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ORIGINAL ARTICLE

Impact of Trinal Histological Glandular Differentiation Grade on the Prognosis of Patients with Intrahepatic Cholangiocarcinoma: a Multicenter Retrospective Study

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Abstract

Introduction It is unclear whether the histological glandular differentiation (HGD) score that evaluates the tumor grade of two dominant components is prognostic for survival in patients with intrahepatic cholangiocarcinoma (ICC).

Method We retrospectively analyzed the clinical and histopathologic data of 235 consecutive patients with histologically confirmed ICC following hepatectomy at 5 university hospitals in the Kansai region of Japan.

Results Survival was statistically significantly stratified by trinal HGD grade ($p < 0.05$). Median disease-free survival (DFS) of patients with high HGD grade was significantly shorter compared with moderate HGD grade (13.0 vs 31.2 months, respectively; $p = 0.004$). By Cox proportional hazards regression analysis, HGD grade had the fifth-highest hazard ratio (HR = 1.77, $p = 0.002$) for DFS after vascular and/or biliary invasion, extrahepatic invasion, lymph node metastasis and multiple tumors. Multivariate logistic regression analysis revealed four predictors of early recurrence after hepatectomy (lymph node metastasis: odds ratio [OR] = 3.74, $p = 0.001$; tumor size > 50 mm: OR = 2.80, $p = 0.002$; HGD grade, high: OR = 2.11, $p = 0.012$; and vascular or biliary tract invasion: OR = 2.11, $p = 0.048$).

Conclusion Trinal HGD grade had a significant prognostic impact on the survival of patients with ICC after radical hepatectomy.

Keywords Cholangiocarcinoma · Histological glandular differentiation · Intrahepatic Cholangiocarcinoma · Biliary tract neoplasms · Hepatectomy

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer, and its incidence has increased over the past three decades.[1] Because the prognosis of advanced ICC remains dismal,[2] a reliable staging system that accurately predicts patient outcomes is crucial for designing a treatment strategy and assessing disease outcomes.[3, 4] Tumor grade reflects how normal cells or abnormal cancer cells look under a microscope. However, cancers often contain more than one pattern of cancer cells. The histological heterogeneity is a problem in the evaluation of tumor grade.

The Gleason score is the grading system used to determine the aggressiveness of prostate cancer, with excellent correlation with clinical outcomes.[5] The Gleason score is made up of evaluating the differentiation degree of two dominant components of the tumor. In addition, a previous

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report indicated that the histological glandular differentiation (HGD) score that evaluates the tumor grade of two dominant components had a significant relationship with prognosis in patients with extrahepatic bile duct cancer.[6] In contrast, the prognostic impact of tumor grade and HGD score in ICC is not well understood. In this study, we evaluated the prognostic impact of tumor grade and HGD score by comparing them with the determinants of tumor, node, metastasis (TNM) cancer staging.

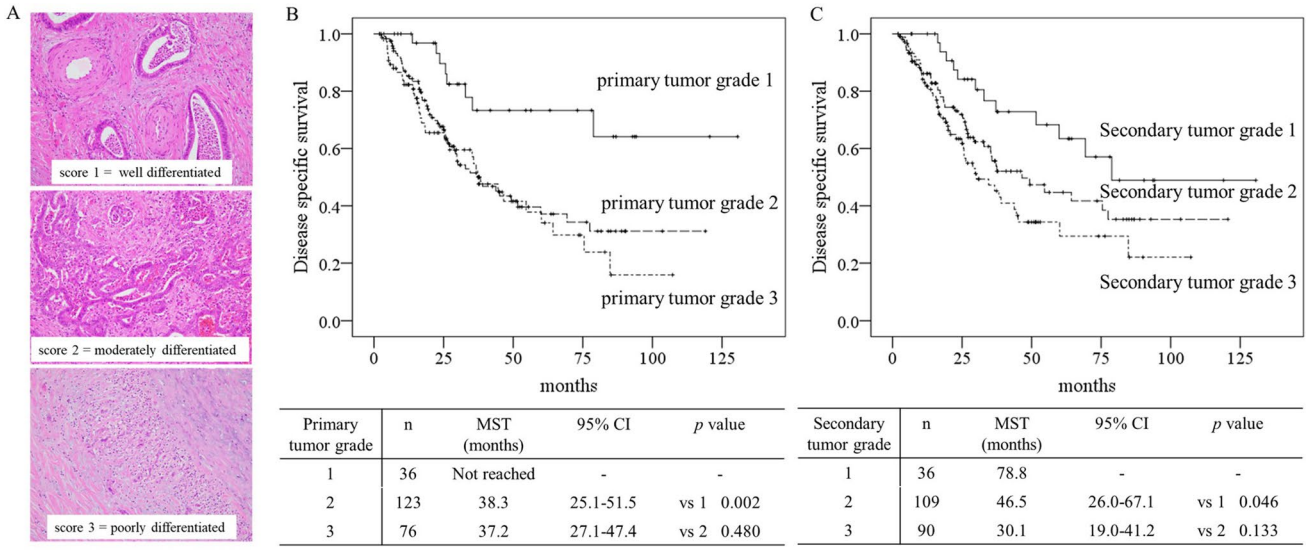
Materials and Methods

Patients

We retrospectively analyzed the clinical and histopathologic data of 235 consecutive patients with histologically confirmed ICC following hepatectomy at 5 university hospitals in the Kansai region of Japan between January 2009 and December 2020. Clinical data were collected from each hospital and compiled and analyzed at Kansai Medical University. The albumin-bilirubin (ALBI) score was calculated using only serum albumin and total bilirubin ($\log_{10}$ bilirubin [μmol/L] × 0.66) + (albumin [g/L] × − 0.085).[7] The Fibrosis-4 (FIB-4) index was calculated as (age [yr] x aspartate aminotransferase [AST] concentration [U/L]) / (Platelets [10^9/L] x sqr (alanine aminotransferase [ALT] concentration [U/L])).[8] The CALLY index was calculated as (albumin [g/L] × absolute lymphocyte count)/(C-reactive protein [CRP] concentration [mg/dL] × 10^4).[9] The disease-specific survival (DSS) was used for survival evaluation instead of overall survival to minimize the bias of our small cohort. DSS and disease-free survival (DFS) were calculated from the time of hepatectomy to the time of disease-specific death or any disease recurrence. The disease-specific death was defined as patients who died from tumor growth or recurrence. The DFS was determined from an analysis of 231 study patients who had R0 or R1 resection margins among 235 patients, as the remaining study patient had an R2 resection margin was excluded from the analysis. Early recurrence was defined as recurrence within a year after hepatectomy.

Histopathologic Assessment

Tumors were excised from patients at each of the 5 university hospitals, fixed in 10% formalin, and embedded in paraffin. Serial sections of each tumor were stained with hematoxylin and eosin. The stained sections were collected and analyzed at Kansai Medical University. Tumor grade was evaluated blindly by two pathologists, in accordance with the previously described manner.[6, 10] Namely, at the two major components of each tumor, primary and secondary tumor grade was scored as 1 (well differentiated), 2 (moderately differentiated) or 3 (poorly differentiated or undifferentiated), as shown in Fig. 1A. Both scores were summed to obtain the total HGD score. A papillary component was defined as well differentiated. In accordance with the previously described manner, a tumor showing cribriform growth was defined as



Primary tumor grade	n	MST (months)	95% CI	*p* value
1	36	Not reached	-	-
2	123	38.3	25.1-51.5	vs 1 0.002
3	76	37.2	27.1-47.4	vs 2 0.480

Secondary tumor grade	n	MST (months)	95% CI	*p* value
1	36	78.8	-	-
2	109	46.5	26.0-67.1	vs 1 0.046
3	90	30.1	19.0-41.2	vs 2 0.133

Fig. 1 Disease-specific survival stratified by tumor grade. Hematoxylin and eosin staining of typical tumor grade patterns (×200 magnification) is shown (**A**). The log-rank test was used to estimate the differences between the disease-specific survival of patients by primary tumor grade (**B**) and secondary tumor grade (**C**). HGD histological glandular differentiation, MST median survival time, CI confidence interval

moderately differentiated.[6] Signet ring cell carcinoma, adenosquamous carcinoma and clear cell carcinoma were all defined as poorly differentiated.[6]

Statistical Analysis

Data are expressed as numbers with percentages or medians with interquartile ranges (IQRs). The Shapiro–Wilk test was used to assess the normality of continuous variables. The Student *t* test or Welch test were performed after the Levene test for normally distributed data, and the Mann–Whitney *U* test was performed for non-normally distributed data. Fisher's exact test was used for nominal scale data. Comparisons were considered statistically significant at $p < 0.05$. The Kaplan–Meier method and log-rank test were performed to assess DSS and DFS. Receiver-operating characteristic (ROC) analysis was performed to identify the cut-off value of continuous variables. A multivariate Cox proportional hazards regression analysis was performed with a forward stepwise method to identify independent risk factors of disease-specific death and any recurrence. Hazard ratios with 95% confidence intervals (CIs) were estimated. A multivariate logistic regression analysis was performed with a forward stepwise method to identify predictors of early recurrence after hepatectomy. All statistical analyses were performed with the IBM SPSS ver. 22 software package for Windows (IBM Japan Ltd., Tokyo, Japan).

Results

Background Characteristics

Patient background characteristics are shown in Table 1. The median follow-up duration of the study cohort was 25.0 months. Median age was 71 years, and the liver function of the majority of patients was normal, as the median ALBI score was − 2.82. The rate of laparoscopic approach was 24.6% which was gradually increasing in recent years. Major hepatectomy was carried out in 63.4%, and the rate of postoperative severe complications was 28.1%. The 90-day mortality rate was 2.6%. Adjuvant chemotherapy was carried out in 51.1%, and most frequent regimen of adjuvant chemotherapy was gemcitabine based regimen through the study period. By the histopathological evaluation, 83.0% of the tumors were more than 20 mm. Vascular and/or biliary tract invasion were observed in 68.9%. The rate of serosal invasion of tumors was 29.8%, and that of extrahepatic invasion of tumors was 2.6%. The majority of both primary and secondary tumors were grade 2.

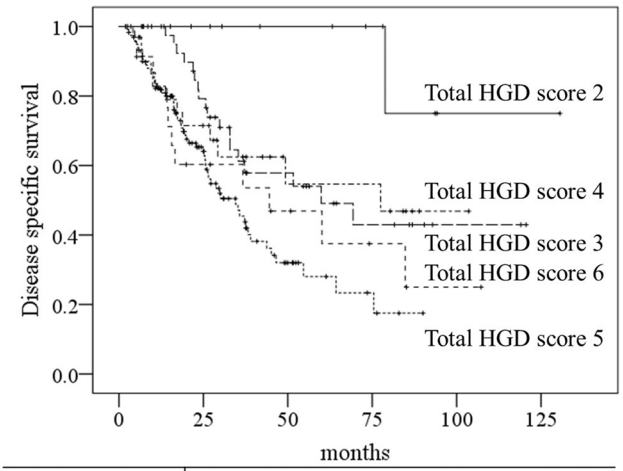
Table 1 Background characteristics

Variable	*N* (%) or median (IQR)
N	235
Follow-up duration, months	25.0 (13.7–43.8)
Age, years	71.0 (66.0–76.0)
Gender, male	162 (68.9)
Hepatitis, HBV/HCV/both	34/20/3 (14.5/8.5/1.3)
ALBI score	− 2.82 (− 3.04 to − 2.48)
FIB4 index	2.05 (1.45–2.85)
CA 19–9 (U/mL)	44.0 (13.0–225.0)
CALLY index	3.70 (1.31–8.55)
Laparoscopic approach	57 (24.6)
Range of hepatectomy *Sectionectomy and less* *Bisectionectomy and more*	86 (36.6) 149 (63.4)
Extrahepatic bile duct resection	45 (19.1)
Regional lymphadenectomy	115 (48.9)
Resection margin, negative	202 (86.0)
Clavien-Dindo score, IIIa and more	66 (28.1)
Mortality within 90 days after surgery	6 (2.6)
Adjuvant chemotherapy	120 (51.1)
Determinants of LCSGJ and AJCC staging	
Multiple tumors	36 (15.3)
Vascular/biliary invasion	162 (68.9)
Tumor size > 50 mm	68 (28.9)
Tumor size > 20 mm	195 (83.0)
Serosal invasion	70 (29.8)
Extrahepatic invasion	6 (2.6)
Lymph node metastasis	47 (20.0)
Histological glandular differentiation score	
Primary tumor grade, 1/2/3	36/123/76 (15.3/52.3/32.3)
Secondary tumor grade, 1/2/3	36/109/90 (15.3/46.4/38.3)

IRQ interquartile range, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *ALBI score* albumin-bilirubin score, *FIB4 index* Fibrosis-4 index, *CA19-9* carbohydrate antigen 19–9, *CALLY index* CRP–albumin–lymphocyte index, *HGD* histological glandular differentiation, *LCSGJ* Liver Cancer Study Group of Japan, *AJCC* American Joint Committee on Cancer

Histological Glandular Differentiation Grade Precisely Stratified Patient Survival

DSS stratified by primary and secondary tumor grade is shown in Fig. 1B and C. There was no statistically significant difference between a score of 2 and 3 for both primary and secondary tumor grade ($p > 0.05$, respectively). DSS stratified by total HGD score, which is determined by adding the primary and secondary tumor grade, also was not statistically significantly different between scores, except for between scores of 2 and 3 ($p = 0.027$), as shown in Fig. 2. ROC analysis was performed to detect the cut-off value for disease-specific death using the total HGD score. Results



Total HGD score	n	MST (months)	95% CI		*p* value
2	12	Not reached	-		-
3	47	59.9	20.9-98.9	vs 2	0.027
4	34	77.5	-	vs 3	0.791
5	119	34.5	25.3-43.8	vs 4	0.053
6	23	44.5	0.0-89.5	vs 5	0.486

Fig. 2 Comparison of disease-specific survival stratified by total histological glandular differentiation score. The log-rank test was used to estimate the differences between the disease-specific survival of patients by total histological glandular differentiation score. HGD histological glandular differentiation, MST median survival time, CI confidence interval

Table 2 Definition of histological glandular differentiation grade

Total HGD score (primary tumor grade + secondary tumor grade)	HGD grade
2	Low
3	Moderate
4	
5	High
6	

HGD histological glandular differentiation

demonstrated that the area under the curve was 0.60 ± 0.037 ($p = 0.011$, CI: 0.53–0.67), and the cut-off value was 4.5. Based on these results, the total HGD score was divided into a trinal HGD grade as low (total HGD score of 2), moderate (total HGD scores of 3 and 4), and high (total HGD scores of 5 and 6), as shown in Table 2.

DSS and DFS stratified by trinal HGD grade are shown in Fig. 3. Survival, in terms of both DSS and DFS, was statistically significantly stratified by HGD grade ($p < 0.05$, respectively). The median DFS of patients with high HGD grade was significantly shorter compared with that of patients with moderate HGD grade (13.0 vs 31.2 months, respectively; $p = 0.004$).

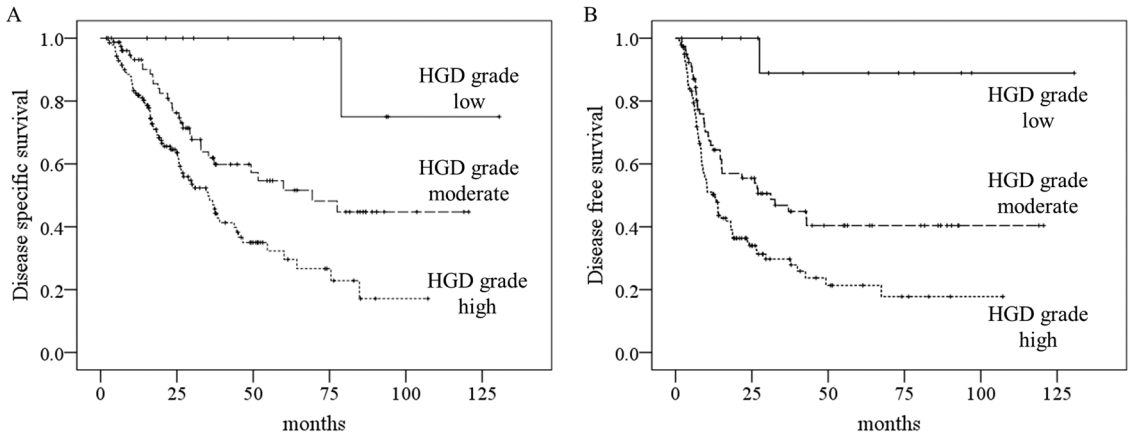
Supplemental Table 1 shows the detailed characteristics depend on the HGD grade. The patients with moderate or high HGD grade demonstrated lower CALLY index and higher CA19-9 level ($p < 0.05$) compared with the patients with low HGD grade. In addition, the rate of mass forming type and vascular invasion were frequently observed in patients with moderate or high HGD grade ($p < 0.05$). Even though the rate of adjuvant chemotherapy was similar among patients ($p > 0.05$), early recurrence was frequently observed in patients with moderate or high HGD grade ($p < 0.05$).

Cox Proportional Hazards Regression Analysis of the Prognostic Ability of Peri-operative and Histopathological Findings

Table 3 shows the results of a Cox proportional hazards regression analysis that investigated the predictive factors of DSS and DFS by comparing trinal HGD grade, perioperative findings, and determinants of cancer staging systems. HGD grade had the fifth-highest hazard ratios (HRs) for DSS and DFS after vascular and/or biliary invasion, extrahepatic invasion, lymph node metastasis, and multiple tumors, with statistical significance (DSS: HGD grade: HR = 2.03, $p = 0.001$; DFS: HGD grade: HR = 1.77, $p = 0.002$). HGD grade had a significant impact on survival, as with some determinants of the TMN staging system, whereas primary nor secondary tumor grade did not.

Factors Predictive of Early Recurrence After Hepatectomy

An understanding of the risk of early recurrence contributes to precise decision-making on the postoperative therapeutic strategy. Results of a multivariate logistic regression analysis performed to identify predictive factors for early recurrence after hepatectomy are shown in Table 4. Among the peri-operative findings and histopathological findings, four factors, including high HGD grade, were identified as independent predictors for early recurrence (lymph node metastasis: OR = 3.74, $p = 0.001$; tumor size > 50 mm: OR = 2.80, $p = 0.002$; HGD grade, high: OR = 2.11, $p = 0.012$; and vascular or biliary tract invasion: OR = 2.11, $p = 0.048$). Subsequently, an early recurrence score for patients with ICC who underwent hepatectomy was created by using the four factors (Table 5). The early recurrence score increases depending on the number of these four determinants that are present (vascular or biliary tract invasion, tumor size > 50 mm, lymph node metastasis, and high HGD grade). The rate of early recurrence increased gradually depending on the increase in the early recurrence score ($p < 0.001$). An early recurrence score of 4 demonstrated an early recurrence rate of 78.9%, whereas a score of zero demonstrated an early recurrence rate of only 3.2%.



HGD grade	n	MST (months)	95% CI	*p* value
low	12	Not reached	-	-
moderate	81	69.3	36.7-101.9	vs low 0.027
high	142	35.3	26.7-43.8	vs mod 0.004

HGD grade	n	Median DFS (months)	95% CI	*p* value
low	12	Not reached	-	-
moderate	80	31.2	14.0-48.4	vs low 0.007
high	139	13.0	9.7-16.2	vs mod 0.004

Fig. 3 Disease-specific survival and disease-free survival stratified by trinal histological glandular differentiation grade. Kaplan–Meier curves demonstrate the disease-specific survival (**A**) and the disease-free survival (**B**) stratified by trinal histological glandular differentiation grade. HGD histological glandular differentiation, MST median survival time, DFS disease-free survival, CI confidence interval

Table 3 Cox proportional hazards regression analysis of the prognostic ability of perioperative and histopathological findings

Variable	Disease-specific survival		Disease-free survival	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Age	–	0.753	–	0.398
Gender, male	–	0.878	–	0.808
Hepatitis, positive	–	0.407	–	0.285
ALBI	–	0.333	–	0.301
FIB4 index	–	0.252	–	0.408
CALLY	–	0.283	–	0.602
CA19-9	1.68 (1.39–2.04)	< 0.001	1.32 (1.10–1.58)	0.003
LCSGJ and AJCC staging				
Multiple tumors	2.20 (1.37–3.54)	0.001	2.05 (1.33–3.17)	0.001
Vascular/biliary invasion	3.28 (1.78–6.04)	< 0.001	1.98 (1.22–3.21)	0.006
Tumor size > 50 mm	–	0.072	–	0.061
Tumor size > 20 mm	–	0.084	–	0.191
Serosal invasion	–	0.667	–	0.756
Extrahepatic invasion	3.22 (1.27–8.17)	0.014	4.55 (1.76–11.76)	0.002
Lymph node metastasis	2.35 (1.47–3.74)	< 0.001	2.25 (1.46–3.46)	< 0.001
Primary tumor grade	–	0.932	–	0.431
Secondary tumor grade	–	0.965	–	0.648
HGD grade	2.03 (1.35–3.06)	0.001	1.77 (1.24–2.52)	0.002
Resection margin, positive	–	0.332	–	0.472
Adjuvant chemotherapy	0.63 (0.42–0.95)	0.027	–	0.194

CI confidence interval, *ICG* indocyanine green, *ALBI* score albumin-bilirubin score, *FIB4 index* Fibrosis-4 index, *LCSGJ* Liver Cancer Study Group of Japan, *AJCC* American Joint Committee on Cancer, *HGD* histological glandular differentiation

Table 4 Results of multivariate logistic regression analysis to identify factors predictive of postoperative early recurrence within a year after hepatectomy

Variable	Odds ratio (95% CI)	*p* value
Age	–	0.791
Gender, male	–	0.602
Hepatitis, positive	–	0.180
ALBI	–	0.832
FIB4 index	–	0.294
CALLY	–	0.295
CA19-9	–	0.130
LCSGJ and AJCC staging		
Multiple tumors	–	0.233
Vascular/biliary invasion	2.11 (1.01–4.43)	0.048
Tumor size > 50 mm	2.80 (1.44–5.45)	0.002
Tumor size > 20 mm	–	0.346
Serosal invasion	–	0.420
Extrahepatic invasion	–	0.093
Lymph node metastasis	3.74 (1.70–8.21)	0.001
Primary tumor grade	–	0.588
Secondary tumor grade	–	0.847
HGD grade, high	2.11 (1.18–3.79)	0.012
Resection margin, positive	–	0.052
Adjuvant chemotherapy	–	0.838

CI confidence interval, *ALBI score* albumin-bilirubin score, *FIB4 index* Fibrosis-4 index, *CALLY index* CRP–albumin–lymphocyte index, *CA19-9* carbohydrate antigen 19–9, *LCSGJ* Liver Cancer Study Group of Japan, *AJCC* American Joint Committee on Cancer, *HGD* histological glandular differentiation

Table 5 Rate of early recurrence depends on the early recurrence score

Early recurrence score	0	1	2	3	4
n	31	63	79	36	19
Early recurrence, *n* (%)	1 (3.2)	17 (27.0)	35 (44.3)	22 (61.1)	15 (78.9)

Definition of early recurrence score:
The score increase depends on the positive number of these four determinants
Determinants: Histological vascular or biliary tract invasion
Tumor size > 50 mm
Lymph node metastasis, positive
HGD grade, high

HGD histological glandular differentiation

Discussion

In this study, the prognostic impact of tumor grade in patients with ICC was evaluated by comparing determinants of the TNM staging system. As a result, tumor grade itself did not demonstrate prognostic significance for patient survival, whereas trinal HGD grade had a significant impact on survival, as with some of the determinants of the TMN staging system (DSS: HGD grade: HR = 2.03, $p = 0.001$; DFS: HGD grade: HR = 1.77, $p = 0.002$). One reason why tumor grade itself could not demonstrate a significant difference for prognosis was intratumoral heterogeneity.[5] On the other hand, HGD grade, which is composed of two dominant components, might minimize the intratumoral heterogeneity.

The TNM factors have been improved with the discovery of new biologic and histologic characteristics. The 6th edition of the Liver Cancer Study Group of Japan (LCSGJ) staging system excluded serosal invasion from a determinant of the T category, whereas a cutoff size of 20 mm and major biliary invasion were added as new determinants.[4, 11] The determinants of the T category in the 8th edition of the American Joint Committee on Cancer (AJCC) staging system included tumor number, cutoff size of 50 mm, vascular invasion, visceral peritoneum invasion, and involvement of local extrahepatic tissue, whereas periductal invasion was excluded.[12] In this study, we compared the prognostic impact on patient survival between HGD grade and determinants of the 6th edition of the LCSGJ staging system and the 8th edition of the AJCC staging system by Cox proportional hazards regression analysis. As result, HGD grade had statistical significance, with the fifth-highest HR after vascular/biliary invasion, extrahepatic invasion, lymph node metastasis, and multiple tumors. This result might indicate that tumor grade-based HGD grade has the potential to be a future candidate for a determinant of a staging system.

Even though patients underwent radical hepatectomy with R0 resection, unexpected early recurrence was experienced at times. Results of a previous multicenter study revealed that tumor characteristics, including increasing tumor size, satellite lesions and lymph node metastasis, were associated with an increased likelihood of early recurrence (within two years after hepatectomy), whereas tumor grade, such as poorly differentiated, was not ($p = 0.166$).[13] Another multi-institutional analysis revealed that CA19-9, tumor size, major vascular invasion, microvascular invasion, and lymph node metastasis were independent risk factors for early recurrence in patients with ICC after radical resection, whereas tumor differentiation did not demonstrate a prognostic impact ($p = 0.106$).[14] On the other hand, the early recurrence score, composed of four determinants (vascular/biliary invasion, tumor size more than 50 mm, lymph node metastasis, and high HGD grade), was created in this study. When all four determinants were present, the potential rate of early recurrence was 78.9%. Even so, tumor grade itself did not demonstrate a prognostic impact; HGD grade, which is composed of two dominant components of tumor grade, might minimize intratumoral heterogeneity.

Limitations

Although this was a multicenter study, the number of patients with ICC was limited. A larger study may be needed to confirm the prognostic significance of HGD.

Conclusions

Trinal HGD grade had a significant prognostic impact on the survival of patients with ICC who underwent radical hepatectomy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11605-023-05852-0.

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Author Contribution HK designed and performed statistical analysis and edited the manuscript. MK and MS supervised the study. MI evaluated all histopathological data. MU, KK, SY, HM, and KM collected the clinical data from each university hospital.

Declarations

Ethics Approval This study was approved by the institutional review board of Kansai Medical University (Approval number: 2019322). It was performed in accordance with the Declaration of Helsinki.

Conflict of Interest The authors declare no competing interests.

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