Pathological Spectrum and Prognostic Significance of Underlying Liver Disease in Hepatocellular Carcinoma*.

Gregory Y. Lauwers, M.D.
Director GI Pathology Service
Massachusetts general Hospital
Harvard Medical Scholl
Boston, MA, USA

***Pubished in Surg Oncol Clin N Am. 2003 Jan;12(1):13-24.**

INTRODUCTION

Already recognized as one of the most common cancer worldwide, the rising incidence of hepatocellular carcinoma (HCC) in the West including the United States has been attributed to a significant increase in chronic hepatitis C virus (HCV) infection.[11, 14] Concurrently, early detection, improved perioperative management, and advanced surgical techniques have allowed surgical resection to become a suitable therapeutic modality. However, several large clinical series have shown that many patients do not benefit from a long-term survival because of recurrences during the first few years after surgery. It is now recognized that not only tumor-related factors (i.e. vascular invasion, size and multiplicity) but also the quality of the surrounding hepatic parenchyma (i.e. cirrhosis and chronic hepatitis) influence the outcome.[5, 27]

It is well established that cirrhosis represents a fertile ground for the development of HCC. According to an autopsy series, 90% of HCCs arise in cirrhotic livers.[42] Even if some recent surgical series report that between 25% and 49% of HCCs arise in non-cirrhotic livers, it is important to point out that the underlying fibrosis or hepatitis, and subtle morphologic changes appreciated only by a thorough histologic evaluation of the

hepatic parenchyma were overlooked.[7, 13, 46] Thus, one can safely state that the majority of HCCs arise in the setting of chronic liver disease even in the non-cirrhotic liver (i.e., chronic viral hepatitis C and B, alcohol intoxication, and metabolic disorders). Rarely, the host liver is completely free of any subjacent chronic liver disease. In these cases the neoplastic sequence is poorly understood, although an intermediary benign neoplastic process, such as adenoma, has been suspected in female patients.

In this chapter we review the prognostic pathologic characteristics of HCC with specific emphasis on how they relate to the quality of the surrounding hepatic parenchyma, and we also analyze the importance of the underlying chronic liver disease with regard to prognosis.

MACROSCOPIC FEATURES OF HEPATOCELLULAR CARCINOMAS

- **Growth patterns of hepatocellular carcinoma**

HCCs are classified in three types according to their macroscopic appearance[32]. These patterns (nodular, massive and diffuse) are variably associated with cirrhosis and have different predictive value with regard to disease free survival and overall survival.[17] For example, diffuse HCCs (multiple small nodules no larger than 1.0 cm and scattered throughout the parenchyma) are uniquely seen in cirrhotic livers. This variant is associated with portal vein thrombosis and lymph node metastasis in about 70% and 53% of the cases, respectively, and thus associated with grim prognosis.[60] Massive HCCs are large neoplasms that are poorly demarcated from the surrounding parenchyma. The majority (95%) measures over 10 cm and is more frequently found in non-cirrhotic livers.[42, 49] They are frequently observed in young patients and accompanied by portal

vein tumor thrombi.[60] Nowadays, most of the surgically resectable HCCs are of the nodular variant. This type is subclassified in three subtypes: a single nodular type, characterized by a sharp interface with the benign parenchyma (Type 1) (Fig. 1), a single nodular type with extranodular growth (Type 2), and a contiguous multinodular type (Type 3).[23] Nodular type 1 and 2 tumors tend to be observed in advanced cirrhosis. In contrast, 60% of nodular type 3 tumors occurr in non-cirrhotic livers.[60] Importantly, the rate of microvascular invasion is significantly increased from type 1 (17%) to type 2 (25%), and from type 1 to type 3 (53%).[17] Consequently, hematogenous extrahepatic metastatases are observed in only about 14% of type 1 but about 48% of type 2 and 70% of type 3. However, this difference is significant only between type 1 and type 3.[60] Nodular HCCs are associated with better prognosis than the massive and diffuse ones. Type 1 nodular tumors have the best prognosis with only a 20% recurrence rate at two years compared to 60% for type 3, and higher overall survival.[17]

- **Multiplicity of Hepatocellular Carcinoma**

Multiplicity is of HCCs is related to the quality of the surrounding parenchyma, reported in 16% to 74% of cases resected in cirrhotic livers.[28, 35, 36, 60] In comparison, the rate of multiple HCCs is only between 12% and 17% in non-cirrhotic livers.[6, 7] Two mechanisms can result in the multiplicity of tumors, either multicentric carcinogenesis or intra-hepatic metastases.[43, 48] The distinction is difficult and arguments in favor of intrahepatic metastases are: 1) if they represent portal vein tumor thrombi or grew contiguously with vascular thrombi, 2) if they are small compared to the tumor they surround, 3) if a single tumor is present near the main tumor but is much smaller in size

and exhibits the same histology.[43] Intrahepatic metastases can be observed both in cirrhotic and non-cirrhotic livers. However, multicentric carcinogenesis is a characteristic of cirrhotic livers and is supported by biologic and histologic evidence. With regard to the former, molecular studies have demonstrated the multicentric origin of different tumors by analysis of hepatitis B virus (HBV) integration and detection of HCV RNA.[27, 43] In terms of prognosis, multiplicity predicts intrahepatic recurrence after hepatectomy and of shorter postoperative overall survival.[3]

- **Size of Hepatocellular Carcinoma**

The size of HCCs is one of the most important prognostic factors with vascular invasion. As we have recently re-emphasized the 5 cm mark is significant cut off point with regard to survival.[55] HCCs measuring less than 5 cm are also associated with less frequent intra- and extra-hepatic metastases as well as portal vein thrombosis.[29] HCCs occurring in non-cirrhotic livers are generally larger in size[25] and have higher tumor stages[30] than those in developing cirrhotic livers. Kishi reported that average tumor size in non-cirrhotic livers is 9.2 cm, in contrast to 4.7 cm in cirrhotic livers.[25]

The difference in size between HCCs arising in cirrhotic and non-cirrhotic liver may be due to the biology of the neoplasm. Etiologic difference (viral vs. non-viral) may be responsible for various growth rates. In addition, the quality of the functional hepatic reserve may contribute to the difference. Healthy liver parenchyma allow longer survival and hence larger growth and/or faster growth of HCCs.[42] Conversely, because of the limited functional reserve of cirrhotic livers, earlier symptoms lead to the detection of

smaller tumors. Moreover, surveillance programs of chronic hepatitic patients at risk for developing cirrhosis and HCCs undoubtedly play a role in the detection of small lesions.

MICROSCOPIC FEATURES OF HEPATOCELLULAR CARCINOMA

- **Variation of tumor architecture**

Among the five representative architectural growth patterns (microtrabecular, macrotrabecular, compact, acinar and mixed), HCCs in non-cirrhotic livers tend to exhibit a microtrabecular architecture, whereas HCCs arising in a background of cirrhosis show mostly a macrotrabecular arrangement.[25]

In addition, the fibrolamellar variant, composed of large eosinophilic granular and polygonal tumor cells embedded in abundant fibrous stroma, is strongly associated with non-cirrhotic livers. About 10% of non-cirrhotic patients, especially in the younger population, demonstrate fibrolamellar histology and better prognosis.[7, 41, 46]

- **Histologic classification (grading) of HCC**

Edmondson's classification, originally designed in 1954, is based on the degree of differentiation of HCCs.[10] Although widely used, the prognostic predictability of histologic grading has been long debated. Better prognosis for low grade HCC (Fig. 2) is reported by some, while others contest a positive correlation between high grade (Fig. 3) and prognosis.[3, 15, 29, 41, 57] The same is true with regard to the prediction of intrahepatic metastasis.[3, 15, 41]

An association between the grade of HCC and the quality of the surrounding parenchyma has been described. In one series, the odds of having a high grade HCC (grade 3/4) was 1.7 times greater for patients with cirrhosis than patients without

cirrhosis.[41] This observation is important since it may in part account for the worse prognosis of HCCs arising in cirrhotic livers, compared to the tumors arising in non-cirrhotic livers. However, this association could not be confirmed in two large surgical and autopsy series of over 400 cases each.[29, 42]

- **Microscopic Growth Interface**

Four microscopic types of interface between surrounding parenchyma and HCCs can be recognized.[37] These are sinusoidal, replacing, pseudocapsular, and capsular (which can be identified macroscopically). In the sinusoidal pattern, the interface is irregular with malignant hepatocytes extending along the sinusoids into the surrounding parenchyma. The replacing pattern shows an expansile interface between tumor cells and benign hepatocytes that they replace. A pseudocapsule is recognized by the deposition of a thin layer of fibrous bundles between an expansile tumor and the surrounding parenchyma. In comparison, a capsule is defined as a fibrous layer several millimeters thick (Fig. 4).[38] The formation of a capsule is a function of the size of the neoplasm. Capsules are observed in 84% of HCCs measuring between 2-5 cm and in about 45% of those measuring less than 2 cm and more than 5 cm. A fibrous capsule is usually associated with lower nuclear grades, reduced incidence of venous invasion and daughter nodules.[38, 41] Some authors reported that patients with encapsulated HCCs without capsular invasion (or beyond) have improved overall survival and a lower intrahepatic recurrence rate.[3, 41] However, difference in survival based on the type of interface was not recognized in a large multivariate analysis.[29]

Also, whether tumor encapsulation is more often present in non-cirrhotic livers than in cirrhotic livers remains a debated issue.[23, 38, 41]

- **Vascular Invasion**

It is well established that macroscopic vascular invasion portends a poor prognosis with, in most patients, recurrence within one year post-surgery and death within two years after resection.[18, 21] Most importantly, multivariate analyses have emphasized the importance of microscopic vascular invasion as one, if not the most important predictor of overall survival after curative resection or orthotopic liver transplantation (OLT). [16, 29, 39, 53] In addition, since intrahepatic metastases occur through portal vein invasion, microvascular invasion is an indicator of disease-free survival, and this whether the vascular invasion is present in the capsule or beyond the capsule.[48] Risk factors for microscopic portal vein invasion include: diameter of tumor larger than 3cm to 5 cm, higher histologic grade, and mitotic rate > 4 to 10 mitoses per 10 high power fields.[2, 29, 50] With regard to patient management, in an study of 245 patients with HCC that fulfilled the criteria for OLT, Esnaola et al. re-emphasized the strong correlation between size and grade and advocated the pathologic grading of HCCs at the time of pretransplantation ablative therapy to improve the selection of candidates for OLT.[12]

Finally, the relation between cirrhosis and vascular invasion is debated. One series reports that venous invasion is 1.6 times more likely in HCCs arising in cirrhotic liver than non-cirrhotic liver, but these findings have not been confirmed by others.[2, 29, 41]

- **Lymphatic Invasion**

The presence of lymph node metastases is associated with poor prognosis with most patients dying within 18 months post surgery.[51] The incidence of nodal metastases in autopsy series reaches between 25% and 33% of cases, while it is only between 2.2% and 3.2 % in surgical series.[31, 55, 56, 60] The reasons for these lower figures possibly relate to the exclusion of patients for hepatectomy if nodal metastasis is detected on pre-operative imaging studies but also of the absence of systematic lymphadenectomy during hepatectomy. In our own series of over 500 resected HCCs, lymph nodes excision was performed in only 22% of cases.[55]

A lower incidence of lymph node metastases in cirrhotic livers compared to non-cirrhotic livers is reported. Since cirrhosis induces lymphatic obstruction, it may be directly responsible for the decreased rate of nodal metastases.[51] Concurrently, since cirrhosis leads to the formation of collateral lymphatic changes, it may also explain the skip metastases sometimes detected.

- **Mitosis**

Few clinicopathological series have evaluated the prognostic importance of mitotic activity. However, some have reported it as a valid prognostic indicator.[15, 22, 29, 41] Some have also indicated that high mitotic activity is a predictor of portal vein invasion (see above) and that it correlates with a higher nuclear grade.[2, 29] Whether the presence of cirrhosis is associated with higher mitotic activity or not remains debated.[41, 46]

IMPORTANCE OF SURROUNDING HEPATIC PARENCHYMA

As alluded in the introduction, much interest has been recently given to the effect of the subjacent chronic liver disease (cirrhosis and hepatitis) in addition to tumor factors with regard to recurrence and survival.

- **Role of cirrhosis**

The influence of cirrhosis on intrahepatic recurrence and long-term survival has also been debated. In the short term, and despite an initially increased operative risk, cirrhotic patients with a good hepatic reserve (Child-Pugh A) fare as well as non-cirrhotic HCC patients.[53] However, the unfavorable effect of cirrhosis upon recurrence and overall survival becomes apparent over time. In a recent analysis of 145 HCC patients who survived 5 years or more after curative resection, Bilimoria et al. have shown that the presence of moderate to severe fibrosis in the liver remnant was the most important predictor of additional survival.[5] The originality of their approach was to grade the hepatic fibroasis according to the Ishak's guidelines.[20]

Several clinical and tumor characteristics appear to be linked with the degree of fibrosis in the host parenchyma (Figure 5 A and B). For example, cirrhotic patients with HCCs are significantly older on average than patients without cirrhosis.[6, 10, 41] It has also been shown that HCCs arising in non-cirrhotic livers grow faster and are larger than those in cirrhotic livers.[6, 25, 31] However, controversies exist as to the influence of cirrhosis on the histologic grade and the prevalence of microscopic vascular invasion. Some have reported that HCCs arising in non-cirrhotic livers were less well differentiated than HCCs in fibrotic livers, while others have demonstrated that cirrhotic patients had higher odds

of presenting with high grade tumors.[41, 42] With regard to microscopic vascular invasion, recent data fail to support the previously held opinion that it is more prevalent in HCCs arising in cirrhotic livers.[2, 29, 41]

The validity of obtaining a wide surgical margin is also debated in relation to the surrounding parenchyma. Several series have demonstrated that a margin of less than 1 cm is associated with higher rates of intrahepatic recurrence, with most patients experiencing a recurrence within 3 to 5 years after resection.[4, 8] Conversely, others did not find a significant difference in patients with a 1 cm clearance or less.[3] One critical argument undermining the validity of a wide clearance is the frequent discovery of distant synchronous satellites rendering complete tumor eradication impossible. Accordingly, in a series of cirrhotic patients, Lai has demonstrated that 74% of patients had either satellites and / or venous invasion beyond 1cm from the main tumor.[28] This was true whether the tumors measured more or less than 5 cm. However, it is reasonable to assert that a wide surgical clearance is necessary to prevent recurrence along the plane of resection.

- **Role of hepatitis**

Histologic chronic hepatitis is recognized in about a third of patients with HCCs arising in cirrhotic livers and 20% of patients without cirrhosis.[41] Whether the inflammatory activity is an indicator of intrahepatic recurrence and survival remains debated in minor hepatectomy.[1, 26, 39, 44] Interestingly, the increased hepatocytic replication resulting from major hepatectomy has been hypothesized as enhancing multicentric hepatocarcinogenesis in patients with chronic hepatitis.[26] Apparently, the

higher risk for recurrence was observed in patients with the highest regenerative capacity of the residual parenchyma.[1, 9] However, others suggested that it reflects only an increased incidence of intrahepatic metastasis rather than multicentric occurrence.[52]

- **Differences based on the etiology**

Differences between HCCs developing in patients with hepatitis B and those with hepatitis C exist. HCV patients are usually older and have a poorer liver function. Advanced fibrosis / cirrhosis and chronic active hepatitis also characterize this group.[45] With regard to pathology, the mean diameter of HCCs is usually larger in HVB patients than in HCV (6.2-7.9 cm vs. 3.2-5.1 cm). There is also a higher incidence of satellite nodules in HBV patients. Conversely, multicentric tumors are more frequent in HCV positive patients.[34, 47, 58] Overall, HVB patients have a shorter disease-free interval but a better actual survival rate, especially in those treated by surgery.[58] By comparison, for patients with HCV-related HCC, the risk of intrahepatic recurrences never subsides even in later years after complete resection.[19, 59]

In the case of genetic hemochromatosis-related HCCs, a recent publication reported a wider range of histologic features with frequent biliary differentiation in livers with or without cirrhosis.[33]

CONCLUSION

Although controversies persist as to the influence of cirrhosis on the incidence of portal vein invasion and other prognostic indicators of recurrence and survival (histologic grade, mitotic activity, multiplicity), it is becoming clear that the degree of cirrhosis is

important with regard to the long-term survival of HCCs patients . Multicentricity is especially important since it reflects the field carcinogenesis associated with viral hepatitis and particularly HCV chronic infection.[54] A better understanding of the different mechanisms linked to tumor recurrence will help select best candidate for curative surgery as a well as tailor adjuvant therapy such as interferon therapy to each individual patient.[40] To date, the recognition of the importance of vascular invasion, number of tumors and size as well as effect of fibrosis led us to propose a simplified staging of HCC with better survival prognostication of survival.[55]

REFERENCE LIST:

1. Adachi E, Maeda T, Matsuma T, et al. Risk factors for intrahepatic recurrence in human small hepatocellular carcinoma. Gastroenterology 108:768-775, 1995

2. Adachi E, Maeda T, Kajiyama K, et al. Factors correlated with portal venous invasion by hepatocellular carcinoma: univariate and multivariate analyses of 232 resected cases without preoperative treatments. Cancer 77:2022-2031, 1996

3. Arii S, Tanaka J, Yamazoe Y, et al. Predictive factors for intrahepatic recurrence of hepatocellular carcinoma after partial hepatectomy. Cancer 69:913-919, 1992

4. Belghiti J, Panis Y, Farges O, et al. Intrahepatic reccurence after resection of hepatocellular carcinoma complicating cirrhosis. Ann Surg 214:114-117, 1991

5. Bilimoria MM, Lauwers GY, Doherty DA, et al. Underlying liver disease, not tumor factors, predicts long-term survival after resection of hepatocellular carcinoma. Arch Surg 136:528-535, 2001

6. Bismuth H, Chiche L, Castaing D. Surgical treatment of hepatocellular carcinomas in noncirrhotic liver: experience with 68 liver resections. World J Surg 19:35-41, 1995

7. Bralet M-P, Regimbeau J-M, Pineau P, et al. Hepatocellular carcinoma occuring in nonfibrotic liver: epidemiologic and histopathologic analysis of 80 French cases. Hepatology 32(2):200-204, 2000

8. Chen M-F, Hwang, T-L, Jeng L-B, et al. Postoperative reccurence of hepatocellular carcinoma: two hundred five consecutive patients who underwent hepatic resection in 15 years. Arch Surg 129:738-42, 1994

9. Chiu JH, Wu LH, Kao HL, et al. Can determination of the proliferative capacity of the nontumor portion predict the risk of tumor recurrence in the liver remnant after resection of human hepatocellular carcinoma. Hepatology 18:96-102, 1993

10. Edmonson H, Steiner P. Primary carcinoma of the liver: a study of 100 cases among 48,900nnecropsies. Cancer 7:462-503, 1954

11. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 340:745-750, 1999

12. Esnoala NF, Lauwers GY, Mirza NQ, et al. Predictors of microvascular invasion in patients with hepatocellular carcinoma who are candidates for orthotopic liver transplantation. J Gastrointest Surg 5:251-259, 2002

13. Grando-Lemaire V, Guettier C, Chevret S, et al. Hepatocellular carcinoma without

cirrhosis in the West: epidemiological factors and histopathology of the non-tumorous liver. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. J Hepatol 31:508-13, 1999

14. Greenlee RT, Murray T, Bolden S, et al. Cancer statistics, 2000. CA Cancer J Clin 50:7-33, 2000

15. Haratake J, Takeda S, Kasai T, et al. Predictable factors for estimating prognosis of patients after resection of hepatocellular carcinoma. Cancer 72:1178-1183, 1993

16. Hemming AW, Cattral MS, Reed AI, et al. Liver transplantation for hepatocellular carcinoma. Ann Surg 233:652-659, 2001

17. Hui AM, Takayama T, Sano K, et al. Predictive value of gross classification of hepatocellular carcinoma on recurrence and survival after hepatectomy. J Hepatol 33:975-979, 2000

18. Ikai I, Yamaoka Y, Yamamoto Y, et al. Surgical intervention for patients with stage IV-A hepatocellular carcinoma without lymph node metatasis: proposal as a standard therapy. Ann Surg 227(3):433-439, 1998

19. Ikeda K, Saitoh S, Tsubota A, et al. Risk factors for tumor recurrence and prognosis after curative resection of hepatocellular carcinoma. Cancer 71:19-25, 1993

20. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. J Hepatol 22:696-699, 1995

21. Izumi R, Shimizu K, Ii T, et al. Prognostic factors of hepatocellular carcinoma in patients undergoing hepatic resection. Gastroenterology 106:720-27, 1994

22. Iwatsuki S, Dvorchik I, Marsh J W, et al. Liver transplantation for hepatocellular carcinoma: a proposal of a prognostic scoring system. J Am Coll Surg 191:389-94, 2000

23. Kanai T, Hirohashi S, Upton MP, et al. Pathology of small hepatocellular carcinoma. A proposal for a new gross classification. Cancer 60:810-819, 1987

24. Kemeny F, Vadrot J, Wu A, Smadja C, Meakins JL, Franco D. Morphological and histological features of resected hepatocellular carcinoma in cirrhotic patients in the West. Hepatology 9:253-257, 1989

25. Kishi K, Shikata T, Hirohashi S, Hasegawa H, Yamazaki S, Makuuchi M. Hepatocellular carcinoma. A clinical and pathologic analysis of 57 hepatectomy cases. Cancer 51:542-548, 1983

26. Ko S, Nakajima Y, Kanehiro H, et al. Significant influence of accompanying chronic hepatitis status on recurrency of hepatocellular carcinoma after hepatectomy: result of multivariate analysis. Ann Surg 224:591-595, 1996

27. Kobayashi S, Hayashi H, Itoh Y, et al. Detection of minus-strand hepatitis C virus RNA in tumor tissues of hepatocellular carcinoma. Cancer 73:48-52, 1994

28. Lai ECS, You KT, Ng OL, Shek TW. The pathological basis of resection margin for hepatocellular carcinoma. World J Surg 17:786-791, 1993

29. Lauwers G, Balis U, Regimbeau J-M, et al. Prognostic histologic Indicators of curatively resected hepatocellular carcinomas: a multi-institutional analysis of 425 patients with definition of a histologic prognostic index. Am J Surg Pathol 26(1):25-34, 2002

30. Le Treut YP, Pons J, Hardwigsen J, et al. Hepatocellular carcinoma in a non-cirrhotic liver. Presentation of series of 77 operated patients. Chirurgie 124(5):485-493, 1999 French.

31. Liver Cancer Study Group of Japan. Primary liver cancer in Japan. Clinicopathological features and results of surgical treatment. Ann Surg 211:277-287, 1990

32. Liver Cancer Study Group of Japan. Classification of Primary Liver Cancer. Tokyo, Kanehara, 1997, pp5-6

33. Marcos M, Dubois S, Bralet MP, et al. Primary liver carcinoma in genetic hemochromatosis reveals a broad histologic spectrum. Am J Clin Pathol 116:738-743, 2001

34. Miyagawa S, Kawasaki S, Makuuchi M, et al. Comparison of the Characteristics of hepatocellular carcinoma between hepatitis B and C viral infection: tumor multicentricity in cirrhotic liver with hepatitis C. Hepatology 24:307-310, 1996

35. Nagao T, Inoue S, Goto S, Mizuta T, Omori Y, Kawano N et al. Hepatic resection for hepatocellular carcinoma. Clinical features and long-term prognosis. Ann Surg 205:33-40, 1987

36. Nagao T, Inoue S, Yoshimi F, Sodeyama M, Omori Y, Mizuta T et al. Postoperative recurrence of hepatocellular carcinoma. Ann Surg 211:28-33, 1990

37. Nakashima T, Kojiro M. Pathologic characteristics of hepatocellular carcinoma. Semin in Liver Disease 6:259-66, 1986

38. Ng IO, Lai EC, Ng MM, Fan ST. Tumor encapsulation in hepatocellular carcinoma. A pathologic study of 189 cases. Cancer 70:45-49, 1992

39. Nigam A, Zhurak M, Boitnott JR, et al. Factors affecting survival in western patients following curative resection for hepatocellular carcinoma. [abstruct] Gastroenterology 108:A1235, 1995

40. Nishiguchi S, Kuroki T, Nakatani S, et al. Randomized trial of effects of interferon-

alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. Lancet 346(8982):1051-1055, 1995

41. Nzeako UC, Goodman ZD, Ishak KG. Hepatocellular carcinoma in cirrhotic and noncirrhotic livers. A clinico-histopathologic study of 804 North American patients. Am J Clin Pathol 105:65-75, 1996

42. Okuda K, Toshiro N, Sakamoto K, et al. Hepatocellular carcinoma arising in noncirrhotic and highly cirrhotic livers: A comparative study of histopathology and frequency of hepatitis B markers. Cancer 49:450-455, 1982

43. Sakamoto M, Hirohashi S, Tsuda H, et al. Multicentric independent development of hepatocellular carcinoma revealed by analysis of hepatitis B virus integration pattern. Am J Surg Pathol 13(12):1064-67, 1989

44. Shirabe K, Takenaka K, Taketomi A, et al. Postoperative hepatitis status as a significant risk factor for recurrence in cirrhotic patients with small hepatocellular carcinoma. Cancer 77:1050-1055, 1996

45. Shiratori Y, Shiina S, Imamura M, et al. Characteristic difference of hepatocellular carcinoma between hepatitis B- and C- viral infection in Japan. Hepatology 22:1027-1033, 1995

46. Smalley SR, Moertel CG, Hilton JF, Weiland LH, Weiand HS. Hepatoma in the noncirrhotic liver. Cancer 62(7):1414-1424, 1988

47. Tanabe G, Nuruki K, Baba Y, et al. A comparison of hepatocellular carcinoma associated with HBV or HCV infection. Hepato-Gatroenterology 46:2442-2446, 1999

48. Toyosaka A, Okamoto E, Mitsunobu M, et al. Pathologic and radiographic studies of intrahepatic metastasis in hepatocellular carcinoma: the role of efferent vessels. HPB Surg 10:97-104, 1996

49. Trevisani F, Caraceni P, Bernardi M, et al. Gross pathologic types of hepatocellular carcinoma in Italian patients. Relationship with demographic, environmental, and clinical factors. Cancer 72:1557-1563, 1993

50. Tsai HP, Lee WC, Jeng LB, et al. Clinicopathologic factors influencing long-term survival after resection for hepatocellular carcinoma. Changgene Yi Xue Za Zhi 23:529-535, 2000

51. Uenishi T, Hirohashi K, Shuto T, et al. The clinical significance of lymph node metastasis in patients undergoing surgery for hepatocellular carcinoma. Surg Today 30:892-895, 2000

52. Ueno S, Tanabe G, Yoshida A, et al. Postoperative prediction of and strategy for metastatic recurrent hepatocellular carcinoma according to histologic activity of

hepatitis. Cancer 86:248-254, 1999

53. Vauthey JN, Klimstra D, Franceschi D, et al. Factors affecting long-term outcome after hepatic resection for hepatocellular carcinoma. Am J Surg 169:28-34, 1995

54. Vauthey JN, Walsh G, Vlastos G, Lauwers G. Importance of field cancerisation in clinical oncology. Lancet Oncol 1:15-16, 2000

55. Vauthey JN, Lauwers GY, Esnaola NF, et al. Simplified staging for hepatocellular carcinoma. J Clin Oncol 20:1527-1536, 2002

56. Watanabe J, Nakashima O, Kojiro M. Clinicopathologic study on lymph node metastasis of hepatocellular carcinoma: a retrospective study of 660 consecutive autopsy cases. Jpn J Clin Oncol 24:37-41, 1994

57. Wayne JD, Lauwers GY, Ikai I, et al. Preoperative predictors of survival after resection of small hepatocellular carcinomas. Ann Surg 235:1-10, 2002

58. Wu CC, Tang JS, Lin MC, et al. Comparison of liver resection for hepatocellular carcinoma in hepatitis B and hepatitis C-related cirrhotic patients. Hepato-Gastroenterology 46:651-655, 1999

59. Yamanaka N, Tanaka T, Tanaka W, et al. Correlation of hepatitis virus serologic status with clinicopathologic features in patients undergoing Hepatectomy for Hepatocellular Carcinoma. Cancer 79:1509-1515, 1997

60. Yuki K, Hirohashi S, Sakamoto M, Kanai T, Shimosato Y. Growth and spread of hepatocellular carcinoma. A review of 240 consecutive autopsy cases. Cancer 66:2174-2179, 1990