The accuracy and prognostic value of radiological tumor staging compared with pathological staging in hepatocellular carcinoma

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<ABSTRACT>

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Background & Aims: A staging discrepancy can exist between the preoperative radiological status and the postoperative pathological status after surgical resection of hepatocelluar carcinoma, since radiological studies have a limited ability to detect microvascular invasion and satellite nodules. This study compared the accuracy of radiological and pathological tumor staging, and each-long term outcome.

Methods: Total 196 patients undergoing curative resections between 2000 and 2006 were enrolled. TNM staging of the American Joint Commission on Cancer (6th ed.) was adopted. Radiological staging was based upon computed tomography and hepatic angiography, with or without liver magnetic resonance imaging. Predictors of survivals were identified using the Kaplan–Meir test and the Cox model. The prognostic value of each staging was further evaluated by entering each stage into the Cox regression model. The median follow-up duration was 32.5 months after surgery.

Results: When tumors were re-staged after surgery, 76 patients (38.8%)

experienced stage shifts, most likely due to the newly diagnosed vascular invasions (68 patients, 89.4%). When tumors were stratified by pathological stage, the differences in overall survival (OS) and disease-free survival (DFS) were notable between stages I and II (p = 0.017/0.045, respectively) and between stages II and III (p = 0.023/0.047, respectively), whereas there were no differences in either OS or DFS between stages II and III, by radiological staging. Therefore, pathological staging were superior in prediction of survivals. Independent factors for OS included tumor number, size and vascular invasion, while those for DFS were only tumor number and size. Regarding vascular invasion, tumor number, size, and Edmondson grade were identified as independent determinants. When tumors recurred, vascular invasion at surgery increased the incidence of multiple tumors, portal vein invasion, and diffuse-infiltrative patterns (all $p<0.001$), resulting in the significantly poorer OS.

Conclusions: The accuracy of radiological staging in hepatocelluar carcinoma compared with pathological staging was only 61.2%, most likely due to newly confirmed vascular invasions, and the latter was a better predictor of survival. Additionally, vascular invasion increased incidences of adverse relapse patterns with multiple tumors, portal vein invasion, and diffuse-infiltrative patterns. Therefore, these clinicopathological patterns are crucial to predict prognosis, which could be also useful for determining prognosis and treatment plans, especially in non-surgical candidates.

Key words : hepatocellular carcinoma, radiological staging, pathological staging, prognosis, vascular invasion

The accuracy and prognostic value of radiological tumor staging compared with pathological staging in hepatocellular carcinoma

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I. Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide.[1,2] Unlike in other malignancies such as cancers of the lung, breast, stomach, and colorectum, various staging systems have been applied in HCC, as the prognosis is affected not only by the anatomical features of the tumor but also by the underlying disease of the organ itself.[3] Currently, the Okuda staging system, the tumor node metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), the Cancer of the Liver Italian Program (CLIP) staging system, the Japanese Integrated System (JIS), and the Barcelona Clinic Liver Cancer (BCLC) staging system are all in use.[3-8] In particular, the TNM system, which analyzes the pathological features of the surgical specimen, has been widely used in HCC patients undergoing hepatectomy, despite a lack of consensus as to which staging system is best. [3, 5, 7-9]

Hepatic resection or transplantation is still the mainstay of treatment, so a staging discrepancy can exist between a patient's pre- and postoperative

status.[2, 10] In addition, the preoperative stage determined from radiological and laboratory tests cannot produce an exact estimate of the postoperative pathological status. Radiological studies have a limited ability to detect microvascular invasion, satellite nodules, and the invasion of other organs. The combined use of imaging modalities, including magnetic resonance imaging (MRI), computed tomography (CT), and ultrasonography, can detect tumor invasion of the major branches of the portal and hepatic veins in 81 to 95% of cases at the time of diagnosis, but the presence of microvascular and satellite nodules cannot be established before resection or transplantation.[11-14] Therefore, following surgery, a change in tumor number or size, or the presence of vascular invasion, which determine tumor stage, can upstage or downstage the tumor.[15] Accurate tumor staging guides patient assessment and therapeutic decisions, and thus it is important to establish optimal tumor staging and decrease the discrepancy between the preoperative and postoperative tumor status. Problems related to preoperative understaging have been reported in several studies involving explanted livers.[16, 17] However, few studies have compared the radiological and pathological status of tumors with the long-term outcome in HCC patients undergoing tumor resection.

This study evaluated the accuracy of preoperative radiological staging in predicting the postoperative pathological staging of tumors, in order to determine which method is better at predicting the long-term clinical in HCC patients undergoing hepatic resection.

II. Materials and Methods

1. Patients

Between January 2000 and April 2006, 196 HCC patients who underwent curative resections as the first line of therapy at Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, were enrolled in this study. An experienced radiologist (MS Park) evaluated all of the preoperative imaging data, and a hepatopathologist (YN Park) evaluated the postoperative liver tissue samples; both were blind to the patients' clinical histories. For the preoperative status, vascular invasion was defined as gross vascular invasion only, as detected on imaging modalities. Conversely, it was defined postoperatively as vascular invasion on pathology, which meant microscopic vascular invasion, with or without macroscopic vascular invasion seen at surgery.

Based on the surgeon's consideration of tumor size, number, and remaining liver function, either lobectomy or segmentectomy was performed with a curative aim and no micro- or macroscopic residual disease. Those patients who underwent preoperative interventions such as radiofrequency ablation, transarterial chemo-embolization, percutaneous ethanol injection, or radiotherapy were excluded from the study because these treatments could change the initial pathological status of the tumors, resulting in shrinkage in size, tumor necrosis, or fibrosis of the tumor itself and its borders.

We adopted the TNM staging system of the AJCC (6th edition, 2002) because the study population was limited to patients undergoing surgical treatment alone as first-line therapy and to patients with good liver function (evaluated as Child-Pugh A). Tumor grade was assessed using the nuclear grading scheme outlined by Edmondson and Steiner.[18]

2. Initial work-up and follow-up

The initial evaluation included a complete medical history and physical examination, paying special attention to symptoms often associated with HCC or chronic liver disease. Chest radiography and laboratory tests were performed, including a complete blood cell count, blood urea nitrogen, creatinine, liver function tests, tumor markers such as alpha-fetoprotein (AFP), and protein induced by vitamin K absence or antagonist II (PIVKA-II). The entire study population underwent dynamic CT of the liver and hepatic arteriography (HA), and liver MRI was performed as necessary. The patients were seen postoperatively at 3-month intervals. Dynamic CT of the liver and the laboratory tests performed in the initial work-up were repeated at each follow-up visit.

3. Statistical analysis

The major end points of this study were tumor recurrence and patient death. Overall survival (OS) was measured from the date of surgery until either the day of death or the day of the last follow-up visit. Disease-free survival (DFS) was measured from the date of surgery until the date of recurrence. Differences between continuous and categorical variables were examined statistically using the Student's t-test and Chi-square test, respectively. If necessary, logistic regression was used to validate the independent factors. In addition, the differences in continuous and categorical variables pre- and postoperatively were evaluated using the paired t-test and McNemar test, respectively.

To determine the predictive factors, including the pre- and postoperative TNM stages, we relied on the Kaplan-Meier method, with comparison using a log rank test for the initial analysis. Subsequent multivariate analysis was performed using the Cox regression model to identify the independent prognostic factors.

The performance of a prognostic system is related to the homogeneity (small differences in survival among patients at the same stage within each system), discriminatory ability (greater differences in survival among patients at different stages within each system), and monotonicity of gradients (longer survival of patients at earlier stages than of patients at more advanced stages within the same system). Therefore, the likelihood ratio (LR) χ^2 and linear trend χ^2 were calculated using the Cox regression model to determine the homogeneity and discriminatory ability, respectively. Both the LR χ^2 and linear trend χ^2 were also used to measure the monotonicity of the gradients of survival. To neutralize potential bias in the two staging methods (preoperative radiological and postoperative pathological staging), the results of the Cox regression were expressed as the Akaike information criterion (AIC), which shows how each staging method affects OS and DFS. The lower the AIC, the more explanatory and more informative the model is.

A probability level (*p*) of 0.05 was chosen for statistical significance. Statistical analyses were performed using SPSS software version 12.0 (SPSS, Chicago, IL).

III. Results

1. Baseline clinical characteristics

The patients' characteristics are summarized in Table 1. The median patient age was 54 years (range, 27-76 years), and 145 patients were male. All patients had good liver function (Child-Pugh class A) at the time of surgery, and 45 patients had evidence of portal hypertension, including splenomegaly, thrombocytopenia, or esophageal-gastric varices. Etiologically, 166 (85%) patients were hepatitis B virus (HBV) carriers, and seven (3.5%) were hepatitis C virus (HCV) carriers. Seven patients (3.5%) had alcoholic liver disease, and five (3%) had steatosis. Within a median follow-up time of 32.5 months (range, 4-84 months), 40 patients died.

2. Stage shift

The changes in important tumor factors and the resultant stage shift before and after surgery are described in Tables 2 and 3. The tumor size, tumor number, and frequency of vascular invasion increased significantly after surgery. As a result, tumors from 72 patients (36.8%) were upstaged (58 for vascular invasion, 7 for number, and 7 for both), and four tumors (2.0%) were downstaged (3 for vascular invasion and 1 for number) postoperatively.

These results indicate that the most prominent stage shift occurred from stage I to II (62 patients, 31.6%), followed by a shift from stage II to III (9 patients, 4.6%).

Table 1. Patient characteristics

Variable	Value
Median Age, yr (range)	54.0 (27-76)
Sex (M:F)	145:51
Biochemical values, median (range):	
Platelet count (/μL)	160 (48-509)
Creatinine (mg/dL)	0.9 (0.5-7.4)
Aspartate aminotransferase (IU/L)	35 (12-206)
Alanine aminotransferase (IU/L)	32 (7-151)
Albumin (mg/dL)	4.1 (3.1-5.1)
Bilirubin (mg/dL)	0.7 (0.1-1.9)
Prothrombin time (s)	12.5 (1-15.5)
R15 (%)	9.2 (1.1-44.0)
AFP (ng/mL)	96.8 (0.5-60500)
PIVKA-II (mAU/mL)	53 (0-2000)
Splenomegaly, no. (%)	35 (18%)
Portal hypertension, no. (%)**	45 (23%)
Etiology:	
HBV	166 (85%)
HCV	7 (3.5%)
Alcohol	7 (3.5%)
Steatosis	5 (3%)
Cryptogenic	11 (5%)
Median Size, cm (range)*	3.5 (0.6-15)
Glisson's Capsule involvement, no. (%)*	
Absent	59 (30%)
Abutting	116 (59%)
Invasion	21 (11%)
Bile duct invasion, no. (%)*	6.0 (3%)
Median follow-up duration, months	32.5 (3.2-84)

* The results were confirmed pathologically.
**It includes splenomegaly, thrombocytopenia, or esophageal-gastric varices.

Table 2. The differences in tumor factors before and after surgery

Tumor factor	Preoperative	Postoperative	*p*-value
Multiple tumor number, no. (%)	13 (6.6%)	26 (13.3%)	<0.001
Tumor size (cm)*	4.03 ± 2.1	4.2 ± 2.1	0.02
Vascular invasion, no. (%)	9 (4.6%)	84 (42.8%)	<0.001

* The data are expressed as means ± standard deviation.

Table 3. Stage shift

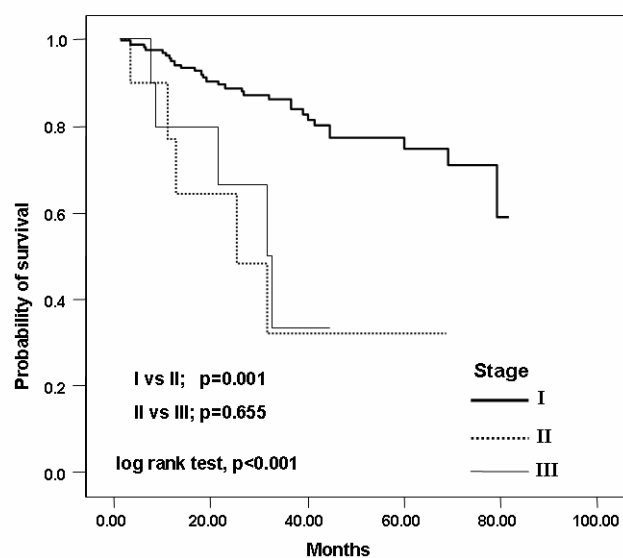| Radiological stage	Pathological stage			
	I	II	III	Total
I	102	62	9	173
II	1	8	1	10
III	0	3	10	13
Total	103	73	20	196

3. Overall and disease-free survival

The overall and disease-free survival curves based on the preoperative radiological and postoperative pathological staging are shown in Figs. 1 to 4. Stratifying OS according to radiological stage revealed a significant difference between stages I and II ($p = 0.001$), but no difference between stages II and III ($p = 0.655$). The 5-year OS rates in radiological stages I and II were 77.6 and 32.1%, respectively, and the 3-year OS in stage III was 33.3%. Conversely, with pathological staging, there were significant differences in OS between both stages I and II ($p = 0.017$) and stages II and III ($p = 0.023$); the 5-year OS rates in stages I and II were 81.1 and 67.7%, respectively, and the 3-year OS in stage III was 33.1%.
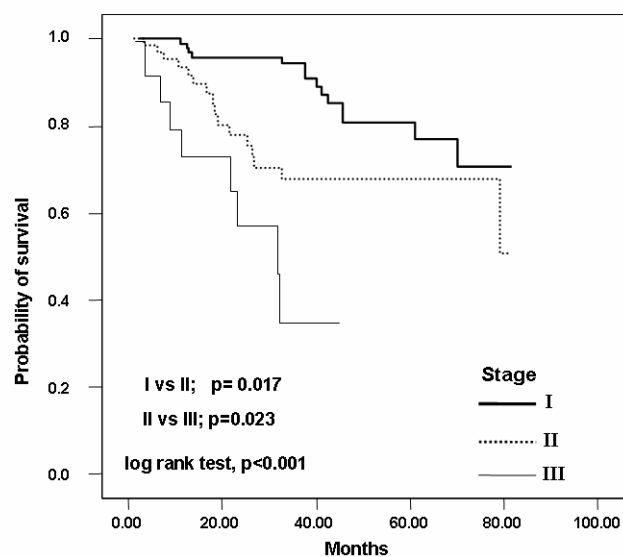
We found a significant difference in DFS between stages I and II ($p = 0.003$) but no difference between stages II and III ($p = 0.452$) based on radiological staging (Fig 3). The 5-year DFS rates in stages I and II were 42.3 and 26.0%, respectively, and the 3-year DFS in stage III was 29.7%. With pathological staging, differences in DFS were found between both stages I and II ($p = 0.045$) and stages II and III ($p = 0.047$); and the 5-year DFS rates in stages I and II were 44.9 and 37.2%, respectively, and the 3-year DFS in stage III was 30.8% (Fig 4).

In addition, the pathological stage had a higher degree of homogeneity (LR χ^2), a higher discriminatory score (liner trend χ^2), better monotonicity of gradients based on LR χ^2 and linear trend χ^2, and a lower Akaike information criterion, compared with the radiological stage (Table 4).

Fig. 1. Overall survival (OS) curves stratified by radiological stage

Fig. 2. Overall survival (OS) curves stratified by pathological stage

Fig. 3. Disease-free survival (DFS) curves stratified by radiological stage

Fig. 4. Disease-free survival (DFS) curves stratified by pathological stage

Table 4. Comparison of the prognostic stratification of the staging systems affecting overall survival and disease-free survival

	Discriminatory Ability Linear Trend χ^2	Homogeneity LR χ^2 Test	Akaike Information Criterion (AIC)
Overall survival:			
Radiological TNM	10.59	13.46	324.6
Pathologic TNM	18.20	18.47	314.1
Disease-free survival:			
Radiological TNM	5.42	7.91	818.2
Pathologic TNM	10.74	11.09	812.9

4. Prognostic factors for survival

Table 5 shows the results of univariate and multivariate analyses of the prognostic factors related to OS and DFS.

For OS, the tumor size, tumor number, vascular invasion on pathology (microvascular invasion, with　or without macrovascular invasion), Edmondson grades, Glisson's capsule invasion, diffuse patterns at recurrence, portal vein thrombosis at recurrence, and multiple tumors at recurrence were identified as significant, and subsequent multivariate analysis showed that tumor size, tumor number, vascular invasion on pathology, diffuse patterns at recurrence, portal vein thrombosis at recurrence, and multiple tumors at recurrence were significant.

For DFS, tumor size, number and Edmondson grades were significant in the univariate analyses. When these factors were entered into a multivariate analysis, tumor size and tumor number were confirmed as independent factors for DFS.

Table 5. Factors affecting the overall survival and disease-free survival

Variable	Overall survival		Disease-free survival	
	Univariate Analysis*	Multivariate Analysis*	Univariate Analysis*	Multivariate Analysis*
Age (<55 yrs vs. >55 yrs)	0.771	-	0.492	-
Sex (female vs. male)	0.164	-	0.726	-
Platelet count (<100 k/μL vs. >100 k/μL)	0.415	-	0.531	-
Splenomegaly (yes vs. no)	0.888	-	0.098	-
Albumin (<3.5 g/dL vs. >3.5 g/dL)	0.571	-	0.087	-
R15 (<20% vs. >20%)	0.125	-	0.088	-
AFP (<400ng/mL vs. >400ng/mL)	0.683	-	0.776	-
Size (<5 cm vs. >5 cm)	0.002	0.006	0.001	0.031
Tumor number (single vs. multiple)	0.001	0.001	0.001	0.002
Vascular invasion on pathology (yes vs. no)	0.005	0.033	0.068	-
Edmondson grades	0.032	NS	0.042	NS
Fibrosis (1~3 vs. 4)	0.287	-	0.272	-
Glisson's capsule Invasion (yes vs. no)	0.015	NS	0.089	-
Bile duct invasion (yes vs. no)	0.963	-	0.483	-
Resection Margin (<2 cm vs. >2 cm)	0.153	-	0.197	-
Diffuse patterns at recurrence (yes vs. no)	0.001	0.001	-	-
Portal vein thrombosis at recurrence (yes vs. no)	0.001	0.019	-	-
Multiple tumors at recurrence (yes vs. no)	0.001	0.02	-	-

Note: Tumor factors are based on the pathological rather than radiological results.

*Data are expressed as p-values.

5. Independent predictors of vascular invasion on pathology

To determine the factors influencing vascular invasion on pathology (microvascular invasion, with or without macrovascular invasion), tumor size ($p = 0.011$), tumor number ($p = 0.001$), patient age ($p = 0.116$), patient sex ($p = 0.963$), patient etiology ($p = 0.673$), alpha fetoprotein level ($p = 0.064$), capsular invasion ($p = 0.213$), and Edmondson grade (p=0.001) were evaluated using univariate analyses, and then the univariate predictors were entered into a stepwise logistic regression model. Ultimately, tumor size, tumor number, and Edmonson grade were confirmed as independent predictors of vascular invasion (Table 6). Patients with grade 1 had few vascular invasion, if any, in even a large size, while patients with grade 2 or higher had relatively high incidences of vascular invasion (at least more than 23%) even in small size (Table 7).

Table 6. Factors affecting vascular invasion on pathology

Variables	Incidence of Vascular invasion on pathology	
Tumor size		p=0.043*
<2cm	7/23 (30.4%)	
2~5cm	45/117 (38.5%)	
>5cm	32/56 (57.1%)	
Tumor numbers		p=0.007*
Single	65/170 (38.2%)	
Two	11/17 (64.7%)	
Three or more	8/9 (88.8%)	
Histologic grades		p=0.001*
Edmondson grade 1	2/23 (8.7%)	
Edmondson grade 2	25/80 (31.2%)	
Edmondson grade 3-4	57/93 (61.3%)	

*Calculated by multivariate analysis

Table 7. Association of vascular Invasion and histologic grades stratified by tumor size

Variables	Incidence of Vascular invasion on pathology		
	Edmondson grade 1	Edmondson grade 2	Edmondson grade 3-4
Tumor size < 2cm	0/2 (0%)	3/13 (23.1%)	4/8 (50.0%)
Tumor size 2~5cm	0/16 (0%)	14/46(30.4%)	31/55(56.4%)
Tumor size > 5cm	1/5 (20.0%)	9/24 (37.5%)	22/27(81.5%)

6. Patterns of recurrence according to vascular invasion on pathology

To validate the superiority of pathological staging over radiological staging and to explain the poorer OS but similar DFS in patients with vascular invasion on pathology, as observed by multivariate analysis, we analyzed the effects of vascular invasions, most of which were radiologically undetected microvascular invasion. The recurrence patterns according to vascular invasion in pathology are presented in Table 8. The pr⌐esence of vascular invasion at surgery significantly (all $p < 0.001$) increased the incidence of portal vein invasion (hazard ratio: 9.43, 95% CI: 1.95-45.6), multiple tumor number (hazard ratio: 11.03, 95% CI: 4.05-30.0), and diffuse-infiltrative patterns at recurrence (hazard ratio: 14.8, 95% CI: 3.9-56.0).

Table 8. Recurrence patterns according to vascular invasion seen on pathology

Recurrence pattern	Vascular invasion on pathology	
	No	Yes
Portal vein invasion at recurrence*	2 (4%)	11 (28%)
Multiple tumor number at recurrence*	13 (26%)	31 (79.5%)
Diffuse recurrence pattern*	3 (6%)	19 (49%)

*Data are expressed as no. (%). All $p < 0.001$.

IV. Discussion

Surgical treatment of HCC, either by resection or transplantation, remains the mainstay of curative therapy, although non-surgical treatment modalities, including transarterial chemoembolization (TACE), radiofrequency ablation (RFA), and percutaneous ethanol or holmium injection (PEI or PHI, respectively), have been increasingly applied with a curative aim and with comparable outcomes.[2, 19-23] Following surgical treatment, clinicians can confirm various prognostic factors such as satellite nodules, microvascular invasion, histological grade, and capsule invasion, which could not be confirmed using preoperative radiological studies. Of these factors, the presence of satellite nodules or microvascular invasion can upstage the tumor being examined. In fact, accurate staging is the most important issue in transplant candidates.[15] In addition, several reports have examined the efficacy of radiological studies in distinguishing small HCC from dysplastic nodules in transplant candidates to confirm the "number" criterion; however, the ability of radiological tools to detect overall vascular invasion as well as the presence of tiny nodules and their predictive value for the long-term prognosis have not yet been evaluated.[24-26] In this study, we analyzed how accurately the preoperative tumor stage determined from radiological evaluation matched the tumor stage determined from postoperative evaluation of the surgical specimen, and we validated the ability of each staging method to predict the long-term clinical outcome. Furthermore, to validate the superiority of pathological staging and to explain the poorer OS but similar DFS in patients with vascular invasion, which was the major factor for discrepancy for two stagings, we analyzed the determinants of radiologically undetected microvascular invasion and their ultimate effect on survival.

In our study, because of changes in tumor factors, that is, vascular invasion (the major factor for discrepancy between two stagings), and tumor number, 38.8% of the patients had experienced stage shifts after surgery, and

the majority were upstaged. Among 76 patients with stage shift, 68 (89.4%) had the newly diagnosed vascular invasions. Despite the statistical significance, tumor size increased only slightly after surgery compared with before surgery, and did not influence the change in tumor stage. Freeman et al.[15] also reported that, even with the use of combined radiological modalities, overall accuracy reached only about 50% compared with the pathological accuracy. A shift from stage I to stage II was most prominent because of confirmed microvascular invasion. As a result, this shift resulted in better survival outcomes in patients with pathological stage I tumors, by improving the homogeneity. Similarly, better patient survival was observed for tumors at pathological stage II than for tumors at radiological stage II. The problem of understaging in radiological staging should be considered when comparing treatment outcomes between resection and local ablative therapy, since there might be actually considerable portions of stage II in patients given local ablative therapy, who were regarded as stage I.

Concerning prognostic factors, tumor size and tumor number, which are well-known prognostic factors, were confirmed to independently influence both OS and DFS.[27-30] However, histologic grades had no independent impacts on OS and DFS in multivariate analysis in this study, although it had been reported as significant predictors on survival outcomes in several studies.[35, 36] It may be most likely due to trends toward the higher frequency of grade 3-4 in patients with a larger tumor size. Therefore, we suggest that tumor size was more influential on survival outcomes rather than histologic grade itself.

In addition, although other investigators have reported that vascular invasion is a potential prognostic variable because HCC often spreads within the intrahepatic vasculature, leading to microscopic occult intrahepatic metastases via the portal system, our results were somewhat different in that the frequency of vascular invasion was a significant prognostic factor in

determining only OS only, and not DFS.[30-32] Vascular invasion on pathology did not have a marked effect on DFS in our study, even in the univariate analysis. Therefore, we analyzed the relapse patterns according to vascular invasion on pathology to explain the similar recurrence rate that was found despite the poorer OS of patients with vascular invasion. As a result, we observed its harmful effects, which include increased incidence of portal vein invasion, multiplicity, and diffuse infiltrative patterns, when tumors recurred. These effects make further treatment difficult in the event of recurrence. To prevent fatal recurrence in this situation, surgery alone might not be enough. The efficacy of adjuvant treatments in patients with poor prognostic factors using conventional cytotoxic agents and agents capable of blocking vascular endothelial growth factors are under investigation.[14, 34]

It may be meaningful to physicians to predict presence of vascular invasion due to its clinical impacts on recurrence pattern and overall survival. In general, the frequency of vascular invasion is increased dramatically in larger, multiple tumors and high grades of histology, according to the investigations of Pawlick et al.[33] and Esnaola et al.[14], which are consistent with our results. Patients with grade 1 had few vascular invasion, if any, in even a large size, while patients with grade 2 or higher had relatively high incidences of vascular invasion even in small size. Since many of HCC patients don't have surgical staging, these findings should be considered for prediction of prognosis and establishment of treatment strategy, especially in non-surgical candidates.

This study had several limitations. First, owing to its retrospective nature, patients with small HCC (tumor size <3 cm) who underwent percutaneous interventions such as TACE, PEI, or RFA instead of resection were excluded. If they had undergone surgery instead of percutaneous management, the accuracy of the radiological staging might have been

improved, because small HCCs have a lower incidence of vascular invasion and multiplicity.[19, 37]

Another limitation was that hepatic function was not considered a survival-related factor in our investigation because all of the patients had relatively good liver function (Child-Pugh A) and all were eligible for surgery. Even early cirrhotic changes seen on pathology did not influence the survival outcome. Therefore, if prognosis were stratified using other staging systems such as CLIP or BCLC, which reflect hepatic function, then the comparison itself would need to be approached differently.

V. Conclusions

The accuracy of radiological staging was only about 60% that of pathological staging, owing primarily to the undetected vascular invasion and multiple small tumors in preoperative settings. This problem of understaging in radiological staging should be considered in evaluating efficacy of local ablative therapy, since there might be actually considerable portion of stage II in those who were regarded as stage I. Large tumor size and tumor multiplicity were poor prognostic variables for OS and DFS. Furthermore, presence of vascular invasion was correlated with adverse relapse patterns. Factors for its presence included histologic grades in addition to size and number. These clinicopathologic patterns might be useful for determining prognosis and treatment plans, especially in non-surgical candidates.

References

1.   Hanazaki K, Kajikawa S, Shimozawa N, Mihara M, Shimada K, Hiraguri M, et al. Survival and recurrence after hepatic resection of 386 consecutive patients with hepatocellular carcinoma. J Am Coll Surg 2000;191(4):381-8.

2.   Song TJ, Ip EW, Fong Y. Hepatocellular carcinoma: current surgical management. Gastroenterology 2004;127(5 Suppl 1):60.

3.   Huang YH, Chen CH, Chang TT, Chen SC, Wang SY, Lee HS, et al. Evaluation of predictive value of CLIP, Okuda, TNM and JIS staging systems for hepatocellular carcinoma patients undergoing surgery. J Gastroenterol Hepatol 2005;20(5):765-71.

4.   Georgiades CS, Liapi E, Frangakis C, Park JU, Kim HW, Hong K, et al. Prognostic accuracy of 12 liver staging systems in patients with unresectable hepatocellular carcinoma treated with transarterial chemoembolization. J Vasc Interv Radiol 2006;17(10):1619-24.

5.   Marrero JA, Fontana RJ, Barrat A, Askari F, Conjeevaram HS, Su GL, et al. Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. Hepatology 2005;41(4):707-16.

6.   Cillo U, Vitale A, Grigoletto F, Farinati F, Brolese A, Zanus G, et al. Prospective validation of the Barcelona Clinic Liver Cancer staging system. J Hepatol 2006;44(4):723-31.

7.   Kudo M, Chung H, Haji S, Osaki Y, Oka H, Seki T, et al. Validation of a new prognostic staging system for hepatocellular carcinoma: the JIS score compared with the CLIP score. Hepatology 2004;40(6):1396-405.

8.   Vauthey J, Lauwers G, Esnaola N, Do K, Belghiti J, Mirza N, et al. Simplified staging for hepatocellular carcinoma. J Clin Oncol 2002;20(6):1527-36.

9.   Lei HJ, Chau GY, Lui WY, Tsay SH, King KL, Loong CC, et al. Prognostic value and clinical relevance of the 6th edition 2002 american joint

committee on cancer staging system in patients with resectable hepatocellular carcinoma. J Am Coll Surg 2006;203(4):426-35.

10.   Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. The lancet 2003;362(9399):1907-17.

11.   Bach AM, Hann LE, Brown KT, Getrajdman GI, Herman SK, Fong Y, et al. Portal vein evaluation with US: comparison to angiography combined with CT arterial portography. Radiology 1996;201(1):149-54.

12.   Hann LE, Schwartz LH, Panicek DM, Bach AM, Fong Y, Blumgart LH. Tumor involvement in hepatic veins: comparison of MR imaging and US for preoperative assessment. Radiology 1998;206(3):651-6.

13.   Nelson RC, Chezmar JL, Sugarbaker PH, Murray DR, Bernardino ME. Preoperative localization of focal liver lesions to specific liver segments: utility of CT during arterial portography. Radiology 1990;176(1):89-94.

14.   Esnaola NF, Lauwers GY, Mirza NQ, Nagorney DM, Doherty D, Ikai I, et al. Predictors of microvascular invasion in patients with hepatocellular carcinoma who are candidates for orthotopic liver transplantation. J Gastrointest Surg 2002;6(2):224-32; discussion 32.

15.   Freeman RB, Mithoefer A, Ruthazer R, Nguyen K, Schore A, Harper A, et al. Optimizing staging for hepatocellular carcinoma before liver transplantation: A retrospective analysis of the UNOS/OPTN database. Liver transplantation 2006;12(10):1504-11.

16.   Kaihara S, Kiuchi T, Ueda M, Oike F, Fujimoto Y, Ogawa K, et al. Living-donor liver transplantation for hepatocellular carcinoma. Transplantation 2003;75(3 Suppl):40.

17.   Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. The New England journal of medicine 1996;334(11):693-9.

18.   Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study

of 100 cases among 48,900 necropsies. Cancer 1954;7(3):462-503.

19.   Ng KK, Vauthey JN, Pawlik TM, Lauwers GY, Regimbeau JM, Belghiti J, et al. Is hepatic resection for large or multinodular hepatocellular carcinoma justified? Results from a multi-institutional database. Ann Surg Oncol 2005;12(5):364-73.

20.   Ramsey DE, Kernagis LY, Soulen MC, Geschwind JF. Chemoembolization of hepatocellular carcinoma. J Vasc Interv Radiol 2002;13(9 Pt 2):S211-S21.

21.   Befeler AS, Di Bisceglie AM. Hepatocellular carcinoma: diagnosis and treatment. Gastroenterology 2002;122(6):1609-19.

22.   Sangro B. Refined tools for the treatment of hepatocellular carcinoma. J Hepatol 2005;42(5):629-31.

23.   Zhou L, Rui JA, Wang SB, Chen SG, Qu Q, Chi TY, et al. Clinicopathological features, post-surgical survival and prognostic indicators of elderly patients with hepatocellular carcinoma. Eur J Surg Oncol 2006;32(7):767-72.

24.   Lim JH, Choi D, Park CK, Lee WJ, Lim HK. Encapsulated hepatocellular carcinoma: CT-pathologic correlations. Eur Radiol 2006;16(10):2326-33.

25.   O'Malley ME, Takayama Y, Sherman M. Outcome of small (10-20 mm) arterial phase-enhancing nodules seen on triphasic liver CT in patients with cirrhosis or chronic liver disease. The American journal of gastroenterology 2005;100(7):1523-8.

26.   Lee KH, O'Malley ME, Haider MA, Hanbidge A. Triple-phase MDCT of hepatocellular carcinoma. AJR, American journal of roentgenology 2004;182(3):643-9.

27.   Wu FS, Zhao WH, Liang TB, Ma ZM, Teng LS, Wang M, et al. Survival factors after resection of small hepatocellular carcinoma. Hepatobiliary & pancreatic diseases international 2005;4(3):379-84.

28.   Poon RT, Fan ST, Lo CM, Liu CL, Ng IO, Wong J. Long-term prognosis after resection of hepatocellular carcinoma associated with hepatitis B-related cirrhosis. J Clin Oncol 2000;18(5):1094-101.

29.   Cha C, Fong Y, Jarnagin WR, Blumgart LH, DeMatteo RP. Predictors and patterns of recurrence after resection of hepatocellular carcinoma. J Am Coll Surg 2003;197(5):753-8.

30.   Vivarelli M, Cucchetti A, Piscaglia F, La Barba G, Bolondi L, Cavallari A, et al. Analysis of risk factors for tumor recurrence after liver transplantation for hepatocellular carcinoma: key role of immunosuppression. Liver transplantation 2005;11(5):497-503.

31.   Ercolani G, Grazi GL, Ravaioli M, Del Gaudio M, Gardini A, Cescon M, et al. Liver resection for hepatocellular carcinoma on cirrhosis: univariate and multivariate analysis of risk factors for intrahepatic recurrence. Ann Surg 2003;237(4):536-43.

32.   Ramacciato G, Mercantini P, Cautero N, Corigliano N, Di Benedetto F, Quintini C, et al. Prognostic evaluation of the new American Joint Committee on Cancer/International Union Against Cancer staging system for hepatocellular carcinoma: analysis of 112 cirrhotic patients resected for hepatocellular carcinoma. Ann Surg Oncol 2005;12(4):289-97.

33.   Pawlik TM, Delman KA, Vauthey JN, Nagorney DM, Ng IO, Ikai I, et al. Tumor size predicts vascular invasion and histologic grade: Implications for selection of surgical treatment for hepatocellular carcinoma. Liver transplantation 2005;11(9):1086-92.

34.   Poon RT, Ng IO, Lau C, Zhu LX, Yu WC, Lo CM, et al. Serum vascular endothelial growth factor predicts venous invasion in hepatocellular carcinoma: a prospective study. Ann Surg 2001;233(2):227-35.

35.   Zhou L, Rui JA, Wang SB, Chen SG, Qu Q, Chi TY, et al. Factors predictive for long-term survival of male patients with hepatocellular carcinoma after curative resection. J Surg Oncol 2007;95(4):298-303.

36.   Sasaki Y, Yamada T, Tanaka H, Ohigashi H, Eguchi H, Yano M, et al. Risk of recurrence in a long-term follow-up after surgery in 417 patients with hepatitis B- or hepatitis C-related hepatocellular carcinoma. Ann Surg 2006;244(5):771-80.

37.   Zhou XD, Tang ZY, Ma ZC, Wu ZQ, Fan J, Qin LX, et al. Surgery for large primary liver cancer more than 10 cm in diameter. J Cancer Res Clin Oncol 2003;129(9):543-8.

< ABSTRACT(IN KOREAN)>

간세포암종에서의 방사선학적 병기의 정확성과 임상적 의의

<지도교수 안 상 훈 >

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배경: 간세포암종 (이하 간암) 환자에 있어서 영상의학적 검사로는 미세혈관침윤이나 위성결절을 발견할 수 없기 때문에, 수술 전 방사선학적 병기와 수술 후 병리학적 병기 간에 차이가 존재할 수 있다. 본 연구는 간암 환자에 있어서 병리학적 병기에 대해 방사선학적 병기와 일치하는 정도와 각각의 장기간 예후 분석의 차이를 비교하였다.

방법: 2000년도에서 2006년도 사이에 초치료로서 근치적 간절제술을 시행받은 196명의 환자를 대상으로 하였고, 병기는 TNM병기(the American Joint Commission on Cancer, 6판)를 사용하였다. 방사선학적 병기는 간 역동적 전산화단층촬영과 간동맥조영술을 근거로 하였으며, 선택적인 경우 간 자기공명영상을 시행하였다. 생존에 미치는 예후인자는 Kaplan Meier 방법과 Cox 회귀모델을 이용하여 산정하였다. 또한 각 병기 간의 생존결과 예측은 Cox 회귀모델을 이용하여 비교하였다. 중앙추적관찰기간은 32.5개월이었다.

결과: 수술 후 76명(38.8%)은 병기에 변동이 있었으며, 이 중 89.4% (68명)는 혈관침윤이 있었다. 병리학적 병기에 근거해 산출하였을 때,

각각 전체생존기간과 무병생존기간은 1기와 2기(p = 0.017/0.045), 2기와 3기(p = 0.023/0.047)에서 의미 있는 차이를 보였다. 반면 방사선학적 병기에 근거했을 때, 전체생존기간과 무병생존기간은 2기와 3기에서 통계학적으로 의미 있는 차이가 없었다. 따라서, 병리학적 병기가 예후예측에 더 유리함을 보였다. 전체생존기간에 영향을 미치는 독립적인 인자는 종양의 크기와 갯수, 혈관침범이었으며, 무병생존기간에는 종양의 크기와 개수가 유의미한 인자로 확인되었다. 또한 혈관침범의 빈도를 결정하는 독립적인 인자는 종양 크기, 개수, 분화도였다. 진단 당시 혈관침범이 있는 경우, 재발 시 다발성, 문맥침범, 미만성으로 침윤하는 양상을 보일 가능성이 의미있게 높았으며(all p<0.001), 이러한 현상들이 궁극적으로 예후를 좋지 않게 하였다.

결론: 방사선학적 병기와 병리학적 병기는 61.2%에서 일치하였으며, 이는 수술 후 새로 진단받은 혈관침범에 주로 기인하였다. 따라서 병리학적 병기가 예후예측에 보다 우수하였으며, 혈관침범은 재발 당시 다발성, 문맥침범, 미만성 침윤의 발생을 증가시켜 악영향을 미치는 것으로 확인되었다. 따라서, 이러한 임상·병리학적 특징은 간암의 예후 예측에 중요하며, 특히 비수술적 치료를 받는 환자에서도 임상 경과 예측에 유용하게 적용될 수 있다.

핵심되는 말 : 간세포암종, 방사선학적 병기, 병리학적 병기, 예후, 혈관침범