Acıbadem Univ. Sağlık Bilim. Derg. 2023; 14 (4): 587-593
https://doi.org/10.31067/acusaglik.1160673

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Radiology / Radyoloji

Can Cellular Differentiation and Microvascular Invasion in Hepatocellular Carcinoma be Predicted by Contrast-Enhanced Computed Tomography?

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Received: 11 August 2022
Accepted: 03 August 2023

ABSTRACT

Purpose: The purpose of our study was to examine the contrast-enhanced computed tomography (CECT) characteristics of hepatocellular carcinoma (HCC) in explanted liver, the association between microvascular invasion (MVI) and cellular differentiation, and to predict the severity of HCC.

Methods: CECT images of 54 surgically proven HCCs were evaluated with abdominal radiologist. Our CECT protocol was composed of precontrast, arterial, portal and delayed venous phases. The radiologist analysed the CT images for; tumor size, tumor margin, presence of intratumoral vessels; presence of capsule; intratumoral fat accumulation; and macroinvasion. The imaging features were correlated with cellular differentiation and MVI using Fisher's exact test or the χ^2 test.

Results: The results of our study indicated that there was a significant inverse correlation between the presence of capsule and MVI ($p<0,05$, $r= -0, 37$) and the grade of HCC ($p=0,001$, $r = -0,42$) while a positive correlation was observed between macroinvasion and the grade of HCC ($p=0,02$).

Conclusion: CECT-observed incomplete tumor capsule and macroinvasion accurately predict MVI and tumor grade prior to surgery and provide a more precise prognosis without a tissue sample, which will benefit in the management of cirrhosis and HCC patients.

Keywords: Hepatocellular carcinoma, liver transplantation, microvascular invasion, prognosis, tomography

Hepatoselüler Karsinomda Hücresel Diferansiyasyon ve Mikrovasküler İnvazyon Kontrastlı Bilgisayarlı Tomografi ile Öngörülebilir mi?

ÖZET

Amaç: Çalışmamızın amacı, eksplante karaciğerde hepatoselüler karsinomun (HCC) kontrastlı bilgisayarlı tomografi (CECT) özelliklerini, mikrovasküler invazyon (MVI) ve hücresel farklılaşma arasındaki ilişkiyi incelemek ve HCC'nin derecesini tahmin etmektir.

Yöntem: Cerrahi olarak kanıtlanmış 54 HCC' nin CECT görüntüleri, batın radyoloğu tarafından değerlendirildi. CECT protokolümüz kontrast öncesi, arteriyel, portal ve geç venöz fazlardan oluşuyordu. BT görüntüleri tümör boyutu, tümör sınırı, tümör içi damarların varlığı; kapsülün varlığı;nintratümöral yağ birikimi; ve makroinvazyon olarak analiz edildi. Görüntüleme özellikleri, Fisher exact test ve χ^2 testi kullanılarak hücresel farklılaşma ve MVI ile ilişkilendirildi.

Bulgular: Çalışmamızın sonuçları, kapsül varlığı ile MVI varlığı ($p<0,05$, $r= -0, 37$) ve HCC derecesi ($p=0,001$, $r = -0,42$) arasında anlamlı bir ters korelasyon olduğunu, makroinvazyon ile HCC derecesi arasında ise, pozitif korelasyon olduğunu göstermiştir ($p=0,02$).

Sonuç: CECT ile tanı alabilen makroinvazyon varlığı ve tümör kapsülü yokluğu, operasyon öncesinde MVI ve tümör derecesini doğru bir şekilde belirleyerek doku örneklemesine gerek kalmadan siroz ve HCC hastalarının tedavisinde prognozu öngörebilir.

Anahtar kelimeler: Hepatosellüler karsinom, karaciğer nakli, bilgisayarlı tomografi, mikrovasküler invazyon, prognoz

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related death worldwide and the sixth most prevalent malignancy overall (1). HCC is a rare type of cancer that can be identified by radiological imaging methods without requiring a confirmed biopsy. The current practice guidelines state that imaging modalities can diagnose HCC with high specificity and acceptable sensitivity (2).

Because the prognosis of HCC depends on the stage at which it is identified, imaging techniques are important factors in selecting the best course of treatment for patients among a variety of alternatives. The primary objective in the early phases is the cure. In this situation, liver transplantation and total or partial hepatectomy are performed. Transarterial chemoembolism (TACE) or radiofrequency ablation (RFA) or microwave ablation are suggested when surgical removal is not an option (3).

Contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) imaging criteria for HCC are early contrast uptake in the arterial phase, followed by washout in the portal venous or equilibrium phases. Dynamic computed tomography is commonly utilized in the diagnosis, staging, and monitoring of HCC (4). The development of imaging technology and intensive follow-up in high-risk populations have enabled the early detection of HCCs, which has improved prognosis. CECT has the benefit of being a quick imaging technique.

The two most important risk factors for the recurrence of HCC after surgical treatment are tumor grade and microvascular invasion. A preoperative evaluation of microvascular invasion (MVI), which could be utilized to guide therapy in patients with HCC, has received a lot of attention recently (5, 6).

Studies have revealed that MVI is a distinct histopathological prognostic feature linked to survival in patients with all stages of HCC (7). Additionally, compared to the Milan criteria, MVI has been shown to be a more accurate predictor of tumor recurrence and overall survival (8).

The aim of this study was to find accurate CT markers of MVI and tumor grade in patients undergoing living donor liver transplantation, including tumor sizes, multinodularity, macrovascular invasion, tumor margin, fat accumulation and capsule.

MATERIALS AND METHODS

Patients

Ethical approval was obtained from local ethics committee on clinical research. We analysed 220 cirrhotic patients between June 2015 and 2021 underwent liver transplantation. Exclusion criteria was tumors smaller than 1 cm, history of radiofrequence ablation, trans-arterial chemoembolization or systemic therapy before operation. A total of 220 patients; 54 patients (43 male,11 female patients; with a mean age of 58,91±7,89) could be included in the study based on the inclusion criteria. The age, gender, serum preoperative and postoperative AFP level, cause of the cirrhosis were collected from medical records. Clinical features and demographics of patients enrolled in the study are shown in Table 1.

CT Protocol

CT was performed using 100 mL of Omnipaque (Omnipaque, GE Healthcare) with multiphasic 256–section multi-detector CT (Siemens Definition Flash CT, Siemens Healthineers, Erlangen, Germany) at baseline before liver transplantation. The hepatic study protocol phases for imaging were precontrast, arterial, portal and delayed venous phases.

All images were loaded to picture and communication system (PACS, GE Healthcare). Two abdominal radiologists with 10 years experiences (AAK, BKS) qualitatively evaluated all CT images. According to Liver Imaging Reporting and Data System version 2018 (LIRADS) all lesions were reported based on imaging appearance that reflect the probability of HCC or malignancy with or without tumor in vein (9).

Image Analysis

There were totally of 54 HCCs that were detected on CT imaging and recorded by the radiologist. Blinded to pathology reports, the imaging findings of HCC such as, capsule appearance, the diameter of HCC, smooth margin or irregular margin, fat accumulation, macrovascular invasion, visualization of the internal arteries, and multifocality were evaluated for per patient during image analysis.

Figure 1 illustrates evidence of the capsule, with a surrounding hyperattenuation linear structure. Fat accumulation was depected with measuring the density of tumor on precontrast CT images. The tumors were classified as smooth or irregular according to their margins. Smooth margin includes a smooth interface between the tumor and normal liver parenchyma. Figure 2 shows the irregular-edged tumor, with infiltration into the surrounding liver parenchyma.

The HCC attenuation in each phase was characterized as nodular, heterogenous, and halo enhancement patterns in order to assess the enhancement pattern of different histological grades of HCC. Each lesion was examined for washout during the delayed phase observation.

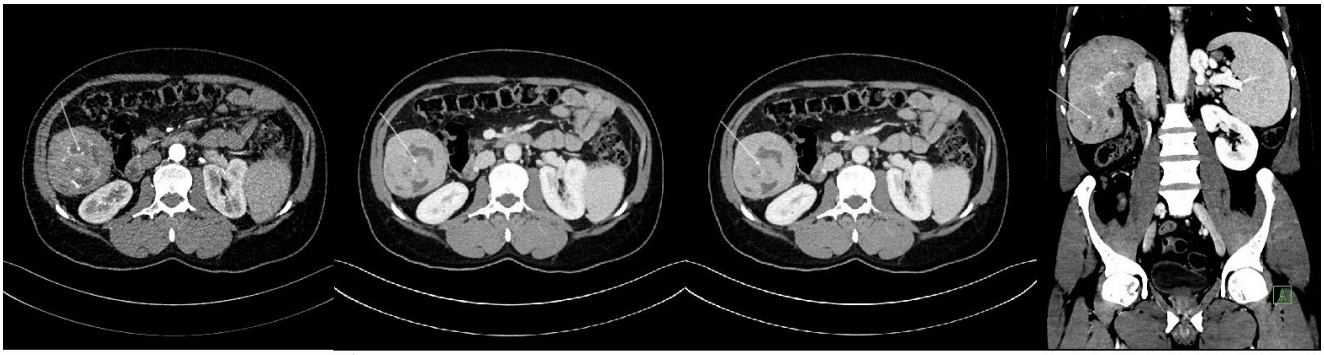

Fig. 1. *A 61-year-old man with cryptogenic cirrhosis. Axial contrast-enhanced arterial (a), portal (b), delayed (c) and coronal delayed (d) phase contrast-enhanced Computed Tomography scans show a heterogenous encapsulated mass, that is histopathology proven to be Grade 3 Hepatocellular carcinoma after liver transplantation.*

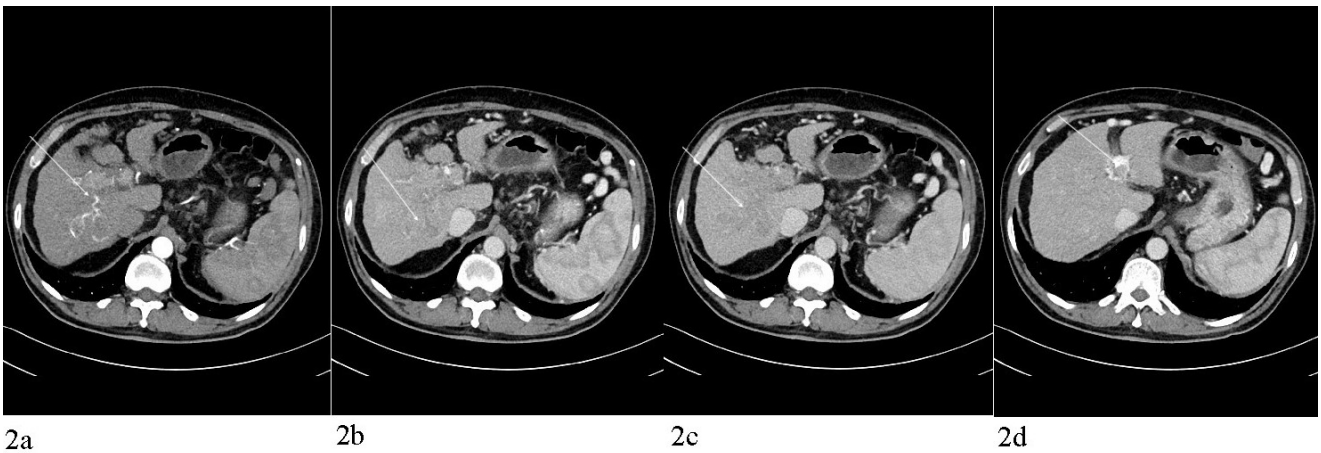

Fig. 2. *Images in a 63-year-old man with Hepatocellular carcinoma and Hepatitis B related cirrhosis. Early hepatic arterial (a) phase image shows heterogenous hypodense mass in segments VI - VII with arterial supply, relative to liver; mass enhances on portal (b) phase. In delayed venous phase it becomes hypoattenuating. Mass has irregular-edge shown to best in delayed venous phase. Malignant tumor trombus is shown in axial portal phase (d). Histologic examination showed Edmondson-Steiner Grade II tumor.*

Histopathological Assessment

A senior pathologist with 20 years experience evaluated the whole specimen and noticed the grade of HCCs according to Edmondson–Steiner (E-S) and microinvasion of the patients. E-S system also divides HCC in 4 grades based on an assessment of cellular atypia and nuclear- cytoplasm ratio (10).

According to E-S; Grade 1 and 2 lesions were included in low-Grade group; Grade 3 and 4 lesions were included in high-Grade group.

Statistical Analysis

Statistical analyses were done using SPSS v. 21 (SSPS, IBM Inc.) package programme and $p < 0.05$ was considered significant. Numerical variables were expressed as mean and standard deviation (SD) if distributed normally; median and minimum–maximum values if not. Categorical variables were given as numbers and percentages.

The Shapiro-Wilk test was used to decide whether the data (age, preoperative and postoperative AFP) were normally distributed or not. The Chi-square test and Fisher's exact test were performed to compare the grade and MVI. Student's t test was performed to compare the two means for both paired and unpaired data.

Performance of the diagnostic criteria compared to pathology was evaluated using the group of one largest HCC per patient. E-S Grade group and microvascular invasion were compared with CT features including tumor size, visualization of internal arteries, smooth or irregular margin, capsule presence, intralesional fat and macrovascular invasion using Fisher's Exact test.

RESULTS

54 patients with a pathological diagnosis of HCC were included in this study. Of these patients, 43 (79.63%) were male. The mean age of the patients was 58,91±7,89. AFP levels were 43,04±74,20 ng/ml while postoperative AFP levels were 2,64±2,53 ng/ml. All lesions were divided into E-S grade groups [Grade 1 (2 lesions); grade 2 (10 lesions); grade 3 (33 lesions) and grade 4 (9 lesions)]. 12 lesions were in low grade group and 42 lesions were in high grade group. 38 of the HCC lesions were in the right lobe of the liver and 16 of them were in the left lobe of the liver.

Demographic features and laboratory values are shown in Table 1.

Table 1. Demographic features and laboratory values of patients

Variables	Patients with surgically confirmed Hepatocellular Carcinoma (n=54)
Age (mean±SD)	58,91±7,89
Sex (M:F)	43 (79,63 %) :11 (20,37%)
Underlying cause of liver disease	
Hepatitis B	20
Hepatitis C	12
Cryptogenic	7
Hepatitis B and Hepatitis D coinfection	6
Hepatitis D	2
Non-alcoholic fatty liver disease	3
Autoimmune hepatitis	2
Wilson disease	1
Alcoholism	1
Preoperative alpha-fetoprotein (ng/ml)	43,04±74,20
Postoperative alpha-fetoprotein (ng/ml)	2,64±2,53
Edmonson- Steiner grade	
Grade 1	2
Grade 2	10
Grade 3	33
Grade 4	9

Intratumoral feeding artery was visualized in 49 HCC nodules on CECT. 28 HCCs have nodular, 15 HCCs have halo and 11 HCCs have heterogenous contrast enhancement. More than half of the HCCs (35 of 54) exhibited the characteristic CT features of HCC. 29 of 54 HCCs had smooth margin and the others have irregular margin.

Smooth or irregular margin, intralesional fat, presence of satellite lesion, multifocality, size and visualization of feeding artery on CT images were not correlated with the grade of HCC and MVI. However there was a significant inverse correlation between the tumor grade and capsule present (p=0,001) while a significant positive correlation between the tumor grade and macroinvasion (p=0,02). Capsule was absent in 72,5 % of high grade group, while the capsule was present in all of low grade group.

Macroinvasion was present 40 % of high grade group. MVI was inverse correlated with the presence of capsule according to radiology features (p<0,05). Correlation of grade and CT findings was reviewed in Table 2.

Table 2. Correlation of tumor grade and Computed Tomography Features

Computed Tomography Features	Group 1 N=12	Group 2 N=42	p
Smooth margin	8	21	0,41
Capsule	10	11	0,001
Multifocality	5	17	0,72
Size (mm)	33,10±13,69 (mm)	31,20±17,11 (mm)	0,75
Fat accumulation	2	6	0,67
Feeding artery	5	21	0,94

According to the pathology reports; the presence of microinvasion was correlated with the tumor grade (p=0,01). MVI is more common in poorly differentiated HCCs than well differentiated. MVI was founded of 64.1 % of high grade group while MVI was not founded in low grade group. Correlation of MVI and imaging features was reviewed in Table 3.

Table 3. Correlation of microinvasion and Computed Tomography features

Computed Tomography Features	Group 1*	Group 2**	p
Smooth margin	20	15	0,15
Capsule	18	2	0,01
Multifocality	16	8	0,06
Size (mm)	28,5±9,13	30,3±13,12	0,89
Fat accumulation	4	4	0,9
Feeding artery	14	14	0,9

**Group 1 Pathologically microinvasion negative*
***Group 2 Pathologically microinvasion positive*

DISCUSSION

This study revealed findings that might be used as prognostic CT characteristics of HCC. For the purpose of directing treatment plans and enhancing therapeutic results for HCC patients, a preoperative noninvasive prediction of grade and MVI may be crucial. In this work, we demonstrated a positive correlation between the tumor's macrovascular invasion and its cellular differentiation, which was inversely connected with the tumor capsule. Inverse association was also found between MVI and capsule presence. MVI and the other imaging characteristics of HCC did not correlate.

After resection or transplantation, the recurrence incidence is greater in patients with vascular invasion. According to Rodriguez et al. (11), 3 years following liver transplantation, MVI reduces overall survival and disease-free survival. Furthermore, Huang et al. (12) observed that the presence of MVI was associated with higher tumor recurrence following resection (hazard ratio (HR) = 4.07; p <0.001) and decreased overall survival following a second resection.

Consequently, the development of noninvasive imaging tools to reliably and safely determine the pathological grade of HCC and estimate the presence of MVI will increase patient survival rates. In several recent investigations, the presence of MVI in HCC has been predicted using radiological or radiomics parameters. According to these research, radiographic characteristics such the tumor margin, internal arteries, peritumoral enhancement, and hypodense halos play a significant role in the prediction of MVI. Along with our study, cellular differentiation and MVI were inversely correlated with capsule presence. Internal arteries, intralesional fat, the existence of satellite lesions, the uneven border, and tumor size were not linked to cellular differentiation and MVI.

In a study comparable to ours, Lim et al. (13) showed that there was a strict association between the grading of the HCC and the occurrence of microvascular emboli; MVI was more prevalent in moderately differentiated HCCs by E-S grading using a retrospective investigation on 368 patients.

The relationship between MVI and the tumor margin and tumor capsule in HCC has been the subject of numerous investigations, however the findings have been mixed. An irregular tumor border indicates that the tumor has infiltrated the liver parenchyma. According to Chou et al., the presence and location of MVI on the histopathology was linked with irregular tumor borders seen on multiphasic CT scans (14). We found no significant correlation between the irregular border and the histological degree of HCC and MVI in our investigation, despite the fact that this feature has been reported to be substantially associated with high MVI risk. High-Grade HCCs had smooth margins in our study.

In 10%–70% of cases, HCC may have a surrounding fibrous capsule (15). Our findings demonstrate decreased rates of microinvasion in capsulated HCCs, which is consistent with recent research (p=0.02 and p=0.01) (16).

According to Chandarana et al., the only factor that significantly correlated with MVI was tumor multifocality (17). Our study's findings, however, showed that satellite lesions did not correlate with tumor grade or MVI.

In our investigation, there was no statistically significant correlation between tumor size, internal artery identification, or tumor differentiation level. Paradis et al. (18) reported that tumor size is a significant predictive factor, which is contrary to our study's findings. On the other hand, Goh et al. researched patients who had multifocal HCC surgically removed. They claimed that the presence of MVI is a more significant predictive factor than tumor size (19). According to Lim et al. (20), this was most likely caused by its connection to MVI .

The fat content typically regresses in advanced HCC, contrary to what has been previously demonstrated in research on dysplastic nodules and early HCC (21). Patients with fat-containing HCCs may have a better clinical result than patients without fat-containing HCCs, according to research by Siripongsakun et al. (22). In contrast to these investigations, we were unable to demonstrate that the prevalence of fat alterations decreased with histological grade in our study. We believe that this may be because the etiology of HCC in our study were heterogeneous.

In this work, we have demonstrated a statistically significant superiority of capsule appearance and macroinvasion in evaluating the prognosis of HCC compared to other CT features. Radiologists should be knowledgeable about the diagnosis and staging of HCC as well as the imaging characteristics that show the MVI of the tumor. Because local therapies may be beneficial for these patients before liver transplantation. Particularly in situations when the waiting list for a liver transplant exceeds six months, RFA and TACE have been suggested as bridging therapy (23).

Our study had several limitations. Firstly, this is a retrospective study. Secondly, sample size is small. Prospective studies with more lesions should be investigated. On the other hand, prospective studies are required to assess the effectiveness of the Edmondson-Steiner grade and MVI as a marker of post-operative recurrence.

CONCLUSION

The presence of MVI, in addition to tumor grade, is a marker of aggressive biological tumor behavior that significantly changes the prognosis of the disease, particularly following potentially curative treatment. Patients with cirrhosis and HCC will benefit greatly from imaging methods and discoveries that can predict tumor and MVI grade ahead of treatment without the need for a biopsy. Numerous imaging features are highlighted in the present literature, and our investigation found that the presence of a capsule was a significant prognostic indicator of HCC. To improve HCC management and provide an assessment of the prognosis for HCC, large-scale studies are nevertheless required.

DECLARATIONS

Funding

This research did not receive any fundings from any third parties.

Conflicts of interest/Competing interests

Authors declare no conflict of interests/competing interests.

Ethics approval

This study was approved by the local ethics committee on clinical research (Date: 03/12/2020, Number: ATADEK-2020/25).

Availability of data and material

Not applicable.

Authors' contributions

All authors conceived and designed the analysis, collected the data, contributed data analysis and wrote the paper equally.

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