Risk factors for early intra-hepatic recurrence in 240 patients with hepatocellular carcinoma who underwent curative resection: Analysis of preoperative radiologic and laboratory findings and postoperative pathologic findings.

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Directed by Professor Mi-Suk Park

The Master's Thesis
submitted to the Department of Medicine
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

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June 2008

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June 2008

ACKNOWLEDGEMENTS

I would like to express my gratitude to my supervisor Prof. Mi-Suk Park and committee members, Prof. Joon Seok Lim and Prof. Mijin Yun for their sincere directions and encouragement.

I wish to express my gratitude to my old school, Yonsei university, college of medicine, which has provided me with the exceptional privilege of education, opportunities, and most of all pride. I will endeavor in maintaining the pioneering spirit and reluctance towards prejudice, and deeply hope that this institute will remain so.

Honsoul Kim

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<ABSTRACT>

Risk factors for early intra-hepatic recurrence in 240 patients with hepatocellular carcinoma who underwent curative resection: Analysis of preoperative radiologic and laboratory findings and postoperative pathologic findings.

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To identify pre-operative MDCT, laboratory, and pathologic features that indicates higher risk for early intrahepatic recurrence of hepatocellular carcinoma (HCC) after surgery in a large-scale study. We retrospectively reviewed the preoperative three-phase MDCT and laboratory data for 240 HCC patients who underwent curative resection; tumor size, number, gross shape, capsule integrity, margin, portal vein thrombosis (PVT), AFP, and PIVKA-Ⅱ levels were assessed. Histopathological differentiation, capsule, and micro-vessel invasion were recorded. HCC recurred in 61 patients within six months. In univariate analysis, large tumor size, shape, poor capsule integrity, elevated AFP, and PIVKA-Ⅱ, histopathologically proven PVT, Glisson's capsule penetration, microvascular invasion, and poor differentiation showed statistical significance. In multivariate analysis, only histopathological microvascular invasion and poor differentiation achieved statistical significance. Preoperative CT and laboratory parameters showed limited value, while the presence of microscopic vascular invasion, and poorly differentiated HCC correlated with higher risk of early post-operative

recurrence.

Key words : Hepatocellular carcinoma, preoperative CT, postoperative pathologic findings, early recurrence, curative resection.

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I. INTRODUCTION

Hepatic resection is the mainstay of curative treatment for HCC [1-4]. However, debate is ongoing over the best way to select candidates for surgery and how to decide the extent of hepatectomy. The decision whether or not to proceed with surgery depends mainly on the functional reserve of the liver and the estimated risk of recurrence [3, 5-9]. Although an ideal limit of residual liver function to serve as a guideline in choosing a specific treatment modality has not yet been established, preoperative measurement of liver function is not difficult. Meanwhile, preoperative estimation of the risk of tumor recurrence remains ambiguous. Therefore, it seems that the stratification of preoperative risk factors for tumor recurrence is important not only in deciding whether or not to proceed with surgical resection, but also in determining the optimal extent of hepatectomy in HCC if surgery is to proceed.

The purpose of this study was to identify risk factors that could be detected preoperatively and postoperatively for early recurrence of HCC after resection of

curative intention. For the preoperative decision about hepatic resection, we analyzed dynamic contrast-enhanced CT scans and tumor markers. For post-operative treatment planning, we evaluated surgical histopathologic features.

II. MATERIALS AND METHODS

1. Patient selection and review of medical history

We retrospectively reviewed the medical records of 414 consecutive patients who received hepatic resection for HCC between January 2001 and February 2006 in one tertiary medical center. Excluded from the study were patients who either received liver transplantation or lobectomy for palliative treatment (n=22); patients whose preoperative radiologic evaluation was not performed with a three-phase dynamic enhanced multi-detector CT (MDCT) scan within one month before surgery (n=119); patients whose tumor pathology was not that of pure hepatocellular carcinoma, for example combined hepatocellular-cholangiocarcinoma (n=23); and patients who did not complete the six-month follow-up period (n=10). This process defined a study population of 240 patients. 181 men and 59 women between 31 and 76 years old (mean ± standard deviation: 53.51 ± 9.04 years) were included. 101 patients had experience of receiving transarterial chemoembolization prior to surgery, while 139 had no experience of treatment prior to surgery. The study population was later divided into early recurrence and non-recurrence groups on the basis of six-month follow-up results.

2. CT Image acquisition

Preoperative CT images were obtained by one of the following commercially available MDCT; 4, 16, and 64 channel MDCT scanners (Somatom Plus 40, Sensation 16, and Sensation 64, Siemens Medical Systems, Erlangen, Germany). Each patient was injected with 120 to 150 mL of iobitridol (Xenetix 300; Guerbet, Aulnay-sous-Bois, France) or iohexol (Omnipaque 300; Daiichi Pharmaceutical, Tokyo, Japan) through an 18-gauge venous cannula placed at the antecubital fossa for contrast injection using a mechanical injector with a fixed duration of 30 seconds. After unenhanced images were obtained, dynamic three-phase imaging was performed. The hepatic arterial, portal venous, and delayed phases were scanned at 15 seconds, 40 seconds, and 180 seconds after the aorta reached 100 HU, respectively.

3. Preoperative CT finding analysis

The preoperative CT scan of each patient was reviewed by a gastrointestinal radiologist with 8 years of experience in hepatobiliary imaging. No clinical, laboratory, or pathology information other than the presence of HCC was provided during image analysis.

The tumor's size (the longest diameter on the axial plane), shape, capsule, and margin were evaluated. Tumor shape was classified into four categories: nodular (round in shape with size less than 5 cm), massive expanding (round in shape with size equal to or greater than 5 cm), multinodular confluent, or infiltrative type. Tumor capsule integrity was assessed on a five-point scale according to the percentage of the tumor surface covered by the capsule (grade 1: covering more than 75%, grade 2: covering 51 to 75%, grade 3: covering 26 to 50%, grade 4: covering no more than 25% or absent capsule, and grade 5: could not be evaluated because of complete necrosis). The number of

identifiable tumor lesions that appeared to be hyperdense on arterial phase and washed out on equilibrium phase images was counted. Portal vein thrombosis was considered to be present if a filling defect in the portal vein was observed at the portal phase of contrast enhancement.

4. Preoperative laboratory findings

Serology studies of antigen and antibodies with or without supplemental DNA studies revealed evidence of either active or inactive states of underlying B viral hepatitis (HBV) in 217 patients and C viral hepatitis (HCV) in 14 (one patient had both B and C viral hepatitis). Eight patients did not show evidence of either HBV or HCV hepatitis. Two patients had no records of serology tests for reasons that could not be determined.

Alpha-fetoprotein level (AFP) and protein induced by vitamin K absence-Ⅱ (PIVKA-Ⅱ) levels were recorded if blood samples obtained within a month prior to surgery were available.

5. Surgical pathology parameters

The surgical pathology report for each patient was reviewed; and features including the presence or absence of portal tumor thrombi, microscopic vessel invasion, tumor capsule formation, and the success or failure of obtaining a tumor-free surgical resection margin were recorded. The degree of tumor differentiation was categorized according to the Edmondson-Steiner classification as low-grade (Edmondson-Steiner grade I and Ⅱ) and high-grade tumor (Edmondson-Steiner Ⅲ and Ⅳ). Tumor differentiation could not be assessed in 39 patients because of extensive necrosis of the tumor, and these patients

were recorded as having missing data. The extent of tumor necrosis reported by the pathologist was recorded; we considered necrosis of 95% or more of the entire tumor as nearly total necrosis and classified each patient either in the group of nearly total necrosis (≥95% necrosis of the whole tumor) or the low necrosis group (<95% necrosis of whole tumor). The physical relation of the tumor with the Glisson's capsule was categorized according to a three-point scale (grade 1: tumor separated from the Glisson's capsule by normal liver parenchyma, grade 2: direct contact of tumor with the Glisson's capsule without microscopic evidence of tumor penetration, and grade 3: microscopic evidence of tumor penetrating the Glisson's capsule).

6. Follow-up after surgery

Patients were regularly followed up with dynamic CT scans and serum tumor markers (AFP and/or PIVKA-II) at 3 to 6 months after surgery using additional liver MRI, conventional angiography, and/or ultrasound if necessary. Early recurrence was defined as tumor recurrence identified within six months after surgery.

Post-operative HCC recurrence was considered to be present if either a focal lesion was identified measuring at least two centimeters with arterial hypervascularization demonstrated in at least two imaging modalities, or a hypervascular nodule exceeding two centimeters was noted in a single imaging study in the presence of AFP over 400 ng/ml [10]. In addition, any new nodule that had appeared during the follow-up period exceeding 2 cm in size, or a newly appearing nodule showing contrast washout leading to hypoattenuation in the equilibrium phase, regardless of size, was considered to be highly suspicious for HCC recurrence [11] and was confirmed with supplemental biopsy or short-term follow-up CT or MRI.

7. Statistical analysis

The two-sample t-test, Chi-Square, and Fisher's exact tests were performed for univariate analysis, and a logistic regression test was performed for multivariate analysis. Statistical significance was accepted if the p value was less than 0.05.

III. RESULTS

Among the 240 patients who were included in the study, 61 patients were proved to have tumor recurrence within six months. The other 179 patients did not show evidence of tumor recurrence during the same period. No statistically significant difference was found in the age (p=0.226) and sex (p=0.085) profile between the early recurrence and non-recurrence groups.

According to univariate analysis for preoperative findings, no significant difference in early recurrence was noted according to the viral pathogen that caused the hepatitis (p=0.151) or the history of receiving previous trans-arterial chemoembolization (p=0.616). However, the serum levels of AFP (p=0.015) and PIVKA-Ⅱ (p=0.008) were significantly higher in the early recurrence group.

Univariate analysis of the preoperative CT features showed a statistically significant increase in the risk for early post-operative HCC recurrence related to the shape of the tumor (p=0.028; Figure 1), size (p=0.018), and capsule integrity (p=0.046). However, the number of tumors (p=0.118), the number of the liver segments involved with the tumor (p=0.526), the presence of portal vein thrombosis (p=0.216), and tumor margins

(p=0.564) did not show statistical significance (Table 1).

Table 1. Univariate analysis of preoperative CT and laboratory parameters in patients with and without early HCC recurrence after lobectomy.

Risk factors	No early recurrence (n=179)	Early recurrence (n=61)	p value
Age (years, mean ± standard deviation)	53.96±9.11	52.34±8.50	0.226*
Sex (M/F)	130/49	51/10	0.085$
Hepatitis			0.151&
HBV	163	54	
HCV	7	7	
Non-B non-C	7	1	
TACE history (present/absent)	77/102	24/37	0.616$
AFP	791.25±3022.51	7021.37±32982.44	0.015*
PIVKA-II	287.23±556.55	586.60±756.89	0.008*
Size (cm)	4.32±2.23	5.30±2.90	0.018*
Number of tumors (single/multiple)	167/12	53/8	0.118$
Number of involved segments (single/multiple segments involved)	80/99	25/36	0.526$
Shape of tumor			0.028$
Nodular	74	13	
Massive expanding	29	12	
Multinodular confluent	63	27	
Infiltrative	13	9	
CT Portal vein thrombosis (absent/present)	165/14	53/8	0.216$
Margin (well defined/poorly defined)	155/24	51/10	0.564$
Capsule (present/absent or uncertain)	95/84	24/37	0.064$
Capsule integrity (35 patients not assessable due to necrosis)			0.046$
> 75%	57	10	
75 – 50%	38	13	
50 – 25%	25	9	
< 25%	32	21	

*: Student t test
$: Chi-Square test

[&]: Fisher's exact test
(Statistical significance was accepted at p value lower than 0.05)

Univariate analysis showed that histopathology parameters such as the presence of portal vein tumor thrombi (p=0.023), microscopic vascular tumor invasion (p<0.001), physical contact of the Glisson's capsule by the tumor with or without tumor penetration (p=0.033), failure to achieve tumor cell clear resection margins (p=0.019), and Edmondson-Steiner grade Ⅲ & Ⅳ (p=0.001) indicated a higher risk of early post-operative HCC recurrence that was statistically significant. The presence or absence of microscopic capsule formation (p=0.132), and the presence of nearly total necrosis (p=0.212) did not show statistical significance.

Table 2. Univariate analysis of histopathology parameters of surgical specimens in patients with and without early HCC recurrence after lobectomy.

Risk factors	No early recurrence (n=179)	Early recurrence (n=61)	p value
Portal vein tumor thrombi (absent/present)	173/6	54/7	0.023[&]
Glisson's capsule			0.033[$]
No contact with Glisson's	54	11	
Abutting capsule	121	45	
Infiltration of capsule	4	5	
Resection margin (negative/positive)	175/4	55/6	0.019[&]
Microscopic vascular invasion (negative/positive)	132/47	28/33	<0.001[$]
Tumor capsule formation (present/absent)	119/60	34/27	0.132[$]
Necrosis (< 95% / ≥95%)	119/59	47/15	0.212[$]
Edmondson grade (Ⅰ&Ⅱ/Ⅲ&Ⅳ) (39 patients were not assessable due	84/59	19/39	0.001[$]

to extensive necrosis)

*: Student t test
$: Chi-Square test
&: Fisher's exact test
(Statistical significance was accepted at p values lower than 0.05)

Multivariate analysis with backward logistic regression revealed a statistically significant increase of risk for early post-operative tumor recurrence caused by the presence of microscopic vascular invasion proved by histology (Odds ratio=2.557) and Edmondson-Steiner grade Ⅲ & Ⅳ (Odds ratio=2.814) (Table 3).

Table 3. Multivariate analysis of laboratory, preoperative CT, and surgical pathology parameters in patients with and without early HCC recurrence after lobectomy.

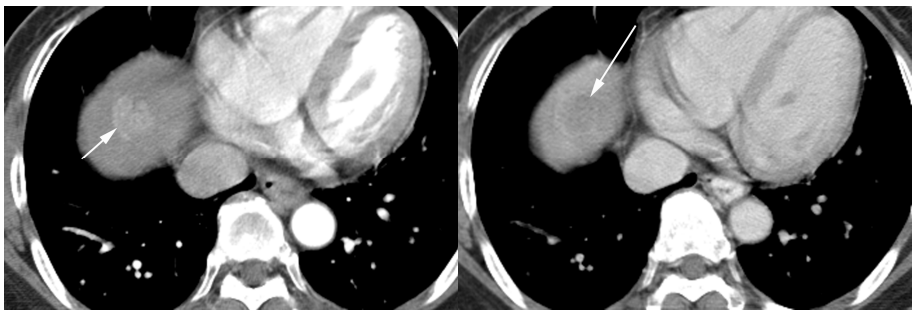
	Coefficient	S.E.	Significance	Odds ratio
Microscopic vascular invasion	0.939	0.358	0.009	2.557
Edmondson grade (Ⅰ&Ⅱ/Ⅲ&Ⅳ)	1.035	0.368	0.005	2.814

IV. DISCUSSION

Intrahepatic tumor recurrence of HCC after treatment has been explained by two different mechanisms, either secondary metastasis or *de novo* development of a separate primary HCC [12]. Chronic viral hepatitis and/or cirrhosis are usually present in HCC patients, and these conditions are risk factors substantially contributing to the development of HCC [12-14]. Therefore, even if a primary HCC is cured, HCC recurrence by newly developed tumors is still more or less inevitable. However, it is very difficult to differentiate intrahepatic metastasis that originated from the primary tumor from

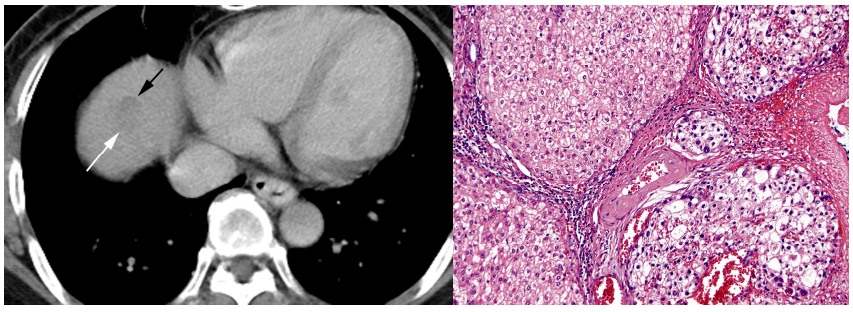
newly developed *de novo* HCC. Imamura et al. suggested that early and late peak recurrence of HCC after resection could roughly represent intra-hepatic metastasis and *de novo* HCC development, respectively [15]. Their suggestion is based on the analysis of the different factors associated with early (non-anatomical resection, presence of micro-vessel invasion, and serum AFP > 32 ng/ml) and late (hepatitis activity, multiple

Figure 1. A 56-year-old female with early recurrent HCC after segmentectomy. The AFP level from a blood sample obtained the same day the CT scan was performed was 1076.84 IU/mL.



A **B**

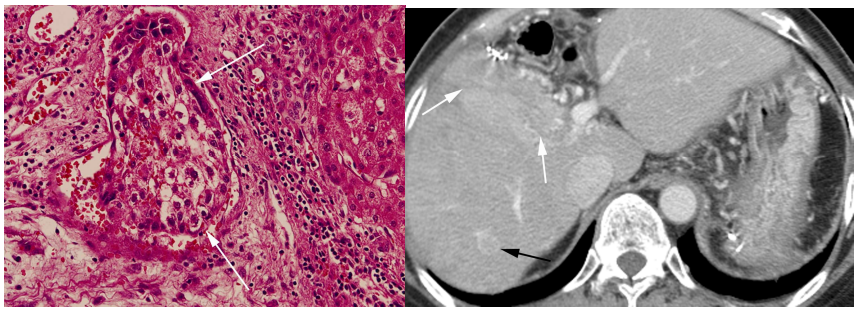
1A. Arterial phase of the preoperative CT obtained by a 4-slice MDCT. A mass measuring approximately 2.2 cm in diameter later proven by surgery to be hepatocellular carcinoma is observed at the dome of liver presenting as a multinodular confulent nodule (arrow). 1B. Early washout (arrow) of contrast of this nodule is observed during the portal venous phase, an enhancement pattern consistent with HCC.



C D

1C. The equilibrium phase of the preoperative CT. A linear enhancement structure (black arrow) is noted which is considered to be the radiological

capsule. The radiological capsule was assessed to cover less than 25% of the tumor circumference (capsule grade 4). The margin of the nodule is poorly defined (white arrow). 1D. Microscopic findings show high grade (Edmondson-Steiner grade Ⅲ) hepatocellular carcinoma, original magnification, x 200; hematoxylin-eosin [H&E].



E F

1E. Microscopic examination revealed frequent microvessel tumor invasion (white arrows), original magnification, x 200; hematoxylin-eosin [H&E]. 1F. Marked increase in AFP level (10865.27 IU/mL) was observed at the fifth postoperative-month blood test. He underwent a CT scan, which revealed an infiltrative hypervascular mass (white arrow). Another 1 cm sized hypervascular nodule (black arrow) is noted, which further increased in size and measured to be 2.2cm at a CT scan performed 4 months afterwards, findings highly suggestive of a HCC nodule.

tumors, and gross tumor classification) recurrence. Although the pathogenesis of recurrence is still under investigation, early recurrence has stronger clinical importance compared with late recurrence considering the morbidity and mortality of surgery, cost-effectiveness, and potential benefits of alternative treatments. To our knowledge, however, reports concerning the evaluation of the radiologic, laboratory, and surgical pathological factors associated with early (within six months) recurrence of HCC after curative resection in a large-scale study remain limited.

Large tumor size [16], absence of the tumor capsule, indistinct margins [17], and elevated serum levels of AFP [15, 18] have been reported as parameters increasing the risk of early

tumor recurrence. In the current study, univariate analysis showed AFP (p=0.015) and PIVKA-II (0.008) levels to have statistical significance for predicting the risk of HCC recurrence within six months. However, the role of tumor markers seems to be limited because statistical significance was not reproduced in multivariate analysis.

Size, gross shape of the tumor, and capsule integrity were other radiological findings that showed significance suggesting higher risk of early tumor recurrence in univariate analysis. However, these factors failed to maintain statistical significance in multivariate analysis.

The presence of portal vein thrombosis identified in preoperative CT scans did not have statistically significant influence in the early HCC recurrence (p=0.216). This unexpected result could be due either to selection bias or the small number of patients with positive portal vein thrombosis in our study. However, the observation that portal vein thrombosis did not show statistical significance in early HCC recurrence is consistent with a previous article [17].

Risk factors reported in previous articles on the basis of surgical pathology are relatively more consistent with each other. The presence of microscopic vascular invasion is a factor repeatedly indicated as a potent risk factor [15, 16, 18, 19]. Advanced histopathologic grade is also reported to have statistical significance for HCC recurrence [18, 20]. Similarly, our study showed microscopic vascular invasion and advanced histopathologic grades to have sustained statistical significance suggesting a higher risk of early recurrence in multivariate analysis. Other factors, including positive portal vein tumor thrombi in the surgical specimen and direct tumor contact with the Glisson's capsule with or without tumor penetration, were parameters with statistical

significance only in univariate analysis.

Previous history of trans-arterial chemoembolization and the presence of nearly total necrosis of the tumor with or without previous treatment did not show statistical significance in relation with the rate of early tumor recurrence. In general practice, more advanced tumors tend to receive more intensive preoperative adjuvant therapies; thus, we believe selection bias with respect to the degree of preoperative adjuvant therapies received does exist in our study population. In spite of the statistically insignificant results produced by the current study, we do not suggest that preoperative adjuvant therapies are unnecessary.

V. CONCLUSION

In conclusion, HCC patients with positive microscopic vascular invasion of the tumor and high Edmondson-Steiner grades have a statistically significantly higher risk of early postoperative recurrence. Most parameters of HCC that are detectable preoperatively, including clinical and radiological features, have limited significance in the prediction of postoperative early recurrence.

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< ABSTRACT (IN KOREAN)>

근치적 간절제술을 시행받은 간암 240 증례의 조기 재발 위험인자: 수술전 영상의학, 임상병리 및 해부병리 소견에 대한 분석

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김 한 솔

본 연구는 수술전 전산화 단층촬영, 임상병리 및 해부병리 소견을 바탕으로 근치적 간절제술을 시행받은 간암 환자에서 대규모의 환자군을 대상으로 조기 재발의 위험인자를 규명하는데 있다. 240 명의 근치적 간절제술을 시행받은 간암 환자를 대상으로 전산화 단층촬영 및 임상병리 소견을 조사하였다; 종양의 크기, 숫자, 모양, 피막의 상태, 종양의 경계, 간 문맥 종양 혈전, AFP, PIVKA-II 혈중 수치가 측정되었다. 병리 소견상 간암의 분화도, 피막 형성, 미세 혈관 종양 침습 여부를 조사하였다. 61례의 환자에서 근치적 수술 후 6개월 이내에 간암이 재발하였다. 단변량 분석시에 종양의 크기, 모양, 불완전한 피막형성, AFP 및 PIVKA-II 수치가 증가된 경우, 해부

병리 소견상 간문맥의 종양 침습, Glisson’s 피막 침습, 미세혈관 종양 침습, 종양 저분화도가 통계적으로 유의한 변수들이었다. 다변량 분석시 해부병리 소견상 미세 혈관 침습과 종양 저분화도만 통계적으로 유의한 변수로 관찰되었다. 수술후 간암의 조기 재발을 예측하는데 있어서 수술전 전산화 단층촬영 및 임상병리 소견의 역할은 제한적인 반면 병리 소견상 미세혈관의 종양 침습과 종양의 저분화도가 유의한 변수로 작용하였다.

핵심되는 말 : 간암, 수술전 전산화 단층촬영, 수술후 병리소견, 조기 재발, 근치적 간절제술.