HISTOPATHOLOGICAL ASSESSMENT OF MICROVASCULAR INVASION IN HEPATOCELLULAR CARCINOMA RESECTION SPECIMENS AND ITS CORRELATION WITH TUMOR SIZE AND GRADE

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How to cite this article

Madiha Z, Jalil S, Iqbal S, Jamil Z, Ali S, Sadiq S, et al. Histopathological Assessment of Microvascular Invasion in Hepatocellular Carcinoma Resection Specimens and its Correlation with Tumor Size and Grade. J Gandhara Med Dent Sci. 2023;10(4):72-75
https://doi.org/10.37762/jgmds.10-4.473

ABSTRACT

OBJECTIVES

To determine the histopathological assessment of microvascular invasion in Hepatocellular Carcinoma Resection Specimens and its correlation with tumour size and grade.

METHODOLOGY

This retrospective cross-sectional study included the biopsy-proven Hepatocellular (HCC) case with microvascular invasion (MVI) noted in the resected specimens evaluated by two independent consultants Histopathologists. The exclusion criteria were; all patients below 18 years, unfixed autolyzed samples, and incomplete requisition-filled forms. Numerical data, i.e., patient age and tumour size, are presented as mean with standard deviation. Categorical variables, i.e., tumour size, grade, and presence or absence of MVI, were submitted as numbers with percentages. Continuous variables, i.e., tumour size and differentiation grade, were assessed using the Chi-square test. A p-value of ≤ 0.05 was considered significant.

RESULTS

Most patients, 34.4%, fall into the age group of 47-70. Most patients were males, 63.6%, and microvascular invasion was noted in 49.09% of cases. Most cases were of moderate to poorly differentiated tumours, 80.0%. MVI was statistically significant with the grade of the tumour.

CONCLUSION

Microvascular invasion is an important prognostic marker noted in a surgical resection specimen. Although the exact definition and risk stratification is unclear, survival studies have proven that MVI is associated with poor outcomes.

KEYWORDS: *Hepatocellular Carcinoma, Microvascular Invasion, Anatomical Liver Resection*

INTRODUCTION

Hepatocellular carcinoma (HCC) is 80% of primary hepatic malignancies and ranked sixth in number.[1] According to the literature review, HCC is the third leading cause of cancer-related demise after lung and gastric carcinoma. The incidence and mortality of HCC in previous years have increased.[2,3] The well-acclaimed risk factors include liver cirrhosis, viral infections (HBV/HCV coinfection), chronic alcoholic steatohepatitis and nonalcoholic steatohepatitis, hereditary hemochromatosis, and HIV. HBV infection is the culprit in 80% of the cases.[4] The generalized symptoms include vague upper abdominal pain, jaundice, anorexia, weight loss, and malaise. Abdominal examination shows hepatomegaly and ascites. HCC acquires its blood supply from the hepatic artery hence, characterized by arterial phase enhancement and faded portal venous phases.[5] The current treatment regimens include anatomical hepatectomy, liver transplant, and targeted therapies, including tumour ablation by radiofrequency, transcatheter arterial chemoembolization (TACE), and immunotherapy.[6] However, despite these varied aggressive surgical and interventional treatment options, the prognosis is dismal due to the high rate of relapse and metastasis. HCC commonly metastasizes to the lung, adrenal glands, peritoneum, and bone.[7] HCC has a high propensity towards macroscopic and microscopic vascular invasion leading to intrahepatic and extrahepatic spread.[8] The estimated relapse rate is relatively high, 70% after anatomical liver resection and 35% after liver transplant at five years. Postoperatively, various histological parameters related to the tumour, such as size, foci, grade, and margins, are clinically significant.[9,10] Much work on HCC management is going on due to aggressive biological behaviours, postoperative relapses, and fugitive survival.[11] In tissue sections, the most important prognostic parameter is the identification of microvascular invasion (MVI), noted

as the attached neoplastic cells to the vascular endothelium of hepatic veins, arteries, and portal veins (Fig 1D). MVI is associated with a high recurrence rate and poor survival.[12] No uniform pathological sampling protocol is currently employed to determine MVI. In a surgical pathology report, MVI is stratified as low-risk, high-risk, and no MVI based on vessel involvement and distance of MVI from adjacent peritumoral liver tissue.[13] MVI has a potential prophetic role in postoperative adjuvant therapy, i.e., transcatheter arterial chemoembolization (PA-TACE), sorafenib, and radiotherapy. Hence identification and reporting MVI is critical for optimized treatment options. The close follow-up of MVI-positive patients leads to the discernment of relapse, or metastasis, leading to timely interventions and further management.[14,15]

METHODOLOGY

The Department of Histopathology, Sheikh Zayed Hospital, Lahore's ethical review board approved this retrospective cross-sectional study. The sample was taken by Non-probability consecutive sampling, and a sample size of 110 patients was calculated using a 95% confidence level and 7% margin of error. The inclusion criteria were; biopsy-proven case of HCC with MVI noted in the resected specimens evaluated by two independent consultant Histopathologists, absence of tumour thrombus in the portal vein, hepatic vein, or bile duct, No metastases, primary resection specimens with wide tumour-free margins evaluated by a histopathologist. The exclusion criteria were; all patients below 18 years, unfixed autolyzed specimens, incomplete requisition filled forms, tumour size less than 1cm, patients presented with recurrence, preoperative chemotherapy, and any concurrent malignancy. The liver specimens were fixed in 10% neutral buffered formalin and grossed as per the American College of Pathologists protocol (Fig 1B). Paraffin-embedded blocks were sectioned at 3-5 micrometres and stained with Hematoxylin and Eosin stains. Data was entered and analyzed using SPSS 23.0. Numerical data, i.e., patient age and tumour size, are presented as mean with standard deviation. Categorical variables, i.e., tumour size, grade, and presence or absence of MVI, were submitted as numbers with percentages (%) (Table I). Continuous variables, i.e., tumour size and differentiation grade, were assessed using the Chi-square test (Table II). A p-value of ≤ 0.05 was considered significant.

RESULTS

Table 1: Main Demographic Data; and Histopathological Features of Patients with HCC Who Have Undergone Anatomical Liver Resections

Age(Years)	Mean Age	49.55	
	Standard Deviation	±12.86	
	Minimum	18	
	Maximum	76	
Tumour Size (cm)	Mean	5.55	
	Standard Deviation	±2.34	
	Minimum	1.0	
	Maximum	10.0	
Parameters		**Number**	**%age**
Gender	Males	70	63.6%
	Females	40	40.0%
Age groups (Years)	18-28	37	33.64%
	29-46	35	31.82%
	47-70	38	34.55%
Subgroups based on tumour size	3cm	26	23.64%
	3.1-5cm	24	21.82%
	5.1-6.5 cm	12	10.91%
	6.5-10cm	48	43.64%
Tumour differentiation	Well-differentiated	22	20.0%
	Moderately differentiated	41	37.27%
	Poorly differentiated	47	42.73%
Frequency of microvascular invasion	Present	54	49.09%
	Absent	56	50.91%
Liver Fibrosis	Present	95	86.3%
	Absent	15	13.6%

Table 2: Main Demographic Data; and Histopathological Features of Patients with HCC Who Have Undergone

		Microvascular Invasion (Positive)	**Microvascular Invasion (Negative)**	**P-Value**
Tumor Size	3.0 cm	06(5.4%)	20 (18.1%)	0.08
	3.1-5 cm	11(10.0%)	13 (11.8%)	
	5.1-6.5 cm	06(5.4%)	06(5.4%)	
	>6.5 cm	31(28.1%)	17 (15.4%)	
Tumor differentiation	Well-differentiated	05(4.5%)	17(15.4%)	0.02
	Moderately differentiated	21(19.0%)	20(18.1%)	
	Poorly differentiated	28(25.4%)	19(17.2%)	
Age groups	18-28	12(10.9%)	13(11.8%)	0.57
	29-46	29(26.3%)	34(30.9%)	
	47-70	13(11.8%)	09(8.1%)	
Gender	Males	31(28.1%)	39(35.4%)	0.18
	Females	27(24.5%)	17(15.4%)	

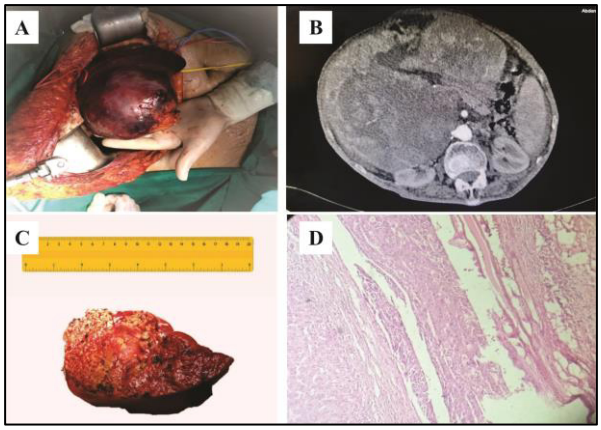

Figure 1: Different images of hepatocellular carcinoma A. Intraoperative image of anatomical resection of hepatocellular carcinoma B. Resected specimen showing tumour with wide margins C. Axial CT images in arterial phase show large lobulated hepatic masses showing patchy enhancement. One of the masses in segment VII is causing a mass effect over the right kidney D. H&E staining shows attached neoplastic cells within the vascular lumina.

DISCUSSION

The management of HCC requires specialists from various disciplines. A dedicated team of professionals is needed to improve the survival of HCC patients postoperatively.[16] After surgical resection, the identification and reporting of MVI is an independent risk factor for relapse and survival.[17] The preoperative assessment of MVI is an essential tool for surgical and medical management.[18] MVI is a major independent prognostic factor for HCC patients, and its frequency increases tumour size.[19,20] The mean age reported in our study was 49.55 years, whereas Lei Z et al. and Zhao J et al. reported higher mean ages of 52.1 and 54.8 years, respectively.[20,24] Wang J et al., Du M et al., and Lu Xy et al.; showed a slightly higher mean age of 50.9 years (27, 29-30). Sun JJ et al. and Li C et al. reported similar mean ages to our study.[25,26] In our index study, most of the patients with HCC were males Xu X et al., Yau T et al., and Lee S et al. Other studies showed a clear male preponderance of 3:1 in HCC patients.[17,18,19,21,22,23,24,25,26,27,28,29,30] The maximum tumour size noted in our study was 10cm; however, Li C et al., Zhao J et al., and Sun JJ et al.; reported tumour sizes of 5.3, 5.7, and 6.9cm, respectively.[24,25,26] The largest tumour size reported is 12.6 cm by DU M et al. and Lu Xy et al. Histologically, MVI is the hallmark of intrahepatic dissemination and extrahepatic metastasis.[29,30] The exact mechanism of MVI formation mechanism is vague.[20] However, MVI is associated with poor prognosis in HCC patients after anatomical liver resections.[21] Neoadjuvant therapies are advised to improve outcomes.[22] There is a lack of consensus among pathologists regarding MVI definition, evaluation, and its correlation with prognosis.[23] Our index study showed that MVI was statistically significant in tumour grade and can significantly affect prognosis.[24] No association was found with tumour size, age, and gender.[25] Regarding MVI, we noted it was present in 86 (95.3%) of cases, however in contrast, Lei Z et al., Hui Zhao et al., and Long Hai Feng et al.; reported 28.8%,32.2%, and 28.3%, respectively, in anatomical liver resections .[20,21,22] A thorough literature review done by Zhang X et al.; showed MVI of 57.1%, 29.6%,58.1%, and 33.8%, respectively (23).In contrast, Lei Z et al., Hui Zhao et al., and Long-Hai Feng et al. also reported 70.2%, 47.4%, and 50.4% of HCC with no MVI.[20,21,22] Well-differentiated tumours noted in our study were 20.0%. MVI was reported in 4.5% of cases; Hui Zhao et al., Long-Hai Feng et al., Li C et al., Wang L et al., DU M et al., and Lu Xy et al.; reported 3.3%,19.9%, and 5.5% of well-differentiated hepatocellular carcinoma.[21,22,26,27,29,30] Our index study showed 42.3% poorly differentiated tumours, of which 25.4% showed MVI. In contrast, Hui Zhao et al.; and Ye JZ et al.; reported slightly higher poorly differentiated tumours, 35.5%; and 47.7 %, respectively.[28] Other authors, i.e., Long-Hai Fen et al., Li C et al., Wang L et al., DU M et al., and Lu XY et al., reported 80.0%, 94.5 %, 94.5%.[22,26,27,29,30]

LIMITATIONS

In the index study, the lack of clinical follow-up regarding relapse is the major drawback of this study.

CONCLUSIONS

The histopathological reporting of microvascular invasion in a surgical resection specimen is prognostically important and associated with poor outcomes in HCC patients. Our index study showed that MVI was statistically significant in tumour grade and can significantly affect prognosis. However, no association was found with tumour size, age, and gender.

CONFLICT OF INTEREST: None

FUNDING SOURCES: None

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