SCIENTIFIC ARTICLE

Tumor-to-background Ratio to Predict Response to Chemotherapy of Osteosarcoma Better than Standard Uptake Values

Jin-peng He, MD^{1*}, Yun Hao, MD^{2*}, Mi Li, MD², Jiang Wang, MD², Feng-jin Guo, MD²

¹Tongji Medical College, and ²Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Objective: According to the current treatment protocol of the Cooperative Osteosarcoma Study, it is mandatory to determine the histological response to neoadjuvant chemotherapy treatment before surgical removal of the tumor, particularly if a limb salvage procedure is planned. The aim of this systematic, retrospective study was to evaluate the ability of 2-(¹⁸F) fluoro-2-deoxy-D-glucose positron-emission tomography/computed tomography to predict chemotherapy response of osteosarcoma and to identify a simple promising method for noninvasive evaluation of neoadjuvant chemotherapy response in osteosarcoma.

Methods: The PubMed database was searched to identify and analyze relevant published reports. In particular, correlations between tumor-to-background ratio (TBR), standard uptake value (SUV) and histological response to chemotherapy were assessed.

Results: It was found that good responses are achieved in patients with TBR after chemotherapy (TBR2)/TBR before chemotherapy (TBR1) < 0.470 (positive predictive value [PPV] = 92.31%, negative predictive value [NPV] = 82.76%, sensitivity [S] = 87.80%, specificity [SP] = 88.89%), whereas poor responses occur in patients with SUV after chemotherapy/before chemotherapy (SUV2/SUV1) > 0.396 (PPV = 73.68%, NPV = 73.33%, S = 63.64%, SP = 81.48%).

Conclusion: Changes in TBR are better predictors of chemotherapy response than SUV in osteosarcoma patients. Therefore, we believe that choice of surgical strategy is optimally based on changes in TBR.

Key words: Evaluation; Histological response; Osteosarcoma; Positron-emission tomography/computed tomography; Prediction

Introduction

Whole-body 2-(¹⁸F) fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) examination, a very important tool for evaluating the stage of a malignant tumor, is now widely used in patients with osteosarcoma¹. In particular, preoperative examination helps clinicians identify metastases^{2,3} and discriminate malignant tumors from benign

tumors⁴. Tumors with high standard uptake values (SUVs) tends to be malignant, the opposite is true for benign tumors.

The histologic response to neoadjuvant chemotherapy is not only an important prognostic indicator for disease free survival after multimodal treatment of osteogenic sarcoma^{5,6}, but should also influence the choice of surgical procedure. Data evaluated by the Cooperative Osteosarcoma Study

Address for correspondence Feng-jin Guo, MD, Affiliated Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Ave, Qiaokou District, Wuhan, Hubei, China 430030 Tel: 0086-15071032254; Fax: 0086-27-83665218; Email: hejinpeng2006@126.com

Disclosure: All the authors declare no conflicts of interest.

*These two authors contributed equally to this work.

Received 1 November 2013; accepted 25 March 2014

(COSS) indicate that the risk of a local recurrence is linked to both the response to preoperative therapy and the type of surgery. A number of studies have shown that patients with inadequate surgical margins but excellent response to neoadjuvant treatment have a lower incidence of local relapse than patients with adequate surgical margins but poor response to preoperative chemotherapy^{7–10}. Therefore, the response to neoadjuvant chemotherapy should be determined and considered as precisely as possible before definitive operative tumor removal¹¹, particularly if a limb salvage procedure is planned. In patients with large tumor volumes and poor responses, ablative surgery or rotation plasty is preferable.

Several studies have analyzed the role of FDG PET scanning in the assessment of therapeutic response in patients with osteosarcoma and analyzed the correlations between various measurements and chemotherapy response^{12–20}. The tumor-to-background ratio (TBR), tumor-to-nontumor ratio (TNT) and SUV are measured routinely in PET/computed tomography (CT) studies. However, their comparative values are as yet unclear.

To measure TNT, a coronary slice is used and a rectangular region of interest (ROI) selected around an area of maximum tumor activity, the boundaries of the ROI being located just within the apparent hypermetabolic zone. An identical ROI is selected around comparable unaffected tissue on the contralateral side to represent background activity¹². TBRs are calculated from identically configured ROIs at the site corresponding to that of the tumor, but in the contralateral extremity, pelvic bone or chest⁸. Thus, they are measurements of the same (contralateral) region.

PET/CT examinations are also widely used to diagnose and assess primary osteosarcomas and detect any metastases²¹. Because it has proved difficult to identify a means other than histological examination for predicting the effect of chemotherapy in osteosarcoma patients, many complex, hybridized and time-consuming methods have been proposed^{22–24}. For example, changes in glucose metabolism can be correlated with the amount of tumor necrosis induced by preoperative treatment²⁵.

Therefore, this study focused on the differences between these varying means of evaluation and their accuracy and reliability in predicting responses to chemotherapy in osteosarcoma patients. The aim of this analysis was to identify a practicable and effective method for choosing optimal treatment strategies.

Materials and Methods

Search Strategy

A comprehensive computer-based search of publications listed in PubMed/MEDLINE databases was conducted to find relevant articles on prediction of histological response to chemotherapy by FDG-PET/CT in patients with osteosarcoma. The words searched were “PET”, “osteosarcoma”, “chemotherapy”; original articles thus selected were downloaded for further analysis.

Inclusion and Exclusion Criteria

The including criteria were:

1. The diagnosis of osteosarcoma must have been established by pathological examination prior to treatment and no metastases have been detected,
2. The PET/CT examinations had used a standard protocol with the same dosage of ¹⁸-FDG, namely, 370 MBq.
3. Each patient had undergone PET/CT examination before commencing chemotherapy.
4. Each patient had undergone PET/CT examination on completion of chemotherapy and prior to surgery or radiotherapy.

Studies with the follow defects were excluded:

1. The patient died before the end of chemotherapy.
2. Details of each patient's PET/CT results and histological responses to chemotherapy were not available.
3. The first PET/CT examination had not been performed before commencing chemotherapy.

Quality Assessment

Two independent reviewers evaluated the methodology of the selected studies using the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS)²⁶. This 14-item tool is composed of five items concerning verification bias, three concerning review bias, two concerning generalizability and context and spectrum bias, and four concerning reporting. The reviewers, who were blinded to the purposes of the systematic review, recorded a score of “1” for “yes” and “0” for “no” for each of the 14 items; all disagreements were resolved by means of consensus. Interrater reliability was also evaluated.

Statistical Analysis

The data was analyzed with SPSS17.0 and Microsoft Excel software. Probability–probability (P–P) plots were used to test the normalized distribution of data and independent samples Student's *t*-tests for mean values, standard value test. $P < 0.01$ was considered statistically significant.

Data Drawn from Published Reports

The studies that met the selection criteria are listed in Table 1a and 1b. Some patients within the selected studies had to be excluded for various reasons, including not meeting our study criteria. In addition, many studies were excluded because they had too few osteosarcoma patients (<10). However, some of the studies that were excluded because they lacked required details about each patient were still helpful for reaching the conclusions of this study.

Quality Assessment

Overall, the studies included in this systematic review were found to have moderate methodological quality according to QUADAS. The selected studies scored between 8/14 and 12/14 (median score 10/14). The index test and the reference standard were often interpreted without blinding; this is the most critical issue concerning the methodological quality of the included studies. Interrater reliability was substantial (kappa = 0.8).

TABLE 1A A list of studies included in analysis of TBR and histological response to chemotherapy

Author	N (n)	Variable	Conclusion
Schulte M, <i>et al.</i> ⁸	27 (27)	TBR	With a TBR ratio cut-off of 0.6, all responders and 8/10 nonresponders could be identified by PET.
Franzius C, <i>et al.</i> ¹²	17 (11)	TNT	FDG PET showed a >30% decrease in TNT ratios in all patients who had good responses. The patients with poor responses either had increasing TNT ratios or ratios that decreased by <30%.
Nair N, <i>et al.</i> ¹³	16 (15)	TBR	Tumor necrosis was accurately predicted on PET scan in 15/16 patients by visual assessment, 14/15 patients by final TBR values on preoperative scans, and 7/15 patients on percent changes in TBR on serial scans.
Ye ZM, <i>et al.</i> ¹⁶	15 (15)	TBR, SUV	SUV2/SUV1, TBR2/TBR1 and TBR2 were significantly correlated with the degree of tumor necrosis ($P < 0.01$, $P < 0.001$, $P < 0.001$, respectively). TBR2/TBR1 was <0.46 in all patients with favorable responses and >0.49 in all patients with unfavorable responses.

N, cases of published report; n, cases included in this study; TBR, tumor-to-background ratio; TNT, tumor-to-nontumor ratio; SUV, standard uptake value.

Results

Characteristics of Data

Our search identified 68 osteosarcoma patients in the TBR had been assessed by PET/CT both before and after neoadjuvant chemotherapy according to the COSS-86c or COSS-96 protocols. The SUVs of 49 patients had been assessed by PET/CT before and after neoadjuvant chemotherapy according to the COSS-86c or COSS-96 protocols. All included patients had undergone surgery and surgical specimens examined for histological evidence of necrosis according to the Salzer-Kuntschik grading system²⁷ (grade I–III with viable tumor cells

< 10% classified as good response, and grade IV–VI as poor response). Good responses had been achieved in 41/68 (60.29%) of patients with mean values of TBR before chemotherapy (TBR1) of 8.75, TBR after chemotherapy (TBR2) of 2.37 and TBR2/TBR1 of 0.309. Poor responses had occurred in 27/68 patients (mean values: TBR1 7.73, TBR2 5.75, TBR2/TBR1 0.274). Good responses had been achieved in 22/49 patients (44.90%), mean values of the ratio of SUV after and before chemotherapy (SUV2/SUV1) being 0.391. Poor responses had occurred in 27/49 patients (Mean SUV2/SUV1 0.645). TBR2, TBR2/TBR1, SUV2/SUV1 differ markedly between the good response and poor response groups (Fig. 1).

TABLE 1B A list of studies included in analysis of SUV and histological response to chemotherapy

Author	N (n)	Observe	Conclusion
Hawkins DS, <i>et al.</i> ¹⁴	33 (14)	SUV	Mean SUV2 for osteosarcoma patients was greater than the values for Ewing sarcoma family of tumors patients (3.3 vs. 1.5, $P = 0.01$). Both SUV2 and the ratio of SUV2 to SUV1 (SUV2/SUV1) were correlated with histologic response ($P = 0.01$ for both comparisons).
Hamada K, <i>et al.</i> ¹⁷	11 (11)	SUV	Changes in tumor size did not correlate with histologic response ($P > 0.05$). SUV2 was significantly lower on patients with good responses than in those with poor responses (1.93 ± 0.50 , 5.86 ± 2.55 , respectively). Both positive and negative predictive values of SUV2 of <2.5 for a good response were 100%. Patients with good responses had significantly higher ratios of SUV2 to SUV1 (SUV2/1) than patients with poor responses (0.74 ± 0.11 , 0.26 ± 0.39 , respectively, $P < 0.05$). The positive and negative predictive values of SUV2/1 ≤ 0.5 for good and poor responses were 80% and 100%, respectively.
Denecke T, <i>et al.</i> ²⁴	27 (11)	SUV	SUV reduction and absolute post-therapeutic SUV (SUV2) derived from FDG PET significantly discriminated responders from non-responders, whereas volume reduction measured by MRI and CT did not.
Ye ZM, <i>et al.</i> ¹⁶	15 (15)	TBR, SUV	SUV2/SUV1, TBR2/TBR1, and TBR2 were significantly correlated with the degree of tumor necrosis ($P < 0.01$). TBR2/TBR1 were below 0.46 in all patients with favorable responses and >0.49 in all patients with unfavorable responses. It was difficult to distinguish good responses from poor responses by SUV2/SUV1.

N, cases of published report; n, cases included in this study; TBR, tumor-to-background ratio; SUV, standard uptake value.

Fig. 1 Comparison of the studied means of predicting response to chemotherapy. The distribution of TBR1 is very similar in the good and poor histological response groups; the distribution of TBR2 or TBR2/TBR1 differs considerably between the good and poor histological response groups; and the distribution of SUV2/SUV1 differs moderately between the good and poor histological response groups.

P-P Plots

Even each research source had relatively small samples, the entire sample of the present study can be considered a normal distributed entity. Because the PET/CT examiner did not know the histological response to chemotherapy before preoperatively and the clinicians also did not know the result before referring the patients to see a surgeon, our findings approximate those of a double-blinded study. The normality of TBR1, TBR2, TBR2/TBR1 and SUV2/SUV1 were analyzed by the P-P Plot method (Fig. 2). Independent samples *t*-tests were used for further analysis.

Critical Point Selection

We used Levene's test to detect variations in standard values and Student's *t*- or *t'*-tests to assess statistical significance between groups with different histological responses (Table 2).

Only the variance of TBR1 was not statistically significant ($P = 0.548$), the other variances were $P < 0.01$. The mean values of TBR1, TBR2, TBR2/TBR1 and SUV2/SUV1 in the good response group were 8.75, 2.37, 0.31 and 0.39, respectively, whereas they were 7.73, 5.75, 0.76 and 0.65, respectively, in the poor response group.

TBR2, TBR2/TBR1, SUV2/SUV1 differed significantly from each other ($P < 0.01$ for all comparisons, Table 2). We therefore drew receiver operating characteristics (ROC) curves to assist in selecting a critical point for each predictive method (Fig. 3). Next, we selected critical points for each variable according to the ROC curves (Fig. 3). By this means, we set the critical point for TBR2 at 2.77, that for TBR2/TBR1 at 0.470 and that for SUV2/SUV1 at 0.396 (Fig. 4) (Greater or equal to the critical point indicates a poor response in all cases).

Fig. 2 Normal P-P plots of TBR1, TBR2, TBR2/TBR1 and SUV2/SUV1. The normality of TBR1 and TBR2 are not acceptable, whereas both TBR2/TBR1 and SUV2/SUV1 have a normal distribution. Cum, cumulative; Prob, probability.

Thus, patients with $TBR2 < 2.77$ would be predicted to have good responses to neoadjuvant chemotherapy and $TBR2 > 2.77$ poor responses. $TBR2/TBR1 < 0.470$ would predict a good response to chemotherapy and greater values a poor response. Patients would be classified into the good response group with $SUV2/SUV1 < 0.396$ (Fig. 4).

Sensitivity and Specificity Test

Many authors have debated the correlations between TBR2, TBR2/TBR1 and SUV2/SUV1 with histological response to chemotherapy, survival rate and disease-free survival. However, according to many studies the histological response is the most important predictor of prognostic factors. We

therefore chose to focus on the prediction of histological response to chemotherapy and accordingly checked the sensitivity, specificity, Youden index, positive predictive value and negative predictive value of such a predicting system (Table 3).

Only 35/43 patients (81.40%) in whom good responses were predicted by TBR2 actually achieved good responses. Similarly, 20/25 patients (80.00%) in whom poor responses were predicted by TBR2 indeed had poor responses confirmed histologically. However, we found that TBR2/TBR1 values predicted response to chemotherapy more accurately. Of 39 patients in whom good responses were predicted by TBR2/TBR1, 36 (92.31%) did have good histological evidence of regression. Conversely, 24/29 patients (82.76%) in whom

TABLE 2 Descriptive statistics for TBR1, TBR2, TBR2/TBR1 and SUV2/SUV1

Variable	Response	N	Mean	S.D.	S. E.	Levene's test	Student's t-test
TBR1	Good	41	8.75	7.41	1.16	$P = 0.503$	$P = 0.548$
	Poor	27	7.73	5.78	1.16		
TBR2	Good	41	2.373	2.68	0.42	$P = 0.005$	$P = 0.002$
	Poor	27	5.75	4.79	0.92		
TBR2/TBR1	Good	41	0.31	0.17	0.03	$P = 0.024$	$P < 0.001$
	Poor	27	0.76	0.27	0.05		
SUV2/SUV1	Good	22	0.39	0.20	0.04	$P = 0.263$	$P < 0.001$
	Poor	27	0.654	0.25	0.05		

poor responses were predicted did have poor responses. Histological evidence of over 90% necrosis (good response, Salzer-Kuntschik grade I–III) occurred in 14/19 patients (73.68%) in whom good responses were predicted by SUV2/SUV1, whereas 22/30 patients (73.33%) in whom poor responses were predicted had less than 90% histological evidence of necrosis (poor response, Salzer-Kuntschik grade IV–VI).

Discussion

Many studies have discussed the value of maximum standardized uptake value (SUVmax) in the evaluation of histological response to chemotherapy²⁸.

Even though $SUV > 2$ is a good criterion for discriminating malignant from benign tumors, it is not as accurate in predicting the histological response as are TBR2/TBR1 or TBR2 (relative positive and negative predictive values: $TBR2/TBR1 > TBR2 > SUV2/SUV1$). SUV2/SUV1 is less sensitive than other methods (sensitivity: $TBR2/TBR1 \approx TBR2 > SUV2/SUV1$), thus it is more likely to predict poor responses in

patients who actually achieve good histological responses. This is an important point: subsequent treatment should be different for patients with good responses than those with poor responses. As a theoretical example, if a poor response was predicted in a patient who actually achieved a good response, the intern would change the chemotherapy strategy, the surgeon would recommend a progressive treatment strategy such as amputation with resultant loss of limb, and that patient and their family would be seriously affected.

On the other hand, SUV2/SUV1 is better than TBR2 but worse than TBR2/TBR1 at predicting poor responses in patients in whom poor responses are actually diagnosed histologically (Table 3) (specificity: $TBR2/TBR1 > SUV2/SUV1 > TBR2$).

Therefore, we believe that the TBR before and after chemotherapy treatment is the optimal measure to derive from PET/CT examination. If no PET/CT examination is performed before chemotherapy, the clinician should be careful about drawing conclusions from the TBR2: this could result in inappropriate decisions, especially in those patients in

Fig. 3 ROC curve analysis of TBR1, TBR2, TBR2/TBR1 and SUV2/SUV1. The areas of TBR1, TBR2, and TBR2/TBR1, under the ROC curve are 0.488, 0.963 and 0.893, respectively. Their 95% confidence intervals are (0.318, 0.659), (0.908, 1.000) and (0.805, 0.981), respectively.

Fig. 4 TBR1, TBR2, TBR2/TBR1 and SUV2/SUV1 quotients of osteosarcoma patients. The green line indicates the level of the critical point of 0.470. There are three patients with poor responses under the line and five with good responses above the line. (S-K grade: I, $n = 6$; II, $n = 15$; III, $n = 20$; IV, $n = 15$; V, $n = 8$; VI, $n = 4$).

TABLE 3 Evaluation of the three predictive methods

Method	S	SP	PPV	NPV	YI
TBR2	0.8750	0.7143	0.8140	0.8000	0.5893
TBR2/TBR1	0.8780	0.8889	0.9231	0.8276	0.7669
SUV2/SUV1	0.6364	0.8148	0.7368	0.7333	0.4512

NPV, Negative predictive value; PPV, Positive predictive value; S, Sensitivity; SP, Specificity; YI, Youden index.

whom a good response to chemotherapy is predicted (the positive predictive value is significant poorer than that of TBR2/TBR1).

In this study, changes in TBR seem to be a better variable than SUVmax for assessing the degree of histological necrosis of osteosarcoma after chemotherapy. The following reasons may account for this. First, the highest metabolic activity point in the ROI determines the SUVmax. Osteosarcoma is heterogeneous, viable tumor may be present in invaded soft tissues, cortex, subcortex, zones in contact with the physis and articular cartilage, ligaments, and areas surrounding “hemorrhagic-necrotic” lacunae²⁹. Because the metabolic activity is also heterogeneous, using the highest metabolic activity point to represent the viable tumor cells of the whole area is not appropriate. In contrast, TBR is a measure of the average activity in the ROI. Second, SUVmax reflects the absolute glucose uptake, whereas TBR is related to both tumor and background metabolic activity. SUVmax is more vulnerable than TBR. For example, circulating glucose concentrations have an impact on tumor FDG uptake³⁰. Injection of insufficient FDG and excessive uptake by certain organs such as the myocardium may result in underestimating tumor viability. Our conclusions may be questioned because we combined results of a number of different studies; however, we believe they are reliable for the

following reasons. First, we set reliable criteria for inclusion in our study. Second, our results seem to be consistent with a recently published study that only included a few patients¹⁶; however, our study included a more adequate number of patients.

In conclusion, FDG-PET is a promising tool for assessing the chemotherapy response of osteosarcoma noninvasively. TBR2/TBR1 is better than SUV2/SUV1 and TBR2 alone for predicting the histological response, which is consistent with the findings of Zhao-min Ye *et al.*¹⁶. However, Ye *et al.* only compared changes in TBR with those in SUVmax and only assessed 15 patients. In Ye *et al.*'s study, changes in TBR were correlated with the grade of histological necrosis, whereas this was only moderately correlated with changes in SUVmax. However, in our study of 68 patients, we found no definite correlation between the grade of necrosis and changes in variables such as SUV and TBR. It is very clear that TBR2/TBR1 values better predict whether the histological response will be good or poor. Thus, we have proved that calculating the ratio of TBR before and after neoadjuvant chemotherapy is a useful means of predicting the response. In turn, appropriate treatment can be selected according to this prediction method.

Even though the positive predictive value is over 90%, the sensitivity and specificity are over 85%, we are still a long way for precisely predicting patients' responses and prognoses. Change in SUV combined with tumor volume is a novel method for predicting the histological response²⁰; tumor volume reflects the amount of necrosis whereas the SUV reflects changes in metabolism. Only by ongoing stringent research can we identify other valuable methods for helping clinicians to make better decision and improve patients' lives.

Acknowledgments

This study was hugely supported by Yun Hao, a friend of Jin-Peng He, who expresses gratitude for her companionship and encouragement. We also greatly appreciate the contributions of our apprentices.

References

1. Caldarella C, Salsano M, Isgrò MA, Treglia G. The role of fluorine-18-fluorodeoxyglucose positron emission tomography in assessing the response to neoadjuvant treatment in patients with osteosarcoma. *Int J Mol Imaging*, 2012, 2012: 870301.
2. Tse N, Hoh C, Hawkins R, Phelps M, Glaspy J. Positron emission tomography diagnosis of pulmonary metastases in osteogenic sarcoma. *Am J Clin Oncol*, 1994, 17: 22–25.
3. Kneisl JS, Patt JC, Johnson JC, Zuger JH. Is PET useful in detecting occult nonpulmonary metastases in pediatric bone sarcomas? *Clin Orthop Relat Res*, 2006, 450: 101–104.
4. Dehdashti F, Siegel BA, Griffeth LK, *et al.* Benign versus malignant intraosseous lesions: discrimination by means of PET with 2-[F-18]fluoro-2-deoxy-D-glucose. *Radiology*, 1996, 200: 243–247.
5. Fletcher BD. Response of osteosarcoma and Ewing sarcoma to chemotherapy imaging evaluation. *AJR Am J Roentgenol*, 1991, 157: 825–833.
6. Meyers PA, Heller G, Healey J, *et al.* Chemotherapy for nonmetastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. *J Clin Oncol*, 1992, 10: 5–15.
7. Picci P, Sangiorgi L, Rougraff BT, Neff JR, Casadei R, Campanacci M. Relationship of chemotherapy-induced necrosis and surgical margins to local recurrence in osteosarcoma. *J Clin Oncol*, 1994, 12: 2699–2705.
8. Schulte M, Brecht-Krauss D, Werner M, *et al.* Evaluation of neoadjuvant therapy response of osteogenic sarcoma using FDG PET. *J Nucl Med*, 1999, 40: 1637–1643.
9. Franzius C, Bielack S, Flege S, Sciuk J, Jürgens H, Schober O. Prognostic significance of (18)F-FDG and (99m)Tc-methylene diphosphonate uptake in primary osteosarcoma. *J Nucl Med*, 2002, 43: 1012–1017.
10. Brisse H, Ollivier L, Edeline V, *et al.* Imaging of malignant tumours of the long bones in children: monitoring response to neoadjuvant chemotherapy and preoperative assessment. *Pediatr Radiol*, 2004, 34: 595–605.
11. Kumar R, Chauhan A, Vellimana AK, Chawla M. Role of PET/PET-CT in the management of sarcomas. *Expert Rev Anticancer Ther*, 2006, 6: 1241–1250.
12. Franzius C, Sciuk J, Brinkschmidt C, Jürgens H, Schober O. Evaluation of chemotherapy response in primary bone tumors with F-18 FDG positron emission tomography compared with histologically assessed tumor necrosis. *Clin Nucl Med*, 2000, 25: 874–881.
13. Nair N, Ali A, Green AA, *et al.* Response of osteosarcoma to chemotherapy. Evaluation with F-18 FDG-PET scans. *Clin Positron Imaging*, 2000, 3: 79–83.
14. Hawkins DS, Rajendran JG, Conrad EU 3rd, Bruckner JD, Eary JF. Evaluation of chemotherapy response in pediatric bone sarcomas by [F-18]-fluorodeoxy-D-glucose positron emission tomography. *Cancer*, 2002, 94: 3277–3284.

15. Huang TL, Liu RS, Chen TH, Chen WY, Hsu HC, Hsu YC. Comparison between F-18-FDG positron emission tomography and histology for the assessment of tumor necrosis rates in primary osteosarcoma. *J Chin Med Assoc*, 2006, 69: 372–376.
16. Ye Z, Zhu J, Tian M, *et al*. Response of osteogenic sarcoma to neoadjuvant therapy: evaluated by 18F-FDG-PET. *Ann Nucl Med*, 2008, 22: 475–480.
17. Hamada K, Tomita Y, Inoue A, *et al*. Evaluation of chemotherapy response in osteosarcoma with FDG-PET. *Ann Nucl Med*, 2009, 23: 89–95.
18. Hawkins DS, Conrad EU 3rd, Butrynski JE, Schuetze SM, Eary JF. F-18]-fluorodeoxy-D-glucose-positron emission tomography response is associated with outcome for extremity osteosarcoma in children and young adults. *Cancer*, 2009, 115: 3519–3525.
19. Kim DH, Kim SY, Lee HJ, *et al*. Assessment of chemotherapy response using fdg-pet in pediatric bone tumors: a single institution experience. *Cancer Res Treat*, 2011, 43: 170–175.
20. Bajpai J, Kumar R, Sreenivas V, *et al*. Prediction of chemotherapy response by PET-CT in osteosarcoma: correlation with histologic necrosis. *J Pediatr Hematol Oncol*, 2011, 33: e271–e278.
21. Eftekhari F. Imaging assessment of osteosarcoma in childhood and adolescence: diagnosis, staging, and evaluating response to chemotherapy. *Cancer Treat Res*, 2009, 152: 33–62.
22. Cheon GJ, Kim MS, Lee JA, *et al*. Prediction model of chemotherapy response in osteosarcoma by 18F-FDG PET and MRI. *J Nucl Med*, 2009, 50: 1435–1440.
23. Im HJ, Kim TS, Park SY, *et al*. Prediction of tumour necrosis fractions using metabolic and volumetric 18F-FDG PET/CT indices, after one course and at the completion of neoadjuvant chemotherapy, in children and young adults with osteosarcoma. *Eur J Nucl Med Mol Imaging*, 2012, 39: 39–49.
24. Denecke T, Hundsdoerfer P, Misch D, *et al*. Assessment of histological response of paediatric bone sarcomas using FDG PET in comparison to morphological volume measurement and standardized MRI parameters. *Eur J Nucl Med Mol Imaging*, 2010, 37: 1842–1853.
25. Franzius C, Schober O. Assessment of therapy response by FDG PET in pediatric patients. *Q J Nucl Med*, 2003, 47: 41–45.
26. Whiting PF, Weswood ME, Rutjes AW, Reitsma JB, Bossuyt PN, Kleijnen J. Evaluation of QUADAS, a tool for the quality assessment of diagnostic accuracy studies. *BMC Med Res Methodol*, 2006, 6: 9.
27. Salzer-Kuntschik M, Delling G, Beron G, Sigmund R. Morphological grades of regression in osteosarcoma after polychemotherapy—study COSS 80. *J Cancer Res Clin Oncol*, 1983, 106 (Suppl.): 21–24.
28. Kong CB, Byun BH, Lim I, *et al*. ¹⁸F-FDG PET SUVmax as an indicator of histopathologic response after neoadjuvant chemotherapy in extremity osteosarcoma. *Eur J Nucl Med Mol Imaging*, 2013, 40: 728–736.
29. Picci P, Bacci G, Campanacci M, *et al*. Histologic evaluation of necrosis in osteosarcoma induced by chemotherapy, regional mapping of viable and nonviable tumor. *Cancer*, 1985, 56: 1515–1521.
30. Lindholm P, Sutinen E, Oikonen V, *et al*. PET imaging of blood flow and glucose metabolism in localized musculoskeletal tumors of the extremities. *Nucl Med Biol*, 2011, 38: 295–300.