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Original Research

Large Hypovascular Hepatocellular Carcinoma: Non-Classical Type

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Abstract

Objectives: As the frequency of surveillance protocols increases in patients with chronic liver disease, the rate of detection of radiologically atypical lesions such as hypovascular hepatocellular carcinoma (HCC) increases. There is no concensus regarding the frequency, size, differentiation, relationship with biomarkers, treatment and survival of hypovascular tumors.

To examine the clinical characteristics and clinical outcomes of resected hypovascular HCCs with known pathology.

Methods: Data of 62 HCC patients treated with resection between January 2009 and December 2022 were retrospectively examined. Twenty-five of these patients had radiological hypovascular HCC and 37 had hypervascular HCC. Patient characteristics (age, gender, blood count and liver function tests, and AFP), tumor variables (differentiation grade, portal vein invasion, Milan Status), and outcome variables (survival, recurrence) were compared between the two radiological groups.

Results: Comparison of quantitative variables between the 2 groups, showed that only GGT values were significantly higher in the hypovascular HCC group. There were no significant differences between the qualitative variables. Overall survival at 1, 3, and 5-years was 79.2%, 55.9%, and 51.2% in the hypovascular group and 83.1%, 61.8%, and 32.4% in the hypervascular group, respectively (p=0.517). Disease-free survival at 1, 3, and 5 years was 58.5%, 46% and 46% in the hypovascular group and 60.3%, 36.5% and 18.2% in the hypervascular group, respectively (p=0.572).

Conclusion: Unlike smaller HCCs, large-dimension hypovascular HCC cases were found to be biologically similar to hypervascular HCC cases. This result may be due to the larger size of the hypovascular tumors. There is a need for studies on bigger series of large size hypovascular HCC cases.

Keywords: Cirrhosis, Hypovascular HCC, Resection

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Hypovascular HCCs have been reported to be smaller in size and show better differentiation[1,2] than typical hypervascular HCCs (HCC with arterial phase hyperenhancement and portal hepatic phase hypoenhancement - washout - findings).[3] The incidence of hypovascular HCCs is 18% in HCCs less than 3 cm in diameter and 24% in HCCs less than 2 cm in diameter.[4]

Questions regarding the frequency, size, differentiation, relationship with biomarkers, treatment and survival of hypovascular tumors have still not found a consensus answer. Additionally, large-dimention hypovascular HCC has not been a subject studied so far Therefore, in this study, we report our experience of 25 cases treated with resection and thus having pathological confirmation of HCC and who were diagnosed radiologically as hypovascular HCC.

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Methods

The data of 62 HCC patients treated with resection at our institute between January 2009 and December 2022 were retrospectively examined. Twenty-five of these patients had radiological hypovascular HCC and 37 had hypervascular HCC. None of them had a liver transplant. The data were accessed from hospital records. Patient characteristics (age, gender, neutrophil lymphocyte, platelet, AST, ALT, total bilirubin, GGT, AFP), tumor variables (differentiation grade, portal vein invasion, Milan Status), and outcome variables (survival, recurrence) were compared between two groups.

Radiologically suspicious hypovascular tumors were defined as hypovascular or isovascular tumors that did not show hyperenhancement compared with surrounding liver parenchyma in the arterial phase (Histopathologically, the characteristics of these tumors were that fibrous capsule formation was less common).

Before resection, extrahepatic metastases were excluded by CT/MRI or PET CT. For major resections, the ICG retention test was used and R15 was required to be below 15%. After resection, all patients were followed up with thorax and abdomen CT scans as well as blood tests every 3 months for the first 2 years and then every 6 months.

Statistical Analysis

All analyzes were performed using IBM SPSS Statistics 25.0 for Windows (New York; USA). Qualitative data from the variables included in the study were summarized as numbers (percentages). The suitability of quantitative data for normal distribution was evaluated with the Shapiro-Wilk test. Since quantitative data did not show a normal distribution, they were summarized with median values (95 % CI lower and upper limits). In statistical analyses, Mann-Whitney U test, Pearson chi-square test, Yates corrected chi-square test and Fisher's exact chi-square test were used where appropriate. In the statistical analysis applied, $p<0.05$ value was considered statistically significant.

Results

Of the 62 patients examined in this study, 25 were in the hypovascular (atypical) HCC group and 37 were in the hypervascular (typical) HCC group. The median age of the entire group was 60 (23-82) years, the median age in the atypical group was 58 (23-67) years, and in the typical HCC group it was 61 (27-82) years (p=0.156). While the male/female ratio was 37/5 in the atypical group, the male/female ratio was 25/6 in the typical group (p=0.731). Quantitative data of all patients, including age, neutrophil, lymphocyte, platelet, AST, ALT, bilirubin, GGT, MELD-NA and maximum tumor size, are shown in Table 1. Qualitative variables related to groups, gender, Milan status, pathological features, and PV invasion status of the entire cohort are shown in Table 2.

When quantitative variables were compared between the 2 groups, only GGT values were found to be significantly higher in the atypical group (Table 3). When the qualitative variables were compared between the 2 groups, there were no significant differences (Table 4).

The overall survival of the entire group was 755 (24-4589) days, 1252 days in the atypical group and 685 days in the typical group (p=0.062). Disease free survival was 574 days in the entire cohort, 383 (133-775) days in the atypical group and 205 (554-1093) days in the typical group (p=0.265). Overall survival (OS) for 1, 3, and 5-year was 79.2%, 55.9%, and 51.2% in the atypical group, respectively

Table 1. Qualitative variables for entire cohort

Parameters	Subparameters	Number	Percentage
Groups	Normal	37	60.7
	Suspicious	24	39.3
Gender	Female	11	18.0
	Male	50	82.0
Milan Status	Within	23	37.7
	Beyond	38	62.3
Pathological features	Well	15	24.6
	Moderately	30	49.2
	Poorly	16	26.2
PV Invasion	No	45	73.8
	Yes	16	26.2
Recurrence	No	25	41
	Yes	36	59
Outcome	Alive	32	52.5
	Dead	29	47.5

Table 2. Quantitative variables for entire cohort

Parameters	Median	IQR	95 % CI Lower	95 % Upper
Age	60	19	23	82
MELD.Na	8	4	6	21
Preop.AFP	32	481	1	30000
Preop.Neutrophil	3.8	2	1.1	17
Preop.Lymphocyte	1.8	1	0.6	6.5
Preop.Platelets	221	149	60	702
Preop.AST	34	31	10	140
Preop.ALT	30	31	12	178
Preop.TBilirubin	0.6	0	0.2	9.3
Preop.GGT	48	80	10	366
MTS	60	77	5	200
OS (days)	711	1441	24	4589
DFS (days)	574	990	24	3204

Table 3. Comparison of normal and suspicious groups in terms of qualitative variables

Parameters	Subparameters	Hypervascular		Hypovascular		p
		n	%	n	%	
Gender	Female	6	16.2	5	20.8	0.447
	Male	31	83.8	19	79.2	
Milan Status	Within	14	37.8	9	37.5	1.000
	Beyond	23	62.2	15	62.5	
Pathological features	Well	8	21.6	7	29.2	0.631
	Moderately	20	54.1	10	41.7	
	Poorly	9	24.3	7	29.2	
PV Invasion	No	30	81.1	15	62.5	0.189
	Yes	7	18.9	9	37.5	
Recurrence	No	15	40.5	10	41.7	1.000
	Yes	22	59.5	14	58.3	
Outcome	Alive	19	51.4	13	54.2	1.000
	Dead	18	48.6	11	45.8	

Table 4. Comparison of normal and suspicious groups in terms of quantitative variables

Parameters	Hypervascular			Hypovascular			p
	Median	95 % CI (Lower- Upper)		Median	95 % CI (Lower- Upper)		
Age	61	57	65	58	48	62	0.134
MELD.Na	8	8.00	10	8	7	11	0.636
Preop.AFP	22	11	250	84	4	400	0.724
Preop.Neutrophil	3.7	3.4	4.2	3.85	3.4	4.5	0.579
Preop.Lymphocyte	1.6	1.5	1.9	1.85	1.5	2.1	0.344
Preop.Platelets	205	184	247	255	194	296	0.535
Preop.AST	37	29	48	33	27	46	0.550
Preop.ALT	30	25	41	30	23	36	0.442
Preop.TBilirubin	.70	.70	1.10	.60	.60	1.0	0.206
Preop.GGT	43	38	57	86	47	128	0.039
MTS	60	55	85	98	45	140	0.154
OS	685	554	1093	1050	562	2194	0.118
DFS	685	554	1093	344	133	775	0.044

Mann-Whitney U test was used for comparison.

and 83.1%, 61.8%, and 32.4% in the typical group, respectively (p=0.517) (Fig. 1). Diseases-free survival (DFS) for 1, 3, and 5 year was 58.5%, 46% and 46% in the atypical group and 60.3%, 36.5% and 18.2% in the typical group, respectively (p=0.572), (Fig. 2).

Discussion

The incidence of hypovascular HCCs increases as surveillance programs increase in chronic liver patients. However, after such surveillance programs, mostly small-sized hypovascular HCCs are detected which is their purpose. Publications on hypovascular HCCs have always focused on small tumors.[4,5] In this study, the hypovascular types of resected large-dimension HCCs were reviewed and their characteristics were described.

Hypovascular HCCs are generally thought to have good biological behavior, with small tumor size (<3 cm), being well-differentiated tumors, and with low AFP levels.[4,6] The median maximum tumor size of the 25 hypovascular HCC cases in this study was 9.75 cm. Whether large-dimension hypovascular HCC cases have the same characteristics as small-dimension tumors is unexplored, to our knowledge.

We found that hypovascular HCC cases studied here had higher GGT values than hypervascular HCC cases. It has

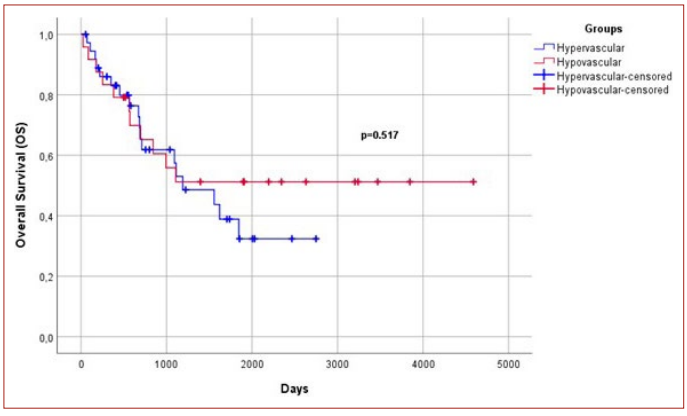

Figure 1. Comparison of overall survival (OS) of both group with Kaplan- Meier estimate.

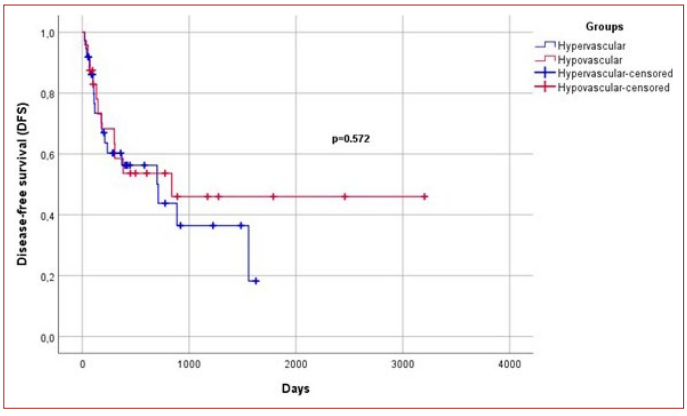

Figure 2. Comparison of disease-free survival (DFS) of both group with Kaplan- Meier estimate.

been shown in many studies how prognostically important high GGT levels have in large HCCs.[7,8] This result may indicate that large hypovascular HCC will have a similar survival rates with hyper vascular HCC.

Gammaglutamyl transpeptidase (GGT), has been thought to play a role in HCC growth and development and in resistance to drug toxicity,[9] being a cell surface enzyme that is involved in glutathione metabolism and is thus important in the maintenance of cellular cysteine levels. Furthermore, it is also considered to be a clinically useful prognostic factor, especially in HCC patients with low levels of AFP.

In the current study, hypovascular HCC cases were observed to have higher AFP values and a higher percentage of portal venous tumor invasion than hypervascular HCC cases. However, they had similar overall and disease-free survival. Although these differences between the two groups are not statistically significant, they may be due to the larger size of the hypovascular tumors as well as the small size of the case series. There is thus a need for studies on a larger series examining large hypovascular HCC cases.

Disclosures

Ethics Committee Approval: Since this study was prepared as a retrospective archive data review, ethics committee approval was not obtained.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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