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Positron emission tomography/computed tomography for osseous and soft tissue sarcomas: A systematic review of the literature and meta-analysis

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Abstract. In order to elucidate the value of positron emission tomography (PET)/computed tomography (CT) in the clinical diagnosis and treatment of osseous and soft tissue malignancies, two authors independently searched the PubMed, Medline, Elsevier, Embase and Cochrane Library databases for literature published between January 2003 and February 2016, using the key words 'PET/CT', 'positron emission tomography/computed tomography', 'osseous sarcoma', 'bone tumor', 'soft tissue sarcoma' and 'neoadjuvant', to identify prospective and retrospective studies on the applicability of PET/CT on the clinical diagnosis of bone and soft tissue lesions, and evaluation of their response to neoadjuvant therapies. Data were independently extracted by the two authors and any disagreements were resolved by a third author when necessary. Extracted data were analyzed by Meta-Disc 1.6 software. As a result, 16 trials with a total of 883 patients and 2,214 lesions were included in the present study. The overall diagnostic accuracy of PET/CT exhibited a sensitivity and specificity of 0.90 (0.86-0.92) and 0.89 (0.85-0.92), respectively, and the effect of neoadjuvant therapy was assessed with a sensitivity and specificity of 0.79 (0.30-0.93) and 0.79 (0.69-0.89), respectively. Thus, it may be concluded from the present study that PET/CT is a reliable imaging method to be applied in the diagnosis and treatment of osseous and soft tissue malignancies.

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Introduction

Osseous and soft tissue sarcomas are rare conditions that may easily be misdiagnosed. Apart from pathological observations of biopsies, imaging studies such as X-rays, whole-body bone scan, computed tomography (CT) and magnetic resonance imaging (MRI) are often used for diagnostic purposes in cases with osseous and soft tissue sarcomas. Positron emission tomography (PET) is an imaging method that semiquantitatively measures the metabolic rate of tissues by measuring the glucose intake level of cells *in vivo*. As malignant tumors normally have a higher metabolic rate compared with benign lesions and normal tissues, PET may theoretically be used to discriminate benign from malignant tumors and, by assessing the metabolic activity of tumor cells following neoadjuvant therapy, it may evaluate the treatment effect without invasive methods, such as biopsy. PET/CT is a combination of the CT and PET techniques, which is able to show the accurate anatomical structure and metabolic activity of the tissues in the whole body. As a new and sophisticated imaging diagnostic tool, PET/CT is gradually used in an increasing number of medical centers. In the current literature, extensive research has been performed on the application of PET/CT in the diagnosis of a variety of tumors, such as lung, colorectal and breast cancer, melanoma and lymphoma (1-3). However, due to the low incidence of primary malignant osseous sarcomas, there are only few reports with large patient samples on the diagnostic accuracy or treatment effect evaluation of PET/CT in osseous and soft tissue sarcomas.

Data collection methods

Literature search. Two independent reviewers performed a computerized search of databases including PubMed (2003-2016), Medline (2003-2016), Embase (2003-2016), Elsevier (2003-2016) and the Cochrane Library (2008-2016) with the mesh words: 'PET/CT', 'positron emission tomography/computed tomography', 'osseous sarcoma', 'bone tumor', 'soft tissue sarcoma' and 'neoadjuvant', for randomized controlled trials, half-randomized controlled studies, prospective and retrospective cohort studies on the accuracy

of PET/CT for the diagnosis of bone and soft tissue sarcomas, and the evaluation of response to neoadjuvant therapy. For studies whose eligibility for the inclusion criteria failed to reach consensus between the two authors, a third author was invited to settle the disputes.

Study quality assessment. Two authors independently assessed the quality of the included studies by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool (4). Each study was scored as '+' (positive), '-' (negative) and '?' (unclear). In case of disagreement, a third author made the final decision. Studies with <7 '+' were considered to be of low methodological quality and high risk of bias. The methodological quality of the included trials is outlined in Table I.

Data extraction. Data in the included trials, including the authors of each study, study design, patient sample size, patient age, origin, time of follow-up and intervention methods, were extracted by two independent reviewers. Patient numbers with true-positive, false-positive, true-negative and false-negative diagnosis and evaluations in each study were extracted and recorded in specific tables. In case that the same patients were analyzed in more than one study, they were extracted and analyzed as one patient population.

Data were analyzed and processed by Meta-Disc software (5). Two authors checked the data input to ensure no errors were made. Considering the possibility of publication bias between the studies, the analyses were performed using the random-effects modes. The I^2 test was used to test heterogeneity and studies were considered to have significant heterogeneity if I^2>50%. Subgroup or sensitivity analysis was used in case of significant heterogeneity due to the methodological quality of the included trials. The differences in each study were defined by odds ratios (ORs) with 95% confidence intervals (95% CIs) of the categorical outcome frequencies in the study groups and the control groups, respectively. The OR of each individual trial was shown in a forest plot.

Table I. Results of quality assessment for 16 eligible studies (indicated by ref. nos.).

Questions	(Refs.)														
	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)	(21)
Was the spectrum of patients representative of the patients who received the test in practice?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Were selection criteria clearly described?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Is the reference standard likely to help correctly classify the target condition?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Is the time between performance of reference standard and index test short enough?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Did the whole sample or a random selection of the sample receive verification by using a reference standard?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Did patients undergo examination with the same reference standard regardless of the index test result?	-	-	-	+	+	-	-	+	-	+	+	+	+	+	+	+
Was the reference standard performed independently of the index test?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Was the execution of the index test described in sufficient detail to permit replication of the test?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Was the execution of the reference standard described in sufficient detail to permit replication of the test?	+	+	-	+	+	-	-	+	-	+	+	+	+	+	+	+
Were the index test results interpreted without knowledge of the results of the reference standard?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Were the reference standard results interpreted without knowledge of the results of the index test?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Were the same clinical data available when test results were interpreted as would be available in practice?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Were uninterpretable and/or intermediate test results reported?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Were withdrawals from the study explained?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Results

Results of the study selection process. Of the 1,310 articles screened, 16 (6-21) were selected for the final analysis (Fig. 1). The meta-analysis included a total of 883 patients and 2,214 lesions (Tables II and III). The majority of the studies were proven to be of relatively high quality according to the QUADAS quality assessment tool (Table I).

Results of the meta-analysis

Diagnostic accuracy. A total of 9 studies, including 738 patients with 2,069 lesions, investigated the diagnostic accuracy of PET/CT in osseous and soft tissue sarcomas (Table IV). On patient-based analysis, the overall sensitivity and specificity were 0.90 (0.86-0.92) and 0.89 (0.85-0.92). The area under the summary receiver operating characteristic (SROC) curve was 0.97, Q=0.91 (Fig. 2). On lesion-based analysis, the overall sensitivity and specificity were 0.96 (0.94-0.97) and 0.95 (0.93-0.96). The area under the SROC curve was 0.97, Q=0.88 (. 3). The meta-analysis indicated that PET/CT is able to diagnose osseous and soft tissue sarcomas with high sensitivity and specificity.

Table II. Demographic characteristics of the included studies.

Authors	Patient no.	Age[a], years	Study type	Patient enrollment	Time of study	(Refs.)
Tateishi *et al*	117	42±21	Prospective	Consecutive	Unclear	(6)
Strobel *et al*	50	36.9 (11-72)	Prospective	Consecutive	Unclear	(7)
Shin *et al*	91	42 (6-79)	Retrospective	Unclear	2004.5-2007.6	(8)
Charest *et al*	212	47±19.2	Retrospective	Consecutive	2004.5-2008.4	(9)
Pepirkova *et al*	93	50.1±14.9	Retrospective	Unclear	2004.1-2007.5	(10)
Fuglø *et al*	89	NA	Retrospective	Unclear	2001.12-2010.12	(11)
Sharma *et al*	53	20.1±10.5	Retrospective	Unclear	2006.3-2012.1	(12)
Xu *et al*	103	59.1±18.6	Retrospective	Unclear	2007.3-2013.2	(13)
Byun *et al*	206	15 (4-71)	Retrospective	Consecutive	2006.1-2011.11	(14)
Iagaru *et al*	14	36±14	Retrospective	Consecutive	1999.1-2004.12	(15)
Evilevitch *et al*	42	17 (7-31)	Prospective	Consecutive	2005.1-2007.1	(16)
Hamada *et al*	11	17 (10.68)	Prospective	Consecutive	2002.6-2006.8	(17)
Benz *et al*	12	31.6±15.0	Prospective	Consecutive	2005.2-2007.11	(18)
Im *et al*	20	15 (10-25)	Prospective	Consecutive	2003.8-2010.7	(19)
Byun *et al*	27	15 (10-23)	Prospective	Consecutive	2010.5-2012.3	(20)
Byun *et al*	31	15 (10-21)	Prospective	Consecutive	2010.5-2013.9	(21)

[a]Presented as mean ± standard deviation of median (range). NA, not available.

Table III. Characteristics of PET/CT imaging and of reference standards.

Authors	FDG (MBq)	Measures	Reference standard	Potential verification bias	(Refs.)
Tateishi *et al*	300-370	Visualization, SUV	Histology and radiological follow-up	Very limited	(6)
Strobel *et al*	350-400	Visualization, SUV	Histology, clinical and imaging follow-up	Very limited	(7)
Shin *et al*	8.1/kg	Visualization, SUV	Histology, clinical and imaging follow-up	Limited	(8)
Charest *et al*	370-500	Visualization, SUV	Histology	Very limited	(9)
Pepirkova *et al*	370-555	Visualization, SUV	Histology	Very limited	(10)
Fuglø *et al*	4.0/kg	Visualization, SUV	Histopathology, clinical and imaging follow-up	Limited	(11)
Sharma *et al*	370	Visualization, SUV	Histopathology, clinical and imaging follow-up	Limited	(12)
Xu *et al*	3.5/kg	Visualization, SUV	Histopathological examination	Very limited	(13)
Byun *et al*	7.4 /kg	Visualization, SUV	Histology, clinical and imaging follow-up	Very limited	(14)
Iagaru *et al*	550	Visualization, SUV	Histopathological examination of surgical specimen	Very limited	(15)
Evilevitch *et al*	333-407	Visualization, SUV	Histopathological examination of surgical specimen	Very limited	(16)
Hamada *et al*	370	Visualization, SUV	Histopathological examination of surgical specimen	Very limited	(17)
Benz *et al*	7.8/kg	Visualization, SUV	Histopathological examination of surgical specimen	Very limited	(18)
Im *et al*	166-666	Visualization, SUV	Histopathological examination of surgical specimen	Very limited	(19)
Byun *et al*	370	Visualization, SUV	Histopathological examination of surgical specimen	Very limited	(20)
Byun *et al*	370	Visualization, SUV	Histopathological examination of surgical specimen	Very limited	(21)

PET, positron emission tomography; CT, computed tomography; SUV, standardized uptake value.

Evaluation of response to neoadjuvant therapy. A total of 7 studies, including 145 patients, investigated the accuracy of PET/CT in assessing the treatment effect of neoadjuvant therapy on patients with osseous and soft tissue sarcomas (Table V). Generally, a ratio of maximum standardized uptake value (SUVmax) after therapy/SUVmax prior to therapy of <0.5 was considered as an indication of effective neoadjuvant therapy in the index test, and necrosis of >90% in the intraoperative specimen was considered as an indication of effective neoadjuvant therapy in the reference test. The overall sensitivity and specificity were 0.79 (0.30-0.93) and 0.79 (0.69-0.89), respectively. The area under the SROC curve was 0.87, Q=0.80 (Fig. 4). The meta-analysis indicated that PET/CT may be used to monitor the effect of neoadjuvant therapy in patients with osseous and soft tissue sarcomas with high sensitivity and specificity.

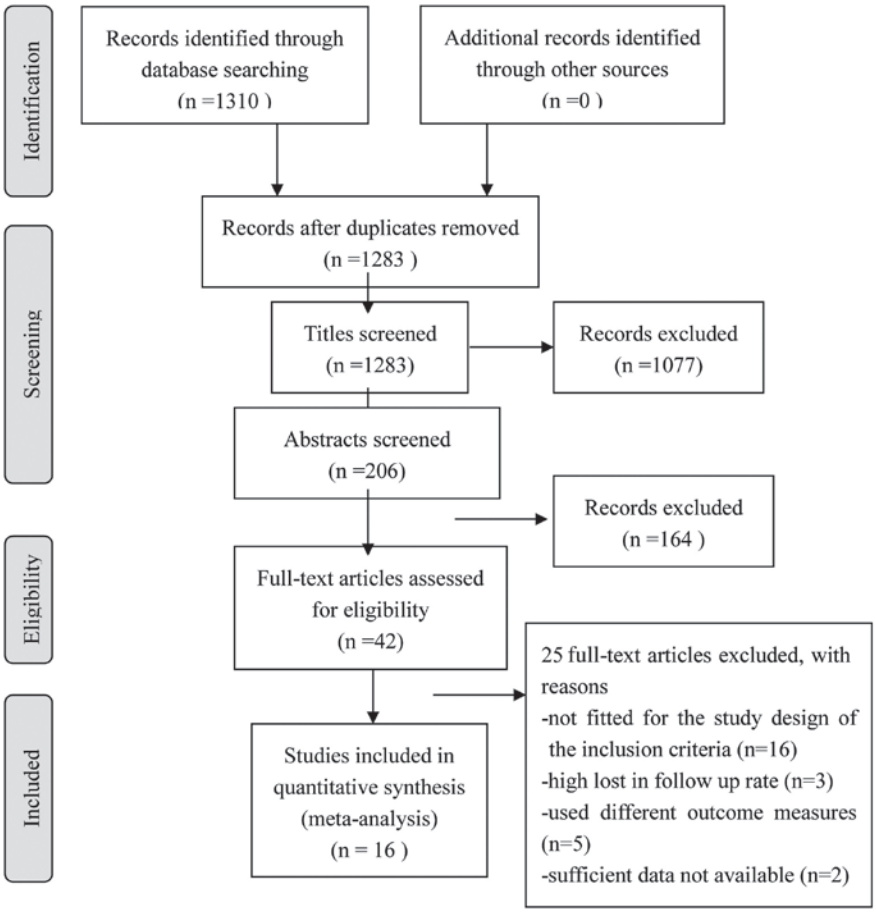

Figure 1. Flow chart of the selection of studies for the meta-analysis.

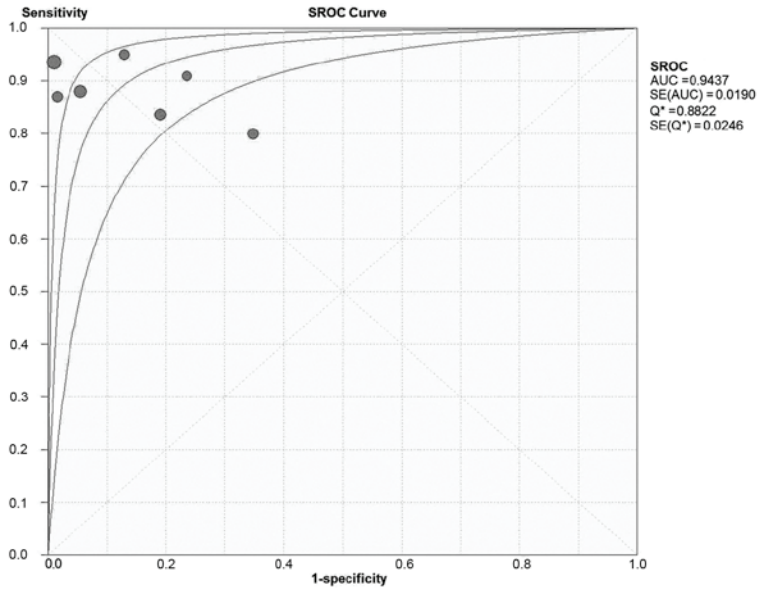

Figure 2. SROC curve of patient based analysis of the included studies. SROC, symmetric receiver operating characteristics curve; AUC, area under the curve; SE, standard error.

Discussion

Imaging studies are important for the diagnosis of various tumors. Currently, radiographic tests such as X-ray, CT and MRI are widely applied for the diagnosis and treatment of musculoskeletal system malignancies (22).

^{18}F-fluorodeoxyglucose (FDG) PET is used for the semiquantification of glucose consumption by cells in the

Table IV. Diagnostic accuracy of PET/CT on osseous and soft tissue sarcomas in the included studies.

Authors	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	(Refs.)
Byun *et al*	52	15	3	763	0.95 (0.85-0.99)	0.98 (0.97-0.99)	(20)
Charest *et al*	153	0	10	49	0.94 (0.89-0.97)	1.00 (0.93-1.00)	(9)
Fuglø *et al*	20	1	3	64	0.87 (0.66-0.97)	0.98 (0.92-1.00)	(11)
Pepirkova *et al*	424	0	3	71	0.99 (0.98-1.00)	1.00 (0.95-1.00)	(10)
Sharma *et al*	38	4	2	27	0.95 (0.83-0.99)	0.87 (0.70-0.96)	(12)
Shin *et al*	36	16	9	30	0.80 (0.65-0.90)	0.65 (0.50-0.79)	(8)
Strobel *et al*	30	4	3	13	0.91 (0.76-0.98)	0.76 (0.50-0.93)	(7)
Tateishi *et al*	44	4	6	69	0.88 (0.76-0.95)	0.95 (0.87-0.98)	(6)
Xu *et al*	51	8	10	34	0.84 (0.72-0.92)	0.81 (0.66-0.91)	(13)
All cases	372	37	43	286	0.90 (0.86-0.92)	0.89 (0.85-0.92)	
All lesions	848	52	49	1,120	0.95 (0.93-0.96)	0.96 (0.94-0.97)	

PET, positron emission tomography; CT, computed tomography; TP, true-positive; TN, true-negative; FP, false-positive; FN, false-negative; CI, confidence interval.

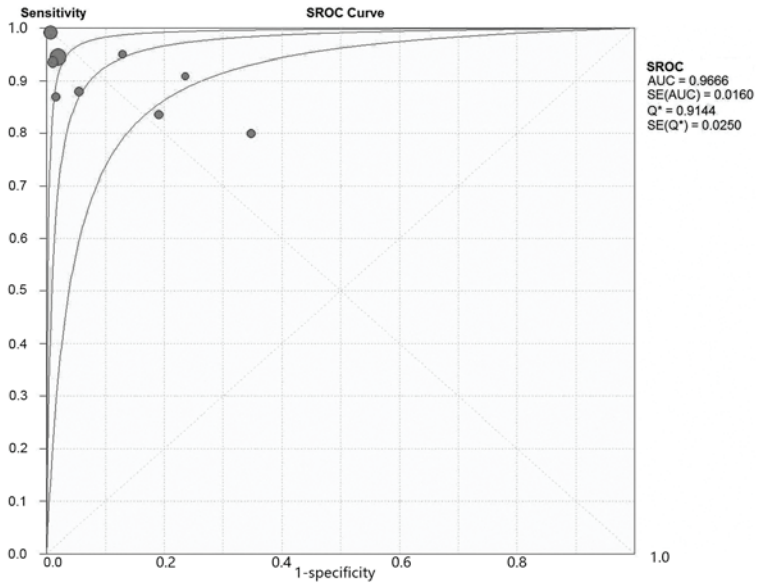

Figure 3. SROC curve of lesion based analysis of the included studies. SROC, symmetric receiver operating characteristics curve; AUC, area under the curve; SE, standard error.

body, which makes it possible to measure the enhancement of metabolic activity in cancer tissue. This is normally performed by calculating the SUVmax. ^{18}F-FDG PET has been successfully used for the diagnosis of several types of cancer, such as lung cancer, melanoma, lymphoma, head and neck tumors, brain tumors, esophageal and colorectal cancer (23). The majority of the studies on the diagnostic value of PET in different types of tumors have concluded that it is a sensitive imaging modality for detection, staging and re-staging in oncology (24-26).

FDG-PET has been applied for diagnostic purposes in various malignant tumors since the early 90s (27). However, although ^{18}F-FDG may locate abnormally functioning anatomical structures, the precise localization of the tumors may not be possible with PET alone. Combining PET with a high-resolution anatomical imaging modality, such as CT, addresses this issue, provided that the images from the two modalities are accurately co-registered. Since 2003, a combination of PET and CT in one imaging device has gained increasing popularity and is referred to as integrated PET/CT. Integrated PET/CT is superior to PET or CT alone, as it can accomplish morphological and functional imaging in one procedure, and the images obtained with PET/CT were more accurate regarding localization of the tumor compared with PET and CT alone, or the fusion of PET and CT with software (28).

There are several reports on predicting the aggressiveness of musculoskeletal tumors by measuring the glucose consumption level using PET/CT (29). However, due to the low incidence of primary malignant osseous sarcomas and

Table V. Accuracy of PET/CT assessment on the effect of neoadjuvant therapy on patients with osseous and soft tissue sarcomas in the included studies.

Authors	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	(Refs.)
Benz *et al*	3	1	1	7	0.75 (0.19-0.99)	0.88 (0.47-1.00)	(18)
Byun *et al*	8	2	4	13	0.67 (0.35-0.90)	0.87 (0.60-0.98)	(20)
Byun *et al*	11	1	1	8	0.92 (0.62-1.00)	0.89 (0.52-1.00)	(21)
Evilevitch *et al*	8	10	0	24	1.00 (0.63-1.00)	0.71 (0.53-0.85)	(16)
Hamada *et al*	5	0	0	4	1.00 (0.48-1.00)	0.88 (0.40-1.00)	(17)
Iagaru *et al*	3	1	3	7	0.50 (0.12-0.88)	0.88 (0.47-1.00)	(15)
Im *et al*	6	4	3	7	0.67 (0.30-0.93)	0.64 (0.31-0.89)	(19)
Total	44	19	12	70	0.79 (0.30-0.93)	0.79 (0.69-0.89)	

PET, positron emission tomography; CT, computed tomography; TP, true-positive; TN, true-negative; FP, false-positive; FN, false-negative; CI, confidence interval.

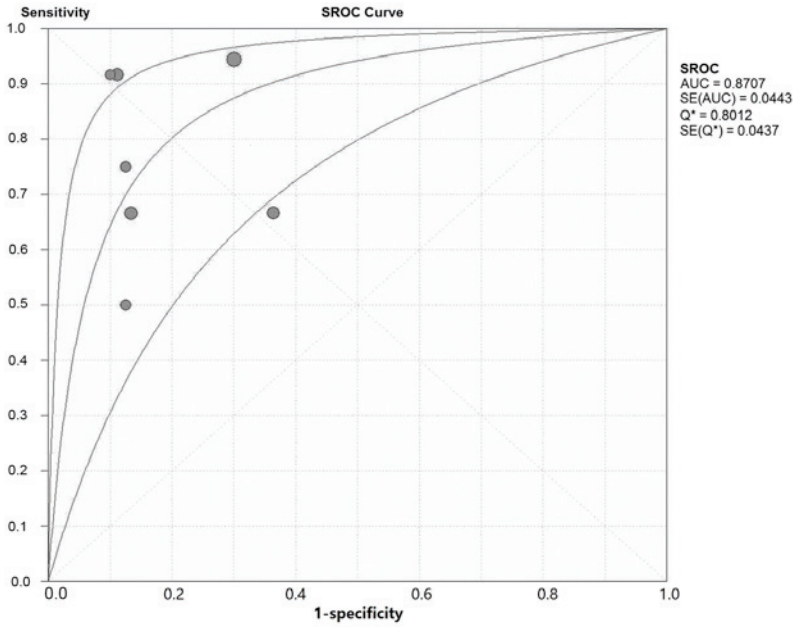

Figure 4. SROC curve on the assessment on the of neoadjuvant therapy effect.

the high cost of PRT/CT imaging, the majority of those studies included only a small number of patients; thus, the level of evidence obtained from those studies was greatly compromised.

The percentage of necrotic tissue following adjuvant therapy of tumors is one of the strongest prognostic factors of osteosarcoma (30). In the present study, PET/CT assessed the effect of neoadjuvant therapy with a sensitivity and specificity of 0.79 (0.30-0.93) and 0.79 (0.69-0.89), respectively, indicating that PET/CT may be a reliable non-invasive method for evaluating the effect of neoadjuvant therapy on patients with osseous and soft tissue sarcomas. However, as only 145 patients were included in the meta-analysis, a larger sample is required to reach a more reliable conclusion.

Although the present study provided evidence on the applicability of PET/CT on the diagnosis and evaluation of response to neoadjuvant therapy for osseous and soft tissue sarcomas using the SUVmax value, and the quality of the included studies was relatively high, the overall sample size may be insufficient. Considering that osseous as well as soft tissue sarcomas are malignancies with a low incidence, multi-center prospective studies with longer follow-up are required to investigate the full potential of PET/CT in the diagnosis and treatment of musculoskeletal tumors.

In conclusion, PET/CT may be a reliable method with high accuracy for the diagnosis and evaluation of treatment efficacy for bone and soft tissue sarcomas, although the present findings require verification by larger-sample studies.

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