Role of 2-deoxy-2-[F-18] fluoro-D-glucose positron emission tomography in the management of bone and soft-tissue metastases

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We retrospectively reviewed 71 histopathologically-confirmed bone and soft-tissue metastases of unknown origin at presentation. In order to identify the site of the primary tumour all 71 cases were examined with conventional procedures, including CT, serum tumour markers, a plain radiograph, ultrasound examination and endoscopic examinations, and 24 of the 71 cases underwent 2-deoxy-2-[F-18] fluoro-D-glucose positron emission tomography (FDG-PET). This detected multiple bone metastases in nine patients and the primary site in 12 of the 24 cases; conventional studies revealed 16 primary tumours. There was no significant difference in sensitivity between FDG-PET and conventional studies.

The mean maximal standardised uptake value of the metastatic tumours was significantly higher than that of the primary tumours, which is likely to explain why FDG-PET did not provide better results. It was not superior to conventional procedures in the search for the primary site of bone and soft-tissue metastases; however, it seemed to be useful in the staging of malignancy.

Malignant tumours frequently metastasise to bone and pain, neurological disturbance or pathological fracture are often the first symptoms of malignancy. The site of the primary tumour is unknown in approximately 30% of patients who present with a bony metastasis.¹⁻³ The identification of the primary tumour is often costly, time-consuming and difficult, and the site of the primary tumour can remain elusive after thorough and repeated examinations. Carcinoma of unknown primary origin, defined as a histologically-confirmed metastatic tumour of unknown primary site even after detailed medical history, complete physical examinations, blood count and biochemistry, urinalysis and stool occult blood testing, chest radiography, mammography and computed tomography of the abdomen and pelvis, accounts for 3% to 5% of all new cancer patients.⁴⁻⁷ It is the fourth most common cause of cancer death in both men and women and its prognosis is less than one year.⁵ Consequently, any procedure that can help to localise the site of the primary tumour is of great value.

2-deoxy-2-[F-18] fluoro-D-glucose positron emission tomography (FDG-PET) can be expected to be of help in this regard because FDG, a PET tracer, is an analogue of glucose, the metabolism of which is up-regulated in malignant tumours.⁸ Several authors have reported the usefulness of FDG-PET in the

detection of unknown primary tumours, especially in patients with metastatic tumours around the neck. The site of the primary tumour was detected in 30% to 60% of carcinoma of unknown primary origin.⁹⁻¹³ However, these reports did not focus on tumours that metastasised to the musculoskeletal system. The purpose of this study was to evaluate the role of FDG-PET in staging and detecting the primary origin of bone and soft-tissue metastases.

Patients and Methods

Patients. Ethical approval for the study was granted from our institution and informed consent was obtained. We retrospectively reviewed 99 patients with histologically-proven metastases to bone and soft tissue treated in our hospital between 1997 and 2009. These did not include haematopoietic malignancies, such as malignant lymphoma of bone or multiple myeloma, because these usually have no apparent primary site other than in bone. We excluded 28 patients because the primary site of their tumour had already been identified and treated. The remaining 71 patients were studied. There were 49 men and 22 women with a mean age of 64.4 years (19 to 87). There were 67 with bone metastases and four with soft-tissue metastases. All 71 cases were examined with conventional procedures, including thoracic, abdominal and

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©2010 British Editorial Society
of Bone and Joint Surgery
doi:10.1302/0301-620X.92B3.
23131 \$2.00

J Bone Joint Surg [Br]
2010;92-B:419-23.

Received 22 July 2009;
Accepted after revision 17
November 2009

pelvic CT, serum tumour markers (carcinoembryonic antigen, α -fetoprotein, carbohydrate antigen 19-9, carbohydrate antigen 15-3, squamous cell carcinoma-related antigen, cancer antigen 125, prostate-specific antigen, a plain radiograph of the chest, ultrasound examination of the abdomen and endoscopic examinations. Whole body FDG-PET scanning was carried out on 24 of the 71 patients (16 men, 8 women, mean age 56.9 years (19 to 80)).

PET studies. Detailed methods for PET scanning have previously been published.¹⁴ Briefly, for this study, patients fasted for at least six hours before imaging and were investigated with a whole-body PET scanner, SET2400W (Shimazu Corp., Tokyo, Japan) and two PET/CT systems, Biograph 16 (Siemens, Forchheim, Germany), and Discovery ST 16 Lite (GE Yokokawa Medical Systems, Tokyo, Japan). These PET/CT systems have been used since 2007. A static image, obtained by a simultaneous emission-transmission method with a rotating external source (68 Ge), was initiated 50 minutes after the injection of 5 MBq/kg body-weight 18F-FDG synthesised by the cyclotron in Gunma University Hospital. Images were reconstructed using Ramp and Butterworth filters and regions of interest were drawn as described below. For semiquantitative analysis, functional images of the standardised uptake value were produced using attenuation-corrected trans-axial images, the injected dose of FDG, patient body-weight, and the cross-calibration factor between the PET scanner and dose calibrator. Regions of interest 1 cm in diameter were drawn on the standardised uptake value images over the area corresponding to the tumour to include the site of maximal FDG uptake. Standardised uptake value, a quantitative index of tissue uptake of 18F-FDG, was computed as follows:

Standardised uptake value = radioactive concentration in the tumour (MBq/kg)/injected dose (MBq)/body-weight (kg).

Statistical analysis. The differences in the rate of unknown primary tumours at the final diagnosis between all cases and the cases examined with FDG-PET were analysed using contingency tables and the chi-squared test. The paired *t*-test was used to examine differences in standardised uptake value between primary tumours and metastatic bone tumours. A *p*-value < 0.05 was considered significant.

Results

The conventional studies used to examine all 71 cases revealed the site of the primary in 54 patients (76.1%) which included the lung in 20, kidney in ten, prostate in nine, thyroid in five, liver in three, oesophagus in two, pancreas in one, rectum in one, colon in one, retroperitoneal melanoma in one and ovary in one. Post mortem studies identified two further sites (pancreas and rectum); however, the site of the primary tumour in the remaining 15 cases (21.1%) remained unknown (Table I).

FDG-PET was used in 24 of the 71 cases (Table II). In the early phase of the study, there was a relatively longer waiting

Table I. Characteristics of the subjects

	Number
Gender	
Male	49
Female	22
Primary site	
Lung	20
Kidney	10
Prostate	9
Thyroid	5
Liver	3
Oesophagus	2
Pancreas	2
Rectum	2
Colon	1
Melanoma	1
Ovary	1
Unknown	15
Mean age in yrs (range)	64.4 (19 to 87)
Site of biopsy	
Bone metastasis	
Clavicle	3
Humerus	5
Radius	1
Femur	13
Tibia	2
Fibula	1
Sternum	1
Rib	4
Cervical spine	3
Thoracic spine	15
Lumbar spine	5
Sacrum	7
Ilium	7
Soft-tissue metastasis	
Shoulder	1
Forearm	1
Thigh	1
Lumbar	1

time for a FDG-PET scan because only one PET scanner was available, however, after two FDG-PET/CT systems were installed in March 2007, most patients could undergo the examination within two weeks. The mean waiting time from a patient's first visit to undergoing FDG-PET was 18.5 days (2 to 76). FDG-PET detected multiple bone metastases in nine cases and a primary site in 12. In addition, four of the 12 cases showed extraskelatal FDG uptake not only in the primary lesion but also in other organs. Two of these four cases were also detected with abdominal CT and were considered to be thyroid metastases to the liver and mediastinum (case 10) and the colon (case 15), respectively. The other two cases were thought to be false positives because they did not grow or provoke any symptoms as the disease progressed. Conventional studies revealed 16 primary sites, including the lung in six, prostate in two, thyroid in two, kidney in two, rectum in one, colon in one, melanoma in one, and ovary in

Table II. Patients examined with FDG-PET

Patient No.	Gender	Age (yrs)	Site of biopsy	No. of metastatic bone lesions	Primary tumour	Days between first visit and FDG-PET	SUV [*] _{max} in the metastatic lesion	SUV _{max} in the primary lesion	Procedures that identify the primary tumour [†]	FDG positive sites except primary
1	F	67	Rib	Single	Lung	13	2.0	2.0	FDG-PET, biopsy	
2	M	44	Femur	Single	Lung	14	4.4	1.4	CT, FDG-PET	
3	M	37	Radius	Single	Lung	30	6.8	3.5	CT, FDG-PET, biopsy	
4	M	64	Ilium	Multiple	Lung	9	11.6	6.9	X-p, CT, FDG-PET	Nasal cavity
5	M	63	Ilium	Single	Lung	29	6.4	3.0	X-p, CT, FDG-PET	Colon
6	M	46	Femur	Single	Lung	14	9.1	3.2	CT, FDG-PET	
7	M	69	Cervical spine	Single	Prostate	2	3.4	NA [§]	Biopsy, PSA	
8	M	55	Ilium	Multiple	Prostate	16	12.3	8.5	FDG-PET, biopsy, PSA	
9	F	54	Humerus	Single	Thyroid	14	3.2	NA	Biopsy	
10	F	35	Sacrum	Multiple	Thyroid	19	4.2	6.0	FDG-PET, biopsy	Liver
11	M	19	Sacrum	Single	Kidney	21	8.3	NA	FDG-PET, biopsy	
12	M	80	Sacrum	Multiple	Kidney	8	5.1	NC	CT, FDG-PET	
13	M	55	Sacrum	Multiple	Rectum	20	NC [‡]	NA	CS, FDG-PET	
14	F	75	Thoracic spine	Single	Rectum	29	NC	9.4	Autopsy	
15	M	60	Humerus	Multiple	Colon	14	11.4	NC	CS, FDG-PET	Mediastinum
16	F	67	Humerus	Single	Melanoma	23	5.8	NA	CT, FDG-PET, biopsy	
17	F	59	Ischium	Single	Ovary	7	7.1	NA	CT, MRI, ultrasound	
18	M	43	Ilium	Single	Pancreas	9	6.8	NA	Autopsy	Liver, rectum
19	F	43	Ilium	Multiple	Unknown	5	3.4	NA		
20	F	72	Rib	Multiple	Unknown	22	4.9	NA		
21	M	68	Ischium	Single	Unknown	12	3.4	NA		
22	M	78	Femur	Single	Unknown	11	3.5	NA		
23	M	55	Thoracic spine	Single	Unknown	76	4.4	NA		
24	M	57	Thoracic spine	Multiple	Unknown	28	4.0	NA		

* SUV, standardised uptake value

† PSA, prostate specific antigen; CS, colonoscopy

‡ NC, not calculated

§ NA, not accumulated

Fig. 1

Mean maximal standardised uptake value of metastatic tumours and primary tumours were 7.65 (SD 3.50) and 5.26 (SD 3.00), respectively, in FDG-PET. The former was significantly higher than the latter ($p = 0.0125$).

primary site, but FDG-PET did not, included a very small thyroid tumour (0.7 cm × 0.5 cm × 0.5 cm), a renal cell carcinoma diagnosed as a normal kidney with FDG-PET, and ovary and prostate carcinoma. Meanwhile, FDG-PET could find no primary site in any case that conventional studies could not; in other words, no primary sites of carcinoma of unknown primary origin in metastatic bone tumours were detected with FDG-PET. In six of the 24 cases (25%) the primary site remained unknown even after conventional studies, post mortem examination and FDG-PET. There was no significant difference in the rate of unknown primary tumours at final diagnosis between all 71 cases and the 24 cases undergoing FDG-PET (21.1% *vs* 25.0%).

In order to investigate the difference in glucose metabolism between primary and metastatic bone tumours, standardised uptake values were analysed in 10 of 12 cases in which FDG-PET could detect both primary and metastatic tumours. They were not calculated in the remaining two cases. The mean maximal standardised uptake value of metastatic tumours was significantly higher than that of primary tumours (7.65 (2 to 12.3) *vs* 5.26 (1.4 to 9.4); $p = 0.0125$ paired *t*-test; Fig. 1).

Discussion

Previous reports have shown that the rate of detection of a primary site is 50% to 90% for bone metastases in which the primary site is unknown at first diagnosis.^{1-3,15} In the current

one, in the 24 cases, although there was no statistically significant difference in sensitivity between FDG-PET (50.0%, 12 of 24) and conventional studies (66.7%, 16 of 24). The four cases in which conventional studies revealed the pri-

study, conventional procedures detected the primary site in 76.1% of tumours that metastasised to bone or soft tissue. Several investigations are known to be useful in the search for the primary site of bone metastases. Thoracic and abdominal CT scans are highly recommended and prostate-specific antigen and protein electrophoresis are useful to diagnose carcinoma of the prostate and myeloma, respectively.^{1,16} FDG-PET has been used successfully for the detection of the primary site of carcinoma of unknown primary origin.⁹⁻¹³ In the expectation that FDG-PET would improve the detection rate of primary tumours, we examined patients with bone metastases with FDG-PET; unfortunately, however, it did not improve the rate of detection of primary sites.

There are several reasons why FDG-PET might not contribute to the search for the primary site of bone metastases. First, metastatic tumour had a significantly higher mean standardised uptake value than primary tumour suggesting that primary sites are difficult to identify with FDG-PET even if metastatic lesions are obvious. Experimentally, metastasised or invaded malignant tumours are known to be more aggressive than primary tumours¹⁶⁻¹⁸ and many authors have reported that the higher the pathological grade of skeletal tumour, the higher their standardised uptake value in FDG-PET.¹⁹⁻²² Taken together, the difference in aggressiveness between metastatic and primary tumours is reflected in the difference in FDG uptake between them.

Secondly, we performed FDG-PET relatively early, after a mean 18.6 days, which is possibly the cause of the low rate of detection of the primary tumour compared with previous reports.⁹⁻¹³ Most of our cases had a FDG-PET scan before the tumours were diagnosed as carcinoma of unknown primary origin, whereas most reports on the usefulness of FDG-PET in identifying a primary site focused on confirmed carcinoma of unknown primary origin. The process of diagnosing a tumour as the latter is as time-consuming as the process required to confirm its primary site and such a time-lag may have disadvantaged FDG-PET in its ability to identify the primary site. Pelosi et al¹³ reported five carcinomas of unknown primary origin in which the primary site was not found with FDG-PET, although subsequent conventional studies performed within three months after the PET scan detected the primary sites, indicating that the timing of the examination is an important factor in identifying the primary site of a tumour of unknown origin.

In our study, the sensitivity of FDG-PET in the identification of primary lesions was 50% (12 of 24), which was not significantly worse than that of conventional procedures (66.7%, 16 of 24); however, FDG accumulated not only in the primary lesion but also in other organs, including two false-positive cases and two other cases of metastasis. It often accumulates physiologically in the pharynx, intestines, urinary track, and the ovary at menstruation, which may sometimes mislead the physician into performing unnecessary investigations which yield false-positive results and make it difficult to differentiate positive accumulation from over-

lapping normal FDG deposits. The physician should evaluate the results of FDG-PET while considering the possibility that physiological FDG accumulation can be an obstacle in the search for primary sites of tumours of unknown origin.

With regard to the staging of malignancies, FDG-PET detected multiple metastases in nine patients and seemed to be very useful in our study as well as those from other authors.^{23,24} Accurate staging is needed to select the appropriate treatment for various malignant tumours and, from this point of view, FDG-PET is still indicated for the investigation of bone metastases from an unknown primary. It can also be used to evaluate the treatment effect by comparing standardised uptake values before and after treatment. Recently, we and other authors concluded that standardised uptake value in FDG-PET after chemotherapy could provide useful prognostic information in patients with primary malignant tumours of bone.²⁵⁻²⁸ Even if the primary lesion remains unknown, bone metastases causing severe pain or fracture should still be treated. In such a situation, the change of standardised uptake values in FDG-PET after treatment can be an important clue to evaluate the effect of that treatment.

It seemed difficult to decide when FDG-PET should be performed for patients with bone metastases. If staging is the main purpose, FDG-PET should be performed as soon as possible. Unfortunately, however, there may be a long wait for FDG-PET studies and it is relatively expensive, which may compel physicians to perform conventional studies first. Further studies, including a cost-benefit analysis, are also needed to decide the optimal timing of FDG-PET for patients with bone metastases.

We conclude that scanning is no better than more conventional procedures in the search for a primary site in patients with bone or soft-tissue metastases; it hardly contributes to the detection of the origin of a carcinoma of unknown primary origin in bone metastases. However, it has a role in the management of bone and soft-tissue metastases in the search for other metastases and in the evaluation of treatment.

This paper is supported in part by Grants-in-Aid for Young Scientists (B) 20791026 from the Ministry of Education, Culture, Sports, Science and Technology, Japanese Government.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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