



## Review Article

# Diagnostic accuracy of functional imaging modalities for chondrosarcoma: A systematic review and meta-analysis

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## ABSTRACT

**Introduction:** The distinction between low-grade (grade 1) chondrosarcoma and its benign counterparts can be challenging. This systematic review aims to quantify the diagnostic accuracies of all functional imaging modalities used in the diagnosis of chondrosarcoma.

**Methods:** Medline and Embase were searched in February 2019. We included studies of either retrospective or prospective design if the results of functional scans were compared with pre-determined reference standards. Studies had to be primary diagnostic reports on patients with chondral tumours at first diagnosis. Two review authors independently performed study selection, extracted data and assessed the methodological quality. We calculated diagnostic accuracy measures for each included study.

**Results:** Four functional imaging modalities were identified across thirteen studies that met the inclusion criteria. 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography (FDG-PET) was a sensitive and specific test. Technetium-99m with methylene diphosphonate (Tc-99m MDP) had an overall low specificity of 4%. Thallium-201 scintigraphy demonstrated high positive predictive values across the studies. The negative predictive values of Technetium-99m pentavalent dimercaptosuccinic acid (Tc-99m DMSA (V)) were consistently 100%.

**Conclusions:** Low-grade chondrosarcomas continue to pose a diagnostic dilemma. FDG-PET demonstrated superior diagnostic accuracy compared to Tc-99m MDP, Thallium-201 and Tc-99m DMSA (V). Characteristic uptake patterns of Thallium-201 and Tc-99m DMSA (V) may provide additional metabolic information to guide the diagnosis in this challenging group of tumours.

## 1. Introduction

Chondrosarcoma is a cartilage forming malignant neoplasm of the bone. It constitutes about a quarter of all primary bone tumours [1], with a peak incidence between the third and seventh decades of life [2]. Reported overall incidence is one in 200,000. The differences in cortical scalloping, expansion or thinning between enchondroma and low-grade (grade 1) chondrosarcoma on anatomical imaging such as plain radiographs or computed tomography (CT) can be subtle [3–7]. Furthermore, biopsy samples are prone to sampling error and under-grading due to the limitations of anatomical imaging in detecting the most malignant area of the tumour [8]. Therefore, the distinction between benign chondroid tumours and chondrosarcomas can be challenging.

Functional imaging is a medical imaging technique to measure or detect metabolic processes through the use of radiotracers [9]. It offers additional and specific metabolic and biological information [10]. There is a growing interest in the use of functional scans to diagnose, guide biopsy and assess therapeutic response after treatment for

cartilaginous tumours [6,10–17]. Management and prognosis may be influenced by the findings of functional imaging, and thus it is important to offer an overview of diagnostic accuracies of these tests.

There is a limited number of systematic reviews on the efficacy of FDG-PET scans in bone and soft tissue tumours [18,19]. Other than one systematic review of FDG-PET scans in chondroid tumours [20], no systematic review of functional scans in general for assessing chondroid tumours has been conducted. Such a review is necessary given that there are multiple small studies of different functional scans each reporting variable results. The purpose of this systematic review is to synthesise and appraise the findings of all available reports on the use of functional imaging in chondroid tumours and to determine the diagnostic accuracy of each functional imaging modality as a single diagnostic test at first diagnosis. The ability of these modalities to grade chondroid tumours based on the intensity of uptake, though important, is not within the scope of this review.

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### 1.1. Rationale

Anatomical imaging alone may be insufficient for diagnosing malignancy in chondroid tumours [3–6,8,20,21]. If a chondrosarcoma can be accurately diagnosed in a tumour that otherwise appears like an enchondroma by utilising functional imaging, then a surgical intervention would be more suitable than a conventional ‘watch and wait’ approach. This would reduce recurrence and metastases from under-treatment. Similarly, the converse is true: if negative scans can predict a low likelihood of malignancy, patients would be spared unnecessary surgery.

## 2. Methods

The PRISMA statement provided a framework for this systematic review [22].

### 2.1. Electronic searches

Following the recommendations of the Cochrane Collaborations [23], the Medline and Embase databases were searched in February 2019. Two authors (IJ and DG) defined search terms shown in Table 1. The Cochrane Library was searched for reviews on diagnostic functional imaging modalities for cartilaginous tumours.

### 2.2. Criteria for considering studies for this review

Before commencing the search, specific inclusion and exclusion criteria were defined. Eligible articles had to meet the following inclusion criteria:

- (1) the target population consisted of at least 10 cartilaginous tumours in the appendicular skeleton;
- (2) the results of functional scans were compared with the tests defined as reference standards (more than 50% of tumours must have histological diagnoses);
- (3) studies had to report sufficient data to generate diagnostic accuracy measures, i.e. either sensitivity or specificity data or the absolute number of positive and negative results;
- (4) studies could be of either retrospective or prospective design; and
- (5) the references are primary diagnostic studies.

**Table 1**  
Search strategies for Medline and Embase.

Medline	
1.	(PET or positron or SPECT or single photon emission computed tomography or bone scan* or scinti* or functional imaging or functional scan* or thallium or Tl-201 or DMSA or dimercaptosuccinic acid or Tc-99* or technetium or nuclear medicine or nuclear scan*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
2.	((cartilag* or chondro*) and (tumour* or tumor*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3.	(chondrosarcoma* or enchondroma*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4.	2 or 3
5.	1 and 4
EMBASE	
1.	(PET or positron or SPECT or single photon emission computed tomography or bone scan* or scinti* or functional imaging or functional scan* or thallium or Tl-201 or DMSA or dimercaptosuccinic acid or Tc-99* or technetium or nuclear medicine or nuclear scan*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
2.	((cartilag* or chondro*) and (tumour* or tumor*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3.	(chondrosarcoma* or enchondroma*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4.	2 or 3
5.	1 and 4

If studies included other types of bone tumours, we retrieved only the data regarding chondroid tumours from those studies. If both early and delayed images were available, we elected to focus on the delayed phase images as they are thought to be more specific for the detection of malignancy [11]. Case reports, diagnostic case-control studies, editorials, review articles, conference proceedings, or studies in relation to osteoarthritis and animal studies were excluded. There were no age restrictions even though it is known that chondrosarcoma is rare in childhood. Studies on recurrence or post chemo- or radiotherapy were excluded. All literature published in the English language was reviewed regardless of the year of publication, due to limited number of studies in this field. There was not blinding of the names of authors, affiliations and journals.

### 2.3. Selection of studies

After applying the search strategy, one review author (IJ) screened titles of retrieved references, excluding studies on animals, cartilage in osteoarthritis and anatomical imaging. Then, two review authors (IJ and DG) independently screened titles, abstracts, and full-texts of the remaining studies. We included only full-texts studies that satisfied all pre-specified inclusion criteria. The reasons for exclusion of any study considered were clearly stated. Final selection required consensus of both review authors and the approval of subject experts within the author team. The reference lists of all included papers were checked.

### 2.4. Reference standards

The ideal reference standard was histopathological diagnosis of the excised lesion or biopsy sample in all eligible lesions. However, given that biopsy or excisions are unlikely to be carried out for all clinically benign lesions, we accepted clinical follow-up of greater than twelve months and repeated radiological assessments as eligible reference standards. Nevertheless, we recognise that misclassification rates of histopathological assessment and clinical follow-up will be different.

### 2.5. Data extraction

Two review authors (IJ and DG) independently performed data extraction on (1) author and year of publication; (2) basic study design; (3) sample characteristics; (4) specifics of imaging modalities; (6) diagnostic criteria; (7) reference standard; and (8) data regarding

discriminative ability of selected imaging modalities. The unit of analysis was the tumour, meaning that if a patient with a negative index test result had multiple tumours, we agreed to consider the number of negative results to be the number of tumours investigated. This is because each tumour may be at a different biological state. If multiple index tests were evaluated in one study, we extracted the number of positive and negative results for each test.

## 2.6. Assessment of methodological quality

Using the revised Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2) [24], two review authors (IJ and DG) independently assessed the methodological qualities of included studies. QUADAS-2 assesses study quality through the assessment of risk of bias in four domains: patient sampling; index test (functional scan); reference standard; and flow and timing. We resolved any discrepancies by discussion.

## 2.7. Statistical analysis and data synthesis

Data analysis was carried out in accordance with guidelines set out by the Cochrane Collaboration for systematic review [23]. The diagnostic performances of the index tests were quantified by sensitivity, specificity, positive (PPV) and negative predictive values (NPV), diagnostic odds ratios (DORs) and likelihood ratio (LR). Meta-analysis was performed using a bivariate random effects model to pool the sensitivities, specificities and DORs. This model allows for the assessment of heterogeneity between studies beyond chance. Heterogeneity was determined statistically by a Cochran Q test and the  $I^2$  statistic and was defined as  $I^2 > 50\%$ .  $p$ -value of less than 0.5 was considered statistically significant. RevMan<sup>®</sup> and Microsoft Excel<sup>®</sup> were used for all statistical analyses.

## 3. Results

### 3.1. Results of the search

We identified a total of 2340 references through electronic searches of Medline (OvidSP;  $N = 451$ ) and Embase (OvidSP;  $N = 1889$ ). After the removal of duplicates, 2318 references remained. 1644 clearly irrelevant references based on title screening were excluded. Two authors (IJ, DG) screened titles and abstracts for 674 publications. We assessed 85 full-text references for eligibility. We included 13 papers and discarded 72 for reasons described in the PRISMA diagram in Fig. 1. Results are presented separately for each functional scan in this review. 2-deoxy-2-[<sup>18</sup>F]fluoro-D-glucose positron emission tomography/X-ray computed tomography (PET/CT) and dedicated FDG-PET were analysed together as our study is concerned with the functional imaging aspect. We could not identify studies that addressed the accuracy of the index tests as add-on tests to the conventional imaging. No studies on functional MR in chondroid tumours met our inclusion criteria.

### 3.2. Methodological qualities of included studies

We assessed methodological qualities of included studies using the QUADAS-2 tool [24] (Table 2). In the participant selection domain, six studies were considered to be at low risk of bias [5,10,13,25–27]. There was insufficient reporting to determine whether the participants were randomly or consecutively enrolled in seven studies [28–34]. We had excluded studies with a case-control design as our focus was on the effectiveness of selected imaging modalities in differentiating between chondrosarcoma and benign chondroid tumours.

The highest level of risk of bias was observed in the index test domain. Four studies [10,15,25,35] set sensitivity and specificity maximising threshold values for diagnosis with the knowledge of reference test results. In six studies [13,27,28,31,32,36], the index test was

performed before the histological assessment hence we inferred that they did not have the knowledge of the reference standard. Eight studies relied on visual assessment of uptake [5,13,28,30–32,36]. Nevertheless, it is the accepted general standard in nuclear medicine. In the reference standard domain, it was unclear whether assessors of the reference standard were blinded to the index test results in 11 studies [5,10,13,15,25,28,30–32,36]. We considered a follow-up for longer than 12 months for benign tumours was sufficient to correctly identify them. Hence, six studies [10,15,29,30,32,33] that used both histopathological assessment and follow-up as reference standards were not considered to pose a high risk of bias.

In the flow and timing domain, one study [26] only reported sensitivity and specificity values without the raw data. Similarly, another study [36] reported percentages of positive uptake in chondrosarcoma and enchondroma only, from which estimates of true positive and false negative results were calculated. This may create a potential for unknown exclusion of data and risk of reporting bias. Therefore, these studies were considered at high risk of bias. All participants were included in the analysis and no missing data was observed across the 11 remaining studies. Only one study [5] specified the time intervals between index test and reference standard, and therefore was considered to be at a low risk of bias.

For assessment of applicability, all included studies met the review question. The patient population, setting, the target condition as defined by the reference standard, index tests were all appropriate. One study [32] had recruited patients who had positive bone scintigraphy within the previous four weeks of the index test. The implication of this was that the patients who tested negative on bone scan were not considered and this can alter the pre-test probability of chondrosarcoma. The authors believed that it poses an unknown level of concern for applicability.

### 3.3. Description of study characteristics

One study [13] investigated two imaging modalities, which made it possible to include the results of 14 patient series. Four studies addressed the value of FDG-PET in the diagnostic work-up for chondroid tumours [15,25,26,30]. Three studies assessed Tc-99 m MDP [5,27,36], four studies focused on Thallium-201 scintigraphy [10,13,28,31], and three studies reported on Tc-99 m DMSA (V) [13,32,37]. All studies reported data at patient level except for two studies that reported on all single lesions [26,32]. A schematic overview of the included studies is presented in Table 3.

We generated a paired forest plot showing sensitivities and specificities of included studies and pooled estimates with 95% confidence intervals (CIs) in Fig. 2. We could not formally investigate the effects of covariates such as study design and patient recruitment on the outcomes (i.e. subgroup analysis) due to the relatively small numbers of included studies. Generating Receiver Operating Curve (ROC) to visualise the results was deemed inappropriate to the limited number of included studies. The results of diagnostic accuracy measures of the individual studies are presented (Table 4). Pooled sensitivity, specificity and DOR for each modality with heterogeneity are shown in Table 5.

#### 3.3.1. FDG-PET

We identified four studies that evaluated the efficacy of FDG-PET or PET/CT in diagnosing chondroid tumours [15, 25, 26, 30]. There was a total of 103 patients with 111 cartilaginous tumours, of which 58 were diagnosed as chondrosarcomas (35 grade 1, 12 grade 1, nine grade 3 and two unknown grade). Among the 111 tumours, 87 (82%) had histopathological assessments as their reference standards. Images were taken 40 to 90 min after the intravenous administration of FDG dose (range 3.7–5 MBq/kg).

The cut-off maximal standardised uptake values (SUV<sub>max</sub>) for diagnosing chondrosarcoma against benign chondroid tumours were variable. Feldman et al. [15] and Jesus-Garcia et al. [30] used 2.0 as

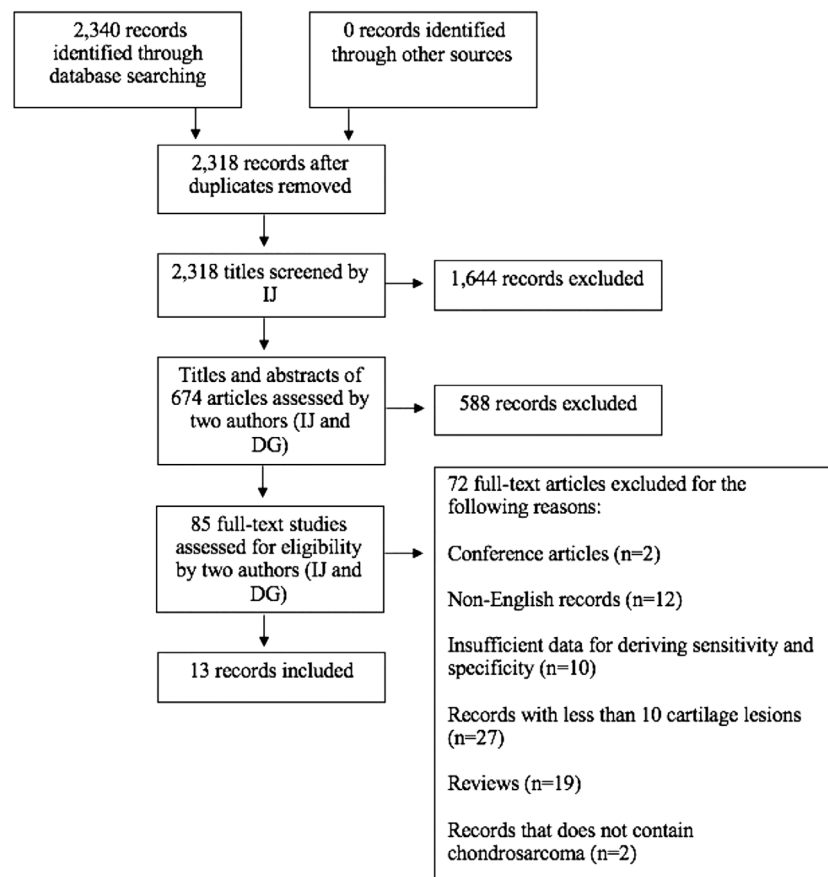


Fig. 1. PRISMA flow diagram.

their SUVmax cut-off values whereas 1.3 was used by Aoki et al. [25]. The SUVmax cut-off point was unclear in Lee et al. [26]'s study. The sensitivity and specificity of FDG-PET for detection of chondrosarcoma ranged from 50% to 100% and from 80% to 100% with pooled estimates of 75% and 90% respectively. Even though the pooled results did not demonstrate significance heterogeneity, they need to be interpreted with the knowledge that there were variations in the diagnostic criteria for index test, reference test and technical details in the included studies.

### 3.3.2. Tc-99m MDP

Three studies on the conventional bone scintigraphy were considered eligible for our review [5,27,36]. There were 110 chondrosarcomas (103 grade 1, one grade 1–2, one grade 2–3 and five unknown) and 65 benign tumours. Histological assessments were performed for 132 tumours (75%). Tc-99m MDP was performed three hours post intravenous injection of 555 MBq (15mCi) in one study [27]. In two studies, the acquisition time and dose were not reported [5,29].

The criteria for Tc-99m MDP positivity were based on visual assessment in all studies. Two studies [5,29] defined increased uptake as uptake more than background. One study [27] adopted a grading system (1–4) for positive uptake and 0 for negative uptake. However, we converted the uptake results into dichotomous outcomes (no uptake vs increased uptake) as intensity of uptake was inconsistently reported across the studies. The pooled sensitivity was high at 95% while the pooled specificity was considerably low at 4%. There was no significant heterogeneity between the studies. The pooled DOR did not demonstrate any significant difference in the odds of positive test in patients with benign chondroid tumours compared to those with chondrosarcomas.

### 3.3.3. Thallium-201 scintigraphy

Four studies fulfilled our inclusion criteria for investigating the role of Thallium-201 scintigraphy for assessing cartilage tumours [10,13,28,31]. Only the data regarding cartilaginous tumours was extracted from one study on bone tumours [10]. 87 chondrosarcomas (38 grade 1, 22 grade 2, 13 grade 3 chondrosarcomas, three mesenchymal chondrosarcoma and one de-differentiated chondrosarcoma, and 10 unknown) and 113 benign chondroid tumours were identified. The reference standard for all chondrosarcomas was based on histopathological assessments. We estimate from the overall sample characteristics that 87 benign tumours were diagnosed histologically and 26 were diagnosed based on a 12-month follow-up.

There were variable time intervals between intravenous thallium administration and imaging across the three studies. Higuchi et al. [28] only considered images at 15 min post administration, which is a major limitation of this study. Choong et al. [13], Inai et al. [10] and Kaya et al. [31] considered images during early (15–30 min) as well as late phase (2–4 h). A dose of 111 MBq was used in two studies [28,31] while the other two studies [10,13] used 148 MBq and 74 MBq respectively. Three studies [13,28,31] assessed images visually while one study [10] used the tumour-to-background ratio as an objective measure.

The pooled sensitivity of 30% and specificity of 91% were observed. High PPVs ranging from 88% to 100% were observed across all studies except for one outlier [10] that had a PPV of 20%. The possible explanation for this difference includes the use of tumour-to-background ratio, the administration of higher dose of Thallium-201, which may account for a high false positive rate in Inai's study [10]. This study was further assessed to be at high risk of bias due to sensitivity maximising diagnostic measure.

**Table 2**

A summary of methodological qualities of included studies determined by review authors' judgement for each domain of QUADAS-2 (colour should be used in print).

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Aoki 1999	+	-	?	?	+	+	+
Choong 2004	+	+	+	?	+	+	+
Feldman 2005	?	-	?	?	+	+	+
Ferrer-Santacreu 2016	?	+	?	-	+	+	+
Hendel 2002	+	+	?	+	+	+	+
Higuchi 2005	?	+	?	?	+	+	+
Inai 2015	+	-	?	?	+	+	+
Jesus-Garcia 2016	?	+	?	?	+	+	+
Kaya 2010	?	+	?	?	+	+	+
Kobayashi 1995	?	+	?	?	?	+	+
Lee 2004	+	-	+	-	+	+	+
Shinya 2015	?	+	?	?	+	+	+
Simon 1980	+	+	?	?	+	+	+
<span style="background-color: red; color: white; padding: 2px;">- High</span> <span style="background-color: yellow; padding: 2px;">? Unclear</span> <span style="background-color: green; color: white; padding: 2px;">+ Low</span>							

**3.3.4. Tc-99m DMSA (V)**

Three studies investigated the efficacy of Tc-99m DMSA (V) in the diagnosis of chondrosarcomas [13,32,37]. There were 144 chondroid tumours present in 124 patients. Tumours comprised of 51 chondrosarcomas (22 grade 1, 14 grade 2, five grade 3, and 10 unknown) and 93 benign chondroid tumours. The histological assessment was carried out in 137 of 144 (95%) tumours. Seven tumours were diagnosed based on a mean 40-month follow-up and radiological findings. In 51 tumours out of 144, images were assessed at 2 h post intravenous administration of a DMSA (V) dose ranging from 370 to 550 MBq. The remaining tumours were assessed at 30 min and 3–4 h post intravenous administration of 557 MBq of DMSA (V). Index test diagnostic criteria was pre-specified in all cases. The uptake results were dichotomised into uptake less than or greater than background or adjacent tissue. Tc-99m DMSA (V) was overall 100% sensitive and 47% specific.

**4. Discussion**

When assessing cartilaginous tumours, radiographs can be helpful in revealing areas of calcification, soft-tissue shadowing and bony destruction [38,39]. Magnetic resonance imaging (MRI) can provide useful information about the size and location of a tumour as well as its proximity to other anatomical structures. Computed tomography is further adopted for staging of chondrosarcomas. However, these anatomical imaging modalities may be limited in distinguishing between grade 1 chondrosarcomas and enchondromas. The sensitivity of plain radiography was only 21% while that of MRI was 58% for correctly diagnosing chondrosarcoma [4]. CT scan has shown limitations in improving diagnostic accuracy [21,40].

Biopsies play an important role in tissue diagnosis. However, targeting the most metabolically active area of tumours can be challenging due to significant heterogeneity of cartilaginous tumours. The concordance between histological analysis from needle biopsy and surgical specimen for histological grade ranging between 36–86% [8].

**Table 3**  
Schematic overview of included studies.

Imaging modality (index test)	Author, year of publication	Methodology	Patient/ Cartilage tumour (n)	Benign tumours/ chondrosarcoma (n)	Specifics on imaging technique (Type, dose, time interval between radiotracer administration and images)	Diagnostic criteria	Time interval between index test and reference standard
FDG-PET	Aoki, 1999	A prospective cohort study. Reference standard: histopathology.	11/11	5/6	FDG-PET, weight-adopted dose (5 MBq/kg), range 185–250 MBq. 40–50 min post injection of FDG.	SUVmax cut-off value = 1.3.	Unclear.
FDG-PET	Feldman, 2005	A prospective cohort study. Reference standard: histopathology (n = 26); otherwise, overall clinical assessment, imaging and follow-up of 1–4 years.	29/29	18/11	FDG-PET, 0.14mCi/kg. 60 min post injection of FDG.	SUVmax cut-off value = 2.0.	Unclear.
<sup>18</sup> F-FDG-PET-CT	Jesus-Garcia, 2016	A prospective cohort study. Reference standard: anatomopathological report (n = 20); otherwise overall clinical assessment and FU with a minimum of 14 months follow-up	36/36	17/19	FDG-PET-CT, weight-adopted dose (3.7 MBq/kg). 60–90 min post injection of FDG.	SUVmax cut-off value = 2.2.	Unclear.
FDG-PET	Lee, 2004	A retrospective cohort study. Reference standard: histopathology.	27/35	13/22	FDG-PET, weight-adopted dose (0.14mCi/kg). 50 min post injection of FDG.	Visual assessment. SUVmax cut-off value unclear.	Unclear.
Tc-99 m with MDP	Ferre-Santacreu, 2016	A prospective cohort study. Reference standard: histopathology (n = 90); otherwise clinical follow-up with a minimum duration of 3 years.	133/133	39/94	Tc-99 m MDP.	Visual assessment: 'Hot or cold'	Unclear.
Tc-99 m with MDP	Hendel, 2002	A retrospective cohort study. Reference standard: histopathology (n = 22).	22/22	11/11	Tc-99 m MDP.	Visual assessment by two nuclear medicine specialists.	Time from imaging to histological assessment within 2 months.
Tc-99 m MDP	Simon, 2018	A prospective cohort study. Reference standard: histopathology (n = 20).	20/20	15/5	Tc-99 m MDP, 15mCi. Three hours post injection of MDP.	Visual assessment, the intensity rated at 0–4.	Unclear.
Thallium-201 scintigraphy	Choong, 2004	A prospective cohort study. Reference standard: histopathology (n = 87).	87/87	45/42	Thallium-201 scintigraphy, 1.48 MBq. 20 min and 3–4 h post injection of Thallium.	Visual assessment: 'no uptake or increased uptake'.	Unclear.
Thallium-201 scintigraphy	Higuchi, 2005	A retrospective cohort study. Reference standard: histopathology (n = 22).	22/22	3/19	Thallium-201 scintigraphy, 111 MBq. 15 min post injection of Thallium.	Visual assessment of intensity of uptake rated at 0–4.	Unclear.
Thallium-201 scintigraphy	Inai, 2015	A retrospective cohort study. Reference standard: histopathology (n = unclear) and 12-month clinical follow up (n = unclear).	68/68	58/10	Thallium-201 scintigraphy, 74 MBq. 15 min and 2 h post injection of Thallium.	Sensitivity and specificity optimising tumour-to-background ratio values for early and delayed imaging set at 0.68 and 0.38 respectively.	Unclear.
Thallium-201 scintigraphy	Kaya, 2010	A retrospective cohort study. Reference standard: histopathology.	23/23	7/16	Thallium-201 scintigraphy, 3 mCi. 20 min and 2 h post injection of Thallium.	Visual assessment of intensity as no or normal uptake and increased uptake.	Unclear.
Tc-99 m DMSA (V)	Choong, 2004	A prospective cohort study. Reference standard: histopathology.	83/83	47/36	Tc-99 m DMSA (V), 557 MBq. 30 min and 3–4 h post DMSA (V) injection.	Visual assessment: 'no uptake or increased uptake'	Unclear.
Tc-99 m DMSA (V)	Kobayashi, 1995	A prospective cohort study. Reference standard: histology (n = 24); otherwise clinic-radiological assessment with a minimum follow-up of 12 months (n = 13)	17/37	27/10	Tc-99 m DMSA (V), 370–550 MBq. 2 h post DMSA (V) injection.	Visual assessment: 'positive or negative'	Unclear. Tc-99 m HMDP was performed within the previous 4 weeks of Tc-99 m DMSA.
Tc-99 m DMSA (V)	Shinya, 2015	A prospective cohort study. Reference standard: histology (n = 14); otherwise clinical and radiological assessment with a mean follow-up of 40 months (n = 10)	24/24	19/5	Tc-99 m DMSA (V), 370 MBq. 2 h post DMSA (V) injection.	Visual assessment of intensity rated 0–2.	Unclear.

Abbreviations: FU: follow-up, FDG-PET: Fluorodeoxy-glucose positron emission tomography, PET-CT: positron emission tomography-computed tomography, MDP: Methylene Diphosphate, Tc-99 m DMSA (V): Technetium-99 m pentavalent dimercaptosuccinic acid, HMDP: hydroxymethylene diphosphonate.

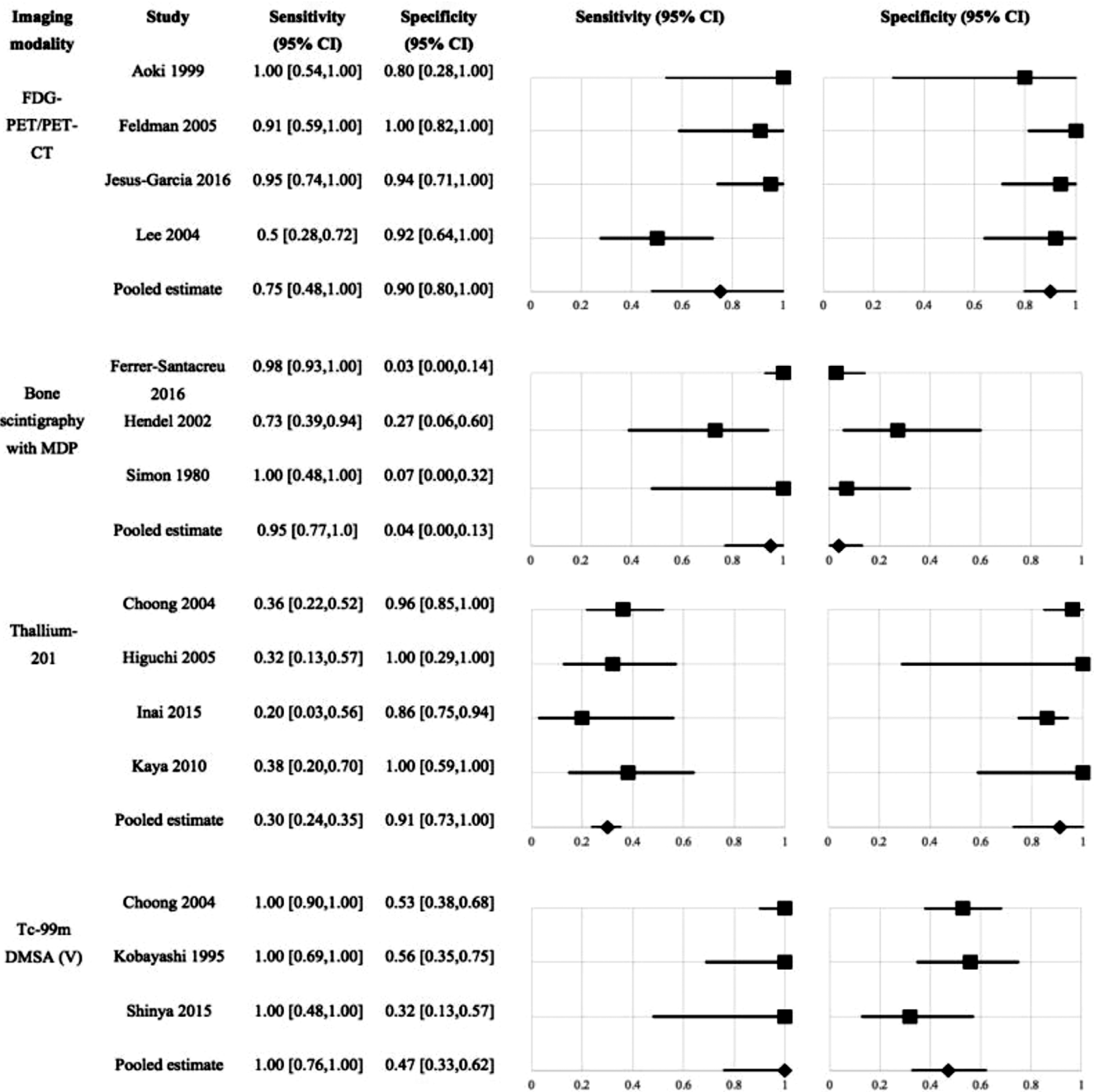


Fig. 2. Forest plots with sensitivity and specificity estimates of the included studies.

The current literature on the use of functional imaging in chondroid tumours is limited by a lack of randomised controlled trials and high-quality large volume studies. This may very well be due to the rarity of chondroid tumours. Therefore, we conducted a systematic review to present the best concurrent comparison of diagnostic accuracies of all functional scans used to discriminate malignancy from benignity in chondroid tumours.

FDG-PET imaging uses FDG that utilises glucose metabolism to detect the primary tumour and metastases. Cancer cells more avidly take up glucose and thus the glucose analogue FDG compared to normal cells, thereby enabling specific visualisation by FDG-PET [41]. Several authors have reported the usefulness of FDG-PET in the oncologic work-up for chondrogenic tumours [42–45]. Based on our results, FDG-PET had the highest pooled DOR of 62.04 amongst the four modalities evaluated in this study. Therefore, when structural imaging findings are

non-diagnostic, it may be a useful adjunct to identify malignancy. Furthermore, FDG-PET has been utilised to guide biopsy at the most metabolically active lesion of the tumour (Fig. 3).

Despite its efficacy, there are concerns with applicability and risk of test review bias. Only one study [30] pre-specified a diagnostic cut-off value. Deciding on a cut-off value based on the results of reference tests can falsely alter sensitivity and specificity of the index tests. Furthermore, there were considerable differences in the reported cut-off values of SUVmax (range 1.3–2.0) to distinguish between benign chondroid lesions and chondrosarcomas. This means a chondroid tumour with an SUVmax value of 1.4 would be considered a chondrosarcoma in Aoki et al. [25]’s study that would otherwise be a benign tumour according to Feldman et al. [15] and Jesus-Garcia et al. [30]’s cut-off value. Similarly, a systematic review and meta-analysis involving eight articles demonstrated substantial overlap of SUVmax values between benign

**Table 4**  
Diagnostic accuracy measures.

Imaging modality	Author	TP	FP	FN	TN	PPV	NPV	LR+	LR-	Accuracy	DOR
FDG-PET & PET/CT	Aoki 1999	6	1	0	4	0.86	1.00	5.00	0.00	0.91	39.00
	Feldman 2005	10	0	1	18	1.00	0.95	NE	0.09	0.97	259.00
	Jesus-Garcia 2016	18	1	1	16	0.95	0.94	16.11	0.06	0.94	288.00
	Lee 2004	11	1	11	12	0.92	0.52	6.5	0.54	0.66	12.00
Tc-99 m MDP	Ferrer-Santacreu 2016	92	38	2	1	0.71	0.33	1.00	0.83	0.70	1.21
	Hendel 2002	8	8	3	3	0.50	0.50	1.00	1.00	0.50	1.00
	Simon 1980	5	14	0	1	0.26	1.00	1.07	0.00	0.30	1.43
Thallium-201	Choong 2004	15	2	27	43	0.88	0.61	8.04	0.67	0.67	11.94
	Higuchi 2005	6	0	13	3	1.00	0.19	NE	0.68	0.41	3.37
	Inai 2015	2	8	8	50	0.20	0.86	1.45	0.93	0.77	1.56
	Kaya 2010	6	0	10	7	1.00	0.41	NE	0.62	0.57	9.29
Tc99m-DMSA (V)	Choong 2004	36	22	0	25	0.62	1.00	2.14	0.00	0.74	82.73
	Kobayashi 1995	10	12	0	15	0.46	1.00	2.25	0.00	0.68	26.04
	Shinya 2015	5	13	0	6	0.28	1.00	1.46	0.00	0.46	5.30

Abbreviations: FDG-PET: 2-deoxy-2-[<sup>18</sup>F]fluoro-D-glucose positron emission tomography, PET/CT: 2-deoxy-2-[<sup>18</sup>F]fluoro-D-glucose positron emission tomography/X-ray computed tomography, MDP: Methylene Diphosphate, Tc-99 m DMSA (V): Technetium-99 m pentavalent dimercaptosuccinic acid, TP: true positive, FP: false positive, FN: false negative, TN: true negative, PPV: positive predictive value, NPV: negative predictive value, LR+: positive likelihood ratio, LR-:negative likelihood ratio, DOR: diagnostic odds ratio, NE: not estimable.

and malignant chondroid tumours [20]. While FDG-PET may be a useful diagnostic test for chondroid tumours, further research with a pre-specified, reliable cut-off value with a large patient cohort is needed before definitive conclusions can be made.

Tc-99 m MDP is the most commonly used bone scintigraphy when bone malignancies are suspected [7]. In our review, positive uptake on Tc-99 m MDP was not significantly associated with the odds of chondrosarcoma. The uptake of MDP has been reported to be dependent on an osteoblastic response to a tumour by the adjacent bone. This response can be just as intense for a benign tumour as chondrosarcoma, which may account for tracer uptake being almost identical between the two groups [29]. A highly sensitive but non-specific test may be considered for a screening test; however, such a test has a limited value in diagnostic work-up. Patients without disease are potentially subjected to unnecessary procedures, often invasive and costly treatment, and emotional stress [46]. Given that 94% (103/110) of chondrosarcomas were grade 1, it is possible that this sample represents a diagnostically challenging group. Nevertheless, we conclude that Tc-99 m MDP has a low diagnostic value for detecting chondrosarcoma.

Thallium-201 scintigraphy involves the use of Thallium-201 chloride, a monovalent cationic agent with similar properties to potassium. It makes use of the property that cancer cells often take up more potassium in cellular metabolic cycles compared to normal cells [47]. Contrary to the conventional bone scan, Thallium-201 scintigraphy had high specificities above 86% across all studies and relatively poor sensitivities ranging from 20% to 38%. This is in concordance with the findings of previous studies [15,48] that chondrosarcoma has a relatively low uptake of scintigraphic agents compared to other bone malignancies such as osteosarcoma. False negative Thallium-201

scintigraphy has been reported in cases of chondrosarcoma, especially those of low-grade [28,31,49]. Nevertheless, a positive test may be useful for predicting malignancy based on its high PPVs (Fig. 4). Furthermore, a positive test has been associated with chondrosarcoma, particularly those of higher grade and more aggressive nature [28,31].

DMSA (V) is a radiopharmaceutical that was designed to metabolically mimic phosphate and accumulates within the more acidic neoplastic cells by the means of hydrolysis [50]. Based on our results, we postulate that almost all patients with chondrosarcoma and about half of the patients with benign cartilaginous tumours would test positive on this modality. Although an increased DMSA (V) uptake may have a limited role in discriminating chondrosarcoma from benign chondroid tumours, its strength lies in its negative results. An NPV of 100% means that it can effectively rule out chondrosarcoma when the test is negative. One study [13] proposed a step-wise algorithm based on the uptake characteristics of both Thallium-201 and DMSA (V). The authors postulated that when Tc-99 m DMSA (V) is negative, chondrosarcoma is less likely. For DMSA (V) positive tumours, Thallium-201 scintigraphy is subsequently performed to differentiate higher grade chondrosarcomas.

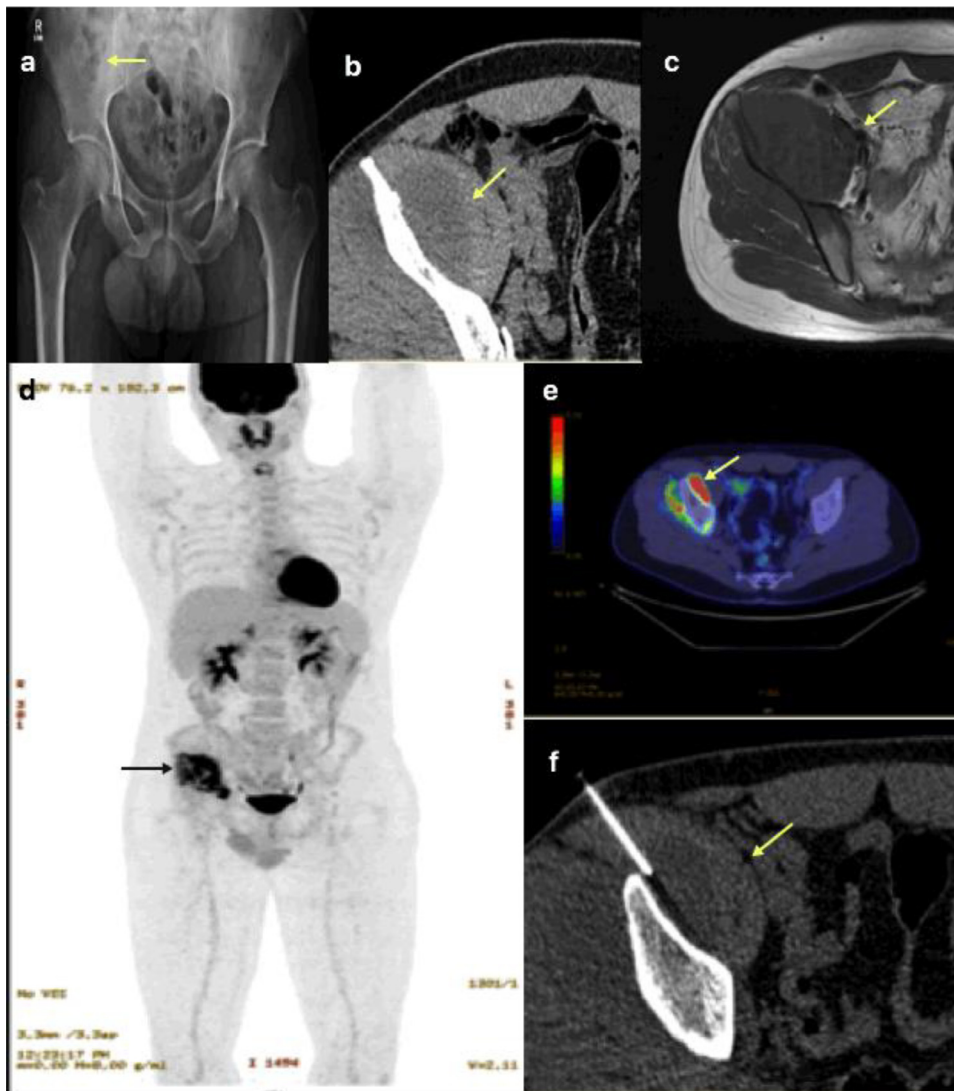
Choosing the most appropriate diagnostic technique for chondroid tumours remains difficult as each test within the field of radiology, nuclear medicine and pathology has its own added value to either diagnosis or therapeutic decisions. For example, functional imaging modalities offer metabolic and biological information about tumour [10]. Nonetheless, they may provide insufficient information about the location, shape, size and relationship to neighbouring organs and structures, which can be offered by structural imaging [13]. The value of multi-disciplinary discussions of all findings from these

**Table 5**  
Pooled sensitivity, specificity and DOR with heterogeneity measures.

Imaging modality	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Pooled DOR
FDG-PET & PET/CT	0.75 [0.48,1.00]	0.90 [0.80,1.00]	62.04 ( $p < 0.00001$ )
Heterogeneity ( $I^2$ )	25.99%	0.00%	26%
Tc-99 m MDP	0.95 [0.77,1.00]	0.04 [0.00,0.13]	1.13 ( $p = 0.86$ )
Heterogeneity ( $I^2$ )	69.97%	10.52%	0%
Thallium-201 scintigraphy	0.31 [0.24,0.35]	0.91 [0.73,1.00]	4.94 ( $p = 0.04$ )
Heterogeneity ( $I^2$ )	48.26%	0.00%	8%
Tc99m-DMSA (V)	1.00 [0.76,1.00]	0.47 [0.33,0.62]	23.92 ( $p = 0.0002$ )
Heterogeneity ( $I^2$ )	NE. $Q^2 = 0$ , given 0 false negatives.	0.11%	0%

Abbreviations: FDG-PET: 2-deoxy-2-[<sup>18</sup>F]fluoro-D-glucose positron emission tomography, PET/CT: 2-deoxy-2-[<sup>18</sup>F]fluoro-D-glucose positron emission tomography/X-ray computed tomography, MDP: Methylene Diphosphate, Tc-99 m DMSA (V): Technetium-99 m pentavalent dimercaptosuccinic acid, CI: confidence interval, DOR: diagnostic odds ratio, NE: not estimable.





**Fig. 3.** a–f. Application of PET for diagnosing and targeting biopsy in chondrosarcoma.

A 29-year-old male who presents with a few month history of right hip pain. (a) Plain radiograph demonstrating subtle sclerosis involving the right ilium. (b) Axial CT shows extraosseous soft tissue mass and periosteal reaction. (c) T1 axial MR demonstrates soft tissue mass with associated marrow infiltration. (d) FDG uptake in the lesion in right ilium on PET/CT. (e) Axial PET/CT shows intense uptake within the lesion correlating to the most metabolically active lesion. (f) Core needle biopsy targeted at the areas with greatest uptake. Histology of surgical specimen: grade 3 chondrosarcoma.

investigations to determine diagnosis should not be undermined [51]. While targeted investigations may assist in distinguishing benign chondroid tumours from chondrosarcomas in challenging situations, the initial clinical, radiological and histological assessments of chondroid tumours are important first steps for diagnosing cartilaginous lesions correctly. A careful combination of diagnostic techniques, each serving a specific purpose, may improve diagnostic confidence and therapeutic planning.

#### 4.1. Limitation

We recognise some limitations to our study. Firstly, due to the relatively small number of included studies for each modality and variations in the execution of index tests and thresholds, the effect of pooling of data may be less meaningful. Secondly, Thallium-201 and DMSA (V) scintigraphs have relatively limited use in modern medicine. However, the findings of the review suggest that some specialist centres may benefit from their use in diagnostically challenging cases. Furthermore, these tracers are easily obtainable for most hospitals as they are used in other investigations in the field of cardiology and renal medicine respectively. This is particularly useful in resource poor setting where access to a PET scan may be limited.

Thirdly, whilst we combined FDG-PET and PET/CT together, they may have a different diagnostic performance. Lastly, this review provides limited information on the use of functional imaging as an add-on

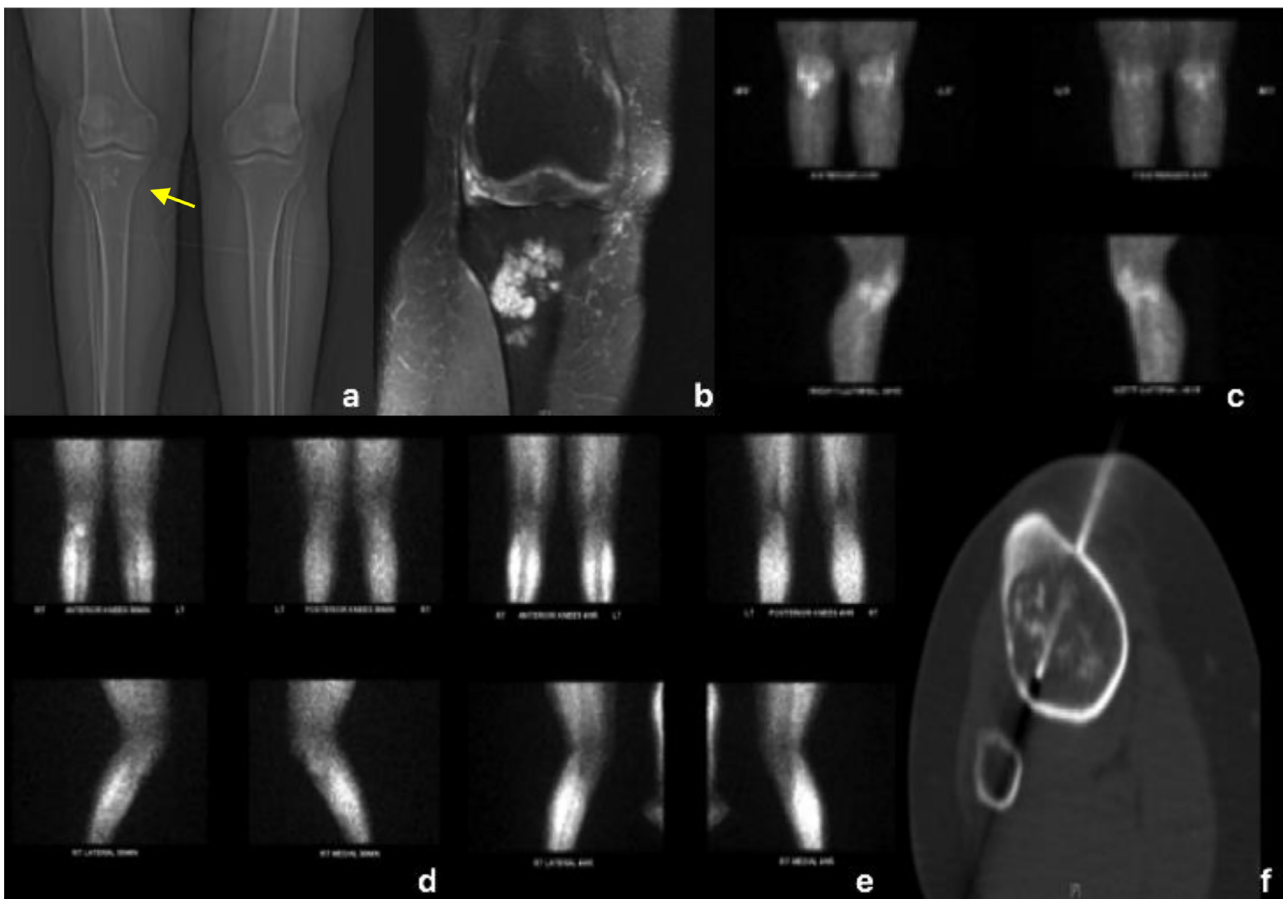
test to the conventional diagnostic work-up for detecting chondrosarcoma. Further studies may focus on this aspect as functional imaging is often performed in conjunction with other investigatory modalities.

## 5. Conclusions

We identified 13 studies that investigated the efficacy of functional imaging scans in assessing chondroid tumours. Four modalities were involved, and sufficient data was available to address the review question on whether functional scans can accurately diagnose chondrosarcoma. FDG-PET or PET/CT is a sensitive and specific diagnostic test. If a reliable SUVmax cut-off value can be determined with further research, it has the potential to significantly increase the diagnostic accuracy. Tc-99m MDP has a limited role in distinguishing benign and malignant chondroid tumours. Thallium-201 scan may be used as a ‘rule-in’ test while DMSA (V) scintigraphy may be an effective ‘rule-out’ test for chondrosarcoma.

## Declaration of Competing Interest

I Jo, D Gould, K Taubman, and S Schlicht declared there are no conflict of interest.



**Fig. 4.** a–e. Role of Thallium-201 scintigraphy and Tc-99 m DMSA (V) in diagnosing low grade chondroid lesion.

A 68-year-old woman who presents with a mass in right distal femur. (a) Plain radiograph of right femur shows punctate calcification without cortical breach. (b) Axial MR demonstrates multiple punctate lesions with endosteal scalloping. There is no associated periosteal oedema. Differential diagnosis include enchondroma and grade 1 chondrosarcoma. (d) DMSA (V) retention at 4 h. (d) The early images at 30 min demonstrate intense early Thallium-201 accumulation involving the proximal right tibial lesion. (e) At 4 h, there is generally a washout pattern, though there is some minimal retention of Thallium-201. Close surveillance is recommended. Histology: grade 1.

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### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jbo.2019.100262.

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