A meta-analysis supports core needle biopsy by radiologists for better histological diagnosis in soft tissue and bone sarcomas

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Abstract

Background: Although surgical biopsy has historically been considered to be the standard diagnostic biopsy for soft tissue and bone sarcomas, recent literature suggests that percutaneous core needle biopsy yields similar results. Therefore, an evaluation of the exact diagnostic accuracy and associated influential variables of core needle biopsy that is based on a large data set would be useful.

Methods: We searched MEDLINE, Web of Science, and EMBASE to identify core needle biopsy studies for predicting final histological subtypes of musculoskeletal lesions. The diagnostic accuracies of core needle biopsy and of surgical biopsy were assessed and compared by using random-effect meta-analyses. The factors relevant to diagnostic accuracy were evaluated by meta-regression and subgroup analyses.

Results: We selected 32 studies comprising 7209 musculoskeletal lesions. The pooled proportion estimate for the diagnostic accuracy of core needle biopsy was 0.84 (95% confidential interval, CI: 0.81–0.87), which indicated an approximate 84% concordance between core needle biopsy results and final histological diagnoses. The findings of meta-regression and subgroup analyses suggested that radiologists were better core needle biopsy operators than surgeons. An additional meta-analysis for direct comparison between core needle biopsy and surgical biopsy demonstrated that diagnostic accuracy was significantly lower for core needle biopsy than for surgical (pooled odds ratio: 0.39, 95% CI: 0.20–0.76).

Conclusion: Our results suggested that core needle biopsy should be performed by expert radiologists and that surgical biopsy should be performed if diagnosis following core needle biopsy does not match the clinical presentation and radiographic findings.

Abbreviations: CI = confidential interval, CNB = core needle biopsy, FNA = fine needle aspiration, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies-2, SB = surgical biopsy, WHO = World Health Organization.

Keywords: bone sarcoma, core needle biopsy, meta-analysis, soft tissue sarcoma, surgical biopsy

1. Introduction

The current 2013 World Health Organization (WHO) Classification of Tumors of Soft Tissue and Bone incorporates much progress regarding the tumor classification and identification of new histological subtypes. The changes in classifying and recognizing the pathogeneses of soft tissue and bone tumors, predominantly based on newly identified genetic findings, have been particularly remarkable as compared with progress made in the pathologies of other cancers.1,2 Sarcomas are a heterogeneous type of rare malignant soft-tissue and bone tumors and account for only approximately 1% of all malignancies in adults and 15% to 20% of pediatric malignancies. More than 50 histological subtypes have been identified, and the differential diagnosis for sarcomas is fairly extensive. Different subtypes can vary in their clinical manifestations and response to treatment. Higher-grade sarcomas exhibit more aggressive behavior and tend to hematogenously metastasize to the lungs, which is the leading cause of disease-specific death. Histological tumor grade has been identified as one of the strongest predictors of metastatic risk and patient prognosis. Despite current intensive and multimodal treatment, including surgery, radiotherapy, and chemotherapy, prognosis has plateaued since the 1990s and remains suboptimal in many high-grade types.3-6 Therefore, prompt and precise diagnostic procedures for these heterogeneous and refractory sarcomas are challenging.

In the management of musculoskeletal lesions, biopsy is the most critical first step in determining treatment strategy and outcomes. Unplanned biopsies can compromise reconstructive procedures and sometimes require amputation to obtain adequate surgical margins. Biopsy is principally utilized to harvest representative and viable tissue specimens for accurate diagnosis. A variety of biopsy techniques, such as fine needle
aspiration (FNA), core needle biopsy (CNB), and incisional or excisional surgical biopsy (SB), are frequently used nowadays. SB has historically been the diagnostic standard; it provides large volumes of tissue sample, which facilitates accurate histological analyses and more precise estimates of patient prognoses. However, biopsy-associated complications involve hematoma, infection, and neurapraxia. A biopsy procedure can also spread tumor cells to surrounding tissue and, therefore, increase the risk of local recurrence. It is imperative that the biopsy tract be placed within the planned resection margins prior to future treatment planning involving surgical resection and radiation. On the contrary, needle biopsies are less invasive techniques, and are less time consuming, have lower costs, and have low morbidity. Because FNA only provides cytology, not true histology, it may be able to distinguish neoplasms from normal tissues, malignant from benign tumors, and high- from low-grade malignancies. CNB, which evolved as an alternative to FNA, improves the determination of the histological subtype and grade. Moreover, the advantages of CNB relative to those of SB include the low risk of contaminating adjacent tissue compartments and minimal invasiveness, which are because of the small biopsy tract and less bleeding.5,6

Although SB has long been considered to be the gold standard for cancer diagnosis, a recent review article suggests that percutaneous CNB yields similar results.6 Thus, an assessment of the exact diagnostic accuracy and relevant influential factors of CNB that is based on a large data set would be useful. The purpose of this review was to provide an up-to-date and unprecedented summary of CNB in soft tissue and bone sarcoma. We conducted a systematic review and meta-analysis for comparing the diagnostic accuracy of CNB. We conducted a systematic review and meta-analysis for comparing the diagnostic accuracy of CNB. We conducted a systematic review and meta-analysis for comparing the diagnostic accuracy of CNB. We conducted a systematic review and meta-analysis for comparing the diagnostic accuracy of CNB. The diagnostic accuracy of CNB was determined as the proportion of lesions that showed concordance between the CNB results and final histological subtypes in the total number of lesions that were tested for CNB; a variety of histological subtypes presented.

2. Materials 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. Search strategy and selection criteria

The literature search was performed in accordance with the guidelines present in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.7 The main research question was defined using the Target Population, Index Test, Comparator Test, Outcome, and Study Design (PICOS) strategy: target population, patients with soft tissue sarcoma, bone sarcoma, or both examined by CNB; index test, results of CNB; comparator test, results of SB; outcome, definitive histological subtypes; and study design, retrospective and prospective cohort studies. Data for this systematic review and meta-analyses were identified by searches of MEDLINE, Web of Science, and EMBASE using the search terms “core needle biopsy” and “sarcoma” on February 1, 2017 without a time search limitation or language restrictions.

We also hand-searched references from relevant articles. We excluded conference abstracts, clinical case series, and review articles.

The inclusion criteria were as follows: original studies reporting CNB conducted to predict final histological subtypes of musculoskeletal lesions and sufficient raw data to calculate the diagnostic accuracy of CNB. The diagnostic accuracy of CNB was calculated using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.8 Risk of bias concerning 4 domains (patient selection, index test, reference standard, and flow and timing) and concerns regarding the applicability of three domains (patient selection, index test, and reference standard) were rated as “low,” “high,” or “unclear.”

2.2. Data analysis

The 2 orthopedic oncologists (TF and MPJ) independently screened and selected the articles. Discrepancies between the 2 reviewers were resolved by a third investigator (TK) via discussion until a consensus was reached. Articles were selected by title, by abstract, and subsequently by full text to fulfill the inclusion criteria. Next, the following information was extracted where available: author name, year of publication, study institutes, clinical characteristics of all participants and tumors, total number included in the meta-analyses, discordant rate of CNB results and the final histological diagnosis at the resection, discordant rate of results of SB and the final histological diagnosis, type of radiological guidance (ultrasound, computed tomography [CT], magnetic resonance imaging [MRI], or fluoroscope), gauge number of biopsy needle, core number of CNB specimens, type of anesthesia, and operator performing the CNB (radiologist or surgeon). The quality of study designs in the eligible articles was evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.8 Risk of bias concerning 4 domains (patient selection, index test, reference standard, and flow and timing) and concerns regarding the applicability of three domains (patient selection, index test, and reference standard) were rated as “low,” “high,” or “unclear.”

2.3. Statistical analysis

In the meta-analysis, a random-effects model was used to calculate a pooled proportion estimate with 95% confidence interval (CI) for the diagnostic accuracy of CNB.9 The inconsistency index I-square ($I^2$) test was used for assessing heterogeneity of the diagnostic accuracy of each study. Variables causing the heterogeneity were identified using the meta-regression method and subgroup analysis.

We also used a random-effect model to calculate the pooled odds ratio and 95% CI for the diagnostic accuracy between CNB and SB. All meta-analyses were conducted using Stata/SE version 14 statistical software (StataCorp LP, College Station, TX). $P < .05$ were considered statistically significant.

3. Results

3.1. Literature search and selection of studies

We used 3 search engines to identify 895 articles, excluding 209 because of duplication. Furthermore, 610 and 27 articles were excluded on the basis of the information in the title and abstract, respectively. We also added eight articles after reviewing references from relevant articles. Lastly, 25 articles were excluded after the review of the full text. A total of 32 studies met all the inclusion criteria for the meta-analysis regarding the diagnostic accuracy of CNB (Fig. 1).10–41 Additionally, 5 eligible articles were selected for directly comparing the diagnostic accuracy of CNB with that of SB.15,18,22,25,36
3.2. Study description and quality

The total human population in the combined studies was 8930 individuals, with an average age of 46.1 years. There were 7209 lesions presenting histological subtypes included in the meta-analyses. The primary characteristics of the 32 studies that were included in the meta-analysis are shown in Table 1.\[10–41\]

According to the QUADAS-2 tool for methodological quality, all studies were rated as having five or more “low” responses and no “high” response in the seven domains. Twenty-five authors did not describe the sampling methods or used inappropriate exclusions in the domain of patient selection, and 31 authors did not state blindness in the domain of reference standard (Table 2).\[10–41\]

3.3. Meta-analysis

Because of high heterogeneity between studies ($I^2 = 93.36\%$), we used a random-effects model for the diagnostic accuracy of CNB. Overall, the pooled proportion estimate for the diagnostic accuracy was 0.84 (95% CI: 0.81–0.87), which indicated an approximate 84% concordance between the CNB results and final histological diagnoses (Fig. 2). In the meta-regression analysis, the type of CNB operator was the only variable significantly associated with heterogeneity ($P = 0.033$). No other possible factors were significantly associated with the diagnostic accuracy (Table 3). Subgroup analysis results indicated that radiologists may be more qualified CNB examiners than surgeons for predicting the histological subtype (Fig. 3).

In addition, 5 articles consisting were eligible for directly comparing the diagnostic accuracy of CNB with that of SB. Because we observed medium heterogeneity between the studies ($I^2 = 68.4\%$), we used a random-effects model for the comparison and found that the diagnostic accuracy of CNB was significantly lower than that of SB (pooled odds ratio: 0.39, 95% CI: 0.20–0.76) (Fig. 4).
Table 1: Key characteristics of the studies included in the meta-analysis.

| Study | Year | Country | Enrollment period | Tumor number | Tumor type |
|-------|------|---------|------------------|--------------|------------|
| Trieu et al. [10] | 2016 | Australia | 1996–2013 | 1131 | Bone, Soft tissue |
| Coletti et al. [11] | 2016 | US | 2009–2015 | 161 | Soft tissue |
| Ferguson et al. [12] | 2016 | United Kingdom | 2008–2013 | 350 | Bone, Soft tissue |
| Conen et al. [13] | 2015 | Italy | 2012–2014 | 27 | Soft tissue |
| Noebauer et al. [14] | 2014 | Austria | ND | 42 | Soft tissue |
| Layfield et al. [15] | 2014 | US | ND | 130 | Bone, Soft tissue |
| Vauth et al. [16] | 2014 | Kuwait | 2010–2012 | 35 | Bone |
| Kiatisevi et al. [17] | 2013 | Thailand | 2006–2010 | 112 | Bone, Soft tissue |
| Joshi et al. [18] | 2013 | Nepal | ND | 50 | Bone |
| layfield et al. [19] | 2013 | Singapore | 1999–2010 | 134 | Bone, Soft tissue |
| Mitton et al. [20] | 2012 | Italy | 2009–2013 | 371 | Soft tissue |
| Coran et al. [21] | 2015 | Italy | ND | 111 | Soft tissue |
| Noebauer et al. [22] | 2015 | Austria | ND | 185 | Bone, Soft tissue |
| Layfield et al. [23] | 2015 | US | ND | 116 | Soft tissue |
| Marchi et al. [24] | 2015 | Italy | 2007–2008 | 104 | Soft tissue |
| Strauss et al. [25] | 2015 | United Kingdom | 2004–2006 | 371 | Soft tissue |
| Narvani et al. [26] | 2015 | United Kingdom | ND | 141 | Bone, Soft tissue |
| Mitsuyoshi et al. [27] | 2015 | Japan | 1990–2004 | 163 | Bone, Soft tissue |
| Lopez et al. [28] | 2015 | Spain | 1999–2004 | 188 | Bone, Soft tissue |
| Yang et al. [29] | 2015 | US | ND | 50 | Bone, Soft tissue |
| Liu et al. [30] | 2015 | China | ND | 37 | Soft tissue |
| Ray et al. [31] | 2015 | Israel | ND | 103 | Soft tissue |
| Issakou et al. [32] | 2015 | US | 1998–2000 | 215 | Bone, Soft tissue |
| Hao et al. [33] | 2015 | China | ND | 258 | Bone, Soft tissue |
| Tomlari et al. [34] | 2015 | Brazil | 1999–2000 | 48 | Bone, Soft tissue |
| Hoefer et al. [35] | 2015 | United Kingdom | 1989–1998 | 257 | Soft tissue |
| Willman et al. [36] | 2015 | US | ND | 43 | Soft tissue |
| Pramesh et al. [37] | 2015 | India | 1999–2000 | 64 | Bone |
| Yee et al. [38] | 2015 | US | ND | 141 | Bone, Soft tissue |
| Dupay et al. [39] | 1999 | Denmark | ND | 186 | Bone, Soft tissue |
| Kosicki et al. [40] | 1997 | US | 1975–1996 | 196 | Bone |

Imaging guidance

| Needle size, gauge | Sample number | Anesthesia | Operator |
|--------------------|---------------|-------------|-----------|
| CT, US, FS | 14,18 | 2–5 cores | ND | ND |
| CT, US | 18,20 | ND | ND | radiologist |
| US, CUS | ND | ND | ND | ND |
| DCEMRI | 14 | 3–4 cores | local | radiologist |
| ND | ND | ND | ND | ND |
| CT, US | ND | ND | ND | ND |
| CT | 12–15,16,18 | Ave. 6 cores | local, general | radiologist |
| CT | 14 | 6–10 passes | local | radiologist, orthopedic |
| ND | ND | ND | ND | ND |
| CT, w/o | 9,12,18 | 2–4 passes | local | Orthopedic surgeon |
| US | ND | ND | ND | ND |
| CEUS | 16,18 | 3–5 cores | local | radiologist |
| w/o | ND | ND | ND | ND |
| ND | ND | ND | ND | ND |
| CT, US, FS | ND | 3–5 passes | local | Orthopedic surgeon |
| NT, US, w/o | 14 | 2–5 passes | local | radiologist, orthopedic |
| CT, w/o | ND | 2–cores | local, general | ND |
| US | 14,18 | Ave. 4 cores | local | ND |
| US | ND | Ave. 6 cores | local | Orthopedic surgeon |
| CT, US | 14,18,20 | 3–4 cores | local | ND |
| CT | 14 | 4 cores | local | radiologist |
| CT | 14 | 3–5 passes | local | radiologist |
| US | ND | ND | ND | ND |
| ND | ND | ND | ND | ND |
| FS, w/o | 15,16,18 | 2–3 cores | local | ND |
| CT, US, FS, w/o | 12,14,16,18 | Multicores | local | radiologist |
| CT | ND | ND | ND | ND |

Ave = average, CECT = contrast-enhanced computed tomography, CEUS = contrast-enhanced ultrasonography, DCEMRI = dynamic contrast-enhanced magnetic resonance imaging, FS = fluoroscopy, ND = not documented, US = ultrasonography, w/o = without guidance.
4. Discussion

Biopsies aim to facilitate definitive pathological diagnoses while minimizing complications, limiting potential tumor seeding, and avoiding interference with subsequent therapies. A diagnosis of sarcoma or benign tumor is generally not sufficient, and the specific histological subtype should be determined from the biopsy to guide therapeutic decision-making. However, to our knowledge, the optimal biopsy procedure for the diagnosis of soft tissue and bone sarcomas is not present in current literature. SB has historically been considered to achieve diagnostic outcomes superior to those of CNB, but the difference in diagnostic accuracy between them was reportedly not significant.

Evidence to recommend one biopsy procedure over another. Thus far, because of the low risk of morbidity and simplicity of the percutaneous procedure, CNB appears to be more suitable as the first choice. This lack of evidence prompted us to conduct a meta-analysis to derive more robust estimates of the diagnostic yield of CNB and to directly compare the diagnostic accuracies between CNB and SB. The present meta-analysis used a large sample of data on soft tissue and bone sarcomas and showed that there was an approximate 84% concordance between the CNB results and SB findings.

Certain anatomical locations and histological subtypes have been associated with the diagnostic difficulty of needle biopsies. Vertebral lesions and deep musculoskeletal tumors as well as myxoid and round-cell histologies have been associated with low-diagnostic accuracy. In addition, certain technical factors such as image-guided needle biopsy targeting representative and viable tumor regions improve the biopsy quality and diagnostic yield. Other recent studies using image-guided percutaneous biopsy provide superior spatial localization of the tumors. SB appears to be the most accurate technique, but there is not enough evidence to recommend one biopsy procedure over another. Thus far, because of the low risk of morbidity and simplicity of the percutaneous procedure, CNB appears to be more suitable as the first choice. This lack of evidence prompted us to conduct a meta-analysis to derive more robust estimates of the diagnostic yield of CNB and to directly compare the diagnostic accuracies between CNB and SB. The present meta-analysis used a large sample of data on soft tissue and bone sarcomas and showed that there was an approximate 84% concordance between the CNB results and SB findings.

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| Study | Risk of bias | Applicability concerns |
|-------|--------------|------------------------|
| Patient selection | Index test | Reference standard | Flow timing | Patient selection | Index test | Reference standard |
| Trieu et al | unclear | low | unclear | low | low | low | low |
| Colletti et al | unclear | low | unclear | low | low | low | low |
| Ferguson et al | unclear | low | unclear | low | low | low | low |
| Coran et al | unclear | low | unclear | low | low | low | low |
| Noebauer et al | low | low | unclear | low | low | low | low |
| Layfield et al | unclear | low | unclear | low | low | low | low |
| Mittion et al | unclear | low | unclear | low | low | low | low |
| No et al | unclear | low | unclear | low | low | low | low |
| Kiatisevi et al | low | low | unclear | low | low | low | low |
| Josh et al | low | low | unclear | low | low | low | low |
| Seng et al | unclear | low | unclear | low | low | low | low |
| Rimondi et al | unclear | low | unclear | low | low | low | low |
| Verheijen et al | unclear | low | unclear | low | low | low | low |
| Manchi et al | unclear | low | unclear | low | low | low | low |
| Strauss et al | low | low | unclear | low | low | low | low |
| Kasraean et al | unclear | low | low | low | low | low | low |
| Sung et al | unclear | low | unclear | low | low | low | low |
| Narvani et al | low | low | unclear | low | low | low | low |
| Mitsuyoshi et al | unclear | low | unclear | low | low | low | low |
| Lopez et al | unclear | low | unclear | low | low | low | low |
| Yang et al | unclear | low | unclear | low | low | low | low |
| Liu et al | low | low | unclear | low | low | low | low |
| Ray et al | unclear | low | unclear | low | low | low | low |
| Issakov et al | unclear | low | unclear | low | low | low | low |
| Hau et al | unclear | low | unclear | low | low | low | low |
| Torrani et al | unclear | low | unclear | low | low | low | low |
| Hoeben et al | unclear | low | unclear | low | low | low | low |
| Willman et al | unclear | low | unclear | low | low | low | low |
| Pramesh et al | unclear | low | unclear | low | low | low | low |
| Yao et al | low | low | unclear | low | low | low | low |
| Dupuy et al | unclear | low | unclear | low | low | low | low |
| Koscick et al | unclear | low | unclear | low | low | low | low |
Table 3. Our analyses did not show any significant influential factors other than the operator type (surgeon or radiologist). This finding indicates that radiologists are more skillful in performing CNB than surgeons when assessed on the ability to predict the final histological diagnosis. This could be because radiologists generally have more experience in some techniques of interventional radiology, such as radiofrequency ablation, embolization, and cryosurgery under radiological guidance. In general, biopsies are technically challenging, and if not performed at a high skill level, the biopsy results can compromise patient outcomes. Therefore, biopsies should only be performed by expert radiologists at referral sarcoma centers to improve diagnostic yield and minimize complications.

Although the present study was based on thorough literature searches and careful data extraction, some limitations should be...
considered. First, compared with the larger sample size used for the meta-analysis of CNB diagnostic accuracy, the sample sizes of the meta-regression analysis regarding operator and the comparison of the diagnostic accuracy between CNB and SB were small. Further studies using larger sample sizes are thus required. Second, the heterogeneity of pooled estimates of diagnostic accuracy and the odds ratio between CNB and SB were high and medium, respectively. $I^2$ represents the percentage of total variability in estimates generated from genuine between-study heterogeneity rather than by random sampling error. The observed heterogeneity may be attributable to numerous other influential factors including location, size, histological subtypes, and other technical procedures. We were unable to collect sufficient data to detect significant differences among the mentioned parameters. In addition, more studies are warranted to evaluate the differences in morbidities, cost, and procedure to determine the optimal biopsy procedure between CNB and SB. Third, bias could not be completely ruled out, although we attempted to judge as fairly as possible. The two reviewers performed this study in an independent blinded manner to minimize bias in the study selection and data extraction. Furthermore, according to the QUADAS-2 tool for methodological quality, all studies were rated as having 5 or more “low” responses and no “high” response in the 7 domains. Prospective randomized clinical trials comparing the diagnostic accuracies between CNB and SB in soft tissue and bone sarcomas would be the optimal method to completely exclude all potential biases, including selection, information, and publication bias.

5. Conclusion

In conclusion, the meta-analysis of this study indicated that the concordance rate between the CNB results and final histological diagnoses was approximate 84%, and suggested that biopsies performed by radiologists are more reliable than those performed by surgeons.

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Author contributions

TK, MO, and NA designed the analysis and had full access to the raw data. TK, FT, and MPJ collected the data and performed the statistical analysis. All authors had the opportunity to review the analysis plan and outcome, participated in writing the article, and provided final approval.
Figure 4. Forest plot of OR for diagnostic accuracy between core needle biopsy and surgical biopsy. The square size of individual studies represents the weight of the study. Error bars indicate 95% CIs of pooled OR. CIs = confidential intervals, OR = odds ratio.

Kubo et al. Medicine (2018) 97:29

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