Systematic Review and Meta-Analysis

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Conventional ^{99m}Tc-(hydroxy) methylene diphosphate remains useful to predict osteosarcoma response to neoadjuvant chemotherapy

Individual patient data and aggregate data meta-analyses

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Abstract

Background: The current standard of chemotherapy response evaluation holds the most important prognostic factor to be the histological assessment of the tumor necrosis of the excised lesion, but the major challenge is to find an early prognostic factor that will allow the adjuvant treatment regimen to be adjusted. The objective of this systematic review is to provide an up-to-date and unprecedented summary of the value of ^{99m}Technetium-methylene diphosphate or -hydroxymethylene diphosphate (^{99m}Tc-MDP/HMDP) scintigraphy for the preoperative evaluation of osteosarcoma response to chemotherapy.

Methods: Studies evaluating the alteration ratio (percentage change of the Tc-99m -MDP/HMDP uptake between before and after neoadjuvant chemotherapy) to predict the histological response of osteosarcoma to chemotherapy were searched for in MEDLINE, EMBASE, and Web of Science. A meta-analysis of individual patient data (IPD) was performed to determine the optimal cut-off point from the receiver operating characteristic (ROC) curve. Additionally, aggregate data (AD) meta-analysis was performed to compare the value of ^{99m}Tc-MDP/HMDP scintigraphy with that of other quantitative modalities, such as dynamic magnetic resonance imaging (MRI), ^{201}Tl scintigraphy, and ^{18}F-FDG PET-CT.

Results: Seven studies with 154 patients were included for the IPD meta-analysis. The optimal cut-off point of the alteration ratio was 31.0%. Five studies with 123 patients were considered for the AD meta-analysis. The pooled sensitivity and specificity were 0.76 (95% CI, 0.63–0.86) and 0.89 (95% CI, 0.79–0.95), respectively. There was a significant difference between the good and poor responders in terms of the diagnostic odds ratio. The summary ROC curve demonstrated that the area under curve (AUC) was 0.892, indicating excellent diagnostic accuracy.

Conclusion: Our findings have suggested that conventional ^{99m}Tc-MDP/HMDP scintigraphy remains as useful as recent quantitative modalities to predict the histological response of osteosarcoma to neoadjuvant chemotherapy.

Abbreviations: (H)MDP = (hydroxy)methylene diphosphate, 18F-FDG = fluorine-18-fluorodeoxyglucose, ^{201}Tl = ^{201}thallium, ^{99m}Tc = ^{99m}technetium, AD = aggregate data, AUC = area under curve, DWI = diffusion-weighted imaging, IPD = individual patient data, MRI = magnetic resonance imaging, PET-CT = positron emission tomography with computed tomography, PICOS = target population, index test, comparator test, outcome, and study design, PRISMA = preferred reporting items for systematic reviews and meta-analyses, QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies-2, sROC = summary receiver operating characteristic.

Keywords: chemotherapy, histological response, meta-analysis, osteosarcoma, technetium scintigraphy

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All authors were involved in the collection and interpretation of data. TK, MO, and NA designed the analysis and had full access to the raw data. TK, FT, and ST collected the data and performed the statistical analysis. All authors had the opportunity to review the analysis plan and outcome, participated in writing the manuscript, and provided final approval.

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1. Introduction

Osteosarcoma is the most common malignant bone tumor in adolescents and young adults, in which the malignant mesenchymal cells produce osteoid. The chemotherapy introduction in the 1970s led to a dramatic improvement in prognosis for patients with localized osteosarcoma. Five-year survival rates of $< 20\%$ improved to 60% to 70%. However, after the mid-1980s, little progress has been made in improving the prognosis, despite attempts to further intensify therapy using conventional chemotherapeutic drugs.[1,2] The histological response to neoadjuvant chemotherapy remains the most reliable prognostic factor used for deciding the treatment strategy of osteosarcoma. Good responders are defined by the percentage of residual viable cells less than 10%.[3] However, this gold standard criterion is available only after surgery. Other prognostic criteria, such as a patient's subjective response and clinical examination, have been investigated, but any clinically useful criteria have never been found thus far.[4] Furthermore, the quantitative assessment using ^{201}thallium (^{201}Tl) scintigraphy, dynamic magnetic resonance imaging (MRI), and more recently Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography with computed tomography (PET-CT) has been developed to predict the histological chemotherapy response.[5–7]

Historically, bone scintigraphy after intravenous administration of ^{99m}Technetium-methylene diphosphate or -hydroxymethylene diphosphate (^{99m}Tc-MDP/HMDP) has been utilized to delineate sites of distant bone metastases and to monitor tumor response to therapy. However, ^{18}F-FDG PET/PET-CT is now being investigated to determine its role in staging and monitoring tumor response and in detecting recurrent and metastatic disease. Therefore, ^{99m}Tc-MDP/HMDP scintigraphy, despite being easily and inexpensively performed in routine work, has been less studied.[8,9] The purpose of this study is to provide an up-to-date and unprecedented summary of the value of ^{99m}Tc-MDP/HMDP scintigraphy for the preoperative assessment of osteosarcoma response to chemotherapy. We performed a systematic review and meta-analysis to compare the ^{99m}Tc-MDP/HMDP uptake between good and poor histological responders in patients with osteosarcoma.

2. Material and methods

This meta-analysis was reported according to the preferred reporting items for systematic reviews and meta-analyses guidelines. All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.1. Study selection

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[10] the main research question was defined using the Target Population, Index Test, Comparator Test, Outcome, and Study Design strategy; Target Population, patients with osteosarcoma treated by chemotherapy and surgery; Index Test, preoperative ^{99m}Tc-MDP/HMDP scintigraphy evaluation for response to chemotherapy; Comparator Test, histological response to chemotherapy; Outcome, the percentage change of ^{99m}Tc-MDP/HMDP uptake between before and after neoadjuvant chemotherapy; Study Design, retrospective and prospective cohort studies. We searched MEDLINE, EMBASE, and Web of Science using the terms "technetium," "chemotherapy," and "osteosarcoma" without a time search limitation on April 18, 2017. We also hand-searched references from relevant articles and Google Scholar. Two investigators (FT and MPJ) reviewed potentially relevant articles independently. In case of disagreement between them, the third investigator (TK) made discussion until a consensus was reached. The inclusion criteria were: Original English articles; Preoperative ^{99m}Tc-MDP/HMDP scintigraphy used to assess the histological response of osteosarcoma to chemotherapy; All raw data of the alteration ratio (percentage change of the ^{99m}Tc-MDP/HMDP uptake between before and after neoadjuvant chemotherapy) for individual patient data (IPD) meta-analysis or sufficient data to make a 2×2 contingency table for aggregate data (AD) meta-analysis. Conference abstracts, case reports, and review articles were excluded.

2.2. Data analysis

The same investigators extract information for the meta-analysis independently where available; author name, publication year and country, study design, total and meta-analysis-included patient number, age, gender, characteristics of ^{99m}Tc-MDP/HMDP scintigraphy settings.

2.3. Quality assessment

The quality of study designs was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.[11] Risk of bias about 4 domains and concerns regarding applicability about 3 domains were rated as "low," "high," or "unclear."

2.4. Meta-analysis

IPD and AD meta-analyses were both adopted.[12] Meta-analysis of IPD was performed to synthesize the receiver operating characteristic curve. The optimal cut-off point was determined by the Youden index.[13] IPD meta-analysis was performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[14] For AD meta-analysis, 2×2 contingency tables were constructed based on the alteration ratio and the histological response of osteosarcoma to neoadjuvant chemotherapy in each study. The DerSimonian–Laird random-effects method was used to determine the pooled sensitivity, specificity, diagnostic odds ratio, and the area under curve (AUC) of the summary receiver operating characteristic (sROC) curve. Heterogeneity was assessed by the inconsistency index I-square. AD meta-analysis was performed using Meta-DiSc statistical software version 1.4 (Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain).[15] $P < .05$ was defined to be statistically significant.

3. Results

We identified a total of 238 relevant articles, of which 57 were excluded because of duplication and 171 were excluded based on information in the title and abstract. Three more articles were excluded after a review of the full text.[16–18] A total of 7 studies, consisting of 154 patients, met all of the inclusion criteria for IPD meta-analysis.[19–25] Five articles,[20,21,23–25] consisting of 123 patients, were included for AD meta-analysis because the cut-off point for making a 2×2 contingency table was available. Figure 1 demonstrated the procedure of study selection and detailed reasons for study exclusion.

Table 1 shows the main characteristics of the 7 studies. All studies were rated to be 5 or more "low risk" answers in the 7

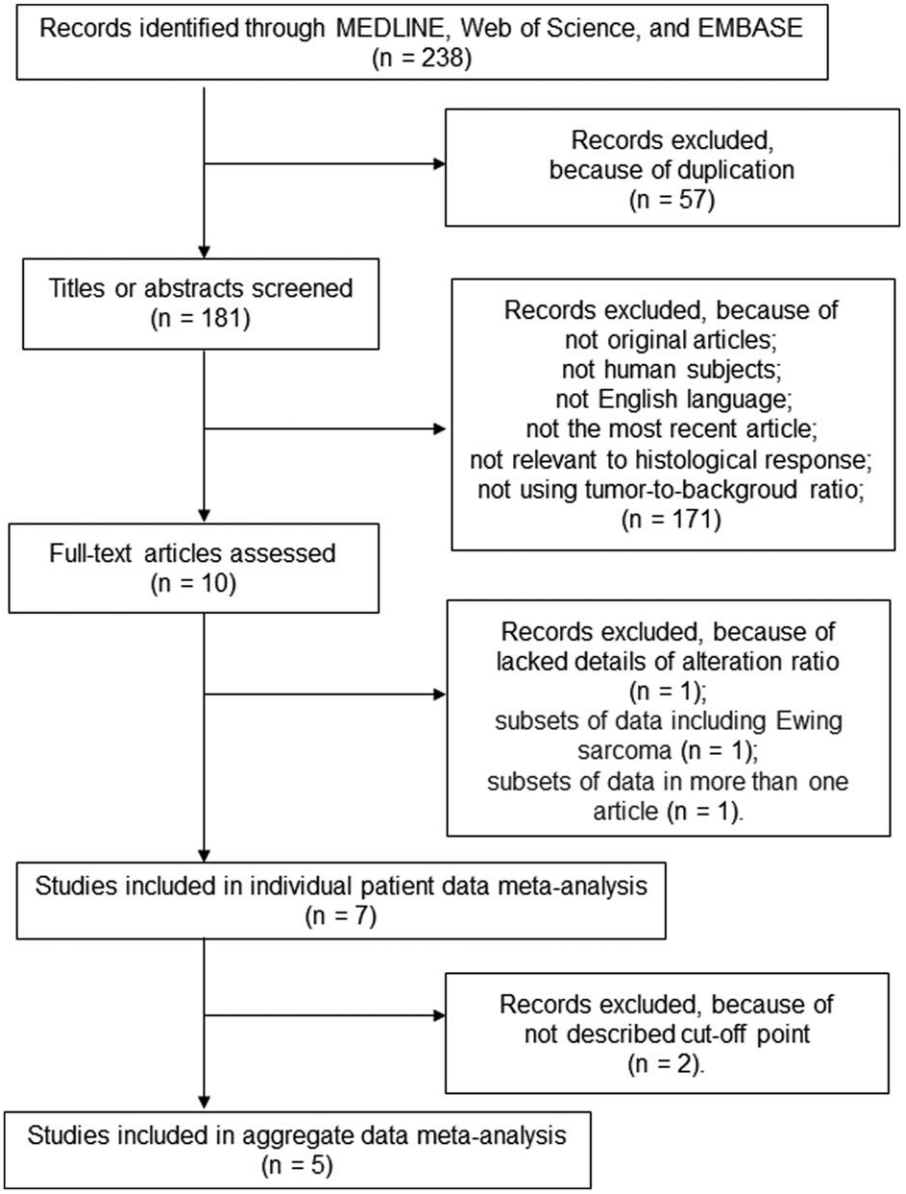

Figure 1. A flowchart of the article-selection process.

Table 1

Description of included studies and comparison of scintigraphy parameters.

Reference	Year	Journal	Country	Study design
Ilhan [19]	2005	*Pediatr Hematol Oncol*	Turkey	ND
Ongolo-Zogo[20]	1999	*Eur Radiol*	France	ND
Winderen [21]	1999	*Acta Orthop Scand*	Norway	ND
Ozcan [22]	1999	*Nucl Med Commun*	Turkey	Retrospective
Kobayashi [23]	1998	*Acta Orthop Scand*	Japan	ND
Edeline [24]	1993	*Eur J Nucl Med*	France	ND
Knop [25]	1990	*Skeletal Radiol*	Germany	ND

Total number	Included number	Male/female	Age (mean/range)
15	11	5/6	14.5/7–18 yr old
12	12	8/4	16/6–27 yr old
51	39	21/18	17.6/6–51 yr old
27	20	12/8	16.2/6–21 yr old
34	25	16/9	19.2/9–66 yr old

(*continued*)

Table 1

(continued).

Total number	Included number	Male/female	Age (mean/range)
19	19	9/10	13/7–17yr old
30	28	18/10	14.9/5–25yr old
Tc-99m	**Phosphate**	**Image**	**Post-injection time**
ND	MDP	Static	3 h
10 MBq/kg BW	HMDP	Dynamic	Every 2.5 s for 160 s
7–10 MBq/kg BW	MDP	Dynamic	Every 2 s for 6 min
500–740 MBq	MDP	Dynamic	Every 1 s for 1 min
740 MBq	HMDP	Static	3 h
7.4 MBq/kg BW	HMDP	Static	3 h
370–550 MBq	MDP	Dynamic	Every 5 s for 70 s

Scan time (pre/postchemotherapy)	ROI (pre/postchemotherapy)
At diagnosis/2 wk after chemo	Unspecified/ND
At diagnosis/13 wk later	Including the whole tumor/ND
Before biopsy/unspecified	Around the tumor/ND
Unspecified/8–10 wk later	Over the lesion/ ND
Before chemo/3 mo later	On the tumor/the same size and position
Just before chemo/6 wk later	Around the tumor/ND
Unspecified/unspecified	ND/the identical reposition

Background (contralateral side)	Calculations	Cut-off point
The contralateral normal area	Count density of the lesion	ND
Unspecified	ND	0%
Unspecified	ND	40%
The contralateral normal tissue	Average counts per pixel	ND
The equally sized region	Average density per pixel	60%
The symmetric bone segment	ND	0%
The corresponding region	Count per minute per pixel	20%

(H)MDP = (hydroxy)methylene diphosphate, BW = body weight, ND = not documented, ROI = region of interest.

domains of the QUADAS-2. No "high risk" response to any domains was found in any studies (Table 2). Five authors did not state the sampling methods or exclusions criteria in the domain of patient selection, and 4 authors did not state blindness in the domain of reference standard.

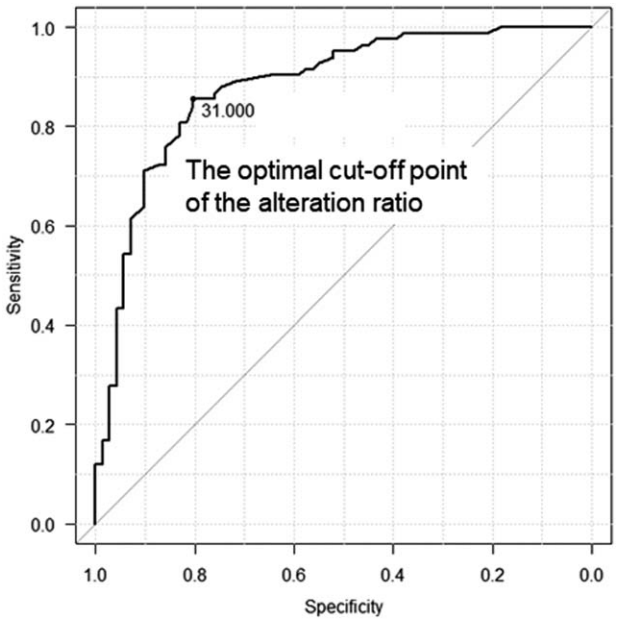

Figure 2. ROC curves for the alteration ratio in individual patient data meta-analysis. The optimal cut-off point was determined to be the point on the ROC curve at which (sensitivity + pecificity − 100%) was maximal. ROC = receiver operating characteristic.

IPD meta-analysis showed that the optimal cut-off point of the alteration ratio was 31.0% (Fig. 2). AD meta-analysis demonstrated that the pooled sensitivity and specificity were 0.76 (95% CI, 0.63–0.86) and 0.89 (95% CI, 0.79–0.95), respectively (Fig. 3A, B). There was a significant difference between the good and poor responders in the diagnostic odds ratio (pooled odds ratio: 23.36, 95% CI, 7.59–71.91) (Fig. 3C). The sROC curve demonstrated that the AUC was 0.892, indicating excellent diagnostic accuracy (Fig. 4). No significant heterogeneity was found among the 5 studies in terms of the pooled diagnostic odds ratio, whereas there was mild heterogeneity in the pooled sensitivity and the pooled specificity. I-squares of the pooled sensitivity, the pooled specificity, and the pooled diagnostic odds ratio were 52.2%, 67.8%, and 0.0%, respectively.

4. Discussion

Conventional bone scintigraphy had been widely used as an essential preoperative examination for patients with osteosarcoma before evolving quantitative modalities, such as dynamic MRI, ^{201}Tl scintigraphy, and ^{18}F-FDG PET-CT, was developed. Although preliminary results have shown that these recent modalities may comprise more sensitive and promising modalities for patients with bone sarcoma than ^{99m}Tc-MDP/HMDP scintigraphy, the number of study participants has been too small population to guarantee a statistically conclusive outcome.[10,16,17,19] Moreover, ^{99m}Tc-MDP/HMDP scintigraphy has some advantages over other modalities because dynamic

Table 2

Quality assessment of diagnostic accuracy studies-2.

	Risk of bias				Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow timing	Patient selection	Index test	Reference standard
Ilhan [19]	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Ongolo-Zogo[20]	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Winderen [21]	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Ozcan [22]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kobayashi [23]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Edeline [24]	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Knop et al[25]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

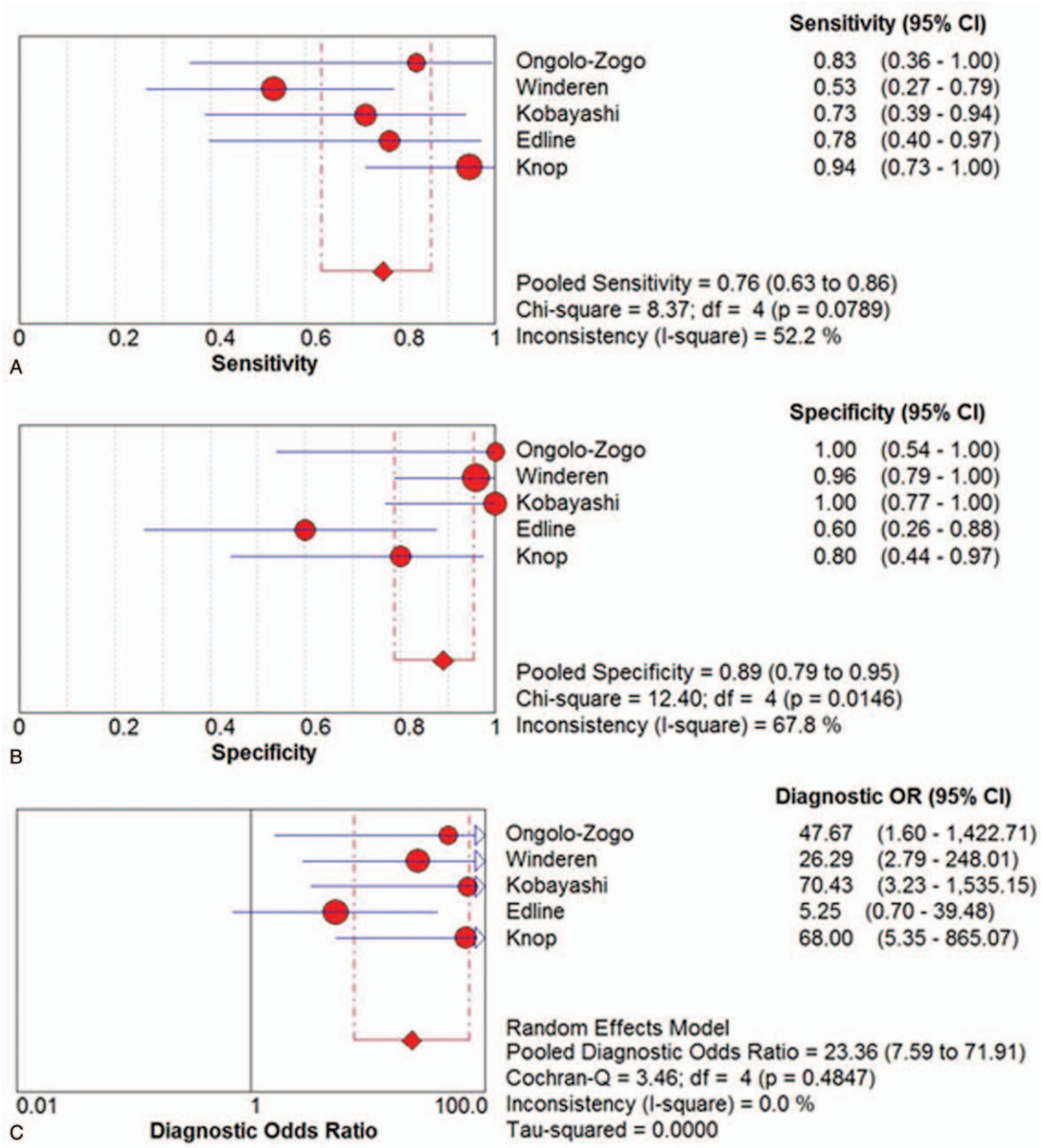

Figure 3. Forest plot of pooled sensitivity (A), specificity (B), and diagnostic odds ratio (C) for the alteration ratio derived from ^{99m}Tc-MDP/HMDP scintigraphy. Size of circles of individual studies represents weight of study. Horizontal lines represent 95% CI of individual studies. Vertical dashed lines represent 95% CI of pooled estimate. MDP = methylene diphosphate, Tc = technetium, (H)MDP = (hydroxy)methylene diphosphate.

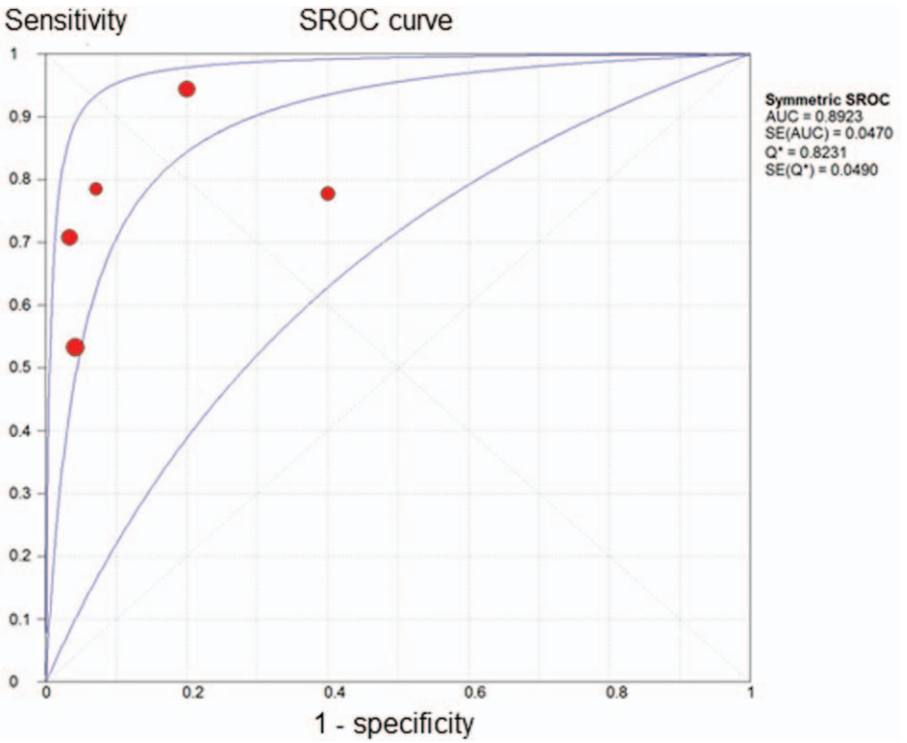

Figure 4. Asymmetric sROC curves for the alteration ratio in aggregate data meta-analysis. Circles in each plot represent individual studies, with size of each circle representing weight of study. Middle curves represent sROC curve, with curves above and below middle curve representing 95% CI. sROC = summary receiver operating characteristic.

MRI is time-consuming and expensive, and cyclotron-produced ^{201}Tl and ^{18}F-FDG are not readily available in many facilities.[21] To obtain more robust estimates of the diagnostic yield of ^{99m}Tc-MDP/HMDP scintigraphy, we pooled published studies, which to our knowledge had not been done previously. According to previous AD meta-analysis studies to predict the histological response of osteosarcoma to neoadjuvant chemotherapy, the pooled sensitivity, specificity, and AUC of percent slope derived from dynamic MRI were 0.73 (95% CI, 0.54–0.88), 0.83 (95% CI, 0.67–0.94), and 0.839, respectively.[5] The pooled sensitivity, specificity, and AUC of the alteration rate derived from ^{201}Tl scintigraphy were 0.93 (95% CI, 0.83–0.98), 0.63 (95% CI, 0.52–0.74), and 0.840, respectively.[6] The pooled sensitivity, specificity, and AUC for the alteration ratio of standardized uptake values from ^{18}F-FDG PET were 0.734 (95% CI, 0.537–0.867), 0.864 (95% CI, 0.510–0.975), and 0.81, respectively.[7] Our AD meta-analysis findings demonstrated that the pooled sensitivity, specificity, and AUC of the alteration ratio derived from ^{99m}Tc- MDP/HMDP were 0.76 (95% CI, 0.63–0.86), 0.89 (95% CI, 0.79–0.95), and 0.892, respectively. These results have suggested that in comparison with these recent quantitative modalities, ^{99m}Tc- MDP/HMDP scintigraphy remains very useful to evaluate the histological response of osteosarcoma to neoadjuvant chemotherapy.

The cut-off point of the alteration ratio derived from the ^{99m}Tc-MDP/HMDP bone scan varied from study to study (Table 1). The ^{99m}Tc-MDP/HMDP uptake can be influenced by various biological and technological parameters, including errors in region-of-interest assignment, the presence of highly vascular granulation tissue or a reactive process, and the presence of pathological fractures.[22] Kobayashi et al[23] defined more than a 60% reduction in the alteration ratio being as a positive response to minimize the false results. However, other authors arbitrarily defined the cut-off point or did not describe the cut-off point for making a 2×2 contingency. Our IPD meta-analysis of the 7 studies comprising 154 patients with osteosarcoma defined 31.0% being as an optimal cut-off point of the alteration ratio. However, since a data-driven cut-off point is not proper for small sample sizes with methodological differences further studies are needed to obtain the standardized and optimized cut-off values.

There are several limitations in this study. Only 7 and 5 studies were included in the IPD and AD meta-analysis study, respectively. Follow-up studies are required to confirm our results. Study selection and data extraction bias could not be excluded completely, although 2 reviewers blindly and independently reviewed all article. Articles with 5 or more "low" answers in the 7 domains of the QUADAS-2 were included. Moreover, mild heterogeneity was found among the 5 studies regarding the pooled sensitivity and specificity (I-squares, 52.6% and 67.8%, respectively) in the AD meta-analysis. This heterogeneity might be attributable to the methodological differences among the studies, such as the ^{99m}Tc-MDP/HMDP scintigraphy acquisition technique and interpretation methods. Also, the relatively low sensitivity of ^{99m}Tc-MDP/HMDP scintigraphy is probably affected by the mechanism of ^{99m}Tc-MDP/HMDP uptake, which is considered to reflect the bone healing process rather than tumor cell viability. Prospective randomized clinical trials with larger cohorts are desirable to completely exclude all potential bias from the ^{99m}Tc-MDP/HMDP scintigraphy assessment of osteosarcoma response to chemotherapy.

In conclusion, this study has proven that conventional ^{99m}Tc-MDP/HMDP scintigraphy remains as useful as recent quantitative modalities to assess the histological response of osteosarcoma to neoadjuvant chemotherapy, suggesting that bone scintigraphy

might be meaningfully and cost-effectively performed in routine work.

Author contributions

Conceptualization: Tadahiko Kubo, Mitsuo Ochi, Nobuo Adachi.
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Formal analysis: Tadahiko Kubo, Taisuke Furuta, Tomohiko Sakuda.
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Writing – review & editing: Tadahiko Kubo, Taisuke Furuta, Mitsuo Ochi, Nobuo Adachi.

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