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Hepatocellular carcinoma in cirrhotic liver: Accuracy of pretransplantation ultrasonography

Sirotik karaciğerde HCC: Pretransplant ultrasonografinin tanısal doğruluğu

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Summary

Aim: To assess the accuracy of ultrasonography in detecting hepatocellular carcinoma in patients with advanced cirrhosis undergoing liver transplantation.

Materials and Methods: Four hundred ninety five patients, who underwent liver transplantation and had histopathologically proved liver cirrhosis, were included in the study. Reports of pretransplantation ultrasonography and histopathologic evaluation of the explanted liver were retrospectively reviewed and compared for the presence of hepatocellular carcinoma.

Results: Hepatocellular carcinoma was detected in the explanted liver in 88 (17,8%) patients. The hepatomas ranged in size from 0.1 to 11cm. One or more solid focal lesions were reported in the pretransplant ultrasonography examination in 58 of these patients. In 16 patients, with a focal lesion reported in the pretransplant US examination, no hepatocellular carcinoma was detected in the histopathologic examination. The patient detection sensitivity of ultrasonography for hepatocellular carcinoma was 66%, specificity was 96%, the positive predictive value was 78% and negative predictive value was 93%.

Conclusion: Sensitivity of utrasonography for hepatocellular carcinoma detection mostly depends on tumor size and is low in liver transplant candidates. On the other hand, the specificity is high and all solid lesions discovered with the ultrasonography should be considered hepatocellular carcinoma until proven otherwise.

Key Words: Liver, fibrosis, carcinoma, hepatocellular, screening, ultrasonography.

Özet

Amaç: *Karaciğer nakil adayı olan sirozlu hastalarda hepatosellüler karsinoma saptamada ultrasonografinin etkinliğinin araştırılması.*

Gereç ve Yöntem: *Ortotopik karaciğer nakli uygulanan 495 hastanın nakil öncesi ultrasonografi bulguları fokal karaciğer lezyonu açısından geriye dönük değerlendirildi. Ultrasonografide saptanan tüm solid lezyonlar olası hepatosellüler karsinoma kabul edildi. Eksplant karaciğer materyalinde hepatosellüler karsinoma odaklarının varlığı ve sayısı nakil öncesi ultrasonografi bulguları ile karşılaştırıldı.*

Bulgular: *Seksen sekiz (%17.8) olguda eksplant karaciğerde hepatosellüler karsinoma saptandı. Hepatosellüler karsinoma boyutları 1mm-11cm arasında değişiyordu. Nakil öncesi ultrasonografi ile bu olguların 58'inde karaciğerde fokal solid lezyon saptanmıştı. Ultrasonografide solid lezyon gözlenen 16 olguda, histopatolojik incelemede hepatosellüler karsinoma saptanmadı. Ultrasonografinin sirotik karaciğerde hepatosellüler karsinoma için duyarlılığı %66, özgüllüğü %96, pozitif öngörü değeri %78, negative öngörğü değeri %93bulundu.*

Sonuç: *Sirotik karaciğerde ultrasonografinin hepatosellüler karsinoma saptamada duyarlılığı tümör boyutu ile ilişkilidir ve düşüktür. Bununla beraber, özgüllüğü yüksektir ve ultrasonografide saptanan tüm solid lezyonlar aksi ispatlanana kadar hepatosellüler karsinoma gibi kabul edilmelidir.*

Anahtar Sözcükler: *Karaciğer, fibrozis, karsinom, hepatosellüler, tarama, ultrasonografi.*

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver tumor and usually develops in a cirrhotic liver. The risk of developing HCC in cirrhotic patients is about 3% to 5% per year (1). Liver transplantation candidates represent a high risk population. The wait lists for transplantation are long, because of a lack of cadaveric donors. Early detection of HCC is important for patient management. Current therapies such as percutaneous ethanol injection, radiofrequency ablation or intra-arterial chemoembolization can alter the natural history of the tumor in patients who develop HCC while waiting for liver transplantation (2-8). In addition, 5 year survival rates reaching 80% are reported after transplantation for HCCs smaller than 2 cm (9,10). Early detection depends mostly on hepatic imaging. Ultrasonography (US) is the most commonly used screening method, with its wide availability, low cost and lack of invasiveness (1,11). The reported sensitivity of US for HCC in cirrhotic liver varies widely, due to the experience of the examiner, different technical factors, the patient population included and the tumor size (12-16).

The purpose of this study is to evaluate the efficacy of US in HCC detection in patients with advanced cirrhosis undergoing liver transplantation.

Materials and Methods

Reports of pretransplantation sonography and histopathologic evaluation of the explanted liver in 650 patients, who underwent liver transplantation between January 1998 and October 2008, were retrospectively reviewed for focal liver lesions. Four hundred ninety five patients, who underwent liver transplantation within 150 days following the US examination and had histopathologically proved liver cirrhosis, were included in the study. The ages of the patients ranged from 4 months to 66 years (mean age 38.2 years). All US examinations were performed by a radiologist experienced in abdominal US with one of ATL HDI-5000 (Advanced Technology Laboratories, Bothell, WA, USA), Siemens Ellegra (Siemens, Erlangen, Germany), Siemens Sonoline Antares (Siemens, Erlangen, Germany) scanners with a 4-1 MHz sector transducer or a 9-4 MHz linear transducer depending on the patient's body habitus. Tissue harmonic imaging was used in particular in obese patients, who were difficult to penetrate sonographically

The presence or absence of HCC in the US was based on the report of the preoperative US examination. All nodular lesions-hyperechoic, hypoehoic, isoechoic, mixed echogenic with or without a hypoechoic halo-were interpreted as potential HCCs. The size of the lesion was measured by an electronic caliper and recorded at the time of the US examination.

Explanted livers were serially sectioned in the transverse plane at 10mm intervals. All hepatocellular carcinomas in the hepatectomy specimens were recorded in terms of number and size, except in 13 patients with multiple lesions. Other incidentally detected masses were also described.

We could not make a one by one correlation of the focal lesions reported in US imaging and histopathologic evaluation, since many patients had multiple lesions and the segment localization of the lesion was not always recorded. Patients with solid focal lesions in the US examination and HCC in histopathologic examination were regarded as true positives. Of the 58 patients, with solid lesions in the US examination and HCC in the histopathologic evaluation, 31 had 1-3 lesions, 14 patients had 4-9 lesions, and 6 patients had more than 10 lesions. Seven patients had multiple lesions, but the number of lesions was not recorded.

The patient detection sensitivity of US was calculated. Lesion detection sensitivity could not be calculated. The patient detectability of HCC was analyzed in terms of the size of the largest tumor in the patient and the liver weight.

Results

HCC was detected in the explanted liver in 88 (17,8%) patients. HCC was unifocal in 28 (32%) patients and multifocal in 60 (68%) patients. More than 5 HCC lesions were detected in 24 (27%) patients. The hepatomas ranged in size from 0.1 to 11cm. The etiology of the cirrhosis in patients with HCC was HBV in 66 patients, HCV in 6, metabolic disease in 4, alcohol in 2 and hemosiderosis in 1 patient. It could not be determined in retrospective review of reports in 9 patients. In 58 patients with HCC detected in the histopathologic examination, one or more solid focal lesions were reported in the pretransplant US examination. No focal lesions were detected in the remaining 30 (34%) patients. In 16 patients, in whom a focal lesion was reported in pretransplant US examination, no HCC was detected in histopathologic examination. A macronodule was reported in 4 patients, a dysplastic nodule in 2, focal nodular hyperplasia like nodule in 1, and no focal lesions in 9 of these patients.

The patient detection sensitivity of US for HCC was 66%, specificity was 96%, positive predictive value was 78% and negative predictive value was 93%.

None of the 11 patients with a largest tumor smaller than 1cm in diameter could be detected in the pretransplant US evaluation. All of the 9 patients with hepatomas

larger than 5cm were detected. The patient detectability of HCC in terms of the size of the largest tumor in the patient is given in (Table-1).

Table 1. The patient detectability of HCC in terms of the size of the largest tumor in the patient.

Tumor size$_a$ (mm)	<1cm	1.1-2cm	2.1-3cm	3.1-5cm	>5cm
US+	0	17	17	14	9
US-	11	6	7	5	0
Patient detection sensitivity	0 (%0)	17/23 (%74)	17/24 (%71)	14/19 (%74)	9/9 (%100)

$_a$ Size of the largest tumor in the patient.

The 88 patients with HCCs were grouped as US (-) and US (+) and these two groups were analyzed in terms of patient age, size of the largest tumor in the patient, liver weight and the time interval between the US examination and transplantation with student's t test. There was no statistically significant difference as regards the patient age, liver weight and the time interval between the US examination and transplantation between the two groups. The only statistically significant difference was the tumor size (Table-2).

Table-2. Comparison of US(-) and US(+) groups in terms of mean patient age, liver weight, time interval between the US examination and operation and tumor size.

	US (-)	**US (+)**	***P***
Mean patient age	48.69	49.93	0.68
Liver weight (gr)	1018.79±305.93	1093.40 ± 337.58	0.32
Time interval$_a$ (days)	33.17 ± 36.98	34.09 ± 37.81	0.92
Tumor size$_b$ (mm)	20.17 ± 13.27	32.61 ± 18.02	0.0015

$_a$Time interval between the US examination and transplantation.
$_b$Size of the largest tumor in the patient

Advanced cirrhosis may cause the liver to shrink and affect sonographic detectability of HCC. Explant liver weight, instead of volume was measured in our study group. We propose that liver weight can also represent the degree of shrinkage of the liver. In order to analyze the effect of liver weight on patient detectability of HCC, the livers were categorized in two groups: Liver weight<800gr, liver weight≥800gr. Pediatric patients were excluded. HCC was detected in pretransplant sonography of 6 of 12 adult patients (sensitivity 50%) with a liver<800gr and 50 of 72 adult patients (sensitivity %69) with a liver≥800gr. According to the chi-square test, the patient detectability of HCC was not significantly influenced by liver weight (P = 0.20).

Discussion

Cirrhotic patients constitute a high risk group for developing HCC. The American association for the study of the liver diseases and the European association for the study of the liver recommend surveillance of patients with cirrhosis and carriers of chronic viral hepatitis. Abdominal US every 6 to 12 months is the most commonly used method for screening (17-19). A shorter interval of 3 to 6 months may be required in patients with a high risk of developing HCC (20,21). Sonographic detection of HCC nodules in a cirrhotic liver is not always straightforward, because of coarse parenchymal echo texture secondary to fibrosis, fatty infiltration, necrosis and regenerative nodules. In addition, the liver is shrunken and high in the subdiaphragmatic region and the sonic window is usually limited. The reported sensitivity of US for HCC varies from 33% to 96% (22-29). This wide variability is secondary to the patient population selected, the experience of the examiner, the technical factors and the method used for correlation of the imaging findings. It is falsely increased in studies in which surgical specimens or percutaneous biopsies are used for correlation, because satellite nodules distant from the tumor go undetected. The results of several reports investigating the sensitivity of US for detecting HCC, on the basis of explanted liver for transplantation are given in (Table-3). Shapiro et al. have reported a patient detection sensitivity of 67%. Lesion detection sensitivity is lower (51%) due to the undetected small satellite tumors, identified at histopathologic examination only (30). In this study we evaluated the sensitivity of US for HCC in patients with advanced cirrhosis on the basis of explanted livers and found a patient detection sensitivity of 66%.

Table-3. Result of several studies investigating the sensitivity of US for detecting HCC, on the basis of explanted liver for transplantation.

	Patient detection sensitivity (%)
Bennett et al. (31)	29.6
Shapiro et al. (30)	67
Kim et al. (29)	38
Dodd et al. (28)	50
Maciel et al. (32)	72
Miller et al. (23)	81

The most important factor affecting the sensitivity of US is the size of the hepatocellular carcinoma. The sensitivity is lower in patients with end stage cirrhosis and small tumors. Bennett et al. have reported an overall sensitivity of 20.5%; 75% (3 of 4) in cases with tumors being>5cm; 50% (1 of 2) between 3-5cm; 20% (1 of 5) between 2-3cm; 14% (3 of 22) between 1-2cm; and 0% (0 of 8) in cases with tumors being smaller than 1cm (31). Maciel et al. have reported a patient detection sensitivity of 72% and a lesion detection sensitivity of 12.1% for tumors being smaller than 1cm, 37% for tumors being 1-3cm and 100% for tumors being larger than 3cm (32). We could not detect tumors smaller than 1cm in any of the 11 patients. On the other hand, all of the 9 patients with tumors larger than 5cm were detected in pretransplant US. We found a patient detection sensitivity of 72.7% in cases with tumors being 1.1 to 5cm. We analyzed the sonography negative and positive groups in terms of tumor size with the student's t test and found a statistically significant difference (p = 0.0015). Another factor affecting sensitivity is the time interval between the US examination and transplantation. Maciel et al. have reported a higher sensitivity in patients assessed less than 6 months before transplantation (32). Patients who were examined less than 150 days before transplantation were included in our study. There was no statistically significant difference, in terms of the time interval between the US examination and transplantation, between the ultrasonography negative and positive groups (P = 0.92)

Liu et al. (33) investigated the effect of decreased liver volume on the sensitivity of US. They concluded that sensitivity did not depend on liver volume. Liver weight, instead of liver volume was recorded in our study. We hypothesized that the liver weight may represent the degree of liver injury and shrinkage. Patient detection sensitivity was 50% in patients with a liver<800gr and %69 in those with a liver≥800gr and the difference was not statistically significant (P = 0.20).

Our study is a retrospective one and has some important limitations. First of all, one by one correlation of the sonographically reported and histopathologically detected lesions was not possible. We assumed that solid lesions reported on sonographic examination corresponded to HCCs on histopathologic evaluation. It is possible that some of these lesions represented solid lesions other than HCC or did not have a corresponding lesion on pathologic examination. Our assumption might have resulted in a falsely increased sensitivity and specificity.

Another limitation resulting from the retrospective nature of the study was that there was a time interval up to 150 days between the US examination and the histopathologic evaluation. In similar studies in the literature, patients with up to 300 days between the two examinations were included in the study (26). This long time interval might have resulted in falsely decreased sensitivity.

Since the study was conducted over the course of 10 years and US examinations were performed with three different scanners, specification of type of equipment used and standardization of the examination technique was not possible. Our retrospective review reflects the accuracy in our standard clinical practice.

Our results may not represent the accuracy of sonography in the general cirrhotic population, because only patients with advanced cirrhosis awaiting liver transplantation were included in our study.

Sonographic contrast agents would probably increase sensitivity and specificity, but could not be used in this study, as they are not yet available in our country.

In conclusion, US without contrast agents is not sensitive enough for HCC detection in liver transplant candidates. However, this does not apply to all cirrhotic patients in whom US is the recommended imaging modality for surveillance. The sensitivity mostly depends on tumor size, being 0% for tumors being less than 1cm in diameter. This low sensitivity with small tumors is valid for all imaging modalities. On the other hand, the specificity of US is high and all solid lesions discovered with US should be considered HCC until proven otherwise.

References

1. Oka H, Kurioka N, Kim K, et al. Prospective study of early detection of hepatocellular carcinoma in patients with cirrhosis. Hepatology 1990;12:680-7.
2. Ebara M, Ohto M, Sugiura N, et al. Percutaneous ethanol injection for the treatment of small hepatocellular carcinoma. Study of 95 patients. J Gastroenterol Hepatol 1990;5:616-26.
3. Redvanly RD, Chezmar JL, Strauss RM, Galloway JR, Boyer TD, Bernardino ME. Malignant hepatic tumors: safety of highdose percutaneous ethanol ablation therapy. Radiology 1993;188:283-5.
4. Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete responce and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? Hepatology 2008;47(1) 82-95.
5. N'Kontchou G, Mahamoudi A, Aout M, E, et al. Radiofrequency ablation of hepatocellular carcinoma: Longterm results and prognostic factors in 235 Western patients with cirrhosis. Hepatology 2009;50(5):1475-83.

6. Stuart K. Chemoembolization in the management of liver tumors. Oncologist 2003;8(5):425-37.
7. Trevisani F, De Notaris S, Rossi C, Bernardi M. Randomized control trials on chemoembolization for hepatocellular carcinoma. J Clin Gastroenterol 2001;32:383-9.
8. Pulvirenti A, Garbagnati F, Regalia E, et al. Experience with radiofrequency ablation of small hepatocellular carcinomas before liver transplantation. Transplant Proc 2001;33:1516-7.
9. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-9.
10. Regalia E, Coppa J, Pulvirenti A, et al. Liver transplantation for small hepatocellular carcinoma in cirrhosis: analysis of our experience. Transplant Proc 2001;33(1-2):1442-4.
11. Takayasu K, Moriyama N, Muramatsu Y, et al. The diagnosis of small hepatocellular carcinomas: efficacy of various imaging procedures in 100 patients. AJR Am J Roentgenol 1990;155:49-54.
12. Sherman M, Peltekian KM, Lee C. Screening for hepatocellular carcinoma in chronic carriers of hepatitis B virus: incidence and prevalence of hepatocellular carcinoma in a North American urban population. Hepatology 1995;22:432-8.
13. Chalasani N, Horlander JC Sr, Said A, et al. Screening for hepatocellular carcinoma in patients with advanced cirrhosis. Am J Gastroenterol 1999;94:2988-93.
14. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394-1403.
15. Gambarin-Gelwan M, Wolf DC, Shapiro R, Schwartz ME, Min AD. Sensitivity of commonly available screening tests in detecting hepatocellular carcinoma in cirrhotic patients undergoing liver transplantation. Am J Gastroenterol 2000;95:1535-8.
16. Teefey SA, Hildeboldt CC, Dehdashti F, et al. Detection of primary hepatic malignancy in liver transplant candidates: prospective comparison of CT, MR imaging, US, and PET. Radiology 2003;226:533-42.
17. Solmi L, Primerano AM, Gandolfi L. Ultrasound follow up of patients at risk for hepatocelular carcinoma:results of a pospective study on 360 cases. Am J Gastroenterol 1996;91(6):1189-94.
18. Sangiovanni A, Del Ninno E, Fasani P, et al. Increase survival of cirrhotic patients with a hepatocelular carcinoma detected during surveillance. Gastroenterology 2004;126(4):1005-14.
19. Trevisani F, Santi V, Gramenzi A, et al. Surveillance for early diagnosis of hepatocellular carcinoma: is it effective in intermediate/advanced cirrhosis? Am J Gastroenterol 2007;102(11):2448-57.
20. Zoli M, Magalotti D, Bianchi G, et al. Efficacy of a surveillance program for early detection of hepatocellular carcinoma. Cancer 1996;78:977-85.
21. Fasani P, Sangiovanni A, De Fazio C, et al. High prevalence of multinodular hepatocellular carcinoma in patients with cirrhosis attributable to multiple risk factors. Hepatology 1999;29:1704-7.
22. Cottone M, Turri M, Caltagirone M, et al. Screening for hepatocellular carcinoma in patients with Child's A cirrhosis: an 8-year prospective study by ultrasound and alpha-fetoprotein. J Hepatol 1994;21:1029-34.
23. Miller WJ, Federle MP, Campbell WL. Diagnosis and staging of hepatocellular carcinoma: comparison of CT and sonography in 36 liver transplantation patients. AJR 1991;157:303-6.
24. Rizzi PM, Kane PA, Ryder SD, et al. Accuracy of radiology in detection of hepatocellular carcinoma before liver transplantation. Gastroenterology 1994;107:1425 -9.
25. Tanaka S, Kitamura T, Nakanishi K, et al. Effectiveness of periodic checkup by ultrasonography for the early diagnosis of hepatocellular carcinoma. Cancer 1990;66:2210-4.
26. Larcos G, Sorokopud H, Berry G, Farrell GC. Sonographic screening for hepatocellular carcinoma in patients with chronic hepatitis or cirrhosis: an evaluation. AJR 1998;171:433-5.
27. Rode A, Bancel B, Douek P, et al. Small nodule detection in cirrhotic livers: evaluation with US, spiral CT, and MRI and correlation with pathologic examination of explanted liver. J Comput Assist Tomogr 2001;25:327-36.
28. Dodd GD III, Miller WJ, Baron RL, Skolnick ML, Campbell WL. Detection of malignant tumors in end-stage cirrhotic livers: efficacy of sonography as a screening technique. AJR 1992;159:727-33.
29. Kim CK, Lim JH, Lee WJ. Detection of hepatocellular carcinomas and dysplastic nodules in cirrhotic liver: accuracy of Ultrasonography in transplant patients. J Ultrasound Med 2001;20:90-104.
30. Shapiro RS, Katz R, Mendelson DS, Halton KP, Schwartz ME, Miller CM. Detection of hepatocellular carcinoma in cirrhotic patients: sensitivity of CT and Ultrasonography. J Ultrasound Med 1996;15:497-502.
31. Bennett GL, Krinsky GA, Abitbol RJ, Kim SY, Theise ND, Teperman LW. Sonographic detection of hepatocellular carcinoma and dysplastic nodules in cirrhosis: Correlation of pretransplantation sonography and liver explant pathology in 200 patients. AJR 2002;179:75-80.
32. Maciel AC, Cerski CT, Moreira RK, Resende VL, Zanotelli ML, Matiotti SB. Hepatocellular carcinoma in patients undergoing orthotopic liver transplantation: Radiological findings with anatomopathological correlation in Brazil. Arq Gastroenterol 2006;43(1):24-9.
33. Liu WC, Lim JH, Park CK, et al. Poor sensitivity of sonography in detection of hepatocellular carcinoma in advanced liver cirrhosis: accuracy of pretransplantation sonography in 118 patients. Eur Radiol 2003;13(7):1693-8.