Utility of ^{18}F -FDG PET and PET/CT in diagnosis and staging of chondrosarcoma: a meta-analysis

Qingyu Zhang

Shandong Provincial Hospital

Yongming Xi

Affiliated Hospital to Qingdao University

Dong Li

Shandong Provincial Hospital

Zenong Yuan

Shandong Provincial Hospital

Jun Dong (✉ slyydj2019@163.com)

Shandong Provincial Hospital <https://orcid.org/0000-0002-5626-975X>

Research article

Keywords: chondrosarcoma, ^{18}F -FDG PET, PET/CT, diagnosis, meta-analysis

Posted Date: October 29th, 2019

DOI: <https://doi.org/10.21203/rs.2.16535/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Journal of Orthopaedic Surgery and Research on June 22nd, 2020. See the published version at <https://doi.org/10.1186/s13018-020-01748-w>.

Abstract

Background Chondrosarcoma is the second most common primary bone sarcoma; 18 F-FDG PET and PET/CT are increasingly proposed as tools to evaluate the status of chondrosarcoma but their accuracy remains disputable. The study aims to evaluate the utility of 18 F-FDG PET and PET/CT to differentiate chondrosarcoma from benign cartilaginous lesions and to predict the histopathological grade of chondrosarcoma.

Methods A comprehensive search was performed in three electronic databases including Medline/PubMed, the Cochrane library and Embase to retrieve diagnostic studies evaluating the role of 18 F-FDG PET or PET/CT for appraising status of chondrosarcoma. The reference lists of related articles were also scrutinized manually. Useful data were extracted to calculate the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odd ratio (DOR), the summary receiver operating characteristic curve (sROC) as well as the area under the curve (AUC) of 18 F-FDG PET or PET/CT in diagnosing chondrosarcoma, and pooled weighted mean differences (WMD) of maximum standardized uptake value (SUVmax) between different entities of cartilaginous neoplasms by using Stata 15.0.

Results A total of 12 studies provided sufficient data for the quantitative analysis. For the diagnosis of chondrosarcoma, the pooled sensitivity, specificity and DOR of 18 F-FDG PET were 0.84 (95% confidence interval [CI] 0.46 to 0.97), 0.82 (95% CI 0.55 to 0.94) and 24.244 (95% CI 1.985 to 96.148), respectively while those of 18 F-FDG PET/CT were 0.94 (95% CI 0.86 to 0.97), 0.89 (95% CI 0.82 to 0.93) and 112.999 (95% CI 41.341 to 308.866), respectively. The pooled WMD of SUVmax were -0.89 (95% CI -1.67 to -0.10) between benign cartilaginous lesions and grade 1 (G1) chondrosarcoma, -1.94 (95% CI -2.76 to -1.12) between G1 and grade 2 (G2) chondrosarcoma, and -2.37 (95% CI -5.79 to 1.05) between G2 and grade 3 (G3) chondrosarcoma.

Conclusions In a word, 18 F-FDG PET/CT revealed excellent accuracy in the diagnosis of chondrosarcoma and might assist in clinical decision-making. However, SUVmax alone showed restricted ability to differentiate benign cartilaginous lesions and chondrosarcoma, as well as between G2 and G3 chondrosarcoma. More large-scale studies are still needed to further warrant current findings.

Background

Chondrosarcoma is the second most common primary malignant bone sarcoma characterized by the production of atypical cartilage matrix and invasive growth inside the pre-existing cortical and medullary bone tissue [1]. This malignant disorder could be further subcategorized to low-grade (LGCS; G1), intermediate-grade (IGCS; G2), high-grade (HGCS; G3) and dedifferentiated chondrosarcoma (DedCS), which manifest diverse histological features and clinical behaviors[2]. Tumor histology and grade (Evans grading) are the decisive factors of recurrence and prognosis of cartilaginous neoplasms[3]. Grade I have little risk of metastasis and excellent prognosis [4] while an unfavorable outcome is generally associated

with G2 and G3 chondrosarcoma, revealing a 5-year cumulative survival rate being 63–92% and 39–77%, respectively[4]. DedCS exhibits a biphasic differentiated nature (a conventional chondrosarcoma and a high-grade, non-cartilage-producing sarcoma) of tumor cells, predisposing patients with the worst prognosis [5, 6]. The widely-accepted regimen for managing benign cartilaginous neoplasms (e.g., enchondroma and exostosis) are follow-up, and margin excision when symptoms appear[7]. Alternative options advocated for LGCS include rigorous follow-up until the lesion progresses, wide excision or curettage, albeit the last approach may be accompanied by relapse [8]. Besides, a neoadjuvant chemotherapy before surgery can be reserved for DedCS [9] while radiotherapy for unresectable lesions [10].

Therefore, therapeutic strategy of cartilaginous bone neoplasms should be established on the accurate diagnosis and staging. Up to date, the differential diagnosis of various cartilaginous tumors is predominantly based on biopsy of the lesions for pathological analysis; nevertheless, tissue samples acquired by core needle biopsy may not be representative of the whole cartilaginous lesion and the final results are often subjected to a substantial interobserver variability [11]. Moreover, the image-guided percutaneous biopsy shows a low predictive value in assessing the grade of chondrosarcoma[11]. According to Laitinen et al's report enrolling 343 patients with osteochondroma, the concordance between the preoperative biopsy grading and the final histological grading of resected tumor tissue was observed in only 43% cases [12]. Conventional imaging methods such as X-ray, computed tomography (CT) scan, magnetic resonance imaging (MRI) and bone scintigraphy have been used as adjuvants for evaluating patients with suspected chondrosarcoma but often result in false-negatives or false-positives[13].

^{18}F -fluorodeoxyglucose(^{18}F -FDG) avidity presents useful information regarding tumor biology and sarcomatous transformation by depicting glucose metabolism and identifying hyper-metabolic foci[14]. Meanwhile, a hybrid of ^{18}F -FDG positron emission tomography (PET) and computed tomography (CT) combines metabolic and anatomic data and may further improve the diagnostic efficiency[14]. A series of studies have investigated the utility of ^{18}F -FDG PET and/or PET/CT in the diagnosis and staging of chondrosarcoma and revealed contradictory conclusions[15–17]. A systematic review[18] published in 2017 attempting to summarize the optimal maximum standardized uptake value (SUVmax) to differentiate different group of cartilaginous bone sarcoma but the reliability of its result was compromised due to several flaws. First, only 8 studies involving 166 chondroid neoplasms were included. Second, the investigators did not appraise the diagnostic accuracy of ^{18}F -FDG PET or ^{18}F -FDG PET/CT for chondrosarcoma. Third, the differences of ^{18}F -FDG avidity between various chondroid neoplasms were not compared by a standard method of evidence-based medicine. Multiple high-quality studies[15–17] on this topic were published in recent years and in current study, we further assess the ability of ^{18}F -FDG PET and PET/CT to diagnose chondrosarcoma and to predict the histological grade by performing a meta-analysis.

Methods

The methodological approach described later was in compliance with the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA)[19]. Ethical approval or informed consent was waived given that all data were retrieved from published literatures. Database searching, eligibility assessment, data extraction and methodological quality evaluation were performed by two investigators (QY Zhang and YM Xi) independently and repeatedly. Any disagreement was resolved through discussion and consensus among research team.

Search strategy

A systematic literature search was performed in three electronic databases including Medline/Pubmed, Embase and Cochrane library using combinations of following key words: (“PET” OR “positron emission tomography”) AND (“chondroid” OR “cartilaginous” OR “cartilage” OR “chondrosarcoma”) with no language limitations. The last search was performed on September 15, 2019. Meanwhile, reference lists of relevant articles (diagnostic studies, reviews, meta-analyses and editorials) were carefully checked to avoid missing additional eligible studies.

Inclusion and exclusion criteria

Studies eligible for our meta-analysis must confirm following criteria: 1) studies assessing the diagnostic or staging value of ^{18}F -FDG PET or PET/CT in cartilaginous neoplasms; 2) final diagnosis were confirmed by histopathological examination, follow-up or other predefined reference methods, and 3) raw data such as the number of true-positive (TP), false-positive (FP), false-negative (FN) and true negative (TN) cases, or maximum standardized uptake value (SUVmax) of enrolled participants were provided. Exclusion criteria for this meta-analysis included: 1) animal studies; 2) studies with less than five participants, and 3) posters displayed at congress, abstracts, letters and comments due to the lack of essential information.

If more than one article contained overlapping data, the most comprehensive or recent one was included.

Data extraction and methodological quality evaluation

Following information were extracted from original articles and entered into a standardized excel file: first author's surname, publication year, study design, number and characteristics of participants (age and gender), tumor histology, reference methods, details of index tests (^{18}F -FDG PET or PET/CT, injection dose, methods of analysis and so on), SUVmax and final diagnosis. Numbers of TP, FP, TN and FN were extracted directly or recalculated through data presented by original articles. Risk of bias of included studies was appraised by using the QUADAS-2 tool[20], which consisted of four key domains (i.e.,

patient selection, index test, reference standard, and flow and timing) involving 14 questions. These questions were answered with “yes” for a low risk of bias, “no” for a high risk of bias and “unclear” if associated information was not clearly presented[20].

Statistical analysis

Pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) were calculated using the bivariate meta-analysis framework (a random-effects model). In addition, summarized receiver operating characteristic (sROC) curves were constructed, with a larger area under curve (AUC) indicating a better diagnostic accuracy of tests. Meanwhile, pooled weighted mean difference (WMD) as well as related 95% confidence intervals (CIs) were generated to evaluate continuous data (SUVmax), and a 95% CIs not covering 0 revealed a difference with statistical significance. Heterogeneity among included studies was assessed using the I^2 statistic. An I^2 value of 0% implied no observed heterogeneity, and values of > 50% suggested substantial heterogeneity. All data were analyzed by using Stata version 15.0 (StataCorp, College Station, TX).

Results

Study selection and description

By searching electronic databases and reviewing reference lists of relevant publications, we retrieved a total of 398 records, among which 324 apparently ineligible articles were firstly discarded by screening titles and abstracts. Subsequently, full-texts of remaining ones were downloaded and scrutinized against the predefined criteria. Eventually, 12[13, 15–17, 21–28] studies were included in the quantitative analysis. The selection process and reasons for exclusion were described in Figure 1.

Study characteristics

All included studies are published in English and among them, three[13, 15–17, 21–28] were prospective, whereas nine[15–17, 21–23, 25–27] were retrospective. Sizes of these studies ranged from 7 to 95 and a total of 375 participants with suspected chondrosarcoma were involved. Main characteristics of included studies were summarized in table 1. As for the risk of bias, only two[24, 25] studies was judged as low risk in the section of index tests because the rest did not predefine the cutoff value of SUVmax for diagnosing chondrosarcoma. Meanwhile, nine[13, 15–17, 21–25] studies were judged as high risk of bias in flow and timing for the lack of a uniform reference tests for all enrolled participants, which was hardly an easy and may be ethically questionable in some situations. In these studies[13, 15–17, 21–25], the golden standard to diagnose cartilaginous tumors was biopsy for those highly suggestive of malignancy and follow-up for those with benign manifestation. Results of risk of bias assessment were summarized in Figure 2.

5[15, 24, 25, 27, 28] studies provided data about the diagnostic accuracy of ^{18}F -FDGPET for chondrosarcoma. As shown in Figure 3A and 3B, the pooled sensitivity and specificity of ^{18}F -FDG PET for diagnosing chondrosarcoma were 0.84 (95%CI, 0.46 to 0.97) and 0.82 (95% CI, 0.55 to 0.94), respectively. The pooled PLR, NLR and DOR were 4.633 (95% CI, 1.443 to 14.875), 0.191 (95% CI, 0.037 to 0.986) and 24.244 (95% CI, 1.985 to 296.148), respectively, while the AUC was 0.89 (95% CI, 0.86 to 0.92) (Figure 4A). The I^2 statistics for sensitivity and specificity values were 86.90% (95% CI, 76.80% to 97.00%) and 70.32% (95% CI, 42.57% to 98.07%), respectively, which indicated that substantial heterogeneity existed among included studies.

Accuracy of ^{18}F -FDG PET/CT for the diagnosis of chondrosarcoma

7[13, 15–17, 21–23] studies provided data about the diagnostic accuracy of ^{18}F -FDGPET/CT for chondrosarcoma. As shown in Figure 3C and 3D, the pooled sensitivity and specificity of ^{18}F -FDG PET/CT for diagnosing chondrosarcoma were 0.94 (95%CI, 0.86 to 0.97) and 0.89 (95% CI, 0.82 to 0.93), respectively. The pooled PLR, NLR and DOR were 8.265 (95% CI, 5.012 to 13.628), 0.073 (95% CI, 0.034 to 0.157) and 112.999 (95% CI, 41.341 to 308.866), respectively, while the AUC was 0.92(95% CI, 0.89 to 0.94) (Figure 4B). The I^2 statistics for sensitivity and specificity values were 15.79% (95% CI, 0% to 77.52%) and 0% (95% CI, 0% to 100%), respectively, indicating that no substantial heterogeneity existed among included studies.

Accuracy of ^{18}F -FDG avidity for the staging of chondrosarcoma

4[13, 15, 25, 27] studies recorded the ability of ^{18}F -FDG avidity to differentiate between benign cartilaginous lesions and G1 chondrosarcoma. The combined results (pooled WMD = -0.89 95% CI: -1.67 to -0.10, $p = 0.027$; I^2 statistic = 85.1%, p for heterogeneity < 0.001) suggested that SUVmax of benign cartilaginous lesions were slightly lower than that of G1 chondrosarcoma (Figure 5A). The SUVmax of G1 chondrosarcoma was also significantly lower than that of G2 chondrosarcoma (pooled WMD = -1.94 95% CI: -2.76 to -1.12, $p < 0.001$; I^2 statistic = 20.5%, p for heterogeneity = 0.287) (Figure 5B). However, there is no significant difference of SUVmax between G2 and G3 chondrosarcoma (pooled WMD = -2.37 95% CI: -5.79 to 1.05, $p = 0.174$; I^2 statistic = 68.3%, p for heterogeneity = 0.024) (Figure 5C).

Discussion

The optimal therapeutic strategy (observation or active treatment) for chondrosarcoma depends on not only the prompt identification but also the correct differentiation between high-grade and low-grade ones. Although chondrosarcoma normally presents with increased pain, these symptoms and signs can be nonspecific and misdiagnosed as other musculoskeletal disorders such as osteomyelitis and osteoarthritis[2]. Up to date, the classification of this heterogeneous entity mainly relies on comprehensive considering clinical, imaging and histological information, but a definitive diagnosis is often difficult to achieve due to the discrepant interpretation among clinicians [29]. In this study, it is demonstrated that overall ^{18}F -FDG PET/CT has a high accuracy of differentiating chondrosarcoma from benign cartilaginous lesions (pooled DOR = 112.999, 95% CI: 41.341 to 308.866) in comparison with ^{18}F -FDG PET (pooled DOR = 24.244; 95% CI: 1.985 to 296.148) alone. To our knowledge, this is the first meta-analysis systematically investigating the utility of ^{18}F -FDG PET and PET/CT for the diagnosis and staging of chondrosarcoma.

Generally, it was reported that benign chondroid lesions such as enchondromas and osteochondromas are not FDG avid[15–17]. According to the pooled results, although there was a statistically significant WMD of SUVmax between G1 chondrosarcoma and benign cartilaginous lesions, differential diagnosis of these two variants can be challenging owing to their histologically analogical nature and overlapped SUVmax[30]. The confidence intervals of the pooled sensitivity and specificity were relatively large, which was possibly on account of the little scale of sample size and small number of included studies as well as the significant between-study heterogeneity. Meanwhile, it may not be possible to arrive a universally-acknowledged SUVmax threshold (ranging from 1.3 to 3.1 in retrieved articles) that explicitly distinguish benign from malignant cartilaginous tumors. The present study also aimed to investigate the potential role of SUVmax to predict CS grading. Distinguishing LGCS from IHGCS is crucial considering that the biological behavior of these tumors varies greatly and the 2013 WHO classification of bone and soft tissue sarcoma clearly separates locally aggressive chondrosarcoma (atypical cartilaginous tumor or G1 chondrosarcoma) from definitely malignant cartilaginous tumors (G2 and G3 chondrosarcoma)[2]. It was postulated that the SUVmax values increased with the tumor grade[25] and the pooled result indeed demonstrated that ^{18}F -FDG PET can accurately discriminate LGCS from IHGCS with a pooled WMD of SUVmax being -3.25 . Unfortunately, there is evident overlap in SUVmax values between G2 and G3 chondrosarcoma. Significant heterogeneity of included studies could be contributed to the differences of the injected radiotracer dose, the time between injection and the initiation of detection, patient weight, body surface area, predictive cutoff value, detection equipment and the individual characteristic of enrolled patients across included studies. Institution-specific threshold established through cooperation of nuclear medicine specialist, orthopedic surgeons and pathologists was recommended in clinic practice.

Despite limited value of ^{18}F -FDG PET for diagnosis and staging, SUVmax did offer crucial information for the management of chondrosarcoma. First, ^{18}F -FDG PET scanning identifies tumor aggressiveness and extent visually and quantitatively, and therefore can aid in deciding whether biopsy is needed or directing the biopsy sampling [31]. This reduces the risk of false-negative result and rebiopsy as well as related

complications. Second, SUVmax serves as an adjuvant for image-guided percutaneous biopsy. For a cartilaginous lesion manifesting low potential of malignancy but high SUVmax, caution should be taken regarding the potential of elevating histologic grade based on postoperative tissue. Third, due to the ability of concentrating in biologically aggressive area, ^{18}F -FDG can accurately predict and localize dedifferentiation[15], prompting adjuvant treatment besides surgical excision. Last but not least, alteration of ^{18}F -FDG avidity is an indicator of relapse or sarcomatous transformation of cartilaginous neoplasms.

The combination of CT with ^{18}F -FDG PET (^{18}F -FDG PET/CT) facilitates the analysis of size and aggressive characteristics (i.e., cortical bone invasion, periosteal reaction, bone expansion, periostitis and extraosseous soft tissue) of the cartilaginous tumor and therefore may increase the diagnostic accuracy[32]. The size of cartilaginous tumors was closely correlated with their histologic grade; for example, the majority of IHGCS (79.3%) presented with a maximum diameter over 5 cm [33]. Meanwhile, if there were signs of invasion, it is most likely that these cartilaginous lesions are chondrosarcomas[2]. In addition, CT scan of other parts of the body, especially the chest, is necessary for conducting a comprehensive staging of patients with chondrosarcoma. Besides the higher pooled DOR of ^{18}F -FDG PET/CT for diagnosing chondrosarcoma in comparison with PET alone, promising pooled sensitivity (94%) and specificity (89%) of ^{18}F -FDG PET/CT were also revealed in current study. The relatively narrow confidence intervals and small heterogeneity indicated that these results were stable and [persuasive](#). However, PET/CT is not without disadvantages. First is the additional radiation of the computed tomography. Second, PET/CT is a costly and labor-consuming procedure that is not yet available in all hospitals. Third, compared with thin-section dedicated CT, the CT section integrated with PET behaves poorly in presenting fine details such as deep of scalloping[15]. For the aim of getting a definitive diagnosis of a cartilaginous neoplasm, all available information such as patient age, clinical manifestation, lesion location and the tumor growth rate must be taken into consideration. Creating a score that comprehensively summarize these data as well imaging and nuclear medicine findings will shed new light on the noninvasive diagnosis of cartilaginous neoplasms.

There are several limitations meriting consideration. The first is the lack of a standardized reference test for the diagnosis of chondrosarcoma. Either follow-up without an anatomopathological examination or biopsies may result in false negatives. The duration of follow-up differed from study to study, exceeding 12 months in most of included ones but in Shin et al.'s investigation[15], the minimum follow-up was only six months. Another major limitation is that during merging of diagnostic data, subgroup analyses on the basis of important indicators such as types of chondrosarcoma, cutoff value and study design was not conducted due to the limited number of studies. Only 12 studies were included in this meta-analysis and most (75%) of them were retrospective in nature. Third, sample size of these studies was quite small and hence this meta-analysis might be subject to variability and inadequacy in data collection. Lastly yet importantly, evidence of heterogeneity in data concerning ^{18}F -FDG PET existed throughout included studies, and therefore we emphasized the pooled DOR, which was a global measure encompassing

sensitivity, specificity, PLR and NLR, as our main outcome of interest to compare the diagnostic performance of ^{18}F -FDG PET and PET/CT.

Conclusions

In a word, ^{18}F -FDG PET/CT revealed excellent accuracy in the diagnosis of chondrosarcoma and might assist in clinical decision-making. However, SUVmax alone showed restricted ability to differentiate benign cartilaginous lesions and chondrosarcoma, as well as between G2 and G3 chondrosarcoma. More large-scale studies are still needed to further warrant current findings.

Declarations

Availability of data and materials

All data analyzed during this study are included in this published article.

Authors' contributions

DJ contributed to the idea of this study. ZQY and XYM searched literatures and screened them independently. ZQY, XYM and LD screened data from the twelve final articles and make Tables. LD and YZN played an important role in analyzing the outcomes. LD, YZN and DJ conducted the data analyses and make graphs. ZQY and XYM wrote the first draft. LD, YZN and DJ revised the manuscript. ZQY, XYM, LD, YZN and DJ approved the final version.

Acknowledgement

None.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

Not applicable.

Funding

None.

Competing interests

The authors declare that they have no competing interests.

References

- 1.Damron TA, Ward WG, Stewart A. Osteosarcoma, chondrosarcoma, and Ewing's sarcoma: National Cancer Data Base Report. Clin Orthop Relat Res. 2007; 45940–47.
- 2.Christopher DM, Fletcher JA, Krishnan U. WHO classification of tumours of soft tissue and bone. International agency for research on cancer 4th edition Lyon. 2013; 250–252.
- 3.Ducimetiere F, Lurkin A, Ranchere-Vince D, Decouvelaere AV, Isaac S, Claret-Tournier C, et al. [Incidence rate, epidemiology of sarcoma and molecular biology. Preliminary results from EMS study in the Rhone-Alpes region]. Bull Cancer. 2010; 97(6):629–641.
- 4.Nota SP, Braun Y, Schwab JH, van Dijk CN, Bramer JA. The Identification of Prognostic Factors and Survival Statistics of Conventional Central Chondrosarcoma. Sarcoma. 2015; 2015623746.
- 5.Staals EL, Bacchini P, Mercuri M, Bertoni F. Dedifferentiated chondrosarcomas arising in preexisting osteochondromas. J Bone Joint Surg Am. 2007; 89(5):987–993.
- 6.Strotman PK, Reif TJ, Kliethermes SA, Sandhu JK, Nystrom LM. Dedifferentiated chondrosarcoma: A survival analysis of 159 cases from the SEER database (2001–2011). J Surg Oncol. 2017; 116(2):252–257.
- 7.Marco RA, Gitelis S, Brebach GT, Healey JH. Cartilage tumors: evaluation and treatment. J Am Acad Orthop Surg. 2000; 8(5):292–304.
- 8.Zoccali C, Baldi J, Attala D, Rossi B, Anelli V, Annovazzi A, et al. Intralesional vs. extralesional procedures for low-grade central chondrosarcoma: a systematic review of the literature. Arch Orthop Trauma Surg. 2018; 138(7):929–937.
- 9.Dickey ID, Rose PS, Fuchs B, Wold LE, Okuno SH, Sim FH, et al. Dedifferentiated chondrosarcoma: the role of chemotherapy with updated outcomes. J Bone Joint Surg Am. 2004; 86(11):2412–2418.
- 10.Waisberg DR, Abrao FC, Fernandez A, Terra RM, Pego-Fernandes PM, Jatene FB. Surgically-challenging chondrosarcomas of the chest wall: five-year follow-up at a single institution. Clinics (Sao Paulo). 2011; 66(3):501–503.
- 11.Mankin HJ, Lange TA, Spanier SS. THE CLASSIC: The hazards of biopsy in patients with malignant primary bone and soft-tissue tumors. The Journal of Bone and Joint Surgery, 1982;64:1121–1127. Clin Orthop Relat Res. 2006; 4504–10.

- 12.Laitinen MK, Stevenson JD, Parry MC, Sumathi V, Grimer RJ, Jeys LM. The role of grade in local recurrence and the disease-specific survival in chondrosarcomas. *Bone Joint J.* 2018; 100-B(5):662–666.
- 13.Jesus-Garcia R, Osawa A, Filippi RZ, Viola DC, Korukian M, de Carvalho CNG, et al. Is PET-CT an accurate method for the differential diagnosis between chondroma and chondrosarcoma? *Springerplus.* 2016; 5236.
- 14.Lim HJ, Johnny OC, Tan JW, Ching TM. Utility of positron emission tomography/computed tomography (PET/CT) imaging in the evaluation of sarcomas: A systematic review. *Crit Rev Oncol Hematol.* 2019; 1431–13.
- 15.Annovazzi A, Anelli V, Zoccali C, Rumi N, Persichetti A, Novello M, et al. (18)F-FDG PET/CT in the evaluation of cartilaginous bone neoplasms: the added value of tumor grading. *Ann Nucl Med.* 2019.
- 16.Purandare NC, Puranik A, Shah S, Agrawal A, Puri A, Gulia A, et al. Can 18F-FDG PET/CT diagnose malignant change in benign chondroid tumors? *Nucl Med Commun.* 2019; 40(6):645–651.
- 17.Vadi SK, Mittal BR, Gorla A, Sood A, Basher RK, Sood A, et al. 18F-FDG PET/CT in Diagnostic and Prognostic Evaluation of Patients With Suspected Recurrence of Chondrosarcoma. *Clin Nucl Med.* 2018; 43(2):87–93.
- 18.Subhawong TK, Winn A, Shemesh SS, Pretell-Mazzini J. F–18 FDG PET differentiation of benign from malignant chondroid neoplasms: a systematic review of the literature. *Skeletal Radiol.* 2017; 46(9):1233–1239.
- 19.Frank RA, Bossuyt PM, McInnes M. Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy: The PRISMA-DTA Statement. *Radiology.* 2018; 289(2):313–314.
- 20.Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS–2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med.* 2011; 155(8):529–536.
- 21.Costelloe CM, Chuang HH, Chasen BA, Pan T, Fox PS, Bassett RL, et al. Bone Windows for Distinguishing Malignant from Benign Primary Bone Tumors on FDG PET/CT. *J Cancer.* 2013; 4(7):524–530.
- 22.Purandare NC, Rangarajan V, Agarwal M, Sharma AR, Shah S, Arora A, et al. Integrated PET/CT in evaluating sarcomatous transformation in osteochondromas. *Clin Nucl Med.* 2009; 34(6):350–354.
- 23.Shin DS, Shon OJ, Han DS, Choi JH, Chun KA, Cho IH. The clinical efficacy of (18)F-FDG-PET/CT in benign and malignant musculoskeletal tumors. *Ann Nucl Med.* 2008; 22(7):603–609.
- 24.Strobel K, Exner UE, Stumpe KD, Hany TF, Bode B, Mende K, et al. The additional value of CT images interpretation in the differential diagnosis of benign vs. malignant primary bone lesions with 18F-FDG-PET/CT. *Eur J Nucl Med Mol Imaging.* 2008; 35(11):2000–2008.

- 25.Feldman F, Van Heertum R, Saxena C, Parisien M. 18FDG-PET applications for cartilage neoplasms. *Skeletal Radiol.* 2005; 34(7):367–374.
- 26.Brenner W, Conrad EU, Eary JF. FDG PET imaging for grading and prediction of outcome in chondrosarcoma patients. *Eur J Nucl Med Mol Imaging.* 2004; 31(2):189–195.
- 27.Lee FY, Yu J, Chang SS, Fawwaz R, Parisien MV. Diagnostic value and limitations of fluorine–18 fluorodeoxyglucose positron emission tomography for cartilaginous tumors of bone. *J Bone Joint Surg Am.* 2004; 86(12):2677–2685.
- 28.Aoki J, Watanabe H, Shinozaki T, Tokunaga M, Inoue T, Endo K. FDG-PET in differential diagnosis and grading of chondrosarcomas. *J Comput Assist Tomogr.* 1999; 23(4):603–608.
- 29.Reliability of histopathologic and radiologic grading of cartilaginous neoplasms in long bones. *J Bone Joint Surg Am.* 2007; 89(10):2113–2123.
- 30.Eefting D, Schrage YM, Geirnaerd MJ, Le Cessie S, Taminiau AH, Bovee JV, et al. Assessment of interobserver variability and histologic parameters to improve reliability in classification and grading of central cartilaginous tumors. *Am J Surg Pathol.* 2009; 33(1):50–57.
- 31.Purandare NC, Kulkarni AV, Kulkarni SS, Roy D, Agrawal A, Shah S, et al. 18F-FDG PET/CT-directed biopsy: does it offer incremental benefit? *Nucl Med Commun.* 2013; 34(3):203–210.
- 32.Logie CI, Walker EA, Forsberg JA, Potter BK, Murphey MD. Chondrosarcoma: A Diagnostic Imager's Guide to Decision Making and Patient Management. *Semin Musculoskelet Radiol.* 2013; 17(2):101–115.
- 33.Parlier-Cuau C, Bousson V, Ogilvie CM, Lackman RD, Laredo JD. When should we biopsy a solitary central cartilaginous tumor of long bones? Literature review and management proposal. *Eur J Radiol.* 2011; 77(1):6–12.

Figures

Figure 1

Selection process of included studies.

	<u>Risk of Bias</u>				<u>Applicability Concerns</u>		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Annovazzi, 2019	+	-	+	-	+	+	+
Aoki, 1999	+	-	+	+	+	+	+
Brenner, 2004	?	-	+	+	+	+	+
Costelloe, 2013	-	-	+	-	+	+	+
Feldman, 2005	+	+	+	-	+	+	+
Jesus-Garcia, 2016	?	-	+	-	+	+	+
Lee, 2004	+	-	+	+	+	+	+
Purandare, 2009	+	-	+	-	+	+	+
Purandare, 2019	-	-	+	-	+	+	+
Shin, 2008	+	-	+	-	+	+	+
Strobel, 2008	+	+	+	-	+	+	+
Vadi, 2018	?	-	+	-	+	+	+

High
Unclear
Low

Figure 2

Quality assessment of included studies using QUADAS-2 tool criteria. Red in figure indicates high risk, yellow represents unclear risk and green means low risk.

Figure 3

Forest plots of the pooled sensitivity and specificity with corresponding 95% confidence interval for the diagnosis of chondrosarcoma. (A) Pooled sensitivity of 18F-FDG PET; (B) pooled specificity of 18F-FDG PET; (C) pooled sensitivity of 18F-FDG PET/CT and (D) pooled specificity of 18F-FDG PET/CT. CI, confidence interval.

Figure 4

The pooled DOR with corresponding 95% confidence interval for the diagnosis of chondrosarcoma. (A) Pooled DOR of 18F-FDG PET and (B) pooled DOR of 18F-FDG PET/CT. CI, confidence interval; DOR, diagnostic odd ratio.

Figure 5

Forest plot of the comparison about SUVmax between (A) benign cartilaginous lesion and G1 chondrosarcoma, (B) G1 and G2 chondrosarcoma and (C) G2 and G3 chondrosarcoma. WMD, weighted mean difference; CI, confidence interval.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementarymaterialPRISMAChecklist.doc](#)