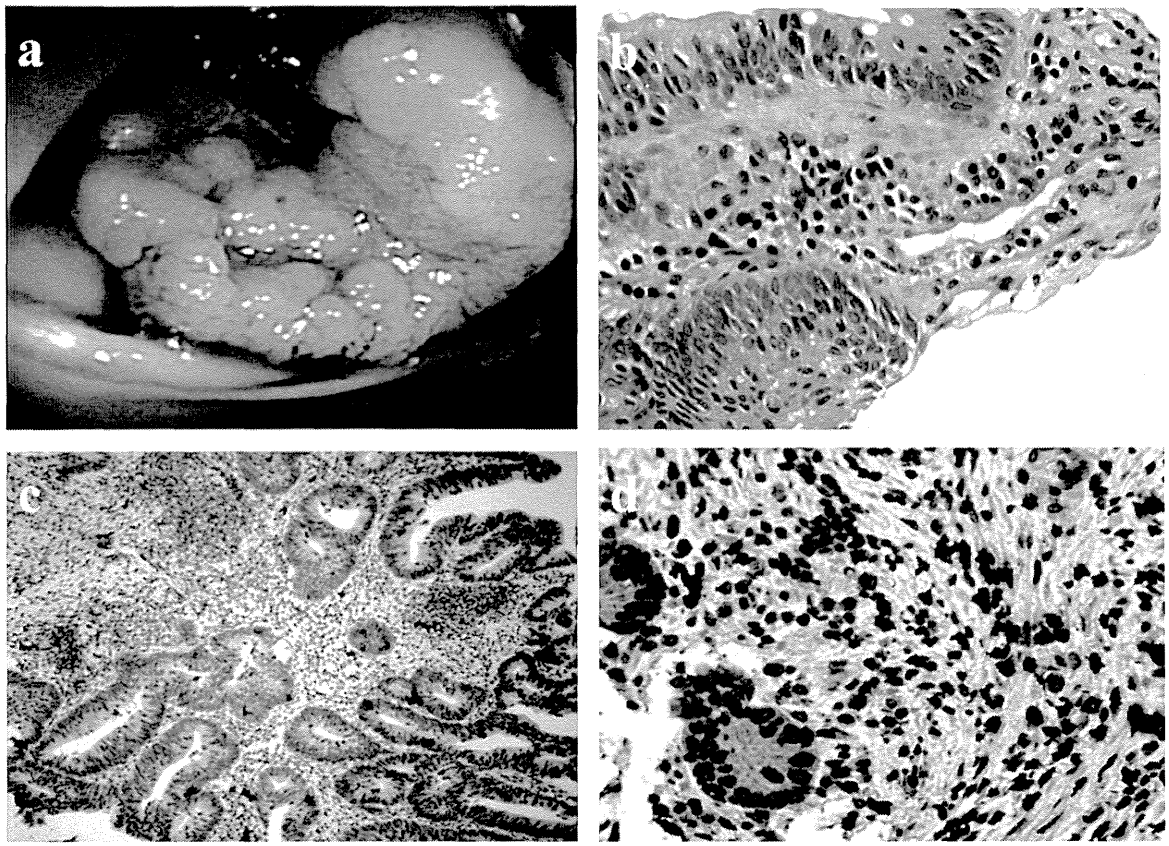

Fig. 2. **a**: The colonoscopic examination revealed a tumor accompanied by a giant ulcer on the ascending colon. **b**: Multiple biopsies showed a well-differentiated tubular adenocarcinoma (X 400). **c**: Immunohistochemical determination of PIVKA-II expression in the area of the adenocarcinoma was negative (X 100). **d:** Immunohistochemical determination of PIVKA-II expression in the non-cancer area of plasma cells was non-specifically positive (X 400).

cally [11]. Hepatoid-differentiated cells are derived from germ cell tumors located close to the embryonic association of the foregut endoderm and yolk sac [12]; the foregut derivation of both liver and stomach and their embryologic proximity likely have a role. Hepatocellular metaplasia of tumor cells is suggested to be the mechanism of PIVKA-II production. Carcinomas that histologically resemble hepatocellular carcinoma (hepatoid adenocarcinomas) have been described at various sites, including the colon [13].

By contrast, PIVKA-II has been reported to be positive in 26% of non-cancer tissues adjacent to HCC. The expression of PIVKA-II in non-cancer tissue adjacent to the HCC is stronger than the expression in the tumor. The explanation for this phenomenon might be that accelerated production of the prothrombin precursor in HCC causes a deficiency of vitamin K in the local region surrounding the HCC [14]. It is suggested that non-cancer tissue including liver parenchyma adjacent to the HCC may produce PIVKA-II [14]. The expression of PIVKA-II was detected in non-cancer areas, with non-specific expression observed in plasma cells in our case. Most hepatoid adenocarcinomas are associated with the production of alpha-fetoprotein (AFP), but not all AFP-producing carcinomas show hepatoid features histologically [15,16]. In our case, serum AFP level was not high, and hepatoid cells were not detected in the biopsy specimen. In many gastric cancer cases, biopsy specimens show only the histological appearance of poorly or moderately differentiated adenocarcinoma, but hepatoid cells are detected by the examination of surgical or autopsy materials [11]. There might be some possibility that hepatoid differentiation exists in other regions of the colon tumor or in the liver tumor, parenchymal cells or lung metastases, which were composed of PIVKA-II-positive and AFP-negative cells.

CA 19–9 has been developed for the diagnosis of digestive tract malignancies. Recent reports indicated that serum CA19–9 is frequently elevated in subjects with various gastrointestinal malignancies, such as pancreatic, colorectal, gastric and hepatic carcinomas [17] The antibody has been obtained by immunizing mice with a human colorectal cell line [18]. The epitope is expressed on the cell surface as glycolipids and glycoproteins. In patients with digestive malignancies, the antigen is found in serum, where it is associated with a high molecular weight carbohydrate-rich mucin fraction. Serum CA19–9 concentration was most increased in a patient with pancreatic cancer or cholangiocarcinoma. CA 19–9 resembles carcinoembryonic antigen in colorectal carcinoma and various different gastrointestinal adenocarcinomas. Expression of CA19–9 has been studied in normal and malignant gastrointestinal tissues. The antigen was found by immunoperoxidase staining in 40% to 80% of carcinomas from gallbladder, stomach, pancreas, and colon [19].

The oncofetal antigen glypican 3 (GP 3) is a heparin sulfate proteoglycan that is expressed in more than 70% of HCCs. They are the first transcripts to appear during malignant hepatocyte transformation [20]. An immunohistochemical analysis showed that the cells present in the colonic lesion were GP3 negative in our case.

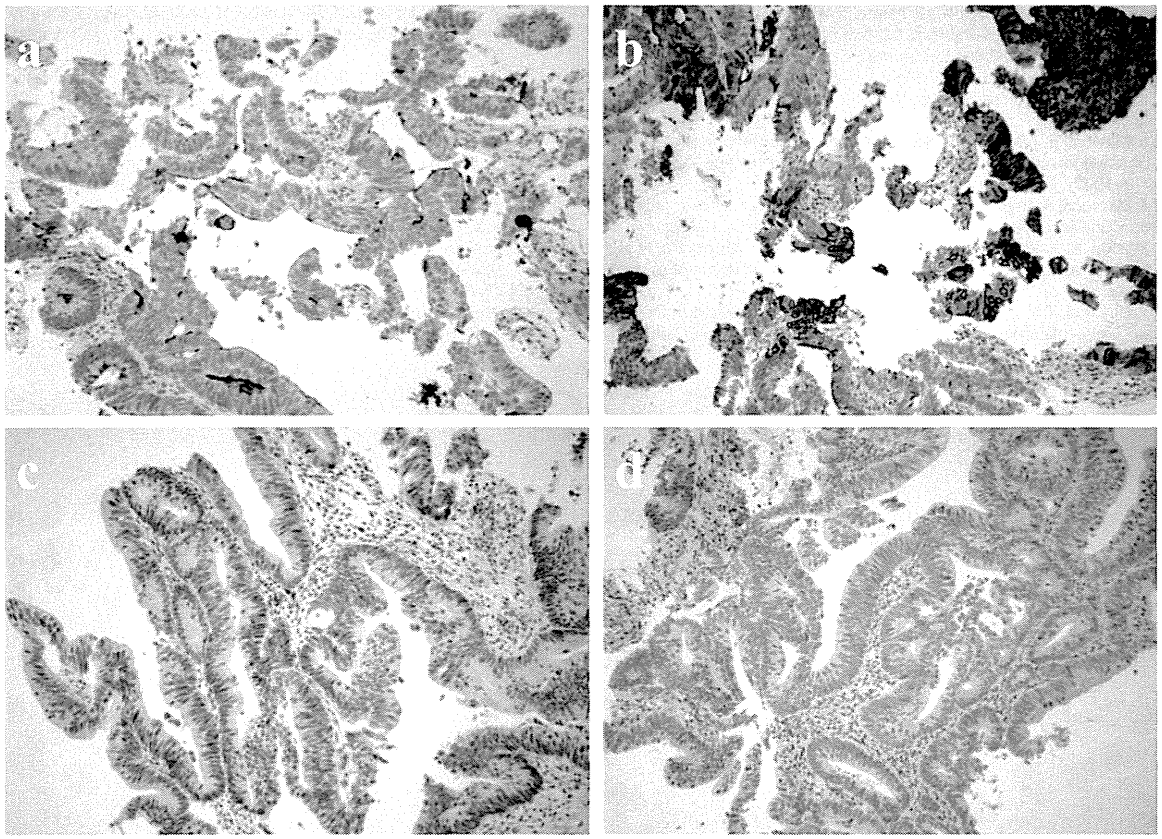

Fig. 3. **a** and **b**: Immunohistochemical determination of CEA and CA 19–9 expression in the area of the adenocarcinoma was positive (X 100). **c** and **d**: Immunohistochemical determination of AFP and GP-3 expression in the area of the adenocarcinoma was negative (X 100).

4. Conclusion

We have reported a rare colon cancer in a patient with high serum levels of multiple serum tumor markers. PIVKA-II-producing colon cancer is an extremely rare subtype of colon cancer.

Conflict of interest

The authors declare that they have no competing interests.

Funding

Written consent was obtained from the patient's relatives for publication of the study. No funds supported this study.

Consent

Written informed consent was obtained from the patient's relatives for publication of this case report and any accompanying images. Copies of the written consent are available for review by the Editor-in-Chief of this journal.

Authors' contributions

KK, TK, and KO conceived and designed the study, analyzed all the reports and drafted the manuscript. MH, YI, YK and KiK drafted the manuscript and searched the literature. MM performed colonoscopy on the patient and participated in designing the study. MT, KK and HF participated in designing the study. All authors read and approved the final manuscript.

Key Learning Points

- PIVKA-II-producing colon cancer is an extremely rare subtype of colon cancer.

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RETROSPECTIVE STUDY

Hepatic clearance measured with ^{99m}Tc-GSA single-photon emission computed tomography to estimate liver fibrosis

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Abstract

AIM: To evaluate the clinical utility of hepatic clearance (HC) measured with technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin (^{99m}Tc-GSA) single-photon emission computed tomography (SPECT) to estimate the degree of liver fibrosis.

METHODS: Seventy-eight consecutive patients who underwent initial hepatectomy due to hepatocellular carcinoma were enrolled in this study. Indocyanine green clearance (ICG R15), quantitative indices estimated by ^{99m}Tc-GSA [the receptor index (LHL15 and HH15) and HC *via* SPECT analysis], and conventional liver function tests were performed before hepatectomy. Correlations among the quantitative indices for liver functional reserve, conventional liver function tests, and the degree of liver fibrosis were evaluated.

RESULTS: The degree of liver fibrosis was correlated with ICG R15, HH15, LHL15, and HC. HC showed the best correlation with conventional liver function tests. According to multivariate analysis, HC and LHL15 were significant independent predictors of severe fibrosis. HC was the most valuable index for predicting severe fibrosis.

CONCLUSION: HC measured with ^{99m}Tc-GSA SPECT is a reliable index for assessing liver fibrosis before hepatectomy.

Key words: Fibrosis; Technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin; Single-photon emission computed tomography; Hepatic clearance; Liver resection

Core tip: This retrospective study evaluated the clinical utility of hepatic clearance measured with technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin (^{99m}Tc-GSA) single-photon emission computed tomography for estimating the degree of liver fibrosis. We demonstrated that ^{99m}Tc-GSA hepatic clearance showed strong correlations with the degree of liver fibrosis and conventional liver function tests. It is a reliable index for assessing severe liver fibrosis. We believe that this quantitative index can yield a more accurate estimation of liver fibrosis compared with currently used measures before hepatectomy for hepatobiliary surgeons.

Taniguchi M, Okizaki A, Watanabe K, Imai K, Uchida K, Einama T, Shuke N, Miyokawa N, Furukawa H. Hepatic clearance measured with ^{99m}Tc-GSA single-photon emission computed tomography to estimate liver fibrosis. *World J Gastroenterol* 2014; 20(44): 16714-16720 Available from: URL: http://www.wjgnet.

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INTRODUCTION

Liver fibrosis is a negative predictive factor for postoperative hepatic failure[1-3]. Cirrhosis is a well-known risk factor for postoperative hepatic failure[1,3,4]. Moreover, morbidity and mortality are high for patients with severe liver fibrosis undergoing liver resection[2,5,6]. Therefore, the accurate preoperative estimation of the extent of hepatic fibrosis is essential for successful liver surgery. Although many liver fibrosis indicators have been proposed for preoperative evaluation[7-10], the best indicator for evaluating liver fibrosis has not yet been established.

Technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin (^{99m}Tc-GSA) liver scintigraphy reflects the liver functional reserve and is reported to correlate with several hepatic function tests[11,12]. However, few available analyses can determine the degree of liver fibrosis. Single-photon emission computed tomography (SPECT) analysis in ^{99m}Tc-GSA liver scintigraphy, which can evaluate GSA accumulation in the liver, was also developed to investigate liver function[13]. These analyses calculate hepatic clearance (HC) with the outline extraction method, using a program based on a radiopharmacokinetic model, as described by Shuke *et al*[14,15].

In this study, we investigate the contribution of HC measured with ^{99m}Tc-GSA SPECT to assess liver fibrosis.

MATERIALS AND METHODS

Patients

Between January 2011 and March 2014, 78 consecutive patients who underwent an initial hepatectomy due to hepatocellular carcinoma were enrolled in this study. The surgery was performed within 1 wk after ^{99m}Tc-GSA liver scintigraphy examination, and conventional tests were performed. All procedures were performed after informed consent was received from the patients and after approval from the Ethics Committee of Asahikawa Medical University Hospital was obtained. This study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

^{99m}Tc-GSA liver scintigraphy and the receptor index

^{99m}Tc-GSA liver scintigraphy was scheduled for the patients on the day before their hepatectomy. ^{99m}Tc-GSA was supplied by Nihon Medi-Physics (Nishinomiya, Japan). After the intravenous injection of 185 MBq ^{99m}Tc-GSA, dynamic imaging was performed with the patient in the supine position. LHL15 was calculated by dividing the radioactivity of the region of interest (ROI) of the liver by the radioactivity of the ROI of the liver and the heart 15 min after injection. HH15 was calculated by dividing the radioactivity of the ROI of the heart 15 min after injection by the radioactivity of the ROI of the heart 3 min after injection[16,17].

SPECT analysis in ^{99m}Tc-GSA liver scintigraphy

Dynamic SPECT was performed using a dual-head gamma camera system equipped with low-energy, general-purpose collimators and a dedicated data processing unit (Millennium VG, GE, Tokyo, Japan). The in-plane spatial resolution of this system was 14 mm full width at half-maximum. After fasting overnight, the patient was placed in a supine position to ensure that the liver and lower part of the heart were within the detectors' field of view. ^{99m}Tc-GSA (185 MBq) was injected intravenously as a bolus. After it was confirmed that the entire liver was covered by the detector's view, dynamic SPECT data acquisition was started 1 min after injection and continued for 20 rotations in a 180° continuous rotation mode with an acquisition time of 1 min per rotation. In each rotation, the data from 60 projections were recorded in a 64 × 64 matrix (pixel size = 68.84 mm × 8.84 mm). SPECT images were reconstructed with a filtered back-projection method using a ramp filter after preprocessing with a Butterworth filter (cutoff frequency = 0.40 cycle per centimeter; order of 8) to obtain 8.84-mm-thick transaxial SPECT images. HC was determined from the SPECT data and was calculated with the outline extraction method using a program based on a radio pharmacokinetic model, as described by Shuke *et al*[14,15].

Conventional liver function tests

The serum albumin (Alb), total bilirubin (T-bil), and cholinesterase (Ch-E) levels; prothrombin time international normalized ratio (PT-INR); and platelet count (Plt) were measured in the peripheral blood before hepatectomy. The indocyanine green (ICG) test was conducted preoperatively, and the ICG clearance (ICG R15) was calculated using standard methods. The model for end-stage liver disease (MELD) score[18] and the Child-Turcotte-Pugh (CTP) score[19] were used as indices of liver dysfunctions.

Histopathological features of liver specimens

Liver fibrosis was diagnosed using surgical specimens, which were resected at a distance from the tumors. The degree of hepatic fibrosis was assessed and graded 0-6 according to the Ishak classification for chronic hepatitis[20]: 0: no fibrosis; 1: fibrous expansion of some portal areas, with or without short fibrous septa; 2: fibrous expansion of most portal areas, with or without short fibrous septa; 3: fibrous expansion of most portal areas with occasional portal-to-portal bridging; 4: fibrous expansion of portal areas with marked bridging (portal to portal as well as portal to central); 5: marked bridging (portal to portal and/or portal to central) with occasional nodules; and 6, cirrhosis, probable or definite. Scores of 0, 1, 2, and 3 were considered to reflect nonsevere fibrosis. Scores of 4, 5, and 6 were recorded as severe fibrosis. Tumor size, tumor number, and tumor vascular invasion (portal vein, hepatic artery, and hepatic vein) were evaluated using surgical specimens.

Table 1 Patient characteristics

Variables	*n* = 78
Age (yr)	66.7 ± 10.3
Gender (male/female)	63/15
HBs-Ag (+/-)	26/52
HCV-Ab (+/-)	21/57
Alcohol abuse (+/-)	10/68
NASH (+/-)	14/64
Diabetes mellitus (+/-)	25/73
Hyperlipidemia (+/-)	18/60
Platelets (× 10^4/mm^3)	16.6 ± 7.0
Prothrombin time (INR)	1.05 ± 0.11
Albumin (g/dL)	4.0 ± 0.6
Total bilirubin (mg/dL)	0.8 ± 0.3
Cholinesterase (U/L)	248 ± 70
Tumor size (cm)	49.6 ± 36.9
Tumor number	1.2 ± 0.5
Tumor vascular invasion (+/-)	21/57
Ishak classification 0/1/2/3/4/5/6	14/11/8/18/4/13/10
MELD score	5.3 ± 1.3
CTP score	5.2 ± 0.2
ICG R15 (%)	11.6 ± 6.0

HBs-Ag: Hepatitis B surface antigen; HCV-Ab: Hepatitis C virus antibody; NASH: Nonalcoholic steatohepatitis; MELD score: Model for end-stage liver disease score; CTP score: Child-Turcotte-Pugh score; ICG R15: Indocyanine green dye retention at 15 min.

Statistical analysis

The data are expressed as the mean ± SD unless otherwise stated. The data were analyzed using the Mann-Whitney *U* test, Pearson's correlation coefficient, and linear regression. These statistical analyses were performed using SPSS 11.0 for Windows (SPSS, Chicago, IL, United States). The receiver operating characteristic (ROC) curve for calculating the area under the ROC curve (AUC) and interactive dot diagrams were created using MedCalc (software, 12.7.4; Ostend, Belgium).

RESULTS

Patient characteristics

The clinical characteristics of all participating patients are listed in Table 1. The mean age of the 78 patients was 66.7 ± 10.3 years, and there were 63 men. Of the 78 patients, 71 had chronic liver disease (chronic hepatitis B, $n = 26$; chronic hepatitis C, $n = 21$; non-alcoholic steatohepatitis, $n = 14$; and alcoholic hepatitis, $n = 10$). The remaining patients were diagnosed with normal livers. Concerning the degree of hepatic fibrosis, 10 patients were graded 6, 13 were graded 5, 4 were graded 4, 18 were graded 3, 8 were graded 2, 11 were graded 1, and 14 were graded 0. The mean ICG R15 was 11.6 ± 6.0.

Correlations between the degree of liver fibrosis and quantitative indices of liver functional reserve

Table 2 shows the correlations between the degree of liver fibrosis and preoperative liver function parameters. The degree of liver fibrosis was positively linearly correlated with ICG R15 and HH15 and negatively linearly correlated with HC.

Table 2 Correlations between the degree of liver fibrosis and quantitative indices for liver functional reserve

	r	*P* value
ICG R15	0.330	0.003
HH15	0.272	0.016
LHL15	-0.198	0.083
HC	-0.598	< 0.00001

The degree of liver fibrosis was correlated with ICG R15, HH15, and HC. ICG R15: Indocyanine green dye retention at 15 min; HC: Hepatic clearance.

Correlations between quantitative indices for liver functional reserve and conventional liver function tests

As Table 3 shows, we evaluated the correlations between the preoperative parameters for liver function and conventional liver function tests. LHL15 was correlated with platelet count ($r = 0.235$, $P = 0.038$) and albumin level ($r = 0.263$, $P = 0.020$), and HH15 was correlated with total bilirubin level ($r = 0.289$, $P = 0.010$) and cholinesterase level ($r = -0.263$, $P = 0.020$). HC was correlated with all conventional liver function tests after liver resection: platelet count ($r = 0.348$, $P = 0.002$), prothrombin time ($r = -0.287$, $P = 0.011$), albumin level ($r = 0.233$, $P = 0.040$), total bilirubin level ($r = -0.345$, $P = 0.002$), and cholinesterase level ($r = -0.419$, $P = 0.0001$).

Univariate and multivariate stepwise regression analysis of various factors affecting liver fibrosis

Univariate analysis showed that platelet count ($P < 0.001$), prothrombin time ($P = 0.032$), total bilirubin level ($P = 0.001$), tumor size ($P = 0.042$), MELD score ($P = 0.009$), ICG R15 ($P = 0.019$), LHL15 ($P = 0.042$), HH15 ($P = 0.0004$), and HC ($P < 0.0001$) were significant predictors of severe cirrhosis. When we entered platelet count, prothrombin time, total bilirubin level, tumor size, MELD score, ICG R15, LHL15, HH15, and HC into a multivariate logistic regression model to identify variables with independent predictive value for severe fibrosis, we found that HC and LHL15 were the significant independent predictors (Table 4).

ROC curve and interactive dot diagrams of HC and LHL15 for the diagnosis of severe fibrosis

In Figure 1, we present the ROC curves for each of the 2 variables, HC and LHL15, that were identified as the significant independent predictors of severe fibrosis. The AUC of the ROC curves for HC and LHL15 were 0.826 and 0.641, respectively. There was a significant difference between the two values ($P = 0.0146$). Based on the analysis employing interactive dot diagrams, the cutoff values for predicting severe cirrhosis with the highest sensitivity and specificity were 298 (sensitivity, 77.8%; specificity, 84.3%) for HC and 0.926 (sensitivity, 74.1%; specificity, 60.8%) for LHL15.

Table 3 Correlations between quantitative indices for liver functional reserve and conventional liver function tests

	ICG R15		LHL 15		HH 15		HC	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
Platelets (× 10^4/mm^3)	-0.160	0.161	0.235	0.038	-0.185	0.105	0.348	0.002
Prothrombin time (INR)	0.082	0.473	-0.122	0.289	-0.016	0.888	-0.287	0.011
Albumin (g/dL)	-0.044	0.703	0.263	0.020	-0.123	0.285	0.233	0.040
Total bilirubin (mg/dL)	0.204	0.073	-0.217	0.057	0.289	0.010	-0.345	0.002
Cholinesterase (U/L)	-0.113	0.324	0.221	0.052	-0.263	0.020	0.419	0.0001

LHL15 was correlated with platelet count and albumin level. HH15 was correlated with total bilirubin level and cholinesterase level. HC was correlated with all conventional liver function tests. ICG R15: Indocyanine green dye retention at 15 min; HC: Hepatic clearance.

Table 4 Univariate and multivariate analyses of variables predictive of severe fibrosis

Variable	Severe fibrosis		*P* value	
	Yes (*n* = 27)	No (*n* = 51)	Univariate analysis	Multivariate analysis
Gender (male/female)	23/4	Nov-40	0.474	
Age (yr)	66.5 ± 10.0	66.8 ± 10.5	0.950	
HBs-Ag (+/-)	10/17	16/35	0.616	
HCV-Ab (+/-)	10/17	11/40	0.145	
Alcohol abuse (+/-)	2/25	8/43	0.301	
NASH (+/-)	4/23	10/41	0.602	
Platelets (× 10^4/mm^3)	12.7 ± 3.9	18.7 ± 7.4	< 0.001	0.096
Prothrombin time (INR)	1.09 ± 0.12	1.03 ± 0.10	0.032	0.223
Albumin (g/dL)	4.0 ± 0.6	4.1 ± 0.6	0.388	
Total bilirubin (mg/dL)	0.9 ± 0.3	0.7 ± 0.3	0.001	0.354
Cholinesterase (U/L)	234 ± 75	255 ± 68	0.229	
Tumor size (cm)	3.5 ± 1.6	5.7 ± 4.2	0.042	0.137
Tumor number	1.1 ± 0.4	1.2 ± 0.6	0.543	
Tumor vascular invasion (+/-)	5/22	16/35	0.226	
MELD score	5.8 ± 1.1	5.1 ± 1.2	0.009	
CTP score	5.3 ± 0.6	5.2 ± 0.4	0.685	
ICG R15 (%)	14.3 ± 6.1	10.2 ± 5.5	0.019	0.183
LHL 15	0.901 ± 0.044	0.935 ± 0.024	0.042	0.041
HH 15	0.648 ± 0.068	0.556 ± 0.067	0.004	0.053
HC	263.3 ± 90.4	381.1 ± 96.7	< 0.001	0.030

Platelet count, prothrombin time, total bilirubin level, tumor size, MELD score, ICG R15, LHL15, HH15, and HC were significant predictors of severe cirrhosis in the univariate analysis. In the multivariate analysis, HC and LHL15 were the significant independent predictors. HBs-Ag: Hepatitis B surface antigen; HCV-Ab: Hepatitis C virus antibody; NASH: Nonalcoholic steatohepatitis; MELD score: Model for end-stage liver disease score; CTP score: Child-Turcotte-Pugh score; ICG R15: Indocyanine green dye retention at 15 min; HC: Hepatic clearance.

DISCUSSION

In the current study, we demonstrated correlations between the degree of liver fibrosis and ICG R15, HH15, LHL15, and HC. Among these indicators, HC showed the best correlation with conventional liver function tests. HC was the most valuable index for predicting severe cirrhosis. An HC of 298 could be used to predict severe cirrhosis.

The degree of liver fibrosis is a negative predictor of liver regeneration and the restoration of liver function after liver resection[9]. Therefore, estimating the liver functional reserve, which is a reflection of liver fibrosis, is important. Several laboratory variables, such as prothrombin time and cholinesterase, have prognostic value in chronic liver disease[21]. In addition, the Alb level, T-bil level, and prothrombin time are the most useful routine laboratory tests for establishing a prognosis for hepatitis patients[22]. However, none of these laboratory variables reflects liver fibrosis directly. As a result, these variables cannot be used as indices for determining the extent of liver resection for patients with liver tumors. In contrast, several studies have evaluated the liver functional reserve before hepatectomy[23-25]. In particular, the indocyanine green (ICG) clearance test has been widely used to evaluate liver functional reserve[25,26] for liver resection. However, it does not provide quantitative parameters. Moreover, there are occasional discrepancies between the ICG clearance values and histologic findings in the liver because of the imbalance of portal inflow or portasystemic shunts. Such discrepancies make direct assessments of the extent of liver fibrosis difficult. Therefore, a new method to estimate the liver functional reserve that accurately reflects the degree of fibrosis is required.

The asialoglycoprotein receptor (ASGPR) is localized on hepatocytes and is involved in the clearance of glycoproteins containing terminal galactose residues from the circulation[27,28]. The expression of this receptor decreases according to the number of functional hepatocytes. Therefore, liver scintigraphy with ^{99m}Tc-GSA,

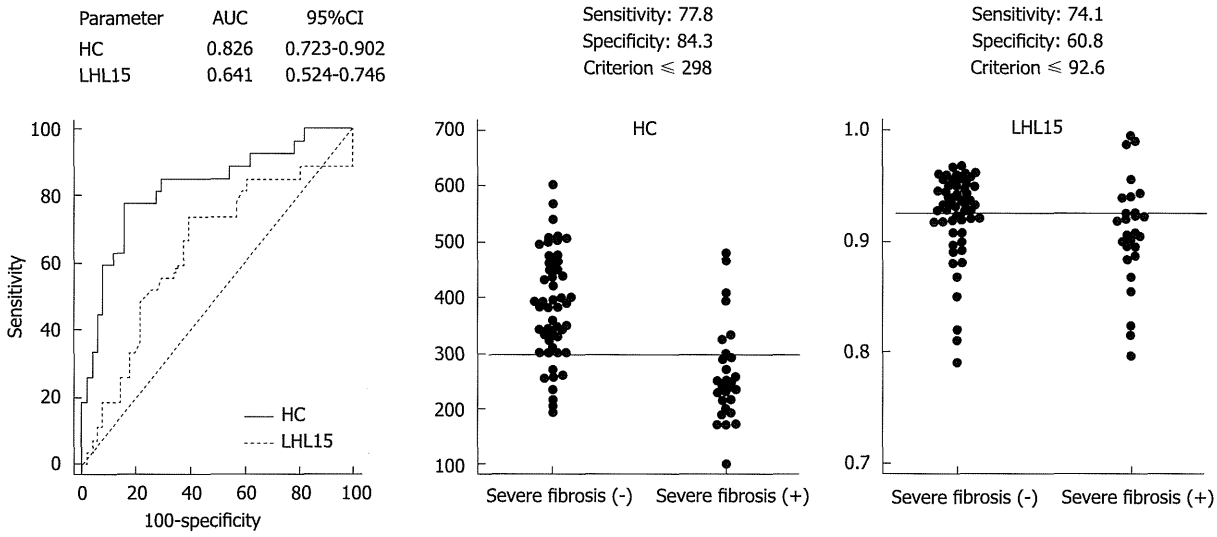

Figure 1 Receiver operating characteristic curve and interactive dot diagrams of hepatic clearance and LHL15 for the diagnosis of severe fibrosis. A: ROC analysis for HC and LHL15. There was a significant difference between the two values (P = 0.0146); B: Interactive dot diagrams showing HC predicts severe cirrhosis. The cutoff value for predicting severe cirrhosis with the highest sensitivity and specificity was 298 (sensitivity, 77.8%; specificity, 84.3%) for HC. The horizontal line indicates the cutoff point with the best separation between the 2 groups (severe fibrosis+, severe fibrosis-); C: Interactive dot diagrams showing LHL15 predicts severe cirrhosis. The cutoff value for predicting severe cirrhosis with the highest sensitivity and specificity was 0.926 (sensitivity, 74.1%; specificity, 60.8%) for LHL15. The horizontal line indicates the cutoff point with the best separation between the 2 groups (severe fibrosis+, severe fibrosis-). AUC: Area under the ROC curve; ROC: Receiver operating characteristic; HC: Hepatic clearance.

an analog of asialoglycoprotein, enables the quantitative evaluation of liver functional reserve. SPECT analysis in ^{99m}Tc-GSA liver scintigraphy, which allows the evaluation of GSA accumulation in the liver, was also developed to investigate liver function[13]. ^{99m}Tc-GSA HC, which is determined based on SPECT data, demonstrates the precise distribution of ASGPR in the liver, thereby providing an accurate calculation of liver functional reserve[29]. In this study, ^{99m}Tc-GSA HC showed a correlation with conventional liver function tests and the extent of liver fibrosis that was better than that of LHL15 or HH15. LHL15 and HH15, which are hepatic uptake and blood clearance ratios in ^{99m}Tc-GSA liver scintigraphy, are the simplest and most commonly used variables. However, they may be insufficient for accurately estimating the degree of liver fibrosis because these indices are calculated from planar scintigraphic images, which do not correctly reflect hepatocyte volume. In contrast, ^{99m}Tc-GSA HC measured by SPECT analysis contains volumetric information and may correctly estimate the hepatocyte volume, thus reflecting the degree of liver fibrosis.

In liver surgery, the risk of perioperative complications is generally believed to increase when the remnant liver volume (RLV) is excessively small[30]. Therefore, reports have advocated preoperatively assessing RLV with CT volumetry[31]. However, CT volumetry can never reflect the function of the remnant liver, especially in patients with parenchymal disease[30,32], such as chronic hepatitis or cirrhosis. Additionally, several reports concerning ^{99m}Tc-GSA SPECT findings have indicated that regional function is not necessarily uniform throughout the liver[33,34], suggesting that an accurate estimation of regional liver function is more important for predicting postoperative liver functional reserve. In this study, ^{99m}Tc-GSA HC strongly reflected the degree of liver fibrosis. Therefore, we believe that using the combined ^{99m}Tc-GSA HC and CT volumetric measurements of the remnant liver can evaluate remnant liver functional reserve after hepatectomy[35]. Further studies are needed to test this hypothesis.

In conclusion, we demonstrated that HC measured with ^{99m}Tc-GSA SPECT showed correlations with the degree of liver fibrosis and conventional liver function tests. ^{99m}Tc-GSA HC was the most valuable index for predicting severe fibrosis. It could yield a more accurate estimation of liver fibrosis compared with currently used measures before hepatectomy for hepatobiliary surgeons.

COMMENTS

Background

Liver fibrosis is a negative predictive factor for postoperative hepatic failure. Therefore, the accurate preoperative estimation of the extent of hepatic fibrosis is essential for successful liver surgery. Although many liver fibrosis indicators have been proposed for preoperative evaluation, the best indicator for evaluating liver fibrosis has not yet been established.

Research frontiers

Technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin (^{99m}Tc-GSA) liver scintigraphy reflects the liver functional reserve and is reported to correlate with several hepatic function tests. In addition, single-photon emission computed tomography analysis in ^{99m}Tc-GSA liver scintigraphy, which can evaluate GSA accumulation in the liver, was also developed to investigate liver function.

Innovations and breakthroughs

Hepatic clearance which was measured with ^{99m}Tc-GSA single-photon emission computed tomography (SPECT) is a reliable index for assessing liver fibrosis.

Applications

Hepatic clearance which was measured with ^{99m}Tc-GSA SPECT could yield a

more accurate estimation of liver fibrosis compared with currently used measures before hepatectomy for hepatobiliary surgeons.

Terminology

^{99m}Tc-GSA liver scintigraphy: Technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin liver scintigraphy. SPECT analysis: Single-photon emission computed tomography analysis.

Peer review

The manuscript evaluates the utility of ^{99m}Tc-GSA SPECT to reliably predict the degree of liver fibrosis in patients for liver resection is planned. Comparisons are made to particularly state that hepatic clearance is superior to other measurements (LHL15 and HH15), other techniques (ICGR15), and clinical parameters of liver function when predicting fibrosis. The study has relevance and is interesting in its concept; however some conclusions are made that need to be justified by more rigorous data analysis.

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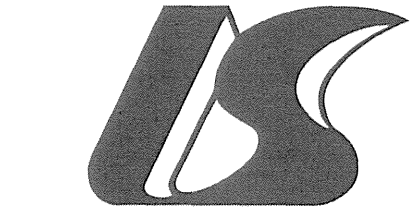

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Successful curative resection of gallbladder cancer following S-1 chemotherapy: A case report and review of the literature

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Abstract. The symptoms of gallbladder cancer (GBC) are vague and non-specific. Therefore, GBC is often detected at an advanced or metastatic stage. The most effective treatment for GBC is surgical resection, however the majority of GBC cases are unresectable at the time of diagnosis. Therefore, numerous GBC patients undergo chemotherapy. This study reports the case of a 60-year-old female with GBC who underwent successful surgical curative resection following a single dose of the chemotherapeutic agent, S-1, twice daily for 4 weeks followed by a 14-day rest period for 36 months. S-1 is a novel orally administered drug composed of a combination of the 5-fluorouracil (5-FU) prodrug, tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP) and oteracil potassium in a 1:0.4:1 molar concentration ratio. The focus of the present study was the candidate factors that affect the therapeutic efficacy of S-1-based chemotherapy. In particular, the gene expression involved in the S-1 metabolic pathway was investigated by assessing the intratumoral dihydropyrimidine dehydrogenase (*DPD*), thymidylate synthase (*TS*) and orotate phosphoribosyltransferase gene expression. The surgical specimen exhibited high intratumoral *DPD* gene expression levels compared with those observed in previously reported non S-1 responsive cases of biliary tract cancer. Due to the results obtained in the current study, we hypothesize that CDHP enhanced the anti-tumor efficacy of 5-FU by inhibiting the excess DPD protein produced by the tumor.

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Key words: gallbladder cancer, S-1, gene expression

Introduction

Gallbladder cancer (GBC) is the most aggressive type of biliary tract cancer (BTC) and exhibits the shortest median survival time worldwide. Complete surgical resection offers the only chance of complete remission; however, GBC is characterized by local invasion, extensive regional lymph node metastasis, vascular encasement and distant metastases. Therefore, only 10% of patients present with early-stage disease are considered to be candidates for surgery (1). Therefore, chemotherapy serves as the primary treatment in the majority of GBC cases. Previous studies have found that patients with metastatic GBC who receive palliative therapy have a median survival time of approximately six months (2,3). Therefore, more effective chemotherapies are required for the management of GBC.

S-1 is a novel orally administered drug composed of a combination of the 5-fluorouracil (5-FU) prodrug, tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP) and oteracil potassium (OXO) in a 1:0.4:1 molar concentration ratio (4). Based on the results obtained from randomized phase III trials, S-1 has become a key drug in the treatment of advanced gastric cancer in Japan and is considered to be the standard option for chemotherapy (5,6). Furthermore, gemcitabine and S-1 have also been approved for clinical use in the treatment of BTC by the Ministry of Health, Labour and Welfare in August 2007 (7).

The current study presents a case of GBC in which the patient underwent successful surgical curative resection following a single dose of S-1. The focus of this study was the candidate characteristics that affect the therapeutic efficacy of S-1-based chemotherapy. In particular, the gene expression involved in the S-1 metabolic pathway was investigated by analyzing dihydropyrimidine dehydrogenase (*DPD*), thymidylate synthase (*TS*) and orotate phosphoribosyltransferase (*OPRT*) gene expression. The patient provided full written informed consent prior to the initiation of the study.

Case report

A 60-year-old female was admitted to Asahikawa City Hospital (Asahikawa, Japan) with a primary complaint of

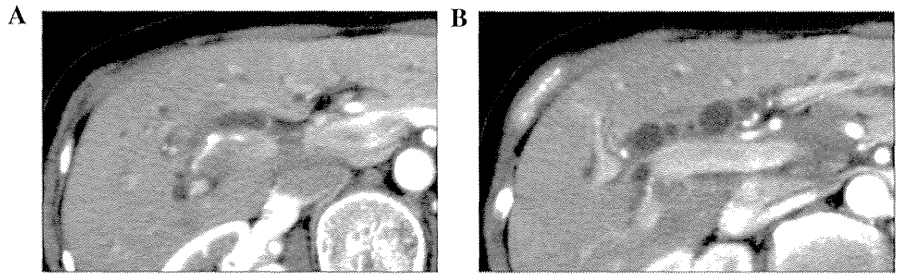

Figure 1. Computed tomography scans revealing (A) direct invasion of the right hepatic artery and (B) perineural invasion of the common hepatic and celiac arteries.

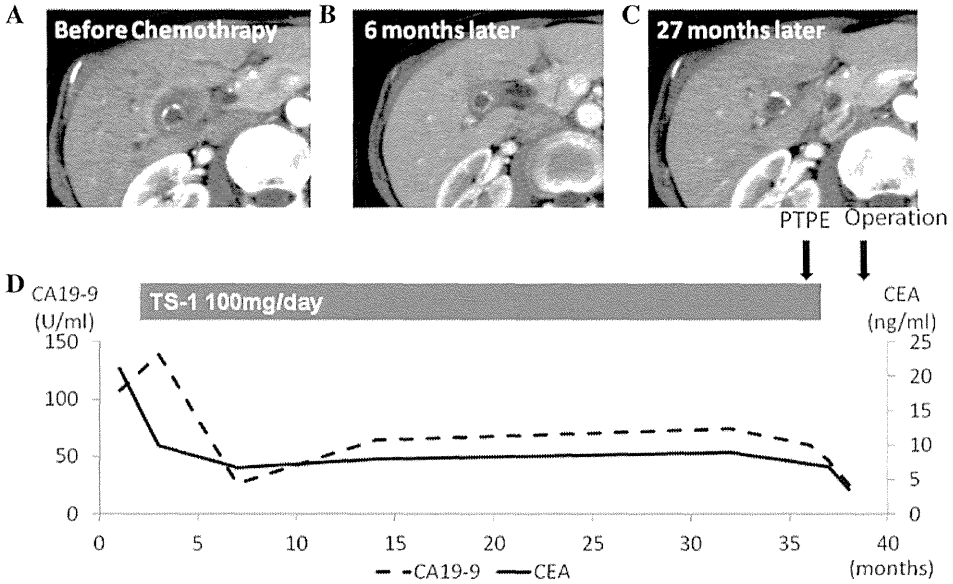

Figure 2. Changes in the patient CEA and CA19-9 levels (A) prior to chemotherapy and (B)six and (C) 27 months following chemotherapy, and computed tomography findings. (D) Clinical course of S-1 treatment. CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; TS-1, thymidylate synthase; PTPE, percutaneous transhepatic portal embolization.

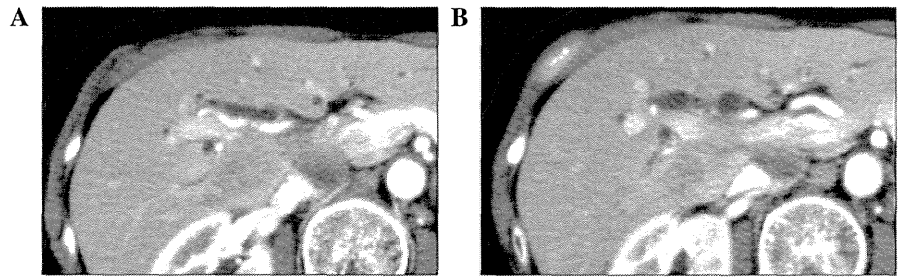

Figure 3. Changes after chemotherapy (A) in the gallbladder tumor and (B) in terms of neural invasion, shown by computed tomography imaging. (A) A clear reduction in size and decreased invasion was observed in the right hepatic artery. (B) Decreased perineural invasion of the common hepatic and celiac arteries was observed.

jaundice in 2008. The patient's medical history was unremarkable and, with the exception of the jaundice, the physical examination revealed no abnormalities. The results from the laboratory tests indicated abnormal values for total bilirubin (7.9 mg/dl; normal range, 0.2-1.0 mg/dl), serum glutamic oxaloacetic transaminase (124 IU/l; normal range, 6-40 IU/l) and serum glutamic pyruvic transaminase (228 IU/l; normal range, 6-37 IU/l). On admission, tumor marker levels were as follows: Carcinoembryonic antigen, 21.1 ng/ml (upper normal limit, 4.9 ng/ml) and carbohydrate antigen 19-9, 107.6 IU/ml (upper normal limit, 39 IU/ml). An abdominal computed tomography (CT) scan revealed the presence of advanced GBC, which had invaded the liver, as well as regional lymph node metastasis and perineural invasion of the common hepatic and celiac arteries (Fig. 1). The tumor was considered to be inoperable due to the presence of perineural invasion of the common hepatic and celiac arteries. With informed consent from the patient, chemotherapy with S-1 was initiated at a dose of

Table I. Intratumoral *DPD, TS* and *OPRT* gene expression in biliary tract cancer patients.

Author (ref.)	TS	DPD	OPRT
Present case	3.26	8.21	0.91
Kitajima *et al* (14)	1.88	8.21	0.91
Case 1	14.42	3.16	1.35
Case 2	2.73	2.78	0.73

TS, thymidylate synthase; DPD, dihydropyrimidine dehydrogenase; OPRT, orotate phosphoribosyltransferase. Case 1, 39 year-old female: intrahepatic bile duct cancer, post right lobectomy with liver and bone metastasis; case 2, 71 year-old-male: extrahepatic bile duct cancer, post pylorus preserving pancreatoduodenectomy with a recurrence of supra mesenteric artery nerve plexus. Case 1 and case 2 patients received treatment with S-1 and had progressive disease.

Table II. Surgical resection following chemotherapy for unresectable gallbladder cancer.

Author (ref.)	Regime	Time to surgery after chemotherapy, months	Regime after surgery	Prognosis
Kitajima *et al* (14)	S-1	8	Unknown	Unknown
Morimoto *et al* (18)	Gem	12	Gem	No recurrence for 20 months
Takita *et al* (19)	Gem + S-1	9	S-1	No recurrence for 12 months
Present case	S-1	36	S-1	No recurrence for 30 months

Gem, gemcitabine.

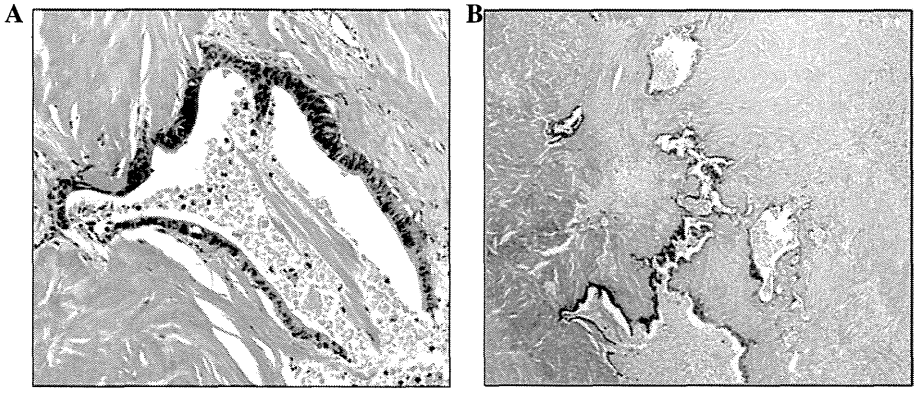

Figure 4. Pathological examination demonstrated that the tumor was (A) a scirrhous adenocarcinoma and (B) predominantly consisted of fibrosis and necrosis tissue [stain, hematoxylin and eosin; magnification (A) x200 and (B) x40.

100 mg twice daily for four weeks, followed by a 14-day rest period, for a total of 25 cycles.

Clinical course of treatment. The patient was followed up every six weeks for a total of 36 months. The tumor marker levels decreased after two months(Fig. 2), and a CT scan demonstrated a clear reduction in size in the regions of the liver that were invaded by the GBC, as well as those affected by lymph node metastasis and perineural invasion (Fig. 3). A partial response was maintained for over 30 months and, subsequently, surgical resection with curative intent was planned for 36 months following the initiation of treatment with S-1.

The patient underwent percutaneous transhepatic portal embolization and, three weeks following this, a right lobectomy with extrabiliary duct resection and lymphadenectomy was performed. The pathological findings of the tumor were compatible with a diagnosis of adenocarcinoma of the gallbladder. The tumor had directly invaded the liver and cancer cells were found in the perineural area; however there was no metastatic lesion in the liver and no regional lymph node metastasis. All surgical margins were negative (Fig. 4) and

a pathological R0 resection was achieved. The postoperative course was uneventful, and the patient was discharged 25 days following surgery.

Intratumoral gene expression levels of DPD, OPRT and TS. The resected gallbladder specimen was analyzed to determine the intratumoral gene expression levels of DPD, OPRT and TS, which encode the corresponding key enzymes that are involved in the metabolism of 5-FU (8,9). The expression levels of these genes were all measured by Response Genetics (Los Angels, CA, USA) using the Danenburg Tumor Profile method and laser capture microdissection, as described previously (10,11). The specimen exhibited high intratumoral *DPD* gene expression levels compared with those observed in the BTC cases who were non-responders of S-1 treatment (Table I).

Discussion

The symptoms of GBC are vague and non-specific; therefore, GBC is often detected at an advanced or metastatic stage. The most effective treatment for GBC is surgical resection; however, the majority of GBCs are unresectable at the time of diagnosis (1,12,13) and, hence, numerous GBC patients undergo chemotherapy (14).

In colorectal cancer, primary systemic chemotherapy appears to be a promising approach to the management of patients with initially unresectable liver metastases, as it leads to a reduction in the lesion size, which facilitates the surgical resection in a high proportion of cases (15). Patients who are able to undergo complete resection following chemotherapy tend to achieve improved outcomes (15-17).

A review of the literature identified only three case reports with regard to surgical resection following chemotherapy for unresectable GBC (Table II) (14,18,19). Two of the four cases survived for >1 year without recurrence (one survived for a year and no information is available for one case). Compared with unresectable GBC cases, the patients reported in these cases had a good prognosis. In the present case, surgery was performed three years following treatment with S-1. To date, no evidence of recurrence has been observed for 30 months following surgery.

The novel antitumor drug S-1 contains a prodrug of 5-FU and was developed based on the biochemical effects of CDHP, a DPD inhibitor, and OXO, an OPRT inhibitor, in the small intestine. The principal roles of these modulators are to inhibit the degradation of 5-FU and to protect against 5-FU-induced gastrointestinal toxicity. TS is a major target of 5-FU, which inhibits DNA synthesis. High TS activity in cancer tissue is considered to reduce the efficacy of 5-FU and it is likely that the DPD mRNA level is also a significant predictor of the response to 5-FU. Low TS and DPD expression levels are associated with poor outcomes in colorectal cancer patients who are treated with surgery alone, whereas these low expression levels are associated with improved outcomes in patients who are treated with 5-FU chemotherapy (20).

The tumor tissue of the patient in the present case and of a patient in a previous case (14) exhibited markedly higher DPD mRNA levels compared with those observed in two BTC patients who did not respond to S-1 treatment (Table I). Conversely, the use of a 5-FU agent in the absence of CDHP is likely to exhibit a decrease in the efficacy, with the agent rapidly becoming inactive due to degradation by the excess DPD produced by the tumor. In the current study, while no conclusive evidence was obtained that the S-1 treatment resulted in the downstaging of the cancer, it is reasonable to speculate that the CDHP in S-1 was significant, and may have enhanced the antitumor efficacy of 5-FU through the inhibition of the excess DPD produced by the tumor, although, additional studies may be required to confirm this.

In conclusion, the current study reports the case of a patient with advanced GBC for whom the anticancer agent, S-1, was effective and a pathological R0 resection was achieved. The results of the present study indicate that the CDHP in S-1 may enhance the antitumor effect of 5-FU by inhibiting the excess DPD protein produced by the tumor. The use of S-1 in patients with GBC warrants further clinical studies. The present study suggests that the CDHP in S-1 may have enhanced the antitumor efficacy of 5-FU by inhibiting the excess DPD produced by the tumor. Analysis of the intratumoral gene expression levels of DPD may be useful to predict the efficacy of S-1 treatment.

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TABLE 1. Previously reported cases of renal transplantation in WAS patients

References	Immunosuppression	Complications	Outcome	Cause of death
Webb et al. (*4*)	ATG, azathioprine, prednisone, CsA	CMV disease	Death at month 35 after transplantation	Postmortem examination showed coronary artery disease without any evidence of malignancy
Meisels et al. (*5*)	Azathioprine, methylprednisolone then prednisone, CsA	Rejections treated by steroids	N/A	N/A
Fischer et al. (*6*)	ATG, azathioprine, prednisone, CsA	Many infections and malignant high grade B-cell non-Hodgkin lymphoma	Death at day 98 after transplantation	Autopsy refused by family. Postmortem liver biopsy showed persistent lymphoma

ATG, antithymocyte globulin; CsA, cyclosporine A; ATG, antithymocyte globulin; CMV, cytomegalovirus; WAS, Wiskott-Aldrich syndrome; N/A, not applicable.

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A Technique for Orthotopic Liver Transplantation in Cynomolgus Monkeys

In our previous studies, we showed markedly prolonged hepatic allograft survival in nonhuman primates (NHPs) (*1*). Experiments using NHPs are of significant value to improve our understanding and facilitate the design of ethically acceptable human trials (Table 1). However, only few liver transplantation (LTx) studies have been reported in NHPs (*2–4*). Moreover, these reports did not describe operative procedures and perioperative management in detail. Although the efficacy of venovenous bypass for LTx during an anhepatic phase (AH) has been reported in human (*5*), application of such bypass in cynomolgus monkeys is very difficult because of the animal size. Herein, we show for the first time that without using venovenous bypass, LTx can be successfully performed in NHPs by clamping the superior mesenteric artery (SMA) during an AH that prevents excessive congestion of the intestine and ameliorates metabolic acidemia after reperfusion of liver graft.

Purpose-bred male cynomolgus monkeys were used. Donor-recipient pairs were previously described in detail (*6*). All procedures were performed in accordance with the standards described in the Guide for the Care and

TABLE 1. Hepatic allograft survival and laboratory data in animals treated with or without SMA clamping during the anhepatic phase

SMA clamp	n	AH, min	pH	24 hr Survival, %	ALT (1 POD)
(−)	9	43.6	7.131	3/9 (33.3%)	1324±744
(+)	15	41.5	7.312*	13/15 (86.7%)**	424±227**

Liver transplantation was performed in cynomolgus monkeys without (n=9) or with (n=15) SMA clamping during the AH. No significant differences in the anhepatic time were observed between the two groups. However, postoperative low pH because of metabolic acidosis, 24-hr survival, and ALT levels on postoperative day 1 were significantly improved by this technique. *$P<0.01$, **$P<0.05$ (Mann-Whitney's U test).

AH, anhepatic phase; ALT, alanine aminotransferase; SMA, superior mesenteric artery; POD, postoperative day.

Use of Laboratory Animals from the National Institutes of Health.

After a 24-hr fast, anesthesia was induced with ketamine (10 mg/kg) (Daiichi Sankyo Co., Ltd, Tokyo, Japan) and atropine (0.01 mg/kg) (Mitsubishi Tanabe Pharma, Osaka, Japan) and maintained by mechanical ventilation. During the recipient operation, donor blood (5 mL/kg) was transfused to the recipient, and the recipient was infused with dopamine (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) (ISEI Co., Inc, Yamagata, Japan), ephedrine hydrochloride (1 mg/kg) (Sumitomo Dainippon Pharma Co., Ltd, Tokyo, Japan), 7% sodium bicarbonate (5 mL/kg) (Takasugi Pharma Co., Ltd, Fukuoka, Japan), and 8.5% calcium gluconate hydrate (0.5 mL/kg) (Nichi-Iko Pharma Co., Ltd, Toyama, Japan) during an AH.

Donor operation: The abdominal aorta is free from the retroperitoneal tissue. The proximal common bile duct is ligated and cut proximal to the insertion of the cystic duct. The portal vein (PV) is divided to the junction of the splenic vein and superior mesenteric vein. The continuity of the hepatic artery with the celiac trunk and abdominal aorta is maintained up to the iliac bifurcation. The ETP-2 (JSM LTD., Tokyo, Japan) tube is inserted from the iliac bifurcation. Before perfusion, donor blood is harvested from the aorta. In situ liver perfusion with cold histidine-tryptophan-ketoglutarate solution (Odyssey Pharmaceuticals, Inc., NJ) supplemented with heparin (2 units/mL) is established through the aorta immediately after clamping the infrahepatic vena cava (IHVC), cross-clamping the thoracic aorta, and cutting the suprahepatic vena cava. For the placement of the ETP-2 tube, the anterior splenic vein wall is cut, and the tube is inserted; portal perfusion is also initiated. Total perfusion requires approximately 150 to 200 mL.

Recipient operation: Just before removal of the native liver, the SMA is clamped. In the normal anatomic case, only an applying SMA clamp is enough to prevent the intestinal congestion. However, it is necessary to add the middle colic artery clamp, in case of anatomic anomaly that the middle colic artery is directly derived from abdominal aorta. The blood flow from the SMA during an AH gets worse the intestinal congestion which results in intrinsic endotoxemia, caused by a no drainage vein. Using a vascufil 7-0 (Tyco Healthcare Group L.P.) suture, a running suture line is used to anastomose the donor and the recipient SHVC in an end-to-end fashion (taking approximately 10 min). The PV anastomosis is performed with vascufil 8-0 suture, suturing the anterior layer first from the inside to produce intimal apposition. Just before the completion of the portal anastomosis, the IHVC and PV clamp are removed, allowing blood to perfuse the liver and wash out the histidine-tryptophan-ketoglutarate. Finally, the SHVC clamp is removed, the PV is kneaded softly, and the last tie is performed. Blood (5–10 mL) is drained by means of the IHVC to wash out acid metabolites coming from mainly congested intestine. The clamp is removed from the SHVC, and the PV is unclamped (for approximately 30 minutes), allowing the liver to be perfused with portal blood just after removing the SMA clamp. Before the IHVC anastomosis, systemic acid metabolites coming from the lower extremity are washed out from the recipient's IHVC (5–10 mL). The graft aorta conduit is pulled through in a retrocolic fashion. A 10-mm incision is made anterior to the aorta just below the infrarenal artery, and the donor aorta is sutured to this defect with an 8-0 arterial running vascufil stitch. Biliary reconstruction by cholecystoduodenostomy is performed between the fundus of gallbladder and the first portion of the duodenum adjacent to the pylorus. The anastomosis is performed using a running 6-0 PDS II (Ethicon; Johnson and Johnson, Belgium) suture in a single layer. Within this AH time (40–50 min), bowel congestion is recovered after reperfusion.

An intravenous infusion is initiated as soon as the catheter has been inserted into the right intermediate cephalic vein and the lactate Rigure's solution (5 mL/kg/hr) is administered. A central vein catheter and aorta blood pressure monitoring catheter are not necessary. The animals are allowed a normal diet just after the operation.

It is remarkable how well the cynomolgus monkey withstands this formidable procedure without venovenous bypass. In our earlier experiments, there was a high incidence of animal death within 24 hr after transplantation. However, by clamping the SMA during an AH, we were able to achieve a successful LTx. In this study, we performed 24 orthotopic LTx in cynomolgus monkeys with (n=15) or without (n=9) clamping the SMA during an AH (Table 1). Thirteen liver recipients survived for over 24 hr after LTx when the SMA clamp technique was applied: two animals in this group died at 2 days after LTx because of surgical complications, abdominal bleeding and stenosis of IHVC, and the other 11 liver recipients, except for three animals without immunosuppressant and one who died at 11 postoperative day because of a biliary complication, survived for more than 2 weeks under cover of immunosuppression. In contrast to the liver-recipients with SMA clamping, six monkeys died within 24 hr after LTx without clamping the SMA. The other three monkeys survived for over 2 weeks with immunosuppressant administration. Because the cynomolgus monkey is very susceptible to a total liver ischemia, this technique is prerequisite for establishment of LTx model.

Statistical Analysis

All values are represented as mean (standard deviation). An intergroup statistical analysis was performed using the Mann-Whitney *U* test. The differences were considered statistically significant when a *P* value was less than 0.05 or 0.01.

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Patent Foramen Ovale and Gut Ischemia in Potential Intestinal Transplant Recipients

The presence of a patent foramen ovale (PFO) is associated with paradoxical embolism (*1*). In turn, this can cause stroke (*2*) and, less commonly, ischemia of the limbs, eyes, and the heart (*3*).

Intestinal ischemia is a common surgical pathology which may require extensive intestinal resection. This can lead to short gut syndrome, a major indication for intestinal transplantation. Typically, gut ischemia because of acute occlusion of the superior mesenteric artery (SMA) is the result of embolic events secondary to atrial fibrillation, valvular defects, cardiac failure, or thrombophilia.

However, the association between acute SMA occlusion, gut ischemia, and a PFO has not been specifically described. We present our experience of potential intestinal transplant recipients with short gut syndrome and reveal the high incidence of PFO in patients with previous intestinal ischemia.

All patients with short gut syndrome referred to a single major transplant center between June 2008 and March 2013 were assessed for suitability for intestinal transplantation. Each individual underwent formal cardiac evaluation, which included transthoracic echocardiography and myocardial perfusion scintigraphy. Those patients in whom an ischemic event caused short gut syndrome were further assessed with a thrombophilia screen and bubble contrast echocardiography.

Twenty-five patients were considered for intestinal transplantation during the time frame described. Nineteen (76%) subsequently proceeded to surgery. The median age was 43 years (range, 31–50) and 15 (60%) were men. Causes of short gut syndrome are shown in Table 1.

Ten patients (40%) were listed for transplantation after previous proven acute SMA occlusion and consequent gut ischemia. In eight such individuals (80%), a PFO was identified with right to left shunting. In one patient, this was combined with an antithrombin III deficiency. In the remaining two cases without PFOs, one (10%) had a thrombophilia diagnosed, whereas the second (10%) had evidence of isolated extensive atherosclerosis. Among those with SMA occlusion, no valvular pathology, deep vein thrombosis, haematological disorders or atrial fibrillation was detected. No patient was a smoker at the time of presentation, and none had a lipid abnormality. Only the individual with the antithrombin III deficiency was obese (body mass index=35). The remainder of the study population was of healthy weight or underweight (body mass index<25).

TABLE 1. Causes of intestinal failure in 25 patients assessed for intestinal transplantation

Diagnosis	n (%)
SMA occlusion	10 (40)
Inflammatory bowel disease	6 (24)
Dysmotility disorders	3 (12)
Neoplasia	3 (12)
Other	3 (12)

SMA, superior mesenteric artery.

In no patient was a PFO diagnosed without a history of gut ischemia. All individuals in whom a PFO was detected had a closure using a transcatheter method.

There was no difference in inducible myocardial ischemia or left ventricular function between the SMA occlusion group and individuals who presented with other causes of short gut syndrome.

Within this cohort, the majority of patients who presented with intestinal ischemia were diagnosed with a PFO. Eighty percent of those with SMA occlusion had a PFO, compared to a normal incidence in the adult population of approximately 25% (*4*). A relationship between PFOs and SMA occlusion was therefore suggested.

These findings may be important because they identify a specific pathology amenable to therapeutic intervention, thereby potentially reducing the risk of further episodes of thrombosis and graft loss after transplantation (*5*). Accordingly, we recommend investigating for a PFO in all patients with intestinal ischemia, with a view to seeking a specialist cardiology opinion. Although traditionally the treatment of a PFO was closure of the defect, increasingly medical therapy is the management of choice (*6*).

Clearly, these observations are limited to small numbers from a single center, whereas the relationship demonstrated is associative, not causal. Validation of our findings is required in larger studies, which should also determine which precise characteristics of a PFO might mandate

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Impact of Intestinal Transplantation for Intestinal Failure in Japan

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ABSTRACT

Introduction. The prognosis of intestinal failure has improved dramatically in the past few decades with the development of parenteral nutrition (PN). However, PN-dependent patients still have numerous complications. Intestinal transplantation can significantly improve their prognosis and quality of life. We report on the impact of intestinal transplantation for intestinal failure in Japan.

Methods. Intestinal transplantations have been performed in Japan since 1996. Standardized forms were sent to all known intestinal transplantation programs, asking for information on intestinal transplantations performed between 1996 and June 31, 2012. All programs responded. Patient and graft survival estimates were obtained using the Kaplan-Meier method and analyzed with the Wilcoxon statistic.

Results. Five institutions provided data on 24 grafts in 21 patients. There were 12 cadaveric and 12 living related donor transplants. Causes of intestinal failure included short gut syndrome ($n = 9$), intestinal motility function disorders ($n = 11$), retransplantation ($n = 3$), and other ($n = 1$). The overall 1- and 5-year patient survival rates were 86% and 68%, respectively. In cases ($n = 15$) after 2006, the 1-year patient survival rate was 92%, and the 5-year survival rate was 83%. One- and five-year graft survival rates were 87% and 78%, respectively. More than 80% of all current survivors discontinued PN.

Conclusions. Intestinal transplantation has become an effective therapy for patients with intestinal failure who cannot tolerate PN. After 2006, patient and graft survival rates approached rates associated with standard treatment for end-stage intestinal failure. Further improvements are expected with early referral due to suitable donor organ and pretransplant management.

THE PROGNOSIS of intestinal failure has improved dramatically in the past few decades with the development of parenteral nutrition (PN). However, PN-dependent patients still have numerous complications. Intestinal transplantation can significantly improve their prognosis and quality of life. We assessed the impact of intestinal transplantation on intestinal failure in Japan based on data from the Japanese intestinal transplant registry.

METHODS

Standardized forms were sent to all known intestinal transplantation programs requesting information on intestinal transplantations performed between 1996 and June 30, 2012. Requested data included age, sex, date of birth, date of transplantation, pretransplant status (home or hospital), underlying disease, procedure, ABO blood type, immunosuppression regimen (induction and maintenance therapy), and post-transplant status (PN requirement, intravenous [IV] fluid requirement, and daily life restrictions). The

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