Diffuse-Type Hepatoma: A Grave Prognostic Marker

Rohan C. Siriwardana a  Chandika A.H. Liyanage a  Bhagya Gunetilleke a  Madunil A. Niriella b  Janaka de Silva b  Anuradha S. Dassanayake c  Subani P. Jayatunge a

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Hepatocellular carcinoma, pathology, diagnosis · Neoplasm, invasiveness · Survival rate · Neoplasm staging · Prognosis

Abstract
Background: Data on diffuse-type hepatocellular carcinoma (HCC) are rare. HCC in Sri Lanka is rising, and the majority is related to nonalcoholic fatty liver disease. This study was planned to compare nodular- and diffuse-type HCC in this cohort. Methods: CT scans of 227 patients with HCC negative for infective hepatitis were analyzed and grouped as nodular and diffuse from July 2011 to July 2014. Diffuse-type cancer was defined as a tumor without convex/distinct margin, diffusely infiltrating the hepatic parenchyma. There were 45 (20%) cases. The baseline liver functions, etiology, treatment, and the outcome were compared with nodular-type cancers. Stage III diffuse cancers were matched with 2 stage III nodular cancers looking at the T stage and background liver. Results: There was no difference in the age (63 vs. 62 years, \( p = 0.937 \)) and gender. Diffuse cancers had a low BMI (24 vs. 22, \( p = 0.009 \)), a higher alpha fetoprotein (AFP) level (\( p < 0.001 \)), a higher incidence of major vascular invasion (14 vs. 80\%, \( p < 0.001 \)), and a history of significant alcohol consumption (39 vs. 67\%, \( p = 0.001 \)). The baseline liver functions were similar in diffuse and nodular cancers. A large proportion (27 vs.77\%, \( p < 0.001 \)) of diffuse cancers were not candidates for active treatment. Overall survival was poor in the diffuse type (4.7 vs. 25 months, \( p < 0.001 \)). Diffuse-type stage III cancers had a poor survival compared to matched nodular cancers (2.5 vs. 15.8 months, \( p = 0.001 \)). Conclusion: HCC without a background of infective hepatitis were common in our cohort. These tumors are associated with high AFP levels, major vascular invasion, and a poor prognosis.

Dr. Rohan C. Siriwardana  
Department of Surgery, Faculty of Medicine, University of Kelaniya  
PO Box 6, Thalagolla Road  
Ragama GQ 11010 (Sri Lanka)  
E-Mail rohansiriwardana@yahoo.com

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Background

Macroscopic tumor appearance of hepatocellular carcinomas is useful in staging and prognostication. Tumor size and the number of tumor nodules are the 2 parameters commonly used. Okuda et al. [1, 2] described a different morphology: diffuse type cancers as tumors without a distinct boundary between the tumor and the hepatic parenchyma. This division is based on the preoperative imaging. The few published data on diffuse-type cancers highlight the difficulties in radiological diagnosis, advanced stage of tumors at the time of diagnosis, and poor prognosis [3–5]. However this morphological variety has not been widely discussed and published in the literature. Most of the published series on diffuse-type HCC are on populations with hepatitis B- or C-related HCC [6]. In Sri Lanka, hepatitis B and C are uncommon. Most of our cirrhotic diseases are related to alcoholic or nonalcoholic steatohepatitis (NASH) or a combination of both [7, 8]. With this background, we have noticed that a larger proportion of our HCC are diffuse in type. This study is aimed at comparing the incidence, clinicopathological characteristics, and outcome in a cohort of patients with non-hepatitis B- or C-related diffuse-type HCC with a nodular variety.

Methods

Design

This is a single-center clinical cohort study carried out in the University Surgical Unit, Faculty of Medicine, Ragama, Sri Lanka.

Patients

A total of 227 patients were referred to the unit in the 3-year period between July 2011 and July 2014. There were 2 patients with positive hepatitis B surface antigen in the nodular-type and 1 in the diffuse-type cancers. All were negative for hepatitis C antibody. The 224 patients who were negative for hepatitis B and C were the subjects of the study.

Diagnosis of HCC

The diagnosis of HCC was based on the diagnostic criteria of the European Association for the Study of Liver Diseases (EASL). In lesions >2 cm, an alpha-fetoprotein (AFP) level >200 μg/L was also considered diagnostic. Liver biopsy was performed only when imaging was not conclusive.

Data Collection

Data were collected prospectively onto preformed proformas and included details on the demographic profile, viral status, clinical distribution of the tumors, and outcome. Two radiologists experienced in reporting hepatobiliary imaging reviewed the patient’s CT or MRI. Based on the imaging characteristics, tumors were divided into diffuse or nodular type. A diffuse-type cancer was defined as a tumor without a defined margin and with a normal hepatic parenchyma [1]. Nodular-type cancer was defined as a tumor having a discrete boundary between itself and the hepatic parenchyma (Fig. 1) irrespective of the number of nodules present. Patients with mixed-type tumors, having partly nodular and partly diffuse components in a solitary or multinodular HCC, were excluded from the study due to confusion in the diagnosis. Presence of macroscopic vascular invasion was defined as having an enhancing thrombus continuous with the main tumor mass. Selected patients underwent a Doppler scan to assess intrathrombus blood flow. Extension of the tumor thrombus was classified according to Shi et al. [9]. Once the diagnosis was made, presence of cirrhosis was diagnosed based on the clinical and biochemical status of the liver and CT appearance. Cirrhotic patients were further investigated to find out the etiology of cirrhosis. Patients who had a history of consuming alcohol above the accepted safe limits (Asian standards: <14 units of alcohol per week in men and <7 units per week in women) prior to the diagnosis of cirrhosis were considered as having alcoholic cirrhosis. Performance status was measured using the Karnofsky Performance Index [10]. The tumors were staged according to the AJCC/TNM Cancer Staging Manual (ed 7) [11].
Clinical Management

The decision regarding the best form of treatment was taken in a multidisciplinary meeting. Noncirrhotic patients having at least 30% residual liver volume and Child-Pugh class A cirrhotic patients having 40% residual liver volume were offered surgery. Selected Child-Pugh class B patients were offered nonanatomical resection. Presence of type 3 and 4 portal vein invasion was considered a contraindication for surgery. In others, alcohol or radiofrequency ablation was used. Alcohol ablation was preferred for radiologically accessible tumors <2 cm and those located close to the vascular pedicle. Radiofrequency ablation was offered for tumors up to 5 cm. Transarterial chemoembolization was offered to patients who did not have contraindications. Having type 3 or 4 portal vein invasion was considered a contraindication for TACE. Other patients were offered best palliative care.

Follow-Up

The follow-up protocol included CT scan or MRI scan every 3 months in the first year and every 6 months in the second and third years. AFP was done only in patients who had an initial rise.

Analyses

The etiology of HCC, baseline liver function, tumor characteristics, and treatment given were compared between nodular- and diffuse-type cancers. First, 30 stage III diffuse cancer were matched with 2 nodular-type cancers matching the cirrhotic status and the T stage (comparison was not done in stage I, II, and IV patients due to smaller numbers in the diffuse group). The overall survival was compared in the 2 groups. Survival was assessed using the Kaplan-Meier method and was compared with the log-rank test. In the 2 groups, Cox regression analysis was done on factors affecting survival. In the model, treatment status (whether treatment was given or not), AFP level, macrovascular invasion, performance index, and diffuse nodular status were used as covariates. Receiver-operating characteristic (ROC) curve analysis was done to find out the different levels of AFP in predicting the diffuse-type cancer. Nonparametric data were compared using the Mann-Whitney U test. A \( p \) value <0.05 was considered significant. Data were analyzed using SPSS software, version 18.0 for Microsoft Windows (SPSS, Chicago, IL, USA).

Statement of Ethics

Informed written consent was obtained from all patients who participated, and they were given full freedom to leave the study at any time during the research period. The study protocol was approved by the Ethics Review Committee of the Faculty of Medicine, University of Kelaniya, Sri Lanka. This article does not contain any animal experiments, and this trial was not registered.

Results

Of the 224 patients, 45 (20%) had diffuse-type tumors and 184 had nodular-type cancers. The median follow-up period was 18 months (range 1–36). Patients with diffuse cancers presented at a median age of 62 years (range 47–76). The majority [39 (87%)] were males.
Table 1. Comparison of nodular and diffuse cancers

|                          | Nodular (n = 183) | Diffuse (n = 45) | p       |
|--------------------------|-------------------|-----------------|---------|
| Age, years               | 63 (12–88)        | 62 (47–76)      | 0.937   |
| Gender, males            | 157 (85.8)        | 39 (86.7)       | 0.795   |
| Weight, kg               | 63.5 (28–109)     | 60 (43–83)      | 0.094   |
| BMI                      | 24.0 (12.96–40.0) | 22.75 (15.3–35) | 0.009   |
| Karnofsky Performance Index (>80%) | 137 (74.8)       | 30 (66.7)       | 0.286   |
| Diabetics                | 104 (56.8)        | 23 (51.1)       | 0.609   |
| Alcohol consumption      | 71 (38.8)         | 30 (66.7)       | 0.001   |
| Bilirubin, mg/dl         | 1.25 (0.2–967)    | 1.15 (0.2–5.29) | 0.179   |
| Aspartate transaminase, U/L | 56 (15–1122)     | 81 (32–354)     | 0.581   |
| Alanine transaminase, U/L | 42.5 (9–585)     | 41 (8.9–199)    | 0.452   |
| International normalized ratio | 1.25 (0.97–3.54) | 1.26 (1.0–2.8)  | 0.371   |
| Platelets, ×10³/µL       | 144 (31–652)      | 143 (44–424)    | 0.683   |
| The Model for End Stage Liver Disease score | 12 (5–24)       | 12 (4–21)       | 0.810   |
| Child-Pugh score         | 6 (5–14)          | 7 (5–11)        | 0.908   |
| Cirrhotic diseases       | 146 (89.8)        | 40 (88.9)       | 0.274   |
| Presence of encephalopathy | 15 (8.2)        | 5 (11.1)        | 0.368   |
| Absence of ascites       | 128 (70)          | 26 (57.8)       | 0.232   |
| Alpha-fetoprotein, µg/L  | 15.9 (1.1–94,120) | 1,610 (1.8–50,000) | <0.001 |
| Venous invasion          | 26 (14)           | 36 (80)         | <0.001  |
| Grade 1                  | 64 (35)           | 7 (16)          |         |
| Grade 2                  | 73 (40)           | 17 (39)         |         |
| Grade 3                  | 28 (15)           | 15 (32)         |         |
| Grade 4                  | 18 (10)           | 6 (14)          |         |
| Stage                    |                   |                 |         |
| Stage I                  | 73 (39.9)         | 2 (4.4)         |         |
| Stage II                 | 24 (13.1)         | 4 (8.9)         |         |
| Stage III                | 80 (43.7)         | 36 (80)         |         |
| Stage IV                 | 6 (3.3)           | 3 (6.7)         |         |
| Treatment                |                   |                 |         |
| Resection/liver transplantation | 44 (24)       | 2 (4)           | <0.001  |
| Ablation                 | 28 (15)           | 8 (18)          |         |
| Transarterial            | 62 (34)           | –               |         |
| No treatment             | 49 (27)           | 35 (78)         |         |

Values are expressed as median (range) or n (%) unless otherwise indicated.

(Table 1). The median BMI was 22.75 (15–35) in the diffuse type compared to 24.0 (12.96–40, p = 0.009) in the others. A history of alcohol consumption was documented in 30 (66.7%) cases of the diffuse type compared to 71 (38.8%) of the nodular type, showing a significant difference (p = 0.001). The median AFP level in the diffuse and nodular types was 1,610 µg/L (1.8–50,000) and 15.9 µg/L (1.1–94,120), respectively, showing a significant difference (p < 0.001). Macroscopic vascular invasion was present in a higher proportion of diffuse-type cancers (n = 36, 80% vs. n = 26, 14%, p < 0.001). When looking at the tumor stage, most of the diffuse-type cancers were stage III (81.8%) compared to 43.9% in the nodular group. There were larger proportions of T1 tumors in the nodular group (40.6 vs. 4.5%). The majority of patients with diffuse cancers were candidates for palliative treatment (n = 42, 27%, vs. n = 35, 78%). There was no difference in the Karnofsky Performance Index, the Model for End Stage Liver Disease (MELD) score at presentation, the median Child-Pugh score, clinical indicators of decompensated cirrhosis (ascites and encephalopathy at presentation), and percentage of non-cirrhotic diseases. In diffuse-type cancers, 3 patients underwent resection, 1 patient...
underwent ablation, and 9 patients had transarterial treatments. The median survival of diffuse-type HCC was 4.7 months (range 1–15); the longest survival was 15 months (Fig. 2).

Subsequent analysis was done in 30 diffuse and matched 60 nodular cancers. When the treatment pattern was compared, 23.3% (n = 14) of the nodular and 6.7% (n = 2) of the diffuse cancers underwent surgery. Transarterial chemoembolization was done in 20% (n = 6) of the diffuse and 28.3% (n = 17) of the nodular group. Ten percent (n = 6) of the nodular- and 3.3% (n = 1) of the diffuse-cancer patients underwent ablation. Active treatment was not offered in 70% (n = 21) with diffuse and 38.3% (n = 23) with nodular cancers. When the overall survival of 30 stage III diffuse tumors were compared with the matched 60 stage III nodular tumors, the median survival of those with diffuse tumors was 2.5 months (1.8–3.2) compared to 15.8 (11–20) in those with nodular tumors, showing a significant difference within the stage (p < 0.005, Fig. 3). On multivariate Cox regression analysis, whether treatment was given or not (p = 0.489, OR = 0.769, 95% CI = 0.365–1.619), the AFP level (p = 0.977, OR = 1.011, 95% CI = 0.482–2.119), macrovascular invasion (p = 0.225, OR = 1.559, 95% CI = 0.761–3.194), and performance index (p = 0.268, OR = 1.422, 95% CI = 0.762–2.650) did not show a significant association. The tumor morphology as diffuse or nodular was the only variable significantly associated with the survival (p < 0.001, OR = 0.356, 95% CI = 2.371–12.137). In receiver-operating characteristic curve analysis, the area under the curve for the serum AFP was 0.748 (95% CI = 0.640 to 0.856). At the upper limit of AFP (10 ng/mL), it had a sensitivity of 87% and a specificity of 42%. At an AFP level >200 ng/mL, it had a sensitivity of 66% and a specificity of 71% (Fig. 4).

**Discussion**

In this cohort, 1 out of 5 patients had diffuse-type cancers. Diffuse-type HCC had a higher proportion of cases with a history of high alcohol consumption, higher AFP levels, higher incidence of venous invasion, and a lower BMI. They also had a poor survival.
Data on diffuse-type HCC are sparse. In the largest previous series of 147 patients with HCC, 75 were described as having the diffuse type [4]. However, in this study, a disproportionately higher percentage of patients were included under diffuse HCC. It is likely that multinodular tumors were also considered to be diffuse-type tumors. A similar approach was taken in another study comparing results of trans-arterial therapy [12]. In this study, tumors having >3 nodules were considered to be diffuse. In our classification of diffuse and nodular, 23 patients who had a mixed morphology were not included into either group. They were not studied separately due to a smaller sample size. Hence, the two groups consisted of pure
nodular and diffuse tumors. Morphologically, diffuse cancers consist of a diffusely infiltrating tumor front without a definite capsule. The nodular type has a different architecture. Even in multinodular cancers, the margin between the tumor and the normal parenchyma is preserved. One of the initial descriptions of diffuse-type HCC by Okuda et al. [1] described the macroscopy as the absence of a convex tumor edge and having diffuse intraparenchymal spread. Subsequently, in a larger detailed study that analyzed the morphology of tumors from different geographical regions, a clear distinction was made between the infiltrative type and expanding nodular type [2]. We believe that diffuse cancers need to be considered separately from any form of nodular cancer given their distinct morphology and behavior. Few other studies have investigated HCC using this strict classification [5, 13]. These studies report a frequency of diffuse HCC ranging from 7–13%, which is lower than in our cohort.

Previous studies on nonalcoholic fatty liver disease and cirrhosis from Sri Lanka have shown that nonalcoholic fatty liver disease is common (a prevalence of >30% in adults in an urban population) and that cryptogenic cirrhosis (probably related to NASH) is a leading cause of cirrhosis and referral for liver transplantation [7, 8, 14]. In this study, high alcohol consumption was significantly more common in patients with diffuse HCC. Alcohol even in moderate amounts in patients with NASH has been identified as a risk factor in the development of HCC [15]. This may be the possible reason for the high percentage of diffuse-type cancers in this cohort.

When the outcomes were compared, overall survival was poor in the diffuse-type tumors compared to nodular HCC. None of the prognostic factors found to be important in nodular-type tumors had an impact on survival in diffuse HCC. Even treatment did not seem to affect the outcome. A benefit of transarterial treatment in diffuse HCC has been reported only in 1 study [4]. In this study, multinodular tumors were also classified as diffuse tumors. However, another study that defines diffuse HCC very specifically showed no survival benefit with transarterial therapy in these patients [12]. In fact this study showed a high rate of procedure-related complications and readmissions. Though surgery is rarely performed, the outcome of surgical resection in diffuse HCC has also been found to be poor [4]. In our series, surgery was performed only in 2 cases. One had postoperative liver failure and the second had a diffuse recurrence in the remaining liver after 2 months. These facts need to be considered when offering any active treatment for diffuse HCC.

Another interesting observation we made was the advanced stage at the presentation of diffuse-type HCC. This has been previously reported in other studies with diffuse HCC [4]. HCC are tumors with vague symptoms. In the large majority, the diagnosis is made by visualizing a mass in good-quality imaging. The absence of a well-defined nodule and the typical pattern of enhancement could make the diagnosis difficult [3]. However, we do not have the data on the percentage of patients on HCC surveillance, hence whether it was initially missed. It is difficult to judge whether there was a difference in symptomatology or a failure in screening in diffuse-type HCC.

Current staging systems, tumor size, number of nodules, and macroscopic vascular invasion are taken into account in assessing the T stage. Multinodular tumors indicate a field change with multiple primary nodules still preserving the tumor boundary. However, diffusely infiltrating tumors need to be gauged separately as the interaction between the liver and the tumor is different. A similar distinction is seen with Paget disease in breast cancer. Centers with larger cohorts of patients need to focus on the impact of this distinct morphology on tumor staging. However, our cohort is too small to arrive at a meaningful conclusion.

In conclusion, diffuse-type HCC was common in our cohort of patients with non-hepatitis B and non-hepatitis C HCC. The majority of patients with diffuse cancers were beyond the stage of active treatment. These stage III tumors have a poor outcome. Larger cohort studies need to be done considering the possibility of using tumor morphology as a predictor of stage.
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Disclosure Statement

Dr. R.C. Siriwardana, Dr. C.A.H. Liyanage, Dr. B. Gunetilleke, Dr. M.A. Niriella, Prof. H.J. de Silva, Dr. A.S. Dassanayake, and Dr. S.P. Jayatunge confirm that there are no conflicts of interest to disclose.

References

1. Okuda K, Noguchi T, Kubo Y, Shimokawa Y, Kojiro M, Nakashima TA: Clinical and pathological study of diffuse type hepatocellular carcinoma. Liver 1981;1:280–289.
2. Okuda K, Peters RL, Simon IW: Gross anatomic features of hepatocellular carcinoma from three disparate geographic areas. Proposal of new classification. Cancer 1984;54:2165–2173.
3. Kanematsu M, Semelka RC, Leonardou P, Mastropasqua M, Lee JK: Hepatocellular carcinoma of diffuse type: MR imaging findings and clinical manifestations. J Magn Reson Imaging 2003;18:189–195.
4. Kneuertz P, Demirjian A, Firoozmand A, Corona-Villalobos C, Bhagat N, Herman J, et al: Diffuse infiltrative hepatocellular carcinoma: assessment of presentation, treatment, and outcomes. Ann Surg Oncol 2012;19:2897–2907.
5. Trevisani F, Caraceni P, Bernardi M, D’Intino PE, Arienti V, Amorati P, et al: Gross pathologic types of hepatocellular carcinoma in Italian patients. Relationship with demographic, environmental, and clinical factors. Cancer 1993;72:1557–1563.
6. Myung SJ, Yoon JH, Kim KM, Gwak GY, Kim YJ, Yu JW, et al: Diffuse infiltrative hepatocellular carcinomas in a hepatitis B-endemic area: diagnostic and therapeutic impediments. Hepatogastroenterology 2006;53:266–270.
7. Siriwardana RC, Niriella MA, Liyanage CAH, Wijesuriya SR, Gunathilaka B, Dassanayake AS, et al: Cryptogenic cirrhosis is the leading cause for listing for liver transplantation in Sri Lanka. Indian J Gastroenterol 2013;32:397–399.
8. Dassanayake AS, Kasturiratne A, Rajindrajith S, Kalubowila U, Chakrawarthi S, De Silva AP, et al: Prevalence and risk factors for non-alcoholic fatty liver disease among adults in an urban Sri Lankan population. J Gastroenterol Hepatol 2009;24:1284–1288.
9. Shi J, Lai EC, Li N, et al: A new for classification hepatocellular carcinoma with portal vein tumor thrombus. J Hepatobiliary Pancreat Sci 2011;18:74–80.
10. Karnofsky D, Burchenal J: The clinical evaluation of chemotherapeutic agents in cancer; in Macleod CM (ed): Evaluation of Chemotherapeutic Agents. New York, Columbia University Press, 1948, pp 191–205.
11. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (eds): AJCC Cancer Staging Manual, ed 7. New York, Springer, 2010.
12. Lopez RR, Pan S-H, Hoffman AL, Ramirez C, Rojter SE, Ramos H, et al: Comparison of transarterial chemoembolization in patients with unresectable, diffuse vs focal hepatocellular carcinoma. Arch Surg 2002;137:653–657; discussion 657–658.
13. Demirjian A, Peng P, Geschwind JFH, Cosgrove D, Schutz J, KamelIR, et al: Infiltrating hepatocellular carcinoma: seeing the tree through the forest. J Gastrointest Surg 2011;15:2089–2097.
14. Silva H, Siriwardana R, Niriella M, Dassanayake A, Liayange CH, Gunathilake B, et al: Nonalcoholic fatty liver disease among potential live liver donors – a preliminary experience from Sri Lanka. Indian J Gastroenterol 2014;33:573–574.
15. Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN: The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology 2010;51:1972–1978.