

Selective transitional zone sampling approach versus random biopsy in cases with malignant liver masses: Is there any superiority?

Kosti Can ÇALIŞKAN¹, Banu ÖZGÜVEN², Mehmet Sait BUĞDAÇ³, Emin ÇAKMAKCI¹,
 Umut Perçem ORHAN¹, Mehmet ERTÜRK¹, Zeki KARPAT¹, Muzafer BAŞAK¹, Fatih SELÇUKBİRİCİK⁴

Departments of ¹Radiology, ²Pathology and ³Gastroenterohepatology, Şişli Etfal Training and Research Hospital, İstanbul
 Department of ⁴Oncology, İstanbul University Cerrahpaşa School of Medicine, İstanbul

Background/aims: Currently, the diagnostic sensitivity of malignant liver mass biopsies is an important problem in the definitive diagnosis. In this study, we aimed to investigate the role of selective peripheral approach to lesion biopsies for diagnostic sensitivity of liver masses. **Materials and Methods:** Between June 2007 and March 2011, totally 88 patients (50 male, 38 female), referred to our Interventional Radiology Department for sonographically guided Tru-cut biopsies for liver lesions, were examined. All biopsies were performed by an experienced radiologist with an 18-gauge Tru-cut biopsy needle with a spring-loaded biopsy gun under sonographic guidance. We describe two locations (peripheral and central) for liver lesions, with the inner 2/3 part of the mass as central and the outer 1/3 part as peripheral. We obtained biopsy from both of these locations, and samples were transferred to the Pathology Department separately. **Results:** According to pathological and immunohistochemistry studies, there were 42 hepatocellular carcinomas and 46 metastases. All of the metastatic tumors were stained by cytokeratin (10 lung adenocarcinoma, 15 breast adenocarcinoma, 16 gastrointestinal tract, 4 prostate, and 1 malignant melanoma of these 46 metastases were reported as primary). According to histopathological results, diagnostic sensitivity was 97.7% in peripherally located biopsies and 86.3% in biopsies taken from the center of the masses ($p=0.0063$). **Conclusions:** Selective peripheral biopsy approach in Tru-cut biopsies of liver lesions has better sensitivity rates for histopathologic diagnosis compared to the centrally located and random biopsies.

Key words: Tru-cut biopsy, hepatocellular cancer, metastasis, exact diagnosis, central biopsy

Selektif geçiş zonu biyopsilerinin rastgele alınan karaciğer biyopsilerine üstünlüğü var mıdır?

Giriş ve Amaç: Günümüzde malign karaciğer kitle biyopsilerinde kesin tanı konmasında tanısal duyarlılık önemli bir sorundur. Bu çalışmada selektif periferik yaklaşım ile alınan kitle biyopsilerinin tanısal duyarlılıktaki rolünü araştırmayı amaçladık. **Gereç ve Yöntem:** 2007-2011 yılları arasında ultrasonografi altında karaciğer kitlelerinden biyopsi uygulanmak üzere invaziv Radyoloji Kliniğine yönlendirilen toplam 88 hasta (50 erkek ve 38 kadın) çalışmaya alındı. 18 gauge karaciğer biyopsisi deneyimli radyolog tarafından uygulandı. Bu biyopsilerde iki lokalizasyon tanımlandı: Santral ve periferik. Kitlenin 2/3 merkezi santral, 1/3 dış kısmı ise periferik olarak tanımlandı. Bu çalışmada her iki yerden de biyopsiler ayrı ayrı alınarak değerlendirildi. **Bulgular:** Patolojik ve immunohistokimyasal çalışmalara göre 42 hastada hepatosellüler kanser ve 46 olguda metastaz saptandı. Tüm metastatik tümörler sitokeratin ile boyandı (10 akciğer adenokarsinomu, 15 meme kanseri, 16 gastrointestinal kaynaklı, 4 prostat ve 1 malign melanom öncü odak olarak belirlendi). Histopatolojik sonuçlar dikkate alındığında tanısal duyarlılık %97.7 periferik örneklerde, %86.3 santral biyopsilerde saptandı ($p=0.0063$). **Sonuç:** Karaciğer kitle biyopsilerinde selektif periferik biyopsi santralden alınan biyopsilerden daha fazla tanısal duyarlılığa sahiptir.

Anahtar kelimeler: Tru-cut biyopsi, hepatosellüler kanser, metastaz, kesin tanı, santral biyopsi

Address for correspondence: Kosti Can ÇALIŞKAN

Şişli Etfal Training and Research Hospital, Department of Radiology,
 İstanbul, Turkey
 E-mail: caliskancan@gmail.com

Manuscript received: 01.10.2011 **Accepted:** 26.07.2012

Turk J Gastroenterol 2012; 23 (6): 708-713
 doi: 10.4318/tjg.2012.0590

INTRODUCTION

Hepatic metastasis and hepatocellular cancer are the most common malignant masses of the liver. The liver is the most frequent target location for metastatic spread of tumors. Therefore, hepatic metastases are the most common masses of the liver worldwide. It has been reported that hepatic metastases occur in up to 40% of adult patients with extrahepatic primary malignancies. Hepatic metastases commonly originate from primary sites in the distribution of the portal venous system. Lung and breast cancer are the most common origins of hepatic metastases. Metastases are commonly gray-white and may show scattered hemorrhages or central apoptosis and necrosis (1). Biopsy is the essential diagnostic cornerstone for revealing the differentiation of metastases and primary liver cancers. In the presence of metastasis, it is well known that metastasectomy extends the survival (2-4). Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. It is the fifth most common cancer, with high annual cancer mortality rates (5,6).

Conventional liver biochemical tests do not distinguish HCC from other hepatic mass lesions or cirrhosis. Although alpha fetoprotein (AFP) is the most commonly used tumor marker for the screening of HCC, in 25% of all patients, it remains under the diagnostic value (200 ng/ml) (7-10).

For these reasons, Tru-cut biopsy has a very substantial role in the pathologic diagnosis of focal liver masses. Apoptosis and necrosis can occur in the central part of these masses, especially in lar-

ge primary or metastatic lesions (Figure 1a and b). This necrotic tissue can be problematic for the pathologic diagnosis, necessitating repetition of biopsy, but it should not be forgotten that liver biopsies have a 0.32% risk for mortality and 35% for morbidity (11,12). Therefore, it must be aimed to obtain diagnostic sensitivity for the pathologic diagnosis in one attempt and to preclude repetition of the biopsy.

To the best of our knowledge, there has been no trial in the literature that compares the diagnostic sensitivity of peripheral versus centrally located liver biopsies. In this study, we aimed to investigate the role of peripheral liver lesion biopsies in the diagnostic sensitivity of liver masses.

MATERIALS AND METHODS

Between June 2007 and March 2011, totally 88 patients (50 male, 38 female), referred to our Interventional Radiology Department for ultrasonography (US)-guided Tru-cut biopsy from their solid focal liver masses with malignant suspicion according to imaging modalities and laboratory results, were examined. The size of the masses was measured in real-time US and the largest diameter was considered. All lesions included in the study were larger than 25 mm and all the patients were over 18 years. From all patients, we obtained written informed consent before the procedure.

Exclusion criteria were as follows: age under 18 years, unconsciousness, history of hypersensitivity for local anesthetic drugs, bleeding diathesis, masses without demarcation lines, lesions smaller

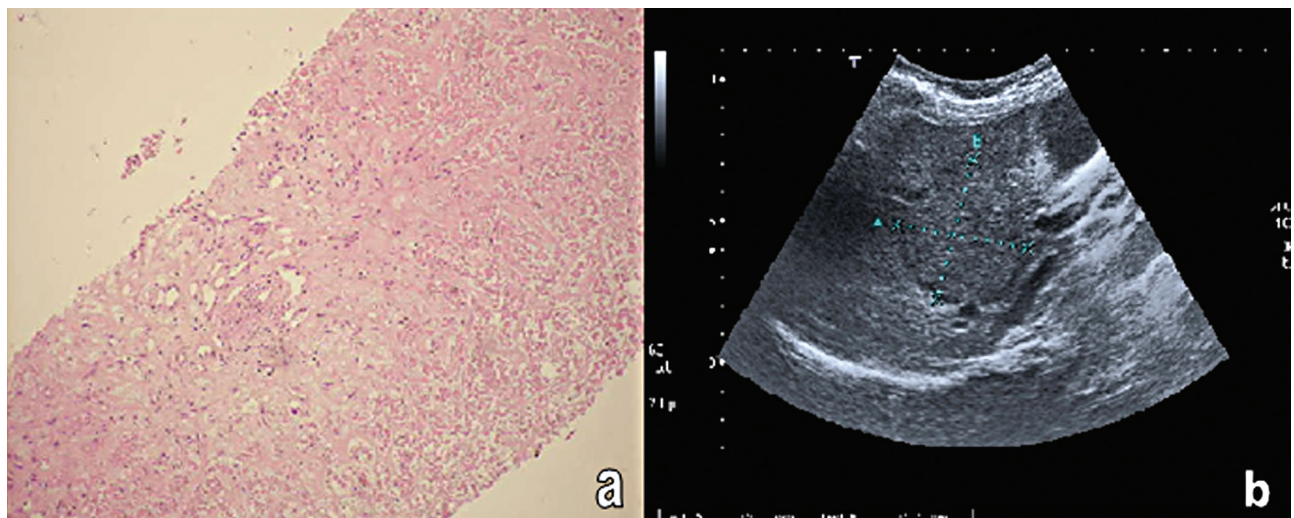


Figure 1. a. Histopathologic section representing the central necrotic area of the tumor. H&E staining, x100) b. The same lesion in sonographic image.

than 25 mm, histopathologically benign solid masses, atypic hemangiomas, adenomas, and calcified and predominantly cystic lesions.

Prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), and number of thrombocytes were monitored in all of the patients. Patients with high risk of bleeding were included into the study after normalization of coagulation parameters.

All biopsies were taken by the same radiologist with the assistance of two residents in their second and fourth years of education. Biopsies were performed after local dermal anesthesia, with an 18-gauge Tru-cut needle and automatically triggered biopsy gun with Toshiba Nemio 20 and Applio ultrasound scanner (Toshiba Medical Systems Co, Ltd, Tokyo, Japan) equipped with a 3.5 - 5 MHz convex probe. The specimen length of the

Tru-cut needle was 17 mm and the movement distance was 22 mm.

The biopsy specimens were obtained from peripheral and central zones of the liver masses. We accepted that the inner 2/3 part of the lesion was central and the outer 1/3 was peripheral zone, and peripheral specimens also had to include the transition zone, between the lesion and normal liver parenchyma (Figure 2a,b,c and d). The central part illustrates that the specimen can be taken only from the mass (Figure 3a,b,c and d). After obtaining biopsy from these two locations, patients were kept under observation by the radiologist in the operating room for 4 hours for possible complications. We classified all complications into two groups as major and minor (11). Major complications were described as hemorrhage, bile leakage, biliary peritonitis, hemobilia, pneumothorax, sep-

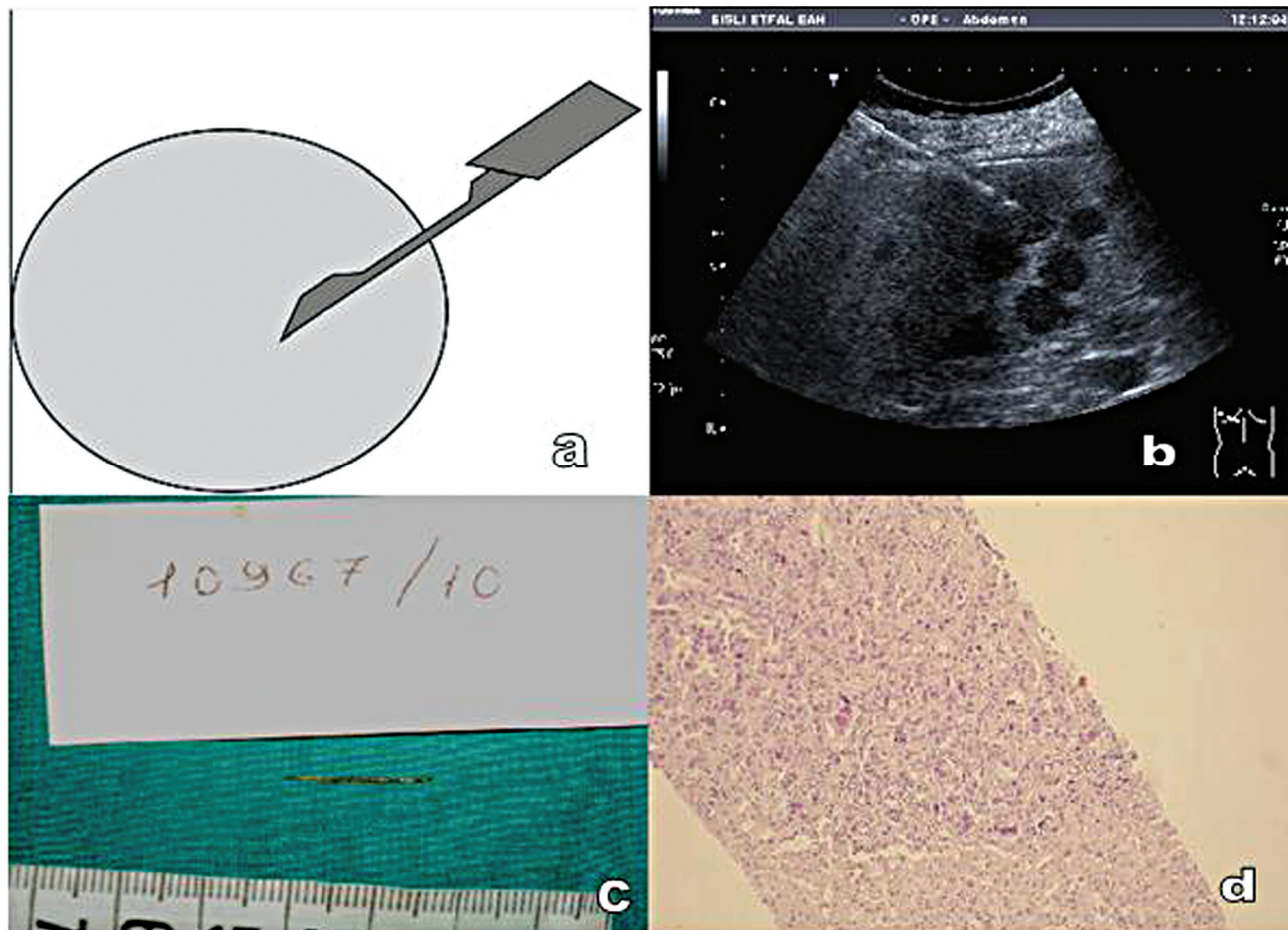


Figure 2. a. The artwork of Tru-cut biopsy needle and schematic outlook of biopsy; note that the needle passes from normal parenchyma, border zone between the mass and parenchyma and the mass, b. Sonographic image of the hypoechoic solid masses in liver parenchyma; the largest measured 26x25 mm, c. Ultrasonically guided biopsy sampling from the peripheric part of the lesion d. The sample: note that the lesion and parenchyma can be differentiated.

tic shock, and death. Minor complications included transitional pain and epigastric discomfort.

Histopathological Evaluation

After obtaining biopsy specimens from both central and peripheral zones of the masses, specimens were placed in different Eppendorf tubes filled with formol and sent to the Pathology Department; all materials were evaluated by the same pathologist. All biopsy materials were stained with hematoxylin-eosin (HE). Some materials that were appropriate for immunohistochemical study were selected. Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue sections, 5-micrometer in thickness. All of the metastatic masses were stained for cytokeratin (CK) 7, 19 and 20, polyclonal carcinoembryonic antigen (CEA), thyroid transcription factor-1 (TTF1), and

HMB 45. Immunohistochemistry for glypican 3 and HepPar1 were performed on Tru-cut biopsies including HCC (13-15).

Statistics

Scale variables were presented as mean±standard deviation (mean±SD). Statistical analysis was made using McNemar test, and inadequate biopsy sample rates of the two different locations were compared. A p value <0.05 was considered statistically significant. The Statistical Package for the Social Sciences (SPSS) (for Windows, release 12.0.0 standard version) software was used for statistical evaluations.

RESULTS

Between June 2007 and March 2011, malignant solid focal liver lesion Tru-cut biopsies were per-

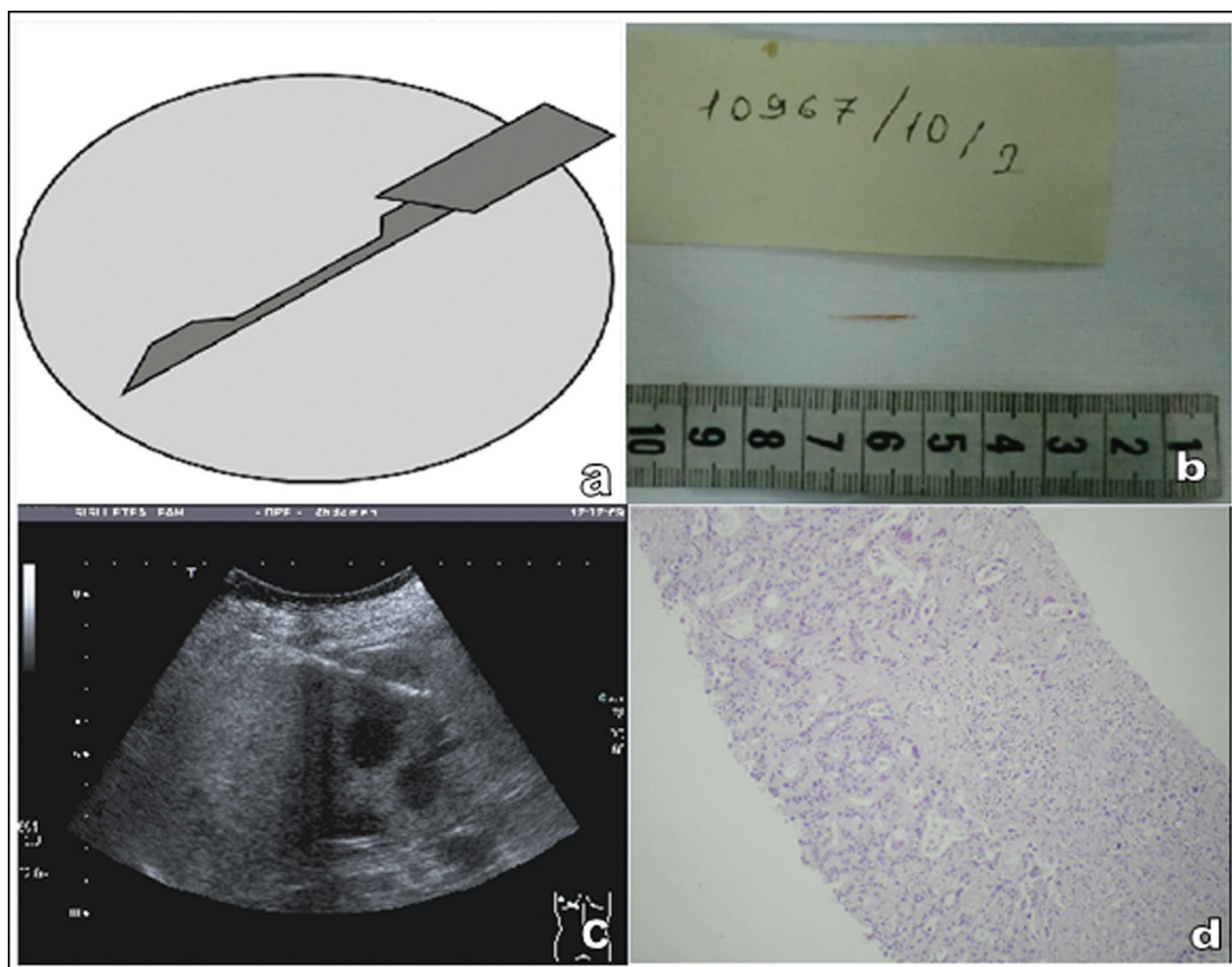


Figure 3. a. The artwork of Tru-cut biopsy needle and schematic outlook of biopsy: note that needle only takes sample from the lesion, b. Ultrasonically guided biopsy sampling from the central part of the lesion c. Sonographic image of biopsy performance from central part of the lesion, d. Histopathologic imaging of the lesion was consistent with metastatic adenocarcinoma, (H&E, x100).

formed with US guidance in 50 males and 38 females, totally 88 patients, in the Interventional Radiology Department. Their mean age was 57 ± 13 (range: 28-79) years.

The mean size of biopsy material was 43.9 mm (range: 30-89 mm). Forty patients had 1 lesion and the others had ≥ 2 ; in the latter patients, biopsy was obtained from the largest lesion. According to the histopathological analysis, 76 (86.3%) central biopsies and 86 (97.7%) peripheral biopsies were diagnostic. This difference between the two locations was statistically highly significant ($p=0.0063$, McNemar Test). In centrally located biopsies, the diagnostic sensitivity was 88% ($n=37$) in HCC and 84.7% ($n=39$) in metastatic lesions. These rates were 97.6% ($n=41$) in HCC and 97.8% ($n=45$) in peripherally located biopsies.

According to immunohistochemistry studies, there were 42 (47.7%) HCCs and 46 (52.3%) metastases. All of the 46 metastatic tumors were stained by CK, and primary pathologic diagnoses were reported as follows: 10 lung adenocarcinoma, 15 breast adenocarcinoma, 16 gastrointestinal tract, 4 prostate, and 1 malignant melanoma (Figure 4).

Complications were evaluated as epigastric discomfort in 5 patients and transient pain in 5 patients, and were reported as minor complications (11.3%). There was no major complication in this study. Thus, the complication rate was only 11.3%. Necrotic tissue sample was determined in the lesions that were larger than 4 cm, and mostly in metastatic lesions.

In one patient, both the peripheral and central biopsy samples were insufficient for a pathologic diagnosis, with only steatosis specified pathologically (Figure 5), and the biopsy was repeated.

DISCUSSION

Despite developments in imaging modalities and laboratory tests, histopathologic assessment is still essential for the definite diagnosis. Thus, US-guided Tru-cut liver biopsy maintains its diagnostic value currently. Although the diagnostic sensitivity rate has increased over time, it remains only 92% with the conventional methods. According to our experiences, we observed that, for large lesions, the diagnostic sensitivity rate was decreased due to central necrosis. In this study, we found the diagnostic sensitivity as 97.7% and 86.3% in peripherally and centrally located biopsies, respectively. In addition, the sensitivity rates were found as 88% for HCC and 84.7% for metastases in cen-

trally located biopsies. In peripheral biopsies, these rates were 97.6% in HCC and 97.8% in metastatic masses (Table 1).

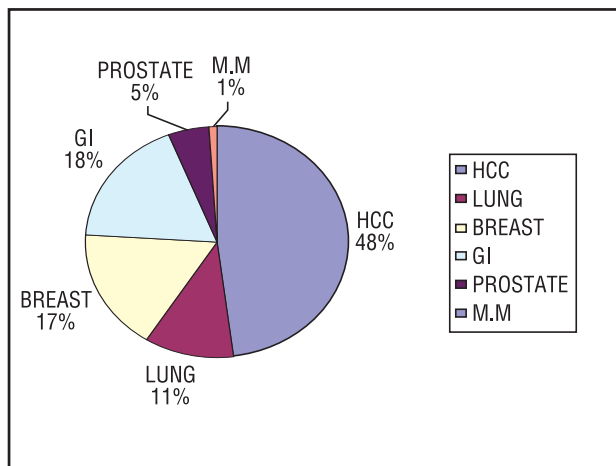


Figure 4. Distribution of definitive diagnoses of metastases. HCC: Hepatocellular carcinoma. GI: Gastrointestinal tumors. MM: Malignant melanoma.

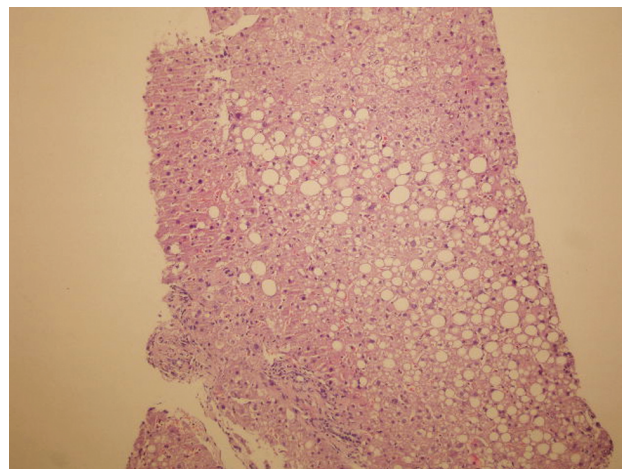


Figure 5. Grade 2 macrovesicular steatosis in the liver parenchyma, H&E, $\times 100$

Table 1. Diagnostic sensitivity of liver biopsies in the other studies

Studies in the literature	Diagnostic sensitivity (%)
Jakobsen et al.	80
Cochand et al.	69
Bedenne et al.	81
Lin et al.	89
Dusenbery et al.	85
Wu et al. (CEUS group)	99
Wu et al. (Classic US group)	92

CEUS: Contrast-enhanced ultrasonography. US: Ultrasonography method without contrast enhancement.

To our knowledge, the diagnostic sensitivity of liver mass biopsies ranges between 69% and 92% in the literature (1-5). These values are relatively better than our results related to centrally located biopsies, but in peripherally located biopsies, we found better sensitivity rates than in the literature. These better results may be associated with the experience of the practitioner, exclusion of predominantly cystic lesions, and the selective approach for the masses. According to the literature, random biopsies are recommended in patients with solid liver masses. Additionally, in other studies, it is recommended to obtain a biopsy specimen preferably in the center of the mass in random biopsies due to concern for missing/inadequate material.

Sparchez et al. (16) reported the diagnostic sensitivity of Tru-cut biopsy as 95.3% in their study, which they made with contrast enhancement US. Another author, Wu et al. (17), reported this value as 98.7%. According to these studies, biopsies

which were made with contrast enhancement have sensitivity values closer to those of our peripherally located biopsies than the random biopsies. It is also clear that contrast enhancement US has a risk of toxicity and increases the cost; however, peripheral biopsy sampling is a cost-effective method without risk of toxicity and major complications.

The limitations of this study were exclusion of benign lesions, lesions smaller than 25 mm and predominantly cystic masses. We excluded the small lesions because of possibility of minimal or no necrosis.

In conclusion, peripheral biopsy approach in Tru-cut biopsies of liver lesions has better sensitivity rates for histopathologic diagnosis compared to the centrally located and random biopsies as described in the literature. We thus suggest that peripheral sampling of focal malignant liver masses must be performed to decrease the repetition of biopsy and to prevent a delay in the diagnosis.

REFERENCES

1. Pickren JW, Tsukada Y, Lane WW. Liver metastasis: analysis of autopsy data. In: Weiss L, Gilber HA, eds. Liver metastases. Boston: CK Hall, 1982; 2-18.
2. Sheiner PA, Brower ST. Treatment of metastatic cancer to the liver. *Semin Liver Dis* 1994; 14: 169-77.
3. Barr LC, Skene AI, Thomas JM. Metastasectomy. *Br J Surg* 1992; 79: 1268-74.
4. Hughes K, Scheele J, Sugarbaker PH. Surgery for colorectal cancer metastatic to the liver. Optimizing the results of treatment. *Surg Clin North Am* 1989; 69: 339-59.
5. Parkin D, Muir C, Whelan S. Cancer incidence in five continents. IARC publication no. 120. Lyon, France: IARC, 1997.
6. Bosch FX, Ribes J, Borrás J. Epidemiology of primary liver cancer. *Semin Liver Dis* 1999; 19: 271-85.
7. Cedrone A, Covino M, Caturelli E, et al. Utility of alpha-fetoprotein (AFP) in the screening of patients with virus-related chronic liver disease: Does different viral etiology influence AFP levels in hepatocellular carcinoma? A study in 350 Western patients. *Hepatogastroenterology* 2000; 47: 1654-8.
8. Nguyen MH, Garcia RT, Simpson PW, et al. Racial differences in effectiveness of alpha-fetoprotein for diagnosis of hepatocellular carcinoma in hepatitis C virus cirrhosis. *Hepatology* 2002; 36: 410-7.
9. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005; 42: 1208-36.
10. Trevisani F, D'Intino P, Morselli-Labate A, et al. Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status. *J Hepatol* 2001; 34: 570-5.
11. Cevik FC, Aykin N, Naz H. Complications and efficiency of liver biopsies using the Tru-Cut biopsy gun. *J Infect Dev Ctries* 2010; 4: 91-5.
12. Türkay C, Elagöz S, Yönm O, et al. The diagnostic value of ultrasonography-guided fine needle aspiration biopsy from liver and pancreas. *Turk J Gastroenterol* 2002; 13: 53-5.
13. Minami Y, Kudo M. Hepatic malignancies: correlation between sonographic findings and pathological features. *World J Radiol* 2010; 2: 249-56.
14. Tot T, Samii S. The clinical relevance of cytokeratin phenotyping in needle biopsy of liver metastasis. *APMIS* 2003; 111: 1075-82.
15. Kakar S, Gown AM, Goodman ZD. Best practices in immunohistochemistry: hepatocellular carcinoma versus metastatic neoplasms. *Arch Pathol Lab Med* 2007; 131: 1648-54.
16. Sparchez Z, Radu P, Zaharia T, et al. Usefulness of contrast enhanced ultrasound guidance in percutaneous biopsies of liver tumors. *J Gastrointest Liver Dis* 2011; 20: 191-6.
17. Wu W, Chen MH, Yan K, et al. Application of contrast-enhanced ultrasound to increase the diagnostic rate of liver tumor by biopsy. *Zhonghua Yi Xue Za Zhi* 2006; 86: 116-20.