

## Clinical Studies



# **$^{11}\text{C}$ -Methionine vs. $^{18}\text{F}$ -FDG PET in Soft Tissue Sarcoma Patients Treated with Neoadjuvant Therapy: Preliminary Results**

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**Abstract.** Objective: In patients with soft tissue sarcoma (STS) the histological response (tumour grade regression: TGR) to neoadjuvant chemoradiotherapy (CRT) may influence the outcome. The main aim of the study was to evaluate the predictive value of  $^{11}\text{C}$ -methionine (MET) and  $^{18}\text{F}$ -FDG PET/CT in patients with STS treated with neoadjuvant CRT, correlating TGR with SUV<sub>max</sub> (standardized uptake value) percentage variation before and after CRT. Patients and Methods: Nine patients with STS already scheduled for a neoadjuvant CRT and surgery were enrolled. They underwent MET and FDG PET/CT in a one-day procedure before and after the CRT. Pre-therapy SUV<sub>max</sub> and the percentage variation of SUV<sub>max</sub> for MET and FDG were correlated with TGR according to the Huvos grade. Grades I-II were considered as partial responders (PR) and grades III-IV as complete responders (CR). Results: FDG pre-treatment mean SUV<sub>max</sub> in PR patients was 7.1, while in CR patients it was 13.2. Pre-treatment mean MET SUV<sub>max</sub> in PR patients was 7.5, while in CR patients it was 4.9. The mean percentage variation in FDG SUV<sub>max</sub>, was -21.2% in PR patients and -74.5% in CR patients while that for MET SUV<sub>max</sub> was 48% in PR patients and -53.9% in CR patients. Conclusion: According to this preliminary study, the percentage variation in FDG before and after CRT seems to discriminate between PR and CR better than MET.

Soft tissue sarcomas are a heterogeneous group of tumours that arise from tissues of mesenchymal origin. They comprise approximately 0.7-1% of adult malignancy (1) and 6.5% of

all cancers in children younger than 15 years of age (2). About 45% of all soft tissue sarcomas are found in the extremities, especially in the lower limb, and 20% intra-abdominally (3).

The metastatic spread of sarcomas is mainly hematogeneous to the lungs (50%), bone, liver and brain (40%), and sometimes to the retroperitoneum and other soft tissue. Lymphatic diffusion to regional nodes may also occur (1, 3, 4). The presence or the absence of metastasis, the tumour histology and the malignancy grade mainly influence the treatment of choice.

Diagnostic imaging plays a key role in the evaluation of patients with sarcoma; the site and size of the primary tumour can be determined using magnetic resonance imaging (MRI) and conventional computed tomography (CT) but benign soft tissue masses and soft tissue sarcomas may appear to be very similar on clinical and radiological examination (1). Biopsy of the mass is the most specific method for diagnosis and grading and this is usually directed by anatomical imaging (1, 5). Positron emission tomography (PET) with  $^{18}\text{F}$ -FDG has been proposed as a tool which may be useful in the management of soft tissue sarcomas (2-17). In fact, several studies have also shown significant differences in FDG uptake values between low- and high-grade soft tissue sarcomas (3, 7, 8, 12-14).

Furthermore, FDG PET could be useful in the detection of recurrent (6-8, 11, 12) and metastatic disease (2, 6, 15, 16), or in guiding biopsy into the most metabolic area and finally in the prediction and/or monitoring response to therapy (3, 6, 9, 17). Nevertheless, it should be remembered that the use of  $^{18}\text{F}$ -FDG PET in soft tissue sarcoma (as in any other tumour) could be limited by the relatively high rate of false-positive results caused by inflammatory tissues.

For this reason some authors have addressed investigations to the potential use of some other radiopharmaceuticals which involve proteic or fatty acid metabolism such as fluorine-18alpha methyltyrosine (FMT),  $^{11}\text{C}$ -methionine (MET),  $^{11}\text{C}$ -choline, and  $^{11}\text{C}$ -tyrosine (18-20).

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Table I. Patients population characteristics.

Patient no.	Age (year)	Gender	Site	Histological diagnosis	Grade
1	51	F	Left thigh	Spindle and polymorphic cell sarcoma	4
2	44	F	Right thigh	Leiomyosarcoma	3
3	16	F	Left hip and gluteus	Synovial monophasic sarcoma	3
4	50	M	Left thigh	Spindle cell sarcoma	4
5	51	F	Right gluteus	Synovial monophasic sarcoma	4
6	62	F	Left limb	Spindle and polymorphic cell sarcoma	3
7	64	M	Right paravertebral area	Spindle cell sarcoma	3
8	34	F	Right leg	Round cell sarcoma indifferentiated	3
9	39	M	Left knee	Synovial biphasic sarcoma	u.r.

u.r., unreported.

Hence, the main aim of this study was to investigate if PET/CT (with FDG or MET) correlates to tumour grade regression (TGR) in a group of patients with soft tissue sarcoma treated with neoadjuvant chemoradiotherapy and to determine the best tracer for this purpose.

## Patients and Methods

Between September 2003 and February 2005, 9 patients (6 women and 3 men, aged between 16 and 64 years) were prospectively studied with different histological types of high-grade soft tissue sarcomas, mainly found in limbs (patient population characteristics are summarized in Table I). All patients underwent a pre-surgical neoadjuvant treatment with radio and chemotherapy. Before starting therapy, all patients underwent FDG and/or MET PET/CT: 7 patients underwent FDG and MET PET on the same day; 1 patient underwent only MET PET, and 1 patient only <sup>18</sup>F-FDG PET/CT (Table II).

Chemotherapy consisted of 3 cycles, one cycle every three weeks after hematological examination, of epirubicine (60 mg/mq) plus ifosfamide (3,000 mg/mq) on the first and second day, and ifosfamide (3,000 mg/mq) alone on the third day.

Radiotherapy treatment was performed after chemotherapy with 3D conformal radiotherapy (3DCR), up to a total dose of 4,400 cGy in 22 days (200 cGy/day).

All patients underwent neoadjuvant chemotherapy, while only 6 patients were also subjected to radiotherapy.

After about 20 days from the end of the treatment, all patients underwent a second PET scan: 7 patients had both FDG and MET PET scan on the same day, 1 patient only MET PET and 1 only FDG PET (Table II). In every PET scan, standardized uptake value (SUV) of all lesions, expressed in g/ml, was evaluated and only the highest SUV<sub>max</sub> value was recorded.

All scans were carried out on a dedicated PET/CT tomograph (Discovery, GE, Milwaukee, WI, USA), following standard procedures. PET acquisition was performed in the 6 hours'-fasted patient, after intravenous injection of 5.3 MBq/kg of <sup>18</sup>F-FDG or <sup>11</sup>C-MET; uptake time was 60 min for FDG and 10 min for MET. PET images were evaluated on the basis of visual inspection by three experienced readers; in all cases agreement among readers was obtained for the final report.

After post-therapy PET scan, all patients were addressed to surgery and every tumour mass was analyzed by the pathologist.

Table II. PET scans performed on each patient.

Patient no.	PET <sup>11</sup> C-MET	PET <sup>18</sup> F-FDG	PET <sup>11</sup> C-MET	PET <sup>18</sup> F-FDG
	Pre-treatment	Pre-treatment	Post-treatment	Post-treatment
1	X	X	X	X
2	X		X	
3	X	X	X	X
4		X		X
5	X	X	X	X
6	X	X	X	X
7	X	X	X	X
8	X	X	X	X
9	X	X	X	X

The Huvos grade was applied (which considers the percentage of necrosis after the treatment) (Table III) to evaluate the histological tumour response (TGR) (21). Grades I-II were considered as partial responders (PR) and grades III-IV as complete responders (CR).

After surgery, some patients completed the treatment with adjuvant chemo and/or radiotherapy. Chemotherapy included 2 cycles with the same schedule as the neoadjuvant therapy; radiotherapy was performed using 3DCR and/or brachytherapy (BRT): 4 patients underwent chemotherapy, 4 patients chemotherapy and external radiotherapy (RTE), and 1 patient interstitial BRT.

The objectives of this study were firstly to evaluate the correlation between the pre-treatment uptake of FDG and MET (measured by SUV<sub>max</sub>) with the TGR; secondly, to evaluate the correlation between the variation expressed in percentage of the FDG and MET uptake before and after CRT with the TGR.

## Results

Histological response criteria according to Huvos grade were: 4 patients grade I, 1 patient grade II, 2 patients grade III and 2 patients grade IV. Histological results are summarized in Table IV.

Table III. Connection between Huvos grade, percentage of post-treatment necrosis and type of response.

Response	Huvos grade	Percentage of necrosis	Response to the treatment
Partial	I	0-50	Little or no effect identified.
	II	51-90	Areas of acellular tumor osteoid, necrotic, or fibrotic material attributable to the effect of chemotherapy, with other areas of histologically viable tumor.
Complete	III	91-99	Predominant areas of acellular osteoid, necrotic, or fibrotic material attributable to the effect of chemotherapy, with only scattered foci of histologically viable tumor cells identified.
	IV	100	No histologic evidence of viable tumor identified within the entire specimen.

In order to meet the first objective of the study, pre-treatment FDG uptake (expressed as SUV<sub>max</sub> value: FDG-SUV1) was correlated with histological response according Huvos grade. The mean SUV1 in 4 patients considered PR was 7.1 g/ml while that in 4 patients considered CR was 13.2 g/ml. Results are summarized in Figure 1. Pre-treatment MET uptake (MET-SUV1) was also correlated with histological response according to Huvos grade. The mean SUV1 in 4 patients considered PR was 7.5 g/ml while that in 4 patients considered CR was 4.9 g/ml. Results are summarized in Figure 2.

In order to determine the correlation between percentage variation of the FDG SUV<sub>max</sub> and Huvos grade, only 8 patients could be considered. Results are summarized in Figure 3. In particular in PR patients, the percentage variation in SUV<sub>max</sub> ranged between +44.4% and -27.9%, except in one case (-84.21%), with a mean percentage of -21.2% (standard deviation, SD=52.7%). In CR patients, the range was between -61.9% and -83.3, with a mean percentage of -74.5% (SD=10.3%).

Correlating pre and post neoadjuvant percentage variations in SUV<sub>max</sub> and Huvos grade, the results are summarized in Figure 4. In particular in PR patients, the range was between +194.8% and -75.14% with a mean percentage of 48% (SD=139.7%); in CR patients, the range was between -15.78% and -72.2%, with a mean percentage of -53.9% (SD=25.7%).

## Discussion

Jones *et al.* proposed a study with 9 patients who were subjected to different kinds of neo-adjuvant treatment (chemotherapy/radiotherapy/hyperthermia) deducing that FDG PET may be of benefit in the monitoring of sarcoma response to neoadjuvant therapy (22).

Schuetze *et al.* demonstrated that patients with a baseline tumour SUV<sub>max</sub>≥6 and a <40% decrease in FDG uptake were at high risk of systemic disease recurrence, while patients whose tumours had a ≥40% decline in the SUV<sub>max</sub> in response to chemotherapy were at a significantly lower risk of recurrent disease and death after complete resection and

Table IV. Huvos grade of each patient.

HUVOS grade	Patients
I	4 (Patient no. 2-3-5-7) Partial response: 5 patients
II	1 (Patient no. 4)
III	2 (Patient no. 1-8) Complete response: 4 patients
IV	2 (Patient no. 6-9)

adjuvant radiotherapy. In this way, they showed which patients could benefit from neo-adjuvant treatment (6). Bredella *et al.* proposed a study in which they found that FDG PET is better than MRI in evaluating the viable tumour after post-therapeutic changes (9). Only limited data are currently available concerning FDG PET for preoperative assessment of response to chemotherapy and they are essentially derived from retrospective studies. In all reported cases, there is a correlation between uptake intensity after chemotherapy and the percentage of viable cells (23, 24). The long-term prognosis of patients considered to be “good responders” by FDG PET is unknown at present and therefore cannot be compared to that of patients with a good histological response.

In a recent study, Evilevitch *et al.* (25) demonstrated that a change in tumour glucose metabolic activity is a significantly more accurate parameter than a change in size for assessing histopathological response to neoadjuvant therapy in patients with high-grade soft tissue sarcoma.

The present study has shown that the patients of the PR group (Huvos grade I-II) presented similar pre-therapy FDG and MET SUV1 values as well as similar standard deviation (SD): mean SUV1 FDG value was 7.1 g/ml, SD 5.6; mean MET SUV1 value was 7.5 g/ml, SD 6.7. Instead, patients in the CR group (Huvos grade III-IV) presented higher FDG than MET SUV1 values, with a smaller MET standard deviation (mean FDG SUV1: 13.2 g/ml, SD 5.7; mean MET SUV1: 4.9 g/ml, SD 2.1). The high grade of flogosis within the tumour mass may be the cause of the relatively high FDG SUV1 value in CR patients.

Discussing the second objective of the study, if a cut-off percentage decrease of SUV<sub>max</sub> FDG of 45% is considered,

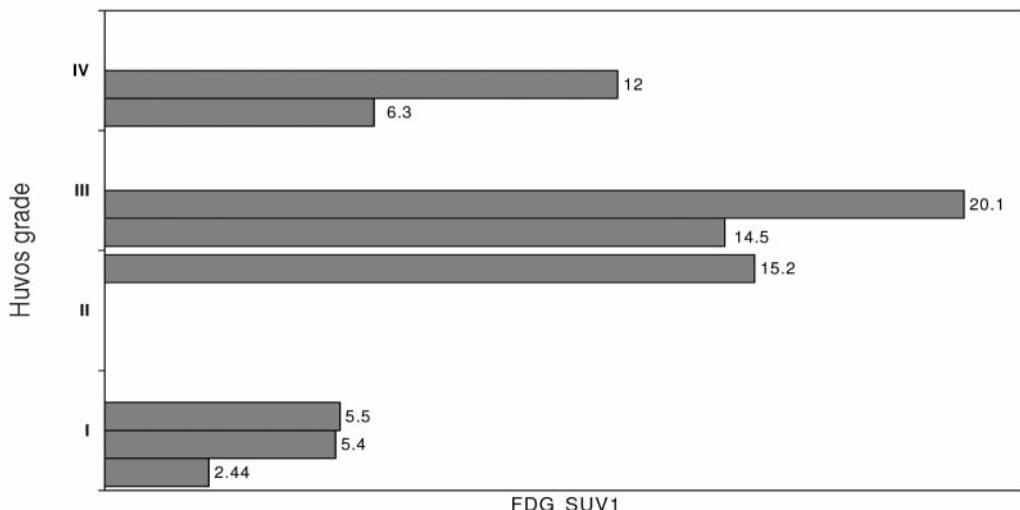


Figure 1. Pre-treatment FDG uptake (expressed as  $SUV_{max}$ : FDG SUV1) and histological response according to Huvos grade.

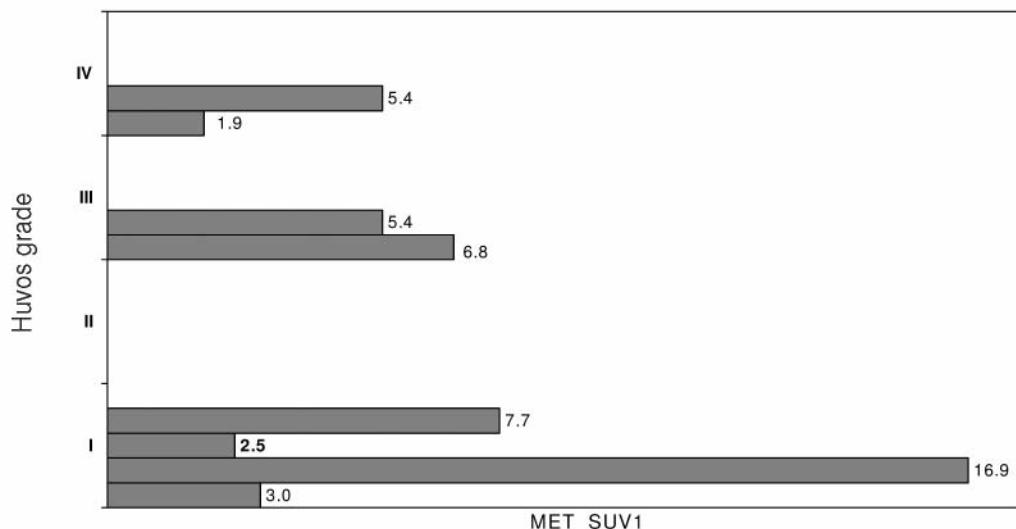


Figure 2. Pre-treatment MET uptake (expressed as  $SUV_{max}$ : MET SUV1) and histological response according to Huvos grade.

it is possible to discriminate between CR and PR patients: in fact in the PR group, 3 out of 4 patients had a  $SUV_{max}$  decrease of less than 27.09% and in the CR group all patients presented a decrease of  $SUV_{max}$  of more than 61.9% [positive predictive value (PPV) 100%; negative predictive value (NPV 75%)]. Even if preliminary, these data could testify that there is a good correlation between metabolic (FDG  $SUV_{max}$  value) and histological (TGR) behaviour. On the other hand, it is not possible to identify an SUV1 cut-off value of percentage variation of MET  $SUV_{max}$  between CR and PR groups (PPV 75%; NPV 50%; with the 45% cut-off). In fact, similar percentage decreases in  $SUV_{max}$  both in

PR and CR groups were observed (-67.53%, -75.14% and -64.7%, -72.2% respectively). Nevertheless, a remarkable augmentation of  $SUV_{max}$  percentage was present only in the PR group, for both MET (two patients: +140% and +194.8%) and FDG tracers (one patient: +44.4%).

Comparing results obtained with FDG and MET PET/CT scans prior to neoadjuvant CRT, the use of  $SUV_{max}$  to predict TGR is not recommended. In fact, neither radiotracer shows different uptake behaviour between PR and CR.

Instead the use of the percentage variation in FDG PET  $SUV_{max}$  between pre and post therapy could give a good differentiation between PR and CR patients. On the contrary,

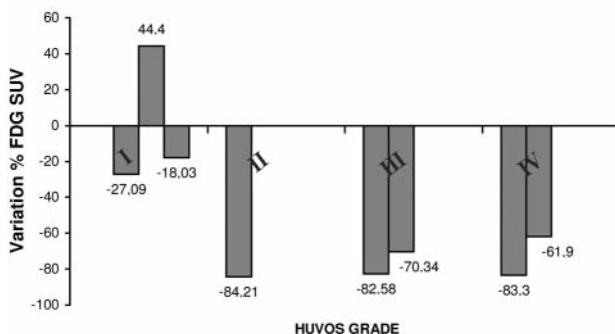


Figure 3. Percentage variation of FDG SUV (pre and post-neoadjuvant RCT) and histological response according to Huvos grade.

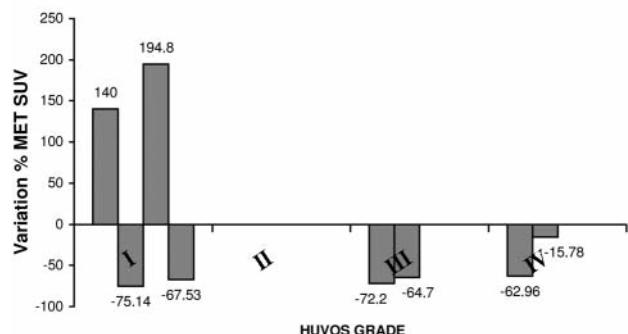


Figure 4. Percentage variation of MET SUV (pre and post-neoadjuvant RCT) and histological response according to Huvos grade.

the percentage variation in MET PET SUV<sub>max</sub> did not show a clear differentiation between PR and CR. Therefore, FDG PET (and in particular the percentage variation of the SUV<sub>max</sub> value) is better than MET PET in discriminating PR and CR patients.

As several previous studies in soft tissue sarcoma have shown, FDG seems to be a good tracer for monitoring the response to therapy. It is clear that further studies with a larger number of patients are necessary to validate these preliminary assertions.

## References

- Santoro A and Sarcomi I (ed.). Medico-Scientifiche Pavia, 1994.
- Iagaru A, Quon A, McDougall IR and Gambhir SS: F-18 FDG PET/CT evaluation of osseous and soft tissue sarcomas. Clin Nucl Med 31: 754-760, 2006.
- Bastiaannet E, Groen H, Jager PL, Cobben DC, van der Graaf WT, Vaalburg W and Hoekstra HJ: The value of FDG-PET in the detection, grading and response to therapy of soft tissue and bone sarcomas; a systematic review and meta-analysis. Cancer Treat Rev 30: 83-101, 2004.
- Lucas JD, O'Doherty MJ, Wong JC, Bingham JB, McKee PH, Fletcher CD and Smith MA: Evaluation of fluorodeoxyglucose positron emission tomography in the management of soft-tissue sarcomas. J Bone Joint Surg Br 80: 441-447, 1998.
- Lodge MA, Lucas JD, Marsden PK, Cronin BF, O'Doherty MJ and Smith MA: A PET study of <sup>18</sup>FDG uptake in soft tissue masses. Eur J Nucl Med 26: 22-30, 1998.
- Schuetze SM, Rubin BP, Vernon C, Hawkins DS, Bruckner JD, Conrad EU 3rd and Eary JF: Use of positron emission tomography in localized extremity soft tissue sarcoma treated with neoadjuvant chemotherapy. Cancer 103: 339-348, 2005.
- Schwarzbach MH, Dimitrakopoulou-Strauss A, Willeke F, Hinz U, Strauss LG, Zhang YM, Mechtersheimer G, Attigah N, Lehnert T and Herfarth C: Clinical value of (<sup>18</sup>F) fluorodeoxyglucose positron emission tomography imaging in soft tissue sarcomas. Ann Surg 231: 380-386, 2000.
- Dimitrakopoulou-Strauss A, Strauss LG, Schwarzbach MH, Burger C, Heichel T, Willeke F, Mechtersheimer G and Lehnert T: Dynamic PET <sup>18</sup>F-FDG studies in patients with primary and recurrent soft-tissue sarcomas: impact on diagnosis and correlation with grading. J Nucl Med 42: 713-720, 2001.
- Bredella MA, Caputo GR and Steinbach LS: Value of FDG positron emission tomography in conjunction with MR imaging for evaluating therapy response in patients with musculoskeletal sarcomas. Am J Roentgenol 179: 1145-1150, 2002.
- Feldman F, van Heertum R and Manos C: <sup>18</sup>FDG PET scanning of benign and malignant musculoskeletal lesions. Skeletal Radiol 32: 201-208, 2003.
- Griffith LK, Dehdashti F, McGuire AH, McGuire DJ, Perry DJ, Moerlein SM and Siegel BA: PET evaluation of soft-tissue masses with fluorine-18 fluoro-2-deoxy-D-glucose. Radiology 182: 185-194, 1992.
- Ioannidis JP and Lau J: <sup>18</sup>F-FDG PET for the diagnosis and grading of soft-tissue sarcoma: a meta-analysis. J Nucl Med 44: 717-724, 2003.
- Kern KA, Brunetti A, Norton JA, Chang AE, Malawer M, Lack E, Finn RD, Rosenberg SA and Larson SM: Metabolic imaging of human extremity musculoskeletal tumors by PET. J Nucl Med 29: 181-186, 1988.
- Nieweg OE, Pruijm J, van Ginkel RJ, Hoekstra HJ, Paans AM, Molenaar WM, Koops HS and Vaalburg W: Fluorine-18-fluorodeoxyglucose PET imaging of soft-tissue sarcoma. J Nucl Med 37: 257-261, 1996.
- Lucas JD, O'Doherty MJ, Cronin BF, Marsden PK, Lodge MA, McKee PH and Smith MA: Prospective evaluation of soft tissue masses and sarcomas using fluorodeoxyglucose positron emission tomography. Br J Surg 86: 550-556, 1999.
- Vernon CB, Eary JF, Rubin BP, Conrad EU 3rd, and Schuetze S: FDG PET imaging guided re-evaluation of histopathologic response in a patient with high-grade sarcoma. Skeletal Radiol 32: 139-142, 2003.
- Inoue T, Kim EE, Wong FC, Yang DJ, Bassa P, Wong WH, Korkmaz M, Tansey W, Hicks K and Podoloff DA: Comparison of fluorine-18-fluorodeoxyglucose and carbon-11-methionine PET in detection of malignant tumors. J Nucl Med 37: 1472-1476, 1996.

- 18 Yanagawa T, Watanabe H, Inoue T, Ahmed AR, Tomiyoshi K, Shinozaki T, Oriuchi N, Endo K and Takagishi K: Carbon-11 choline positron emission tomography in musculoskeletal tumors: comparison with fluorine-18 fluorodeoxyglucose positron emission tomography. *J Comput Assist Tomogr* 27: 175-182, 2003.
- 19 Watanabe H, Inoue T, Shinozaki T, Yanagawa T, Ahmed AR, Tomiyoshi K, Oriuchi N, Tokunaga M, Aoki J, Endo K and Takagishi K: PET imaging of musculoskeletal tumors with fluorine-18 alpha-methyltyrosine: comparison with fluorine-18 fluorodeoxyglucose PET. *Eur J Nucl Med* 27: 1509-1517, 2000.
- 20 Kole AC, Plaat BE, Hoekstra HJ, Vaalburg W and Molenaar WM: FDG and L-[1-<sup>11</sup>C]-tyrosine imaging of soft-tissue tumors before and after therapy. *J Nucl Med* 40: 381-386, 1999.
- 21 Rosen G, Marcove RC, Huvos AG, Caparros BI, Lane JM, Nirenberg A, Cacavio A and Groshen S: Primary osteogenic sarcoma: eight-year experience with adjuvant chemotherapy. *J Cancer Res Clin Oncol* 106: 55-67, 1983.
- 22 Jones DN, McCowage GB, Sostman HD, Brizel DM, Layfield L, Charles HC, Dewhirst MW, Prescott DM, Friedman HS, Harrelson JM, Scully SP and Coleman RE: Monitoring of neoadjuvant therapy response of soft-tissue and musculoskeletal sarcoma using fluorine-18-FDG PET. *J Nucl Med* 37: 1438-1444, 1996.
- 23 Brisse H, Ollivier L, Edeline V, Pacquement H, Michon J, Glorion C and Neuenschwander S: Imaging of malignant tumours of the long bones in children: monitoring response to neoadjuvant chemotherapy and preoperative assessment. *Pediatr Radiol* 34: 595-605, 2004.
- 24 Hawkins DS, Rajendran JG, Conrad EU III, Bruckner JD and Eary JF: Evaluation of chemotherapy response in pediatric bone sarcomas by [F-18]-fluorodeoxy-D-glucose positron emission tomography. *Cancer* 94: 3277-3284, 2002.
- 25 Evilevitch V, Weber WA, Tap WD, Allen-Auerbach M, Chow K, Nelson SD, Eilber FR, Eckardt JJ, Elashoff RM, Phelps ME, Czernin J and Eilber FC: Reduction of glucose metabolic activity is more accurate than change in size at predicting histopathologic response to neoadjuvant therapy in high-grade soft-tissue sarcomas. *Clin Cancer Res* 14: 715-720, 2008.

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