
Noninvasive Grading of Musculoskeletal Tumors Using PET

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Twenty-five patients with mass lesions involving the musculoskeletal system were studied with positron emission tomography (PET) in order to determine if a relationship exists between histologic grade and tumor uptake of [fluorine-18] 2-deoxy-2-fluoro-D-glucose (FDG). There were 6 benign lesions and 19 malignant lesions of various grades. A high correlation ($Rho = 0.83$) was found between the normalized uptake of tracer and the NCI grade. The high-grade malignancies had significantly greater ($p = 0.0091$) uptake of FDG than the combination of benign lesions and low-grade malignancies. All lesions with a normalized uptake value of 1.6 or greater were high-grade, while all lesions less than 1.6 represented either benign tumors or low grade malignancies. This strong relationship between FDG uptake and grade among neoplasms from a wide variety of cell types within a single organ system suggests that the technique may be useful in predicting grade even when the cell type is unknown.

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Since Som et al. (1) first proposed the use of [fluorine-18] 2-deoxy-2-fluoro-D-glucose (FDG) as a tumor imaging agent, a variety of different neoplasms have been imaged using this radiopharmaceutical in conjunction with positron emission tomography (PET) (2-12). The ability of PET with FDG to non-invasively grade neoplasms was first demonstrated with cerebral gliomas (13). Two small series have suggested a similar relationship exists between FDG uptake and histological grade in tumors of the musculoskeletal system (9,11). The purpose of this research was to study the relationship of FDG uptake and tumor grade in a broad variety of neoplasms involving the musculoskeletal system.

MATERIALS AND METHODS

Patients

Patients referred to the Department of Orthopaedics at University Hospitals of Cleveland for known or suspected malignan-

cies of the musculoskeletal system were considered for enrollment in this study. The selection criteria consisted of age greater than or equal to 18 yr, a tumor of at least 2 cm in diameter, known histologic diagnosis or planned biopsy and, the ability and willingness to complete a PET scan. Following the approval of our Institutional Review Board for Human Subject Experimentation and the obtaining of informed consent, 25 patients were studied. All patients received an anatomical, cross-sectional imaging study, either CT or MR, as part of their clinical evaluation. Malignant lesions were classified using the NCI grading system (14). Benign lesions were assigned a grade of 0 to distinguish them from malignant tumors in an ordinal fashion.

Scanning Technique

Studies were performed using the Super PETT 3000 (PETT Electronics, St. Louis, MO), a commercially available PET scanner. After obtaining an attenuation scan using a $^{68}Ge/^{68}Ga$ rotating sector source, 110-410 MBq (3-11 mCi) of FDG was administered intravenously. The injection syringe was counted immediately before and after injection in order to determine the net activity administered. Following a 15 min delay, a 1-hr list mode time-of-flight acquisition was performed. The scanner was operated in low-resolution mode, producing seven contiguous slices, each 14 mm thick, spanning 9.8 cm in the axial dimension. Axial resolution of the instrument varied between 11 and 13 mm depending on location. The in-plane resolution of the scanner is 4.2 mm. Quantitative images of average activity per cc were reconstructed using a two-dimensional sigma filter with a 12-mm cut off frequency supplied by the manufacturer.

Data Analysis

After comparing the PET images with the patients' CT and/or MR scans, regions of interest (ROIs) were drawn around each tumor by an experienced nuclear physician (LPA). Though clinical information was available, the results of biopsy and/or surgery were not known to him at the time of region drawing. Areas of decreased or absent tracer uptake in the center of the tumor, when present, were excluded from the ROI. If the tumor could not be identified on the PET scan, an ROI was drawn in its expected location. A background ROI was then drawn as a mirror image of the original on the contralateral extremity or body part for the purpose of calculating a tumor-to-background ratio (TBR). The average activity within each tumor was subsequently corrected for radioactive decay and normalized for the dose administered and the patient's weight to yield the average dose uptake ratio (DUR) according to the formula $DUR = activity \times weight/dose$ (15).

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Statistical Methods

Statistics were calculated using a commercially available statistics package (StatView 512+, Brain Power, Inc., Calabasas, CA). Spearman's Rho rank-order correlation coefficient, corrected for ties, was conducted to study the strength of the relationship between tumor grade and the TBR and DUR, respectively. Student's t-Test (two-tailed) was used to look for significant differences between tumor grades. A significance level of 0.01 was set to control for multiple comparisons.

RESULTS

The patients ranged in age from 18 to 86 yr (49 ± 20). There were six benign tumors, three Grade 1 tumors, six Grade 2 tumors, and ten Grade 3 tumors. All 19 malignancies and three out of six benign lesions were easily visualized with PET as areas of increased FDG accumulation. Figures 1 and 2 show examples of high- and low-grade malignancies, respectively. Note that while there is a marked increase in tumor uptake of FDG in the malignant tumor, a Grade 2 osteosarcoma, the low-grade lesion, a liposarcoma, showed only mildly increased uptake. Figure 3 illustrates one of the most FDG-avid benign lesions, a nonossifying fibroma. The amount of FDG accumulation within this tumor is similar to that of the low-grade malignancies in our series, possibly because of the abundant histiocytic reaction found during histological examination. There were nine lesions involving bone including a rare case of intraosseous pigmented villonodular synovitis (PVNS) and 16 tumors involving soft tissue. The results are summarized in Table 1. In the case of the patient with the abscess (MD), the large, fluid-filled areas on CT were seen to correspond to regions of diminished or absent FDG uptake on PET (DUR = 0.61), and so only the relative thin wall of the abscess was included in the ROI.

Both the TBR and the DUR were positively correlated with tumor grade, although the relationship was stronger

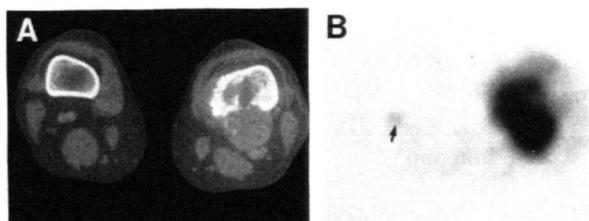


FIGURE 1. A 55-yr-old woman (IB) with a high-grade (Grade 2) osteosarcoma of the distal left femur. (A) A CT scan through the level of the tumor demonstrates destruction of the marrow space and of the posterior margin of the cortex with extension of the mass posteriorly. There is penetration of the mass through the medial aspect of the cortex as well. (B) A PET scan through approximately the same level shows markedly increased FDG accumulation in a pattern that corresponds to the extent of tumor involvement by CT. Uptake within the mass is mildly nonuniform. The contralateral extremity is only faintly visualized due to its relatively low uptake. A small amount of intravascular activity is identified in the right popliteal vessels (arrow).

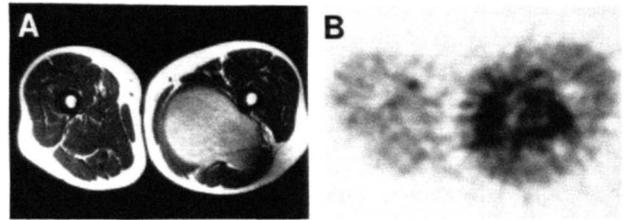


FIGURE 2. A 58-yr-old man (WC) with a low-grade myxoid liposarcoma. (A) Spin density weighted MR images (TR/TE = 2500/25) demonstrate a large, posteromedial mass arising from the adductor magnus with signal intensity intermediate between that of fat and muscle. (B) The PET scan shows mildly increased but nonuniform FDG uptake throughout the lesion. Other levels showed a large, central area of absent tracer accumulation that was felt to represent a cystic or necrotic area and was excluded from the ROI.

for the DUR (Rho = 0.83) than for the TBR (Rho = 0.54). There was a highly significant difference ($p = 0.0008$) in DUR between benign lesions and Grade 2 malignancies. Although Grade 1 and Grade 3 malignancies had higher mean DURs than the benign tumors, these differences were not significant ($p = 0.30$ and 0.022 respectively). For the Grade 3 tumors, this lack of significance could be attributed to a single patient (HT), whose malignancy was so FDG avid that the standard deviation of this group was markedly elevated. If this patient is excluded from our analysis, the small drop in this group's mean (from 4.57 to 3.59) is more than offset by a relatively larger drop in the standard deviation (from 3.29 to 1.24), resulting in a highly significant difference between the benign tumors and the remaining nine Grade 3 lesions ($p = 0.0004$). The average DUR for the malignant neoplasms (3.4 ± 2.7) was greater than the DUR for the benign lesions (1.0 ± 0.53), although this difference was not significant ($p = 0.042$). By excluding the same outlying patient, the small drop in DUR and the relatively larger drop in standard deviation (2.88 ± 1.23) again resulted in a highly significant difference ($p = 0.0019$) between the benign and malignant tumors.

A great deal of overlap existed between the benign and the Grade 1 tumors as well as between the Grade 2 and Grade 3 tumors. There was, however, complete separation

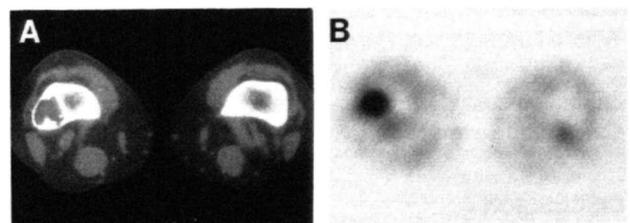


FIGURE 3. An 18-yr-old female (CC) with a recently fractured nonossifying fibroma of the distal femur. (A) The CT scan shows a well-circumscribed lesion involving the lateral aspect of the distal femoral metaphysis. (B) The PET scan demonstrates moderately increased FDG accumulation in the same location.

TABLE 1
Summary of Data

Patient	Diagnosis	Grade	TBR	DUR
DL	Pigmented villonodular synovitis	0	1.29	0.65
CC	Non-ossifying fibroma	0	4.50	1.47
GL	Synovial cyst	0	1.05	0.73
MD	Abscess	0	1.70	1.52
FK	Fibroma	0	1.92	1.47
LA	Pigmented villonodular synovitis	0	0.46	0.31
	mean ± s.d.	0	1.82 ± 1.41	1.03 ± 0.52
WC	Liposarcoma	1	2.05	1.41
SB	Liposarcoma	1	1.92	1.33
EH	Liposarcoma	1	2.74	1.40
	mean ± s.d.	1	2.24 ± 0.44	1.38 ± 0.04
MR	Angiosarcoma	2	2.39	1.93
RP	Malignant fibrous histiocytoma	2	3.30	3.48
EE	Liposarcoma	2	4.02	2.28
IB	Osteosarcoma	2	6.43	2.92
JN	Neurosarcoma	2	1.35	2.73
SW	Osteosarcoma	2	4.69	2.00
	mean ± s.d.	2	3.70 ± 0.179	2.56 ± 0.60
AB	Liposarcoma	3	3.34	2.62
RK	Ewing's sarcoma	3	7.07	4.90
DM	Neurosarcoma	3	4.74	5.46
ID	Malignant fibrous histiocytoma	3	3.27	4.76
JW	Malignant fibrous histiocytoma	3	11.5	3.43
CB	Synovial sarcoma	3	2.39	1.67
GH	Synovial sarcoma	3	3.28	3.21
NP	Chondrosarcoma	3	1.28	2.65
RS	Malignant fibrous histiocytoma	3	2.28	3.60
HT	Lymphoma of bone	3	12.2	13.2
	mean ± s.d.	3	5.14 ± 3.87	4.57 ± 3.29

between the high-grade tumors (Grades 2 and 3) and the benign and Grade 1 tumors taken in combination. All high-grade malignancies had DURs > 1.6, while all benign and all Grade 1 tumors had DUR < 1.6. The DURs for these two groups were significantly different ($p = 0.0091$). Using a DUR of 1.0 as an arbitrary cut off, e.g., predicting that all tumors with DURs less than 1.0 are benign and all tumors greater than 1.0 are malignant, the sensitivity of PET for correctly diagnosing malignancy was 100% with a specificity of 50% and an overall accuracy of 88%. With a cutoff of 1.6, the sensitivity fell to 81%, while the specificity rises to 100%. Using the TBR, no significant differences could be found between any of the tumor grades alone or in combination.

DISCUSSION

As glucose is metabolized or stored as glycogen, more glucose must be transported intracellularly. Since the active transport mechanism can not distinguish between glucose and its analogue, FDG, the amount of labeled

tracer transported intracellularly is greater in cells with a high metabolic rate. While both glucose and FDG can be phosphorylated by hexokinase to glucose-6-phosphate and FDG-6-phosphate respectively, only glucose-6-phosphate can be stored as glycogen or undergo aerobic or anaerobic glycolysis. The only way that the labeled FDG-6-phosphate can leave the cell is for it to be dephosphorylated by glucose-6-phosphatase. FDG localization within tissue is therefore a function of the rate of glucose utilization and the ratio of the enzymes hexokinase and glucose-6-phosphatase (16). Since more aggressive malignancies tend to have higher rates of glycolysis and higher ratios of these enzymes than less aggressive malignancies and benign lesions (17-20), the degree of FDG uptake should be positively correlated with grade.

Within tumors of a single cell type, researchers have demonstrated a positive correlation between grade and FDG uptake (11,13). Unfortunately, the cell type of a neoplasm cannot always be predicted using noninvasive techniques and once a biopsy has been performed, there may no longer be a need to noninvasively determine the

grade. If a noninvasive grading technique can be shown to work across a variety of histologies afflicting the same organ system, then it may have greater utility. Accurate determination of histologic grade could, in some cases, alter the patient's management. If a lesion is determined to be benign, biopsy may not be needed. Biopsy of malignant lesions can cause tumor seeding, in addition to infection, hemorrhage, and wound problems. (21,22). If a noninvasive test such as PET can document malignancy, an en bloc resection without initial biopsy would eliminate these potential complications.

In our study, a strong correlation ($Rho = 0.83$) was found between tumor grade and DUR, despite the inclusion of neoplasms originating from many different types of tissues. This suggests that PET may give useful information about neoplasm grade noninvasively even when the cell type of the lesion is unknown. All malignancies and most benign tumors were easily identified as areas of increased tracer uptake. PET was able to accurately distinguish between high-grade malignancies and benign or low-grade tumors. Of 25 musculoskeletal tumors examined with PET, all lesions with a DUR greater than 1.6 were high-grade malignancies and all tumors with DURs less than 1.0 were benign. Lesions with DURs between these two values were either benign or represented low-grade malignancies. Of the three benign lesions with DURs above 1.0, the abscess wall and the nonossifying fibroma had high numbers of histiocytes present. Perhaps inflammatory cells can result in a mild elevation of FDG uptake when compared to benign tissue. The lack of significance between the Grade 2 and Grade 3 lesions may be explained at least in part by the larger degree of necrosis present in Grade 3 tumors (14). The relatively weaker correlation of TBR to grade can be explained by the variability in FDG uptake between different tissues within the same patient. Muscle was more avid for this tracer than fat, causing differences in the denominator of the TBR depending on the tumor location.

Our data suggest that the normalized uptake of FDG by musculoskeletal tumors can be used to separate lesions into three groups: low uptake tumors that are likely to be benign, high uptake tumors that are likely malignant, and lesions that fall in between these two groups and may be either malignant or benign. Since all three malignancies that fell into this range were liposarcomas, we cannot be sure whether their relatively low level of FDG uptake was due just to their low grade or was also a function of their cell type. Certainly more experience is necessary before PET scanning can be used to determine the need for biopsy or en bloc resection. PET may be useful in the presurgical evaluation of patients in other ways. An FDG study can guide the surgeon to the sites of the most metabolically active tissue for biopsy (11). This is potentially most helpful in high-grade tumors with large, necrotic areas or in lesions in which there is regional heterogeneity where high-grade and low-grade or even benign tissue exists

within the same mass. When coupled with a labeled water or ammonia study, PET may also yield useful information about tumor perfusion (12). While this research was performed on neoplasms involving a single organ system, the results may eventually be found to generalize to tumors of other origins. As techniques for whole-body imaging (23) become more readily available, noninvasive grading of tumor masses can be coupled with a search for distant metastases, further increasing the utility of PET in the preoperative evaluation of mass lesions.

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REFERENCES

- Som P, Atkins HL, Bandyopadhyay D, et al. A Fluorinated glucose analog, 2-fluoro-2-glucose (F-18): nontoxic tracer for rapid tumor detection. *J Nucl Med* 1980;21:670-675.
- Di Chiro G, De LaPaz RL, Brooks RA, et al. Glucose utilization of cerebral gliomas measured by [¹⁸F]fluorodeoxyglucose and positron emission tomography. *Neurology* 1982;32:1323-1329.
- Yonekura Y, Benua RS, Brill AB, et al. Increased accumulation of 2-deoxy-2-[¹⁸F]fluoro-D-glucose in liver metastases from colon carcinoma. *J Nucl Med* 1982;23:1133-1137.
- Kiyosawa M, Ohmura M, Mizuno K, et al. ¹⁸F-FDG positron emission tomography in orbital lymphoid tumor. *Nippon Ganka Gakkai Zasshi* 1985;89:1329-1333.
- Nolop KB, Rhodes CG, Brudin LH, et al. Glucose utilization in vivo by human pulmonary neoplasms. *Cancer* 1987;60:2682-2689.
- Di Chiro G, Oldfield E, Bairamian D, et al. Metabolic imaging of the brain stem and spinal cord: studies with positron emission tomography using ¹⁸F-2-deoxyglucose in normal and pathological cases. *J Comput Assist Tomogr* 1983;7:937-945.
- Di Chiro G, Hatazawa J, Katz DA, Rizzoli HV, De MDJ. Glucose utilization by intracranial meningiomas as an index of tumor aggressivity and probability of recurrence: a PET study. *Radiology* 1987;164:521-526.
- Kuwabara Y, Ichiya, Y, Otsuka M, et al. High [¹⁸F]FDG uptake in primary cerebral lymphoma: a PET study. *J Comput Assist Tomogr* 1988;12:47-48.
- Kern KA, Brunetti A, Norton JA, et al. Metabolic imaging of human extremity musculoskeletal tumors by PET. *J Nucl Med* 1988;29:181-186.
- Strauss LG, Clorius JH, Schaig P, et al. Recurrence of colorectal tumors: PET evaluation. *Radiology* 1989;170:329-332.
- Adler LP, Blair H, Makley J, et al. Noninvasive grading of liposarcomas using PET with FDG. *J Comput Assist Tomogr* 1990;14:960-962.
- Adler LP, Blair HF, Makley JR, Pathria MN, Miraldi F. Comparison of PET with MR and conventional scintigraphy in a benign and in a malignant soft-tissue tumor. *Orthopaedics* 1991:in press.
- Di Chiro G, De LaPaz R, Smith B. [¹⁸F]fluoro-deoxy-glucose positron emission tomography of human cerebral gliomas. *J Cereb Blood Flow Metab* 1981;1(suppl 1):11-12.
- Costa J, Wesley RA, Gladstein E, Rosenberg SA. The grading of soft-tissue sarcomas. *Cancer* 1984;54:530-541.
- Kubota K, Matsuzawa T, Ito M, et al. Lung tumor imaging by positron emission tomography using C-11-L-methionine. *J Nucl Med* 1985;26:37-42.
- Gallagher BM, Fowler JS, Gutterson NI, MacGregor RR, Wan CN, Wolf AP. Metabolic trapping as a principle of radiopharmaceutical design: some factors responsible for the biodistribution of [¹⁸F]2-deoxy-2-fluoro-D-glucose. *J Nucl Med* 1978;19:1154-1161.

17. Warburg O. On the origin of cancer cells. *Science* 1956;123:309-314.
18. Weber G. Enzymology of cancer cells (part 1). *N Engl J Med* 1977;296:486-541.
19. Weber G. Enzymology of cancer cells (part 2). *N Engl J Med* 1977;296:541-551.
20. Weber G. Biochemical strategy of cancer cells and the design of chemotherapy. G.H. A. Clowes memorial lecture. *Cancer Res* 1983;42:3466-3492.
21. Mankin HJ, Lange TA, Sanier SS. The hazards of biopsy in patients with malignant primary bone and soft-tissue tumors. *J Bone Joint Surg* 1982;64A:1121-1127.
22. Simon MA. Biopsy of musculoskeletal tumors (current concepts review). *J Bone Joint Surg* 1982;64A:1253-1257.
23. Schiepers C, Hawkins RA, Hoh C, et al. Total-body imaging with fluoro-deoxyglucose (FDG) and PET in patients with malignancies [Abstract]. *J Nucl Med* 1990;31:803.

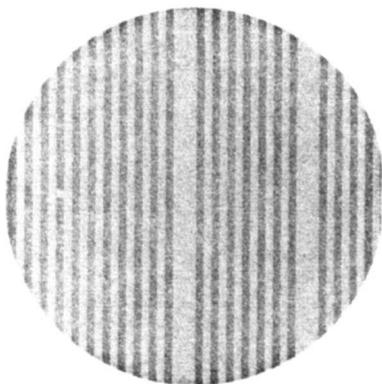
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FIRST IMPRESSIONS



PURPOSE:

A bar phantom mysteriously appeared superimposed on a routine bone scan (Fig. 1). A flood field image revealed the underlying "phantom" (Fig. 2). A new uniformity correction flood was accumulated and the "phantom" disappeared. Routine scanning continued, but the "phantom" reappeared when the next patient was imaged. It was observed that when the sheet from the imaging table was changed it occasionally made contact with the formatter. The noticeably high static electricity discharged onto the formatter caused the timer and scaler to be reset to zero and appears to have erased half of the uniformity correction memory. The proximity of the imaging table to the formatter and the dry weather conditions resulted in this interesting and unusual phenomenon.



INSTRUMENTATION

General Electric MaxiCamera II

CONTRIBUTORS

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