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Original Paper

Pylorus-preserving Pancreatoduodenectomy: Preoperative Pancreatic Function and Outcome

Jiro Ohuchida MD[1], Kazuo Chijiiwa MD, FACS[1], Takao Ohtsuka MD[2]
Hiroyuki Konomi MD[2], Masao Tanaka MD, FACS[2]
[1]Department of Surgery 1, Miyazaki University School of Medicine
Miyazaki, and [2]Department of Surgery and Oncology, Graduate School of Medical Sciences
Kyushu University, Fukuoka, Japan
Corresponding Author: Kazuo Chijiiwa, MD, PhD, FACS, Department of Surgery 1
Miyazaki University School of Medicine, Miyazaki, Japan
Tel: +81 985 85 2905, Fax: +81 985 85 2808, E-mail: kazuochi@med.miyazaki-u.ac.jp

ABSTRACT
Background/Aims: To investigate the effects of preoperative pancreatic function on gastric emptying, body weight, and quality of life after pylorus-preserving pancreatoduodenectomy.
Methodology: Thirty-one patients who underwent pylorus-preserving pancreatoduodenectomy were divided into 2 groups according to preoperative pancreatic exocrine and endocrine function (normal *vs.* abnormal). Gastric emptying, body weight, and quality of life were evaluated before surgery, 1-2 months after surgery (short term), and 6-12 months after surgery (long term).
Results: Short-term body weight was significantly decreased in comparison to preoperative body weight regardless of preoperative exocrine and endocrine pancreatic function. Body weight returned to the preoperative level by 12 months after surgery in patients with normal preoperative pancreatic function but not in patients with abnormal pancreatic function. In both groups, gastric emptying was delayed at 1-2 months after surgery and then returned to the preoperative value by 12 months. Short-term quality of life did not differ from preoperative quality of life in either group, but long-term quality of life improved to beyond the preoperative level in both groups.
Conclusions: Preoperative pancreatic function appears to significantly influence long-term body weight after pylorus-preserving pancreatoduodenectomy.

KEY WORDS:
Pancreatic function; Gastric emptying; PPPD

ABBREVIATIONS:
Pylorus-Preserving Pancreatoduodenectomy (PPPD); Quality Of Life (QOL); Pancreatoduodenectomy (PD); Delayed Gastric Emptying (DGE)

INTRODUCTION

Traverso and Longmire introduced pylorus-preserving pancreatoduodenectomy (PPPD) in 1978 (1), and it is now the standard surgical procedure for treatment of periampullary lesions. It is thought that PPPD prevents long-term complications such as dumping and anorexia by preserving the reservoir function of the stomach and the duodenum-derived intestinal hormones and that, in comparison to standard pancreatoduodenectomy (PD), it improves nutritional status and quality of life (QOL) (2-5). However, complications can occur after PPPD. For example, delayed gastric emptying and impaired pancreatic function can result from the resection, and nutritional status may remain insufficient. Few studies have investigated the relation between pancreatic function and gastric emptying, nutritional status, and QOL over the long term after PPPD even though pancreatic function and gastric emptying are important indicators of postoperative nutritional status and QOL. The aim of this study was to investigate the effects of preoperative pancreatic exocrine and endocrine function on gastric emptying and recovery of body weight over the long term after PPPD.

METHODOLOGY

The present study included 31 Japanese patients who underwent PPPD in the Department of Surgery and Oncology at Kyushu University Hospital January 1994 through December 2001. The group comprised 19 men and 12 women who ranged in age from 46 to 81 years, with a mean age of 63.2 years. PPPD was performed for 19 malignant and 12 benign diseases: ampullary carcinoma, n=9; bile duct carcinoma, n=6; pancreas carcinoma, n=4; intraductal papillary adenoma of the pancreas, n=6; chronic pancreatitis, n=4; serous cystadenoma of the pancreas, n=1; and chronic cholangitis, n=1. All patients were followed up, and cancer recurrence was ruled out for more than 1 year after PPPD.

Of the 31 patients, 27 underwent gastrointestinal reconstruction by the Imanaga method (6) and 4 by the Traverso method (1). The proximal duodenum was transected 2-6cm distal to the pyloric ring. The Imanaga reconstruction procedure has been described previously (7-11): end-to-end duodenojejunostomy, end-to-side pancreatojejunostomy and hepaticojejunostomy, in that order. In Traverso reconstruction, pancreatojejunostomy is performed 5cm from the closed end of the jejunum, this is followed by hepaticojejunostomy 10cm distally and end-to-side duodenojejunostomy 30cm more distally.

Before surgery, the fecal chymotrypsin level (cutoff value: 13.2 U/g) and fasting blood sugar level (cut-

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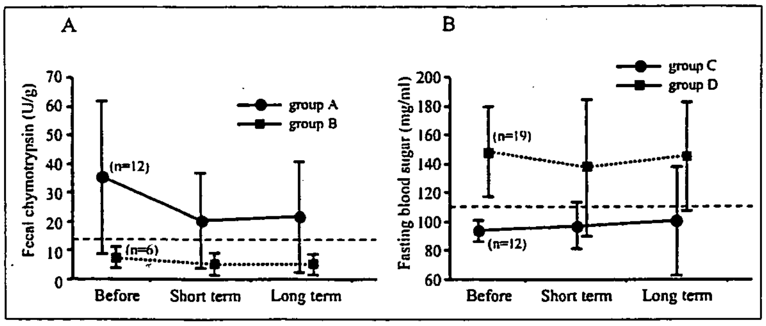

FIGURE 1 Changes in pancreatic **(A)** exocrine (fecal chymotrypsin) and **(B)** endocrine (fasting blood sugar) function.

off value: 110mg/mL) were examined in each patient for evaluation of pancreatic exocrine and endocrine function, respectively. Patients were divided into 2 groups according to preoperative pancreatic exocrine and endocrine function, and they were classified in subgroups of normal and abnormal group: group A, fecal chymotrypsin level was normal, group B, fecal chymotrypsin level was abnormal, group C, fasting blood sugar level was normal, group D, fasting blood sugar level was abnormal. Gastric emptying, body weight, and QOL were determined before surgery, 1-2 months after surgery (short term) and 6-12 months after surgery (long term). Gastric emptying was evaluated by the acetaminophen method as previously reported (7). The indices of gastric emptying were calculated from the area under the serum acetaminophen concentration curve for 90 minutes (AUC 90). Changes in each patient's body weight were calculated by referring to the preoperative level as 100%. QOL was assessed by means of a modified Kurihara questionnaire (12), which we have used previously (11,13). The questionnaire consisted of 23 items divided into 2 categories: physical (questions 1-13) and psychosocial (questions 14-23).

All values are expressed as means ± standard deviation (SD). Statistical analyses were carried out with unpaired *t*-test. A *P* value of less than 0.05 was considered significant.

RESULTS

Pancreatic Exocrine and Endocrine Function

The mean fecal chymotrypsin level in group A was decreased in the short term after surgery, but kept within normal limit in the short and long term. The level in group B with pancreatic exocrine insufficiency did not differ between time points. The mean fasting blood sugar levels in groups C and D did not differ between time points. Thus, normal or abnormal preoperative pancreatic exocrine and endocrine function did not appear to influence postoperative pancreatic function **(Figure 1A, B)**.

Influence of Preoperative Pancreatic Exocrine Function

Short-term gastric emptying was delayed in both groups (group A: before surgery, 550.8±243.9 μg·90min/mL; short term, 412.4±146.3μg· 90min/mL, and group B: before surgery, 649.8±294.6μg·90 min/mL; short term, 478.5±348.9μg· 90min/mL). Long-term gastric emptying returned to the preoperative state in both groups (group A: long term, 702.2±284.4μg·90min/mL, and group B: long term, 761.7±345.7μg·90min/mL **(Figure 2A)**. Short-term body weight significantly decreased in both groups, while long-term body weight returned to the preoperative value in group A (short term, 90.9±4.3%; long term, 95.1±5.1%) but not in group B (short term, 89.5±5.3%; long term, 90.7±7.1%) **(Figure 2B)**. Short-term QOL was decreased in group B (group A: before surgery, 70.1±16.3%; short term, 71.0±9.5%, and group B: before surgery, 71.3±15.3%; short term, 62.5±10.2%), but long-term QOL increased to greater than the preoperative level in both groups (group A: long term, 84.5±9.6%, and group B: long term, 78.4±8.2%) **(Figure 2C)**.

Influence of Preoperative Pancreatic Endocrine Function

Short-term gastric emptying was delayed in both groups (group C: before surgery, 679.1±267.0μg·90min/mL; short term, 456.1±220.1μg·90min/mL, and group D: before surgery, 596.8±262.2μg·90min/mL; short term, 410.4±150.8μg·90min/mL), and long-term gastric emptying returned to the preoperative level in both groups (group C: long term, 789.4±259.4μg·90min/mL, and group D: long term, 711.3±212.2μg·90min/mL) **(Figure 3A)**. Short-term body weight was decreased significantly in both groups. Whereas long-term body weight significantly recovered and returned to the preoperative value in group C (short term, 90.6±4.4%, long term,

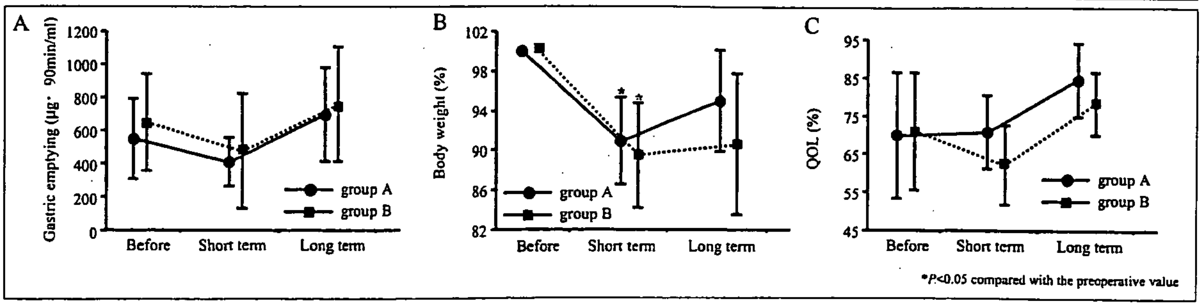

FIGURE 2 Changes in **(A)** gastric emptying (AUC 90), **(B)** body weight, and **(C)** QOL in groups A and B.

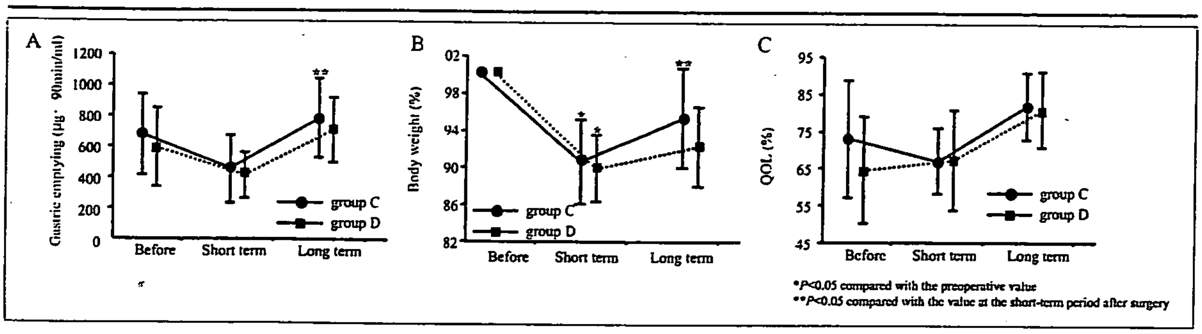

FIGURE 3 Changes in **(A)** gastric emptying (AUC 90), **(B)** body weight, and **(C)** QOL in groups C and D.

95.3±5.4%, $P<0.05$), there were no significant changes in group D (short term, 89.9±3.5%, long term, 92.2±4.2%) **(Figure 3B)**. Short-term QOL decreased in group C (before surgery, 73.0±15.8%, short term, 67.0±8.9%) and was similar in group D (before surgery, 64.5±14.4%, short term, 67.1±13.5%). However, long-term QOL increased to greater than the preoperative level without a significant difference in both groups (group C: long term, 81.9±9.0%, and group D: long term, 80.9±10.3%) **(Figure 3C)**.

DISCUSSION

Several reports have suggested that body weight is better after PPPD than after standard PD. Kozuschek *et al.* reported that 43% of patients who underwent standard PD reached preoperative body weight after 1 year, whereas 86% of patients who underwent PPPD reached their preoperative weight (2). Braasch *et al.* reported that 28 patients who underwent PPPD reached 93% pre-illness weight and 106% preoperative weight at the time of follow-up (14). Zerbi *et al.* reported that patients who underwent PPPD had reached a mean 92% of the usual pre-illness body weight at 6 months after surgery, showing significantly better recovery of body weight than that of patients after standard PD (15). Yamaguchi *et al.* reported that postoperative loss of more than 3kg body weight was evident in 62% of patients after PPPD, that the maximum body weight loss was seen about 4.2 months after PPPD, and that body weight returned to the preoperative level 4.8 months thereafter (16). In our PPPD patients, long-term body weight was greater than 90% in all groups, and these results resembled those of previous reports. Short-term body weight decreased significantly after PPPD in patients with normal preoperative pancreatic function and in patients with abnormal preoperative pancreatic function. However, long-term body weight returned to the preoperative level in patients with normal preoperative pancreatic function, but not in patients with abnormal preoperative pancreatic function. Recovery of body weight is an important determinant of nutritional status, and our results suggest that the relation between pancreatic function and body weight is also important.

Gastric emptying is also an important determinant of nutritional status. Early delayed gastric emptying (DGE) is one of the most relevant and frequent postoperative complications and has been reported to range between 20% and 50% (17-23). The cause of DGE is not yet clear, and several factors are thought to play a role in DGE. These include gastric dysmotility after PPPD attributed to disruption of the gastroduodenal neural connection (24) and gastric dysrhythmia due to postoperative complications such as anastomotic leakage, intraabdominal abscess, and bleeding (25,26). Murakami *et al.* reported that residual pancreatic fibrosis is the most important cause of DGE after PPPD without complications (27). We previously reported that gastric emptying was delayed but returned to the preoperative level by 6 months after surgery (7). We obtained similar results in the present study, and there was no significant difference in postoperative gastric emptying between patients with normal and abnormal preoperative pancreatic function. Long-term gastric emptying was restored to the preoperative level, whereas recovery of body weight was poor in patients with abnormal preoperative pancreatic function. This suggests that preoperative pancreatic function is more important determinant of postoperative nutritional status.

Short-term QOL was the same or slightly lower than preoperative QOL. However, long-term QOL was high in comparison to preoperative and short-term QOL. It is likely that the QOL score improved with the increases in food intake and nutritional status. It is also possible that patients' anxiety over their disease state was relieved after surgery, positively influencing QOL. The difference in long-term QOL between our patients with normal and abnormal preoperative pancreatic functions suggests on indirect link between preoperative pancreatic function and improvement in QOL.

In conclusion, preoperative pancreatic function influenced the recovery of body weight after PPPD, however, it did not influence the recovery of gastric emptying or QOL.

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Original Paper

Vertical Retrocolic Duodenojejunostomy Decreases Delayed Gastric Emptying after Pylorus-Preserving Pancreatoduodenectomy

Kazuo Chijiiwa MD, FACS, Jiro Ohuchida MD, Masahide Hiyoshi MD, Motoaki Nagano MD
Masahiro Kai MD, Kazuhiro Kondo MD
Department of Surgery 1, Miyazaki University School of Medicine, Miyazaki, Japan
Corresponding Author: Kazuo Chijiiwa MD, PhD, FACS, Professor and Chaiman, Department of Surgery 1
Miyazaki University School of Medicine, Kiyotake, Kihara 5200 Miyazaki, Japan
Tel: +81 985 85 2905, Fax: +81 985 85 2808, E-mail: kazuochi@med.miyazaki-u.ac.jp

KEY WORDS:
Delayed gastric emptying; Vertical duodenojejunostomy; Pylorus-preserving pancreatoduodenectomy

ABBREVIATIONS:
Delayed Gastric Emptying (DGE); Pylorus-Preserving Pancreatoduodenectomy (PPPD); Pancreatoduodenectomy (PD)

ABSTRACT

Background/Aims: With the aim of preventing delayed gastric emptying (DGE) after pylorus-preserving pancreatoduodenectomy (PPPD), the new reconstruction method namely vertical retrocolic duodenojejunostomy in which the stomach and duodenum are brought down through the left side of the transverse mesocolon in a straight line thereby allowing these organs apart from the excised and anastomosed field and food passage by gravity is presented.

Methodology: The preoperative and intraoperative factors, and short-term outcomes with special reference to DGE were compared between the two groups, PPPD (n=12) and standard pancreatoduodenectomy (PD, n=9). PD was similarly carried out except for hemigastrectomy for comparison. DGE was defined as a need for nasogastric tube decompression for 10 days or more.

Results: Preoperative and intraoperative factors were not significantly different between the two groups. DGE was absent in both groups because nasogastric tube was removed within 7 days in all patients with a mean of postoperative day 3 in both groups. The days until liquid diet in the PPPD group were similar, but those until regular diet were significantly faster compared with the PD group. Postoperative hospital stay was similar between the two groups.

Conclusions: The current reconstruction method may minimize DGE after PPPD.

INTRODUCTION

Pylorus-preserving pancreatoduodenectomy (PPPD) has taken the place of conventional pancreatoduodenectomy (PD) (with hemigastrectomy so called Whipple's procedure) as a generally accepted standard operation for both benign and malignant periampullary diseases. The biggest advantage in PPPD has been reported to improve the quality of life, nutritional state and body weight gain without any differences in operative morbidity and mortality and in postoperative survival compared with PD (1-4).

Delayed gastric emptying (DGE), however, has been reported to be the most common and frustrating complication after PPPD. Despite the lack of a certain definition for DGE, the reported incidence varies from 20% to 60% (5-12). We have recently collected 1,066 patients who had undergone PPPD in 74 Japanese institutions and found the incidence of DGE being 54.5% when defined as the need for nasogastric decompression for more than 10 days (13). Although this seems to be high, DGE results in the late start of food intake and prolonged hospital stay, hence some surgeons still prefer the standard PD (6,10). Although the several reasons for DGE have been reported, the way for its prevention has not been established enough.

We have speculated that the main reason for DGE might be ascribed to gastric dysrhythmias or atony secondary to some clinical or even subclinical inflammatory change in the excised- and anastomosed-region and/or to a torsion or angulation of the reconstructed alimentary tract rather than the pylorus preservation itself. The possible reconstruction methods to solve these factors are 1) the placement of the stomach and duodenum apart from the excised and anastomosed field and 2) the vertical and straight reconstruction of the stomach and duodenum. To prove this hypothesis, we have applied the reconstruction method, namely vertical retrocolic duodenojejunostomia that the stomach and remnant of the duodenum are brought down through the left side of the transverse mesocolon apart from the anastomotic region in a straight and vertical manner. The antrum is fixed to the transversemesocolon and duodenum is anastomosed to the jejunum below the mesocolon. We herein report that the method is useful to prevent DGE after PPPD.

METHODOLOGY

Operative Technique

The area resected during the PPPD included the

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gallbladder, common hepatic duct, head of the pancreas, duodenum, and approximately 10cm of the proximal jejunum. A few archades of the right gastric artery and right gastroepiploic artery to the stomach were divided along the wall of antrum (approximately 2-3cm from the pylorus ring) to dissect the peripyloric lymph nodes. The duodenum was free from the surrounding tissue and transected approximately 4-5cm distal to the pylorus ring. The lymph nodes in the hepatoduodenal ligament and along the common hepatic artery were dissected. The right gastric artery was divided at its origin in all. The left gastric artery and vein were carefully preserved. The lesser omentum close to the liver was dissected to preserve neurovascular supply to the stomach. As a result, vagal nerve except the hepatic and pyloric branches was preserved. These procedures allowed the stomach and the duodenum to be mobilized to the left and brought down through the left side of the transverse mesocolon in a straight and vertical manner.

As a first step in the gastrointestinal reconstruction, the proximal jejunum was brought through the right side of the transverse mesocolon retrocolically. An end-to-side pancreatojejunostomy was carried out. The pancreatic duct was anastomosed to the whole layer of the small opening in the jejunum to approximate the duct to the jejunal mucosa An end-to-side hepaticojejunostomy was then performed 5 to 10cm distally followed by an end-to-side duodenojejunostomy 40cm more distally. Left side of the transverse mesocolon (left side of the middle colic vessels) was opened and the duodenum was brought down together with the stomach in a straight and vertical manner. A retrocolic end-to-side duodenojejunostomy was done at the caudal side of the transverse mesocolon and side-to-side jejunojejunostomy was added at 5 to 10cm apart from the duodenojejunostomy in the Braun manner. Finally, the jejunum brought up retrocolically was fixed to the right side of the mesocolon, the opening of the old Treitz was closed and the antrum approximately 4 to 5cm proximal to the pylorus was fixed to the left side of mesocolon with a few sutures

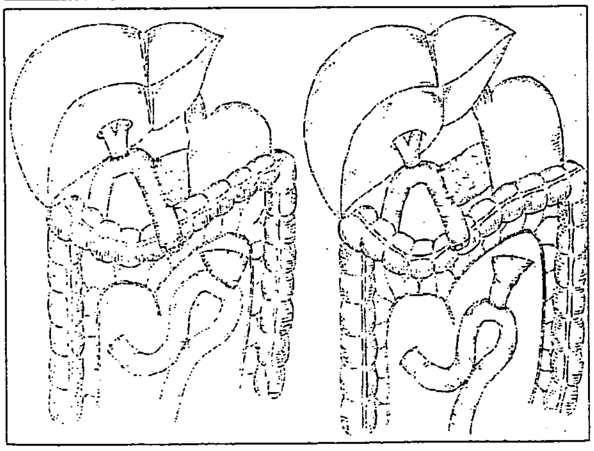

FIGURE 1 Reconstruction method after PD and PPPD. Vertical retroclic duodenojejunostomy and gastrojejunostomy were employed.

TABLE 1 Preoperative and Operative Factors in the PD and PPPD Groups

	PD (n=9)	PPPD (n=12)	*p* value
Age (years)	66.8±11.6	66.3±10.9	0.916
Male/Female	7/2	8/4	0.577
Final diagnosis			
Bile duct cancer	3	3	
Pancreatic cancer	2	3	
Ampullary cancer	1	3	
Duodenal cancer	1	0	
IPMN	2	1	
Benign	0	2	
Hemoglobin (g/dL)	12.6±1.8	12.2±1.5	0.549
Total protein (g/dL)	6.6±0.5	6.6±0.4	0.772
Albumin (g/dL)	3.5±0.4	3.8±0.3	0.508
Total cholesterol (mg/dL)	167.1±42.6	184.0±36.8	0.343
Diabetes mellitus (+/-)	3/6	3/9	0.676
BT-PABA test (%)	63.0±18.7	70.0±16.9	0.417
Operation time (minutes)	599±83	578±109	0.627
Intraoperative blood loss (mL)	1540±440	1664±908	0.711
Residual duodenum (cm)	-	4.2±0.6	
Division of right gastric artery	9	12	
Hepatoduodenal node dissection	9	12	
Gastrostomy tube decompression	0	0	

IPMN: Intraductal papillary mucinous neoplasm; Benign: Ampullary adenoma and serous cystadenoma of the pancreas; BT-PABA: N-benzoyl-L-tyrosyl-p-aminobenzoic acid.

TABLE 2 Short-term Outcomes

	PD (n=9)	PPPD (n=12)	*p* value
Delayed gastric emptying	0	0	
Nasogastric tube (days)	3.4±1.5	2.8±1.7	0.412
Water intake (days)	13.2±5.4	9.5±4.7	0.108
Liquid meal (days)	17.8±9.7	12.8±5.5	0.100
Regular diet (days)	26.8±12.6	17.3±5.6	0.030
Postoperative morbidities			
P-J leakage	1	0	
Wound infection	1	1	
Amylase level from the peripancreatic drain (IU/L)	434.8±308.6	760.4±760.7	0.243
Postoperative hospitalization (days)	46.9±13.5	41.7±9.5	0.341
Mortality	0	0	

(**Figure 1**). Pancreatoduodenectomy was carried out in an essentially similar manner except for distal hemigastrectomy for comparison.

After employing this new reconstruction method in 2002, 21 patients were enrolled in this study during a 2-year period based on the full information explaining the possible advantage and disadvantage of PD and PPPD. Another 15 patients who underwent subtotal stomach-preserving pancreatoduodenectomy, or the surgery combined with hepatectomy were excluded from the present study. All surgery was performed by the first author (K.C). All patients received prophylactic antibiotics, but none received prokinetic drugs such as erythromycin. Delayed gastric emptying (DGE) was defined as a need for nasogastric tube decompression for 10 days or more as recently described by Sugiyama *et al.* (14). Postoperative days of a nasogastric decompression and those until liquid diet and regular diet were recorded. The amylase levels from the peri-pancreatojejunostomy drain were also determined.

Preoperative and operative factors, and postoperative complications with a special reference to DGE were compared between the standard PD and PPPD group. All values are expressed as means ± SD and statistical difference between the groups were examined by the unpaired Student's *t*-test and Welch's test.

RESULTS

Preoperative and operative factors in the PPPD and PD groups are shown in **Table 1**. Age, gender, histopathological final diagnosis, and serum chemistry are similarly distributed between the two groups. The presence of diabetes mellitus and pancreatic exocrine function assessed by the N-benzoyl-L-tyrosyl-p-aminobenzoic acid test were comparable between the PD and PPPD groups. Operation time and intraoperative blood loss did not differ significantly. Hepatoduodenal lymph node dissection and right gastric artery division at its origin were carried out in all patients. None received gastrostomy tube for gastric decompression. The mean length of the residual duodenum in the PPPD group was 4.2cm.

Postoperative short-term results are shown in **Table 2**. The nasogastric tube was removed with a mean of 3 days postoperatively in each group. None needed a repeated nasogastric decompression. The days until of water intake and liquid diet were not significantly different. Postoperative days to have a regular diet were longer in the PD group because one patient in this group had leakage of pancreatojejunostomy although this complication could be conservatively managed. There was no mortality and the period of postoperative hospital stay was not different between the two groups. The amylase level in the discharged fluid from the peripancreatic drain on days 2 to 4 after surgery are shown in **Table 2**. The mean amylase level in the PD and PPPD group was 435 and 760 IU/L, respectively without a statistical significance. In both groups, the amylase level ranged from 20 to 2662 IU/L.

None of the PD group and PPPD group showed DGE defined as a need for gastric tube decompression for more than 10 days **(Figure 2)**.

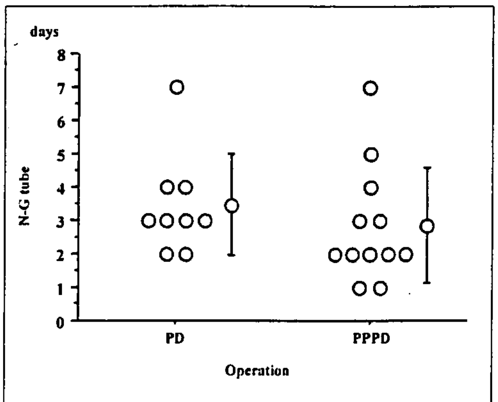

FIGURE 2
Postoperative days until the removal of nasogastric tube in the PD and PPPD groups.

DISCUSSION

The present study demonstrated that our new reconstruction method, namely vertical retrocolic duodenojejunostomy, eliminated DGE after PPPD. This was likely due to the reduced effect of subclinical inflammation on gastroduodenal motility by placing the stomach and duodenum apart from the anastomotic regions and to the easy passage of gastric contents.

PPPD is now widely accepted as a standard treatment for benign and malignant periampullary diseases. Its advantages over conventional PD have been reported to be a better quality of life, nutritional state and body weight gain with similar operative morbidity and postoperative survival (1-4). We have also reported similar results (15,16).

DGE has been considered as the specific complication after PPPD because it has been specifically attributed to pylorus-sparing resection of the pancreatic head (5-7,10). Although the definition of DGE has not been used consistently, it is generally used by the need for gastric decompression tube on day 7-14 after PPPD. Using this definition, the reported incidence of DGE has ranged from 20 to 60% (5-12). We have previously employed the standard reconstruction where all these anastomoses are done on the right side above the transverse mesocolon described as a conventional reconstruction method (14), and found the DGE in 29% of the patients after PPPD (16). Moreover, oral liquid meal was started on the mean of 28 days after PPPD (15). These reported operations at Kyushu University hospital and the current new reconstruction procedure have been mainly performed by the same surgeon (K.C) after moving to Miyazaki University. In the present study, none needed nasogastric decompression for more than 10 days and liquid meal could be started much faster after PPPD.

Several reasons for DGE have been proposed, (a) gastric atony or gastroparesis after resection of the duodenal pacemaker and disruption of the gastroduodenal neural connections (11,17), (b) ischemic injury and intraoperative trauma of the antrum and pylorus (7,18), (c) gastric atony in response to a reduced circulating levels of motilin (12). We also reported that leucin 13-motilin (19), cisapride (20), and erythromycin (21) improved DGE after PPPD. These causes of DGE, however, could not be eliminated because the duodenum is excised and the branches of the right gastric and gastroepiploic arteries to the antrum are dissected for peri-pyloric lymph nodes dissection. Our present results suggest that these factors are not responsible for DGE after PPPD.

The other possible reasons for DGE that could be managed surgically are torsion or angulation of the reconstructed alimentary tract (7) and gastric dysrhythmias or gastroparesis secondary to intraabdominal complication such as an anastomotic leak, abscess or local inflammation (22,23). Recent studies have demonstrated that DGE does not occur as a result of pylorus preservation but occurs as a consequence of postoperative complications (24-26). Our results support these observations. Moreover, new reconstruction method namely antecolic duodenojejunostomy, has been proposed to prevent DGE after PPPD just recently (14,25,26). Their reported incidences of DGE are 8% and 24% as defined the need for nasogastric decompression for 10 days or more (14,25). Our current method is vertical retrocolic duodenojejunostomy to place the stomach and duodenum in a straight line and apart from the possible regions where clinical and/or subclinical inflammation take place, resulting in the reduced effect of intraabdominal complication on gastrointestinal motility. The mean amylase level in the discharged fluid from the peripancreatic drain on days 2, 3 and 4 postoperatively was 435 and 760 IU/L in the PD and PPPD groups, respectively. The results support our hypothesis that subclinical inflammation takes place even in the absence of clinical complications. In addition to reduce the effect of subclinical inflammation on gastrointestinal motility, our vertical and retrocolic reconstruction method may help the passage of gastric contents more easily than the antecolic duodenojejunostomy. However, days of gastric suction, until liquid diet and regular diet in the present study were similar to those of the antecolic duodenojejunostomy (4, 8, and 17 days, respectively) (14). Therefore, the further prospective comparative study using more number of the patients is necessary to draw the final conclusion.

In conclusion, we have applied the new reconstruction method namely vertical retrocolic duodenojejunostomy and found that the method is useful to prevent DGE after PPPD.

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A Curative Resection Improves the Postoperative Survival Rate Even in Patients with Advanced Gallbladder Carcinoma

Masahiro Kai · Kazuo Chijiiwa · Jiro Ohuchida · Motoaki Nagano · Masahide Hiyoshi · Kazuhiro Kondo

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Abstract The aim of this study was to evaluate the results of our series of 90 operations for gallbladder carcinoma according to the Japanese Society of Biliary Surgery (JSBS) classification system and to clarify the appropriate surgical strategy for advanced gallbladder carcinoma based on the depth of primary tumor invasion and lymph node metastasis. Generally, only a surgical resection can achieve a prognostic improvement of the advanced gallbladder carcinoma. The survival of patients with this neoplasm depends strictly on the depth of histological primary tumor invasion and lymph node metastasis. A retrospective analysis was conducted on 90 patients from 1990 to 2004 who underwent a surgical resection of gallbladder carcinoma. The factors influencing survival were examined. Thirty-nine patients with palliative treatment (not resected cases), which was diagnosed as T3 or T4 by preoperative imagings, were also included in this study. The significance of the variables for survival was examined by the Kaplan–Meier method and the log-rank test followed by multivariate analyses using Cox's proportional hazard model. Portal invasion, lymph node metastasis, the surgical margin (+ vs. −) and the final curability (fCurA, B vs. C) were all found to be independent prognostic factors in the multivariate analysis. In pT2 gallbladder carcinoma, a better survival was achieved in an aggressive surgical approach, in order of a S4a+S5 hepatic resection, an extended cholecystectomy and a cholecystectomy. In pT3 and pT4, although radical extended surgery did not provide the opportunity for good survival even after lobectomy of the liver, the survival of patients with curative surgery was statistically better than in those without curative surgery. In addition, the nodal involvement of pN1 to pN2 was better than that with pN3. A S4a+S5 hepatectomy, therefore, appears to be adequate for the treatment of pT2 gallbladder carcinoma. Even in patients with pT3 and pT4 gallbladder carcinoma, long-term survival can be expected by an operation with a tumor-free surgical margin. The role of radical surgery, however, is considered to be limited in patients with pN3 lymph node metastasis.

Keywords Gallbladder carcinoma · Surgical resection · S4a+S5 hepatectomy · Prognostic factors

Gallbladder carcinomas, the most frequent form of bile duct cancer, is usually detected at an advanced stage because of the absence of specific symptoms and signs, despite recent progress in diagnostic modalities.[1] Recent advances in ultrasonography, computed tomography, magnetic resonance cholangiography, direct cholangiography, and endoscopic ultrasonography, however, have contributed to the increased detection of gallbladder carcinoma at a resectable stage.[1–3]

The prognosis in patients with early gallbladder carcinoma (tumors restricted to the mucosa or muscle layer) is associated with a 5-year survival rate ranging from 90% to 100%.[4–6] These lesions are most frequently diagnosed incidentally after a cholecystectomy for symptomatic diseases such as gallstones.[7] For the early gallbladder carcinoma including undiagnosed cases incidentally detected by macroscopic and microscopic examinations after open or laparoscopic cholecystectomy, most surgeons

M. Kai · K. Chijiiwa (✉) · J. Ohuchida · M. Nagano · M. Hiyoshi · K. Kondo
Department of Surgical Oncology and Regulation of Organ Function, Miyazaki University School of Medicine, 5200 Kihara, Kiyotake, Miyazaki 889-1692, Japan
e-mail: kazuochi@med.miyazaki-u.ac.jp

agree that such patients do not require any surgery other than a simple cholecystectomy because no lymph node metastasis is evident.[4,8–11]

On the other hand, advanced gallbladder carcinoma is characterized by a very poor survival rate, and its surgical treatment ramains a matter of controversy. Recent papers from Japan have reported that radical surgery for advanced gallbladder carcinoma improve survival[12–14]; however, most Western authors have so far failed to establish any benefit in patients with advanced gallbladder carcinoma.[15,16]

It is well-known that a surgical resection provides the only hope for a long-term survival of patients with gallbladder carcinoma. An improvement in the outcome after a resection for the gallbladder carcinoma may thus depend on the selection of appropriate surgical strategies for advanced lesions. The depth of primary tumor invasion (pT) and lymph node metastasis (pN) have all been reported to be significant prognostic factors.[3,12,17–21]

Because pT can now be diagnosed either pre- or intraoperatively,[5,21,22] the choice of surgical procedure should thus be evaluated based on pT especially for advanced carcinoma greater than pT2. The aim of this study was to evaluate the results of curative resections for the advanced gallbladder carcinoma and to clarify the optimal surgical strategies, especially for the advanced gallbladder carcinoma.

Patients and Methods

Ninety patients with gallbladder carcinoma who had undergone a surgical resection from January 1990 to December 2004 at our University Hospital were retrospectively analyzed. They included 41 men and 49 women with a mean age of 65 years old (range 36–89 years). Thirty-nine patients with palliative treatment (not resected cases), diagnosed as T3 or T4 by preoperative imagings, were also included in this study. pT, pN, and the final stage (fStage) was examined based on the Japanese Society of Biliary Surgery (JSBS) classification system.[23]

The depth of primary tumor invasion (pT) was classified into the following four groups: pT1, tumors restricted to the mucosa or muscle layer, a lack of direct invasion of the liver and hepatoduodenal ligament, and also no invasion of the portal veins and hepatic arteries; pT2, tumors invading the perimuscular connective tissue, no extension beyond the serosa or into the liver parenchyma and no invasion of the hepatoduodenal ligament, portal veins, and hepatic arteries; pT3, tumors perforating the serosa (visceral peritoneum) and/or directly invades liver, extension 5 mm in depth or less into the liver, and/or invading the right margin of the hepatoduodenal ligament, but not the left margin, without vascular (portal vein and hepatic artery) invasion; pT4, tumors extending more than 5 mm into the liver parenchyma and/or invades the left margin of the hepatoduodenal ligament and/or invading the portal veins or hepatic arteries. Lymph node metastasis (pN) was classified as follows: pN0, no regional lymph node metastasis; pN1, metastasis in cystic duct and/or pericholedochal node; pN2, metastasis in the hepatoduodenal ligament except pN1 and/or posterosuperior pancreas head and/or along the common hepatic artery; pN3, metastasis in the peripancreatic (head except posterosuperior pancreatic), celiac, superior mesenteric, and/or paraaortic lymph node metastasis. fStage and

Table 1 Classification Systems for the Staging and Curability by the JSBS

Final Stage (fStage)	H0, P0, M(−)						H1, 2, 3, P1, 2, 3, M(+)	
	pN_0	pN_1	pN_2	pN_3				
pT_1	I	II	III	IVa				
pT_2	II	III	III	IVa				
pT_3	III	III	IVa	IVb			IVb	
pT_4	IVa	IVa	IVb	IVb				
Final curability (fCur)	H	P	pN-D	pBM	pHM	pEM	M	Residual tumor
Final curability A (fCurA)	H0	P0	pN<D	pBM0	pHM0	pEM0	M(−)	(−)
Final curability B (fCurB)	H0	P0	pN=D	pBM1	pHM1	pEM1	M(−)	(−)
Final curability C (fCurC)	H1, 2, 3	P1, 2, 3	pN>D	pBM2	pHM2	pEM2	M(+)	(+)

H0 = no evidence of liver metastasis; H1 = metastasis limited to one lobe; H2 = a few metastases to both lobes; H3 = numerous metastases to both lobes; P0 = no evidence of peritoneal metastasis; P1 = metastasis to the peritoneum adjacent to extrahepatic bile ducts; P2 = a few metastases to the distant peritoneum; P3 = numerous metastases to the distant peritoneum; M = distant metastasis other than peritoneal and/or liver metastases; pN = histological lymph node metastasis; D = lymph node dissection; pBM = distal (cystic or bile duct) cut end; pHM = proximal (hepatic) cut end; pEM = dissected periductal structure; pBM0, pHM0, pEM0 = cancer-free margin of more than 5 mm in width; pBM1, pHM1, pEM1 = cancer-free margin of 5 mm or less in width; pBM2, pHM2, pEM2 = definite invasion of each surgical margin.

Table 2 Significant Prognostic Factors for the Patients with Gallbladder Carcinoma Based on Univariate and Multivariate Analyses*

Variables	Odds Ratio	95% Confidence Interval	*p* Value
Univariate analysis			
Tumor factor			
pT(1, 2 vs 3, 4)	4.808	2.488–9.346	0.0001
Serosal invasion (− vs +)	3.935	2.124–7.192	0.0001
pHinf (− vs +)	3.234	1.652–6.330	0.0006
pBinf(− vs +)	4.554	2.434–8.521	0.0001
pPV (− vs +)	12.14	3.230–45.63	0.0002
H (− vs +)	7.559	2.808–20.35	0.0001
Lymph node metastasis (− vs +)	5.458	2.769–10.76	0.0001
Operative factor			
Bile duct resecton except pT1(− vs +)	1.939	0.973–3.863	0.0598
Lymph node dissection except pT1 (D1 vs D2)	2.049	0.894–4.695	0.0902
Surgical margin (− vs +)	4.046	2.128–7.692	0.0001
Final curability (AB vs C)	5.650	2.994–10.64	0.0001
Multivariate analysis			
pPV(− vs +)	10.61	1.753–64.19	0.0101
Lymph node metastasis (− vs +)	3.247	1.504–7.010	0.0027
Surgical margin (− vs +)	12.98	1.030–166.7	0.0474
Final curability (AB vs C)	8.929	1.314–62.50	0.0252

*Cox's proportional hazard model; pT = depth of primary tumor invasion; pHinf = direct invasion of the liver; pBinf = invasion of the hepatoduodenal ligament; pPV = invasion of the portal veins; H = liver metastasis; D1 = complete dissection of group 1 lymph nodes; D2 = complete dissection of group 1 and 2 lymph nodes; Final curability A, B, C = refer to Table 1.

final curability (fCur) were classified according to the final histopathological diagnosis. A curative resection was defined as a complete removal of the cancer cells with negative histological margins without the presence of any residual tumor. The classification of fStage and fCur according to the JSBS system is shown in Table 1.

The significance of the variables for survival was examined by the Kaplan–Meier method and the log-rank test followed by multivariate analyses using the Cox's proportional hazard model. A probability value of less than 0.05 was considered to be significant.

Results

Univariate and Multivariate Analyses of the Prognostic Factors

Significant prognostic factors in the univariate analysis of the tumor factors were primary tumor invasion (pT), serosal invasion, direct invasion of the liver, invasion of the hepatoduodenal ligament, portal vein invasion, liver metastasis, and lymph node metastasis. Regarding surgical factors, the surgical margin (negative vs. positive) and final

Table 3 Histopathological Findings of Gallbladder Carcinoma Depending on the Depth of Primary Tumor Invasion (pT)

	pT1	pT2	pT3	pT4
Number of patients	17	34	9	30
Lymphatic invasion (ly) (%)	0	26/32(81)	6/8(75)	24/25(96)
Venous invasion (v) (%)	0	17/32(53)	8/8(100)	20/25(80)
Perineural invasion (pN) (%)	0	9/28(32)	4/8(50)	20/24(83)
Presence of lymph node metastasis (%)	0	16/34(47)	5/8(62)	20/29(69)
pN1	0	8/34(24)	1/8(13)	5/29(17)
pN2	0	7/34(21)	2/8(25)	10/29(34)
pN3	0	1/34(3)	2/8(25)	5/29(17)
Liver metastasis (H) (%)	0	1/34(3)	1/9(11)	5/30(17)
Peritoneal dissemination (P) (%)	0	0	0	2/30(7)
fStage I/II/III/IVa/IVb	17/0/0/0/0	0/17/15/1/1	0/0/4/2/3	0/0/0/12/18
Positive of surgical margin (%)	0	1/34(3)	3/9(33)	14/30(47)
Final curability C(fCurC) (%)	0	2/34(6)	4/9(44)	19/30(63)

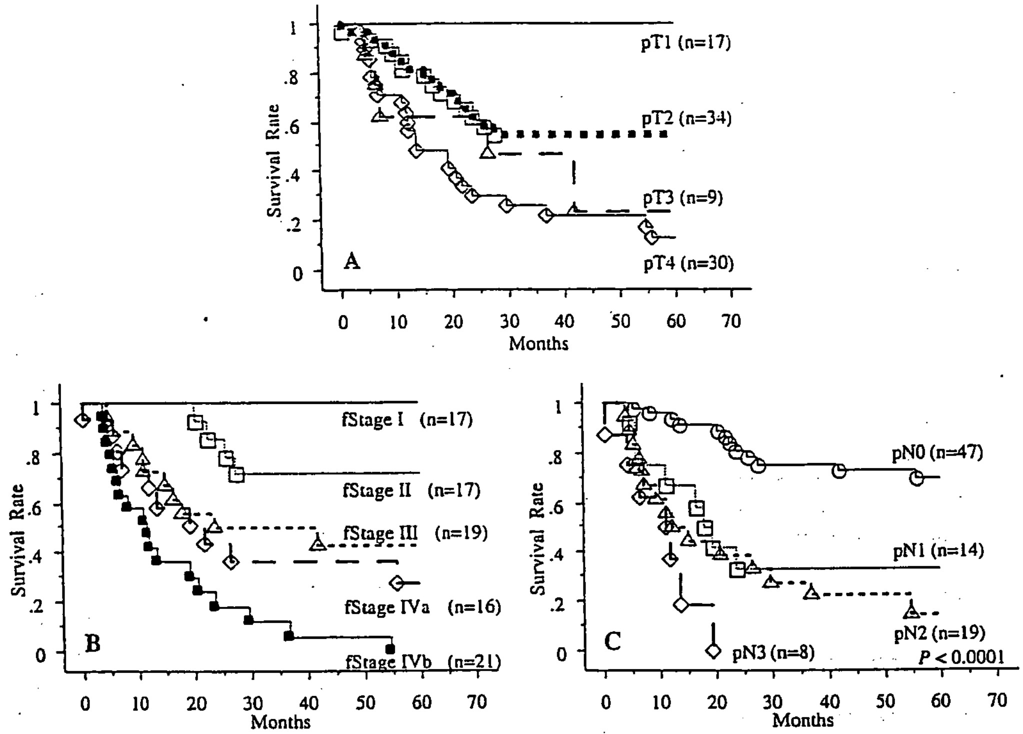

Figure 1 (A) The postoperative survival rate depending on the primary tumor invasion (pT) in patients with gallbladder carcinoma. (B) The postoperative survival rate depending on the final stage (fStage) in patients with gallbladder carcinoma. The classification of the final stage is shown in Table 1. (C) The postoperative survival rate depending on the extent of lymph node metastasis in patients with gallbladder carcinoma ($p<0.0001$, log-rank test).

curability (fCurA, B vs. fCurC) were significant prognostic factors by the univariate analysis. Bile duct resection and the degree of lymph node dissection (D1 vs. D2), except pT1 gallbladder carcinomas, had no significant effect on the postoperative survival. The absence of portal invasion (odds ratio [OR] 10.61, p=0.0101), the absence of lymph node metastasis (OR 3.247, p=0.0027), surgical margin (− vs. +, OR 12.98, p=0.0474), final curability (fCurA, B vs. C, OR 8.929, p=0.0252) were all independent prognostic factors based on a multivariate analysis (Table 2).

The Histopathological Findings of Gallbladder Carcinoma Depending on Primary Tumor Invasion (pT)

The number of patients were: pT1, 17; pT2, 34; pT3, 9; pT4, 30. Early gallbladder carcinoma (pT1) was 17 cases (19%) and advanced disease (pT2 to pT4) was 73 cases (81%).

The incidences of lymphatic (ly), venous (v), perineural (pn) invasions, lymph node metastasis, liver metastasis, and peritoneal dissemination, and also the distribution of the final stage, positive rate of surgical margin, and final curability depending on the pT classification are shown in Table 3. All of these factors were absent in pT1 gallbladder carcinoma. In the pT2 gallbladder carcinoma, the rates of ly, v, and pn were 81%, 53%, and 32%, respectively. In the pT3 and pT4, these rates were higher than those of pT2; the rates of ly, v, and pn were 75%, 100%, and 50%, respectively, in pT3 and 96%, 80%, and 83%, respectively, in pT4. The rates of lymph node metastasis were 47% in pT2, 62% in pT3, and 69% in pT4. Even in pT2, pN2 lymph node metastasis was seen in 21% of cases. In pT3 and pT4, the rates of pN2 and pN3 lymph node metastases were both 25% in pT3, and 34% and 17%, respectively, in pT4. The rate of a noncurative resection (fCurC) was 6% in pT2, 44% in pT3, and 63% in pT4.

From lymph node metastasis, 47 patients were classified as pN0, 14 as pN1, 19 as pN2, and 8 as pN3. The number of fStage I, II, III, IVa, and IVb patients was 17, 17, 19, 15 and 22, respectively.

The 5-year survival rates of the gallbladder carcinoma in patients with pT1, pT2, pT3, and pT4 were 100%, 58%,

Table 4 Surgical Procedures According to the pT Classification in the Patients with Gallbladder Carcinoma

Surgical Procedure	Cx	Ext. Cx	S4a+S5	Hx
pT1	11	4	2	–
pT2	9	21	4	–
pT3	3	6	–	–
pT4	3	7	16	4

Cx; Cholecystectomy, Ext. Cx; Extended Cholecystectomy, S4a+S5; anatomic resection of liver segment 5 and of the lower part of segment 4 together with the gallbladder, Hx; Hepatic lobectomy

Table 5 Bile Duct Resection in Patients with Gallbladder Carcinoma

Bile Duct Resection	BDR+(with PD)	BDR-
pT1	6 (1)	11
pT2	17 (2)	17
pT3	5 (1)	4
pT4	25 (3)	5

BDR = Bile duct resection, PD = pancreaticoduodenectomy

23%, and 12%, respectively (Fig. 1A). Those with pN0, pN1, pN2, and pN3 were 70%, 32%, 14%, and 0%, respectively (Fig. 1B), and with fStage I, II, III, IVa, and IVb were 100%, 77%, 42%, 28%, and 0%, respectively (Fig. 1C).

The Role of Surgery for Advanced Gallbladder Carcinoma

Because all 17 patients with pT1, irrespective of the surgical procedure, were alive without recurrence, the role of surgery was thus examined in the patients with pT2, pT3, and pT4 gallbladder carcinoma. The surgical procedures according to the pT classification are shown in Tables 4 and 5.

Of the 34 patients with pT2, a cholecystectomy was applied to nine, a resection of the gallbladder liver bed (extended cholecystectomy) to 21, a resection of the segments 4a and 5 of the liver to four. The postoperative 5-year survival rates after each procedure in the patients with pT2 gallbladder carcinoma are shown in Fig. 2A. A better survival was achieved in order of a S4a+S5 hepatic resection, an extended cholecystectomy, and a cholecystectomy. A cholecystectomy showed a significantly shorter survival than an extended cholecystectomy and a S4a+S5 hepatic resection (p=0.0481). According to the degree of lymph node dissection in pT2 gallbladder carcinoma except for one patient with pN3 lymph node metastasis, the patients with D1 (dissection of N1 lymph nodes) or more lymph node dissections statistically showed a longer survival than the patients with no dissection of the regional lymph nodes, but there was no statistically significant difference between a D1 and a D2 (dissection of N1 and N2 lymph nodes, respectively; Fig. 2B). A bile duct resection in pT2 gallbladder carcinoma had no significant effect on the postoperative survival (p=0.6694).

Of the 39 patients with pT3 or pT4 gallbladder carcinomas, a cholecystectomy was performed in six patients, an extended cholecystectomy in 13, a resection of the segments S4a and S5 of the liver in 16, and a hepatic lobectomy in four. In spite of the retrospective nature and the heterogenicity of the surgical approaches employed, the postoperative survival of the patients with pT3 or pT4 carcinoma who underwent curative surgery (fCurA+B) was significantly better than that in those undergoing fCurC (Fig. 3A). In addition, even if the fCurC was applied to pT3 or pT4 gallbladder carcinomas, its survival rate was significantly better than that in the nonresected patients (diagnosed as T3 and T4 by preoperative imaging; Fig. 3A). The clinicopathological features of pT3 and pT4 gallbladder carcinoma according to the cases of fCurA+B, fCurC, and not resected tumors are shown in Table 6. The backgrounds in these three groups were different. The incidences of peritoneal dissemination, distant metastasis, and pT4 were significantly higher in the nonresected group than those in the fCurC group. In pT3 and pT4, the survival of patients with nodal involvement of pN1 to pN2 was better than that in those with pN3 (Fig. 3B). A surgical resection provided no survival benefit for the patients with pN3 lymph node metastasis. The survival of the patients with pN3 lymph node metastasis was not better than that of the nonresected patients.

Discussion

The depth of primary tumor invasion (pT) and lymph node metastasis (pN) are critical prognostic factors in patients with gallbladder carcinoma.[3,12,17–21] To select an appropriate procedure either before or during an operation,

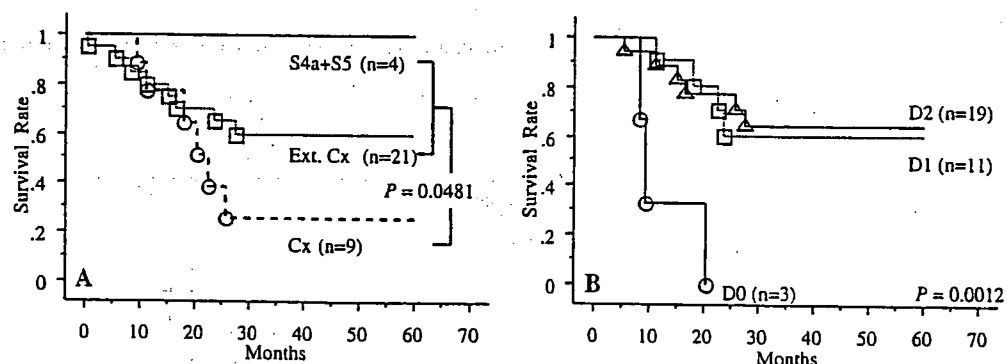

Figure 2 (A) The postoperative survival rate depending on the surgical procedure in patients with pT2 gallbladder carcinoma. S4a+S5; S4a+S5 hepatic resection (anatomic resection of the segment 5 and of the lower part of segment 4 of the liver together with the gallbladder, Ext. Cx; an extended cholecystectomy (resection of the gallbladder together with the gallbladder bed of the liver 2 cm or more in depth), Cx; cholecystectomy. A cholecystectomy was a significantly shorter survival than either an extended cholecystectomy or a S4a+S5 hepatic resection (p=0.0481, log-rank test). (B) The postoperative survival rate depending on the extent of lymph node dissection in patients with pT2 gallbladder carcinoma except for one patient with pN3 lymph node metastasis (p=0.0012, log-rank test). D0; No dissection of the regional lymph nodes, D1; a complete dissection of group 1 lymph node, D2; complete dissection of group 1 and 2 lymph nodes.

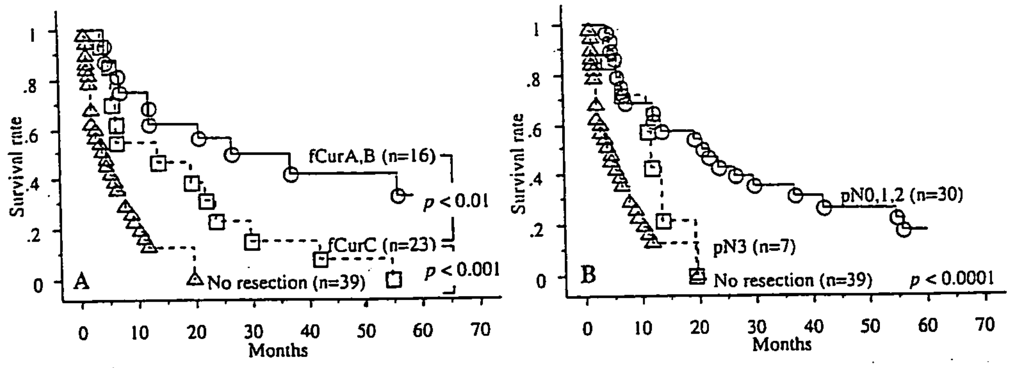

Figure 3 (A) The postoperative survival rate depending on the final curability in patients with pT3 and pT4 gallbladder carcinoma ($p<0.0001$, log-rank test). The classification of final curability (fCurA, B and C) is shown in Table 1. (B) The postoperative survival rate depending on the extent of lymph node metastasis in patients with pT3 and pT4 gallbladder carcinoma ($p<0.0001$, log-rank test).

such factors as the depth of primary tumor invasion (pT) and lymph node metastasis (pN) are extremely useful variables, because the primary tumor with or without the gross invasion of adjacent structures, some sites of metastasis and lymph node metastasis can be recognized by preoperative imaging techniques, endoscopic ultrasonography, and computed tomography, and operative ultrasonography.[24] The optimal surgical procedure according to the depth of primary tumor invasion, especially regarding the extent of a hepatic resection, bile duct resection, and radical lymph node dissection still remains controversial.[14,18,25–27]

A surgical resection is effective for tumors limited to the gallbladder wall, which are defined as pT1, whereas the surgical treatment for advanced lesions, especially pT3 or pT4, remains unsatisfactory. An aggressive approach is thus required to resect advanced carcinomas. Extensive surgery has been reported to result in a long-term survival in patients with advanced gallbladder carcinoma.[12–14,25] On the other hand, Donohue et al.[28] reported the patient outcome to be not demonstrably affected by aggressive therapy for the advanced gallbladder carcinoma, and a multicenter study has reported no long-term survivors among the patients with node-positive disease.[27] Cubertafond et al.[29] reported that no patients with T3 and T4 (based on the staging criteria of the American Joint Committee on Cancer) gallbladder carcinoma survived more than 36 months after an extended cholecystectomy.

We and some authors have thus proposed surgical management for pT2 gallbladder carcinoma.[3,12,17–21,25] In patients with pT2 gallbladder carcinoma treated with a simple cholecystectomy alone, postoperative survival remains pessimistic.[19,30,31] We have proposed an extended cholecystectomy or more aggressive surgery, a S4a+S5 hepatic resection or extended right lobectomy of the liver, for patients with pT2 gallbladder carcinoma.[3,17,19–21] A simple cholecystectomy is not adequate for pT2 gallbladder carcinoma, because the rate of lymph node metastasis is 47%, with a 21% rate of pN2-node-positive in our surgical series; moreover, some studies heve reported that even in the absence of hepatic invasion, metastases to the liver (mainly the segment 4a and 5) are possible.[32] In our study, the survival of patients with a simple cholecystectomy showed a poorer prognosis than that of an extended cholecystectomy and a S4a+S5 hepatic resection, which confirmed the previous result.[21] In the present study, the

Table 6 Clinicopathological Features of pT3 and pT4 Gallbladder Carcinoma Include Not Resected Cases Diagnosed as T3 or T4 by Several Types of Imaging

Number of Patients	fCurA, B 16	fCurC 23	Not Resected 39
Presence of lymph node metastasis(%)	9/16/(57)NS*	16/21(76)NS	24/30(80)
(p)N1(%)	2/16(13)	4/21(19)	4/30(13)
(p)N2(%)	7/16(44)	5/21(24)	6/30(20)
(p)N3(%)	0†	7/21(33)NS	14/30(47)
Liver metastasis (H)(%)	0†	6/23(26)NS	19/38(50)
Peritoneal dissemination (P)(%)	0NS	2/23(9)‡	12/23(52)
Distant Metastasis (%)	0NS	0†	9/39(23)
(p)T3/(p)T4	5/11NS	4/19†	1/38
(f)Stage III/IVa/IVb	3/8/5†	1/6/16NS	0/5/34

An asterisk indicates significance (†, $p<0.05$; ‡ $p<0.01$) of the difference compared with fCurAB and fCurC or fCurC and not resected group.
*NS = not significant

pT2 patients with a D1 (dissection in cystic duct and pericholedochal lymph node) or greater lymph node dissection showed a statistically prolonged survival in comparison to that of patients without lymph node dissection (D0), but no statistically significant difference was seen with or without resection of the extrahepatic bile duct. Based on the results, preserving the bile duct seems preferable. However, a lymph node dissection in the hepatoduodenal ligament without bile duct resection is difficult to perform while keeping the blood supply. Therefore, to perform a complete dissection of the lymph node in the hepatoduodenal ligament, we believe that the combined resection of the common bile duct is necessary and suitable for the pT2 gallbladder carcinoma.

For patients with pT3 and pT4 gallbladder carcinomas, a curative resection is the only chance of a long-term survival. Fong et al.[33] have reported that radical resection offers significantly greater chance of long-term survival than the less radical procedures or nonoperative therapy in selected patients even with advanced gallbladder carcinoma. Taner et al.[34] also have presented that radical surgical resection can improve patient survival. Lymph node metastasis is common, and in our surgical series the rate of lymph node metastasis was 62% in pT3 tumors and 69% in pT4 tumors. In the pT3 or pT4 gallbladder carcinomas, the survival of patients with curative surgery (fCurA+B) was significantly better than that in those with no curative resection (fCurC). In addition, the survival in patients with nodal involvement of pN1 to pN2 was better than that in those with pN3. The role of radical surgery cannot be concluded from the present study because the backgrounds were different, but seems to be limited in patients with pN3 lymph node metastasis. Although the clinical course of pT3 and pT4 gallbladder carcinoma remains dismal, a curative resection of tumor (fCurA+B), excluding cases with pN3 lymph node metastasis, statistically prolonged the survival in comparison to those without curative resection (fCurC) and also in those with no resection of the tumor. We propose that even in the patients with pT3 or pT4 gallbladder carcinoma without pN3 lymph node metastasis, a long-term survival can be expected by surgery with a tumor-free surgical margin. We believe that pN3 lymph node metastasis, especially para-aortic lesions, are thus not indicated for a curative resection.

Recently, an extended right hepatic lobectomy with a pancreaticoduodenectomy has been advocated for advanced gallbladder carcinomas such as pT3 or pT4 tumors because of the frequent presence of lymph node metastasis posterior to the head of the pancreas and along the root of the mesentery.[35–37] However, the perioperative mortality rate is high and few patients have shown any survival advantage after such extensive surgery.[36–38] Therefore, the indications for this radical procedure remain limited.

Conclusion

In conclusion, a S4a+S5 hepatic resection, lymph node dissection, and bile duct resection for a complete lymph node dissection of hepatoduodenal ligament are therefore mandatory for pT2 gallbladder carcinoma. Although the clinical course of pT3 or pT4 gallbladder carcinoma remains dismal, long-term survival can be expected by a curative surgery with a tumor-free surgical margin. Survival depends on the ability to achieve a curative resection, including a hepatectomy and lymph node dissection in patients with local extended tumors according to the depth of primary tumor invasion. In addition, a multidisciplinary approach including radiochemotherapy should be considered to prevent either local recurrence or hepatic metastasis after a surgical resection for patients with pT3 or pT4 gallbladder carcinoma.

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Journal of HBP Surgery

Topics: Treatment of patients with advanced gallbladder carcinoma with special reference to stage IV

Outcome of radical surgery for stage IV gallbladder carcinoma

Kazuo Chijiiwa, Masahiro Kai, Motoaki Nagano, Masahide Hiyoshi, Jiro Ohuchida, and Kazuhiro Kondo

First Department of Surgery, Miyazaki University School of Medicine, Miyazaki 889-1692, Japan

Abstract

Background/Purpose. The role of aggressive surgery for patients with stage IV gallbladder carcinoma was examined.
Methods. Cancers were classified according to the TNM system of the Japanese Society of Biliary Surgery. The survival of 37 patients with stage IV cancer (stage IVa, $n = 15$; stage IVb, $n = 22$) treated by surgical resection during the period January 1990 to December 2004 was examined and compared with the survival of 41 patients with stage IV disease not treated by surgical resection during the same period.
Results. The postoperative survival rate was significantly better for patients with resected stage IVa cancer than for patients with resected stage IVb disease and for those with nonresected stage IV disease. Survival in patients with N3 lymph node metastasis, liver metastasis, peritoneal dissemination, or vascular invasion was poor, like that in the nonresected group. Surgical resection without residual tumors (curability A and B) yielded a significantly better outcome than that with residual tumor (curability C). There were three 5-year survivors that were treated successfully by curative resection (curability A and B) and all had T4N0 disease.
Conclusions. These results suggest that surgical resection significantly improves survival even in patients with stage IV gallbladder carcinoma when N3 metastasis, liver metastasis, peritoneal dissemination, and vascular invasion are absent. Curative resection can be expected to produce long-term survival in selected patients with stage IV gallbladder carcinoma.

Introduction

The prognosis for gallbladder carcinoma, the most frequent biliary tract cancer,[1] remains dismal even with recent advances in diagnostic modalities and surgical techniques. This is mainly because the disease is usually advanced before it is diagnosed and treated; there is a lack of symptoms and signs in the early stages.

It is generally recognized that surgical resection provides the only hope of long-term survival. The advantage of surgical resection has been reported for advanced gallbladder carcinoma even in the presence of lymph node metastasis.[2–6] However, Benoist et al.[7] and Bartlett et al.[8] report poor results once lymph node metastasis occurs. The primary tumor (T), lymph node metastasis (N), and stage are well-known prognostic factors, with stage IV being the most advanced disease stage, and characterized by lymph node metastasis, direct liver invasion, vascular involvement, and/or distant metastasis. However, few studies have focused on the role of surgical resection for stage IV gallbladder carcinoma.

The aim of this study was to examine whether surgical resection affects the outcome of patients with stage IV gallbladder carcinoma. Therefore, outcomes and actuarial 5-year survival after surgical resection were examined. The outcomes and 5-year survival of patients with stage IV cancer who had not undergone surgical resection were examined as a reference.

Patients and methods

Ninety patients with gallbladder carcinoma underwent surgical resection at our University hospital between January 1990 and December 2004. Of these 90 patients, 37 patients with pathologically proven stage IV carcinoma, classified according to the TNM system of the Japanese Society of Biliary Surgery[9] (Table 1) were identified and became the subjects of the study. Their medical records were analyzed, and final follow-up data were obtained in July 2005.

The 37 patients comprised 19 men and 18 women, with a mean age of 65 years (range, 38 to 84 years). Disease was stage IVa in 15 patients and stage IVb in

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Table 1. Classification system and disease stages of gallbladder cancer[a]

Primary tumor (T)
- T1: Tumor invasion limited to the mucosa or muscularis propria
- T2: Tumor invasion limited to the subserosa
- T3: Tumor perforates the serosa or directly invades the liver <5 mm
- T4: Tumor extends more than 5 mm into the liver and/or into the hepatoduodenal ligament, portal vein, or hepatic arteries

Lymph node (N)
- N0: No regional lymph node metastasis
- N1: Metastasis in cystic duct and/or pericholedochal lymph node
- N2: Metastasis in hepatoduodenal ligament, except N1, posterosuperior pancreatic head, and/or along the common hepatic artery
- N3: Metastasis in peripancreatic head (except posterosuperior pancreatic head), celiac, superior mesenteric, and/or paraaortic lymph node

Liver (H), peritoneal (P), and distant (M) metastasis
- H(−), P(−), M(−): No evidence of liver metastasis, peritoneal metastasis, or of distant metastasis, other than P and/or H, respectively
- H(+), P(+), M(+): The presence of liver metastasis, peritoneal metastasis, and distant metastasis other than P and/or H, respectively

Final stage (judged on the basis of surgical and pathological findings)
- Stage IVa: T3N2, T4N0,1, T2N3 without H, P, M
- Stage IVb: T3N3, T4N2,3 without H, P, M
  Any T any N with H, P, M

[a] According to the Japanese Society of Biliary Surgery[9]

22 patients. The 15 cases of stage IVa were classified pathologically as T4N0 (n = 7), T4N1 (n = 4), T3N2 (n = 2), and T2N3 (n = 2) disease. The 22 cases of stage IVb disease were classified as T3 (n = 3) and T4 (n = 19) disease. Of the 22 patients who underwent surgical resection, 7 had liver metastasis and 2 had peritoneal dissemination. The remaining 13 patients with stage IVb disease had no liver metastasis, peritoneal dissemination, or distant metastasis (T3N3, n = 2; T4N2, n = 8; T4N3, n = 3).

The surgical procedures used in the 37 patients with stage IV disease were cholecystectomy (n = 6), excision of the gallbladder and liver bed (n = 11), anatomical resection of segments IV below and V of the liver (n = 16), and extended right or left hepatic lobectomy (n = 4). The extrahepatic bile duct was excised in 27 patients, and pancreatoduodenectomy was added in 4 patients. In general, anatomical resection of the segments IV below and V of the liver and lymph node dissection were performed as previously described[3,10]. In brief, lymph node dissection in the hepatoduodenal ligament, below the pancreas head, along the common hepatic artery, and in the paraaortic region was carried out with or without resection of the extrahepatic bile duct. Six of the 37 patients (16%) underwent postoperative chemotherapy: 4 patients were given tegafur-uracil (UFT) orally, and 2 were given 5-fluorouracil (5-FU) + cisplatin (CDDP) intravenously.

An additional 41 patients with stage IV disease not treated by surgical resection were included for comparison. This group comprised 19 men and 22 women, with a mean age of 67 years (range, 37 to 89 years), and they were given "best supportive care". Laparotomy was performed in 12 of these patients, probe laparotomy in 8 and gastrojejunostomy or hepaticojejunostomy in the other 4. Peritoneal dissemination was confirmed in 8 of the 12 patients. Disease stage was determined mainly on the basis of results of clinical imaging, such as direct cholangiography (endoscopic retrograde cholangiography, percutaneous transhepatic cholangiography), computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), or fluorodeoxyglucose-positron emission tomography (FDG-PET). The disease was classified as T4 in all 41 patients. Liver metastasis was present in 20 patients, and peritoneal dissemination was present in 12 patients, and most cancers were classified as stage IVb. Fifteen patients (37%) in this group received either intravenous 5-FU+CDDP or oral UFT, as in the surgically resected group.

Postoperative survival curves in relation to surgical resection, TN factors, vascular invasion, liver metastasis, peritoneal dissemination, and curability were constructed by the Kaplan-Meier method, and differences in survival were examined by the log-rank test. Curability was classified as A, B, and C, based on the pathological examination. Curability A indicated a cancer-free surgical margin of more than 5 mm and greater extent of lymph node dissection than that of N metastasis. Curability B indicated a cancer-free surgical margin of 5 mm or less and the same extent of lymph node dissection and N metastasis. Curability C was a cancer-positive surgical margin; greater extent of N metastasis than that of lymph node dissection; or the presence of peritoneal dissemination, liver metastasis, or distant metastasis. Probability values less than 0.05 were considered significant.

Results

Postoperative survival of patients with stage IVa and IVb disease

The postoperative survival of patients with stage IV carcinoma who underwent surgical resection and the survival of those who did not undergo surgical resection are shown in Fig. 1. Survival was significantly better

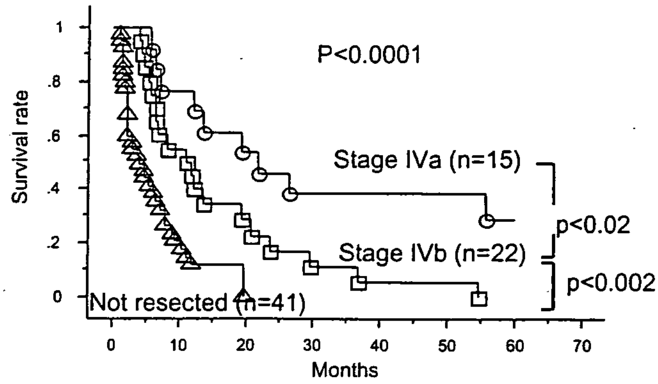

Fig. 1. Postoperative survival of patients with stage IV gallbladder carcinoma. Stage IVa,T2N3, T3N2, T4N0,1; stage IVb, T3N3, T4N2,3, liver metastasis (+), peritoneal dissemination (+), distant metastasis (+). A significant difference in survival was observed among resected patients with stage IVa, resected patients with stage IVb, and the not-resected groups

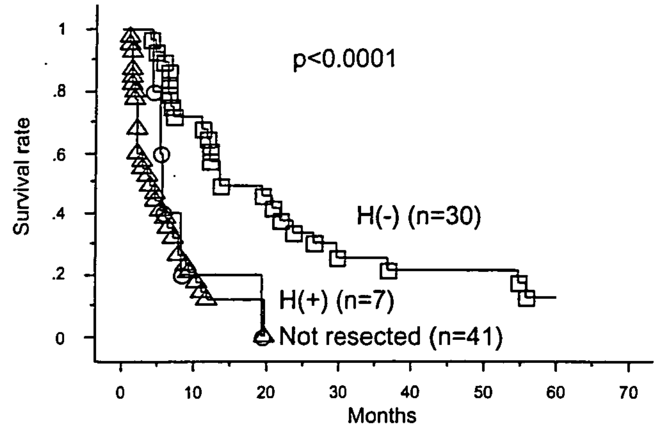

Fig. 2. Postoperative survival of patients with stage IV gallbladder carcinoma with or without liver metastasis (*H*). Patients with liver metastasis (*H*+) showed a significantly poorer survival than those without (*H*–) ($P < 0.0001$)

among patients with stage IVa cancer treated by surgical resection than among patients with stage IVb cancer treated by surgical resection ($P < 0.02$). Both stage IVa and stage IVb patients who underwent surgical resection showed significantly better survival than patients with stage IV disease who did not undergo surgical resection.

Of the 22 patients with stage IVb disease treated by resection, 7 had liver metastasis and 2 had peritoneal dissemination. The liver metastases were removed by extended lobectomy in 1 patient, concomitant resection of segments IV below and V of the liver in 4 patients, and by partial hepatic resection in 2 patients. The 7 patients who presented with liver metastasis and underwent hepatectomy together with resection of the primary tumor had a survival rate similar to that of the nonresected stage IV patients (Fig. 2). Surgical resection had no effect in patients with liver metastasis. Similarly, the 2 patients with peritoneal dissemination had poor outcomes, similar to the outcomes of patients who did not undergo resection.

Because the survival of patients who presented with liver metastasis and/or peritoneal dissemination was poor, the outcomes of the 28 patients without liver metastasis and peritoneal dissemination who underwent surgical resection were examined according to the T and N factors (Fig. 3). The best outcome was observed in patients with T4N0 disease. Outcomes were poor in patients with N3 lymph node metastasis, regardless of the T factor.

Four of the 37 patients who underwent surgical resection showed vascular invasion (portal vein invasion, $n = 2$; hepatic artery invasion, $n = 1$; both portal vein and hepatic artery invasion, $n = 1$). Outcomes in patients with vascular invasion were poor, and were similar to those of patients who did not undergo resection (Fig. 4).

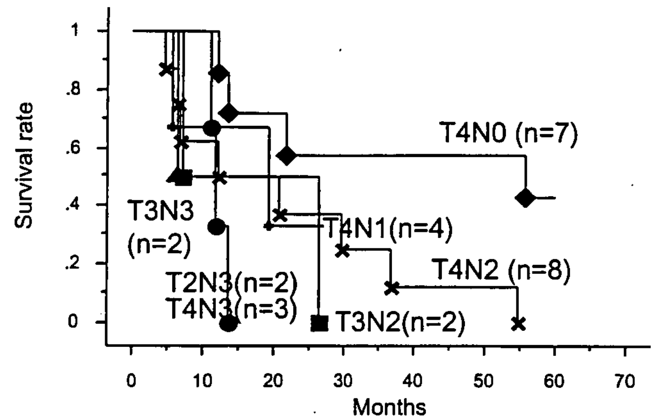

Fig. 3. Postoperative survival of patients with stage IV gallbladder carcinoma with respect to TN factors (liver metastasis, peritoneal dissemination, and distant metastasis were excluded)

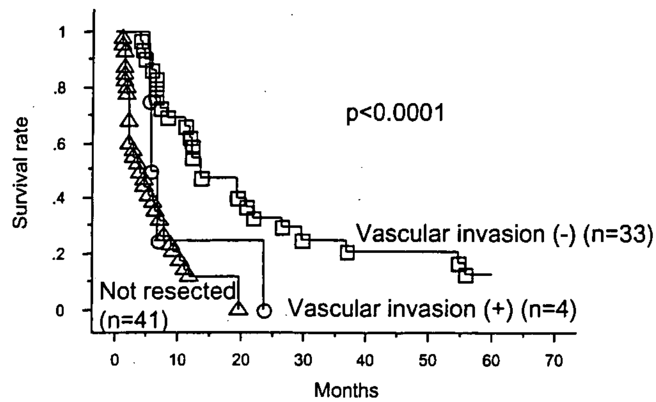

Fig. 4. Postoperative survival of patients with stage IV gallbladder carcinoma with respect to vascular (portal vein, hepatic artery) invasion. A significantly better survival was observed in patients without vascular invasion ($P < 0.0001$)