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Review

18F-FDG positron emission tomography for the assessment of histological response to neoadjuvant chemotherapy in osteosarcomas: A meta-analysis

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ABSTRACT

Purpose: The purpose of this meta-analysis was to evaluate the predicting value of fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography (18F-FDG PET-CT) in the assessment of histological response to neoadjuvant chemotherapy in patients with osteosarcomas.
Methods: A detailed search was made in MEDLINE, EMBASE and the Web of Knowledge for relevant original articles published in English; methodological quality of the included studies were also assessed. Two reviewers extracted data independently. Sufficient data was presented to construct a 2×2 contingency table. Pooled sensitivity and specificity, positive and negative likelihood ratios were estimated. A summary receiver operating characteristic curve (SROC) was constructed with the Moses' constant of linear model. A χ^2 test was performed to test for heterogeneity.
Results: Eight studies comprising 178 patients met the inclusion criteria. The pooled sensitivity and specificity for standardized uptake values (SUV) after chemotherapy (SUV2) $\leq$ 2.5 were 0.734 (95% CI, 0.537–0.867) and 0.864 (95% CI, 0.510–0.975), for the ratio of standardized uptake values after (SUV2) to before (SUV1) chemotherapy SUV 2:1 $\leq$ 0.5 were 0.690 (95% CI, 0.497–0.833) and 0.653 (95% CI, 0.492–0.786), the positive and negative likelihood ratio (LR+/LR−) for SUV2 $\leq$ 2.5 were 5.397 (95% CI, 1.169–24.920) and 0.308 (95% CI, 0.165–0.577), for SUV 2:1 $\leq$ 0.5 were 1.989 (95% CI, 1.145–3.457) and 0.475 (95% CI, 0.247–0.915). There was no significant difference between-study heterogeneity for either LR + or LR− in any of these analyses. The area under the SROC curve for SUV2 $\leq$ 2.5 and SUV 2:1 $\leq$ 0.5 were 0.81 and 0.72, respectively.
Conclusions: The present meta-analysis showed that 18F-FDG PET-CT scan, as measured by the SUV before and after treatment, SUV2 $\leq$ 2.5 and SUV 2:1 $\leq$ 0.5 are valuable for predicting the histological response to chemotherapy. SUV2 $\leq$ 2.5 have better predicting performance than SUV 2:1 $\leq$ 0.5.

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Abbreviations: OS, Osteosarcoma; 18F-FDG PET-CT, Fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography; SUV, standardized uptake value; TBR, tumor to background ratios; ROI, region-of-interest; SROC, summary receiver operating characteristic; LR+/−, positive/negative likelihood ratios; AUC, area under curve.

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Introduction

Osteosarcoma (OS) is the most common bone cancer in children and young adults [1,2]. In the past decades, the combination of multi-agent chemotherapy has improved long-term survival in patients with OS [3,4]. Histological response or tumor necrosis rate to neoadjuvant chemotherapy has been shown to be associated with survival [5]. Tumor response to neoadjuvant chemotherapy has important implications in subsequent patient management. However, histopathological examination of tumor response can be assessed only after resection. Therefore, an accurate and noninvasive preoperative marker of response would be ideal for planning surgical margins and as a prognostic tool.

Fluorine-18-fluorodeoxyglucose (18F-FDG) positron emission tomography with computed tomography (18F-FDG PET-CT) is now widely used with promising results in the initial diagnosis, staging, and detection of recurrence in many kinds of cancer [6]. Furthermore, some studies revealed that a decreased 18F-FDG uptake after chemotherapy or radiotherapy is associated with good pathological response [7–14]. However, there have been conflicting results. The other studies have not found a significant association between 18F-FDG uptake and tumor necrosis [15–17]. Therefore, the results of predictive value of 18F-FDG uptake remained undetermined.

In the present study, we conducted a comprehensive review of relevant studies and a meta-analysis of data to determine the predictive value of 18F-FDG uptake in determining histological response to treatment in patient with osteosarcoma.

Methods

Search strategy

Medline, PubMed, Embase, and the Web of Science were searched (last search was updated on 24 May 2011, using the search terms: "positron emission tomography", "prognosis" and "sarcoma"). All searched studies were retrieved, and their bibliographies were checked for other relevant publications. References of selected articles and reviews were also searched manually for additional relevant studies. When more than one of the same patient populations was included in several publications, only the most recent or complete study was used to avoid duplication of information.

Selection criteria

Two independent reviewers assessed the eligibility of studies by reviewing titles and abstracts identified by the search, differences were resolved by discussion. The inclusion criteria required that the specified articles were studies that included: at least 10 patients, 18F-FDG PET-CT scan before and/or after chemotherapy, 18F-FDG PET-CT performed with the intention of monitoring the histological response to neoadjuvant chemotherapy, attenuation-corrected 18F-FDG PET-CT studies. Duplicate studies on the same patients, studies written in a language other than English, and reviews and abstracts were excluded. No unpublished data or data from abstracts were used. "Good" histopathologic response was defined as tumor necrosis of more than 90% according to Salzer-Kuntschik's grading systems [18], whereas the presence of 10% or more viable tumor after chemotherapy was defined a "poor" response.

Data extraction

Two investigators extracted data from eligible studies independently, discussed discrepancies and reached consensus for all items. The following data were collected from each study: first author's name, year of publication, study design, total number of patients, age, sex, and 18F-FDG PET-CT parameters such as standardized uptake value (SUV). We considered the description of 18F-FDG PET-CT as adequate if the publication reported details on the scanner type, the timing of scanning after injection, a clear description of quantitative procedures including region-of-interest (ROI) methodology, and the performance of attenuation correction.

Study character

The QUADAS quality assessment tool, an evidence-based quality assessment tool for diagnostic accuracy studies, was used to extract relevant study design characteristics from each study. This tool and the definitions of the characteristics have been fully described by Whiting et al. [19].

Statistical analysis

Data on the diagnostic performance of the SUV after chemotherapy (SUV2), the ratio of SUV2 to SUV before chemotherapy (SUV1) (SUV 2:1) for determining histological response to chemotherapy were analyzed separately. Pooled sensitivity and specificity for each study were calculated by extracting data into 2×2 tables including the numbers of true positive (TP), true negative (TN), false positive (FP) and false negative (FN) results in each study. A value of 0.5 was added to all cells of studies that contained a count of zero to avoid potential problems in odds calculations for studies with sensitivities or specificities of 100%, and a summary receiver operating characteristic (SROC) curve was constructed. Combined positive and negative likelihood ratios (LR+ and LR−, respectively) were also estimated. Heterogeneity was assessed with the $\chi 2$-test using a random effects model. All analyses were performed by using Rev Manager V5.1, and STATA [19].

Results

Study selection and characteristics analysis

We initially identified 26 articles including discussion of the role of 18F-FDG PET-CT scan in patients with OS. Of those, 18 reports were excluded (5 studies due to reviews [20–24], 2 studies aiming

at staging or grading [25,26], and 3 focused on survival [13,27,28], four for not providing detailed data of enrolled patients [25,29–31], 2 for discussing Ewing sarcoma [8,16], one had less than 10 patients [32],and one used T:NT (tumor to non-tumor background) as parameter [33]). In all, 8 independent eligible studies, which had detailed data of 18F-FDG PET-CT scan and pathological grade score for each patient, were included in the quantitative synthesis [9,10,12,15,17,34–36]. Different methods to quantify 18F-FDG uptake were used: the SUV approach was used in 10 studies (maximum SUV in 9 studies; mean SUV in 1 study), tumor to background ratios (TBR) was used in 3 studies. All analyzed patients were treated with combination chemotherapy regimens. These 18F-FDG PET-CT characteristics are listed in Table 1.The QUADAS quality assessment result is presented in Table 2. The mean time intervals of second 18F-FDG PET-CT scan were provided in 7 studies: 2–3 weeks after treatment and before surgery in brief, while it was not mentioned in the other 4 studies. Five studies mentioned that 18F-FDG PET-CT scan was evaluated blindly to histopathological results, whereas detailed observation methods were not provided in 6 studies.

Predictive value of SUV2

Eight studies investigated the prediction value of SUV after therapy (SUV2) to tumor necrosis rate. As showed in Fig. 1b, the results of estimation of 8 studies involving 138 patients were included in this comparison. There was no significance between-study heterogeneity for these analyses ($I^2 = 34.39\%$). At a cut-off level at ≤2.5, the pooled sensitivity and specificity estimated for SUV2 ≤ 2.5 were 0.734 (95% CI, 0.537–0.867) and 0.864 (95% CI, 0.510, 0.975) respectively, and pooled LR+ and LR− were 5.397 (95% CI, 1.169–24.920) and 0.308 (95% CI, 0.165–0.577) respectively (Fig. 1a,b). The SROC curve for SUV ≤ 2.5 showed that area under curve (AUC) was 0.81 (95% CI, 0.77–0.84), indicating a lower diagnostic accuracy (Fig. 2a).

Predictive value of SUV2:1

The diagnostic performances for the ratio of SUV after treatment (SUV2) to SUV before treatment (SUV1) were assessed in nine eligible studies. These studies involving 178 patients were analyzed in comparison. There was no significance between-study heterogeneity for these analyses ($I^2 = 0.00\%$) The results were showed in Fig. 1c. In this meta-analysis, when the cut-off value were set at ≤0.5, the pooled sensitivity and specificity estimated were 0.690 (95% CI, 0.497–0.833) and 0.653 (95% CI, 0.492–0.786) respectively, and pooled LR+ and LR− estimated were 1.989 (95% CI, 1.145–3.457) and 0.475 (95% CI, 0.247–0.915) respectively. The SROC curve for SUV2:1 showed a median diagnostic accuracy. The AUC was 0.72 (95% CI, 0.68–0.76) (Fig. 2b).

Table 2
Results of the distribution of study design characteristics in 8 studies.

	Question about study design characteristic	Response		
		Yes	No	Unclear
1	Was the spectrum of patients representative of the patients who will receive the test in practice?	8	0	0
2	Were selection criteria clearly described?	8	0	0
3	Is the reference standard likely to correctly classify the target condition?	8	0	0
4	Is the time period between reference standard and index test short enough to be reasonable?	6	0	2
5	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	8	0	0
6	Did patients receive the same reference standard regardless of the index test result?	8	0	0
7	Was the reference standard independent of the index test?	8	0	0
8	Were the reference standard results interpreted without knowledge of the results of the index test?	8	0	0
9	Were the index test results interpreted without knowledge of the results of the reference standard?	4	0	4
10	Was the execution of the reference standard described in sufficient detail to permit its replication?	8	0	0
11	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	8	0	0
12	Was the execution of the index test described in sufficient detail to permit its replication?	8	0	0
13	Were uninterpretable/intermediate results reported?	8	0	0
14	Were withdrawals from the study explained?	8	0	0

Data were the numbers of responses from the QUADAS tool. The numbers indicated how many articles were assigned a score of "Yes", "No" or "Unclear".

Disscusion

18F-FDG PET-CT imaging is a useful, noninvasive method for staging tumors and detecting disease recurrence. Lines of studies have evidenced that the decrease of SUV2 is significantly correlated to percent of necrosis. Quarles et al. demonstrated that the change in 18F-FDG uptake was the strongest indicator for histological response to neoadjuvant chemotherapy through a meta-analysis of 19 studies [6], indicating that 18F-FDG PET-CT scan might be plausible for predicting tumor necrosis after treatment. The present meta-analysis explored the association between the 18F-FDG uptake and histological response after neoadjuvant chemotherapy focusing on a population with osteosarcoma. Since previous studies used an SUV2 cutoff value of 2.5 and an SUV2:1 cutoff value at 0.5 to discriminating histological response, we also selected the same

Table 1
Comparison of PET parameters in patients with osteosarcoma.

No.	Study	R/N*	PET	Design	Age(mean, median)	Sex(M/F)	Time interval after treatment(d)	Time interval before surgery(d)	Observer /Blinded	Reference
1	Cheon 2009	33/37	SUV2/SUV2:1	Prospective	14(5–59)	48/22	14	14	1/nm	[35]
2	Denecke 2010	17/10	SUV2	Prospective	13(3–18)	15/12	21	nm	2/blinded	[12]
3	Gaston 2011	16/15	SUV2	Retrospective	26.75 (18–62) 24.11 (14–38)	13/18	nm	nm	1/blinded	[10]
4	Hamada 2009	5/6	SUV2	Retrospective	27(10–68)	7/4	nm	nm	nm/nm	[34]
5	Hawkins 2002	5/9	SUV2	Unclear	13(6.2–19.2)	22/11	nm	18.2(2–84)	nm/nm	[9]
6	Huang 2006	2/8	SUV2	Prospective	19(4–47)	8/2	7	nm	nm/nm	[17]
7	Ye 2008	8/7	SUV2	Prospective	17(7–31)	9/6	8 (4–14)	12 (2–22)	2/blinded	[15]
8	Bajpai 2011	10/21	SUV2/SUV2:1	Prospective	17(5–66)	25/6	21–28	nm	2/blinded	[36]

N: numbers of patients that included, R/N: number of patients with necrosis ≥90%/number of patients with necrosis <90%, SUV: standardized uptake value, SUV2 : standardized uptake value after chemotherapy, SUV 2:1: the ratio of standardized uptake values after chemotherapy (SUV2) to before (SUV1) chemotherapy, *:for patient with pathological evaluation, nm: not mentioned.

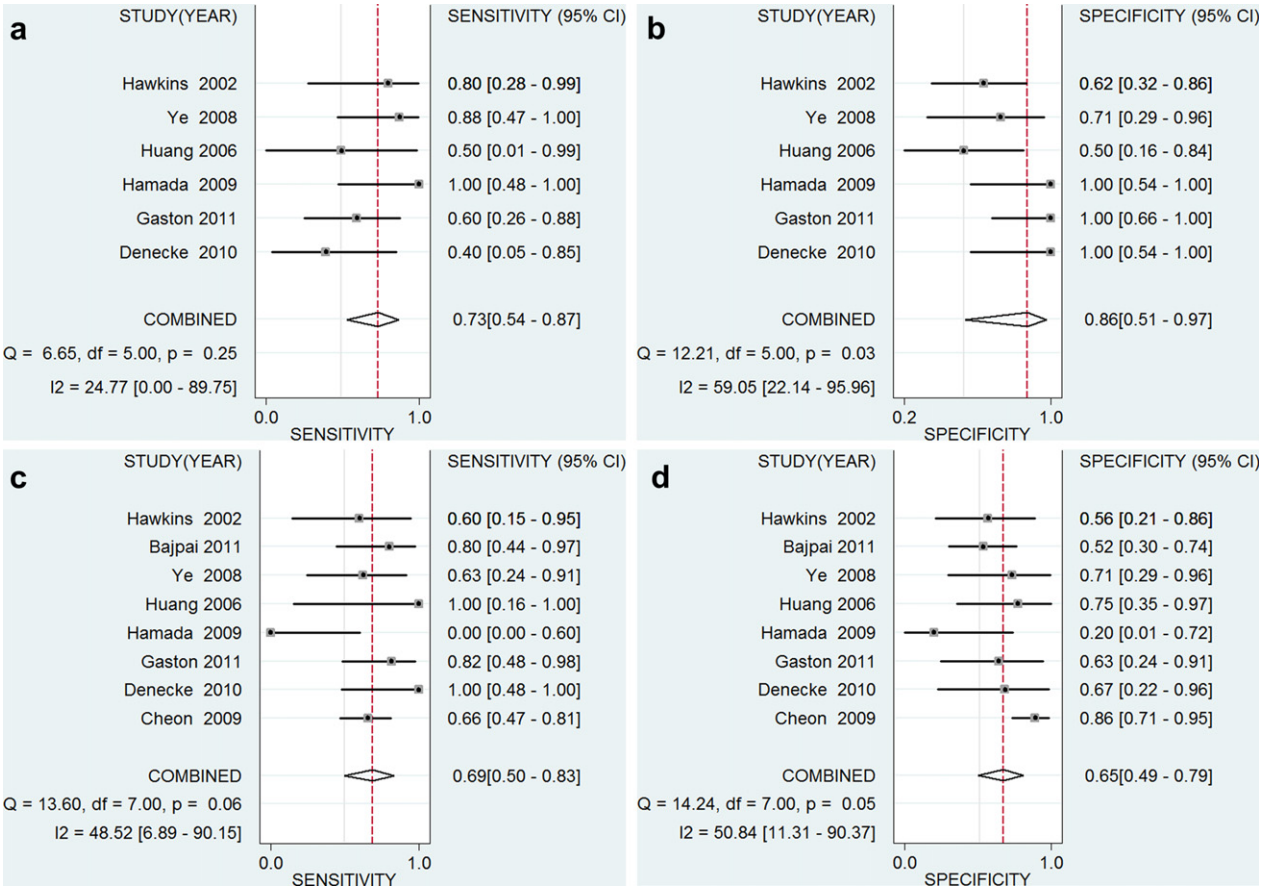

Figure 1. The forest plots of sensitivity and specificity for SUV2 $\leq$ 2.5 (a, b), SUV2:1 $\leq$ 0.5 (c, d). Each solid represents each study in the meta-analysis. The pooled sensitivity and specificity for SUV2 $\leq$ 2.5 were 0.734 and 0.864, for SUV 2:1 $\leq$ 0.5 were 0.690 and 0.653.

cutoff point [9,34]. The results showed that 18F-FDG PET-CT parameters, SUV2 $\leq$ 2.5 and SUV2:1 $\leq$ 0.5, were of predictive value for tumor response to chemotherapy and/or radiotherapy, and SUV2 $\leq$ 2.5 exhibited better performance than SUV2:1 $\leq$ 0.5 according to AUC of SROC (0.81–0.72).

According to widely accepted interpretation of AUC values, an AUC of 0.5 is classified as no value for diagnosis; 0.6–0.69 provides poor discrimination; 0.7–0.79 provides acceptable discrimination; 0.8–0.89 provides excellent discrimination and 0.9–1.0 provides outstanding discrimination. The AUC estimates for SUV2 $\leq$ 2.5 was 0.81, while for SUV2:1 $\leq$ 0.5 was 0.72, indicating a relatively high level of accuracy of SUV2 $\leq$ 2.5 than SUV2:1 $\leq$ 0.5 in predicting treatment response.

Since likelihood ratios are considered to be more clinically meaningful than SROC [37], LR+/− were also analyzed in this review. A good test should have LR+ above 5 and LR− below 0.2, even there is no absolute cut-off. Our results showed the value of LR+ for SUV2 $\leq$ 2.5 and SUV2:1 $\leq$ 0.5 were 5.397 and 1.989, suggesting that SUV2 $\leq$ 2.5 is more valuable than SUV2:1 $\leq$ 0.5 in discriminating tumor necrosis rate >90% after treatment. In the other hand, the value of LR− for SUV2 $\leq$ 2.5 and SUV2:1 $\leq$ 0.5 were 0.308 and 0.475, indicating that a negative examination result could not to rule out good response of neoadjuvant therapy.

Some limitations of this meta-analysis should be acknowledged. Firstly, although eleven studies were included in present analysis, the numbers of patients enrolled in these studies were relatively small, with a mean of 25 patients per study. Therefore, large number of patient enrollment would be more powerful to improve this statistical result. Secondly, there was no single reference standard strategy for 18F-FDG PET-CT imaging. For example, the time intervals between neoadjuvant therapy and 18F-FDG PET-CT scan, and the scan to surgery were varied at most of the studies, different time window would inevitably make result conflicting between studies. Thirdly, since tumor volumes and time of 18F-FDG PET-CT scan are showed to influence scan results, these parameters should be adjusted in estimation. However, they are not taken in this analysis.

In conclusion, this meta-analysis suggests that 18F-FDG PET-CT parameters SUV2 $\leq$ 2.5 and SUV2:1 $\leq$ 0.5 are valuable predictor to assess the chemotherapy-induced tumor necrosis. However, more patients should be enrolled to improve statistical power and avoid clinical heterogeneity; moreover it will be necessary to define the prognostic assessment system in combination with other factors to develop the more precise strategies to improve discriminating ability for better treatment of patients.

Author contribution

Guarantor of the integrity of the study: Li Hongtao, Zhao Hui, Yao Yang, Shen Zan.

Study concepts: Li Hongtao, Shen Zan.

Study design: Yao Yang, Shen Zan, Zhao Hui.

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Clinical studies: Li Hongtao, Zhao Hui.

Experimental studies: Li Hongtao.

Data acquisition: Li Hongtao, He Aina.

Data analysis: Li Hongtao, Wang Bingshun, Wang Xiaojin.

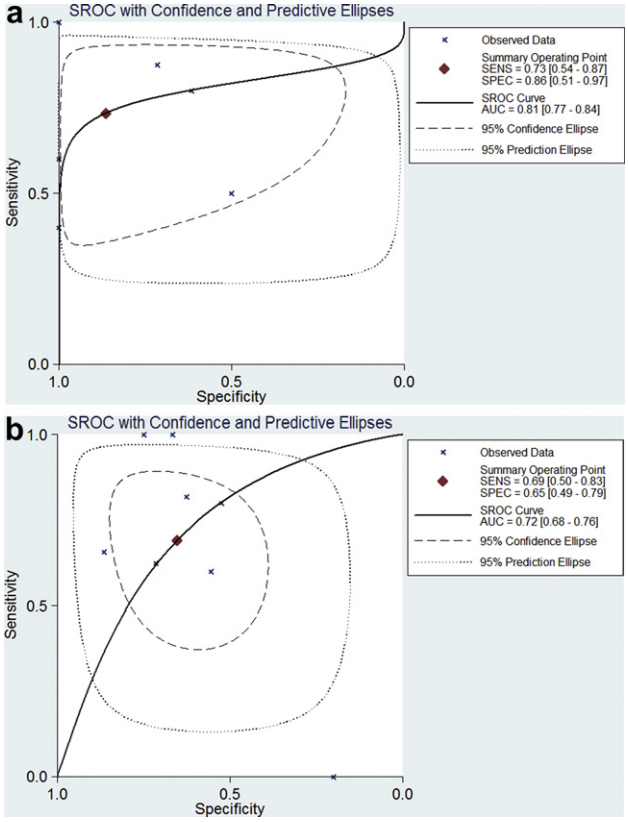

Figure 2. The summary receiver operating characteristic (SROC) curves for SUV2 $\leq$ 2.5 (a), SUV2:1 $\leq$ 0.5 (b) on a per-patient basis. Each cross represents each study in the meta-analysis. The size of the circle indicates the study size. The AUC estimate for SUV2 $\leq$ 2.5 and SUV2:1 $\leq$ 0.5 were 0.81 and 0.72 respectively. AUC: area under the curve.

Statistical analysis: Li Hongtao, Wang Xiaojin.
Manuscript preparation: Li Hongtao.
Manuscript editing: Li Hongtao, Sun Yuanjue.
Manuscript review: Li Hongtao, Shen Zan, Min Daliu.

Conflict of interest statement

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled "18F-FDG positron emission tomography for the assessment of neoadjuvant therapy reponse in osteosarcomas: A meta-analysis".

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