

Comparison Between F-18-FDG Positron Emission Tomography and Histology for the Assessment of Tumor Necrosis Rates in Primary Osteosarcoma

Teng-Le Huang^{1,2}, Ren-Shyan Liu^{2,3}, Tain-Hsiung Chen^{2,4}, Winby York-Kwan Chen^{2,5},
Horng-Chaung Hsu^{1*}, Yen-Chih Hsu²

¹Department of Orthopedics, China Medical University and University Hospital, Taichung,

²National Yang-Ming University School of Medicine, and Departments of ³Nuclear Medicine,

⁴Orthopedics and Traumatology, and ⁵Pathology, Taipei Veterans General Hospital, Taipei, Taiwan, R.O.C.

Background: The purpose of this prospective study was to identify if F-18-fluorodeoxy-D-glucose positron emission tomography (F-18-FDG PET) was a reliable noninvasive surrogate of histologic response in determining the efficacy of neoadjuvant chemotherapy before surgical resection in primary osteosarcoma.

Methods: Between January 2003 and December 2003, 10 patients with primary osteosarcomas were examined using F-18-FDG PET before neoadjuvant chemotherapy and surgery. The mean age at the time of first intervention was 19 years (range, 4–47 years). Positive prognostic significance was defined as more than 90% tumor necrosis response following neoadjuvant chemotherapy. The parameters of FDG uptake were correlated with histologic findings. The intraclass correlation coefficient was used to validate the tumor necrosis rates determined by PET and histology.

Results: The tumor necrosis rate determined by PET was comparable with that determined histologically. The mean standardized uptake value before and following neoadjuvant chemotherapy were 8.2 and 4.4, respectively. The average tumor necrosis rate determined by PET was 22%. However, the mean tumor necrosis rate determined histologically was 54.5%. According to the intraclass correlation coefficient models, the intraclass correlation coefficient equaled 0. The relationship of tumor necrosis rates determined by F-18-FDG PET and histology seems to be statistically insignificant.

Conclusion: In this preliminary study, FDG PET did not seem to be a promising tool for evaluating the response of primary osteosarcoma to neoadjuvant chemotherapy. [*J Chin Med Assoc* 2006;69(8):372–376]

Key Words: fluorodeoxy-D-glucose, histology, neoadjuvant chemotherapy, positron emission tomography, sarcoma

Introduction

By reducing tumor vascularity, viability, and peritumor edema, neoadjuvant chemotherapy may facilitate limb-sparing resections and reduce the number of amputations. The combination of multiagent chemotherapy and surgery has dramatically improved the prognosis for patients with primary bone and soft tissue sarcoma. Neoadjuvant chemotherapy also allows histologic assessment of the tumor response. Furthermore, neoadjuvant chemotherapy permits the design of reconstruction method after surgical resection.

Short-term assessment of tumor response generally involves the sequential measurement of tumor size either clinically or by imaging. These assessments may not always reflect the quantity of residual viable tumor cells because of edema, hemorrhage, and necrosis.^{1,2} Also, because osseous lesions, such as osteosarcoma and Ewing's sarcoma, frequently do not change in size in response to chemotherapy, radiographic evaluation of response by computed tomography (CT) or magnetic resonance imaging (MRI) does not discriminate between responding and nonresponding tumors.³ F-18-fluorodeoxy-D-glucose

*Correspondence to: Dr Horng-Chaung Hsu, Department of Orthopedics, China Medical University and University Hospital, 2, Yuh-Der Road, Taichung 404, Taiwan, R.O.C.

E-mail: tenglehuang@yahoo.com.tw • Received: January 6, 2006 • Accepted: April 6, 2006

positron emission tomography (F-18-FDG PET) is an alternative imaging modality. PET imaging differs considerably from conventional imaging modalities such as MRI, CT, and ultrasonography because it quantifies the functional activity of tissue by using a labeled glucose analog, FDG, but not its morphologic abnormality.⁴ Tumor tissues generally show enhanced glycolysis,⁵ and elevated uptake of FDG determined by PET has been reported in malignant mesenchymal tumors in a limited number of studies.^{6,7} FDG-PET has been proposed as a diagnostic tool for discriminating benign and malignant soft tissue and osseous lesions,⁸⁻¹¹ for the grading of sarcomas,^{10,12} and for the detection of local recurrence.¹³

The aim of the current study was to evaluate the reliability of FDG-PET in the assessment of neoadjuvant chemotherapy response in osteosarcoma patients by correlation with histology.

Methods

Patients

This prospective study was conducted at the Department of Orthopedics and Traumatology, Department of Nuclear Medicine, and Department of Pathology, Taipei Veterans General Hospital. Patients attending our outpatient department who met all the following criteria were included:

1. Biopsy-proven primary osteosarcoma;
2. Newly diagnosed, had not been treated at other hospitals;
3. Solitary lesion; no other bone or lung metastasis;
4. Allowed and planned to be treated with neoadjuvant chemotherapy before the definite tumor resection surgery;
5. No pathologic fracture.

The study was approved by the hospital review board.

Procedure

All patients underwent PET imaging twice with FDG: first, in the week before initiation of neoadjuvant chemotherapy; second, in the week after the completion of neoadjuvant chemotherapy. FDG uptake was quantitated using average standardized uptake value (SUV). All data recording FDG uptake were obtained twice from the 2 PET images. Positive prognostic significance was defined as more than 90% tumor necrosis response following neoadjuvant chemotherapy. The neoadjuvant chemotherapy regimens employed contained high-dose methotrexate, doxorubicin, cisplatin, and ifosfamide, and they generally followed the protocols employed by the Pediatric Oncology Group.¹⁴

All data were subjected to Pearson's correlation coefficient model analysis. SUV, a quantitative index of tissue uptake of FDG, was computed as follows:

$$\text{SUV} = \frac{\text{PET activity}}{\text{Injected dose/body weight}}$$

The tumor necrosis rate was quantified using tumor-to-nontumor ratios from PET-2 imaging. Thus, a region of interest was drawn to follow the contours of the elevated FDG activity in the axial slice with maximum tumor activity. An identical region of interest representing background activity was placed around comparable unaffected tissue on the contralateral side. The PET-2 scans were sliced into pixels and compared with the background activity to quantify the tumor-to-nontumor ratios. The percentage of nontumor area was defined as the tumor necrosis rate.

Comparison between tumor necrosis rates, PET and histology was made with intraclass correlation coefficient model.

PET scanning

Patients fasted for more than 2 hours before the procedure. They then signed informed consent forms for the procedure and received 7–10 mCi of FDG i.v. over 2 minutes. After a 45-minute equilibration period during which the patient was at rest, attenuation-corrected emission images over the tumor were acquired on a Siemens EXACT HR+PET scanner. Typically, the tumor extent was captured in 2 adjoining 15 cm fields of view. Reconstructed attenuation-corrected images were viewed in the transaxial planes and hand drawn regions of interest were placed over the tumor for calculation of the SUV. Regions of interest were drawn to follow the contours of the elevated FDG activity as compared to normal tissue, contralateral to the tumor site (Figures 1 and 2). The SUV was generated by the tomographic software as the ratio mentioned above.

Histologic response to neoadjuvant chemotherapy

Response to chemotherapy was assessed in the postchemotherapeutic surgical specimens according to the well-established and highly reproducible classification of Salzer-Kuntschik (grades I to VI).^{15,16} The percentage of vital areas in relation to the entire tumor area was determined by an experienced pathologist who examined the slices of the resected specimens independently of clinical or imaging findings. The area of tumor necrosis was determined by examining the largest histologic section. A good response to chemotherapy was defined as less than 10% residual

vital tumor area; 10% vital tumor area or more indicated a poor response.

Statistical analysis

Comparison between tumor necrosis rates calculated by different modalities, PET and histology, was made with the intraclass correlation coefficient model. The intraclass correlation coefficient, ρ , ranges from 0 to 1, with $\rho=0$ indicating no correlation at all and $\rho=1$ indicating perfect correlation.

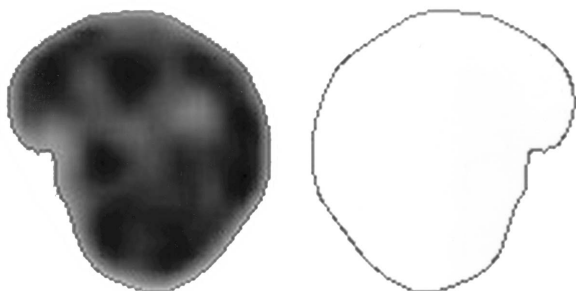


Figure 1. The F18-FDG PET study before neoadjuvant chemotherapy was performed on a 17-year-old boy (Case 4) with osteosarcoma on his right distal femur.

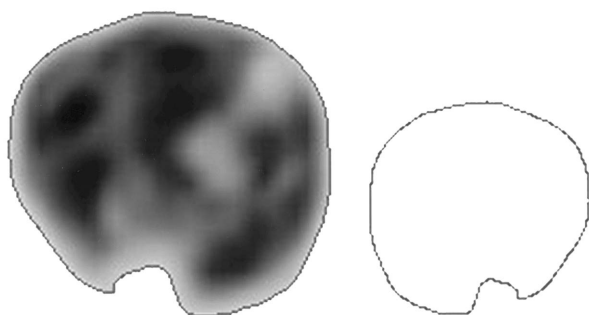


Figure 2. F18-FDG PET study after neoadjuvant chemotherapy in the same patient (Case 4).

Results

Between January and December 2003, 10 patients with primary osteosarcomas were examined using FDG PET before neoadjuvant chemotherapy and surgery. The mean age at the time of first intervention was 19 years (range, 4–47 years). All patients underwent PET imaging twice with FDG: before initiation and after the completion of neoadjuvant chemotherapy.

Eight patients were male, and 2 were female. Four cases involved the distal femurs, 3 proximal tibias, 1 proximal humerus, 1 proximal fibula, and 1 involved the proximal femur. Regarding histology type, 7 were osteoblastic, 1 was fibroblastic, 1 was chondroblastic, and 1 was of mixed type. The tumor necrosis rate determined by FDG PET was compared with that determined histologically. The mean SUV value before neoadjuvant chemotherapy was 8.2 (1.4–13.6), and the mean SUV value following neoadjuvant chemotherapy was 4.4 (1.7–9.6). The average tumor necrosis rates determined by PET and histology were 22% (11–39%) and 54.5% (17.5–100%), respectively (Table 1). According to the intraclass correlation coefficient models, the ρ value was 0 (Table 2). The relationship of tumor necrosis rate between PET and histology seemed to be statistically insignificant.

Discussion

The histologic response to neoadjuvant chemotherapy is an important prognostic indicator of disease-free survival following treatment of primary musculoskeletal malignant neoplasms, in particular osteogenic sarcoma and Ewing's sarcoma.^{1,2,17,18} Furthermore, we also used the histologic response following neoadjuvant chemotherapy to guide the selection of alternative

Table 1. Details of the 10 patients in the current study

Patient	Age (yr)	Sex	Tumor site	SUV1	SUV2	Necrosis rate	
						PET (%)	Histology (%)
1	47	F	Proximal femur	7.3	5.0	26	38
2	15	M	Proximal tibia	11.7	9.6	30	50
3	18	M	Proximal tibia	9.3	3.2	20	100
4	17	M	Distal femur	12.6	5.4	20	33
5	4	M	Proximal tibia	9.4	6.7	24	15
6	24	M	Proximal fibular	2.7	2.5	16	75
7	19	M	Distal femur	13.6	2.2	17	100
8	5	M	Proximal humerus	1.4	1.7	11	66
9	26	M	Distal femur	9.0	4.8	17	17.5
10	15	F	Distal femur	5.4	2.5	39	50

SUV = standardized uptake value; PET = positron emission tomography.

Table 2. Comparison between tumor necrosis rates by PET and histology

	Necrosis rate	
	PET	Histology
Number	10	10
Mean \pm SD	22.0 \pm 8.1	54.5 \pm 30.5
Median (range)	20 (11, 39)	50 (15, 100)
Intraclass correlation coefficient (ρ)	0	

PET = positron emission tomography.

postoperative chemotherapy in an attempt to improve event-free survival rate.^{17,19,20} Less than 90% tumor necrosis response following presurgical treatment denotes a poor response and is associated with a less favorable outcome.¹ Given the surgical and prognostic implication of adequate histologic response, a reliable noninvasive surrogate marker of histologic response would be valuable in determining the efficacy of neoadjuvant chemotherapy before surgical resection.

Recently, PET was shown to be valuable in assessing the therapeutic response in various malignant conditions.^{21,22} Additionally, the ability of PET to detect and grade musculoskeletal sarcomas and their recurrence has been shown in several studies.^{4,6,7} Nieweg et al⁷ described the absence of FDG uptake within a treated soft tissue sarcoma, which correlated histologically with tumor necrosis. Shulkin et al²³ reported decreasing FDG accumulation in a responding Ewing's sarcoma during chemotherapy and radiation. The potential role of FDG PET in monitoring response to therapy has been shown by Jones et al²⁴ in a small, heterogeneous group of patients with soft tissue and bone tumors. Another study from the Netherlands showed substantial decreases in the glucose metabolism of soft tissue sarcomas, with a pathologically complete response after a hyperthermic isolated limb perfusion.²⁵

It is anticipated that tumor activity will be decreased after neoadjuvant chemotherapy. Our results demonstrated the fact that, of our 10 patients, in only 1 (patient 8) was the SUV2 larger than SUV1. We attribute this exception to excess inflammatory process that could also increase glucose uptake. This may occur in some patients after chemotherapy. With regard to the tumor necrosis rate, the necrosis rates calculated by PET were smaller than those by histology in 9 of 10 patients. We ascribe this to PET tending to have a false-positive evaluation, which is supported by other studies.^{26,27}

Our results showed that the correlation between PET and histology in determining the tumor necrosis

rate was statistically insignificant. We attribute this to 2 reasons: the first being the relatively small case number and the other is that the regions of interest might be positioned in a different plane. Conventionally, our pathologists examined the largest histologic section for calculating the tumor necrosis rate. However, the selected plane might be transaxial, coronal, or sagittal and might, frequently, not be the same plane as that used by PET. These 2 factors also contribute to the major drawbacks of the current study.

In the present study, we used the intraclass correlation coefficient model to verify the relationship of the necrosis rates determined by 2 different methods, histology and PDG PET. However, the ρ value was 0. The relationship of tumor necrosis rate between FDG PET and histology seemed to be statistically insignificant. Because the case numbers of this preliminary study were relatively small, they may be insufficient to make such a conclusion. We look forward to larger series to evaluate the clinical significance of FDG PET in osteosarcoma patients.

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