Original Article

OPEN ACCESS

Histopathological Evaluation of Abnormal Hepatic Nodules Detected Radiologically and on Gross Examination of Hepatectomy Specimens and Their Relationship with Alpha Fetoprotein Levels

Mavra Akhtar[1], Shahila Jaleel[2], Nausheen Henna[3], Uzma Shaheen[4], Fareeha Shahid[5], Madiha Ehsanulhaq[6]

[1]Senior Demonstrator, Fatima Memorial Hospital, Lahore
[2]Associate Professor Histopathology department Shaikh Zayed FPGMI Lahore
[3]Specialist Anatomic Pathologist, Tawam Hospital, Purelab, UAE
[4]Assistant Professor Pathology, D G Khan Medical College, Dera Ghazi Khan
[5]Assistant Professor Pathology (histopathology), Akhtar Saeed Medical College Rawalpindi campus
[6]Assistant Professor, Department of Pathology, Sharif Medical and Dental College

Author`s Contribution

[1,4]Substantial contributions to the conception or design of the work; or the acquisition, Active participation in active methodology, [2]analysis, or interpretation of data for the work, [3,5,6]Drafting the work or revising it critically for important intellectual content

Funding Source: None
Conflict of Interest: None

Received: Jan 22, 2024
Accepted: July 05, 2024

Address of Correspondent
Dr. Mavra Akhtar
Senior Demonstrator, Fatima Memorial Hospital, Lahore
Mavrababar11@gmail.com

ABSTRACT

Objective: To determine the frequency and pattern of abnormal nodules in Hepatectomy specimens and to evaluate the frequency of elevated serum alpha-fetoprotein (AFP) levels in abnormal hepatic nodules.

Methodology: A Descriptive, cross-sectional survey was conducted from January 2021 to July 2022 in the Department of Histopathology, Sheikh Zayed Hospital Lahore, A non-probability consecutive sampling technique was used. A total of 60 Hepatectomy samples taken from liver explants were included and data was analyzed by SPSS version 23. A chi-square test with a p-value less than 0.05 was considered significant.

Results: The mean age of patients was 47.33±14.74 years. There were 46 (76.67%) male and 14 (23.33%) female patients. On the frequency of etiology, 30 (50.00%) had viral etiology, 05 (8.33%) autoimmune, 06 (10.00%) cryptogenic, 03 (5.00%) NASH, 05 (8.33%) fibrolamellar CA, 07 (11.67%) bud chiari syndrome and 04 (6.67%) liver disease (Figure 4). There were 15 (25.00%) patients with elevated AFP levels. Abnormal nodules were present in 47 (78.33%) patients. On frequency of type of nodules, 11 (23.40%) macro-regenerative nodules, 04 (8.51%) FNH nodules, 06 (12.77%) adenoma nodules, 06 (12.77%) dysplastic nodules (SCC), 08 (17.02%) dysplastic nodules (LCC) and 12 (25.53%) hepatocellular carcinoma.

Conclusion: Viral causes are commonest in liver explant samples. The common histopathological finding was that HCC was identified in 25.53% of cases, and macro-regenerative nodules were identified in 23.40% of patients.

Keywords: Liver Explant, Hepatectomy, abnormal nodules, Histopathological spectrum.

Cite this article as: Akhtar M, Jaleel S, Henna N, Shaheen U, Shahid F, Ehsanulhaq M. Histopathological Evaluation of Abnormal Hepatic Nodules Detected Radiologically and On Gross Examination of Hepatectomy Specimens and Their Relationship with Alpha Fetoprotein Levels. Ann Pak Inst Med Sci. 2024; 20(SUPPL-1):635-640. doi. 10.48036/apims.v20iSUPPL-1.1230

Introduction

The topic of regenerative nodules and dysplasia continues to be a source of much debate and the distinction between nodular lesions in cirrhosis and hepatocellular carcinoma (HCC) remains unclear.[1] Hepatocellular nodules are classified histologically as regenerative lesions (e.g., regenerative nodules, FNH) or dysplastic lesions.[2-3] the prevalence of liver cell dysplasia in cirrhotic livers and its progression to HCC is still discussed. Prospective studies have suggested that HCC is more common in the presence of dysplasia at a frequency of 24% to 30%.[4-5]

Dysplastic nodules are composed of large and small cell changes. Small cell change is considered to be a more advanced precursor than large cell change. [6].

Specialists have also studied the value of radiological imaging techniques in cirrhotic patients for early detection of HCC and differential diagnosis of hepatic nodular lesions. Moreover, the authors found an association of serum alpha-fetoprotein (AFP) with HCC, AFP was elevated in 91.6% of cases of HCC. [7-8]

A recent study by Bansal et al. conducted a study on liver explants in patients with liver cirrhosis. The authors reported 40 (80%) abnormal nodules in liver explants, out of these 40, 12 (33.0%) were having HCC, 11 (27.5%) macro-regenerative nodules, 08 (20.0%) dysplastic nodules and 9 (22.0%) were having necrotic nodules.[9]

In healthy persons, serum AFP levels generally range from 5 to 10 ng/mL. Conversely, an increased blood level of AFP is often linked to HCC or other hepatic disorders. Research indicates that an AFP level of 400 ng/mL is typically regarded as diagnostic for HCC.[10] HCC monitoring using AFP is common in clinical practice. However, it has low sensitivity and specificity for HCC diagnosis, and some advanced HCC patients do not secrete AFP. Patients with chronic liver disorders, notably cirrhosis, sometimes have prolonged AFP increase without radiographic HCC. For these reasons, AFP should not be used alone to monitor HCC. [11]

The present study aims to determine the pattern of abnormal nodules in hepatectomy specimens and to determine the association of CC with the type of nodules and AFP levels. Because very little work is published regarding the etiological spectrum of these nodules in liver cirrhosis patients. This study will help us gain new insight into the etiopathological association of cirrhosis and hepatocellular carcinoma (HCC). That in the future will help in detecting the suspicion of HCC based on the appearance of nodules.

Methodology

A Descriptive, cross-sectional survey in the Department of Histopathology, Sheikh Zayed Hospital, Lahore from January 2021 to July 2022. A non-probability consecutive sampling was used. The sample size for this study is 60 hepatectomy specimens. The study sample size is calculated by taking a 95% confidence level, 10% margin of error, and taking the estimated frequency of dysplastic nodules as 20% (8).

The patients fulfilling the following criteria were included in the study. Hepatectomy taken from patients with cirrhosis (viral and non-viral cause). Hepatectomy taken from patients without cirrhosis. Hepatectomy taken from adult patients of age 20-85 years. Both male and female patient specimens.

The patients with the following criteria are excluded from the study. Hepatectomies from patients with metastatic nodules or having malignancy other than HCC. Patients who did not give consent to include their data in the study.

After approval of the synopsis, a total number of 60 hepatectomies specimens were included in this study. A written consent was taken from each patient before including their specimens in this study.

Data regarding the patient's age, gender, and etiology of liver cirrhosis was taken from the personal hospital file of the patient.

Any nodules differing in color, composition, and appearance from the liver parenchyma surrounding them were considered aberrant. The three major hepatic veins were opened and cut at 0.5–1 cm intervals following probe insertion. Any aberrant nodule discovered was segmented differently than the typical sections obtained from the right lobe three times, the left lobe two times, the caudate lobe one time, the porta hepatis one time, and the gall bladder once. All of the slices were colored as usual using hematoxylin and Eosin dye. Special stains employed as needed included Orcein, Pearl, Masson's trichrome, PAS, PAS with diastase, and reticulin stain.

The International Working Party Classification 1995 put these nodules into five groups based on their histological features: macro-regenerative nodules, FNH, adenomas, dysplastic nodules, and hepatocellular cancer. All the study relevant information was noted on a pre-designed Proforma.

The data analysis was conducted using SPSS version 23. We will compute the mean and standard deviation of age. The frequency and percentage of gender, cause of liver cirrhosis, increased AFP levels (Yes/No), abnormal nodules (Yes/No), and types of abnormal nodules were computed. Stratification was employed to control for effect modifiers such as age, gender, and the etiology of cirrhosis. A post-stratification chi-square test was used to determine the connection between the frequency and type of aberrant nodules and the effect modifiers. A substantial correlation was shown with a P-value of ≤ 0.05.

Doi.10.48036/apims.v19i2.782

Results

The mean age of patients included in this study was 47.33±14.74 years. The minimum age was 20 years and the maximum age was 70 years. The gender distribution showed a higher number of males than females, with 46 (76.67%) males and 14 (23.33%) females.

The etiology of hepatocarcinoma was categorized as viral (50%), autoimmune (8.33%), cryptogenic (10%), NASH (5%), fibrolamellar CA (8.33%), Budd-Chiari syndrome (11.67%), and liver disease (6.67%) (Figure 1).

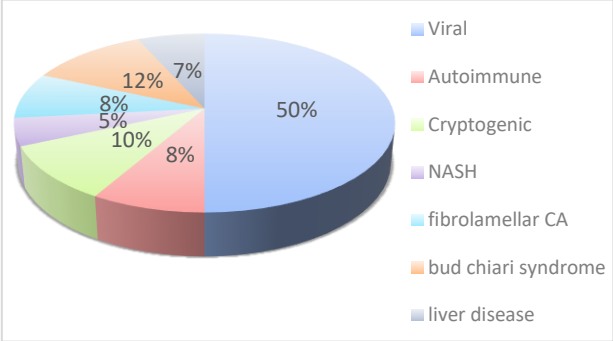

Figure 1. Frequency of Etiology of Hepatocarcinoma.

Of the patients, 15 (25%) had elevated AFP levels, while 45 (75%) did not. Abnormal nodules were present in 47 (78.33%) patients and it was not present in 13 (21.67%)

On frequency of type of nodules, 11 (23.40%) macro-regenerative nodules, 04 (8.51%) FNH nodules, 06 (12.77%) adenoma nodules, 06 (12.77%) dysplastic nodules (SCC), 08 (17.02%) dysplastic nodules (LCC) and 12 (25.53%) hepatocellular carcinoma (Figure 2).

Stratification of age was performed. In patients aged 20-48 years, abnormal nodules were present in 20 (66.7%) patients. In patients aged 49-78 years, abnormal nodules were present in 27 (90.0%) patients with a p-value of 0.028. (Table I).

Table I: Comparison of Age to Determine the Association of Age with Frequency of Abnormal Nodules.

Presence of Abnormal Nodules	Age Group		P-value
	20-48 Years (N=30)	49-78 Years (N=30)	
Yes	20 (66.7%)	27 (90.0%)	
No	10 (33.3%)	03 (10.0%)	0.028

Stratification by age and gender revealed the following: In patients aged 20-48 years, 15% had macro-regenerative nodules, 15% had FNH, 25% had adenoma and dysplastic nodules (SCC), and 20% had dysplastic nodules (LCC). In patients aged 49-78 years, 29.6% had macro-regenerative nodules, 3.7% had FNH, adenoma, and dysplastic nodules (SCC), 14.8% had dysplastic nodules (LCC), and 44.4% had hepatocellular carcinoma (p-value 0.001; Table II). Gender stratification showed that 89.1% of males and 42.9% of females had abnormal nodules (p-value 0.001). In males, 29.3% had hepatocellular carcinoma, while in females, 50% had dysplastic nodules (LCC) (p-value 0.043). Stratification of the etiology of hepatocarcinoma was performed. Patients with abnormal nodules, etiology of hepatocarcinoma was viral in 25 (83.3%) patients, autoimmune in 03 (60.0%), cryptogenic in 05 (83.3%),

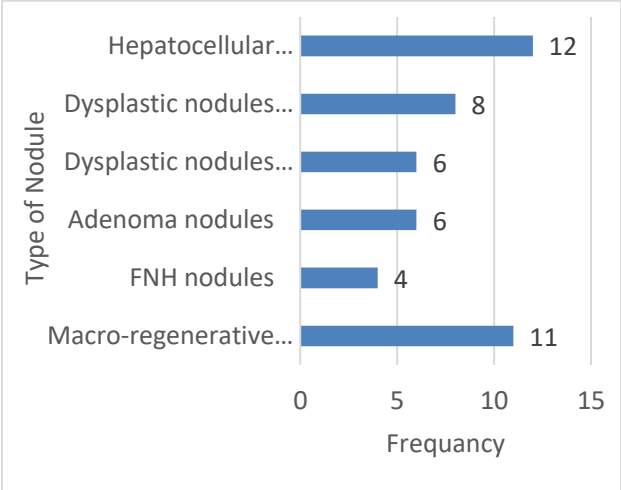

Figure 2. Frequency of Type of Abnormal Nodules.

Table II. Comparison of Age/ Gender to Determine the Association of Age/ Gender with Type of Nodules.

Type of Abnormal Nodules	Age Group		P-value	With Gender		P-value
	20-48 Years (N=20)	49-78 Years (N=27)		Male (N=41)	Female (N=06)	
Macroregenerative Nodules	03 (15.0%)	08 (29.6%)	0.001	11 (26.8%)	00 (0.0%)	
FNH	03 (15.0%)	01 (3.7%)		03 (7.3%)	01 (16.7%)	0.043
Adenoma	05 (25.0%)	01 (3.7%)		04 (9.8%)	02 (33.3%)	
Dysplastic Nodules (SCC)	05 (25.0%)	01 (3.7%)		06 (14.6%)	00 (0.0%)	
Dysplastic Nodules (LCC)	04 (20.0%)	04 (14.8%)		05 (12.2%)	03 (50.0%)	
Hepatocellular Carcinoma	00 (0.0%)	12 (44.4%)		12 (29.3%)	00 (0.0%)	

NASH in 02 (66.7%), fibrolamellar CA in 04 (80.0%), bud chiari syndrome in 05 (71.4%) and liver disease in 03 (75.0%) patients with p-value of 0.920 (Table III).

Stratification of hepatocarcinoma etiology based on abnormal nodules revealed the following: In patients with macro-regenerative nodules, 24% had a viral etiology, 33.3% had autoimmune, 60% had cryptogenic, and 50% had NASH. For FNH nodules, 4% had a viral etiology, 33.3% had autoimmune, and 20% had cryptogenic. In adenoma nodules, 4% had a viral etiology, 33.3% had autoimmune, 20% had cryptogenic, and 25% had fibrolamellar CA. In dysplastic nodules (SCC), 4% had a viral etiology, 50% had fibrolamellar CA, 40% had Budd-Chiari syndrome, and 33.3% had cystic lesions. In dysplastic nodules (LCC), 16% had a viral etiology, 25% had fibrolamellar CA, 40% had Budd-Chiari syndrome, and 33.3% had cystic lesions. In hepatocellular carcinoma nodules, 48% had a viral etiology (p-value 0.043; Table IV).

Discussion

The distribution of different nodules observed during gross inspection of liver explants has long been contentious, particularly regarding their involvement in hepatic carcinogenesis. The objective is to identify hepatic carcinomas in their precursory phases and administer treatment promptly to prevent the progression to advanced malignancy. There is less research on etiology and pathophysiology from South Asia and poor nations, mostly due to the absence of illness registries for liver and other conditions in our community. HCV is the predominant cause of liver cirrhosis in South Asia, accounting for 40% of explant liver cases, followed by hepatitis B virus and alcohol. A Japanese study including 345 individuals indicates that hepatitis B virus infection is a prevalent cause of liver cirrhosis and hepatocellular cancer in Asia and Africa. [12-13]

In the majority of Asia and sub-Saharan Africa, chronic HBV infection has been identified as a dominant risk factor for HCC, with the exception of Japan, where chronic HCV infection is the primary risk factor for HCC. [14]

In our study, the most common etiology in liver explant samples was viral in 30 (50.00%) patients, autoimmune in 05 (8.33%) patients, cryptogenic in 06 (10.00%) patients, NASH in 03 (5.00%) patients, fibrolamellar CA in 05 (8.33%) patients, bud chiari syndrome in 07 (11.67%) patients, and liver disease in 04 (6.67%). The relationships between MRN and HCC have been intensively explored over the last decade, with important studies conducted by the Japanese and American groups. The Japanese group first postulated that MRN was involved in the formation of HCC based on postmortem research on 345 individuals with chronic liver disorders.

Table IIII: Comparison of Etiology of Hepatocarcinoma to Determine the Association of Etiology of Hepatocarcinoma with Type of Nodules

Presence of Abnormal Nodules	Etiology of Hepatocarcinoma							P-value
	Viral (N=30)	Auto-immune (N=05)	Cryptogenic (N=06)	NASH (N=03)	Fibrolamellar CA (N=05)	Bud Chiari Syndrome (N=07)	Cystic Lesions of Liver (N=04)	
Yes	25 (83.3%)	03 (60.0%)	05 (83.3%)	02 (66.7%)	04 (80.0%)	05 (71.4%)	03 (75.0%)	
No	05 (16.7%)	02 (40.0%)	01 (16.7%)	01 (33.3%)	01 (20.0%)	02 (28.6%)	01 (25.0%)	0.920

Table IV: Comparison of Etiology of Hepatocarcinoma to Determine the Association of Etiology of Hepatocarcinoma with Type of Abnormal Nodules.

Type of Abnormal Nodules	Etiology of Hepatocarcinoma							P-value
	Viral (N=25)	Auto-immune (N=03)	Cryptogenic (N=05)	NASH (N=02)	Fibrolamellar CA (N=04)	Bud Chiari Syndrome (N=05)	Cystic Lesions of Liver (N=03)	
Macro regenerative Nodules	06 (24.0%)	01 (33.3%)	03 (60.0%)	01 (50.0%)	00 (0.0%)	00 (0.0%)	00 (0.0%)	
FNH	01 (4.0%)	01 (33.3%)	01 (20.0%)	00 (0.0%)	00 (0.0%)	00 (0.0%)	01 (33.3%)	
Adenoma	01 (4.0%)	01 (33.3%)	01 (20.0%)	01 (50.0%)	01 (25.0%)	01 (20.0%)	00 (0.0%)	
Dysplastic Nodules (SCC)	01 (4.0%)	00 (0.0%)	00 (0.0%)	00 (0.0%)	02 (50.0%)	02 (40.0%)	01 (33.3%)	
Dysplastic Nodules (LCC)	04 (16.0%)	00 (0.0%))	00 (0.0%)	00 (0.0%)	01 (25.0%)	02 (40.0%)	01 (33.3%)	
Hepatocellular Carcinoma	12 (48.0%)	00 (0.0%)	00 (0.0%)	00 (0.0%)	00 (0.0%)	00 (0.0%)	00 (0.0%)	0.043

Other investigations from Japan on 141 liver explants found comparable big regenerating nodules. [15]

In a study it was found 53 cirrhotics with 94 big regenerating nodules. Japanese researchers found ordinary and atypical adenomatous hyperplasia (AAH) in 209 cirrhotics and concluded that AAH may represent a preneoplastic lesion in livers related with non-A non-B hepatitis virus. They also followed up on these surgically removed atypical adenomatous nodules. These nodules were categorized as ordinary adenomatous hyperplasia (OAH) without hepatocellular atypia, atypical AH with structural and cellular atypia inadequate for carcinoma (AAH), and atypical AH with localized malignancy including HCC. On follow-up (range: 12–77 months; mean: 31.4 months), HCC was found in all 3 FM patients, 4 (36%) of 11 AAH patients, and none of 10 OAH patients.[16] It was shown that the incidence of head and neck cancer (HCC) in patients with focal malignancy (FM) or AAH nodules was much greater than that in individuals with OAH nodules, which highlights the preneoplastic character of these nodules. [17]

In our study, abnormal nodules were found in 78.33% of patients. Among those, 11 (23.40%) samples had macro-regenerative nodules, 04 (8.51%) FNH nodules, 06 (12.77%) adenoma nodules, 06 (12.77%) dysplastic nodules (SCC), 08 (17.02%) dysplastic nodules (LCC) and 12 (25.53%) hepatocellular carcinoma.

Later, following additional research on 155 explant specimens (which included 44 from the previous study), they came to the same conclusion: having either type of MRN (type I: dysplasia-free; type II: dysplasia-containing) was linked to a higher incidence of HCC. [18]

Ferrell et al. conducted another investigation in which they examined 110 liver explant specimens, which each had 28 MRNs and three of them included HCC. In addition to this, they suggested that MRN could have a role in HCC. [19]

41 consecutive cirrhotic liver explants from French patients were examined by a French team. Ten livers had 35 adenomatous hyperplasia (prevalence: 24%), of which seven tested positive for HCV. According to their findings, OAH has the ability to proliferate, whereas AAH is thought of as a premalignant lesion in the multistep process of hepatocarcinogenesis. [20]

Our study identified the prevalence of abnormal specimens in Hepatectomy specimens. It provides ground for further studies. It also shows the subtypes of these specimens.

The limitation of our study is that it's a cross-sectional study and doesn't show a correlation between levels of Alfa-fetoprotein and abnormality found in the specimen. Further studies are required to establish the relationship.

Conclusion

Viral causes are commonest in liver explant samples. The commonest Histopathological finding was HCC identified in 25.53% of cases, and macro-regenerative nodules were identified in 23.40% of patients.

References

1. Balogh J, Victor D, Asham EH, Burroughs SG, Boktour M, Saharia A, et al. Hepatocellular carcinoma: a review. *J Hepatocell Carcinoma*. 2016;3:41–53. doi:10.2147/jhc.s61146.
2. Zamor PJ, deLemos AS, Russo MW. Viral hepatitis and hepatocellular carcinoma: etiology and management. *J Gastrointest Oncol*. 2017;8:229–42. doi:10.21037/jgo.2017.03.14.
3. Grąt M, Krasnodębski M, Patkowski W, Wronka KM, Masior Ł, Stypułkowski J, et al. Relevance of Pre-Transplant α-fetoprotein dynamics in liver transplantation for hepatocellular cancer. *Ann Transplant*. 2016;21:115–24. doi:10.12659/aot.894644.
4. Joung J-G, Ha SY, Bae JS, Nam J-Y, Gwak G-Y, Lee H-O, et al. Nonlinear tumor evolution from dysplastic nodules to hepatocellular carcinoma. *Oncotarget*. 2016;8:2076–82. doi:10.18632/oncotarget.10502.
5. Shin H, Jung YW, Kim BK, Park JY, Kim DY, Ahn SH, et al. Risk assessment of hepatocellular carcinoma development for indeterminate hepatic nodules in patients with chronic hepatitis B. *Clin Mol Hepatol*. 2019;25:390–9. doi:10.3350/cmh.2018.0103.
6. Lo RC, Kim H. Histopathological evaluation of liver fibrosis and cirrhosis regression. *Clin Mol Hepatol*. 2017;23:302–7. doi:10.3350/cmh.2017.0078.
7. Almpanis Z. Evaluation of liver fibrosis: "Something old, something new…." *Ann Gastroenterol*. 2016. doi:10.20524/aog.2016.0046.
8. Toyoda H, Tada T, Yasuda S, Mizuno K, Ito T, Kumada T. Dynamic evaluation of liver fibrosis to assess the risk of hepatocellular carcinoma in patients with chronic hepatitis C who achieved sustained virologic response. *Clin Infect Dis*. 2019. doi:10.1093/cid/ciz359.
9. Bansal N, Vij V, Rastogi M. Different nodules identified during liver explant gross examination: relevance and need for sectioning—experience from India. *Int J Hepatol*. 2016;2016:1–6. doi:10.1155/2016/4390434.
10. Lee C-W, Tsai H-I, Lee W-C, Huang S-W, Lin C-Y, Hsieh Y-C, et al. Normal alpha-fetoprotein hepatocellular carcinoma: are they really normal? *J Clin Med*. 2019;8:1736. doi:10.3390/jcm8101736.
11. Hanif H, Ali MJ, Susheela AT, Khan IW, Luna-Cuadros MA, Khan MM, et al. Update on the applications and limitations of alpha-fetoprotein for hepatocellular

carcinoma. *World J Gastroenterol*. 2022;28:216–29. doi:10.3748/wjg.v28.i2.216.

12. Sepanlou SG, Safiri S, Bisignano C, Ikuta KS, Merat S, Saberifiroozi M, et al. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 2020;5:245–66. doi:10.1016/s2468-1253(19)30349-8.
13. Mokdad AA, Lopez AD, Shahraz S, Lozano R, Mokdad AH, Stanaway J, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. *BMC Med*. 2014;12. doi:10.1186/s12916-014-0145-y.
14. Furuya K, Nakamura M, Yamamoto Y, Togei K, Otsuka H. Macroregenerative nodule of the liver. A clinicopathologic study of 345 autopsy cases of chronic liver disease. *Cancer*. 1988;61(1):99–105. doi:10.1002/1097-0142(19880101)61:1<99::aid-cncr2820610117>3.0.co;2-u.
15. Wada K, Kondo F, Kondo Y. Large regenerative nodules and dysplastic nodules in cirrhotic livers: A histopathologic study. *Hepatology*. 1988;8:1684–8. doi:10.1002/hep.1840080636.
16. Terada T, Terasaki S, Nakanuma Y. A clinicopathologic study of adenomatous hyperplasia of the liver in 209 consecutive cirrhotic livers examined by autopsy. *Cancer*. 1993;72(5):1551–6. doi:10.1002/1097-0142(19930901)72:5<1551::aid-cncr2820720511>3.0.co;2-q.
17. Kaji K, Terada T, Nakanuma Y. Frequent occurrence of hepatocellular carcinoma in cirrhotic livers after surgical resection of atypical adenomatous hyperplasia (borderline hepatocellular lesion): a follow-up study. *PubMed*. 1994;89:903–8.
18. Hytiroglou P, Theise ND, Schwartz M, Mor E, Miller C, Thung SN. Macroregenerative nodules in a series of adult cirrhotic liver explants: Issues of classification and nomenclature. *Hepatology*. 1995;21:703–8. doi:10.1002/hep.1840210316.
19. Ferrell L, Wright T, Lake J, Roberts J, Ascher N. Incidence and diagnostic features of macroregenerative nodules vs. small hepatocellular carcinoma in cirrhotic livers. *Hepatology*. 1992;16:1372–81. doi:10.1002/hep.1840160612.
20. Bail BL, Belleannee G, Bernard P-H, Saric J, Balabaud C, Bioulac-Sage P. Adenomatous hyperplasia in cirrhotic livers: Histological evaluation, cellular density, and proliferative activity of 35 macronodular lesions in the cirrhotic explants of 10 adult French patients. *Hum Pathol*. 1995;26:897–906. doi:10.1016/0046-8177(95)90014-4.