研究成果の刊行に関する一覧表

雑誌

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研究成果の刊行物・別刷

Original Paper

Safe Management of the Pancreatic Remnant with Prolamine Duct Occlusion after Extended Pancreaticoduodenectomy

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KEY WORDS:
Pancreatic duct occlusion; Extended pancreatico-duodenectomy; Pancreatic fistula

ABBREVIATIONS:
Pancreatico-duodenectomy (PD)

ABSTRACT

Background/Aims: Occlusion of the pancreatic duct system has been used to prevent pancreatic leakage by abolishing pancreatic exocrine secretion in pancreatic surgery. However, ductal occlusion has not proved satisfactory for preventing pancreatic fistulas in pancreaticoduodenectomy (PD).
Methodology: Pancreatic duct occlusion with a watertight drainage system around the pancreatic stump was performed following extended PD in 17 patients with (n=12) or without (n=5) a dilated pancreatic duct.
Results: Transient pancreatitis during the early postoperative period occurred in all patients with a nondilated pancreatic duct. No patient developed pancreatic fistula or any other serious complication in both groups.
Conclusions: Pancreatic duct occlusion may minimize the risk of pancreatic leakage in patients with a nondilated pancreatic duct and a normal pancreas as well as in those with a dilated, obstructed pancreatic duct without compromising the postoperative quality of life. This is a safe and reliable technique for managing the pancreatic remnant in patients undergoing extended PD for advanced pancreaticobiliary malignancy.

INTRODUCTION

Leakage of the pancreaticoenteric anastomosis remains the major cause of serious complications after pancreaticoduodenectomy (PD). Various anastomotic procedures have been developed, but the incidence of hemorrhagic complications resulting from pancreatic leakage still has been reported to be 2-18% during the last two decades (1-4). Recently extended PD including skeletonization of large vessels, portal vein resection, extended lymphadenectomy, retroperitoneal soft-tissue clearance, and concomitant hepatic lobectomy has been aggressively applied for advanced pancreaticobiliary malignancy (5-7). Patients who undergo extensive surgical resections might be at an increased risk for severe complications following leakage of pancreaticoenteric anastomosis.

Pancreatic duct occlusion is another method for avoiding the fatal complication associated with pancreaticoenteric anastomosis by facilitating atrophy of the pancreatic remnant (8-10). However, occlusion of pancreatic duct has not proved satisfactory for preventing pancreatic fistula (11). As an alternative, we covered the cut surface of the pancreatic remnant with a watertight drainage system after occlusion of the pancreatic duct with prolamine. We applied this technique after extended PD and report our experience in 17 patients with advanced pancreaticobiliary malignancy.

METHODOLOGY

Between January 1998 and April 2000, 15 patients who underwent extended PD for invasive ductal adenocarcinoma, and 2 patients who underwent PD with concomitant right hemihepatectomy (hepatopancreaticoduodenectomy) for gallbladder cancer and bile duct cancer respectively, at the National Cancer Center Central Hospital, were managed with this technique. Patients with cystic or intraductal papillary tumors and adenocarcinoma of the ampulla of Vater, the lower common bile duct, or the duodenum were excluded in this study. There were 9 men and 8 women, and their average age was 57.1 years (range, 33 to 75 years). All patients with invasive ductal adenocarcinoma of the pancreas underwent extended lymphadenectomy, including paraaortic lymph adenectomy, skeletonization of the great vessels, and retroperitoneal soft-tissue clearance. Eight of 17 patients (47%) also underwent portal or superior mesenteric vein resection and reconstruction. Nine patients underwent a classical Whipple resection, and eight patients underwent pylorus-preserving PD. The Institutional Review Board approved this study, and a written informed consent was obtained from all patients or their family prior to participation.

Management of Pancreatic Remnant

After completion of the pancreatic resection, a

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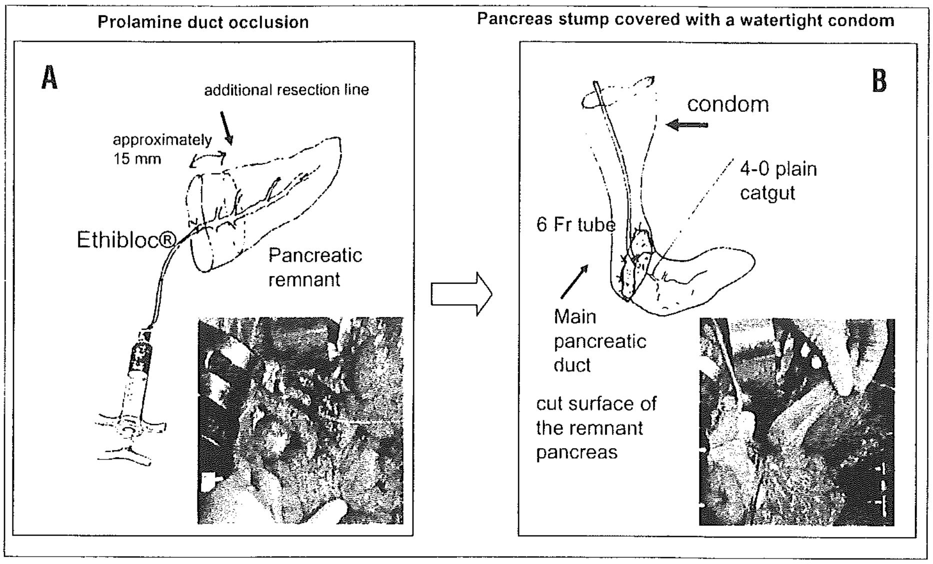

FIGURE 1 **(A)** Schematic diagram showing obliteration of the pancreatic duct occlusion by injection with prolamine. **(B)** The cut surface is covered with a condom. A 6-Fr tube is inserted in the main pancreatic duct and fixed.

pancreatic duct tube (Sumitomo Bakelite Medical, Tokyo, Japan) was inserted into the main pancreatic duct and fixed using a 4/0 polyglycolic acid suture. Prolamine emulsion (Ethibloc®, Ethicon GmBH, Norderstedt, Germany) 4-6mL was injected slowly into the main pancreatic duct until the compound began to extravasate on the transected plane. An additional 15mm of the pancreas was resected to remove incompletely occluded branches near the line of transection 15 minutes after injection of the prolamine **(Figure 1A)**. The injection tube was replaced with a vinyl chloride tube, which was used for external drainage. Then the pancreatic stump was covered by a condom, which was sutured with the edge of the pancreatic stump with 4-0 plain catgut sutures. Saline was poured into the condom and the integrity of the suture line was confirmed **(Figure 1B)**. A silicone penrose drain was inserted into the condom and then they were delivered from the abdomen. Two closed suction drains were placed superiorly and inferiorly to the pancreatic stump, respectively. The condom with the Penrose and the short tube was pulled out on POD 14. When pancreatic leakage or infection from the cut stump persisted 2 weeks after the operation, the condom with a penrose tube was replaced with a silicon drain, which was managed until the leakage or infection subsided.

Correlation between the Diameter of the Pancreatic Duct and Postoperative Management

The diameter of the main pancreatic duct was measured at the line of transections using intraoperative ultrasonography. Seventeen patients were divided into two groups; group A (n=12; a dilated pancreatic duct, >3mm in diameter) or group B (n=5; a nondilated pancreatic duct, ≤3mm in diameter). Three patients in group A had diabetes mellitus needing insulin control before operation.

The serum amylase and amylase concentrations in the fluid collected from each drain was recorded for 10 days postoperatively.

A pancreatic fistula was defined as a persisting secretion of more than 10mL/day of drainage fluid with a high level of amylase (>1000mL) for more than 10 days or the later reoccurrence of amylase rich fluid via the drainage canal.

Statistical significance was determined using the chi-square test. A p value <0.05 was statistically significant.

RESULTS

Twelve patients in group A had a rather hard pancreatic remnant with a dilated pancreatic duct. The diameter of the main pancreatic duct was 5.9±1.4mm. Five patients in group B had a normal, soft pancreatic remnant and the diameter was less than 3mm.

The serum amylase concentration in group A (on day 1, 50.5±29.1 IU/L) did not show significant difference (P=NS). The serum amylase concentration in group B (on day 1, 388±107 IU/L) increased signifi-

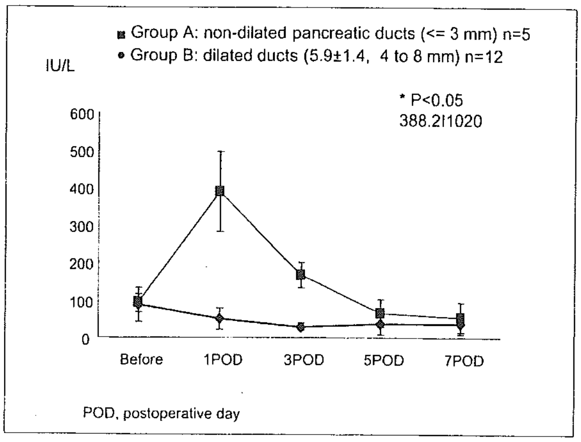

FIGURE 2 Sequential changes in the serum amylase concentration after prolamine occlusion.

cantly ($p<0.05$). However, the serum amylase level returned the preoperative level by day 5 (**Figure 2**). No patient developed clinical symptoms of acute pancreatitis.

The drain amylase concentration in group A remained low by day 5 (on day 1, superior drain; 122±168 IU/L, inferior drain: 105±139 IU/L). However, the drain fluid in group B showed a high level of amylase (on day 1, superior drain; 2183 to 20 181 IU/L, inferior drain; 2402 to 10 003 IU/L). The amylase concentration of the drainage fluid decreased less than 1000 IU/L on day 7 (superior drain; 18 to 970 IU/L, inferior drain; 8 to 355 IU/L).

Postoperatively, 4 of 12 patients in group A (33%) and 3 of 5 patients (60%) in group B required prolonged drainage for minor infection (21-35 days). However no patient developed pancreatic fistula, and there was no serious complication, such as abscess formation or arterial bleeding.

Other Complications and Survivals

Excluding prolonged drainage, delayed gastric empting occurred in five patients, and wound infection in six patients. There was no operative or hospital death. The median survival time (95% Confidence Interval) was 1.06 years (range, 0.38 to 2.66 years). Three patients survived over 2 years.

Glucose Tolerance

Preoperatively, three patients with a dilated pancreatic duct had diabetes mellitus needing insulin control, and they also continued to use insulin postoperatively. Fourteen patients were not diabetic preoperatively, 12 of whom did not require insulin control until they died of their disease. Two patients are alive and do not require insulin administration.

DISCUSSION

Pancreatic duct occlusion with chemical or biological substance to abolishing exocrine pancreatic secretion has been proposed as a safe alternative to pancreaticojejunostomy (8-10). The avoidance of opening the defect in the small bowel and activation of pancreatic enzymes may prevent serious postoperative complications. However, Tran *et al.* (11) recently concluded in their randomized trial that ductal occlusion without pancreaticojejunostomy did not reduce pancreatic fistula and postoperative bleeding. As for their technique, the opening of the duct was ligated and the pancreatic remnant was sewn up after obliteration of the pancreatic duct, and a non-suction silicone drain was placed near the pancreatic remnant and gradually retracted after 7 days. We performed additional resection of the edge of the incompletely occluded pancreatic remnant after ductal occlusion with prolamine and used a condom to cover the pancreatic cut stump to prevent spreading of pancreatic juice leakage during the early postoperative period.

Prolamine occlusion causes edematous pancreatitis a few days later after injection and atrophy of pancreatic parenchyma occurs in 2-3 weeks in the experimental study (11,12). Production of pancreatic juice from the stump may taper and cease within several days after occlusion. A transient pancreatitis occurred in patients with non-dilated pancreatic duct, but not in patients with dilated pancreatic duct (≥3mm) in our study. The elevation of amylase level promptly recovered without clinical symptoms of pancreatitis.

The drain amylase concentration also elevated in patients with a nondilated pancreatic duct. These data reveal prolamine occlusion in patients with a normal pancreas could not abolish pancreatic exocrine secretion within several days after occlusion. Drainage from the pancreatic cut stump seemed to be essential especially during the early postoperative period.

Prolonged drainage due to mild infection was the most common complication in this study. The cause of minor infection might be mainly related to pancreatic leakage around the pancreatic cut stump, in case that ductal occlusion was incomplete and pancreatic exocrine secretion could not be fully abolished. However a persisting secretion of drainage fluid with a high level of amylase and reoccurrence of amylase rich fluid via the drainage canal were not recognized in all patients. Prolamine occlusion probably caused the deterioration of pancreatic exocrine secretion and completely reduced pancreatic fistula in the late postoperative period.

It is believed that patients with a nondilated pancreatic duct and a friable pancreas are especially susceptible to pancreatic anastomotic leakage because of difficulties in surgical technique and a high output of pancreatic juice (1,2). This method caused temporary pancreatitis, but still produces a favorable outcome.

An obvious disadvantage of duct occlusion seems to be the introduction of endocrine pancreatic insufficiency (11). Land *et al.* (12,13) reported that isles of Langerhans were well preserved in their experimental model, and Carlo *et al.* described intraducal injection of Neoprene did not reduce a post-surgical diabetes (9). In this study, from the patients who did not require insulin preoperatively, none required it after occlusion. However long-term follow-up of these patients is necessary before diabetes mellitus can be excluded as a late complication.

Second-stage and two-staged pancreaticojejunostomy have been used in high-risk patients with soft pancreatic parenchyma or liver cirrhosis (7,14,15). These approaches represent another viable method, but require a long-term tube placement and a second operation 2 to 3 months after PD. Even if the pancreatic anastomosis is completed, anastomotic patency cannot be guaranteed for a long time and exocrine pancreatic insufficiency after pancreaticojejunostomy is common in 10-20% of cases (16,17). The strategy described in this report minimized the risk of pancreatic leakage even in patients with a normal, as well as those with a dilated and obstructed pancreatic duct. Furthermore, it preserves the quality of life, by not inducing glucose intolerance. We cannot recommend this method for all patients who undergo PD because exocrine function is lost. However this technique offers a safe and reliable way to manage the pancreatic remnant in patients undergoing extended PD for advanced pancreaticobiliary malignancy, as well as for high-risk patients and patients undergoing emergent surgery.

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A Long-Term Follow-Up and Management Study of Hepatocellular Carcinoma Patients Surviving for 10 Years or Longer after Curative Hepatectomy

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BACKGROUND. The aims of the current study were to elucidate the clinicopathologic characteristics and disease recurrence patterns of patients with hepatocellular carcinoma (HCC) who survived for 10 years or longer after undergoing an initial hepatectomy.

METHODS. Between January 1987 and December 1993, 578 patients underwent potentially curative hepatectomy at the study institution. Disease recurrence and follow-up data were available for 481 of these patients, who then were followed for more than 10 years after the initial hepatectomy. Fourteen clinicopathologic features were compared between the 10-year survivors and those patients who died within 10 years after the surgery. The risk factors for disease recurrence, the recurrence status, time to recurrence, and treatment modalities for recurrence were examined among the 10-year survivors.

RESULTS. There were 105 10-year survivors (21.8%), including 42 disease-free survivors (8.7%). Favorable independent factors found to be correlated with 10-year survival were age < 55 years, a plasma retention rate of indocyanine green at 15 minutes of < 15%, the presence of a solitary tumor, the absence of intrahepatic metastases, the absence of portal vein invasion, and the absence of underlying cirrhosis. A negative test for the the hepatitis C antibody and the absence of intrahepatic metastases were found to be independent predictive factors for 10-year disease-free survival among the 10-year survivors.

CONCLUSIONS. The results suggest that younger patients without underlying cirrhosis who have a solitary HCC that does not demonstrate vascular invasion might survive for longer than 10 years after the initial hepatectomy. In addition to close surveillance in such patients after hepatectomy, repeat hepatectomy, local ablation therapy, and transhepatic arterial chemoembolization may contribute to long-term survival, even if disease recurrence occurs. *Cancer* **2005;104:1939–47.**

KEYWORDS: hepatocellular carcinoma (HCC), survival, hepatectomy, clinicopathologic characteristics, disease recurrence.

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The detection of early hepatocellular carcinoma (HCC) through the screening of high-risk populations[1–3] and precise preoperative and intraoperative diagnosis of macroscopic nodules[4–6] have led to a decrease in the number of patients with occult remnant tumors after surgery. However, the long-term survival still is unsatisfactory and a permanent cure remains difficult to achieve because of the high frequency of postoperative disease recurrence, not only because of intrahepatic metastases but also because of multicentric carcinogenesis.[2,3,6] Therefore, the number of reports of long-term survivors after the initial hepatectomy remains small, especially on the basis of

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long-term observation amounting to longer than 10 years using the actuarial method.[7–9]

Recently, it was reported that a multimodality treatment strategy could improve the survival rate in patients with recurrent HCC after curative hepatectomy.[10] Repeat hepatectomy has been considered to be the most effective treatment choice for recurrent HCC in selected patients.[11,12] Percutaneous ethanol injection (PEIT), ablation therapy, or transarterial chemoembolization (TACE) also are well established treatment modalities for recurrent HCC, and are used taking into consideration the patterns of disease recurrence and functional hepatic reserve.[13,14] To our knowledge, few studies to date have investigated the clinicopathologic factors that might influence actual long-term survival (i.e., those patients surviving for 10 years or longer) among patients with recurrent HCC who are treated with various treatment modalities. It is important to clarify the optimal postoperative management on a timely basis.

In the current study, we evaluated the prognostic factors by analyzing 14 clinicopathologic factors in 105 actual 10-year survivors among 481 patients. The risk factors for disease recurrence, the recurrence status, time to disease recurrence, and the treatment modalities used for disease recurrence were examined among the 10-year survivors.

MATERIALS AND METHODS

Between January 1987 and December 1993, 578 patients undergoing primary hepatic resection for HCC at the National Cancer Center Hospital in Tokyo, Japan were assessed retrospectively. Eleven patients (1.9%) died within 1 month of surgery and 7 patients (1.2%) died during the initial hospital stay. Macroscopic curative hepatectomy was defined as the removal of all macroscopic tumors without tumor exposure. Fifty-seven patients who underwent palliative resection with macroscopic residual tumors, 8 patients who were lost to follow-up, and 14 patients who died of noncancer causes within 10 years of the surgery also were excluded from the study. None of the patients who did not develop disease recurrence was found to have liver failure. The remaining 481 patients were followed for longer than 10 years after the hepatic resection. The median duration of follow-up was 6.0 years (range, 0.1–15.9 yrs). The mean age of the patients (383 men and 98 women) was 60.0 years (range, 17–80 yrs).

Preoperative TACE had been performed in 329 patients (68.4%), in the majority of cases before referral to the study hospital. A preoperative diagnosis of HCC was established on the basis of the findings on ultrasonography (US), dynamic computed tomography (CT), and angiographic CT. The criteria for surgery have been described previously.[3,4,5,15] The maximum liver resection volume was evaluated based on the indocyanine green retention rate at 15 minutes (ICGR15). An ICGR15 of 15% or less is considered to be satisfactory for segmentectomy or lobectomy. The volume of the remnant liver as estimated by CT was taken into consideration when determining the extent of hepatectomy.[16]

No adjuvant therapy was administered. After surgery, the patients were followed by measurement of the serum α-fetoprotein (AFP) levels and abdominal US every 3 months, and dynamic CT was performed every 6 months. If disease recurrence was suspected, angiography was performed for further diagnostic and therapeutic purposes. The diagnosis of disease recurrence was based mainly on imaging modalities; biopsy was routinely performed before PEIT, but not before TACE.

Tumor recurrence with fewer than three nodules was managed for the most part by repeat hepatectomy or PEIT, if possible. Multiple tumor recurrence (more than three nodules) was treated with TACE.

The following clinicopathologic factors were compared between patients who survived for 10 years or longer (10-year survivors) and those who died within 10 years after the initial hepatectomy: age, gender, serum AFP level, ICG R15, status of hepatitis virus infection, preoperative TACE, and surgical procedure performed. (resection of a segment according to the definition of Healey[17]).[3–5] Pathologic factors included the number of nodules and size of the tumor, the presence of portal vein invasion or intrahepatic metastases, and the width of the surgical margin as histologically assessed (with less than 5 mm defined as a positive surgical margin); associated cirrhosis was investigated as a part of the routine histopathologic examination in all the resected specimens.[4,5,18] Noncancerous liver parenchyma was classified as normal liver, chronic hepatitis, and cirrhosis.

The clinicopathologic factors also were compared between 10-year survivors with no disease recurrence and 10-year survivors with recurrence. The disease recurrence status, time to disease recurrence, and treatment modalities used for disease recurrence in the 10-year survivors were examined.

Comparisons were performed using the chi square test with Yates correction (or the Fisher exact test when appropriate) in the univariate analysis, and all significant factors as determined by the univariate analysis were entered into a multivariate regression analysis to identify independent factors. For continuous factors, a preliminary analysis of the prognostic significance of different cutoff values for each of the

TABLE 1
Comparison of Clinicopathologic Factors among Patients Surviving for Fewer than 10 Years and 10 Years and Longer after the Initial Surgery

Factors		Surviving < 10 yrs No. of patients (n = 376)	(%)	Surviving ≥ 10 ys No. of patients (n = 105)	(%)	P value
Age in yrs	≥ 55	292	78	70	67	0.021
	< 55	84	22	35	33	
Gender	Male	296	79	87	83	0.353
	Female	80	21	18	17	
Serum AFP in mg/dL	≥ 100	128	34	31	30	0.395
	< 100	248	66	74	70	
ICGR15 in %	≥ 15	284	76	46	44	< 0.001
	< 15	92	24	59	56	
Hepatitis B virus antigen	Positive	53	14	22	21	0.096
	Negative	323	86	83	79	
Hepatitis C virus antibody	Positive	232	70	54	56	0.044
	Negative	101	30	43	44	
Preoperative treatment[a]	Yes	254	68	75	71	0.478
	No	122	32	30	29	
No. of nodules	Solitary	231	61	90	86	< 0.001
	Multiple	145	39	15	14	
Size in cm	> 3.0	202	54	53	50	0.556
	≤ 3.0	174	46	52	50	
Noncancerous liver parenchyma	Cirrhosis	230	61	32	30	< 0.001
	CH/NM	146	39	73	70	
Surgical margin in mm	> 5	253	67	53	50	0.002
	≤ 5	123	33	52	50	
Portal vein invasion	Present	138	37	23	22	0.004
	Absent	238	63	82	78	
Intrahepatic metastases	Present	139	37	19	18	< 0.001
	Absent	237	63	86	82	
Surgical procedure	Partial resection	232	62	47	45	0.002
	Segmentectomy, lobectomy	144	38	58	55	

AFP: α-fetoprotein; ICGR15: indocyanine green retention rate at 15 minutes; CH: chronic hepatitis; NM: normal liver.
[a] Preoperative treatment was comprised of transarterial chemoembolization.

factors was performed, and the best discriminating cutoff values were used in the univariate and multivariate analysis. All statistical analyses were performed using SPSS software (version 11.51J; SPSS Inc., Chicago, IL). A P value < 0.05 was considered to be statistically significant.

RESULTS

The median survival was 5.2 years in the 481 patients who underwent macroscopic curative hepatectomy compared with 2.7 years in the 57 patients who did not undergo curative resection ($P < 0.0001$). One hundred five patients survived for ≥ 10 years (10-year survivors) after the initial hepatectomy, yielding an actual 10-year survival rate of 21.8%. Thirteen of these 105 10-year survivors who were lost to follow-up during the study period were excluded because their recurrence status could not be evaluated fully. The median follow-up duration of the 10-year survivors was 11.8 years (range, 10.1–15.9 yrs). Of the 481 patients who underwent macroscopic curative hepatectomy in the current study, 376 died within 10 years of the initial hepatectomy as a result of disease recurrence.

Table 1 shows the chi-square test results (univariate analysis) on the 14 clinicopathologic factors between the 10-year survivors and the patients who died within 10 years after undergoing the initial resection. Patient age (< 55 years; $P = 0.021$), ICGR15 (< 15%; $P < 0.001$), the presence of hepatitis C virus infection (P=0.044), and noncancerous liver parenchyma (normal liver or chronic hepatitis) ($P < 0.001$) were found to be significantly favorable patient-related prognostic factors. The number of tumor nodules (solitary; $P < 0.001$), portal vein invasion (absent; $P = 0.004$), and intrahepatic metastases (absent; $P < 0.001$) were found to be significant favorable tumor–related prognostic factors. With regard to therapy-related factors, although the surgical margin status (> 5 mm; P

TABLE 2
Independent Factors Predictive of 10-Year Survival by Multivariate Analysis

	B	S.E.	Wald	*P* value	Exp(B)	95% CI
ICGR15 (≥ 15)	0.9113	0.2907	9.8289	0.0017	2.4876	1.4072–4.3974
Intrahepatic metastases (absent)	0.9074	0.3242	7.8337	0.0051	2.4778	1.3125–4.6776
Portal vein invasion (absent)	0.6842	0.3234	4.4765	0.0344	1.9822	1.0517–3.7360
Noncancerous liver parenchyma (normal liver or chronic hepatitis)	1.1279	0.3068	13.5149	0.0002	3.0893	1.6932–5.6367
No. of nodules (solitary)	1.1387	0.3352	11.5367	0.0007	3.1226	1.6187–6.0239
Age in yrs (< 55)	0.8142	0.3243	6.3027	0.0121	2.2574	1.1955–4.2624

B: regression coefficient; SE: standard error; Exp(B): odds ratio; 95% CI: 95% confidence interval; ICGR15: the indocyanine green retention rate at 15 minutes.

= 0.002) and surgical procedure (segmentectomy or lobectomy; *P* = 0.002) employed were found to have significant affect on prognosis, TACE was not found to be a significant prognostic factor.

A stepwise logistic regression analysis was performed with the 14 clinicopathologic factors to determine the favorable factors for 10-year survival. Table 2 shows the results of the multivariate analysis. Six factors were found to be significant: noncancerous liver parenchyma (normal liver or chronic hepatitis), number of tumor nodules (solitary), patient age (< 55 yrs), absence of intrahepatic metastases, absence of portal vein invasion, and the value of ICGR15 (< 15%).

Forty-two of the 92 10-year survivors (46%) were free of disease whereas 50 patients (54%) had developed disease recurrence within 10 years of the initial surgery. Table 3 shows a comparison of the 12 clinicopathologic factors between the 10-year disease-free survivors and the 10-year survivors who developed disease recurrence within 10 years and underwent treatment for recurrent HCC. The hepatitis B virus antigen and hepatitis C virus antibody status among the 6 host-related factors were found to be associated significantly with the 10-year disease-free survival. The absence of intrahepatic metastases tended to be a favorable factor (*P* = 0.062) on the univariate analysis. No therapy-related factors were found to be statistically significant. On the multivariate analysis, the hepatitis C virus antibody status and the presence and/or absence of intrahepatic metastases were found to be independent predictive factors of 10-year disease-free survival, with *P* values and hazard ratios of 0.036 and 2.556, respectively, (95% confidence interval [95% CI], 1.063–6.146) and 0.031 and 4.561 (95% CI, 1.152–18.067), respectively.

Figure 1 shows the recurrence status and therapeutic modalities used for disease recurrence in the 50 10-year survivors who developed recurrence. Intrahepatic disease recurrence with fewer than 3 nodules and intrahepatic disease recurrence with more than 3 nodules were observed in 38 patients (76%) and 11 patients (22%), respectively. None of the patients was found to have a recurrent tumor exceeding 3.0 cm in greatest dimension or macroscopic portal or hepatic vein involvement. Extrahepatic recurrence (bone metastasis) was observed in one patient who underwent radiation therapy. The mean disease-free survival in the 50 patients with disease recurrence was 5.0 years (range, 0.4–9.8 yrs) after the first hepatectomy. The mean disease-free survival for all other patients who developed disease recurrence within 10 years was 1.9 years (range, 0.3–8.1 yrs). The therapeutic modalities used included repeat hepatectomy in 18 patients (36%), PEIT in 14 patients (28%), and TACE in 17 patients (34%). Seventeen patients (34%) demonstrated no evidence of disease recurrence after undergoing treatment for recurrent HCC until at least 10 years after the initial hepatectomy was performed. The history of disease recurrence in the 33 patients who developed further recurrence was as follows: 14 patients underwent TACE because of their multiple disease recurrences, 6 patients underwent repeat hepatectomy, and 9 patients underwent PEIT because they had fewer than 3 recurrent nodules. Lymph node recurrence occurred in one patient, an abdominal wall recurrence occurred in one patient, an adrenal metastases occurred in one patient, and bone metastases occurred in one patient. Six of 11 patients who had more than 3 recurrent nodules consequently underwent repeat TACE because their recurrences could not be well controlled.

The mode of intrahepatic disease recurrence according to the number of recurrent tumors (Fig. 2) and the time course of disease recurrence according to the hepatitis virus status are shown in Figure 3. The first and second peaks of disease recurrence among the 10-year survivors were observed at 5 years and 9 years, respectively, after the initial surgery. The median time to disease recurrence for the patients with fewer than 3 recurrent nodules and those with 3 or more tumor nodules was 5.4 years (range, 0.6–9.8 yrs) and 3.9 years (range, 0.4–8.9 yrs), respectively. There was no statistical differences noted with regard to the number of

TABLE 3
Comparison of Clinicopathologic Factors between the 10-Year Disease-Free Survivors and Those Patients Who Developed Disease Recurrece within 10 Years

Factors		Disease-free survival ≥10 yrs (*n* = 42)	(%)	Disease-free survival <10 yrs (*n* = 50)	(%)	*P* value
Age in yrs	≥ 55	26	62	35	70	0.416
	< 55	16	38	15	30	
Gender	Male	32	76	38	76	0.983
	Female	10	24	12	24	
ICGR15	≥ 15	30	71	30	60	0.309
	< 15	12	29	19	38	
Hepatitis B virus status	Positive	13	31	7	14	0.049
	Negative	29	69	43	86	
Hepatitis C virus status	Positive	19	45	33	66	0.045
	Negative	23	55	17	34	
No. of nodules	Solitary	34	81	35	70	0.229
	Multiple	8	19	15	30	
Size in cm	> 3.0	17	40	22	44	0.735
	≤ 3.0	25	60	28	56	
Noncancerous liver parenchyma	Cirrhosis	11	26	15	30	0.688
	CH/NM	31	74	35	70	
Surgical margin in mm	> 5	22	52	28	56	0.445
	≤ 5	20	48	22	44	
Portal vein invasion	Present	9	21	11	22	0.948
	Absent	33	79	39	78	
Intraheoatic metastases	Present	4	10	12	24	0.062
	Absent	38	90	38	76	
Surgical procedure	Partial resection	18	43	26	52	0.384
	Segmentectomy, Lobectomy	24	57	24	48	

ICGR15: the indocyanine green retention rate at 15 minutes; CH/NM: chronic hepatitis/normal liver.

recurrent tumors ($P=0.09$). The median time to disease recurrence in patients who were positive for hepatitis B virus antigen and hepatitis C virus antibody was 4.9 years (range, 0.5–9.7 yrs) and 5.6 years (range, 0.6–9.8 yrs), respectively. The recurrence occurred later after the initial hepatectomy in patients with the hepatitis C virus antibody compared with those who were positive for the hepatitis B virus antigen ($P=0.05$).

DISCUSSION

To our knowledge, hepatectomy provides the only chance for potential cure in patients with HCC. However, long-term survival remains unsatisfactory because of frequent disease recurrence.[1–5] Recently, close postoperative follow-up to detect recurrent HCC at an early stage and various management strategies for recurrent HCC (including repeat resection, local ablative therapy, or/and TACE) have contributed to prolonged survival after initial hepatectomy.[10–12] Numerous studies to date have reported cumulative 5-year survival rates of approximately 40–50%, based largely on relatively short-term follow-up,[3–5,10,11,14] and to our knowledge only a few reports of the results of long-term follow-up of more than 10 years have been reported to date. Nagasue et al.[7] reported a cumulative 10-year survival rate of 21.5% among 201 patients, and Shirabe et al.[8] reported 12 10-year survivors (11.7%) among 103 patients. Poon et al.[9] reported 10 10-year disease-free survivors among 230 patients. To our knowledge, there has been no detailed analysis of a large series of HCC patients who survived longer than 10 years after curative surgery. In the current series, 42 patients survived for longer than 10 years without disease recurrence, and 50 patients survived for longer than 10 years despite the detection of disease recurrence, after the initial hepatectomy. Seventeen of the 50 patients (34%) with disease recurrence who received treatment with 1 or more treatment modalities for recurrent HCC survived with no evidence of tumor recurrence for at least 10 years after the initial hepatectomy.

Portal vein invasion and intrahepatic metastases are well known risk factors for early disease recur-