

Efficiency of Preoperative 64-Channel Multidetector Computed Tomography in Detection of Hepatocellular Carcinoma in Patients Undergoing Liver Transplantation due to Liver Cirrhosis: A Comparison of Radiological and Pathological Findings

Karaciğer Sirozu Nedeniyle Karaciğer Nakli Yapılan Hastalarda Hepatosellüler Karsinomun Saptanmasında Ameliyat Öncesi 64 Kanallı Çok Dedektörlü Bilgisayarlı Tomografinin Etkinliği: Radyolojik ve Patolojik Bulguların Karşılaştırılması

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Abstract

Objective: The aim of this study is to demonstrate the efficiency of preoperative 64-channel multidetector computed tomography in detection in detecting hepatocellular carcinoma (HCC) in patients who underwent transplantation due to cirrhosis.

Methods: The study was designed retrospectively, and data were obtained by reviewing patient records at the organ transplant clinic. A total of 37 patients who met the specified criteria were included in the study.

Results: In the study, 9 (24.3%) of the 37 included patients were female. There was no significant difference between the two observers. The correlation between both observers and pathology regarding the presence of lesions showed a strong correlation for both Observer 1 and Observer 2, with r-values of 0.799 and 0.510, respectively. The correlation between Observer 2 and pathology was moderate, with an r-value of 0.441. For Observer 1, the sensitivity of CT was 100% for lesions larger than 2 cm and 64.2% for lesions smaller than 2 cm. For Observer 2, the sensitivity was 100% for lesions larger than 2 cm and 50% for lesions smaller than 2 cm.

Conclusion: Especially in our study, although the sensitivity of CT is low in lesions smaller than 2 cm (50-64%), it is quite successful in lesions larger than 2 cm (100%). However, due to the high spatial and temporal resolution of contrast-enhanced CT, a high false-positive rate should be considered, and patients should not be unnecessarily removed from the transplantation list.

Keywords: Cirrhosis, hepatocellular carcinoma, liver transplantation



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Öz

Amaç: Bu çalışmanın amacı siroz nedeniyle transplantasyon yapılan hastalarda preoperatif 64 kanallı multidetektör bilgisayarlı tomografinin hepatoselüler karsinomu (HCC) saptamadaki etkinliğini göstermektir.

Yöntem: Çalışma retrospektif olarak tasarlandı ve veriler organ nakli kliniğindeki hasta kayıtları incelenerek elde edildi. Belirlenen kriterleri karşılayan toplam 37 hasta çalışmaya dahil edildi.

Bulgular: Çalışmaya dahil edilen 37 hastanın 9'u (%24,3) kadındı. İki gözlemci arasında anlamlı bir fark yoktu. Her iki gözlemci ve patoloji arasında lezyonların varlığına ilişkin korelasyon, sırasıyla 0,799 ve 0,510 r-değerleri ile hem Gözlemci 1 hem de Gözlemci 2 için güçlü bir korelasyon gösterdi. Gözlemci 2 ile patoloji arasındaki korelasyon 0,441 r-değeri ile orta düzeydeydi. Gözlemci 1 için bilgisayarlı tomografinin (BT) duyarlılığı 2 cm'den büyük lezyonlar için %100 ve 2 cm'den küçük lezyonlar için %64,2 idi. Gözlemci 2 için duyarlılık 2 cm'den büyük lezyonlar için %100 ve 2 cm'den küçük lezyonlar için %50 idi.

Sonuç: Çalışmamızda özellikle BT'nin duyarlılığı 2 cm'den küçük lezyonlarda düşük olmasına rağmen (%50-64), 2 cm'den büyük lezyonlarda oldukça başarılıdır (%100). Ancak kontrastlı BT'nin yüksek uzaysal ve zamansal çözünürlüğü nedeniyle yüksek yanlış pozitiflik oranı göz önünde bulundurulmalı ve hastalar gereksiz yere transplantasyon listesinden çıkarılmamalıdır.

Anahtar Kelimeler: Siroz, hepatoselüler karsinom, karaciğer transplantasyonu

Introduction

About 80–90% of primary liver cancers are hepatocellular carcinoma (HCC), accounting for approximately 5% of all malignant cancers. HCC ranks as the fourth leading cause of cancer-related deaths. More than 90% of these patients also have liver cirrhosis⁽¹⁾. In our country, the incidence in 2008 was 2.5 per 100,000, with a mortality rate of 2.3 per 100,000⁽²⁾. HCC can be treated with surgical, percutaneous, and transarterial interventions; however, curative treatment options are resection or transplantation. Unfortunately, curative treatment can be applied to less than 20% of patients due to reasons such as tumor size, presence of metastatic disease, and limited liver reserve^(3,4).

HCC diagnosis, according to the European Association for the Study of Liver (EASL) guidelines, can be classified into two categories: Pathological or non-invasive. The role of radiology is mainly in the non-invasive diagnostic field. According to the EASL guidelines, non-invasive diagnosis can only be performed in cirrhotic patients using 4-phase multidetector computed tomography (MDCT) or dynamic magnetic resonance imaging (MRI)⁽⁵⁾. Typical HCC findings for diagnosis include hypervascularity in the arterial phase and washout of contrast material in the portal or late phase. The diagnostic value of contrast-enhanced ultrasound and angiography remains controversial, while positron emission tomography-computed tomography (PET-CT) is considered unhelpful⁽¹⁻⁵⁾. Most of the studies comparing CT and MRI for HCC diagnosis have not shown statistically significant differences, and MDCT and MRI have been reported to exhibit similar diagnostic performance⁽⁶⁻⁹⁾. However, there are publications suggesting that MRI may be superior, especially for detecting small lesions⁽⁶⁾. Baek et al.⁽⁶⁾ reported

that MDCT and MRI had similar diagnostic power but MRI was more successful in detecting lesions smaller than 1 cm. On the other hand, Pitton et al.⁽⁷⁾ stated that dynamic MRI was superior to MDCT in detecting HCC, and Hwang et al.⁽⁸⁾ claimed that MRI was more effective than MDCT in detecting lesions smaller than 2 cm in their study. The reported sensitivity for HCC diagnosis with CT ranged widely between 44% and 93% in the studies⁽⁹⁾.

The aim of this study is to demonstrate the efficiency of preoperative 64-channel MDCT in detecting HCC in patients who underwent transplantation due to cirrhosis.

Materials and Methods

This study was conducted at Dokuz Eylül University Faculty of Medicine Organ Transplantation Clinic between April 2008 and June 2011. The study included adult patients (18 years and older) who had undergone liver transplantation and had undergone dynamic MDCT scanning before transplantation. The study was designed retrospectively, and data were obtained by reviewing patient records at the organ transplant clinic. A total of 37 patients who met the specified criteria were included in the study. Patients who did not meet the criteria or had missing information were excluded from the study.

Ethics committee approval was obtained from the Local Ethics Committee (Dokuz Eylül University; date: 04.10.2012, number: 2012/32-05).

CT Procedure

All patients underwent contrast-enhanced biphasic or triphasic 64-channel MDCT imaging of the liver using a Brilliance CT scanner (Philips Medical Systems) before

operation at the Department of Radiology, Dokuz Eylül University Faculty of Medicine. An 18/20 G angiocath was placed in the right or left antecubital vein for intravenous contrast administration. The CT examination covered the region from the superior diaphragm to the superior iliac crest. A "bolus tracking" technique was employed for contrast-enhanced CT imaging. A trigger was set at the level of the diaphragm, placed in the aorta, and adjusted to initiate the scan when the attenuation reached 150 HU. A total of 120 mL of non-ionic iodinated contrast material at 350 mgI/mL was used for intravenous contrast administration. The injection rate was 4 mL/s, and the scan began when the contrast attenuation in the aorta reached 150 HU. The CT scan was performed with the following parameters: 120 kV, gantry rotation time of 0.5 seconds, and a parameter of 250 mAs. The arterial phase images were acquired with an 8-second delay after reaching the 150 HU attenuation level in the aorta. For the portal phase, a delay of 45 seconds was used, and for the late phase, a delay of 180 seconds was applied. The pitch factor ranged from 0.89 to 1.1, and the detector collimation was 64x0.625.

Analysis of the Images

The MDCT images were evaluated independently by two different radiologists, one being an experienced abdominal radiologist, without knowledge of the patient records or information. During the assessment, the radiologists were aware that the patients had undergone liver transplantation surgery, but they had no access to any clinical information, AFP levels, or pathological data related to the operation. The CT images were reviewed on the picture archiving and communication system, and all lesions with different densities within the liver parenchyma were assessed for the possibility of HCC. The size, number, and location of detectable lesions were noted for each case. The longest dimension of the lesions seen in any plane was recorded. In the literature, a four-point confidence level has been determined for the detection of HCC⁽⁶⁾. However, in this study, a separate category (Category 3) was specified for uncertain lesions. The radiologists classified the lesions in a five-point scale based on their confidence level regarding the presence of HCC; Category 1: Definitely not HCC, Category 2: Probably not HCC, Category 3: Uncertain, Category 4: Probably HCC, Category 5: Definitely HCC. Lesions falling into Category 4 demonstrated contrast enhancement in the arterial phase and were isodense with the parenchyma in the portal and late phases, whereas those in Category 5 showed contrast enhancement in the arterial phase and washout of contrast

material in the portal or late phase, appearing hypodense compared to the parenchyma. Categories 4 and 5 were considered significant for HCC.

The EASL diagnostic criteria were used for HCC diagnosis⁽⁵⁾. In the diagnosis of HCC, contrast characterization and morphological features of the lesion are important. The typical contrast enhancement pattern includes hyperdensity in the arterial phase for nodular lesions, washout of contrast material in the portal and late phases, or hyperdensity in the arterial phase, isodensity in the portal phase, and hypodensity due to washout in the late phase. Morphologically, features such as mosaic pattern, peritumoral capsule formation, and fat infiltration are observed in HCC. The mosaic pattern refers to the presence of different contrast-enhanced areas, nodules, and septa with varying densities within the tumor. The peritumoral capsule is a thin, well-defined tissue surrounding the tumor. Fat infiltration is characterized by the presence of low-density gross fat tissue within the tumor.

Histopathological Evaluation

The pathology evaluation is performed without knowledge of the CT findings. Native liver is sectioned in the coronal plane with a thickness of 7-10 mm. The transplanted liver specimens are fixed in formalin immediately after surgery and examined. The location, size, and number of visually identifiable nodules are recorded, and samples are taken for microscopic examination. The microscopic examination is used to assess the presence of HCC findings.

Measurements

The nodular lesions observed on CT were compared with pathology reports in terms of the number, location, and size of the lesions on a lesion-by-lesion basis. Lesions seen on CT in the liver were recorded, and those lesions whose location and size were confirmed by pathology data were considered true positives. Lesions that were detected in pathological evaluation but missed on CT were considered false negatives, while lesions that were classified as HCC on CT but determined to be benign in pathological evaluation were considered false positives. Sensitivity was calculated as the ratio of the number of nodules defined as HCC on CT to the number of HCC nodules confirmed by pathology. Specificity was calculated as the ratio of the number of CT-negative cases for HCC to the number of cases negative for HCC according to pathology. The false positive rate represents the ratio of false positive cases on CT to the total number of true and false positive cases. Positive predictive value is the

ratio of the number of true HCC nodules detected in imaging to the total number of lesions detected in imaging. Negative predictive value is the ratio of true negatives to the sum of true and false negative lesions.

Statistical Analysis

In the evaluation of the findings in the study, statistical analyses were performed using the SPSS (Statistical Package for Social Sciences) for Windows 15 program. Chi-square test, McNemar’s test for paired proportions, Fisher’s Exact test, and correlation analysis were used for statistical analysis. A p-value less than 0.05 was considered statistically significant for all tests. Descriptive statistics, such as counts and percentages, were provided for categorical variables.

Results

In the study, 9 (24.3%) of the 37 included patients were female, and 28 (75.7%) were male. The ages of the patients ranged from 23 to 65 years, with a mean age of 50.02. Among the 37 patients, 20 (54.1%) had undergone biphasic CT examination, while 17 cases (45.9%) had undergone triphasic CT examination. The time interval between the preoperative CT examination and the surgery ranged from 0 to 345 days, with a mean of 64.1 days. Out of the 37 cases, 31 had preoperative AFP values, which ranged from 1.12 to 321, with a mean of 23.9.

When assessing the agreement between Observer 1 and Observer 2, the McNemar’s test yielded a p-value of 0.687, indicating no significant difference between the two observers. The Kappa value was 0.797, representing “excellent correlation”. Regarding the pathological data, among the

37 patients, 20 (54.1%) had no lesions consistent with HCC, while 17 (45.9%) had HCC. The size of these lesions ranged from 10 to 70 mm, with a mean of 23.5 mm. According to the evaluations made by the observers based on CT, Observer 1 identified 16 lesions consistent with HCC in 16 out of the 37 patients. The size of these lesions ranged from 6 to 55 mm, with a mean of 21.7 mm. On the other hand, Observer 2 identified 35 lesions consistent with HCC in 16 out of the 37 patients, with lesion sizes ranging from 8 to 65 mm and a mean of 22.8 mm (Table 1).

When the pathological results were considered as the gold standard, the sensitivity of CT according to Observer 1 was 88% (15/17), with a specificity of 95% (19/20). The positive predictive value was 93% (15/16), and the negative predictive value was 90% (19/21). The overall accuracy rate of CT at the patient level was 91.8% (34/37), with a diagnostic odds ratio of 147.1. For Observer 2, the sensitivity of CT was 82.3% (4/17), with a specificity of 90% (18/20). The overall accuracy rate of CT at the patient level was 86.4% (32/37), with a diagnostic odds ratio of 41.2 (Table 2).

The correlation between both observers and pathology regarding the presence of lesions showed a strong correlation for both Observer 1 and Observer 2, with r-values of 0.799 and 0.510, respectively. The correlation between Observer 2 and pathology was moderate, with an r-value of 0.441 (Table 3).

The ROC curve for the detectability of HCC by CT revealed an area under the curve of 0.749 for Observer 1 and 0.718 for Observer 2. Both values fell within the range of 0.70 to 0.80, indicating moderate success of the method (Table 4, Figure 1).

Table 1. HCC distribution and lesion sizes in patients according to pathology and observers

Parametre	Pathology	Observer 1	Observer 2
HCC (n, %)			
Yes	17 (45.9%)	16 (43.2%)	16 (43.2%)
No	20 (54.1%)	21 (56.8%)	21 (56.8%)
Lesion size [mm, (avarage, min, max)]	23.5 (10-70)	21.7 (6-55)	23.43 (8-65)

HCC: Hepatocellular carcinoma

Table 2. Comparison of observers with gold standard

	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %	Diagnostic OR
Observer 1	88 (62-97)	95 (73-99)	93 (67-99)	90 (68-98)	91	147.1
Observer 2	82 (55-95)	90 (66-98)	87 (60-97)	85 (62-96)	86	41.2

PPV: Positive predictive value, NPV: Negative predictive value, OR: Odds ratio

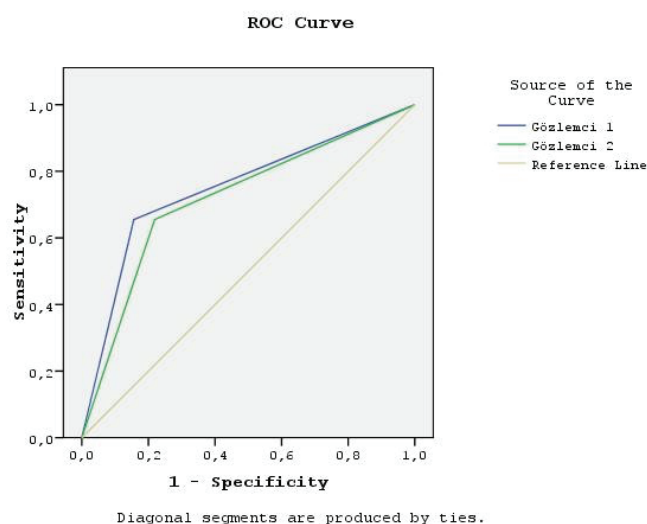
Table 3. Correlation analysis for the presence of lesions

	Observer 1	Observer 2	Pathology
Observer 1 (p-value)	-	0.799 0.000	0.510 0.000
Observer 2 (p-value)	0.799 0.000	-	0.441 0.000
Pathology (p-value)	0.510 0.000	0.441 0.000	-

Table 4. Evaluation of HCC detectability with CT

	Area	Std. mistake	95% confidence interval	
			Lower value	Top value
Observer 1	0.749	0.065	0.622	0.877
Observer 2	0.718	0.067	0.586	0.850

HCC: Hepatocellular carcinoma, CT: Computed tomography

**Figure 1.** Evaluation of HCC detectability with CT

HCC: Hepatocellular carcinoma, CT: Computed tomography

Considering lesion sizes, evaluations were performed for lesions smaller or larger than 2 cm. For Observer 1, the sensitivity of CT was 100% for lesions larger than 2 cm and 64.2% for lesions smaller than 2 cm. For Observer 2, the sensitivity was 100% for lesions larger than 2 cm and 50% for lesions smaller than 2 cm.

Discussion

Cirrhosis is defined as a chronic liver disease characterized by fibrosis and regeneration. Curative treatment for this patient group is liver transplantation. In patients with cirrhosis who undergo transplantation, the prevalence

of HCC not detected during the preoperative period can reach up to 8%⁽¹⁰⁾. This high rate is observed in advanced cirrhosis patients requiring transplantation, and it is not considered applicable to all cirrhosis patients. In fact, the true prevalence of HCC in cirrhosis patients is unpredictable due to difficulties in imaging small HCC lesions.

Although there are different alternatives in radiological evaluation, some studies have reported that contrast-enhanced CT is the most valuable method for detecting malignancy in cirrhotic patients^(11,12). Since the liver morphology changes in cirrhosis, the normal radiological appearance of the liver also changes significantly on CT. On the other hand, non-tumoral small arteriovenous shunts may create a false nodule appearance, making evaluation challenging⁽¹³⁾. While arterial phase images in CT are more useful for detecting hypervascular tumors like HCC, portal venous and delayed phases are more useful for evaluating less vascular tumors with good differentiation or early HCC.

In previous studies, the sensitivity of CT ranged widely from 50% to 99% at the patient level, while specificity ranged from 75% to 96%. Some studies suggested that the reported low sensitivity values may be due to early arterial phase imaging and thicker (5-10 mm) sections. Francis et al.⁽¹⁴⁾ indicated that the best lesion distinction was achieved in delayed arterial phase images (at 30-35 sec delay).

Lopez Hänninen et al.⁽¹⁵⁾ reported the sensitivity of biphasic helical CT in diagnosing HCC as 76% in patients who underwent liver transplantation. In their study, sensitivity values for HCC nodules based on lesion size were 20% for lesions of 0.5-1.0 cm, 82% for 1.1-2.0 cm, 86% for 2.1-3.0

cm, and 100% for lesions larger than 3 cm. Lim et al.⁽¹⁶⁾ reported the patient-based sensitivity of helical CT as 80% and the lesion-based sensitivity as 71%. In their study, 60% of HCCs smaller than 2 cm and 82% of lesions larger than 2 cm were detected. Noguchi et al.^(17,18) reported the overall sensitivity of helical CT in diagnosing HCC as 66%, with 98% for lesions larger than 2 cm and 50.3% for lesions smaller than 2 cm⁽¹⁹⁾. In another series, Zacherl et al.⁽²⁰⁾ reported a sensitivity of 75% and a positive predictive value of 72% for pre-transplantation patients who underwent biphasic helical CT. In this series, a high false-positive rate (27.7%, 15/54) was found, but the authors did not specify the reason for this^(19,20).

In our study, CT data was compared with pathological data, and evaluations were made at the patient and lesion levels by two observers. Looking at the patient-based data, the sensitivity of CT was found to be 88-82%, specificity 95-90%, positive predictive value 93-87%, and negative predictive value 90-85%. Studies on this subject in the literature have reported sensitivity values for lesion-based HCC detection ranging from 37% to 82% with helical CT. In studies using contrast-enhanced CT, lesion-based sensitivity has been reported between 64% and 89%^(10,21-30).

Brancatelli et al.⁽³¹⁾ and Valls et al.⁽⁹⁾ reported false-positive rates of 8% and 12%, respectively. In our study, this rate was higher (27-28%). A possible explanation for this could be that the other two studies used single-detector helical CT, while we used contrast-enhanced CT. Indeed, Addley et al.⁽³²⁾ reported false-positive rates of 30-50% with contrast-enhanced CT. Nadarevic et al.⁽³³⁾ showed that 22.5% of people with HCC would be missed and 8.7% of people without HCC would have a positive diagnosis. Seo et al.⁽³⁴⁾ reported that overall diagnostic accuracy with imaging ranged from 81.5% to 83.3%.

Study Limitations

Limitations in the use of imaging modalities may be that in the setting of cirrhosis, fibrosis surrounding regenerative or dysplastic nodules may mimic the appearance of a "strengthening capsule" and may lead to misinterpretation of benign lesions as HCC.⁽³⁵⁾ The high spatial and temporal resolution of contrast-enhanced CT leads to the identification of more lesions, which in turn increases the false-positive rate. Although our study found sensitivity and specificity within the previously reported range, the specificity was lower than sensitivity due to false-positive lesions.

Addley et al.⁽³²⁾ conducted a study on the role of contrast-enhanced CT in the diagnosis of HCC, including 39 patients, and reported the sensitivity of contrast-enhanced CT to be 65-75% for all lesions and 48-57% for lesions smaller than 2 cm. In this study, as in our study, a diagnosis scale ranging from one to five was used. With evaluation based on confidence levels, as the confidence level increased towards five (i.e., lesions more likely to be HCC), the sensitivity in larger lesions was 26-70%, while it was 4-26% in lesions smaller than 2 cm.

Our study demonstrates that contrast-enhanced CT has an overall acceptable sensitivity for diagnosing HCC and can be used for imaging patients who will undergo transplantation during the preoperative period. Especially, although the sensitivity of CT is low in lesions smaller than 2 cm (50-64%), it is quite successful in lesions larger than 2 cm (100%). Contrast-enhanced CT achieves a general sensitivity of 78-84% and a positive predictive value of 73-71% for the imaging of HCC before liver transplantation. However, due to the high spatial and temporal resolution of contrast-enhanced CT, a high false-positive rate should be considered, and patients should not be unnecessarily removed from the transplantation list.

Conclusion

Our study demonstrates that contrast-enhanced CT has an overall acceptable sensitivity for diagnosing HCC and can be used for imaging patients who will undergo transplantation during the preoperative period. Especially in our study, although the sensitivity of CT is low in lesions smaller than 2 cm (50-64%), it is quite successful in lesions larger than 2 cm (100%). However, due to the high spatial and temporal resolution of contrast-enhanced CT, a high false-positive rate should be considered, and patients should not be unnecessarily removed from the transplantation list.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Local Ethics Committee (Dokuz Eylül University; date: 04.10.2012, number: 2012/32-05).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: F.G.K., F.B.O., Concept: F.B.O., Design: Ö.A., F.B.O., Data Collection or Processing: Ö.A., F.G.K., Analysis or Interpretation: F.G.K., Literature Search: Ö.A., F.G.K., Writing: Ö.A., F.G.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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