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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.[3,4] 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

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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 sarcomas. We conducted a systematic review and meta-analysis for assessing the diagnostic accuracy and relevant influential factors of CNB and for comparing the diagnostic accuracy of CNB with that of SB.

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 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.

2.2. 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, concordant rate of CNB results and the final histological diagnosis at the resection, concordant 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% confidential 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 statistical 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]

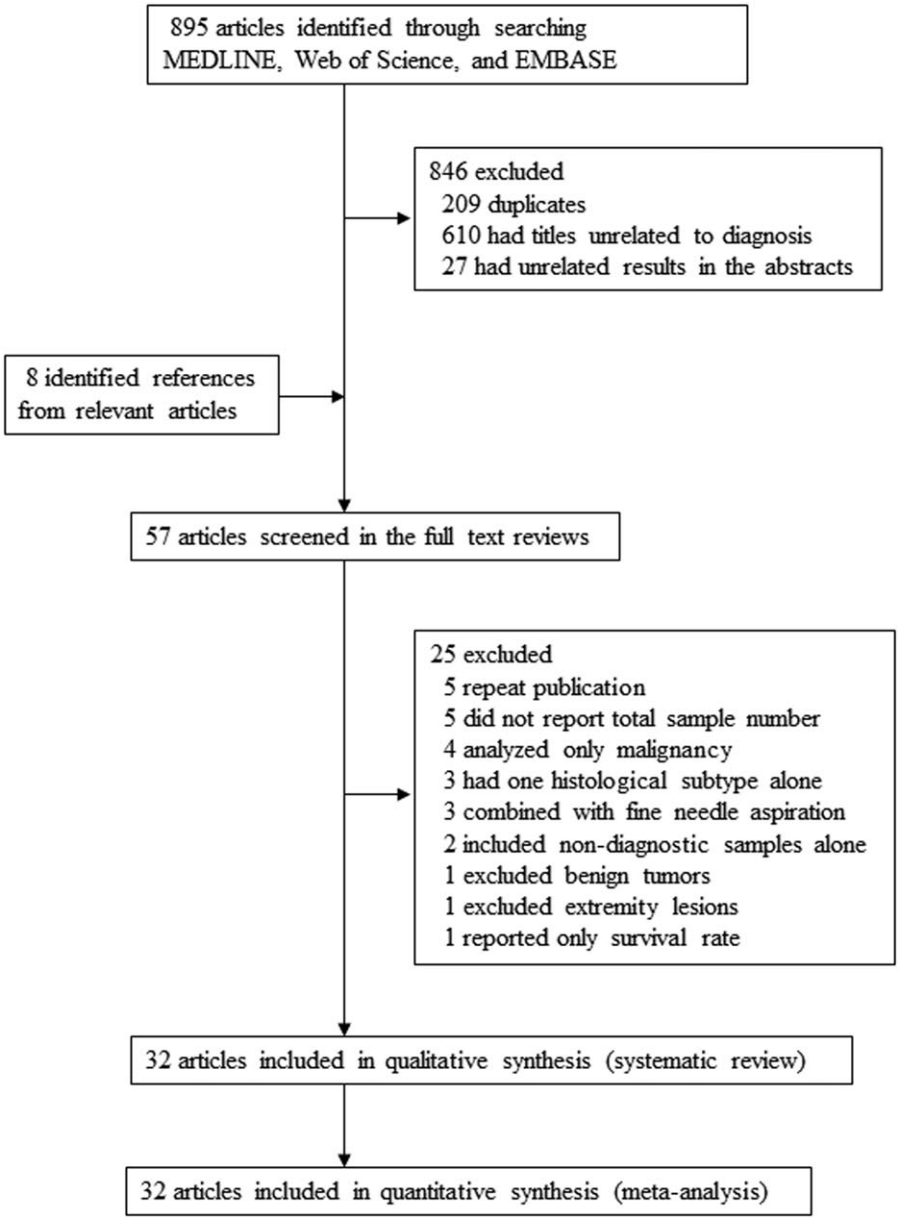

Figure 1. Flowchart of the article-selection process.

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 ($P = .033$). 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
Colletti et al[11]	2016	US	2009–2015	161	Soft tissue
Ferguson et al[12]	2016	United Kingdom	2009–2013	350	Bone, Soft tissue
Coran et al[13]	2015	Italy	2012–2014	27	Soft tissue
Noebauer et al[14]	2015	Austria	ND	42	Soft tissue
Layfield et al[15]	2014	US	ND	130	Bone, Soft tissue
Mitton et al[16]	2014	US	2001–2011	128	Bone, Soft tissue
Nouh et al[17]	2014	Kuwait	2010–2012	35	Bone
Kiatisevi et al[18]	2013	Thailand	2008–2010	112	Bone, Soft tissue
Joshi et al[19]	2013	Nepal	2005–2011	50	Bone
Seng et al[20]	2013	Singapore	1999–2010	134	Bone, Soft tissue
Rimondi et al[21]	2011	Italy	1990–2008	2027	Bone
Verheijen et al[22]	2010	Netherlands	2000–2003	116	Soft tissue
Marchi et al[23]	2010	Italy	2007–2008	104	Soft tissue
Strauss et al[24]	2010	United Kingdom	2004–2008	371	Soft tissue
Kasraeian et al[25]	2010	US	2007–2009	57	Soft tissue
Sung et al[26]	2009	Korea	2004–2007	185	Bone, Soft tissue
Narvani et al[27]	2009	United Kingdom	ND	111	Soft tissue
Mitsuyoshi et al[28]	2006	Japan	1990–2004	163	Bone, Soft tissue
Lopez et al[29]	2005	Spain	1999–2004	188	Bone, Soft tissue
Yang et al[30]	2004	US	ND	50	Bone, Soft tissue
Liu et al[31]	2004	China	1999–2000	37	Soft tissue
Ray et al[32]	2003	France	1999–2000	103	Soft tissue
Issakov et al[33]	2003	Israel	1998–2000	215	Bone, Soft tissue
Hau et al[34]	2002	US	1999–2000	258	Bone, Soft tissue
Torriani et al[35]	2002	Brazil	1999–2000	48	Bone, Soft tissue
Hoeber et al[36]	2001	United Kingdom	1989–1998	257	Soft tissue
Willman et al[37]	2001	US	1992–1998	43	Soft tissue
Pramesh et al[38]	2001	India	1999–2000	64	Bone
Yao et al[39]	1999	US	ND	141	Bone, Soft tissue
Dupuy et al[40]	1998	US	1992–1994	176	Bone, Soft tissue
Koscick et al[41]	1997	US	1975–1996	195	Bone

Imaging guidance	Needle size, gauge	Sample number	Anesthesia	Operator
CT	14,18	2–5 cores	ND	ND
CT, US, FS	18,20	ND	ND	radiologist
CT, US	ND	ND	ND	ND
US, CEUS	14	2–3 cores	local	radiologist, surgeon
DCEMRI	14	3–4 cores	local	radiologist
ND	ND	ND	ND	ND
CT, US	14	Ave. 6 cores	local, general	ND
CT	12–15,16,18	ND	local, general	radiologist
CT	14	6–10 passes	Local	radiologist, orthopedic
ND	16	2–4 passes	local	Orthopedic surgeon
CT, w/o	ND	3–5 cores	local	ND
CT	9,12,18	ND	local, general	ND
ND	ND	ND	ND	ND
CEUS	16,18	ND	ND	radiologist
w/o	ND	4 cores	local	ND
ND	ND	3–5 passes	local	Orthopedic surgeon
CT, US, FS	ND	4–cores	ND	radiologist
CT, 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
ND	ND	Ave. 6 passes	local	Orthopedic surgeon
US	14,16,18,20	3–6 cores	local	ND
CT, US	14	Ave. 4 passes	local	radiologist
CT	11–18	3–10 cores	ND	radiologist
CT	12–18	ND	local, general	radiologist
US	14	5 cores	local	radiologist
ND	ND	ND	ND	ND
ND	15,16,18	2–10 cores	ND	ND
FS, w/o	ND	2,3 cores	local, general	ND
CT, US, FS, w/o	12,14,16,18	Multicores	local	radiologist
CT	14	ND	local, general	radiologist
CT	14	ND	ND	ND

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

Table 2

Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2).

	Risk of bias				Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow timing	Patient selection	Index test	Reference standard
Trieu et al[10]	unclear	low	unclear	low	low	low	low
Colletti et al[11]	unclear	low	unclear	low	low	low	low
Ferguson et al[12]	unclear	low	unclear	low	low	low	low
Coran et al[13]	unclear	low	unclear	low	low	low	low
Noebauer et al[14]	low	low	unclear	low	low	low	low
Layfield et al[15]	unclear	low	unclear	low	low	low	low
Mitton et al[16]	unclear	low	unclear	low	low	low	low
Nouh et al[17]	unclear	low	unclear	low	low	low	low
Kiatisevi et al[18]	low	low	unclear	low	low	low	low
Joshi et al[19]	low	low	unclear	low	low	low	low
Seng et al[20]	unclear	low	unclear	low	low	low	low
Rimondi et al[21]	unclear	low	unclear	low	low	low	low
Verheijen et al[22]	unclear	low	unclear	low	low	low	low
Marchi et al[23]	unclear	low	unclear	low	low	low	low
Strauss et al[24]	low	low	unclear	low	low	low	low
Kasraeian et al[25]	unclear	low	low	low	low	low	low
Sung et al[26]	unclear	low	unclear	low	low	low	low
Narvani et al[27]	low	low	unclear	low	low	low	low
Mitsuyoshi et al[28]	unclear	low	unclear	low	low	low	low
Lopez et al[29]	unclear	low	unclear	low	low	low	low
Yang et al[30]	low	low	unclear	low	low	low	low
Liu et al[31]	unclear	low	unclear	low	low	low	low
Ray et al[32]	unclear	low	unclear	low	low	low	low
Issakov et al[33]	unclear	low	unclear	low	low	low	low
Hau et al[34]	unclear	low	unclear	low	low	low	low
Torriani et al[35]	unclear	low	unclear	low	low	low	low
Hoeber et al[36]	unclear	low	unclear	low	low	low	low
Willman et al[37]	unclear	low	unclear	low	low	low	low
Pramesh et al[38]	unclear	low	unclear	low	low	low	low
Yao et al[39]	low	low	unclear	low	low	low	low
Dupuy et al[40]	unclear	low	unclear	low	low	low	low
Koscick et al[41]	unclear	low	unclear	low	low	low	low

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. [5,6] CNB has been reported to provide limited sample volumes and to be less able to access deep-seated masses, which is problematic particularly for the inherent heterogeneity of sarcoma. Kasraeian et al[25] prospectively studied 57 patients with soft-tissue masses; they performed CNB, preceded by FNA and followed by SB, of the same mass. SB showed 100% diagnostic accuracy in diagnosis, however, the accuracy was only 33.3% for FNA and 45.6% for CNB. Therefore, the authors supported the usage of SB for diagnosing soft-tissue masses. On the contrary, Pohlig et al[42] retrospectively compared CNB with SB in 48 bone tumors. The diagnostic accuracies were 100% for CNB and 93.3% for SB, but the difference was not significant ($P > .05$). Other recent studies using image-guided percutaneous biopsy provide superior spatial localization of the tumors.[5] 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 the final histological diagnoses. We noted a significant difference in the diagnostic accuracies between SB and CNB, which suggested that SB should be performed if diagnosis following CNB does not match the clinical presentation and radiographic 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 and reduce the complications rates. The caliber and type of biopsy needle, number of sample cores, and institute where the biopsy was performed have also been found to influence the outcomes of needle biopsy. [5,6] Therefore, we statistically performed meta-regression and subgroup analyses to assess influential parameters for diagnostic accuracy of CNB (shown in

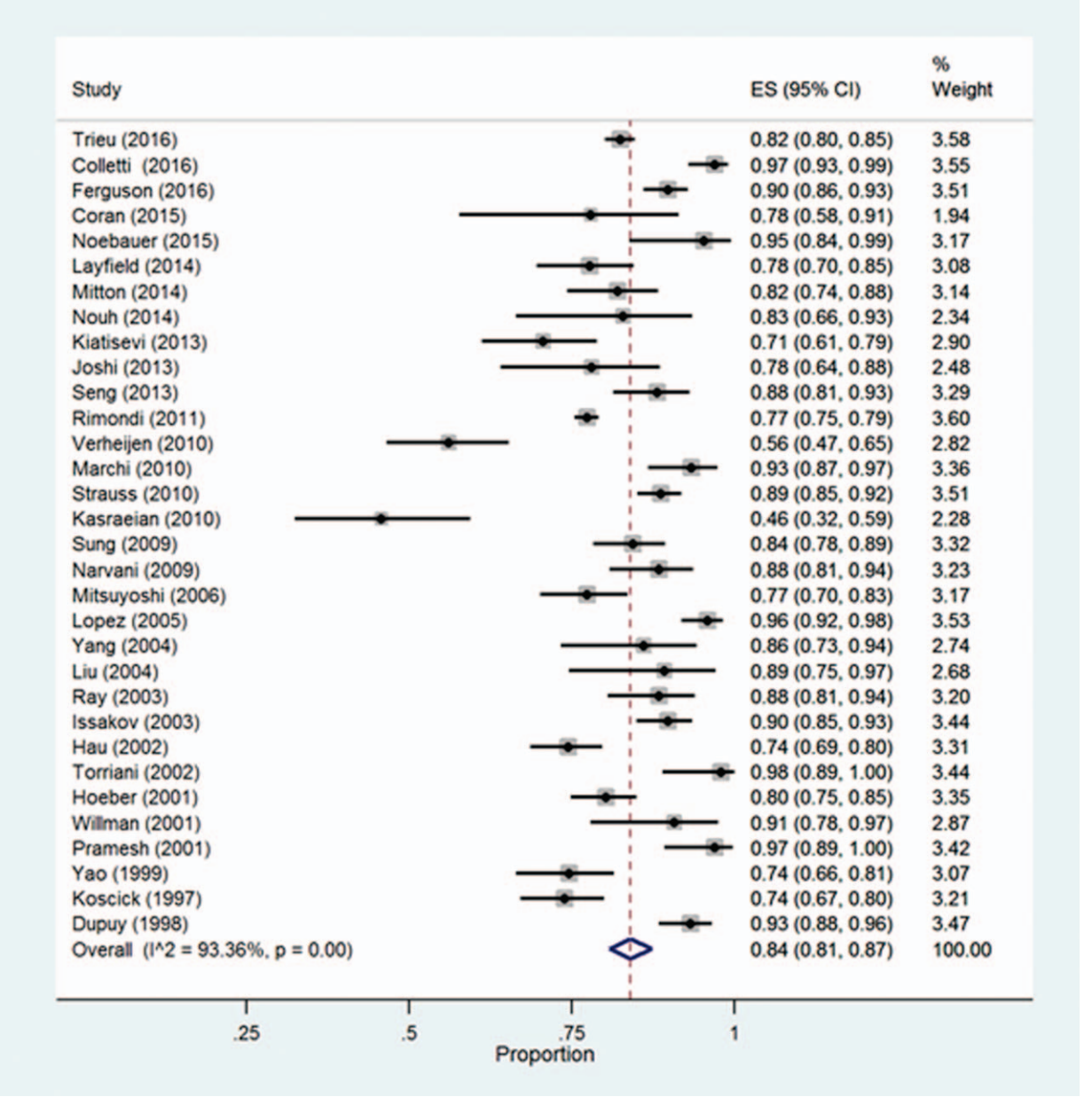

Figure 2. Forest plot showing diagnostic accuracy of core needle biopsy. The square size of individual studies represents the weight of the study. Error bars indicate 95% CIs of pooled estimates. CIs = confidential intervals.

Table 3

Meta-regression analyses.

Variables	N	Coefficient	SE	*P*
Year (<2010/≥2010)	7209	0.053	0.039	.180
Countries (US, Europe, Japan, others)	7209	0.036	0.046	.447
Tumor number (<100/≥100)	7209	−0.022	0.044	.624
Tumor type (bone/soft tissue/either)	7209	0.005	0.022	.824
Guidance (with/without)	6506	−0.006	0.039	.886
Needle size (<15/≥15 gauge)	5332	0.060	0.049	.230
Sample number (≤5/>5 cores or passes)	3400	−0.003	0.049	.956
Anesthesia (local/local or general)	4322	−0.006	0.054	.918
Operator (Radiologist/surgeon or either)	1875	−0.133	0.057	.033

N = tumor number, SE = standard error.

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

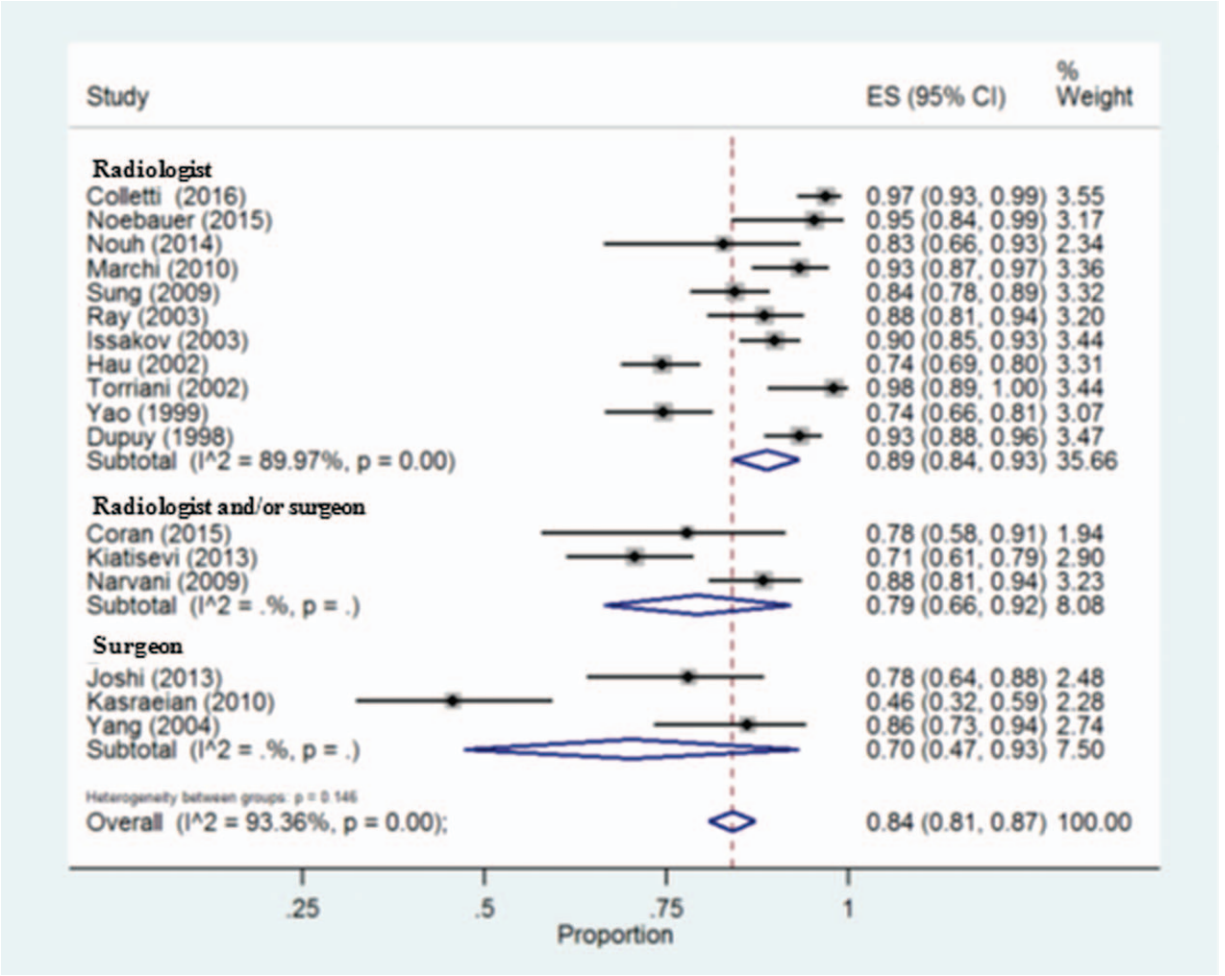

Figure 3. Forest plot showing diagnostic accuracy of core needle biopsy sorted by operators. The square size of individual studies represents the weight of the study. Error bars indicate 95% CIs of pooled estimates. CIs = confidential intervals.

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.

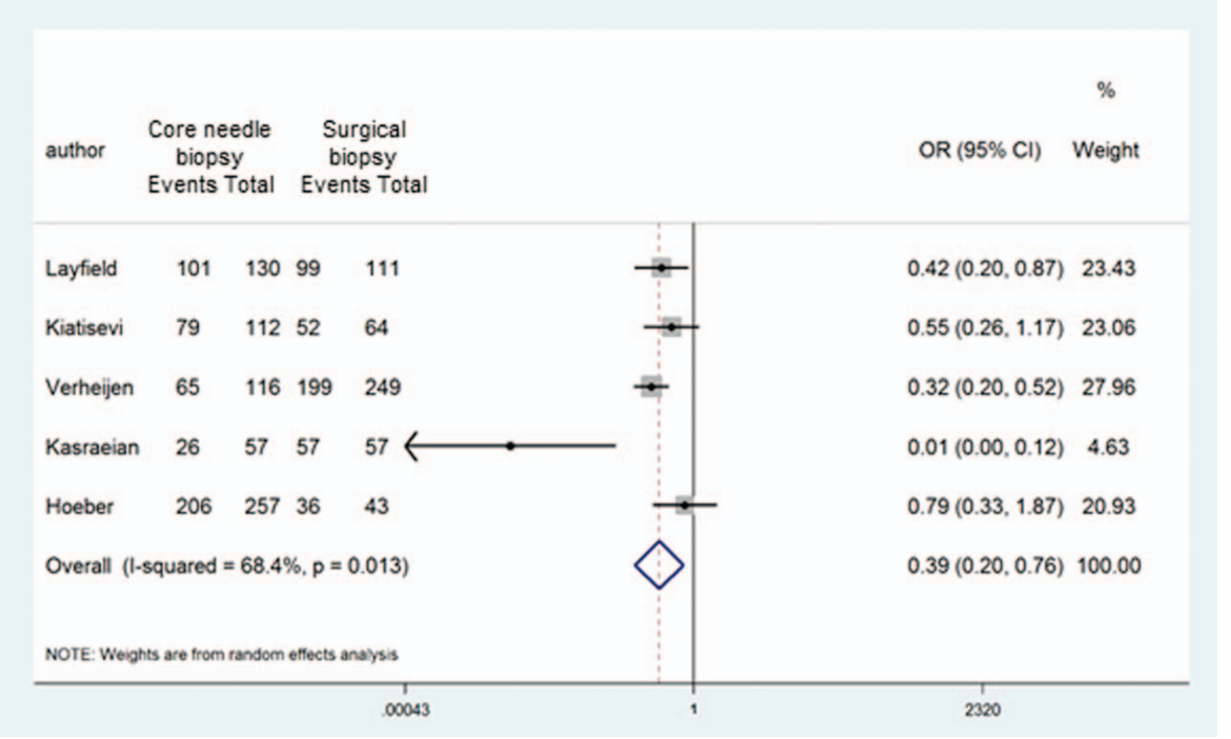

Figure 4. Forest plot of OR for diagnostic accuracy between core needle biopsy and surgical biopsy. The square size of individual studies represents the weight of the study. Error bars indicate 95% CIs of pooled OR. CIs = confidential intervals, OR = odds ratio.

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