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CASE REPORT

Hepatectomy for liver abscess caused by stones spilled during laparoscopic cholecystectomy

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Keywords
Hepatic granuloma; intraperitoneal abscess; liver abscess

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Abstract

An abdominal abscess caused by spilled stones is a serious complication of laparoscopic cholecystectomy that requires drainage or reoperation to remove the scattered stones. Herein, we report the case of a 50-year-old woman, who was on dialysis for renal failure. She underwent major hepatectomy for a liver abscess caused by stones spilled during laparoscopic cholecystectomy.

Introduction

Although laparoscopic cholecystectomy is a standard surgical treatment for gallbladder disease, it is associated with a significant risk of injury to the gallbladder wall and may result in the dispersion of free stones within the peritoneal cavity. An abdominal abscess caused by spilled stones is a serious complication of laparoscopic cholecystectomy that requires drainage or reoperation to remove the scattered stones. The incidence and consequences of the loss of gallstones during laparoscopic cholecystectomy remain unclear (1), but stone spillage might occur with a greater frequency than during open cholecystectomy. Herein, we report a patient who underwent major hepatectomy for a liver abscess caused by stones spilled during laparoscopic cholecystectomy.

Case Presentation

A 50-year-old woman, who was on dialysis for renal failure and had visual impairment and a history of breast cancer, suffered from cholecystitis in October 2008. She was admitted to Toranomon Hospital (Tokyo, Japan) with abdominal pain. Abdominal ultrasonography indicated numerous small stones in the gallbladder, but no bile duct abnormality was found in endoscopic retrograde cholangiography (Figure 1). The patient underwent laparoscopic cholecystectomy. During the procedure, her gallbladder was damaged and some stones were lost into the peritoneal cavity. We retrieved as many of the stones as possible laparoscopically using an oblique view scope and retractor (2). We also performed extensive peritoneal lavage. The stones in the gallbladder were analyzed to be bilirubin calcium stones. The patient was discharged without any evidence of abdominal inflammation.

In July 2009, 9 months after the operation, the patient suffered from fever, and laboratory tests revealed evidence of inflammation. Antibiotic therapy controlled the inflammatory response. Abdominal MRI showed inflammation in the posterior segment of the liver near the right subphrenic space, and diffusion-weighted MRI revealed a slightly high intensity in that region.

In February 2010, the patient was hospitalized with a diagnosis of liver abscess as a result of her recurrence of high fever and inflammation. On CT, there was an irregular region of contrast enhancement in the posterior

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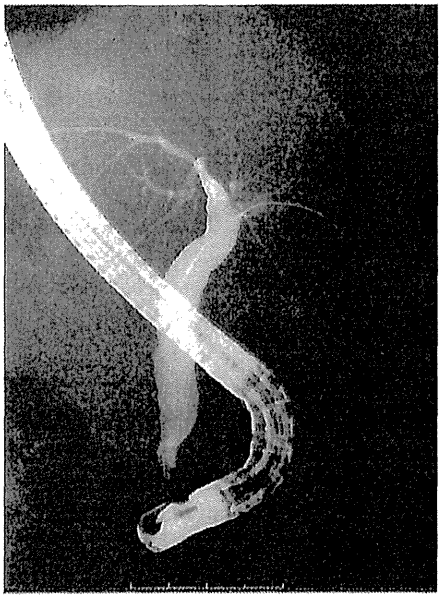

Figure 1 Endoscopic retrograde cholangiography showed no abnormality in the bile duct.

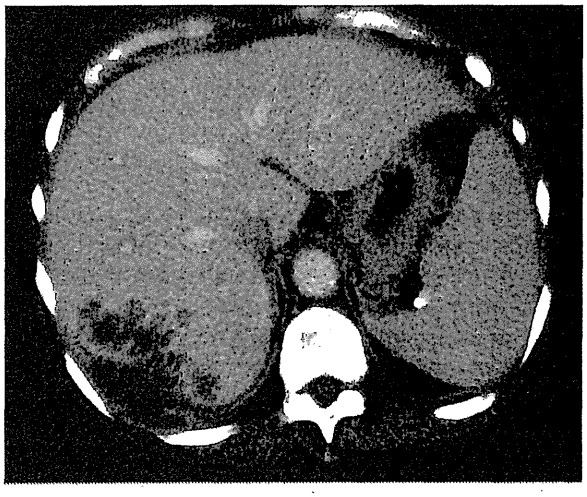

Figure 2 There was an irregular region of contrast enhancement in the posterior segment of the liver on CT scans.

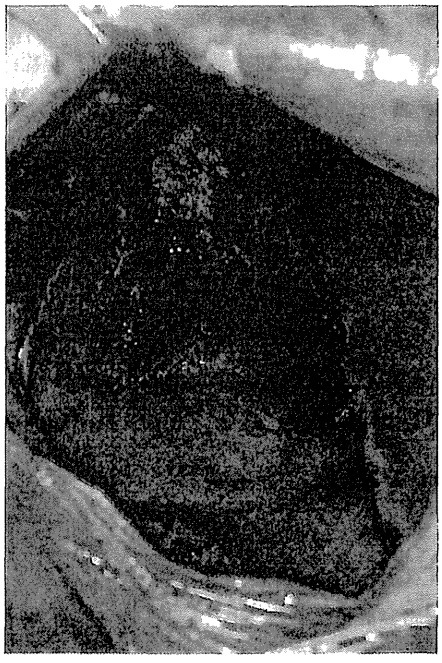

Figure 3 A subphrenic abscess was detected adjacent to the liver abscess during the operation.

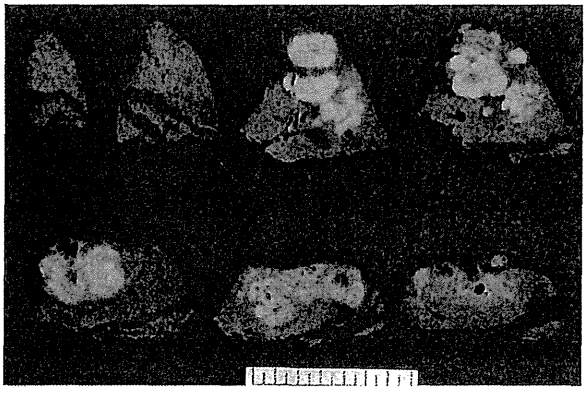

Figure 4 The cut surface of the resected liver specimen had a well-defined whitish tumor.

segment of the liver, and diffusion-weighted MRI showed a higher intensity at that site, suggesting more severe inflammatory changes than at her previous admission (Figure 2). There was no evidence of typical unretrieved gallstones on abdominal ultrasonography. The patient underwent resection of the posterior segment of the liver. During the operation, a subphrenic abscess was detected adjacent to the liver abscess, but there were no obvious stones on the diaphragmatic surface of the liver (Figure 3). The resected liver specimen contained a granulomatous tumor and the cut surface had a well-defined whitish tumor (Figure 4). Histologically, there was granulomatous inflammation surrounding the abscess with necrosis and hemorrhage, which formed the tumor-like lesion (Figure 5). There were only secondary cholangitis and actinomycetes inside the abscess, which suggested the intraperitoneal spread of inflammation instead of via the biliary tract. The postoperative course was uneventful, and there has been no recurrence at 3 years after surgery.

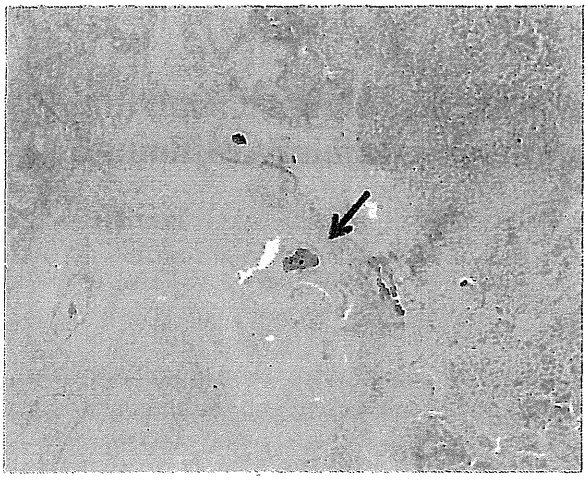

Figure 5 Histologically, there was granulomatous inflammation surrounding the abscess with necrosis, hemorrhage and actinomycetes (arrow). Hematoxylin and eosin staining, ×100.

Discussion

Because the indications for laparoscopic cholecystectomy have been expanded to include severe cholecystitis, the incidence of intraoperative injury to the gallbladder wall has not decreased and is reported to be around 30% (1,3,4). The fate of gallstones that are lost during laparoscopic cholecystectomy has not been elucidated, so the precise number of these unretrieved stones or the incidence of abscess formation due to such stones is unknown. Patients may have silent unretrieved stones in the peritoneal cavity or asymptomatic small abscesses. Indeed, there have been reports of surgery for a silent abscess that was found incidentally by imaging studies as well as for an abscess due to spilled stone 10 years after laparoscopic cholecystectomy (2,5). Retained stones rarely cause problems, but aggressive surgical intervention is usually necessary when complications arise. For example, there is a case report of a patient with inflammatory pseudotumor of the liver and two other extrahepatic masses in association with spilled stones after laparoscopic cholecystectomy who had to undergo posterior segmentectomy of the liver (4).

In the present case, there were no evident spilled stones in the reoperation. We believe the spilled stones were aspirated with pus from the abscess cavity during the operation or migrated into the liver parenchyma because the gallstones were very small. Migration of spilled stones could occur via the mechanism that expels foreign substances from the body. There have been reports of a perihepatic abscess and an empyema of the thorax containing migrating gallstones that may have occurred due to such a mechanism (6–9). The reason that a liver abscess formed in our patient could be the result of immunodeficiency related to hemodialysis.

In conclusion, this case is a rare example of hepatic involvement, with inflammation of the peritoneum, after gallstones were spilled during laparoscopic cholecystectomy.

Acknowledgment

The authors have no conflicts of interest or financial ties to disclose.

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ORIGINAL ARTICLE

Factors associated with early cancer-related death after curative hepatectomy for solitary small hepatocellular carcinoma without macroscopic vascular invasion

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Abstract

Background Unexpected early cancer-related death (ECRD) within 2 years due to recurrence after curative hepatectomy for solitary small (<5 cm) hepatocellular carcinoma without macroscopic vascular invasion (SSHCC) is occasionally observed.

Method A total of 415 patients were enrolled (19 patients with ECRD and 396 patients with non-ECRD) to elucidate the risk factors of ECRD after curative hepatectomy for SSHCC. They were initially compared by limiting variables to preoperative factors to reveal predictors that could enable the modification of primary treatment. Subsequently, the same analysis was performed with all variables, including perioperative and histological factors.

Results In the preoperative factors, tumor size > 3 cm and elevation of tumor marker level were independent predictors of ECRD. In the analysis with all variables, excessive intraoperative blood loss, poor differentiation, and microscopic vascular invasion were predictors of ECRD. In the recurrence patterns, 79% of ECRD presented as advanced (four or more lesions) or extra-hepatic recurrence, whereas these accounted for 18% in the non-ECRD.

Conclusion Excessive blood loss during the operation and histopathological findings of microscopic vascular invasion and poor differentiation are predictive factors of cancer-related death within 2 years of a hepatectomy for SSHCC.

Keywords Early cancer-related death · Hepatectomy · Hepatocellular carcinoma

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Introduction

Hepatectomy for hepatocellular carcinoma (HCC) is considered to be the most reliable treatment and a potential curative treatment; nevertheless, HCC recurrence is observed in up to 70–80% of patients within 5 years of curative resection [1, 2]. The 5-year overall survival rates after curative resection are 50% or more in high-volume centers. However, approximately 20% of patients experience cancer-related death within 2 years after resection [3–5].

A solitary HCC smaller than 5 cm and without macroscopic vascular invasion (SSHCC) in preserved liver function patients is considered the best candidate for hepatectomy in many treatment algorithms, and SSHCC has been reported to have a better prognosis [6–10].

To date, there have been several studies regarding predictors of early cancer-related death (ECRD) among subjects, including patients with multiple HCC and/or macroscopic vascular invasion; however, the predictors of ECRD in SSHCC are still unclear. Although ECRD after curative hepatectomy for SSHCC is uncommon, it has significant clinical relevance because the percentage of these patients has been increasing with advances in imaging modalities and the establishment of screening programs for high-risk patients [6, 7]. This study aimed to reveal the predictors of ECRD in SSHCC to clarify which patients require treatment modification and additional treatment.

Methods

From June 1994 to December 2010, 528 patients received a primary curative hepatectomy (R0 or R1 resection). Of those patients, 425 with a pathologically confirmed solitary HCC smaller than 5 cm that did not have macroscopic tumor invasion were included. The clinical findings, including gender, age, hepatoviral infection status, liver function status, pre-operative tumor marker levels, tumor marker elevation pattern, maximal tumor diameter on preoperative imaging examination, intraoperative blood loss, presence of intra-operative red blood cell transfusion, type of resection, complications, histopathologic results, and prognosis, were retrospectively collected. The histological variables were defined according to the General Rule for the Clinical and Pathological Study of Primary Liver Cancer by the Liver Cancer Study Group of Japan [11]. The macroscopic appearance of the HCC was divided into two groups according to classification by the aforementioned criteria; one was the boundary type, which included the vaguely nodular type and single nodular type, and the other was the non-boundary type, which included the single nodular type with extranodular growth, the confluent multinodular type, and the invasive type. An elevation in the levels of both tumor markers was defined as patients with an alpha-fetoprotein (AFP) > 20 ng/ml and a des-gamma-carboxyprothrombin (DCP) > 40 AU/L simultaneously. Because the current analysis was focused on the oncologic outcome after hepatectomy for HCC, we excluded 10 patients from the current study for the following reasons: four patients with hospital deaths related to the hepatectomy (mortality rate of 1.0%), two patients who died from causes unrelated to liver disease within 2 years, and four patients who were lost to follow-up within 2 years of the primary operation. Eventually, 415 patients with SSHCC were included in the analysis and followed until death or at least 2 years after the primary operation. The median follow-up period for the patients was 75.7 (6.4–218.4) months. None of these patients received adjuvant chemotherapy or radiation treatment.

The 415 patients were divided into two groups: 19 patients with cancer-related death within 2 years of the operation (ECRD) and 396 patients who survived more than 2 years (non-early cancer-related death; NECD). These two groups were compared with respect to preoperative, operative, and histopathological factors and recurrence patterns to reveal the predictors of ECRD after curative hepatectomy for SSHCC. The two groups were first compared by limiting the variables to preoperative factors to reveal predictors that could enable the modification of primary treatment. Subsequently, the same analysis was performed with all variables, including preoperative, operative, and histological factors, to reveal perioperative predictors of ECRD.

The patients were followed-up via tumor marker analysis every month, ultrasonography every 3 months, and dynamic computed tomography (CT) scan or magnetic resonance imaging (MRI) every 6 months during the first 2 years after the operation. Subsequently, the follow-up period was determined according to the likelihood of recurrence. The number of recurrent tumors was determined with dynamic CT/MRI and/or CT angiography. Extra-hepatic recurrence was detected with CT, MRI, and scintigraphy. The site and pattern of the initial recurrence were defined as follows: (1) solitary or oligonodular (two or three tumor nodules) recurrence; (2) advanced recurrence, defined as recurrence with four or more lesions, portal vein invasion, or both; and (3) recurrence at an extra-hepatic site regardless of simultaneous intra-hepatic recurrence. Treatment for the initial recurrence was determined according to the recurrence type and hepatic function reserve. A second curative resection and local ablation therapy were actively indicated for solitary and oligonodular recurrences, including extra-hepatic recurrence considered to be controlled, as reported previously [12]. Trans-arterial chemoembolization (TACE) and trans-arterial chemoinfusion were indicated for patients who were not indicated for curative treatment.

The data were analyzed with SPSS software, ver. 19 (SPSS, Chicago, IL, USA).

All clinical and pathological features depicted in Table 1 were selected for potential relation to ECRD based on previous studies or our own clinical experience [13–19].

They were categorized as continuous or categorical variables. Continuous variables were summarized as medians and ranges. Categorical variables were summarized as frequencies and percentages. Categorical data were analyzed using a χ^2 test or Fisher's exact test as appropriate. A Mann–Whitney *U*-test was used to compare continuous variables between the two groups. Differences in the clinicopathological variables between the two groups were identified with multivariate logistic regression analysis. In the multivariate analysis including prognostic factors, all factors that were $P < 0.15$ in univariate analysis were included. A two-tailed *P*-value of < 0.05 was considered statistically significant.

This study was approved by the Human Ethics Review Committee of Toranomon Hospital.

Results

The patient characteristics, treatments and histopathological characteristics of the ECRD and NECD groups are shown in Table 1. The results of the univariate analysis of the two groups are also shown in Table 1. The results of the multivariate analysis of the differences in preoperative factors between the two groups are shown in

Table 1 Comparison of the patients with early cancer-related deaths and non-early deaths

	ECRD ($n = 19$)	NECD ($n = 396$)	P
Preoperative characteristics			
Gender (male/female)	16/3	296/100	0.43
Age (years)	64 (28–79)	62 (30–87)	0.93
>65 years (yes/no)	9/10	157/239	0.63
HBV infection (yes/no)	8/11	121/275	0.31
HCV infection (yes/no)	11/8	233/163	1.00
Platelet count (μL) ($>10^5$/$<10^5$)	4/15	125/271	0.45
ICG > 30 % (yes/no)	5/14	73/323	0.37
Child–Pugh grade (A/B)	17/2	355/41	1.00
Elevation in the levels of both tumor markers[a,b] (yes/no)	4/15	48/341	<0.01
AFP > 400 ng/ml (yes/no)	4/15	42/354	0.15
DCP > 100 AU/L (yes/no)[b]	5/14	72/317	0.38
Tumor size (cm)	2.9 (1.3–5.0)	2.1 (0.6–5.0)	<0.01
>3 cm (yes/no)	9/10	74/322	<0.01
Operative characteristics			
Anatomical resection (yes/no)	3/16	76/320	1.00
Intraoperative blood loss (ml)	368 (20–2268)	195 (5–5367)	<0.01
>1,000 ml (yes/no)	6/13	10/386	<0.01
Intraoperative RBC transfusion (yes/no)	5/14	12/384	<0.01
Histopathological characteristics			
Macroscopic tumor appearance (boundary/non-boundary)	6/13	248/148	<0.01
Tumor differentiation grade (poorly/non-poorly)	11/8	67/329	<0.01
Capsule formation (yes/no)	16/3	286/110	0.30
Vascular invasion (yes/no)	10/9	80/316	<0.01
Surgical margin (R0/R1)	16/3	345/51	0.73
Liver cirrhosis (yes/no)	14/5	221/175	0.16

AFP alpha-fetoprotein, *DCP* des-gamma-carboxyprothrombin, *ECD* early cancer-related death, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *ICG15* indocyanine green 15-minute retention rate, *NED* non-early death, *RBC* red blood cell

[a] AFP > 20 ng/ml and DCP > 40 AU/L simultaneously

[b] DCP was not measured in seven patients

Table 2. In the multivariate analysis limited to preoperative factors, tumor size > 3 cm and an elevation in the levels of both tumor markers were independent preoperative predictors of ECRD. The results of the multivariate analysis including preoperative, operative, and histopathological variables are also shown in Table 2. Intraoperative blood loss > 1000 ml, poor histological differentiation grade, and microscopic vascular invasion were significantly frequent in the ECRD group. The preoperative factors tumor size and elevation in the levels of both tumor markers were no longer significant in the multivariate model with all variables.

The recurrence patterns and secondary treatments are summarized in Table 3. Advanced recurrence and extra-hepatic recurrence were more prevalent in the ECRD group and mostly occurred within one year of the primary operation. Advanced recurrence and extra-hepatic recurrence accounted for 58% and 21% of the recurrences in the ECRD group, respectively, but only accounted for 16% and 2% in the NECD group, respectively. The median duration between the primary operation and initial recurrence in the ECRD and NECD groups was 7.3 and 26.0 months, respectively ($P < 0.01$). In the secondary treatment after recurrence, only 16% of the ECRD group received a potential curative treatment, such as a second hepatectomy or local ablation therapy, whereas more than half of the NECD group received potentially curative secondary treatment. Other secondary treatments included two cases of radiation therapy and one case of no treatment due to massive tumor progression in the ECRD group and two cases of radiation therapy, two cases of systemic chemotherapy, and eight cases of treatment refusal in the NECD group.

Discussion

The current study examined the risk factors of cancer-related death within 2 years after curative hepatectomy for

Table 2 Comparison of the clinicopathological characteristics of the patients with early cancer-related death (ECRD) and non-early cancer-related death (NECD)

	Multivariate analysis				
	ECRD	NECD	P	HR	95% CI
a) Analysis limited to preoperative factors					
Elevation in the levels of both tumor markers[a,b] (yes/no)	7/12	48/341	***0.02***	***3.38***	***1.23–9.25***
AFP > 400 ng/ml (yes/no)	4/15	42/354	0.96	0.97	0.26–3.61
Tumor size > 3 cm (yes/no)	9/10	74/322	***0.02***	***3.28***	***1.26–8.57***
b) Analysis with all perioperative factors					
Elevation in the levels of both tumor markers[a,b] (yes/no)	7/12	48/341	0.07	2.77	0.91–8.40
AFP > 400 ng/ml (yes/no)	4/15	42/354	0.97	1.03	0.25–4.28
Tumor size > 3 cm (yes/no)	9/10	74/322	0.19	2.06	0.70–6.08
Intraoperative blood loss > 1000 ml (yes/no)	6/13	10/386	***<0.01***	***11.84***	***3.34–41.93***
Intraoperative RBC transfusion (yes/no)	5/14	12/384	0.34	2.32	0.41–13.06
Tumor differentiation grade (poorly/non-poorly)	11/8	67/329	***<0.01***	***4.63***	***1.67–12.88***
Macroscopic tumor appearance (boundary/non-boundary)	6/13	248/148	0.20	2.05	0.69–6.08
Vascular invasion (yes/no)	10/9	80/316	***0.045***	***2.86***	***1.03–7.96***

CI confidence interval, *HR* hazard ratio

[a] Alpha-fetoprotein (AFP) > 20 ng/ml and des-gamma-carboxyprothrombin > 40 AU/L simultaneously

[b] Des-gamma-carboxyprothrombin was not measured in seven patients

Table 3 Comparison of recurrence patterns and secondary treatment types

	ECRD ($n = 19$)	NECD ($n = 396$)	*P*
Total recurrence (%)	19 (100%)	236 (60%)	
Initial recurrence pattern			<0.01
Solitary or oligonodular	4 (21%)	193 (82%)	
Advanced[a]	11 (58%)	38 (16%)	
Extrahepatic	4 (21%)	5 (2%)	
Initial recurrence pattern and duration until recurrence			
Recurrence within one year from operation	17 (89%)	50 (21%)	<0.01
Advanced recurrence within one year	10 (53%)	14 (6%)	<0.01
Extra-hepatic recurrence within one year	4 (21%)	2 (1%)	<0.01
Second treatment type			<0.01
Second hepatectomy	1 (5%)	36 (15%)	
Local ablation therapy[b]	2 (11%)	101 (43%)	
TACE	13 (68%)	87 (37%)	
Others	3 (16%)	12 (5%)	

ECRD early cancer-related death, *NECD* non-early cancer-related death, *TACE* trans-arterial chemo embolization

[a] Advanced recurrence was defined as recurrence with four or more lesion, portal vein invasion, or both

[b] Including local ablation therapy with TACE

SSHCC so that future studies can focus on providing better therapies to this group of patients. In the statistical analysis limited to preoperative factors, tumor size larger than 3 cm and elevation of the levels of both tumor markers were revealed as independent prognostic factors of ECRD. In the analysis using all variables, including perioperative, operative and histopathological factors, none of the preoperative factors were predictors of ECRD. However, one operative factor (excessive intraoperative blood loss) and two histopathological factors (poorly differentiated HCC and the presence of vascular invasion) were found to be predictors of ECRD.

This study focused on SSHCC, which has good survival and a lower recurrence rate. However, even when curative

resection was performed for SSHCC, some patients developed early postoperative recurrence and experienced subsequent cancer-related death. The occurrence of ECRD in patients with SSHCC is relatively uncommon compared to those with large tumors, multiple tumors and/or macroscopic vascular invasion, while the prevalence of hepatectomy for SSHCC has been increasing due to medical innovations. In fact, 72.8% of patients who underwent curative resection had an HCC smaller than 5 cm, and 73.9% of them had a solitary HCC in a nationwide Japanese report including 13772 patients [7]. Therefore, the occurrence of ECRD in SSHCC is uncommon, but the total number of patients is not small.

Although the recurrence of HCC is determined by both recurrence of the resected tumor and multicentric carcinogenesis due to the damaged liver, the resected tumor is considered the main cause of recurrence in the early period after the operation. The recurrence patterns in this study revealed that advanced recurrence and extra-hepatic recurrence were more frequent in the ECRD group, supporting the hypothesis that the aggressive recurrence of the resected tumor is the main cause of ECRD. Therefore, the prognosis of potential ECRD patients may be improved with perioperative treatment modification or additional treatments to effectively control the resected tumor. The main objective of this study was to identify patients who required treatment modification and additional treatments as quickly as possible.

To predict potential ECRD, identifying important preoperative factors would provide the most useful information because it would permit the early customization of the treatment strategy to potentially have the best impact on prognosis. Therefore, we initially performed a statistical analysis limited to preoperative factors and found that tumor size larger than 3 cm and elevation in the levels of both tumor markers were preoperative predictors of ECRD. However, in the multivariate analysis using all factors, those preoperative factors were not significant. The tumor size and elevation in the levels of both tumor markers were considered to be confounded by microscopic vascular invasion and/or poor differentiation in the multivariate analysis. HCC develops in a multistep fashion, and the frequencies of poor differentiation grades and vascular invasion increase as the tumor size increases [20, 21]. Similarly, the elevation in the levels of both tumor markers was previously reported to be an indicator of advanced recurrence, microscopic vascular invasion and poor histological differentiation [13, 22]. Considering the abovementioned observations, the confounding effect among these variables appears to be rational.

We found that poor histological differentiation and the presence of microscopic vascular invasion were significant predictors of ECRD in SSHCC. Those factors have been reported to be predictors of early recurrence and ECRD in previous reports, although the backgrounds of the included patients were different in each of the studies [13–19]. Furthermore, Endo et al. previously reported that reduced E-cadherin expression was correlated with poorly differentiated HCC and that E-cadherin underexpression may reduce the adhesiveness of HCC cells, thereby potentiating invasion and metastasis. Because early cancer-related death appears to be related to the malignancy of the resected tumor, factors that indicate cancer cell invasion into the peripheral circulating blood are reasonable predictors of ECRD [23].

Interestingly, operative blood loss was the most powerful predictor of ECRD in this study. Although excessive blood loss during the operation was known to be an important predictor of the postoperative prognosis, the relationship between excessive blood loss and poor oncologic outcomes has not been clearly identified [24]. In a previous study by Katz et al., the potential reasons for the correlation between excessive blood loss and poor prognosis included tumor spillage and hematogenous spread during the operation, hypoperfusion and impaired oxygen delivery to vital organs, and the introduction of some cytokines by hemorrhagic shock [24].

In addition to the abovementioned possible explanations, we suggest that excessive blood loss is potentially correlated with tumor location, such as near the hepatic hilar and/or major vasculature, poor background liver function, including hemostatic functions, and an insufficient operation due to the massive bleeding. In any case, the surgeon should avoid excessive blood loss for not only operative safety but also oncological benefits.

Because nearly 80% of the initial recurrence in the ECRD group presented as advanced or extra-hepatic recurrence, we propose a correlation between ECRD and tumor dissemination from the resected tumor, although whether these sources of recurrence already existed at the time of operation or subsequently is uncertain. The systemic or hepatic artery infusion of neo-adjuvant and adjuvant chemotherapy appears to be a hopeful treatment for those patients. However, there is currently insufficient evidence to show that those therapies increase the survival rate of HCC, although there is limited evidence suggesting that those therapies may be useful for disease-free survival [25].

Our study had a possible limitation. Because the statistical analyses were performed with only 19 patients who had an event, our findings must be confirmed in a larger prospective study. As mentioned above, the occurrence of ECRD in SSHCC patients is not large, but the detection of those patients and improvement of the subsequent treatment approaches would enable further understanding of tumor control.

In conclusion, excessive blood loss during the operation and histopathological findings of microscopic vascular invasion and poor differentiation are predictive factors of cancer-related death within 2 years of a hepatectomy for SSHCC. The predictors revealed in this study and recurrence patterns of the ECRD group suggest a correlation between ECRD and tumor spillage and/or dissemination from the resected tumor. Reducing the intraoperative blood loss and additional perioperative treatments targeting disseminated tumors are expected to prevent ECRD.

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Conflict of interest None declared.

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In Hepatocellular Carcinomas, any Proportion of Poorly Differentiated Components is Associated with Poor Prognosis After Hepatectomy

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Abstract
Background Hepatocellular carcinoma (HCC) often consists of various differentiation components in a single tumor. However, the categorization of histologic grade in hepatectomy for those tumors has not been standardized. Some studies have determined the differentiation grade of the tumor according to its worst component, whereas others have determined it according to its predominant component. The present study aimed to resolve the controversy about whether the worst component or the dominant component determines the nature of the tumor, especially focusing on the presence of a poorly differentiated component (PDC).
Methods In total, 427 hepatectomized patients with solitary HCC were divided into three groups, tumors without a PDC (NP), tumors with a PDC but dominantly consisting of non-PDC as poorly contained (PC), and tumors predominantly consisted of a PDC as poorly dominant (PD). PC was compared with PD and NP.
Results Statistical analysis revealed that large tumors and high alpha-fetoprotein level were significantly more frequent in PC than in NP ($P < 0.01$ and $P = 0.04$, respectively), although no remarkable difference was observed between PC and PD. Both recurrence-free and overall survival rates were significantly worse in the PC and PD groups than in the NP group (PC vs. NP: $P = 0.01$ and $P < 0.01$, PD vs. NP: $P < 0.01$ and $P < 0.01$, respectively), but there was no significant difference in these parameters between PC and PD.
Conclusions All HCC, including PDC, should be categorized as poorly differentiated HCC regardless of the predominant differentiation component.

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Introduction

Hepatocellular carcinoma (HCC) is well known to develop in a multistep fashion [1, 2]. In general, HCC evolves from hyperplastic nodules into well-differentiated HCC and further grows into moderately and/or poorly differentiated HCC of increasing size, vascularity, and malignancy. The presence of two or more histological patterns and mixed patterns of various grades of differentiation in a single tumor are often observed during multistep development [3].

Numerous previous studies have indicated the clinical importance of histologic grade in the treatment of HCC [4–13]. In particular, the presence of a poorly differentiated component (PDC) has been considered to reflect high tumor malignancy and poor prognosis after radiofrequency ablation (RFA) and liver transplantation [4–9]. However, the categorization of differentiation grade after hepatectomy for HCC has not been well defined or standardized for tumors that consist of more than one histologically differentiated component [14]. The classification system of the World Health Organization and the guidelines of the General Rule for the Clinical and Pathological Study of Primary Liver Cancer Study Group of Japan (guidelines of LCSGJ) do not mention the categorization of heterogeneously differentiated HCC [3, 10]. Some previous studies categorized such tumors according to the worst component

Table 1 Comparison of clinicopathological characteristics after dividing into poorly contained (PC) and poorly dominant (PD) categories

				NP versus PC				PC versus PD			
	NP $N = 339$	PC $N = 41$	PD $N = 47$	Univariate	Multivariate			Univariate	Multivariate		
				P	*P*	HR	95 % CI	*P*	*P*	HR	95 % CI
Patient-related factors											
Male gender (%)	255 (75)	38 (95)	35 (74)	0.01	<0.01	5.49	1.57–19.23	0.03	0.03	4.34	1.13–16.68
Age >65 years (%)	137 (40)	15 (37)	19 (40)	0.74				0.83			
HBV infection positive (%)	98 (29)	15 (37)	12 (26)	0.37				0.35			
HCV infection positive (%)	197 (58)	20 (49)	29 (62)	0.32				0.28			
Liver-related factors											
Platelet count $<10^5$ μl (%)	105 (31)	8 (20)	13 (28)	0.15				0.46			
Child-Pugh grade B (%)	35 (10)	4 (10)	6 (13)	1.00				0.75			
Liver cirrhosis (%)	185 (55)	20 (49)	27 (57)	0.51				0.52			
Treatment-related factors											
Preoperative TACE (%)	46 (14)	5 (12)	5 (11)	1.00				1.00			
Anatomical resection (%)	70 (21)	11 (27)	17 (36)	0.42				0.37			
R0 resection (%)	297 (88)	35 (85)	43 (91)	0.62				0.50			
Tumor-related factors											
AFP >100 ng/ml (%)	65 (19)	14 (34)	18 (38)	0.04	0.04	2.26	1.05–4.86	0.83			
DCP >40 AU/l (%)[a]	86 (25)	17 (41)	27 (57)	<0.01				0.39			
Tumor size >3 cm (%)	67 (20)	20 (49)	19 (40)	<0.01	<0.01	3.42	1.70–6.87	0.52			
Non-boundary macroscopic appearance (%)[b]	124 (37)	24 (59)	23 (49)	0.04	0.01	2.38	1.19–4.76	0.40			
Capsule formation (%)	237 (70)	35 (85)	34 (72)	0.04				0.20			
Microscopic vascular invasion (%)	64 (19)	15 (37)	20 (43)	0.06				0.52			

NP non-poorly, *PC* poorly contained, *PD* poorly dominant, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxyprothrombin, *HR* hazard ratio, *CI* confidence interval, *TACE* transcatheter arterial embolization

[a] DCP was not measured in three patients

[b] Macroscopic appearance was uncertain in 1 patient

of the entire specimen, whereas in other studies determination of the tumor differentiation grade was based on the tumor's dominant components [10–12]. As a result, even though the tumor contained a PDC, it was categorized as moderately or well-differentiated HCC when non-PDC was dominant.

The present study aimed to clarify whether the worst component or the dominant component determines the nature of the tumor, especially focusing on the presence of a PDC.

Methods

Patients

From January 1995 to December 2010, 551 patients underwent primary curative hepatectomy (R0 or R1 resection), and the clinicopathological findings depicted in Table 1 were collected. The number, size, and differentiation grade of the tumors; the distance of the resection margin; and the presence of liver cirrhosis were determined pathologically. Of the initial 551 patients, 469 patients with solitary tumors were enrolled in the study. Of the 469 enrolled patients, 31 were later excluded because of the following diagnoses: combined HCC and cholangiocarcinoma (14 patients), sarcomatoid differentiation (two patients) and an undifferentiated type (one patient); additionally, 14 patients had an uncertain histopathological differentiation grade because the total necrosis due to preoperative TACE prevented determination of the differentiation grade. To accurately assess the influence of tumor differentiation grade on initial tumor recurrence and prognosis, one patient who died from causes unrelated to liver disease within 1 year and ten patients whose outcomes were uncertain within 1 year from primary operation were also excluded. Ultimately, 427 patients with solitary HCC were included in the analyses and were

followed up until death or until at least one year after the primary resection. There were four cases of hospital death related to hepatectomy (0.9 %). The median follow-up period for survivors was 60.8 months.

The etiology of background liver disease was determined as follow; 125 patients had hepatitis B infection, 246 patients had hepatitis C infection, six patients had both hepatitis B and C infection, 19 patients had alcoholic liver cirrhosis, six patients had autoimmune liver disease, and 37 patients had cryptogenic HCC.

Histopathologic features

Surgically resected specimens were routinely processed according to the guidelines of LCSGJ [3]. The resected specimen was fixed with 10 % formaldehyde and embedded in paraffin, and 5 μm sections were stained with hematoxylin and eosin. Histopathological examination of the resected specimens was performed by two experienced pathologists blinded to the patient outcomes after hepatectomy. A poorly differentiated component was defined as follows: "PDC proliferate in a solid pattern without distinct sinusoid-like blood spaces, and only slit-like blood vessels are observed in large tumor nests. Neoplastic cells show an increased nuclear/cytoplasmic ratio and frequent pleomorphism, including bizarre giant cells" [3, 15]. The histopathological variables were defined according to the guidelines of LCSGJ. The macroscopic appearance of HCC was divided into two groups according to classification by the aforementioned criteria; one was the boundary type, which included vaguely nodular and single nodular types, and the other was the non-boundary type, which included the single nodular type with extranodular growth, the confluent multinodular type, and the invasive type. Microscopic vascular invasion was defined as the presence of tumor emboli within the central vein, the portal vein, or large capsular vessels, or as involvement of the lobar or segmental branches of the portal vein or the hepatic veins.

Postoperative follow-up

Patients were followed up monthly via tumor markers such as alpha-fetoprotein (AFP) and des-gamma-carboxyprothrombin (DCP), by ultrasonography every 3 months, and with a dynamic computed tomography (CT) scan or magnetic resonance imaging (MRI) study every 6 months during the first year after the resection. After 1 year, the follow-up period was determined according to the likelihood of recurrence. When recurrence was suspected, patients were examined by extra imaging studies; the number of recurrent tumors was determined by dynamic CT/MRI and/or CT angiography. Extrahepatic recurrence was detected by CT, MRI, and scintigraphy. The site and pattern of the initial recurrence were defined as follows: (1) solitary recurrence; (2) oligonodular (two or three tumor nodules) recurrence; (3) advanced recurrence (recurrence with four or more lesions and/or extrahepatic recurrence).

Design

The 427 patients with solitary HCC were divided into three groups: those with tumors without a PDC (the NP group), those with tumors that included a PDC that predominantly was defined as poorly dominant (the PD group), and those with tumors that included a PDC non-predominantly regardless of the dominant component, which was defined as poorly contained (the PC group). Clinicopathological variables and prognoses were compared among the NP, PC, and PD groups to investigate whether PC tumor should be categorized into poorly differentiated HCC or non-poorly differentiated HCC (Fig. 1).

Statistical analysis and ethical considerations

The data were analyzed with SPSS software v. 19 (IBM SPSS, Chicago, IL, USA). All clinical and pathological features were categorized as categorical variables and summarized by their frequencies and percentages. The χ^2 test or Fisher's exact test was used to compare categorical variables when appropriate. Differences in the clinicopathological variables between the groups were identified by multivariate logistic regression analysis. In the multivariate analysis of the difference, all factors that were marginally significant in the univariate analysis ($P < 0.10$) were entered into the analyses.

Cumulative overall survival and recurrence-free survival were determined by the Kaplan–Meier method. Differences between curves were assessed according to the log rank test. Multivariate analysis with Cox stepwise regression was used to investigate the significant predictor of prognosis. In the multivariate analyses about prognostic factors, all factors depicted in Table 1 and the presence of a PDC were entered into the analyses. A two-tailed P value of <0.05 was considered statistically significant. The study protocol was approved by the Human Ethics Review Committee of Toranomon Hospital.

Results

The patient group included 328 men and 99 women whose mean age at the time of hepatectomy was 61.4 years (range 28–87 years). The mean tumor size was 27.2 mm (median 23.0 mm; range 6 –170 mm).

Of 427 patients with solitary HCC, 339, 41, and 47 were classified into the NP, PC, and PD groups, respectively.

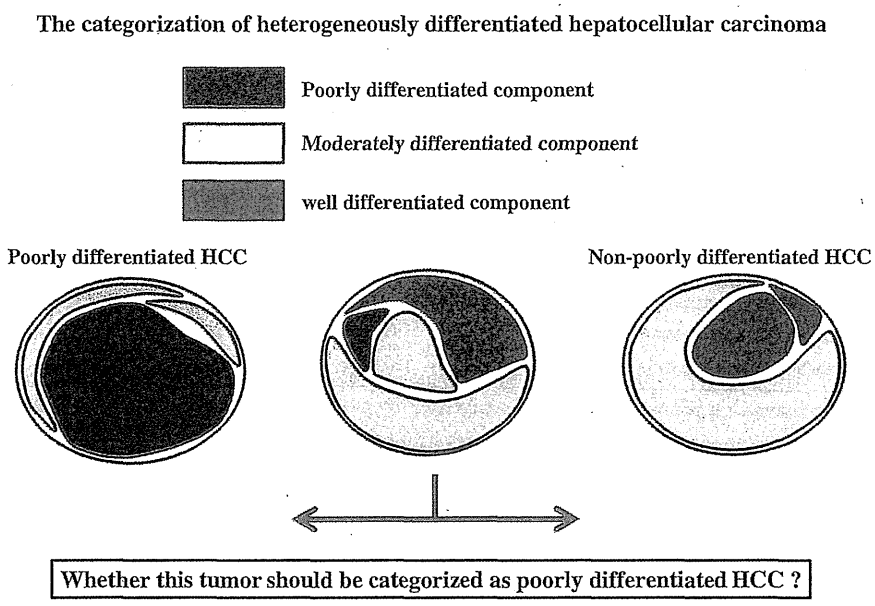

Fig. 1 The categorization of heterogeneously differentiated hepatocellular carcinoma

The results of clinicopathological factor comparison among those three groups are shown in Table 1. In a comparison between the NP group and the PC subgroup, male gender, high AFP level, tumor size greater than 30 mm, and non-boundary macroscopic tumor appearance were significantly more common in the PC subgroup. In contrast, comparison between the PC and PD groups indicated that only male gender was significantly more frequent in the PC group. The etiology of liver disease and indicators of background liver function such as serum platelet count, Child-Pugh classification, and presence of liver cirrhosis did not differ between the NP and PC groups, and those were the same in the comparison between the PC and PD groups.

Of the 427 patients, 256 patients (60 %) had tumor recurrence and the mean time between primary resection and initial recurrence was 33.0 months (median 23.2 months; range 1–186 months). The recurrence patterns of each of the differentiation groups are summarized in Table 2. Advanced recurrence was significantly more frequent in the PC and PD groups than in the NP group. Moreover, the PC group tended to develop recurrence early after primary resection and significantly more frequently with early advanced recurrence than the NP group, although three was no significant difference between the PC and PD groups.

The recurrence-free survival and overall survival curves for each group are shown in Fig. 2. The 1-, 3-, and 5-year recurrence-free survival rates for NP, PC, and PD were 85, 62, and 47; 77, 40, and 31; and 68, 40, and 33 %, respectively. The 5- and 10-year overall survival rates for NP, PC, and PD were 82, 55, and 77 and 41, 63, and 50 %, respectively.

Both recurrence-free and overall survival were significantly poorer in the PC and PD groups than in the NP group (PC vs. NP: $P = 0.01$ and $P < 0.01$, PD vs. NP: $P < 0.01$ and $P < 0.01$, respectively). The recurrence-free and overall survival curves for the PC group were not significantly different from those for the PD group ($P = 0.51$ and $P = 0.99$, respectively).

When the categorical variables listed in Table 1 and the presence of a PDC were included in the Cox regression multivariate analysis, hepatitis C infection, low serum platelet count, high AFP level, presence of a PDC, and presence of microscopic vascular invasion were independent poor prognostic factors for recurrence. A similar analysis of overall survival rate showed that hepatitis C infection, Child-Pugh grade B liver function, liver cirrhosis, presence of a PDC, and presence of vascular invasion were independent poor predictors of survival (Table 3).

Discussion

The present study was conducted to establish the proper categorization of heterogeneously differentiated HCC containing a PDC in hepatectomy. Statistical analyses showed that, in heterogeneous tumors with a PDC, tumor characteristics and malignancy are similar regardless of which component predominates.

The prognostic importance of histologic grade has been reported for many neoplasms [16, 17]. As in HCC, poor histological differentiation has been reported to be a poor prognostic factor [4–9]. Current guidelines recommend not performing RFA for poorly differentiated HCC due to poor prognosis and the possibility of tumor seeding [18]. In liver

Table 2 The comparison of recurrence patterns based on the presence of a poorly differentiated component

Number of recurrences	NP ($N = 189$)	PC ($N = 30$)	PD ($N = 37$)	NP versus PC P	PC versus PD P
Overall recurrence rate	56 %	73 %	79 %	0.04	0.62
Initial recurrence pattern					
Solitary	115	14	16	1.00	1.00
Oligonodular	37	4	9	1.00	0.25
Advanced[a]	37	12	12	<0.01	0.81
Initial recurrence pattern and duration until recurrence					
Recurrence within 2 years of resection	97	17	24	0.10	0.40
Advanced recurrence within 2 years of resection	27	8	12	0.02	0.61

NP tumor without a poorly differentiated component, *P* tumor with a poorly differentiated component

[a] Advanced recurrence was defined as recurrence with four or more lesions and/or extrahepatic recurrence

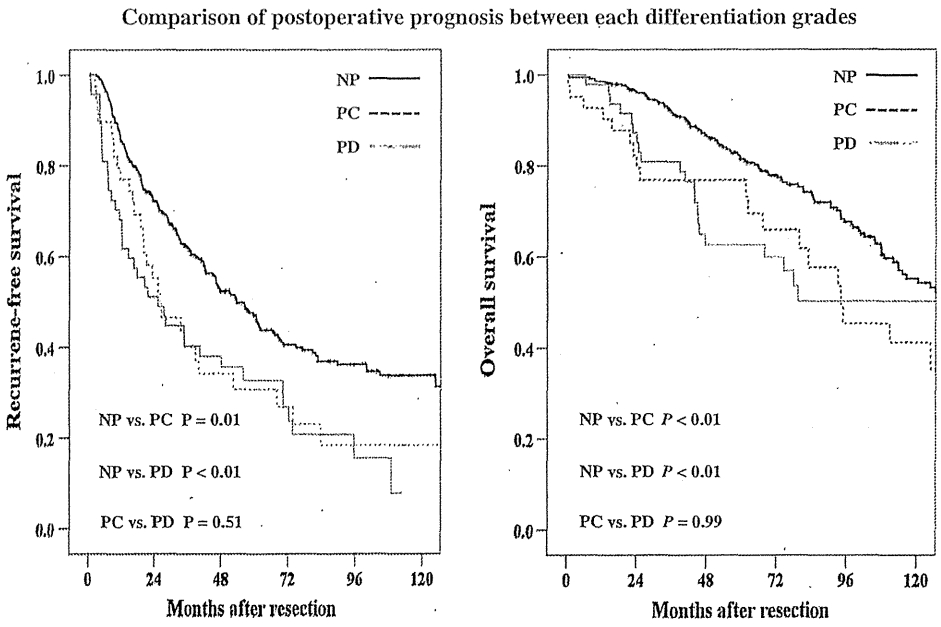

Fig. 2 Comparison of postoperative prognosis between each differentiation grade. *NP* tumor without a poorly differentiated component, *PC* poorly contained, *PD* poorly dominant

transplantation, poorly differentiated HCC has been considered to be a contraindication in some institutions because of its obvious adverse effects on post-transplant recurrence and survival [8, 9]. However, although histologic grade is considered an important prognostic factor, the grading of heterogeneously differentiated HCC remains controversial, and no consensus or guidelines on the best way to approach such categorization are available. Thus this study, which focused on the presence of a PDC, was conducted to determine whether the worst component or the dominant component of the specimen indicates its clinicopathological features and postoperative prognosis more accurately. We categorized HCC with a PDC into PC and PD subgroups and compared the PC group with the PD and NP groups to determine the properties of the PC group. In comparisons among the three groups by univariate and multivariate analyses, the PC group was more frequently associated than the NP group with known predictors of poor prognosis, such as large tumor size, high tumor marker levels, and non-boundary macroscopic tumor appearance [13, 19–21]. In contrast, there were no significant differences between the PC and PD groups in poor prognostic predictors, such as tumor size, tumor marker level, and the presence of microscopic vascular invasion.

Regarding the recurrence pattern, both the PC and PD groups tended to experience recurrence within two years after resection, and HCC tended to recur in an advanced state more often than in the NP group, although no difference was seen in recurrence patterns between the PC and PD groups. This recurrence pattern indicates the high malignancy of HCC with a PDC because recurrence of the resected tumor is considered to be the primary cause of advanced recurrence in the early period following resection [22].

Table 3 The results of Cox regression multivariate analysis regarding recurrence and survival

Variable	*P* value	Hazard ratio	95 % confidence interval
Disease-free survival			
Hepatitis C infection	<0.01	1.54	1.18–2.00
Platelet count $<10^5$ μl	<0.01	1.45	1.11–1.90
AFP >100 ng/ml	0.049	1.34	1.002–1.79
Presence of a PDC	<0.01	1.66	1.25–2.21
Microscopic vascular invasion	<0.01	1.76	1.34–2.32
Overall survival			
Hepatitis C infection	0.04	1.50	1.03–2.19
Child-Pugh grade B	<0.01	2.73	1.69–4.41
Liver cirrhosis	0.04	1.46	1.01–2.12
Presence of a PDC	0.02	1.56	1.03–2.19
Microscopic vascular invasion	0.02	1.57	1.09–2.26

For long-term prognosis, the recurrence-free and overall survival curves for the PC group were similar to those of the PD group and significantly different from those of the NP group. Considering that there was no statistical difference between the NP and PC groups regarding the background liver factors, the difference in recurrence-free and overall survival between the NP and PC groups would derive from such tumor factors as large tumor size, the presence of vascular invasion, and the presence of a PDC. There would be confounding between histological grade and other tumor factors in the postoperative outcomes; namely, the poorer prognosis of the PC group did not derive merely from tumor differentiation grade. However, when considering the properties of the PC group, the tumor characteristics and postoperative outcomes of PC tumors are more similar to PD tumors than to NP tumors. Therefore, we recommended categorizing all tumors, including those with a PDC, as poorly differentiated HCC, regardless of the proportion of the PDC.

The present study has several limitations. First, determination of the presence of a PDC depended entirely on the pathologists' subjective assessment. At present, there is no acknowledged objective evaluation system for the presence of a PDC, although several studies have shown an association between tumor differentiation grade and protein or cytokine expression [23, 24]. Although these methods offer attractive possibilities, they are not sufficiently established for use in a real clinical setting at this moment. The required next step is to establish a simple and objective differentiation grading system and to re-evaluate our results based on that system.

A second limitation is that we did not evaluate the proportion of the PDC area using percentages and cut-off values when we divided the tumors into the PC and PD subgroups. Therefore, particularly in the PC group, the tumors included the PDC in a range of proportions. Evaluation of the objective percentage of the PDC and its cut-off value might have made it possible to grade heterogeneously differentiated HCC more precisely. Unfortunately, as mentioned above, there is no objective method for evaluation of the percentage of the PDC. Thus, we classified tumors with and without a PDC based on the pathologists' subjective assessment in this study. The small sample size regarding PC and PD group tumors is also a limitation of our study. A well-defined, nationwide study is required to accurately assess our findings.

In conclusion, we recommend that all HCC, including a PDC, be categorized into poorly differentiated HCC regardless of the dominant component when categorizing HCC that consists of two or more differentiated components.

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Case Report

Hepatic Mucinous Cystic Tumor Communicating with the Bile Duct

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Keywords
- Hepatic mucinous cystic tumor
- Bile duct communication

ABBREVIATIONS

MCT: Mucinous Cystic Tumor; IPMN: Intraductal Papillary Mucinous Neoplasm; IPNB: Intraductal Papillary Neoplasm of Bile Duct; CT: Computed Tomography; MRI: Magnetic Resonance Imaging

EDITORIAL

Hepatic mucinous tumors are rare and can be difficult to distinguish from intraductal bile duct neoplasms. This tumor usually produces mucin, but it can be a problem to distinguish between a hepatic mucinous cystic neoplasm and an intraductal tumor. Here we report a patient who had a hepatic mucinous cystadenoma with communication between the cyst and bile duct.

A 65-year-old woman developed chronic renal failure of unknown etiology and required hemodialysis. She was scheduled to undergo living-related renal transplantation from her husband. However, a cystic lesion of the liver associated with calcification, gallstones, and dilatation of intrahepatic bile ducts (B2-B3) was found by the referring hospital. Investigation of the cystic tumor was performed at that hospital. Percutaneous transhepatic cyst puncture and infusion of contrast medium showed a communication between the cyst and the bile duct (Figure 1). Endoscopic retrograde cholangiography also revealed a communication with the cystic lesion. After drainage of the cyst was performed, dilatation of the intrahepatic bile ducts diminished.

She was admitted to our hospital for renal transplantation, and was referred for the treatment of her gallstones. Computed tomography (CT) showed an irregular cystic lesion in segment 4 of the liver, which had thickened and partly calcified walls. The contents of the cyst were largely serous and a communication between cyst and bile duct was not visualized. Before renal transplantation, it was decided that her gallstones and the cystic lesion in the liver required treatment.

Therefore, left lobectomy of the liver was performed together with cholecystectomy. The resected specimen contained a multilocular cystic tumor with black stones inside it and calcification of its walls. Microscopic examination showed that the cysts were lined by cuboidal and columnar epithelium with evidence of inflammation (Figure 2). The ovarian-like stroma was positive for estrogen and progesterone receptors on immunohistochemistry (Figure 2). A communication between the cystic tumor and the bile duct was not evident.

Hepatic mucinous tumor is rare and it can be confusing to distinguish between this tumor and an intraductal bile duct tumor. Although this tumor usually has mucin-producing capacity, it can be problematic to differentiate between a hepatic mucinous cystic neoplasm and an intraductal tumor. Recently, the concept of this tumor has changed and it is thought to be a counterpart of the cystic neoplasms of the pancreas, i.e., intraductal papillary mucinous neoplasm (IPMN) and mucinous

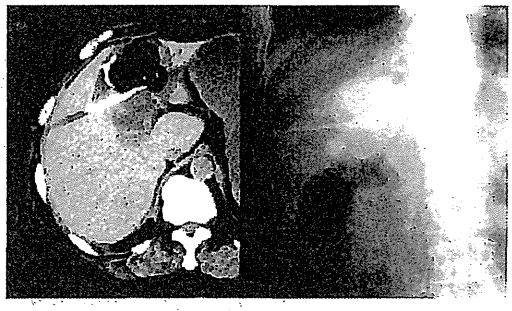

Figure 1 Endoscopic retrograde cholangiography also revealed a communication with the cystic lesion.

Figure 2 The ovarian-like stroma was positive for estrogen and progesterone receptors on immunohistochemistry.

cystic tumor (MCN) [1]. Mucinous cystic tumor of the pancreas rarely has a communication with the pancreatic duct.

Thus, the criteria for classification of hepatic mucinous tumor are usually the absence of a communication between cyst and bile duct and the presence of ovarian-like stroma. Our patient had a hepatic mucinous tumor with ovarian-like stroma, and there was a communication between the cystic lesion and the bile duct.

This was an unusual case of hepatic mucinous tumor. Although the presence of ovarian-like stroma is specific to hepatic mucinous tumor, a communication between cyst and bile duct as well as stones within the cyst cavity are not in accordance with the known features of this tumor. The communication in this patient was thought to be either a true communication between the bile duct and the cystic lesion or else due to rupture of a cyst into the bile duct. CT and MRI are inadequate imaging methods to examine the communication of an intrahepatic cystic lesion with the biliary tree. However, communication of this patient's cystic lesion with the bile duct was confirmed by both percutaneous transhepatic cyst puncture with infusion of contrast medium and endoscopic retrograde cholangiography.

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ORIGINAL SCIENTIFIC REPORT

The Influence of Histological Differentiation Grade on the Outcome of Liver Resection for Hepatocellular Carcinomas 2 cm or Smaller in Size

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Abstract

Background Small hepatocellular carcinomas (HCC) with poorly differentiated components (PDC) are reportedly at risk of dissemination and needle tract seeding after percutaneous radiofrequency ablation, although it is the preferred treatment for HCC $\leq$ 2 cm because of the low rate of vascular invasion. On the other hand, the clinical outcomes after hepatectomy for these tumors are still unclear because of their rarity.

Methods A total of 233 cases of solitary HCC $\leq$ 2 cm were retrospectively reviewed and divided into two groups according to the presence of PDC: 199 without PDC (NP-HCCs) and 34 with PDC (P-HCCs). The clinicopathological characteristics and prognosis were compared.

Results A comparison of clinicopathological characteristics showed that the elevation of the tumor markers alpha-fetoprotein (AFP) (>20 ng/mL) and des-gamma-carboxyprothrombin (DCP) (>40 AU/L) was significantly frequent in P-HCCs. The 3- and 5-year recurrence-free survival rates for P-HCCS were 39 and 29 %, respectively, which were significantly worse than those for NP-HCCs (64 and 50 %, respectively) ($p < 0.01$). Initial recurrence of P-HCCs was significantly more frequent, as well as extrahepatic recurrence and advanced recurrence in the early period after the operation. Recurrences with tumor dissemination were observed in 15 % of P-HCCs and 4 % of NP-HCCs ($p = 0.03$).

Conclusion PDC is present in 15 % of HCC < 2 cm and should be suspected when the both tumor markers are elevated. Moreover, significantly worse post-hepatectomy outcomes such as early advanced recurrence or recurrence with dissemination should be taken into account if PDC is present even in HCCs $\leq$ 2 cm.

Introduction

Classic hepatocellular carcinoma (HCC) is known to develop in a multistep fashion. Well-differentiated areas are gradually replaced by less well-differentiated tissue when the tumor size reaches a diameter of approximately 2 cm [1, 2]. It is now possible to detect small HCCs because of advances in imaging and establishment of screening guidelines for patients with a high risk of HCC, resulting in an increasing number of early HCC that

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undergo treatment [3]. In these situations, surgeons may encounter cases of resected HCCs of a small size (2 cm or smaller) that have poorly differentiated components (PDC). The carcinogenesis process of these tumors deviates greatly from the well-known multistep development theory.

The HCCs that have PDCs are reportedly at risk of dissemination, needle tract tumor seeding, and intrahepatic dissemination after percutaneous radiofrequency ablation (RFA). Based on these observations, several reports recommend hepatectomy rather than RFA for HCCs that contain PDCs and pre-treatment detection of PDCs in HCCs has attracted attention [4–6]. However, the influence of PDCs in small HCCs on outcomes after hepatectomy and the characteristics of these tumors remain unclear.

The aim of the present study was to examine the clinicopathological characteristics of small HCCs $\leq$ 2 cm with PDC, and to determine whether the outcome of hepatectomy is influenced by the histologic grade in small HCCs $\leq$ 2 cm.

Methods

Patients

A total of 649 cases that underwent primary curative hepatectomy for HCC (R0 or R1 resection) between 1994 and 2012 were retrospectively reviewed. Of the 649 cases, 246 had solitary tumors $\leq$2 cm in size and were examined in detail. Cases with solitary tumors were chosen to enable accurate assessment of the influence of histologic grade on operative outcomes. Ten cases with an uncertain histologic grade due to total necrosis secondary to preoperative transcatheter chemoembolization were excluded, as well as three cases with unclear outcomes 1 year after primary resection. Thus, 233 cases of solitary HCC $\leq$ 2 cm were analyzed in this study, which were followed up until death or December 2013. The clinicopathological characteristics of these cases are shown in Table 1, including the number and size of tumors, width of the surgical margin, and presence of liver cirrhosis.

Table 1 Comparison of clinicopathological characteristics between differentiation grades

Differentiation grade[a]	Non-poorly		Poorly $N = 34$	Non-poorly versus poorly
	Well $N = 54$	Moderately $N = 145$		
(a) Patient-related factors				
Male sex % (yes/no)	**72** (39/15)	**75** (109/36)	**79** (27/7)	0.67
Age > 60 years % (yes/no)	**67** (36/18)	**48** (70/75)	**53** (18/16)	1.00
HBV infection positive % (yes/no)	**22** (12/42)	**36** (52/93)	**29** (10/24)	0.84
HCV infection positive % (yes/no)	**70** (38/16)	**57** (82/63)	**62** (21/13)	1.00
(b) Background liver-related factors				
Platelet count $<10^5$ (μL) % (yes/no)	**46** (25/29)	**34** (49/96)	**35** (12/22)	1.00
Child-Pugh grade B % (yes/no)	**22** (12/42)	**8** (12/133)	**12** (4/30)	1.00
Liver cirrhosis % (yes/no)	**70** (38/16)	**66** (95/50)	**79** (27/7)	0.17
(c) Pre-operative tumor markers				
AFP > 100 ng/mL % (yes/no)	**11** (6/48)	**20** (29/116)	**26** (9/25)	0.24
DCP > 100 AU/L %[b] (yes/no)	**2** (1/51)	**12** (17/123)	**15** (5/28)	0.35
Elevation of both tumor markers[b,c] (yes/no)	**4** (2/50)	**10** (14/126)	**27** (9/24)	*<0.01*
(d) Operative factors				
Anatomical resection % (yes/no)	**5** (2/52)	**17** (24/121)	**24** (8/26)	0.12
Surgical margin >5 mm % (yes/no)	**46** (25/29)	**54** (78/67)	**47** (16/18)	0.71
(e) Tumor-related factors				
Non-boundary macroscopic appearance % (yes/no)	**22** (12/42)	**39** (56/89)	**47** (16/18)	0.18
Capsule formation % (yes/no)	**37** (20/34)	**72** (104/41)	**71** (24/10)	0.44
Microscopic vascular invasion % (yes/no)	**9** (5/49)	**18** (26/119)	**24** (8/26)	0.32

HBV hepatitis B virus, *HCV* hepatitis C virus, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxyprothrombin

[a] Differentiation grade was determined by the differentiation component with the worst grade in the entire specimen

[b] DCP was not measured in six patients

[c] Concurrent elevation of alpha-fetoprotein (>20 ng/mL) and des-gamma-carboxyprothrombin (>40 AU/L)