	>10mm	>10mm
	Deep	>10mm	1mm
	Lateral	>10mm	>10mm
	Inferior	>10mm	1mm
	Superior	>10mm	>10mm
Shaving		Superior margin 75x50x15mm. Benign changes	Not applicable
Tumour to background: FDG (± SD; 95% CI)		1.49:1 (±0.08; 0.74-2.25)	1.47:1 (±0.12; 0.88-2.57)
Tumour to background: FCH (± SD; 95% CI)		1.49:1 (±0.70; 0.24-3.21)	1.20:1 (±0.07; 0.54-1.87)

Table 1. Clinical, mammographical, pathological and positron emission tomography findings

limited to the breast and chest wall only but not the axillary nodes. The patient was followed for eight years using mammogram and clinical review with no new lesion, distortion or masses detected and no axillary lymphadenopathy. There were persistent nodular densities throughout both breasts which are stable when compared to previous scans.

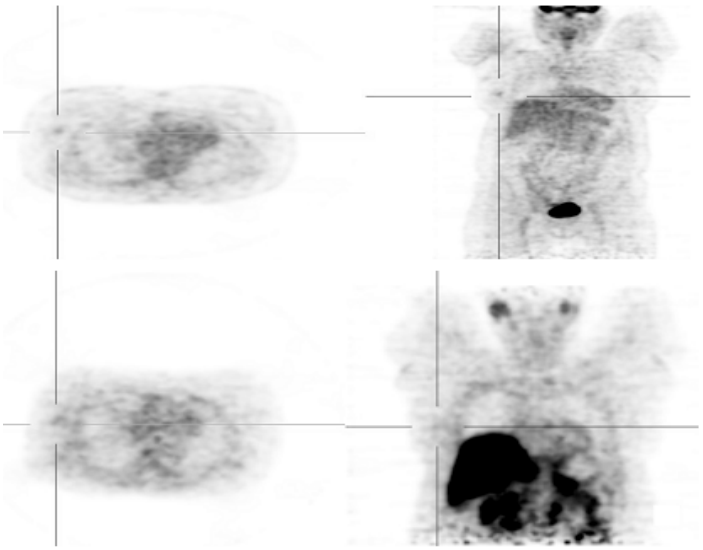

Figure 1. Case 1 ^{18}F-fluorodeoxyglucose (top) and ^{18}F-fluoromethylcholine (bottom) positron emission tomography images for ductal carcinoma in situ.

Case 2

The second patient, aged 56 years, had a lesion measured mammographically as 30mm in the lower outer quadrant of the left breast. A stereotactic core biopsy identified high grade DCIS. Although the tumour was classified as borderline for breast conservation therapy, the patient elected to do so with radiotherapy. The patient was not a diabetic and had a body mass index of 30.4. On the day of the first PET scan she was injected with 361MBq of FDG and rested supine for 42 minutes in a dimly lit stall. Both PET clinicians reported the DCIS could be visualised on the PET image but no other incidental findings were evident. The tumour activity ranged from 1004 (±316) to 1182 (±473) in the tumour and 725 (±306) to 759 (±379) in the contralateral breast, giving a TTB ratio of 1.47:1 (±0.12; 95% CI 0.88–2.57). On the following day, the patient reported no adverse effects and was injected with 202MBq of FCH and imaged immediately. Again the DCIS could be visualised on the FCH-PET image but it was not as intense as the FDG uptake. The tumour activity ranged from 517 (±208) to 589 (±209) in the tumour and 412 (±200) to 512 (±208) in the contralateral breast, giving a TTB ratio of 1.20:1 (±0.07; 95% CI 0.54–1.87). The FDG and FCH-PET images are shown in Figure 2.

The patient underwent a wide local excision two days post imaging. Histology confirmed a 35mm intermediate (not high) grade DCIS. Cell type was classified as comedo/solid, cribriform, with comedo necrosis present. The margin was 1mm from the deep margin, 1mm from the inferior margin and 6mm from the superficial margin. All other margins exceeded 10mm. Tubal score was 4 and Nottingham category A; see Table 1. At a subsequent review it was determined that no further excisions would be necessary; mastectomy and chemotherapy were not needed. Moreover, radiotherapy was recommended to the breast and chest wall only and not the axillary nodes. The patient was followed for eight years using mammogram and clinical review with no new lesion, distortion or masses detected and no axillary lymphadenopathy, indicating she was clinically stable.

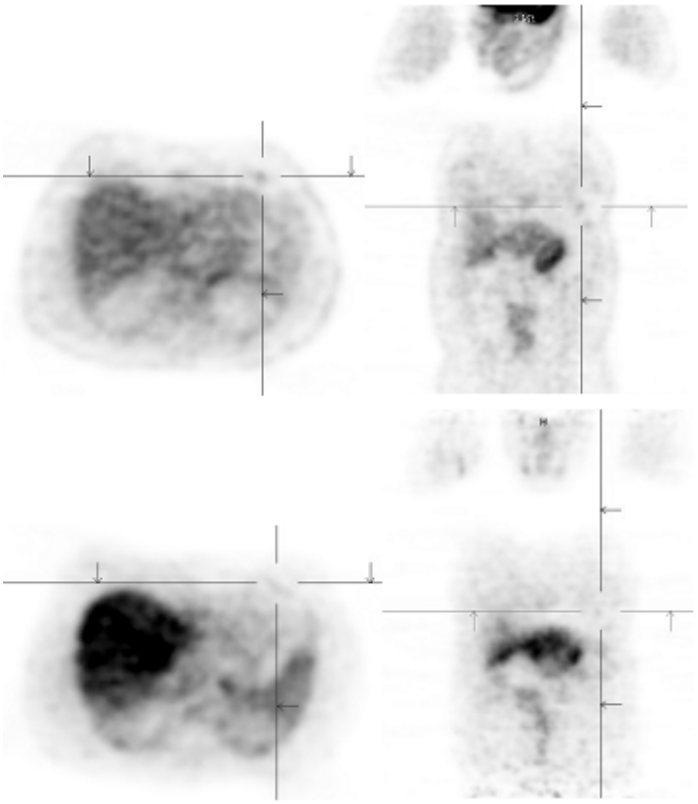

Figure 2. Case 2 ^{18}F-fluorodeoxyglucose (top) and ^{18}F-fluoromethylcholine (bottom) positron emission tomography images for ductal carcinoma in situ.

Discussion

The poor sensitivity of FDG-PET for the detection of DCIS has been reported [2], presumably due to the low spatial resolution of PET and the fact that DCIS has a decreased glycolytic activity and vascularity. Tumour size, histological type and grade, and hormone receptor status can all impact on the uptake of FDG in breast cancer [3]. A study found a significant difference in PET sensitivity between invasive ductal carcinoma (98%) and DCIS (60%), with higher uptake in the former [6]. More-

over, greater uptake of FDG was observed in ductal carcinoma than lobular or other histological types of breast cancer [3].

The use of FDG-PET in the diagnosis of breast cancer has been well reported, but this is not the case with FCH-PET. One identified case reported an incidental finding in a male during the examination of prostate cancer and another study used FCH-PET for metastatic tumour identification in a female who had undergone a mastectomy for invasive breast cancer [7,8]. Whilst FCH-PET is frequently used in the staging of prostate cancer, further exploration of the usefulness of this radiopharmaceutical merited exploration.

In our study, the DCIS for the two patients could be detected by both FDG and FCH-PET. Both cases had tumours >10mm, thus overcoming the limitation of small tumours previously reported for PET in DCIS. The nuclear grade was high and intermediate grade, respectively, and histological type was comedo/solid, which favoured the application of PET [3]. In both cases, the TTB ratio was higher for FDG than FCH-PET, albeit the difference was not statistically significant. However the confidence intervals for the TTB ratios in FDG-PET in both patients showed a greater lower-limit than in the FCH-PET TTB ratio. It suggested a better uptake of FDG by DCIS and is consistent with previous studies [6, 9]. Given FDG-PET performed better than FCH-PET and it is clinically more widely available than FCH, the use of FDG should be recommended.

Conclusion

Whilst both FDG and FCH-PET were able to accurately detect newly diagnosed DCIS, the clinical availability of FDG makes it the preferred radiopharmaceutical for DCIS imaging and handheld PET technology.

Acknowledgement

The authors wish to thank the staff at the Breast Assessment Centre at Royal Perth Hospital, Perth Western Australia, and in particular Dr Christobel Saunders, for their assistance in the recruitment of participants in this study. The authors would also like to thank the staff in the Department of Nuclear Medicine at Sir Charles Gairdner Hospital, Perth Western Australia, for their assistance with the PET scans and staff in the RAPID team in the Department of Medical Technology and Physics at Sir Charles Gairdner Hospital, Perth Western Australia, for the provision of the radiopharmaceuticals. Dr Butler-Henderson wishes to acknowledge Curtin University for the time to work on this research during her employment. No financial support is associated with this study.

Conflict of interest statement

No potential conflict of interest exists for listed authors.

Ethics approval

Ethical approval of the project was obtained from Human Research Ethics Committees of Curtin University (no. HR58/2005) and Royal Perth Hospital (no. 2005/068).

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