Original Article

Role of Core Needle Biopsy in Liver Metastases: A Histopathological and Immunohistochemical Approach

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Abstract

Background: The liver is the second most common organ involved by secondary neoplasms. Core needle biopsy of oncological patients requires an accurate histological diagnosis for the subsequent prescription of adequate management plans. **Objectives:** The aim of this study was to evaluate the diagnostic accuracy of core needle biopsy for suspected hepatic metastasis and to assess factors that influence the accuracy of the procedure. **Materials and Methods:** A cross-sectional study randomly enrolled 74 percutaneous ultrasound-guided core needle biopsies from patients with suspected hepatic neoplasm. A 16-gauge tru-cut biopsy needle was performed for all patients. Patient characteristics, procedure information, histopathology reports, and slides were collected from the Department of Histopathology at Al-Jamhorii Teaching Hospital, Mosul City, Iraq. All cases were analyzed using SPSS software, version 18.0. **Results:** Among 74 patients diagnosed with liver metastasis, the median age was 57 years (range 33–90 years) at the time of biopsy; of them, 61 patients (82.4%) reported a previous history of malignancy, $P = 0.003$. Histologically, metastatic adenocarcinoma was the most common neoplasm identified in 56 patients (75.7%), with the predominance of colorectal carcinoma. Forty-seven (63.5%) patients underwent two–five passes, which was statistically correlated with an increase in diagnostic accuracy ($k = 0.21$, 95% confidence interval [CI]= 0.038–1.189, $P = 0.04$). The overall sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of tru-cut biopsies were 100%, 97.1%, 95.7%, 100%, and 98.2%, respectively. **Conclusions:** The core needle biopsy is a reliable and valid diagnostic option for the histological assessment of suspected liver metastasis, particularly when supplemented by ancillary immunohistochemistry.

Keywords: Carcinoma of unknown primary, core needle biopsy, immunohistochemistry, liver metastases

Introduction

The liver is the second most common organ for metastatic disease, following lymph nodes, accounting for approximately 25% of all secondary neoplasms to solid organs.[1] Liver biopsy (LB) has long been used as a well-established procedure for the diagnosis of hepatic lesions.[2] It is an accurate and safe method that represents the gold standard in the management algorithm for various liver pathologies.[3] There are several approaches to LB, and transvenous or percutaneous approaches are usually used.[4] Furthermore, a wide variety of needles are available as suction needles (Menghini) and cutting needles (Tru-cut). However, the approach and choice of a needle will depend on the patient's clinical presentation and the interventional radiologist's expertise.[1]

Hematoxylin and eosin (HE) is the most widely used strain for histological assessment of LB specimens. The principal point in constricting the diagnosis of the possible hepatic neoplasm type and primary origin is the awareness of the different histological patterns of hepatic primary and metastatic lesions.[5] Therefore, the crucial steps for pathologists in the histopathological interpretation of liver biopsies are deciding the tumor type, differentiating primary hepatic from metastatic neoplasms, suggesting the metastatic primary

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location by using HE-stained sections to clarify a differential diagnosis, and subsequently using a suitable immunohistochemical panel (IHC) to set up the final diagnosis.[2]

The diagnostic validity of liver core needle biopsy (CNB) for neoplasms has long been investigated. The procedure has been shown to yield sensitivity and specificity up to 94 and 100%, respectively, for the detection of suspicious lesions.[1] However, the validity of CNB for pathologic evaluation might be affected by sampling errors or specimen inadequacy related to hepatic lesions.[6]

Different types of needles have been used to increase the diagnostic accuracy. A tru-cut needle is thought to obtain a good quality tissue sample and is easily available.[2] The samples obtained using tru-cut needles are known to provide an opportunity to use ancillary immunohistochemistry and to provide a preserved tissue architecture, thus enhancing the diagnostic validity.[3]

To our knowledge, there have been few published researches about the use of percutaneous ultrasonic guided core needle biopsies (PUS-CNB) for the histopathological assessment of metastatic hepatic lesions.

This study aimed to investigate the diagnostic accuracy of PUS-CNB using a tru-cut needle for suspected hepatic metastasis and to estimate factors that influence the diagnostic validity of the technique for hepatic metastasis.

Materials and Methods

In this prospective and retrospective study, we reanalyzed the clinicopathological records and slides of consecutive patients with suspected hepatic metastasis who experienced percutaneous ultrasonic guided core needle biopsies (PUS-CNB) between January 2021 to May 2022 at the histopathology department of AL-Jamhurii teaching hospital.

Patient characteristics

The database of the patients who undergo liver biopsies for suspected hepatic metastasis was reanalyzed to evaluate patient characteristics, procedure information, and pathology outcomes. Patient-related variables include; patient age at diagnosis, gender, history of primary malignancy, number of metastatic sites, and the number of metastatic foci detected by the imaging study.

Liver core biopsy procedure

A 16-gauge tru- cut biopsy needle was conducted, under real-time ultrasonic guidance, for all selected cases. According to our laboratory protocol, we usually received two–five passes kept in formalin solution for each biopsy from the radiology interventional room. Information was collected regarding the biopsy procedure, such as the location of a targeted liver lesion, number of biopsy passes, and the length of the core sample.

Pathological analysis

The histopathological diagnosis was performed using HE staining with subsequent immunohistochemistry. The histological and immune slides were blindly assessed by two expert pathologists, followed by a review of agreements.

The PUS-CNB histopathology report represented information about the malignant character of the hepatic lesion and the histopathological diagnosis. The final diagnostic report was based on the PUS-CNB result considering compatible radiology, clinical data, and subsequent IHC.

Inclusion criteria include all cases diagnosed as consistent with malignancy, indeterminate with atypical cells, and all supported by immunohistochemistry.

The excluded patients were those who had incomplete information, cases when the final pathology report was diagnostic of benign or primary malignancy, indeterminate results with the inflammatory process, a procedure using other than tru-cut needle, and inadequate biopsies (a core biopsy with ingredients that could not illustrate the presence of hepatic mass, for example, necrotic tissue, predominantly blood, or normal liver cells).

Statistical analysis

All analyses were conducted using SPSS version 18.0 (SPSS, Chicago, Illinois). Continuous variables including the baseline characteristics (mean± standard deviation and range), were analyzed. Categorical parameters (frequency and proportion) were described. The diagnostic accuracy was calculated. A value of $P \leq 0.05$ was set to determine the statistical significance.

Ethical approval

The study received approval from the medical research ethics committee of the College of Medicine, Ninevah University (Ref: NU.CM. 152.2022).

Results

A total of 74 patients who underwent core needle biopsies for liver metastases were included in this study. Table 1 summarizes the clinical characteristics of the sampled patients, procedure, and pathological data.

Patient characteristics

The median age was 57 years (33–90 years range) at the time of LB, with a mean age ± SD (60.26 ± 13.29) years. Patients were divided into three groups regarding their ages, with the predominance of the sixth decade by 40 (54.1%) patients.

The histologically confirmed liver metastasis was noticed more in females than males, with 40 (54.1%) versus 34 (45.9%), respectively. Regarding the history of the primary tumor, 61(82.4%) patients reported positive history, on

the other hand, those with unknown primary history were 13 (17.6%) patients, $P = 0.003$.

Thirty-six (48.6%) patients were presented with the liver metastatic-only site at the time of diagnosis. Forty-seven (63.5%) patients had multiple US-detected liver masses versus 27 patients (36.5%) with a single liver nodule ($k = 0.96$, 95% confidence interval [CI]= 0.875–1.084, $P = 0.647$).

Core biopsy procedure characteristics

The hepatic right lobe scored higher involvement by the metastatic process than the left lobe with 41 (55.4%) and, 33 (44.6%), respectively. Forty-seven (63.5%) patients underwent two–five passes, which was statistically correlated with an increase in the diagnostic accuracy of CNB ($k = 0.21$, 95% confidence interval [CI] = 0.038–1.189, $P = 0.04$). The median length of the liver core biopsy was 13 mm (range 6–18 mm) ($P = 0.0211$).

Table 1: Clinical characteristics, procedure, and pathological data of the sampled patients

Patient-related (n = 74)	
Age mean ± SD (60.26 ± 13.29) years	No. (%)
≤ 50 yr	16 (21.6%)
51–70 yr	40 (54.1%)
> 70 yr	18 (24.3%)
Gender	No. (%)
Female	40 (54.1%)
Male	34 (45.9%)
History of primary malignancy	No. (%)
Yes	61 (82.4%)
No	13 (17.6%)
Number of metastatic sites	No. (%)
One (liver only)	36 (48.6%)
Two (liver and lung)	19 (25.7%)
Three (liver, lung, bone)	8 (10.8%)
≥ Four (liver, lung, bone, brain)	11 (14.9%)
Lesion location (liver lobe involved)	No. (%)
Right	41 (55.4%)
Left	33 (44.6%)
Radiologic liver findings (metastatic foci)	No. (%)
Single	27 (36.5%)
Multiple	47 (63.5%)
Procedure related	
Number of passes	No. (%)
One	18 (24.3%)
Two–five	47 (63.5%)
> Five	9 (12.2%)
Core length, mm	No. (%)
≤ 8	22 (29.7%)
> 8	52 (70.3%)
Pathology details	
PUS-CNB pathology report	No. (%)
Diagnostic	69 (93.2%)
Indeterminate	5 (6.8%)
Available IHC stain on specimens, n (%)	74/74 (100%)

SD = standard deviation, PUS-CNB = percutaneous ultrasonic guided core needle biopsies, IHC = immunohistochemistry

Histopathology characteristics

By using the most widely used HE stain on the PUS-CNB samples, diagnostic results were noted in sixty-nine (93.2%) specimens versus five (6.8%) reports that concluded intermediate results by both pathologists ($P < 0.001$) [Figure 1]. Ancillary IHC was available in all cases (average 6.7 ± 3.8 antibodies), (range, 1 to 16). Carcinoma was the most frequently diagnosed neoplasm in 67 patients (90.5%), followed by sarcoma in 4 patients (5%), lymphoma in 2 patients (3%), and melanoma in 1 patient (1%). Metastatic adenocarcinomas were the most common histological carcinomas identified in 56 patients (75.7%) [Figures 2–4], followed by neuroendocrine carcinoma($n = 6$, 8%), and squamous cell carcinoma($n = 5$, 7%). The majority of adenocarcinoma was colorectal carcinoma in 17cases(30.4%), followed by breast in 11 patients (19.6%), pancreatobiliary in 10 patients (17.9%), lung in 7(12.5%), upper gastrointestinal

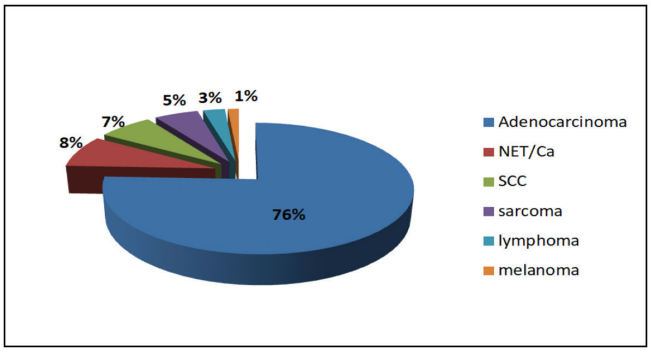

Figure 1: Histological types of liver metastases of the sampled patients

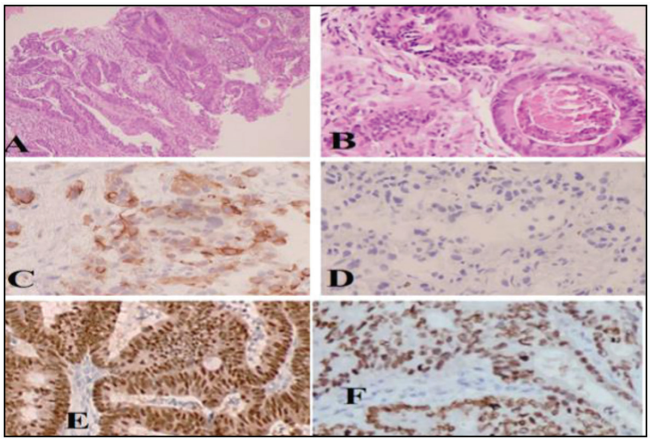

Figure 2: Metastatic colorectal adenocarcinoma in the liver. (A and B) Histopathologic features in hematoxylin and eosin stain (original magnification x100, and x 400). (C) CK20 IHC, positive cytoplasmic staining. (D) CK7 IHC, negative staining. (E) CDX2 IHC, positive nuclear staining. (F) SATB2 IHC, positive nuclear staining (IHC, x100, and x 400)

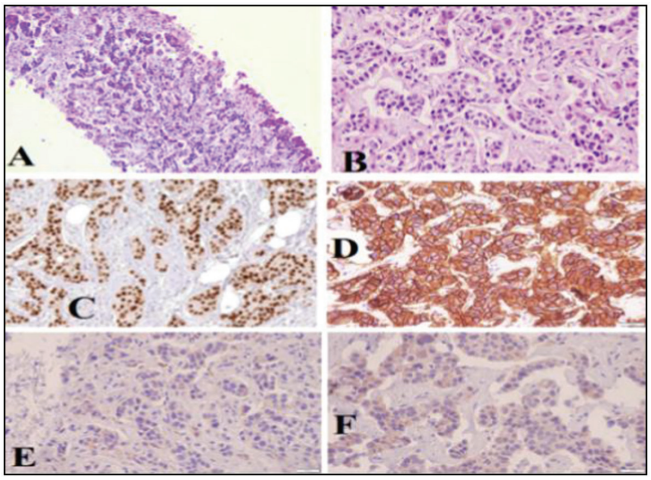

Figure 3: Metastatic breast invasive ductal adenocarcinoma in the liver. (A and B) Histopathologic features in hematoxylin and eosin stain, (original magnification x100, and x 400). (C) GATA3 IHC, positive nuclear staining. (D) HER2 IHC, positive strong and complete membranous staining. (E) ER IHC: negative staining. (F) PR IHC: negative staining (IHC, x100, and x 400)

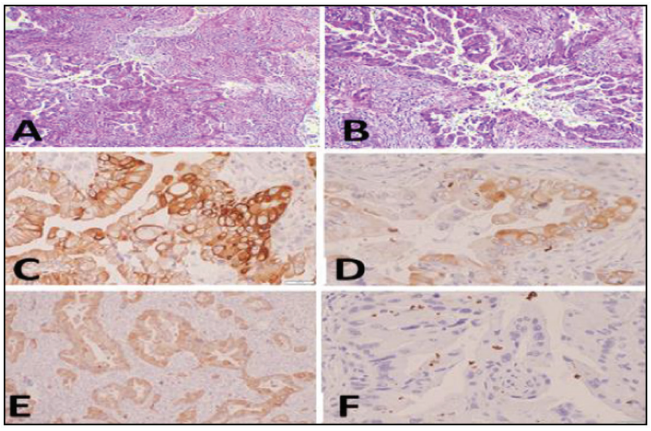

Figure 4: Metastatic pancreatic ductal adenocarcinoma in the liver. (A and B) Histopathologic features in hematoxylin and eosin stain, (original magnification x100, and x 400). (C) CK7 IHC, positive cytoplasmic staining. (D) CK20 IHC, positive cytoplasmic staining. (E) CK19 IHC, positive cytoplasmic staining. (F) SMAD4/DPC4 IHC: loss of staining (negative) (IHC, x100)

tract in 5 cases (8.9%), and prostate carcinoma in 3cases (5.4%). Three core biopsies were ultimately diagnosed as carcinoma of unknown origin(CUP).

Neuroendocrine hepatic metastasis was originated from the gastrointestinal tract (n = 3; 50%), particularly from the pancreas (n = 2; 66.6%), and jejunum (n = 1; 33.3%). Pulmonary primary origin was recorded in 2 cases (33.3%). However, in one patient (16.6%) the primary site was not specified.

Hepatic metastasis squamous cell carcinoma was noticed to originate from the lung (n = 4; 80%) and the gastrointestinal tract from the esophagus (n = 1; 20%).

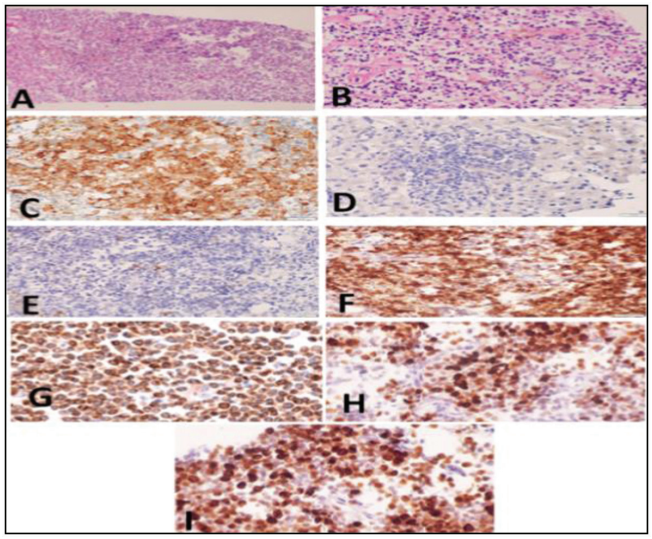

Figure 5: Metastatic non Hodgkin lymphoma in the liver. (A and B) Histopathologic features in hematoxylin and eosin stain (original magnification x100, and x 400). (C) CD20 IHC, positive diffuse cytoplasmic staining. (D) CD3 IHC, negative staining. (E) CD30 IHC, negative staining. (F) CD10 IHC, diffuse positive staining. (G) BCL2 IHC, positive diffuse cytoplasmic staining. (H) BCL6 IHC, positive diffuse nuclear staining. (I) MUM1/IRF4 IHC, positive nuclear staining (IHC, x 400)

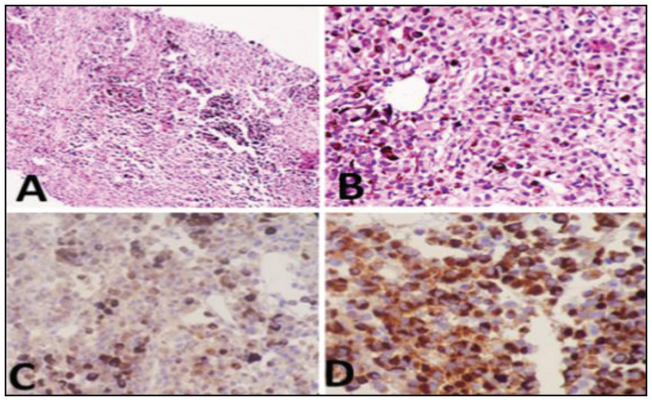

Figure 6: Metastatic Melanoma in the liver. (A and B) Histopathologic features in hematoxylin and eosin stain, (original magnification x100, and x 400). (C) S100 IHC, positive cytoplasmic and nuclear staining. (D) HMB45 IHC, positive cytoplasmic staining (IHC, x100, and x 400)

Secondary hepatic non-Hodgkin lymphoma originated from the gastrointestinal tract (n = 2; 2%) [Figure 5]. Metastatic sarcomas to the liver were detected in 4patients (5%). The most prevalent type was a gastrointestinal stromal tumor (GIST) in 3patients (75%), followed by leiomyosarcoma in 1 case(25%). Metastatic uveal melanoma was observed in 1 patient (1%) [Figure 6].

The discrepancy between HE and IHC was in 3specimens(4.1%). There were two diagnostic cases of metastatic adenocarcinoma in favor of pancreatobiliary

Table 2: Diagnostic accuracy of PUS-CNB pathology reports with the final IHC (gold standard) reports in patients with liver metastasis

Variables	PUS-CNB pathology reports, n(74)	
	Diagnostic 69 (93.2%)	Indeterminate 5 (6.8%)
TP	67	4
FP	2	1
TN	–	–
FN	–	–

TP = true positive, FP = false positive, FN = false negative, TN = true negative, PUS-CNB = percutaneous ultrasonic guided-core needle biopsy. The row-column association is statistically significant (P = 0.0000*), (ANOVA test)

Table 3: Correlation between HE and IHC staining in PUS-CNB in the sampled patients with clinically suspected liver metastasis

Variables	PUS-CNB, n(74)	
	Diagnostic	Indeterminate
HE stain	69 (93.2%)	5 (6.8%)
IHC stain	67 (91%)	4 (5.4%)

HE = hematoxylin and eosin, IHC = immunohistochemistry, PUS-CNB = percutaneous ultrasonic guided core needle biopsies. The row-column association is statistically significant (P ≤ 0.0001*) (ANOVA test)

origin, and one indeterminate case highly suspected a metastatic lymphoma to the liver. The final IHC diagnosis was intrahepatic cholangiocarcinomas, and chronic viral hepatitis, respectively. The overall sensitivity, specificity, PPV, NPV, and accuracy were 100%, 97.1%, 95.7%, 100%, and 98.2%, respectively [Table 2]. The correlation between HE and IHC staining was statistically in influential agreement (k = 0.963, 95% confidence interval [CI] = 0.91–1.02, $P \leq 0.0001$) [Table 3].

Discussion

It is a common situation in oncology to raise doubts about the neoplastic nature of the hepatic lesion, as well as whether it is primary or secondary.[7] Under these circumstances, the US-guided core needle biopsy emerges as an accurate option to establish with as a low-cost and safe procedure.[8] Our findings reveal the diagnostic effectiveness of core-needle biopsy. The sensitivity and specificity values we obtained are consistent with those previously documented studies.[6,9] These results support the prevalent use of core-needle biopsy as the primary invasive procedure of choice for histological characterization of hepatic nodules.

In our analysis, we determined that percutaneous ultrasound-guided core-needle biopsy (PUS-CNB) using a tru-cut needle achieved a notably high diagnostic accuracy of 98.2%, consistent with the 96.4% accuracy reported by Parente *et al*.[9] Although Gheorghiu *et al*.[6] reported even more impressive results with 100% diagnostic validity. It is valid to note that our high result may be justified by the dependence of the biopsy outcome on two crucial elements: first; the radiologist's skills in performing the biopsy procedure, second; the pathologist's experiences in the interpretation of a received sample. Fortunately, both of these vital components were available within our institution.

Furthermore, we improved the validity of core-needle biopsy (CNB) by integrating immunohistochemistry (IHC). This combination enhanced diagnostic reliability and accuracy, providing additional molecular and protein-level insights to complement CNB's histological data. This comprehensive approach reinforces CNB's diagnostic effectiveness and enables a more detailed characterization of suspected metastatic hepatic neoplasms.

As has been documented in a previous study, the sixth decade was the most common age group represented by liver metastasis in this study.[6] By comparison, the fifth decade was dominated by Khadim *et al*.,.[10] Females show a higher incidence of liver metastasis than males, approximating the results of Vernuccio *et al*.,[11] but dissimilar to previous studies.[9,10] Our explanation might be due to the small sample size and the higher frequency and incidence of liver metastases of breast cancer in women in our locality.

In this study, young females up to 50 years old encountered liver metastasis more frequently from breast carcinoma, whereas those older than 70 years scored hepatic metastases frequently from colorectal cancers. The origin of hepatic metastasis in males older than 70 years were often from lung non-small cell carcinomas.

It is known that most liver metastases are multiple, the same was observed in our analysis. Both lobes were involved in the majority of cases (63.5%). This finding is similar to Khadim *et al*.,[10] who identified multiple lesions in 55% of the cases.

In this analyses, the majority of liver metastasis patients presented with a previously known history of malignancy, which is similar to de Ridder *et al*.,.[12] However, 4% of patients show histologically confirmed metastatic carcinomas without any detectable primary tumor in spite of the standardized diagnostic approach. They are called carcinoma of unknown primary (CUP), for which evidence of a primary site of origin is lacking.[13] Since we are dealing with small-sized core biopsies, the diagnostic validity is crucial, especially in the current era of immune-based targeted molecular therapies. In this situation, immunohistochemistry became an essential ancillary method for the diagnosis and classification of liver metastasis.[14] Here, we used

appropriate IHCs to influence the accurate diagnosis of hepatic metastases.

In this work as to be anticipated, carcinoma was by far the most common neoplasm diagnosed in patients with hepatic metastases. Our findings revealed that the most common primary site for liver metastases was from the colorectum, consistent with the findings of de Ridder *et al*.,[12] and Kasper *et al*.,.[15] However, Wang and his colleagues,[16] established the lung as the commonest primary site, followed by the colorectum, whereas Parente *et al*.,[9] revealed metastatic colorectal carcinoma in the third place. Those differences might be attributed to the inclusion criteria set for the participants and the geographical diversity of the studies. Colorectal carcinoma (CRC) is the third most common malignancy worldwide, with 25–30% hepatic metastases during the course of the disease, and more than 50% of CRC cases develop postsurgical recurrence within 2years. The second most common group of liver metastases were neuroendocrine carcinomas (7%), in keeping with those of others.[9,15]

The main factor correlated with the increase in the diagnostic accuracy of our work was the number of needle passes, parallel to that reported by Chon *et al*.,.[2] further, it is well known that the diagnostic validity of the procedure might be compromised by a poor technique. Fortunately, a well-trained radiologist carried out adequate tru-cut biopsy specimens for subsequent histological interpretation.

The core tissue length has been noticed as another influence that improved the accuracy of the study. This observation was mentioned by Gheorghiu *et al*.,.[6] It is a sense that the longest the sample core, the higher chance to contain adequate amounts of tissue from the target lesion. At our institution, tru-cut needles were preferred as it provided longer specimens that are better interpreted by pathologists than suction needles, thus minimizing the requirement for repeat biopsies due to inconclusive results.

The clinical value of the current study might be doubted, but we think it might be used in clinical practice decision-making. In liver metastatic patients, an approximation of the relative frequency of liver metastases could be emanated from the present data. This might guide additional treatment strategies like surgical operation.

The strength of our study is associated with the nature of the inclusions and the use of immunohistochemistry for all specimens. However, some limitations are acknowledged. First, the study included a limited number of cases based on a single institution. Therefore, our findings require further verification in a larger prospective cohort of cases. Second, the absence of a rapid on-site evaluation, because we wanted to assess the exact value of tru-cut needle passes, although its association would increase the accuracy of the procedure. Randomized trials are required in the future to show the reliability and accuracy of the tru-cut biopsy needle.

Conclusions

The core needle biopsy using a tru-cut needle is a reliable and valid diagnostic option for the histological assessment of suspected liver metastasis, particularly when supplemented by ancillary immunohistochemistry.

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Conflicts of interest

There are no conflicts of interest.

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