Table 3 Factors influencing early-phase and late-phase liver regeneration

	Parameter estimate	Standard error	β'	P value (Prob>F)
Early-phase regeneration (0–3 months)				
Operative procedure (right compared to left)	0.119	0.042	0.447	0.010
Sex	−0.073	0.037	−0.296	0.059
Peak ALT(IU/L)	0.000	0.000	−0.274	0.099
Late-phase regeneration (3–12 months)				
None of the variables were entered to the model				

Factors influencing the regeneration process are other issues of interest. Animal studies have shown that senescence, steatosis, and ischemic injury had a negative effect on regeneration, while previous studies in LDLT donors did not confirm these findings, except the study by Yokoi et al., which showed a decreased rate of regeneration in older donors,[17] and that by Pomfret et al., which demonstrated a negative effect of female gender.[13] Our results were partially in agreement with those in previous reports: sex and the postoperative peak ALT value were associated with the magnitude of liver regeneration during the early phase; however, no variables that were identified to be related to liver regeneration were identified in the late phase. Although postoperative ALT value is thought to be an indicator of postoperative liver damage most likely caused by the ischemic injury, and indeed this parameter was linked to warm ischemic time in our series (P=0.02), further investigation using a larger cohort will be needed to clarify the relationship between the postoperative ALT value and liver regeneration.

The question of whether functional recovery after a donor hepatectomy occurs in parallel with the volumetric regeneration is another issue of interest. Former studies addressing this issue using quantitative liver function tests have reported contradictory results: our group showed that liver functional recovery as assessed using the intrinsic plasma clearance of antipyrine preceded volumetric regeneration at 12 days postoperatively,[23] while Nadalin et al. reported that functional recovery as assessed using the serum galactose elimination capacity was delayed, compared with the volumetric recovery, at 10 days postoperatively.[15] In the present study, the biochemical parameters that showed albeit mild alterations at 3 months postoperatively had returned to the preoperative levels at 12 months after the surgery, except for the ALB. All these mild derangements were within the normal range at both timepoints in the study; these results agreed with those reported by Chan et al.[18] and Nadalin et al.[15] Also, the ALB at 12 months postoperatively was not associated with the extent of volumetric regeneration of the liver. Furthermore, Nadalin et al. reported that the serum galactose elimination capacity had returned to the preoperative level at 1 year postoperatively. Hence, the liver function appeared to have recovered to the preoperative level at 1 year after surgery, at least from a clinical point of view.

In conclusion, normal liver regeneration in humans followed a similar pattern, albeit being 20–50 times slower, to that observed in rodent models of liver resection; that is, liver regeneration consisted of an early phase of rapid regeneration and a subsequent late phase characterized by a slower rate of regeneration. Although regeneration continued even after 12 months postoperatively, the process seemed to reach a stage close to its final volumetric goal at 4 years after the hepatectomy, when the liver was restored to approximately 90% of its preoperative TLV.

Table 4 Biochemical parameters before, 3 months after, and 12 months after donor hepatectomy

	Before (n=33)	3 months (n=29)	12 months (n=15)
AST (IU/L)	18.3±4.0 (11–30)	23.2±5.1 (16–36)*	20.5±4.8 (15–34)
ALT (IU/L)	17.0±7.2 (7–41)	24.0±9.8 (12–51)*	18.7±7.5 (10–37)
TB (mg/dl)	0.77±0.32 (0.3–1.8)	0.74±0.22 (0.4–1.3)	0.86±0.36 (0.5–1.8)
ALB (g/dl)	4.48±0.27 (4.0–5.1)	4.14±0.31 (3.5–4.7)*	4.30±0.28 (3.6–4.6)*
PT-INR	1.08±0.10 (0.92–1.42)	1.14±0.15 (0.98–1.47)*	1.11±0.19 (0.98–1.46)

Values are expressed as the mean ± standard deviation with the range in parentheses

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *TB* total bilirubin, *ALB* albumin, *PT-INR* prothrombin time international normalized ratio

*P<0.025

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Original article

Recurrence-free survival more than 10 years after liver resection for hepatocellular carcinoma

S. Eguchi[1], T. Kanematsu[1], S. Arii[2], M. Omata[3], M. Kudo[4], M. Sakamoto[5], K. Takayasu[6], M. Makuuchi[7], Y. Matsuyama[8] and M. Monden[9] for the Liver Cancer Study Group of Japan

[1]Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, [2]Department of Hepato-Biliary-Pancreatic Surgery, Tokyo Medical and Dental University, Graduate School of Medicine, [3]Department of Gastroenterology, Yamanashi Prefectural Central Hospital, Yamanashi, and [4]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Kinki University School of Medicine, [5]Department of Pathology, University of Keio, [6]Department of Diagnostic Radiology, National Cancer Centre Hospital, [7]Department of Surgery, Japanese Red Cross Medical Centre, and [8]Department of Biostatistics, School of Health Sciences and Nursing, University of Tokyo, Tokyo, and [9]Department of Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

Correspondence to: Dr S. Eguchi, Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, 852-8501, Japan (e-mail: sueguchi@nagasaki-u.ac.jp)

Background: High recurrence rates after liver resection with curative intent for hepatocellular carcinoma (HCC) remain a problem. The characterization of long-term survivors without recurrence after liver resection may help improve the therapeutic strategy for HCC.

Methods: A nationwide Japanese database was used to analyse 20 811 patients with HCC who underwent liver resection with curative intent.

Results: The 10-year recurrence-free survival rate after liver resection for HCC with curative intent was 22·4 per cent. Some 281 patients were recurrence-free after more than 10 years. The HCCs measured less than 5 cm in 83·2 per cent, a single lesion was present in 91·7 per cent, and a simple nodular macroscopic appearance was found in 73·3 per cent of these patients; histologically, most HCCs showed no vascular invasion or intrahepatic metastases. Multivariable analysis revealed tumour differentiation as the strongest predictor of death from recurrent HCC within 5 years.

Conclusion: Long-term recurrence-free survival is possible after liver resection for HCC, particularly in patients with a single lesion measuring less than 5 cm with a simple nodular appearance and low tumour marker levels.

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Introduction

Hepatocellular carcinoma (HCC) is a common malignancy in Japan, and often develops in virus-infected cirrhotic liver[1]. The high incidence of recurrence following treatment renders it difficult to cure this disease completely. On the other hand, long-term survival has been reported even beyond 10 years, with or without recurrence, after potentially curative liver resection[2–4]. However, there have been few reports regarding recurrence-free survival (RFS) for more than 10 years after liver resection with curative intent for HCC[5].

The Liver Cancer Study Group of Japan (LCSGJ) has conducted a nationwide survey of patients with primary liver carcinoma since 1969 to evaluate the clinicopathological characteristics and outcomes of these patients[6]. The large-scale registration system of the LCSGJ was used here to evaluate the characteristics of patients who survived without recurrence for at least 10 years after curative liver resection. These patients were compared with patients who died from recurrent HCC within 5 years in order to gain insight into the demography and biological behaviour of HCCs. In addition, such data might be important in determining follow-up strategies, and encouraging patients to undergo treatment, including surgical resection.

Methods

A nationwide follow-up survey of all patients with primary HCC was conducted by the LCSGJ. All patients with

primary malignant liver tumours diagnosed by imaging, preoperative clinical data, and/or histopathological studies at approximately 800 institutions in Japan were registered and followed prospectively every 2 years.

At the time of this analysis, the LCSGJ database contained 142 900 patients diagnosed with a liver tumour and 130 748 patients ultimately diagnosed with HCC. The present study enrolled 20 811 patients with HCC who had undergone liver resection with curative intent before 1993, and were registered in the JCSGJ database between 1988 and 2003 (from the 10th to the 17th surveillance). The indications for hepatic resection and operative procedures were based on both anatomical location of the tumour and liver function. Follow-up ended on 31 December 2003.

Patients who survived more than 10 years without recurrence of HCC and those who died from recurrent HCC within 5 years of liver resection were identified. Patients were further examined according to the degree of background liver damage, as advocated by the JCSGJ as an alternative to the Child–Pugh score (*Table 1*)[7]. The serological presence of hepatitis B antigen was considered evidence of hepatitis B infection, and that of hepatitis C antibody as an indicator of hepatitis C infection. Hepatic resections were classified according to the terminology of the Liver Cancer Study Group of Japan[7]. The macroscopic appearance of HCC was classified into six types: type 1 (simple nodular type), type 2 (simple nodular type with extranodular growth), type 3 (confluent multinodular type), type 4 (multinodular type), type 5 (others, including infiltrative, mass and diffuse types) and unknown[6,8]. Serum levels of α-fetoprotein (AFP) and des-γ-carboxyprothrombin (DCP) were measured as tumour markers. Microscopic portal vein invasion was defined as the presence of tumour emboli within the portal vein. Intrahepatic metastasis was classified into four groups: 0 (no intrahepatic metastasis), 1 (intrahepatic metastasis to the segment in which the main tumour is located), 2 (intrahepatic metastases to two segments), 3 (intrahepatic metastases of the three or four segments). Non-cancerous liver was classified microscopically as normal, or as having chronic hepatitis, fibrosis or cirrhosis.

Hepatic recurrence of HCC was diagnosed at each centre by ultrasonography and/or dynamic computed tomography. Distant metastases were diagnosed by computed tomography (lung) and scintigraphy (bone)[9].

Table 1 Degree of liver damage according to the Liver Cancer Study Group of Japan

	Degree of liver damage		
	A	B	C
Ascites	None	Controllable	Uncontrollable
Serum bilirubin (mg/dl)	> 2·0	2·0–3·0	< 3·0
Serum albumin (g/dl)	> 3·5	3·0–3·5	< 3·0
ICG-R15 (%)	< 15	15–40	> 40
Prothrombin activity (%)	> 80	50–80	< 50

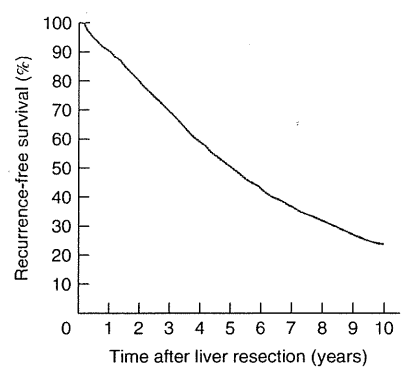
The degree of liver damage was classified as grades A, B and C based on the highest grade containing at least two of five items. Then, if two or more items scoring the same grade occur in the three grades, the higher grade is adopted as the degree of liver damage. ICG-R15, indocyanine green retention rate at 15 min.

Statistical analysis

Continuous data were expressed as mean(s.d.) and analysed by means of Student's t test. The χ^2 test was used to analyse the distribution of nominal variables, and the Wilcoxon rank sum test for analysis of ordered categorical variables. RFS curves were generated by the Kaplan–Meier method. A multivariable logistic regression model was used to investigate odds ratios. $P < 0{\cdot}050$ was considered statistically significant.

Results

Stratification according to the time of recurrence identified 281 patients who survived more than 10 years without recurrence of HCC (10-year RFS group), whereas 918 patients died from recurrent HCC within 5 years of liver resection. Median follow-up was 11·2 and 0·9 years respectively. The RFS rate at 10 years was 22·4 per cent after liver resection with curative intent (*Fig. 1*). Clinical



No. at risk	4977	3399	2253	1423	572	39
Cumulative recurrences	0	543	1047	1349	1533	1704
Cumulative deaths without recurrence	0	471	812	1110	1275	1339

Fig. 1 Recurrence-free survival after liver resection with curative intent for hepatocellular carcinoma

Table 2 Comparison of clinical data between recurrence-free survivors at 10 years and patients who died from recurrent hepatocellular carcinoma within 5 years

	10-year RFS ($n = 281$)	Died within 5 years ($n = 918$)	P§
Age (years)*	57·5(9·4)	60·8(8·5)†	< 0·001¶
Sex ratio (M : F)	219 : 62	755 : 162‡	0·115
Liver damage grade			< 0·001
A	212 (79·1)	553 (65·1)	
B	52 (19·4)	257 (30·3)	
C	4 (1·5)	39 (4·6)	
Unknown	13	69	
HBsAg-positive	82 of 255 (32·2)	179 of 812 (22·0)	< 0·001
HCV Ab-positive	103 of 198 (52·0)	356 of 474 (75·1)	< 0·001
AFP (ng/ml)			< 0·001#
< 20	140 (50·9)	272 (30·8)	
≥ 20 to < 400	73 (26·5)	345 (39·1)	
≥ 400 to < 1000	15 (5·5)	79 (9·0)	
≥ 1000	47 (17·1)	186 (21·1)	
Unknown	6	36	
DCP (mAU/ml)			< 0·001#
< 40	118 (69·4)	222 (50·5)	
≥ 40 to < 500	16 (9·4)	83 (18·9)	
≥ 500 to < 1000	36 (21·2)	135 (30·7)	
≥ 1000	0 (0)	0 (0)	
Unknown	111	478	
Operative method			0·270
> 1 segment	135 (48·2)	410 (44·9)	
Subsegment	71 (25·4)	216 (23·6)	
< 1 subsegment	74 (26·4)	288 (31·5)	
Unknown	1	4	

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). Data missing for †six and ‡one patients. RFS, recurrence-free survival; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C antibody; AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin. §χ^2 test, except ¶Student's t test and #Wilcoxon rank sum test.

Table 3 Comparison of histopathological data between recurrence-free survivors at 10 years and patients who died from recurrent hepatocellular carcinoma within 5 years

	10 year RFS ($n = 281$)	Died within 5 years ($n = 918$)	P*
Maximum tumour size (cm)			0·009
< 2	91 (32·5)	198 (21·7)	
2–5	142 (50·7)	480 (52·6)	
> 5	47 (16·8)	234 (25·7)	
Unknown	1	6	
No. of tumours			< 0·001
1	253 (91·7)	675 (74·1)	
2	20 (7·2)	145 (15·9)	
≥ 3	3 (1·1)	91 (10·0)	
Unknown	5	7	
Macroscopic type			< 0·001
1	198 (73·3)	521 (60·2)	
2	32 (11·9)	174 (20·1)	
3	28 (10·4)	69 (8·0)	
4	6 (2·2)	66 (7·6)	
5	6 (2·2)	35 (4·0)	
Unknown	11	53	
Tumour differentiation			< 0·001
Well	52 (24·0)	95 (13·7)	
Moderate	133 (61·3)	427 (61·4)	
Poor	31 (14·3)	167 (24·0)	
Unclassified	1 (0·5)	6 (0·9)	
Unknown	64	223	
Vascular invasion			0·281
Yes	4 (1·4)	23 (2·6)	
No	272 (98·6)	875 (97·4)	
Unknown	5	20	
Intrahepatic metastases			< 0·001
0	258 (92·5)	673 (75·3)	
1	15 (5·4)	154 (17·2)	
2	6 (2·2)	62 (6·9)	
3	0 (0)	5 (0·6)	
Unknown	2	24	< 0·001
Non-cancerous liver			
Normal	35 (14·4)	50 (6·6)	
Chronic hepatitis/fibrosis	105 (43·2)	189 (25·1)	
Cirrhosis	103 (42·4)	514 (68·3)	
Unknown	38	165	

Values in parentheses are percentages. RFS, recurrence-free survival. *χ^2 test.

and histopathological characteristics of the two groups are compared in *Tables 2* and *3* respectively.

In the 10-year RFS group, at the time of liver resection the background liver damage was grade A in 79·1 per cent, grade B in 19·4 per cent and grade C in 1·5 per cent. Some 32·2 per cent of these patients were positive for hepatitis B virus antigens, whereas 52·0 per cent were positive for hepatitis C virus antibody. Serum levels of AFP and DCP were normal in 50·9 and 69·4 per cent of patients respectively. Surgical procedures comprised resection of less than a subsegment in 26·4 per cent, subsegmentectomy in 25·4 per cent and resection of more than one segment in 48·2 per cent of patients.

The maximum size of HCC at resection was less than 5 cm in 83·2 per cent of patients in the 10-year RFS group. Some 91·7 per cent of these patients had a single HCC at resection. HCCs in this group were of the single nodular type in 73·3 per cent, and 61·3 per cent were moderately differentiated; most showed no vascular invasion (98·6 per cent) or intrahepatic metastases (92·5 per cent). The non-cancerous tissue was cirrhotic in 46·5 per cent.

Comparison of the characteristics of patients who survived for at least 10 years without disease recurrence and those who died from recurrent HCC within 5 years revealed significant differences in age, degree of liver damage, positivity for hepatitis B antigen and hepatitis C antibody, serum levels of AFP and serum levels of DCP

(*Table 2*). Indeed, the 10-year survivors were younger, less frequently positive for hepatitis C and more frequently positive for hepatitis B. Levels of tumour markers (AFP, DCP) were lower in this group, whereas HCCs were smaller and fewer in number. There were also statistically significant differences in macroscopic appearance, tumour differentiation, intrahepatic metastasis and non-cancerous liver histology.

Table 4 Multivariable logistic regression analysis for death from recurrent hepatocellular carcinoma within 5 years

	Odds ratio	*P*
Age (years)		
≥ 60	1·00	
< 60	1·67 (1·06, 2·61)	0·026
Maximum tumour size (cm)		
< 2	1·00	
2–5	1·10 (0·63, 1·93)	0·728
> 5	2·56 (1·16, 5·65)	0·020
No. of tumours		
1	1·00	
≥ 2	1·99 (0·85, 4·62)	0·111
Macroscopic type		
1	1·00	
2	1·44 (0·75, 2·75)	0·270
3	0·76 (0·36, 1·62)	0·473
4	1·31 (0·36, 4·78)	0·687
5	1·68 (0·50, 5·67)	0·405
Tumour differentiation		
Well	1·00	
Moderate	1·59 (0·86, 2·92)	0·138
Poor	3·33 (1·46, 7·60)	0·004
Unclassified	1·01 (0·08, 12·67)	0·995
Vascular invasion		
No	1·00	
Yes	1·21 (0·25, 5·74)	0·813
Intrahepatic metastasis		
No	1·00	
Yes	2·34 (1·02, 5·37)	0·046
Non-cancerous liver		
Normal	1·00	
Chronic hepatitis/fibrosis	0·71 (0·30, 1·72)	0·450
Cirrhosis	2·25 (0·93, 5·40)	0·071
Liver damage grade		
A	1·00	
B or C	1·58 (0·96, 2·62)	0·075
AFP (units/l)		
< 20	1·00	
≥ 20 to < 400	1·96 (1·19, 3·25)	0·009
≥ 400 to < 1000	2·88 (1·19, 6·94)	0·019
≥ 1000	1·63 (0·86, 3·08)	0·134
DCP (units/l)		
< 40	1·00	
≥ 40 to < 500	2·73 (1·28, 5·41)	0·004
≥ 500 to < 1000	0·90 (0·39, 2·08)	0·804
≥ 1000	1·42 (0·76, 2·68)	0·273

Values in parentheses are 95 per cent confidence intervals. AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin.

Multivariable analysis revealed that tumour differentiation had the highest odds ratio related to death from recurrent HCC within 5 years, followed by raised levels of AFP and DCP (*Table 4*). When both the size and number of HCCs were categorized, the frequency of single HCC was significantly higher for any diameter of HCC in the 10-year RFS group than in patients who died from recurrent HCC within 5 years (data not shown).

Among patients whose levels of AFP (400–1000 units/l) and DCP (500–1000 units/l) were moderately raised, those with a single HCC had a lower risk of death from recurrent HCC than those with multiple tumours (data not shown). The number of HCCs yielded a higher odds ratio than the diameter of HCC in this specific group.

Discussion

The present study characterized tumour and patient factors among patients who survived without recurrence for 10 years after liver resection with curative intent for HCC. Although the characteristics of 10-year survivors after liver resection have already been investigated, there are few reports on 10-year RFS[2–5,10]. The present research was conducted as a nationwide large-scale comprehensive study of long-term recurrence-free survivors of HCC following liver resection in Japan.

In the present study, patients in the 10-year RFS group were younger with less background liver damage than patients who died from recurrent HCC within 5 years after liver resection. This was probably because there was less inflammatory change resulting from hepatitis C infection in the 10-year RFS group. The importance of underlying liver disease has been noted previously with regard to the degree of liver fibrosis and cirrhosis[10]. Underlying liver disease has more impact on patient survival than tumour factors[11]. Although two extreme HCC groups were compared in the present study (long-term RFS and short-term relapse), the present findings are of importance in determining possible factors associated with long-term RFS after curative liver resection.

Failure to detect latent intrahepatic HCC before surgery has no prognostic impact on the outcome or recurrence of HCC after liver transplantation[12,13]. The explanted diseased liver may show early HCCs that could not be detected before surgery, which can therefore appear as multicentric HCC on later examination. In the present study, patients in the 10-year RFS group had better liver function, despite a higher rate of positivity for hepatitis B surface antigen. Although the inflammatory activity in the resected liver was not investigated here, it was likely to have been lower in the remnant liver of the long-term survivors.

Tumour markers such as AFP or DCP have been reported to predict the early recurrence of HCC, even in the absence of microvascular invasion in the resected specimen[14,15]. The documentation of microvascular invasion depends on the slice width of the resected specimen and the number of slices investigated. Therefore, early recurrence can occur despite the absence of documented microvascular invasion. However, AFP or DCP levels are raised in nearly 60 per cent of patients with HCC, reflecting the biological behaviour of malignant tumours. The present data indicate that patients with no increase in AFP and DCP levels before surgery have a higher chance of survival without recurrence. In multivariable analysis, both tumour markers were independently associated with death due to recurrence after liver resection with curative intent. Furthermore, patients with a single HCC who had moderately raised AFP and DCP levels still had the prospect of surviving for longer after liver resection than those with high levels of tumour markers.

Considering the number and size of HCCs, a considerable percentage of patients in the 10-year RFS group had a single HCC (91·7 per cent) at the time of liver resection. Even with a raised AFP or DPC level, the risk of early death from recurrent HCC increased when there was more than one lesion. In other words, if a single HCC is found, a patient has an increased chance of surviving for longer after liver resection with curative intent.

Macroscopic HCC appearance was valuable for predicting 10-year RFS after curative liver resection, as shown previously[8]. HCCs of a contiguous multinodular type with clustering of small and contiguous nodules, and simple nodular types with extranodular growth carry a worse prognosis, most likely owing to microvascular invasion. In line with this, patients with these macroscopic types of HCC had a lower chance of long-term survival after liver resection in the present series.

The authors' group previously reported that anatomical resection has therapeutic value for treating patients with HCCs of 2–5 cm in diameter[16]. However, in the present study, this benefit of curative resection was not confirmed, even for HCCs with a diameter of 2–5 cm. This may have been because two extreme patient groups were compared. For example, even for HCC of 2–5 cm in size, the macroscopic appearance, vascular invasion, inflammatory status and fibrosis in the tumour-bearing liver may have been largely different between the two groups.

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Original Article

Demonstration of quality of care measurement using the Japanese liver cancer registry

Takahiro Higashi,[1] Kiyoshi Hasegawa,[2,13] Norihiro Kokudo,[2,13] Masatoshi Makuuchi,[3,13] Namiki Izumi,[4,13] Takafumi Ichida,[8,13] Masatoshi Kudo,[9,13] Yonson Ku,[10,13] Michiie Sakamoto,[5,13] Osamu Nakashima,[11,13] Osamu Matsui,[12,13] Yutaka Matsuyama,[6,13] Tomotaka Sobue[7] and the Liver Cancer Study Group of Japan

Departments of [1]Health Policy/Public Health and [2]Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, [3]Japanese Red Cross Medical Center, [4]Department of Gastroenterology, Musashino Red Cross Hospital, Musashino, [5]Department of Pathology, Keio University School of Medicine, [6]Department of Biostatistics, School of Public Health, University of Tokyo, [7]Division of Cancer Information and Statistics, Center for Cancer Control and Information Services, the National Cancer Center, Tokyo, [8]Department of Gastroenterology, Juntendo University Shizuoka Hospital, Izunokuni, Shizuoka, [9]Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Sayama, Osaka, [10]Division of Hepato-Biliary-Pancreatic Surgery, Kobe University Graduate School of Medicine, Kobe, Hyogo, [11]Department of Pathology, Kurume University School of Medicine, Kurume, [12]Department of Radiology, Kanazawa University Graduate School of Medical Science, Kanazawa, and [13]Liver Cancer Study Group of Japan, Japan

Aim: Despite advances in medical therapy, studies have reported gaps between current evidence and actual practice in many areas of medicine. Process-of-care quality indicators (QIs) are tools to measure the evidence–practice gap. This study aims to examine the feasibility of applying QIs for liver cancer care to the national registry database operated by the Liver Cancer Study Group of Japan.

Methods: Prior research developed a set of process-of-care QIs developed on the basis of the Japanese Clinical Practice Guidelines for hepatocellular carcinoma. Each QI describes target patients and care processes indicated for such patients. Among the 25 developed QIs, six appeared scorable using the information contained in the dataset from the 17th Nationwide Survey of Primary Liver Cancer.

Results: In total, 16 187 patients were eligible for the six QIs for 34 599 times, among which the indicated care was provided 83.9% times. The scores ranged from 64.4% (surgical therapy in patients with HCC 3–5 cm in diameter) to 91.1% (indocyanine green checkup before surgical resection). The information was generally available to determine eligibility (78.3%–100%) and pass/fail (91.9%–99.9%) for the QIs.

Conclusions: Applying QIs to the liver cancer registry, the quality of hepatocellular carcinoma care can be measured. In future, providing feedback regarding the results to the participating society may improve the quality of liver cancer care nationwide.

Key words: cancer registry, hepatocellular carcinoma, quality indicators, quality of health care.

INTRODUCTION

LIVER CANCER IS the third leading cause of cancer deaths worldwide.[1] Eastern countries generally exhibit higher incidences of liver cancer, but many Western countries have experienced a steady increase.[2,3] Liver cancer is prevalent in Japan, and it was the fourth leading cause of cancer deaths in 2009.[4] Despite recent advances in diagnostics and therapeutics, the 5-year survival rates based on population-based cancer registries remains relatively low at 23.1%.[5]

To improve survival, both medical therapeutic advances and their dissemination into clinical practice are necessary. To distribute current knowledge and facilitate clinical decision making for liver cancer treatment, the first evidence-based Clinical Practice

Correspondence: Dr Norihiro Kokudo, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo Bunkyo-ku, Tokyo 113-0033, Japan. Email: KOKUDO-2SU@h.u-tokyo.ac.jp
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Guidelines for Hepatocellular Carcinoma in Japan were published in 2005 with financial support from the Ministry of Health, Labor, and Welfare.[6,7] A follow-up survey of specialists and generalists involved in liver cancer care demonstrated successful outreach and acceptance of these guidelines among frontline practitioners of hepatocellular carcinoma (HCC) care.[8]

The next step in monitoring the effectiveness of the HCC clinical practice guidelines is the assessment of the quality of care. Although the quality of care can be assessed by structure, process, and outcome,[9] an evaluation of the process best fits the context of guideline implementation. Quality assessments that examine the processes of care compare the actual care provided to the patient against the pre-specified standards of care. Although standards may not exist for all aspects of care, examining how well the standards are incorporated into daily practice in those areas that do exist can reveal aspects of quality and create a basis for improvement. In addition, gaps in the process quality highlight areas for the guideline committee to focus on in the next round of revisions. Accordingly, we developed a set of process quality indicators (QIs) that describe standards for HCC patient care.[10,11] Although the QIs were designed to be implemented through the review of medical records, some QIs can be used on the Nationwide Survey of Primary Liver Cancer – the liver cancer registry operated by the Liver Cancer Study Group of Japan. This provided a unique opportunity to pilot test the QIs and examine certain aspects of the quality of care of some liver cancer patients in Japan.

METHODS

Development of the QIs

THE QIS WERE developed using Japanese HCC guidelines, adopting the RAND/University of California, Los Angeles appropriateness methods.[12] Details of processes and results were previously reported in Japanese.[11] Briefly, we first created candidate QIs based on the recommendations of the Japanese HCC guidelines and the medical literature. Each QI described the care standards defining target patients and indicated the care processes. From a literature review, we summarized the rationale for each candidate QI.

Next a nine-member multidisciplinary panel was convened that consisted of two hepatobiliary surgeons, three hepatologists, a gastrointestinal surgeon, a general internist, and two interventional radiologists. The panel members were nationally recognized clinicians from various practice settings, including the university and general hospital settings. The geographic distributions of the clinical practices were also taken into account.

The panel examined candidate QIs by following the modified Delphi process that consisted of two rounds of anonymous rating of the validity (scale of 1–9; 1 = definitely invalid; 9 = definitely valid) coupled with a face-to-face group discussion between rounds. During the process, the panel was allowed to modify the QIs. As per prior studies, QIs that had a median rating of 7 or higher and were rated 3 or lower by two or fewer panelists in the second ratings were accepted.[12,13]

Liver cancer registry database

The Liver Cancer Study Group of Japan operates the Nationwide Survey of Primary Liver Cancer in Japan, which is a cancer registry specifically for liver cancer.[14] Biannually, it collects 178 data items from the newly treated primary liver cancer patients and 46 items for following the previously registered patients. Participation is voluntary and is estimated to cover approximately 20% of all primary liver cancer patients in Japan.[15] We used data on patients receiving therapy for liver cancer at 645 participating institutions during 2002 and 2003. The data consisted of detailed clinical information and included the patients' baseline conditions, imaging findings, treatment modality, and pathological findings. Here, we have limited our analysis to HCC patients ≥20 years of age and have excluded patients who lacked age or diagnosis information.

Quality scores

The expert panel process resulted in 25 QIs,[11] which targeted a wide range of care processes including the pre-therapeutic evaluation, treatment choice, patient explanation of the treatment and results, and follow-ups. Of the 25 QIs, six could be scored using the information in the Liver Cancer Registry Database (Table 1). Patients were eligible for QIs if they met the criteria described in the denominator, and they were considered to have "passed" the QI if they received the care processes stated in the numerator. The quality score was calculated for each QI as the percentage of "passed" patients among those eligible. For example, the first QI in Table 1 was scored as the percentage of the patients whose alpha-phetoprotein (AFP) and protein indiced by vitamin K absence -2 (PIVKA-2) levels were measured before treatment (numerator) among those who were diagnosed with hepatocellular carcinoma (denominator). When necessary information was unavailable (i.e. either missing or coded as "unknown" in the dataset),

Table 1 Quality indicators (QIs) applied to the liver cancer registry, quality scores, and data completeness

Denominator (target patients)	Numerator (standard care processes)	*n*	Quality score (%)	Data availability (%)	
				Denominator	Numerator
Tumor marker before initiation of therapy					
Patients who were diagnosed with hepatocellular carcinoma (HCC)	AFP and PIVKA-2 levels were measured before treatment†	16 187	82.3%	100%	94.3%
ICG check-up before surgery					
Patients who underwent surgical resection of HCC for the first time	15-min ICG retention rate was measured before treatment†	4 802	91.1%	99.2%	94.6%
Local therapy for new HCC (≤3 cm)					
HCC patients with liver damage class A, having three or less tumors of 3 cm or smaller in diameter	Surgical resection or percutaneous local ablation therapy (PEI, MCT, or RFA) was performed.	3 934	76.9%	78.3%	99.5%
Surgical therapy for new HCC (3–5 cm)					
HCC patients with liver damage class A having a solitary tumor of 3–5 cm in diameter	Surgical resection was performed.	1 029	64.4%	78.3%	99.9%
TACE indication					
HCC patients with Stage IVa or earlier, Vp 0–2 and Child–Pugh class A or B, in whom surgery and percutaneous local ablation therapy were not possible (patients who did not receive surgery or percutaneous local ablation therapy within 3 months after diagnosis)	TACE was performed.	3 741	84.5%	82.0%	99.9%
Documentation of after surgical resection					
HCC patients who received surgical resection	Medical record (including pathological report) documented the degrees of vascular invasion‡ and tumor differentiation was postoperatively determined.	4 906	81.4%	99.5%	91.9%

†Timing of the measurement was uncertain because the date of the test was not present in the registry.
Whether surgical resection was the first-line therapy was unclear because the registry did not distinguish the first-line therapy from subsequent therapies. ‡Includes invasion to the portal vein (vp), hepatic vein (vv), hepatic artery (va), and bile duct (b).
HCC, hepatocellular carcinoma; ICG, indocyanine green; MCT, microwave coagulation therapy; PEI, percutaneous ethanol injection; RFA,radiofrequency ablation; TACE, transarterial chemoembolization.

we treated the patients as follows: if QI eligibility information (applicability to the denominator) was missing, we excluded the patients from the denominator; if the information needed to determine the "pass" or "fail" status (the numerator) was unavailable, we considered that the care was not provided, and thus, the patient was counted as "fail" on the QI.

To evaluate the feasibility of applying these QIs to the liver cancer registry, we examined the completeness of the data to determine patient eligibility (the proportion of patients having all data items necessary to examine the denominator criteria [i.e. target patients]) and pass/fail (the proportion of patients having all necessary data items among all eligible patients) for QIs. Because the analysis revealed that the liver damage classification of the Liver Cancer Study Group[16] was the most frequently missing information, we further evaluated the usability of Child–Pugh classification to substitute for the liver

damage classification by examining the agreement between the two classification systems among patients with both sets of data. Because the QIs that target treatment choice focused on patients with class A liver damage, we calculated the sensitivity and specificity of the Child–Pugh class A in predicting liver damage class A. All of the statistical analyses were performed using STATA 11.1 (College Station, TX, USA). The study protocol was approved by the institutional review board of the National Cancer Center of Japan.

RESULTS

Sample characteristics

IN TOTAL, 16 187 patients were included. Table 2 presents the sample characteristics. The mean age of patients was 67 years (71.6% male). Approximately 50% of patients had liver damage of class A and 50% had solitary tumors. Similar numbers of patients underwent surgery, percutaneous local ablation, and transcatheter arterial chemoembolization (TACE).

Table 2 Sample characteristics

	n (%)
Age, mean (SD)	67 (SD = 9.4)
Male *n* (%)	11 592 (71.6%)
Liver damage class	
A	8089 (50.0%)
B	4439 (27.4%)
C	1058 (6.5%)
Unknown/No response	2601 (16.1%)
Child–Pugh class	
A	10 585 (65.4%)
B	3444 (21.3%)
C	867 (5.4%)
Unknown/No response	1291 (8.0%)
Number of tumors	
1	8970 (55.4%)
2	2727 (16.9%)
3	1198 (7.4%)
>3	3733 (15.7%)
Unknown/No response	757 (4.9%)
Tumor diameter (cm), mean (SD)	4.1 (4.0)
Primary treatment modality	
No treatment	1238 (7.7%)
Surgical resection, transplantation	4895 (30.2%)
Percutaneous local ablation	4733 (29.2%)
TACE	4423 (27.3%)
Systemic chemotherapy	718 (4.4%)
Other treatment	110 (0.7%)
No answer	70 (0.4%)

SD, standard deviation; TACE, transarterial chemoembolization.

Table 3 Cross-tabulation of Child–Pugh and Liver damage classes

CP	LD				
	A	B	C	Unknown	Total
A	7729	1813	35	1008	10 585
B	131	2445	290	578	3 444
C	6	56	693	112	867
Unknown	223	125	40	903	1 291
Total	8089	4439	1058	2601	16 187

CP, Child–Pugh classification; LD, liver damage.

Quality scores

On average, quality indicators had 5767 patients applicable, and overall the indicated care processes were provided 83.9% of the time. Table 1 presents quality scores and data completeness for each QI. The score was lowest for the QI "Surgical therapy in patients with HCC 3–5 cm in diameter" (64.4%) and highest for the QI "Indocyanine green (ICG) checkup before surgical resection" (91.1%). Although the availability of data for denominators ranged from 78.3% to 100%, information for numerators was available for more than 90% of patients for all QIs. QIs that use liver damage classification, tumor number, and tumor size were least commonly available for the denominator (78.3%). Liver damage classification, tumor number, and tumor size were missing or unknown for 2601 (16%), 757 (4.7%), and 1134 patients (7.0%), respectively.

Distribution of liver damage and the Child–Pugh classification

Table 3 presents the analysis of the concordance between Child–Pugh and liver damage classifications. These two classification systems agreed in 82.3% of patients for whom sufficient data were available. Child–Pugh A could predict liver damage class A with 98.3% sensitivity and 65.3% specificity.

DISCUSSION

WE HAVE DEMONSTRATED that certain aspects of the quality of care for patients with liver cancer can be measured using the liver cancer registry operated by the Liver Cancer Study Group of Japan. To our

knowledge, this was the first study to measure the quality of care for HCC. Standardizing the care process is challenging given the complexity of HCC care, as a range of treatment modalities from surgical resection to percutaneous and transcatheter therapy exists. The choice of treatment is influenced not only by the cancer stage but also by the baseline liver function. The QIs in this study, developed by the consensus of clinical experts, examined the actual care provided against the standards of pretherapeutic evaluation, the collection of pertinent tumor information, and treatment choice. The quality scores were high for most of the QIs, but there was also room for improvement. Although not all of the QIs developed were used for this analysis, we believe that the identification of a focus for improvement is an important initial step.

The information available in the registry was sufficiently complete for quality measurements to be made. Although information required to determine eligibility for QIs was occasionally missing, the information required to assign each QI a "pass" or "fail" status was generally available, which indicated little ambiguity in the scoring of the eligible patients. Among the missing information, the liver damage classification was the most frequently missing, presumably due to the lack of the ICG test. Although the liver damage classification was used for the QIs that focused on treatment choice in accordance with the Japanese Clinical Practice Guidelines, alternative criteria would be necessary to review actual practices. The comparison of the Child–Pugh class and liver damage class, however, revealed that the former underestimated the liver damage. For example, the Child–Pugh class A includes patients with more severe disease and is broader than liver damage class A. This result was expected, as the prothrombin criteria threshold is lower for the Child–Pugh classification.[16] Furthermore, this is consistent with a previous report that reviewed the medical records of the HCC patients.[17] If the Child–Pugh classification is used in place of the liver damage classification for the patients whose liver damage classification data are missing, the QIs targeting patients with liver damage class A would also include a broader group of the patients with liver damage class B or C. Thus, caution should be exercised when using these liver function classifications interchangeably.

For other types of cancer, we have a predecessor on using the national database for quality measurements and feedback. In the National Cancer Database, the Commission on Cancer of the American College of Surgeons measured six QIs (three for breast cancer and three for colorectal cancer) and provided feedback regarding the scores of the individual participating facilities and the distribution of these scores among other facilities.[18] This program is now developing the Rapid Quality Reporting System, in which the facilities submit and update the information continuously and the quality of care is monitored in real time. Our study indicates that the same service is theoretically possible in Japan using the liver cancer registry.

Some limitations must be considered when interpreting the results of the current study. First, the QIs that examined the appropriate documentation of vascular invasion and tumor differentiation were scored based on the availability of data in the dataset rather than on the actual medical records. This may underestimate or overestimate the quality scores for these QIs. Underestimation occurs when physicians keep appropriate documentation but fail to enter that information into the dataset, and overestimation occurs when physicians enter the information into the dataset but fail to document it in the medical record. Accordingly, caution must be exercised while interpreting these scores. Second, quality assessment requires the consideration of exceptional cases. For example, in some cases where a QI indicated surgery, surgery may not be appropriate due to compromised cardiac or respiratory functions. As the database does not contain information on the reasons why surgery was not performed, it is possible that patients who were appropriately excluded from surgery may be labeled as having received poor quality care. Hence, the results of the measurements of quality from the database should be regarded as starting points for discussions of quality and not as the final conclusions about quality. Third, the fact that the facilities participated in the registry voluntarily must be taken into account, as they are motivated and likely to be more specialized than the average Japanese hospitals. Therefore, the quality scores from these facilities may be higher than those provided by typical hospitals in Japan. Fourth, the QIs were based on the clinical practice guidelines issued in 2005, [6] but our study was comprised of patients diagnosed in 2002 and 2003. Thus, the guidelines used may have already improved some of the aspects of care scored in this analysis, but our study has demonstrated that the Liver Cancer Registry Database can be a useful data source for analyzing quality of care. Finally, the timing of the evaluation and the start of treatment for each patient was uncertain. Although the QIs targeting pretherapeutic laboratory tests (tumor markers and ICG retention) require knowledge of whether these tests were performed before the treatment was initiated, the test dates were not available in the

registry. Thus, we assumed that the tests were performed before the start of the therapy and we therefore overestimated the quality scores.

Despite these limitations, we have demonstrated that the Liver Cancer Registry Database can be a tool for quality measurement. To date, cancer registries have primarily focused on clinical and epidemiological research, and the examination of the quality of care is a new area of research. Professional societies, however, have the responsibility to promote improved quality of patient care. Because the ultimate goal is to improve patient outcome, the role of these societies should not be limited to the discovery of new knowledge but should also include the monitoring of the extent to which the new knowledge is applied to patient care nationwide. This study serves as an initial step for the future growth of such activities.

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APPENDIX

The list of the quality indicators (QIs) approved by the expert panel

	Denominator (target patients)	Numerator (standard care processes)
Pre-treatment work-up		
1	Patients who were diagnosed with hepatocellular carcinoma (HCC)	AFP and PIVKA-2 levels were measured before treatment
2	HCC patients who underwent surgical resection, percutaneous local ablation therapy and transarterial chemoembolization (TACE) therapy	Dynamic CT/MRI study was performed before treatment
3	Patients who were diagnosed with HCC and received treatment	The medical records documented the clinical stage (TNM or TNM factors) and liver function level (the Child–Pugh class or the liver damage class)
4	Patients who underwent surgical resection of HCC for the first time	15-min ICG retention rate was measured before treatment
Treatment choice of local therapy		
5	HCC patients with liver damage class A, having three or less tumors of 3 cm or smaller in diameter	Surgical resection or percutaneous local ablation therapy (PEI, MCT, or RFA) was performed.
6	HCC patients with liver damage class A having a solitary tumor of 3–5 cm in diameter	Surgical resection was performed.
7	HCC patients with liver damage class A or B and three or fewer tumors smaller than 3 cm who had surgical resection or percutaneous local ablation therapy	The advantages and disadvantages of each therapy were explained and documented in the medical records
8	HCC patients with liver damage class C who underwent surgical resection, percutaneous local ablation therapy or TACE	The risks and benefits of the treatments received were explained and documented in the medical records
9	HCC patients receiving percutaneous ethanol injection (PEI) as the initial treatment	Medical records documented the reasons why RFA was not performed
10	HCC patients with Stage IVa or earlier, Vp 0–2 and Child–Pugh class A or B, in whom surgery and percutaneous local ablation therapy were not possible (patients who did not receive surgery or percutaneous local ablation therapy within 3 months after diagnosis)	TACE was performed.
11	Recurrent HCC patients with liver damage class A and a solitary tumor of 3–5 cm in diameter	Surgical resection was performed, or the medical record documented the reasons for not performing surgery
12	Recurrent HCC patients with liver damage class A and solitary tumor of 3 cm or smaller in diameter	Surgical resection or percutaneous local ablation therapy (PEI, MCT or RFA) is performed or the medical record documents the reasons for not performing these therapy
13	Recurrent HCC patients with liver damage class A and two or three tumors of 3 cm or smaller in diameter	Surgical resection, percutaneous local ablation therapy (PEI, MCT or RFA), or TACE was performed, or the medical record documented the reason for not performing these therapies.
14	HCC patients who received TACE	Lipiodol was used in the procedure
15	HCC patients with liver damage class C who satisfied Milan criteria	The option of liver transplantation was explained and documented
Documentation and explanation		
16	HCC patients who underwent surgical resection	Medical record (including pathological report) documented the degrees of vascular invasion and tumor differentiation was postoperatively determined.
17	HCC patients who underwent surgical resection	The medical record documented the physician's judgment on the postoperative risk of recurrence
18	HCC patients who underwent surgical resection	The pathological findings after surgery were explained to patients and were documented in the medical record

	Denominator (target patients)	Numerator (standard care processes)
Systemic therapy		
19	HCC patients who received systemic chemotherapy	Medical records documented the explanation to patients that surgical resection, percutaneous local ablation therapy or TACE could not be performed and that evidence for the efficacy of chemotherapy was lacking.
20	Patients who received treatment for HCC	Hormone therapy was avoided
Follow-up monitoring		
21	HCC patients who underwent surgical resection or percutaneous local ablation therapy	AFP and PIVKA-2 were monitored for at least 4-month intervals for 2 years after the curative treatment
22	HCC patients who received TACE	CT/MRI and tumor marker tests were performed within 2 months after TACE
23	HCC patients who received TACE	Image studies (contrast-enhanced CT/MRI, if not contraindicated) were performed at least every 3 months
24	HCC patients who received TACE	Tumor marker tests (AFP, PIVKA-2) were monitored at least every 3 months
25	HCC patients who received TACE and who showed elevated tumor marker levels, increases in the tumor size from diagnostic imaging or the appearance of new tumors with rich blood flow	TACE was repeated, or the medical record indicates the TACE was considered

AFP, Alpha-fetoprotein; CT, computed tomography; HCC, hepatocellular carcinoma; ICG, indocyanine green; MCT, microwave coagulation therapy; MRI, magnetic resonance imaging; PEI, percutaneous ethanol injection; PIVKA-2, protein induced by vitamin K absence-2; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

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ORIGINAL ARTICLE

RESULTS OF A JAPANESE MULTICENTER, RANDOMIZED TRIAL OF ENDOSCOPIC STENTING FOR NON-RESECTABLE PANCREATIC HEAD CANCER (JM-TEST): COVERED WALLSTENT VERSUS DOUBLELAYER STENT

HIROYUKI ISAYAMA,[1] ICHIRO YASUDA,[4] SHOMEI RYOZAWA,[5] HIROYUKI MAGUCHI,[6] YOSHINORI IGARASHI,[7] YUTAKA MATSUYAMA,[2] AKIO KATANUMA,[6] OSAMU HASEBE,[8] ATSUSHI IRISAWA,[9] TAKAO ITOI,[3] HIDEKAZU MUKAI,[10] YOSHIFUMI ARISAKA,[11] KAZUMU OKUSHIMA,[12] KOJI UNO,[13] MITSUHIRO KIDA[14] AND KIICHI TAMADA[15]

[1]*Department of Gastroenterology, Graduate School of Medicine and* [2]*Department of Biostatistics, Faculty of Medicine, University of Tokyo,* [3]*Department of Gastroenterology and Hepatology, Tokyo Medical University, Tokyo,* [4]*First Department of Internal Medicine, Gifu University Hospital, Gifu,* [5]*Department of Gastroenterology & Hepatology, Yamaguchi University Graduate School of Medicine, Yamaguchi,* [6]*Center for Gastroenterology, Teine-Keijinkai Hospital, Sapporo,* [7]*Division of Gastroenterology and Hepatology, Toho University Omori Medical Center, Tokyo,* [8]*Department of Gastroenterology, Nagano Municipal Hospital, Nagano,* [9]*Department of Gastroenterology, Preparatory office for Aizu Medical Center, Fukushima Medical University, Fukushima,* [10]*Department of Gastroenterology, Yodogawa Christian Hospital and* [11]*Second Department of Internal Medicine, Osaka Medical College, Osaka,* [12]*Department of Internal Medicine, Second Teaching Hospital, Fujita Health University School of Medicine, Aichi,* [13]*Department of Gastroenterology, Kyoto Second Red Cross Hospital, Kyoto,* [14]*Department of Gastroenterology, Kitasato University East Hospital, Kanagawa and* [15]*Department of Gastroenterology and Hepatology, Jichi Medical University, Tochigi, Japan*

Background: No study has compared covered metallic stents with Tannenbaum stents. We evaluated the efficacy of the DoubleLayer stent (DLS) and Covered Wallstent (CWS) in patients with pancreatic head cancer (PHC).

Patients & Methods: This was a multicenter, prospective randomized study. Between October 2005 and December 2007, we enrolled 113 patients (58 DLS, 55 CWS) with unresectable PHC with distal biliary obstructions and observed them for at least 6 months.

Results: No significant difference in patient survival was found between groups, with a median survival of 231 and 248 days in the DLS and CWS groups, respectively. The cumulative stent patency was significantly higher ($P = 0.0072$) in the CWS group. The respective mean and median stent patency was 202 and 133 days in the DLS group and 285 and 419 days in the CWS group. The incidence of DLS occlusion (53.5%) was significantly higher than that of CWS (23.6%; $P = 0.0019$). The respective causes of occlusion were tumor overgrowth (0, 1), ingrowth (0, 2), sludge (24, 2), food impaction (3, 5), kinking bile duct (2, 0), and other (2, 3). Other complications were cholecystitis (0, 4), pancreatitis (0, 1), migration (1, 5), liver abscess (2, 0), and other (1, 2). No significant difference in the incidence of complications between groups was observed.

Conclusion: CWS had significantly longer patency than DLS for the management of PHC with obstructive jaundice. The incidence of complications other than stent occlusion was higher in CWS, but this difference did not reach significance.

Key words: biliary metallic stent, covered metallic stent, endoscopic treatment, obstructive jaundice, pancreas cancer.

INTRODUCTION

Endoscopic biliary stenting is a widely accepted palliative procedure for the management of unresectable malignant biliary obstruction.[1] The covered metallic stent (CMS) was developed to overcome tumor ingrowth through the stent mesh, which is a main cause of stent occlusion in uncovered metallic stents (UMS).[2–8] The covered Diamond stent was patent significantly longer than the uncovered stent in a randomized study.[9] Several studies have compared the CMS and UMS[9–11] and the UMS and plastic stent (PS),[12,13] and one study has compared CMS and PS.[14]

In a randomized study comparing CMS with a conventional PS, the CMS was patent significantly longer.[14] However, studies showed that the Tannenbaum type PS (TTPS) without side holes was patent longer than the conventional PS.[15,16] The DoubleLayer stent (DLS; Olympus Medical Systems, Tokyo, Japan) is a TTPS, and its patency was superior to that of the conventional PS in a prospective randomized study.[17]

Correspondence: Hiroyuki Isayama, Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: isayama-tky@umin.ac.jp

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Migration was not reflected in the calculation of stent patency in the conventional analysis, although this complication impaired the quality of life. To estimate the real quality of life, we calculated the time to dysfunction between stent insertion and stent occlusion or migration.

Many biliary stent studies included various malignancies around the bile duct; however, different diseases may show different tumor behavior and prognoses.[9] Therefore, we need to determine the stent efficacy for a single causative disease. Consequently, we conducted a prospective randomized study of CMS *vs* TTPS in the management of unresectable pancreatic head cancer (PHC) with obstructive jaundice using the DLS and Covered Wallstent (CWS; Microvesive, Boston Scientific, Natick, MA, USA).

METHODS

Patients

Consecutive patients over 18 years of age undergoing a first diagnostic or therapeutic endoscopic retrograde cholangiopancreatography (ERCP) were enrolled in the study on their initial diagnosis of non-resection pancreas head cancer (PHC) with distal biliary obstruction. Their International Union Against Cancer classification was limited to stages 2b, 3, and 4. Neoplasms were diagnosed based on a pathological examination or clinical and imaging findings.

Exclusion criteria were: (i) intraductal papillary mucinous neoplasm (IPMN); (ii) endoscopic approach impossible; (iii) performance status 4; and (iv) an American Society of Anesthesiologists Physical Status Classification System grade of 3 and over. Written informed consent was obtained from all patients before entering the study.

Study oversight

The trial was not sponsored by any company. No endoscopic equipment or stents were donated by manufacturers.

Study design

The study was a multicenter, prospective, open-labeled, randomized, controlled trial. The study protocol was approved by the ethics committees of each participating institute and was performed at 14 Japanese referral centers according to the guidelines described in the Declaration of Helsinki for biomedical research involving human subjects. The protocol appears on UMIN CTR (C000000388). Each of the participating endoscopists in this study had performed more than 200 ERCP examinations per year for more than 5 years.

Randomization

Patients were registered on the study website and subsequently assigned to one of two groups by computer-generated randomization: the CWS or DLS groups. The randomization procedure was a minimization method stratified on tumor stage and institution.

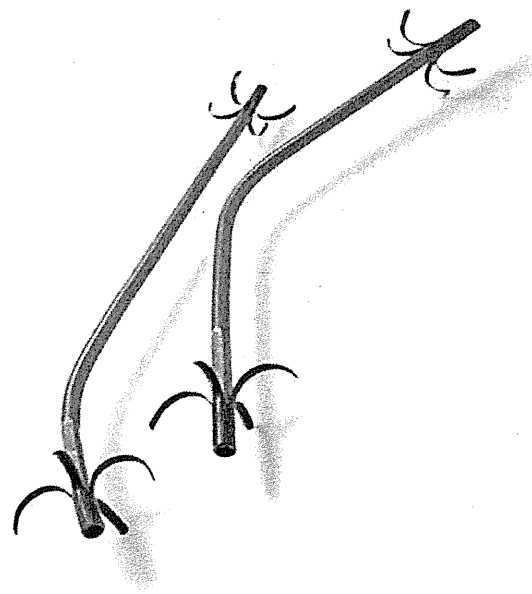

Fig. 1. DoubleLayer stent.

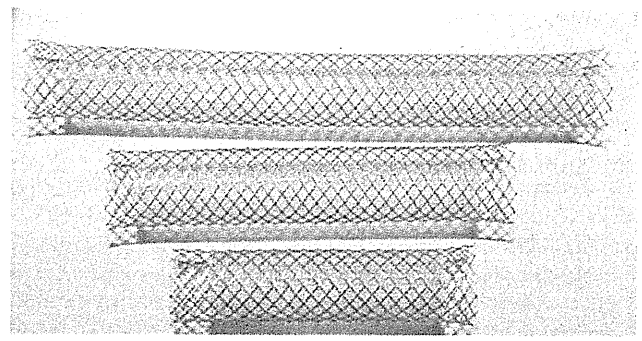

Fig. 2. Covered Wallstent.

Biliary stents

The plastic stent used in this study was a 10-Fr DLS duodenum bending type (Fig. 1). This stent is a Tannenbaum-type plastic stent constructed in three layers – the perfluoroalkoxy, wire mesh, and polyamide elastomer layers in order from the inner lumen – and has four distal and proximal flaps to prevent stent migration. The cost of each DLS was ¥45 000. A CWS with a partial silicone (Permalum) cover was used (Fig. 2), and its cost was ¥23 800. Both ends of this stent were uncovered for 5 mm. All stents were 10 mm in diameter. During the study, three lengths were available in the CWS (40, 60, and 80 mm) and DLS (50, 70, and 90 mm) groups.

Stent insertion

All endoprostheses were usually preceded by insertion of a 6-, 7-, or 8.5-Fr plastic tube stent or a nasobiliary drainage tube at the initial ERCP. After deciding that the tumor was

unresectable, the drainage tube was replaced with a 10-Fr DLS or CWS under fluoroscopic guidance using a therapeutic duodenal endoscope (JF-260V, TJF-200; Olympus, Tokyo, Japan). In patients who were deemed unresectable before the initial ERCP, either a DLS or CWS was inserted at the initial ERCP. An endoscopic sphincterotomy was performed and antibiotics given to all patients before either DLS or CWS insertion.

The length of the DLS was decided according to the stricture location from the papilla. The DLS tends to cause bile duct kinking because of its stiffness.[17] Therefore, we carefully selected the stent size to avoid bile duct kinking at the proximal stent end.

We selected the length of the CWS to be as long as possible to avoid stent occlusion by the tumor overgrowing beyond the stent end and to avoid bile duct kinking due to the strong axial force.[9,18,19] We placed the center of the CWS at the stricture to avoid stent misplacement due to a large shortening ratio.

Follow-up and definition of end-points

Blood biochemistry, clinical signs, and symptoms were monitored on an outpatient basis. Stent occlusion was diagnosed when patients presented with jaundice, cholangitis, or cholestasis. Palliative intervention involving either endoscopic or percutaneous drainage was performed as soon as possible, and the causes of stent obstruction were investigated endoscopically or cholangiographically. Most stents involving complications, either DLS or CWS, were removed, and the cause of occlusion was determined by examining the removed stents. The primary end-points of this study were stent obstruction or patient death with a patent stent. The secondary end-point was patient death.

Statistical methods

The stent patency period was calculated as the interval between stent insertion and its obstruction or patient death with a patent stent. We calculated the time to dysfunction (TTD) between stent insertion and stent dysfunction, including occlusion, cholangitis without stent occlusion, and migration. The cumulative patient survival, stent patency, and TTD were analyzed using the Kaplan–Meier method and the log–rank test for comparisons between two groups. The Mann–Whitney *U*-test was used to compare quantitative variables, and Fisher's exact test was used to analyze qualitative variables.

A previous study found an occlusion rate of 20% for the CWS,[4] which was about 25% less than that for the DLS (43%).[17] For a 5% type I error with 80% statistical power, the required number of patients in each group was estimated to be 60. All analyses were performed using StatView 5.0 software (SAS Institute, Cary, NC, USA).

RESULTS

Patient enrollment and characteristics

We enrolled 120 patients between October 2005 and December 2007. Seven patients were excluded: one patient died from cancer progression before CWS placement, and the papilla could not be reached in the remaining six (two DLS and four CWS) due to duodenal obstruction. The remaining 113 patients were followed until June 2008, and the final data were fixed in May 2009. The clinical features were balanced between the two groups, as shown in Table 1. Pathological confirmation was made in 86.7% of the included cases. No patients were lost during the follow-up period.

Table 1. Patient characteristics

	DoubleLayer stent	Covered Wallstent	
Cases	58	55	
Sex (M/F)	30/28	33/22	NS
Mean age (range)	69.6 (44–86)	71.1 (53–86)	NS
Pathological confirmation	50	48	
Reason for non-resection			NS
Metastasis	23	27	
Locally advanced	26	20	
Advanced age	6	5	
Concomitant disease	1	2	
Patient request	1	1	

NS, not significant.

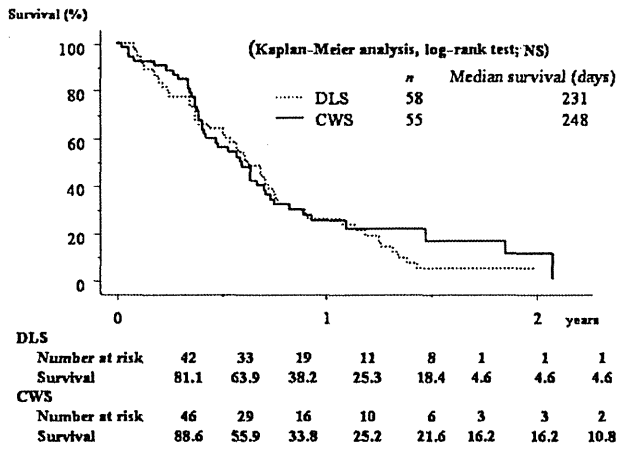

Fig. 3. Cumulative survival time calculated using the Kaplan–Meier method and log–rank test. No significant (NS) difference was found between the Covered Wallstent (CWS) group and the DoubleLayer stent (DLS) group.

Survival and stent patency

No significant difference in overall patient survival was found (Fig. 3), with a median survival of 231 days in the DLS group and 248 days in the CWS group. Twenty cases of duodenal tumor invasion occurred in each group, and the difference in stent patency did not differ significantly from the non-invasion cases. The cumulative stent patency according to the Kaplan–Meier method was significantly higher ($P = 0.0072$) in the CWS group than in the DLS group (Fig. 4). The respective mean and median stent patency was 202 and 133 days in the DLS group and 285 and 419 days in the CWS group.

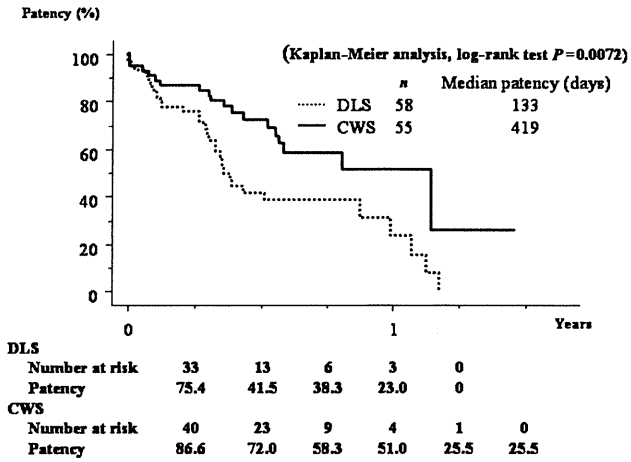

Fig. 4. Cumulative stent patency. The Covered Wallstent (CWS) was patent significantly longer than the DoubleLayer stent (DLS) ($P = 0.0072$).

Table 2. Details of biliary drainage and anti-cancer therapy

	DoubleLayer stent	Covered Wallstent	*P*-value
Cases	58	55	
Median survival (days)	231 (31–586)	248 (8–761)	
Stent patency (days)			
Mean	202 (0–429)	285 (2–536)	
Median	133	419	
Stent occlusion	31 (53.5%)	13 (23.6%)	0.0019
Patent period (days)	110 (0–429)	144 (2–419)	
Cause			
Tumor ingrowth	0	2	0.2347
Tumor overgrowth	0	1	0.2347
Sludge	24	2	< 0.0001
Food impaction	3	5	0.3552
Kinking	2	0	0.4959
Others	2	3	0.6736

Stent occlusion and other complications

Stent occlusion occurred in 31 (53.5%) cases after a median of 110 days in the DLS group and in 13 patients (23.6%) after a median of 144 days in the CWS group. The incidence of DLS occlusion was significantly higher than that of CWS ($P = 0.0019$). The causes of occlusion are summarized in Table 2, and the rate of stent occlusion due to sludge formation in the DLS group (24 cases) was significantly higher than in the CWS group (two cases) ($P < 0.001$). Two DLS were occluded by kinking of the bile duct at the proximal end of the stent, whereas this type of occlusion was not observed in the CWS group. No significant difference in stent occlusion by food impaction between the groups was observed.

The incidence of complications other than stent occlusion in the CWS group was higher than in the DLS group, but the difference did not reach significance (Table 3). No cholecystitis or pancreatitis was observed in the DLS group, but four cases (7.2%) and one case (1.8%) were seen in the CWS group, respectively.

Table 3. Complications

	DoubleLayer stent	Covered Wallstent	*P*-value
Cases	58	55	
Complications	4 (6.9%)	11 (20%)	0.0528
Cholecystitis	0	4 (7.3%)	0.0530
Pancreatitis	0	1 (1.8%)	0.4911
Migration	1	5 (9.1%)	0.1104
Liver abscess	2 (3.4%)	0	0.4959
Others	1	2	0.6117

Table 4. Stent dysfunction and time to dysfunction

	DoubleLayer stent	Covered Wallstent	*P*-value
Stent dysfunction	32 (55.2%)	18 (34.6%)	0.0228
Cause, TTD* (days)			
Stent occlusion			
Tumor ingrowth	0	2 (166, 419)	
Tumor overgrowth	0	1 (217)	
Sludge	24 (mean 154.0)	2 (193, 216)	
Kinking	2 (41, 1)	0	
Food impaction	3 (2, 36, 131)	5 (mean 57.6)	
Others	2	3	
Migration	1 (2)	5 (mean 146)	

TTD, time to dysfunction.

With stent-related complications, 33 DLS and 12 CWS were removed successfully. No complication related to stent removal and no failed case of removal occurred.

Stent dysfunction

Stent dysfunction occurred with stent occlusion or migration. Table 4 lists the causes of dysfunction in both groups and the period from stent insertion to stent dysfunction. The Kaplan–Meier analysis of the TTD, shown in Fig. 5, and median and range of TTD was 133 days (1–429) in the DLS group and 285 days (2–536) in the CWS group, respectively. Cumulative TTD of CWS was significantly longer than that of DLS ($P = 0.0209$), but the difference was shorter than the patency.

DISCUSSION

The CWS was patent significantly longer and had a longer TTD than the DLS for unresectable PHC with obstructive jaundice. Duodenal invasion did not affect the stent patency in either group. The TTD of the CWS was shorter than the patency due to migration.

Both covered metallic stents and plastic stents were able to prevent tumor ingrowth via the stent mesh and were mainly occluded by biliary sludge. In this study, the incidence of stent occlusion by sludge was significantly higher in the DLS group than in the CWS group. The large stent diameter may decrease the incidence of stent occlusion by sludge. Conversely, the large opening on the duodenal stent end may cause a high incidence of stent occlusion by impaction of food scraps. The TTPS may prevent this complication, and it