Meta-Analysis of the Diagnostic Accuracy of Primary Bone and Soft Tissue Sarcomas by ^{18}F -FDG-PET

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Highlights of the Study

- Some sarcomas present substantial diagnostic challenges that demand accurate diagnostic modalities.
- We performed a meta-analysis of available evidence and found the pooled sensitivity and specificity of FDG-PET combined with CT for the detection of sarcomas to be 89.2 and 76.3%, respectively, i.e., higher than those of FDG-PET alone.
- FDG-PET can efficiently differentiate between benign and malignant tumors, with a mean standard uptake value of maximally 2.52 units in benign and 6.81 units in malignant tumors with 89.2% sensitivity and 75.1% specificity.

Keywords

Positron emission tomography · PET · Sarcoma · Meta-Analysis

Abstract

Objectives: The goal of this meta-analysis was to assess the use of FDG-PET in the diagnosis of primary bone and soft tissue sarcomas. **Subjects and Methods:** Several databases, including PubMed, Embase, Cochrane Library, and Web of Science, were searched. In addition to sensitivity and specificity, the diagnostic accuracy region for detecting and grading sarcomas were pooled using bivariate and hierarchical summary receiver-operating characteristic (HSROC) models. Subgroup analysis included pooling soft tissue and bone sar-

comas separately, and sensitivity analysis included high-quality studies. The quality of eligible studies was assessed using QUADAS-2. **Results:** Of the 1,258 papers screened, 21 studies satisfied the inclusion criteria. The pooled sensitivity and specificity of FDG-PET combined with CT for the detection of sarcomas were 89.2 and 76.3%, respectively. These diagnostic accuracy measures were higher when combined with CT than those of PDG-PET alone. Diagnostic accuracy for bone and soft tissue lesions were comparable but slightly better for soft tissue tumors. Pooling only the high-quality studies with low risk of bias yielded a sensitivity of 88.5% and specificity reduced to 65.6%. There was no evidence for publication bias, but significant heterogeneity among the studies was apparent. This study also showed that FDG-PET can efficiently differentiate between benign and malignant tu-

mors, with a mean standard uptake value of maximally 2.52 units in benign and 6.81 units in malignant tumors (89.2% sensitivity and 75.1% specificity). **Conclusion:** Our findings indicate FDG-PET can efficiently differentiate between benign and malignant bone and soft tissue tumors. We also found that FDG-PET improves accuracy in diagnosing soft tissue sarcomas when combined with CT.

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Introduction

Bone sarcomas account for less than 0.2% of malignancies, whereas soft tissue sarcomas constitute less than 1% of all cancers [1]. The radiological tools used in the diagnosis and staging of musculoskeletal sarcomas encounter several challenges as sarcomas form a substantial diagnostic dilemma that demands new modalities to provide better evaluation. Positron emission tomography (PET), a noninvasive imaging technique that detects γ -rays emitted from isotopes, has the potential to increase diagnostic accuracy. In particular, the uptake of fluorine-18 deoxyglucose (^{18}F -FDG) is used to detect the increased metabolic rate of glucose by tumorous cells [2]. ^{18}F -FDG-PET allows visualization of the tumors as it reflects the metabolic rate of metabolically active tumors in human tissues, and tumors of higher grade are more metabolically active than those of lower grade. Although FDG uptake cannot differentiate between the histological tumor subtypes, it was sufficiently accurate to differentiate low- from high-grade sarcomas given different standard uptake values (SUV). However, differentiating between benign tumors and low-grade sarcomas was reported to be difficult [3, 4]. Due to the low incidence of bone and soft tissue sarcoma, and the high costs of PET imaging, most of the published studies had only small numbers of patients; therefore, the level of evidence obtained from these smaller studies were mostly underpowered. Because of that, it was important to pool the effect measures to provide higher-quality evidence that can be used to build guidelines for the diagnosis and management of bone and soft tissue sarcomas.

The aim of this study was to provide an updated review of the published evidence on the level of accuracy of PET in the diagnosis and grading of primary bone and soft tissue sarcomas. Furthermore, this study aims to quantify the added diagnostic accuracy in combining CT with PET.

Subjects and Methods

This study utilizes a meta-analytical approach to synthesize evidence from observational diagnostic studies. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [5] and the checklist for Meta-Analyses of Observational Studies (MOOSE) [6] guided the reporting of this study. This review is registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42018081904).

Search Strategy

A comprehensive search was performed in Medline, Cochrane Central including Cochrane Central Register of Controlled Trials, Embase, and Web of Science, from January 1, 1990, through December 1, 2017, to retrieve all published studies assessing the role of FDG-PET in the detection and grading of musculoskeletal tumors. The search was limited to human subjects and English language publications. A manual search using reference lists of original research and reviews was also carried out. The search terms used were PET OR positron emission tomography) AND (bone tumor OR osseous sarcoma OR sarcoma) as words in the title or abstract.

Inclusion and Exclusion Criteria

Studies that used FDG-PET and pathological confirmation of bone or soft tissue tumors were included. Case reports, reviews, editorials, or animal studies, as well as studies using multiple imaging modalities in combination without a clear way to discern the data evaluating each modality separately were excluded. Reports of musculoskeletal tumors in combination with other tumors, in a way data could not be extracted separately, were also excluded.

Data Extraction

Data were extracted independently by 2 reviewers. Adjudication was done by a third author.

Risk of Bias Assessment

Risk of bias was independently assessed by 2 reviewers using Quality Assessment of Diagnosis Accuracy Studies (QUADAS-2) [7], a validated tool for assessing diagnostic studies.

Data Synthesis

Meta-analyses were used to pool the accuracy measures of FDG-PET in detecting and grading sarcomas. This included analysis of different FDG-PET interpretation methods and combined FDG-PET and CT scan. Accuracy estimates were obtained using both the bivariate and the hierarchical summary receiver-operating characteristic (HSROC) models. Meta-analyses were conducted using comprehensive meta-analysis (CMA, version 3; Biostat, Englewood, NJ, USA), Meta-Disc (version 1.4; Complutense University of Madrid, Spain), and Metandi modules of Stata (release 15; StataCorp LLC, College Station, TX, USA).

In addition to the visual inspection of the forest plots, the bivariate and hierarchical models were used to quantify the amount of heterogeneity. The area of the prediction ellipse allows interpretation of the between-study heterogeneity as a proportion that is naturally bounded in the ROC space area. To assess the publication bias, Hunter's funnel plot was used.

Fig. 1. Flow diagram of studies included in the meta-analysis.

Results

Of the 1,258 articles screened, 21 were selected for the final analysis (Fig. 1). Of these 21 studies, 17 evaluated bone and soft tissue sarcomas using FDG-PET, whereas 5 used PET/CT either alone or in combination with dedicated FDG-PET. Nine studies were on soft tissue sarcomas only, and 7 on bone sarcomas alone. The remaining 5 studies evaluated both sarcomas; however, data on bone and soft tissue tumors could not be separated.

The meta-analysis included a total of 1,198 patients and 1,205 lesions. Sample sizes of the studies ranged from 11 to 202. Patient age ranged from 1 to 89 years, and 55% were males (Table 1). The soft tissue sarcomas were predominantly located in the extremities, while the bone and mixed sarcomas were also located in the trunk. Except for 4 studies, all studies had histopathological examination as the reference test.

In terms of the quality of the studies, the majority of the studies had relatively moderate to high quality (Table 2). The exclusion criteria were described in only 39% of the studies. Most studies used valid reference tests, yet it was unclear if the reference standard was performed blindly from the index test. Most studies described the

index test FDG-PET procedures in sufficient details, yet a cutoff was prespecified in only 2 studies. In 24% of the studies, it was not clear whether the index test was interpreted independently of the reference test or not. In 4 studies, part of the study subjects received a reference standard other than the histopathology. The time interval between the index test and the reference standard was unclear in 14 studies. In 4 studies, not all patients had undergone the reference standard tests, with the proportion ranging from 8 [8] to 45% [9].

Twenty-one studies provided sufficient data for calculation of the sensitivity and specificity for the detection and grading of sarcoma. The overall pooled sensitivity was 89.2% (95% CI: 82.3–93.7%), and pooled specificity was 75.1% (95% CI: 69.8–81.9%) (Fig. 2). The area under the summary ROC curve was 87.5% (Fig. 3). We found sensitivity, specificity, and AUC of bone sarcomas to be 87.2% (95% CI: 78.1–94.8%), 71.4% (95% CI: 58.3–82.6%), and 86.9%, respectively. Likewise, for soft tissue sarcomas, sensitivity was 89.0% (95% CI: 79.4–95.2%), and specificity was 72.1% (95% CI: 60.9–85.9%) with an AUC of 90.2%.

PET scans were interpreted using the semiquantitative method (SUV) in 19 studies, from which we extracted the

Table 1. Characteristics of the 21 studies included in this meta-analysis

Ref. No.	Country	Design	Pat., <i>n</i>	Mean age (range), years	Males/females	Soft tissue, bone, or mixed	Location	Histopathol. confirmed, <i>n</i>
10	USA	prospective	25	49 (18–86)	–	mixed: ST = 16, B = 9	unclear	25
11	USA	prospective	20	55 (5–87)	12/8	B	unclear	20
12	Netherlands	prospective	22	50 (18–82)	13/9	ST	LL = 20, UL = 2	22
13	UK	prospective	30	53 (6–85)	17/13	ST	LL = 22, UL = 5, trunk = 4	31
14	UK	retrospective	29	50 (18–76)	14/15	ST	unclear	29
15	Germany	prospective	102	49 (1–89)	55/47	ST	LL = 49, UL = 25, trunk = 28	102
4	Japan	prospective	11	44 (12–78)	4/7	B (chondrosarcoma)	LL = 5, UL = 3, trunk = 3	11
16	Germany	prospective	202	28 (1–78)	127/75	B	LL = 88, UL = 35, trunk = 79	202
17	UK	prospective	18	23.5 (12–62)	8/10	ST (malig. neurofibroma)	LL = 13, UL = 3, trunk = 7	12
18	Germany	prospective	19	54 (16–78)	–	ST	unclear	19
19	Japan	prospective	52	45.3 (12–77)	26/29	mixed: ST = 35, B = 18	ST: LL = 10, UL = 5, trunk = 3 B: LL = 18, UL = 10, trunk = 7	52
20	Switzerland	prospective	83	–	–	B	unclear	72
21	Japan	prospective	31	45.2 (11–83)	12/19	mixed: ST = 23, B = 10	LL = 22, UL = 7, trunk = 4	33
3	Japan	prospective	44	58.1 (27–87)	29/28	ST (lipomatous tumors)	unclear	44
8	Switzerland	prospective	50	36.9 (11–72)	29/21	B	unclear	46
22	S. Korea	retrospective	91	42 (6–79)	47/44	mixed: ST = 44, B = 47	UL, LL = 71, trunk = 20	83
23	Germany	retrospective	46	–	–	ST	unclear	46
24	India	retrospective	22	22.2 (8–66)	14/8	B	LL = 16, UL = 3, trunk = 2, head = 1	22
25	USA	retrospective	98	–	–	B	unclear	64
26	Japan	retrospective	103	59.1±18.6	53/50	mixed	unclear	103
9	USA	retrospective	100	54 (9–89)	58/42	ST	UL and LL = 100	54

SUV as it was reported in these studies. The analysis showed a sensitivity of 89.8% (95% CI: 81.1–94.7%), specificity of 75.8% (95% CI: 68.8–81.6%), and AUC of 88.1%. On the other hand, visual assessment was used in 4 studies, and showed a sensitivity of 93.2% and AUC of 94.8%, while the specificity dropped to 40%. When the data of studies that used PET/CT in combination were pooled,

sensitivity and specificity slightly increased to 89.2% (95% CI: 83.6–93.1%) and 76.3% (95% CI: 70.4–82.7%) compared to 82.3% (95% CI: 76.8–90.3%) and 73.9% (95% CI: 66.8–80.0%) in FDG-PET alone, respectively.

Seventeen studies provided data concerning SUV. Overall, benign bone and soft tissue tumors had an average SUV of 2.52 (SD = 0.63), while malignant sarcomas

Table 2. QUADAS-2 assessment of the 21 included studies in the meta-analysis assessing the risk of bias and applicability

Ref. No.	Risk of bias				Applicability		
	patient selection	index test	reference standard	flow and timing	patient selection	index test	reference standard
10	low	unclear	unclear	low	low	unclear	low
11	unclear	unclear	unclear	unclear	low	unclear	low
12	low	high	unclear	low	high	unclear	low
13	low	unclear	unclear	low	low	unclear	low
14	low	unclear	unclear	unclear	low	low	low
15	low	unclear	unclear	low	low	unclear	low
4	low	unclear	unclear	low	low	unclear	low
16	low	unclear	unclear	low	low	unclear	low
17	low	unclear	unclear	high	low	unclear	high
18	low	high	unclear	low	low	high	low
19	low	high	unclear	unclear	low	unclear	low
20	low	high	unclear	unclear	unclear	unclear	low
21	unclear	unclear	unclear	low	unclear	unclear	low
3	unclear	unclear	unclear	low	unclear	unclear	low
8	low	low	unclear	unclear	low	unclear	low
22	unclear	unclear	unclear	high	unclear	unclear	unclear
23	low	high	unclear	low	low	unclear	low
24	unclear	high	low	low	low	unclear	low
25	unclear	unclear	unclear	low	high	high	low
26	low	unclear	unclear	low	low	unclear	low
9	high	high	unclear	high	high	low	unclear

had a mean of 6.81 (SD = 1.03). These differences are statistically significant ($p < 0.05$). The range of SUVs was 0.83–11.4 for malignant and 0.63–5.1 for benign cases. Likewise, it was 0.83–1.3 for low-grade sarcomas and 4.5–11.4 when they were of high grade. When pooling the accuracy measure of the high-quality studies with low risk of bias, sensitivity, specificity, and AUC were 88.5% (95% CI 75.6–95.1%), 65.6% (95% CI 47.1–80.3%), and 88.2%, respectively. Hunter's funnel plots showed no evidence to suggest any serious publication bias.

Discussion

The gold standard of diagnosis and grading of bone and soft tissue sarcomas is the histopathological examination of the tumor through biopsy, usually guided by anatomical imaging. Biopsy has a diagnostic accuracy of approximately 80% with a need of a redo-biopsy in 15–20% of cases, and a risk of complications estimated to be 20%, of which 8% carry serious morbidities [13]. Radiographic tests such as X-ray, CT, and MRI are widely used for the diagnosis of musculoskeletal system malignancies. De-

Fig. 2. Sensitivity and specificity for the detection of sarcoma. HSROC, hierarchical summary receiver-operating characteristic.

Fig. 3. Forest plot of the studies included.

spite the good anatomical localization and resolution for these tests, the ability of these methods to define the nature of musculoskeletal sarcomas was unsatisfactory raising the need for a different method for radiological assessment that addresses the histopathological grade of the sarcoma and helps guide treatment. FDG-PET is utilized for the quantification of glucose consumption of cells in the body, which makes it possible to measure the metabolic activity of malignant cells. However, because PET does not provide an accurate resolution of images, the

combination of PET with CT has been long appreciated for providing detailed assessment of functional anatomy [22].

Our meta analyses indicated that FDG-PET is an efficient tool in the assessment of sarcomas with high sensitivity and specificity. We found FDG-PET could be an optimal screening tool for sarcoma to be ruled out. This is further asserted by the statistically and clinically different mean SUV values in sarcomas and benign tumors. Regarding the ability to differentiate benign from malignant

tumors and grading the malignant tumors, FDG-PET showed some promising results, especially among specific histological groups such as chondroid tumors [2]. However, we were unable to discern the differences between different grades of sarcomas due to heterogeneous pathophysiological changes in the sarcoma group. The reported studies reflect the present clinical practice and had many characteristics that render the analysis of data critical for several reasons, most important being the clinical heterogeneity introduced due to varying measurement methods of FDG uptake. Additionally, the acquisition time for the SUV activity varied between studies from 40 to 60 min. This is important as evidence suggests that FDG uptake by high-grade tumors continues to increase until 4 h [14]. It was also noticed that most of the studies using the semi-quantitative SUV method did not specify whether they used the mean or maximum SUV, which is important for daily clinical practice [3, 4, 9, 11–14, 17–19, 21–26]. Moreover, the varying SUV cutoff points used made it difficult to define a test as positive. Furthermore, some studies did not clearly describe the pathological criteria used for diagnosis. It was unclear whether each patient had the index and reference tests interpreted independently to avoid verification bias. Heterogeneity of reported pathology was another challenge where some studies included both soft tissue and bone sarcomas without providing sufficient data to separate them for analyses.

Despite the above-mentioned limitations, sensitivity analysis of high-quality studies of lower risk of bias found that FDG-PET had comparable sensitivity (88.5%); however, the specificity dropped to 65.6%. This further supports the idea that FDG-PET can serve as a good screening tool for sarcomas, bearing in mind the high rate of false-positive results that need to be interpreted carefully.

Our findings are consistent with what has been published in the literature. For instance, in their meta-analysis,

Ioannidis and Lau [27] studied different SUV levels and evaluated the diagnostic accuracy associated with the use of different thresholds: >2.0 and >3.0. In 2004, Bastiaannet et al. [28] pooled the available evidence on the use of PET in the detection of sarcomas. They found that the overall sensitivity and specificity were 91 and 85%, respectively. Etchebehere et al. [1] performed a systematic review to compare the accuracy of FDG-PET versus combined FDG-PET in the diagnosis of soft tissue musculoskeletal sarcoma. They found that FDG-PET/CT is more specific and accurate than dedicated FDG-PET. On the other hand, dedicated FDG-PET was more sensitive in the diagnosis of soft tissue sarcomas. To elucidate the value of PET/CT, Muheremu et al. [29] pooled the data of 16 trials and concluded that PET combined with CT is a reliable imaging method to be applied in the diagnosis of osseous and soft tissue malignancies. New diagnostic modalities including PET-MRI combinations have been investigated. However, the precise role that PET/MRI will play remains to be determined.

Conclusion

This systematic review studying the value of FDG-PET showed that it is a sensitive tool in the detection of primary bone and soft tissue sarcomas and the differentiation between benign and high-grade tumors. Further high-quality studies with standardized FDG uptake measures with varying SUV cutoff values are warranted.

Disclosure Statement

The authors do not have any conflicts of interest to declare.

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