

# Intraductal papillary neoplasm of the bile ducts: Report of 58 cases

Hong Hui Zhang<sup>Equal first author, 1, 2, 3</sup>, Zhen Dong Zhong<sup>Equal first author, 1, 3, 4</sup>, Gao Yin Kong<sup>5</sup>, Junaid Khan<sup>1, 2, 3</sup>, Lian Hong Zou<sup>6</sup>, Yu Jiang<sup>6</sup>, Xie Hong Liu<sup>6</sup>, Yi Xun Tang<sup>5</sup>, Bo Jiang<sup>1, 2, 3</sup>, Chuang Peng<sup>1, 2, 3</sup>, Ying Hui Song<sup>Corresp., 1, 2, 3</sup>, su lai liu<sup>Corresp. 1, 2, 3</sup>

<sup>1</sup> Department of Hepatobiliary Surgery, Hunan Provincial People's Hospital, Changsha, Hunan province, China

<sup>2</sup> Clinical Medical Technology Research Center, Hunan Provincial for Biliary Disease Prevention and Treatment, Changsha, Hunan province, China

<sup>3</sup> Biliary Disease Research Laboratory, Hunan Provincial People's Hospital, Changsha, Hunan province, China

<sup>4</sup> Department of Hepatobiliary Surgery, Changsha County People's Hospital, Changsha, Hunan province, China

<sup>5</sup> Department of Anesthesiology, Hunan Provincial People's Hospital, Changsha, Hunan province, China

<sup>6</sup> Key Laboratory of Study and Discovery of Small Targeted Molecules of Hunan Province, Hunan Provincial Institute of Emergency Medicine, Changsha, Hunan province, China

Corresponding Authors: Ying Hui Song, su lai liu

Email address: sissysyh@163.com, liusulai@hunnu.edu.cn

## Abstract



**Background.** Intraductal papillary mucinous neoplasm of the bile duct (IPMN-B) is considered an uncommon tumor, and there is limited understanding of IPMN-B. This study aimed to investigate the prognosis and influential factors of the IPMN-B from 58 cases.

**Methods.** The clinical data of 58 patients with pathologically confirmed IPMN-B admitted to our hospital from January 1, 2012 to August 2017 were collected and analyzed. The patients were followed up by outpatient or telephone until January 1, 2019. SPSS19.0 software was applied for data analysis. Survival analysis was performed using Kaplan-Meier method and parallel Log-rank test. Prognostic factors were analyzed by univariate analysis and multiple Cox regression model.

**Results.** Among of all the patients, 26 cases were benign tumors and 32 cases were malignant tumors. The preoperative tumor markers CA242 and CEA of malignant IPNM-B patients were significantly higher than those in benign tumors ( $P < 0.05$ ). Survival analysis showed that patients with malignant tumors had a worse prognosis with The median survival time (MST) of malignant IPMN-B patients was  $40.57 \pm 3.015$  months, yet MST of benign IPMN-B patients was not reached ( $P = 0.041$ ). Univariate analysis showed that combined lymph node metastasis, surgical method, and differentiation degree could affect patients' prognosis ( $P < 0.05$ ). Multivariate analysis showed differentiation degree was an independent risk factor affecting prognosis (OR = 0.06, 95% confidence interval: 0.007 ~ 0.486,  $P < 0.05$ ).

**Conclusion.** The levels of CEA and CA242 were helpful to identify benign and malignant of IPNM-B. Moreover, radical surgical resection could prolong patients' survival. Finally, differentiation degree was an independent risk factor affecting malignant IPNM-B prognosis.

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Honghui Zhang<sup>1,2,3#</sup>, Zhendong Zhong<sup>1,2,4#</sup>, Gaoyin Kong<sup>5</sup>, Junaid Khan<sup>1,2,3</sup>, Lianhong Zou<sup>6</sup>, Yu  
jiang<sup>6</sup>, Xiehong Liu<sup>6</sup>, Yixun Tang<sup>5</sup>, Bo Jiang<sup>1,2,3</sup>, Chuang Peng<sup>1,2,3</sup>, Yinghui Song<sup>1,2,3\*</sup>, Sulai  
Liu<sup>1,2,3\*</sup>

<sup>1</sup>Department of Hepatobiliary Surgery/Hunan Research Center of Biliary Disease, Hunan  
Provincial People's Hospital/The First Affiliated Hospital of Hunan Normal University,  
Changsha, 410005 Hunan Province, China

<sup>2</sup>Biliary Disease Research Laboratory of Hunan Provincial People's Hospital, Key Laboratory of  
Hunan Normal University, Changsha, 410005 Hunan Province, China

<sup>3</sup>Clinical Medical Technology Research Center of Hunan Provincial for Biliary Disease  
Prevention and Treatment, Changsha, 410005 Hunan Province, China

<sup>4</sup>Department of Hepatobiliary Surgery, Changsha County People's Hospital/Hunan Provincial  
People's Hospital Xingsha Campus, Changsha, China.

<sup>5</sup>Department of Anesthesiology, Hunan Provincial People's Hospital/Clinical Research Center  
for Anesthesiology of ERAS in Hunan Province, Changsha 410005, China

<sup>6</sup>Key Laboratory of Study and Discovery of Small Targeted Molecules of Hunan Province,  
School of Medicine, Hunan Normal University/Hunan Provincial Institute of Emergency  
Medicine, Hunan Provincial Key Laboratory of Emergency and Critical Care Metabonomics,  
Changsha, Hunan, China

#This author contributes equally to this work.

\*Corresponding author: Yinghui Song PhD, M.D., or Sulai Liu, PhD, M.D., Department of Hepatobiliary Surgery, Hunan Provincial People's Hospital/The First Affiliated Hospital of Hunan Normal University, Changsha, Hunan Province, People's Republic of China. Tel/fax: 08673183929520. E-mail: \*\*sissysyh@163.com and liusulai@hunnu.edu.cn

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**Methods.** The clinical data of 58 patients with pathologically confirmed IPMN-B admitted to our hospital from January 1, 2012 to August 2017 were collected and analyzed. The patients were followed up by outpatient or telephone until January 1, 2019. SPSS19.0 software was applied for data analysis. Survival analysis was performed using Kaplan-Meier method and parallel Log-rank test. Prognostic factors were analyzed by univariate analysis and multiple Cox regression model.

**Results.** Among of all the patients, 26 cases were benign tumors and 32 cases were malignant tumors. The preoperative tumor markers CA242 and CEA of malignant IPNM-B patients were significantly higher than those in benign tumors ( $P < 0.05$ ). Survival analysis showed that patients with malignant tumors had a worse prognosis with The median survival time (MST) of malignant IPMN-B patients was  $40.57 \pm 3.015$  months, yet MST of benign IPMN-B patients was not reached ( $P = 0.041$ ). Univariate analysis showed that combined lymph node metastasis, surgical method, and differentiation degree could affect patients' prognosis ( $P < 0.05$ ). Multivariate analysis showed differentiation degree was an independent risk factor affecting prognosis (OR = 0.06, 95% confidence interval: 0.007 ~ 0.486,  $P < 0.05$ ).

**Conclusion.** The levels of CEA and CA242 were helpful to identify benign and malignant of IPNM-B. Moreover, radical surgical resection could prolong patients' survival. Finally, differentiation degree was an independent risk factor affecting malignant IPNM-B prognosis.

**Keywords:** Papillary mucinous tumor in the bile duct; radical resection; prognosis; risk factor

## Introduction

Intraductal papillary mucinous neoplasm of the bile duct (IPMN-B) is considered an uncommon tumor, which secretes a large amount of mucus to cause significant expansion and obstruction in clinical practice. Kim HJ, et al. described nine cases of bile duct tumors secreting a large amount of mucus and concluded that their clinical, imaging and pathological features were similar to those of papillary mucinous tumors in the pancreatic duct in 2000(Kim HJ et al., 2000). In 2008, the concept of IPMN-B was first proposed to summarize such diseases (Paik KY et al., 2008). There is limited understanding of IPMN-B, which are mostly case reports, and lack of large-scale clinical research (Nakanuma Y et al.,2016; Hokuto D et al., 2017). This study retrospectively analyzed 58 patients with IPMN-B admitted in our hospital from January 2012 to August 2017. Clinical and pathological data were collected and explored to identify the prognosis and influencing factors of IPMN-B in order to provide basis for the clinical diagnosis and treatment of IPMN-B.

## Materials & Methods

### Clinical manifestations

The clinical data of 58 patients with postoperative pathological diagnosis of IPMN-B were collected, including 24 males and 34 females; the median age was 61 years (41-85 years). The clinical manifestations were mainly pain in the right upper abdomen with yellow staining of the skin and sclera. Abdominal ultrasound, CT, or MRI examinations were performed before surgery.

Typical imaging findings were local or intrahepatic and extrahepatic bile duct dilatation, cystic or soft rattle, thickening of the bile duct wall with nodular tissue protrusions, and some patients underwent electronic imaging. Jelly-like bile was seen on duo-scope examination. Thirty-eight patients (65.5%) developed jaundice at the time of consultation, and 6 of them underwent percutaneous liver puncture of the biliary tract to remove jelly-like bile, which had a poor drainage effect. A total of 46 patients underwent radical resection and 12 patients underwent palliative surgery.

### **Surgical methods**

Preoperative auxiliary examinations were performed to evaluate important organ functions, liver reserve functions, and resectability of liver. Pathological histological examinations were performed during and after surgery. According to the results of pathological histological examinations and the degree of tumor invasion, they were divided into three subgroups: atypical hyperplasia, adenoma and adenocarcinoma (including cancerous changes). The first two groups were belonged to benign tumors. The surgical method was hepatic resection or combined tail resection according to the tumor location, and the intraoperative pathological results. The malignant tumors were routinely dissected with lymph nodes in groups 8, 12, 13a. Patients with multiple intrahepatic bile duct tumors by intraoperative choledochoscopy underwent hepatobiliary reconstruction, bile-gut drainage, and T-tube drainage. The specimens submitted including resected liver specimen, resection margins and lymph nodes.

### **Follow up**

The patients' gender, age, jaundice, biliary stones, previous biliary surgery, tumor markers (CA19-9, CA242, CEA), histological characteristics, lymph node metastasis, resection margins, etc. were followed up in outpatient and telephone ways after the operation. Recurrence was defined as the recurrence of jaundice, and imaging examinations such as CT and/or MRI

confirmed recurrence. The end point of follow-up was the death of patients or the follow-up time until January 1, 2019, and those who died for other reasons but not IPMN-B were excluded.

## Statistical methods

SPSS19.0 software was applied for data analysis. Tumor markers were analyzed by variance among subgroups. Survival analysis was performed using Kaplan-Meier method and parallel Log-rank test. Prognostic factors were analyzed by univariate analysis and multiple Cox regression model.  $P < 0.05$  was considered statistically significant.

## Results

### Clinicopathological parameters of IPNM-B patients

45 patients (77.6%) had bile duct stones, 35 patients (60.3%) had previous biliary surgery, and 38 patients (65.5%) had jaundice. The pathological results showed 14 cases (24.1%) were atypical hyperplasia, 12 cases (20.7%) were adenoma, and 32 cases (55.2%) were adenocarcinoma (including canceration). Lymph node metastasis did not occur in benign tumors, and lymph node metastasis occurred in 6 cases (18.8%) of malignant tumors. Radical resection was performed in 46 cases (79.3%), and palliative resection was performed in 12 cases (20.7%). Malignant tumor differentiation grade: 17 cases with high differentiation (53.1%), 9 cases with high-medium differentiation or middle differentiation (28.1%), 6 cases with medium-low differentiation or poor differentiation (18.8%). See Table 1 for details.

### Imaging of IPNM-B

In this study, patients showed typical massive jelly-like mucus biliary drainage before surgery or intraoperative biliary tract. Typical CT manifestations showed obvious cystic dilatation of the intrahepatic bile duct, a small spot-shaped high-density lesion in the bile duct of the right hepatic lobe (Figure 1A). T2 magnetic resonance imaging showed a clear soft vine-like expansion of the intrahepatic bile duct, and a small nodular T2 signal foci in the bile duct (Figure 1B). The

electronic duodenum showed a common bile duct duodenal fistula by below the duodenum above the duodenal papilla, about 1.0 cm in diameter, full filled with full of jelly-like Slime (Figure 1C).

### Survival analysis

51 cases (87.9%) were followed up to the endpoint, no perioperative deaths. 4 patients with benign tumors died, of which two elderly patients survived 3.7 months and 8.7 months, respectively, and were excluded when the survival curve was drawn; two patients survived 7.5 months and 35.2 months due to multiple intrahepatic and extrahepatic bile ducts lesions, respectively. The overall average survival time of this group was  $62.1 \pm 5.1$  months. 10 patients with malignant tumors were died, the median overall survival time was  $41.4 \pm 6.1$  months, the one-year survival rate was 87.5%, and the three-year survival rate was 64.7%. Kaplan-Meier survival curves of two groups were shown in Figure 1. Log-rank test= 4.086,  $P = 0.041$ . Analysis of prognostic factors in patients with malignant tumors revealed that prognostic factors including lymph node metastasis, surgical method, and degree of differentiation ( $P < 0.05$ ). See Table 2 for details. Including lymph node metastasis, surgical method, and degree of differentiation into the COX model and performing multivariate analysis showed that differentiation degree ( $OR = 0.06$ , 95% confidence interval: 0.007-0.486,  $P < 0.05$ ) was an independent factor affecting prognosis.

### Discussion

IPMN-B is one of intraductal papillary neoplasm of the bile duct (IPNB and intrapancreatic a subtype). It secretes a large amount of mucus to block the bile duct and causes obstructive jaundice. Histopathology of IPMN-B is similar to intraductal papillary mucinous neoplasm of the pancreas (IPMN-P) (Nakanuma Y et al., 2017; Fukumura Y et al., 2017). In this study, patients showed typical massive jelly-like mucus by biliary drainage before surgery or intraoperative

biliary tract. Most patients experienced preoperative B-ultrasound showed significant bile duct dilatation, hypoechoic flocculent light masses in the bile duct, and obvious space occupying. Typical CT or MRI imaging features were soft vine-like dilatation of the bile ducts inside and outside the liver, and multiple nodules in the bile duct wall.

Previous studies have suggested that CT play an important role in identifying benign and malignant diseases of IPMN-B (*Okai H et al., 2011; Paik KY et al., 2008*). It is reported that "floating sign" in the bile duct of MRI imaging is a typical manifestation of IPMN-B (*Ying SH et al., 2015*). In general, the imaging characteristics of IPMN-B patients in this study were basically consistent with the reported imaging characteristics.

Most patients were complained jaundice and abdominal pain. 45 patients (77.6%) suffered head biliary calculi. And 35 patients (60.3%) had a previous history of biliary tract surgery. The tumor markers CA242 and CEA of most patients were significantly increased before surgery, and they were helpful to distinguish benign from malignant diseases. It was reported that CA19-9, CA242 and CEA were three recognized plasma tumor markers of cholangiocarcinoma (*Wongkham S et al., 2012*). Moreover, CA242 and CEA were more valuable in the diagnosis of cholangiocarcinoma (*Ni XG et al., 2005*). In this study, it seemed that CA242 was more sensitive and specific than CEA in diagnosing malignant IPMN-B from the ROC curve (date not shown).

IPMN-B often presents multiple lesions. Intrahepatic bile duct is the most common site and accounts for about 84% of all the IPMN-B. When bile duct tumors inside and outside the liver accumulate bile ducts in the hilar region often indicate an enhancement of tumor infiltration. Although the progress of bile duct and pancreatic papillary adenomas is relatively slow, the prognosis is often poor when multiple infiltrates appear (*Luvira V et al., 2016*).



Radical surgical resection is considered the only way to cure bile duct malignancies. All patients in this study underwent radical or palliative surgical treatment. Among them, 13 patients who underwent T-tube drainage and palliative intestinal drainage due to acute obstructive suppurative cholangitis (AOSC) or multiple tumors had a shorter survival time than those who underwent liver resection ( $p < 0.05$ ). The median survival time of patients who achieved R0 resection was significantly longer than those of R1, R2 resection, meanwhile the recurrence rate of patients with R1, R2 resection was significantly higher than that of R0 resection.

The original cells of IPNB are considered to be bile duct gland cells, which are distributed along the intrahepatic bile duct and extrahepatic bile ducts, showing a slowly transition from adenoma to adenocarcinoma with fewer lymph nodes or distant metastases. The prognosis of IPMN-B is significantly better than any other types of cholangiocarcinoma (*Schlitter AM et al., 2014; Gordon Weeks AN et al., 2016*). In this study, IPMN-B often accompanied by biliary stones and it progressed slowly, but once jaundice appeared, it was easy to induce AOSC. So it is necessary for patients with stones or previous history of biliary surgery to perform routine physical examination. Radical surgery could effectively improve the survival rate of patients with IPMN-B. The role of adjuvant treatment for IPMN-B is yet to be established (*Yeh TS et al., 2006*). Therefore, it is particularly essential to take the optimal surgical method. For multiple tumors involving the hilar area, in order to avoid the occurrence of biliary obstruction, bile-intestinal drainage may be necessary to increase the diameter of bile outflow channels.

In this study, there was significantly different of the cumulative survival rate between benign IPMN-B patients and malignant IPMN-B patients. The median survival time (MST) of malignant IPMN-B patients was  $40.57 \pm 3.015$  months, yet MST of benign IPMN-B patients was not

reached ( $P=0.041$ ), which was consistent with the previous studies of IPMN-B survival time (*Wang X et al., 2015; Luvira V et al., 2017*).

## Conclusions

In short, preoperative CT and MRI is helpful to improve the detection rate of IPMN-B. Meanwhile, the levels of CEA and CA242 are helpful to identify benign and malignant of IPMN-B. Moreover, radical surgical resection could prolong patients' survival, when radical surgery is not available, unobstructed drainage is necessary. Finally, more data should be collected from more patients of IPMN-B and long-term survival follow-up to improve the diagnosis and treatment of IPMN-B.

## Acknowledgements

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## Conflict of interest

The authors declare that they have no financial or commercial conflict of interest.

## Ethical approval

The study was approved by the Ethics Committee of the hospital, and all clinical samples were used in accordance with institutional guidelines and the Declaration of Helsinki after obtaining signed informed consent from all participants.

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# 264 **Figure legend**

265 Figure 1 Imaging of IPNM-B: (A)Typical CT manifestations showed obvious cystic dilatation of  
 266 the intrahepatic bile duct, a small spot-shaped high-density lesion in the bile duct of the right  
 267 hepatic lobe. (B) T2 magnetic resonance imaging showed a clear soft vine-like expansion of the  
 268 intrahepatic bile duct, and a small nodular T2 signal foci in the bile duct. (C)The electronic  
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271 Figure 2 The cumulative survival of patients with benign IPNM-B patients and malignant IPNM-  
 272 B patients was determined by the Kaplan-Meier method.

**Table 1** (on next page)

Table 1 Clinicopathological parameters of 58 IPNM-B patients

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Clinical Features	Benign		Malignant		$\chi^2$	P value
	N	%	N	%		
Age (years)					0.017	0.897
≤60	15	44.12	19	55.88		
>60	11	45.83	13	54.17		
Gender					0.500	0.479
Female	17	48.57	18	51.43		
Male	9	39.13	14	60.87		
Stones					0.012	0.913
Negative	6	46.15	7	53.85		
Positive	20	44.44	25	55.56		
Previous biliary surgery					0.139	0.710
Negative	11	47.83	12	52.17		
Positive	15	42.86	20	57.14		
Jaundice					0.330	0.566
Negative	10	50.00	10	50.00		
Positive	16	42.11	22	57.89		
CA19-9					0.051	0.821
Normal	13	44.83	16	55.17		
High	13	41.94	18	58.06		
CA242					7.083	0.008
Normal	21	56.76	16	43.24		
High	5	21.74	18	78.26		
CEA					8.148	0.004
Normal	25	54.35	21	46.65		
High	1	8.33	11	91.67		
Surgical method					0.808	0.369
radical resection	22	47.83	24	52.17		



palliative resection	4	33.33	8	66.67
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- 2  $\chi^2$  test was used to compare the distribution of clinical features between benign IPNM-B patients
- 3 and malignant IPNM-B patients.
- 4 CA19-9 normal reference range: 0-35 U/ mL.
- 5 CA242 normal reference range: 0-20 U/mL.
- 6 CEA normal reference range: 0-5 ng/ mL.
- 7 A P value <0.05 was considered significant.

## Table 2 (on next page)

Table 2 Multivariate analysis of factors contributing to overall survival in 29 malignant IPNM-B patients

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Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (<60 vs. ≥60)	0.114(0.002-6.305)	0.413	—	—
Gender (female vs. male)	0.166(0.012-2.216)	0.838	—	—
Stones (negative vs. positive)	2.007(0.166-12.283)	0.540	—	—
Jaundice (negative vs. positive)	3.890(0.138-25.550)	0.074	—	—
CA19-9 (≤35U /L vs. >35U/L)	0.835(0.061-11.335)	0.099	—	—
CA242 (≤20U /L vs. >20U/L)	0.326(0.063-1.678)	0.116	—	—
CEA (≤5ng/mL vs. >5 ng/mL)	1.143 (0.086-9.181)	0.097	—	—
Lymph node metastasis (negative vs. positive)	0.368(0.054-2.519)	0.015	0.442(0.111-1.755)	0.246
Surgical method (radical resection vs. palliative resection)	5.444(0.337-27.848)	0.018	0.081(0.010-0.673)	0.665
Differentiation degree (high vs. medium-low)	0.056(0.007-0.451)	0.000	0.06(0.007-0.486)	0.008

Univariate and multivariate analysis of prognostic factors in 29 malignant IPNM-B patients

included in the survival analysis.

Statistical analyses were performed by Cox proportional hazards regression. A P value < 0.05

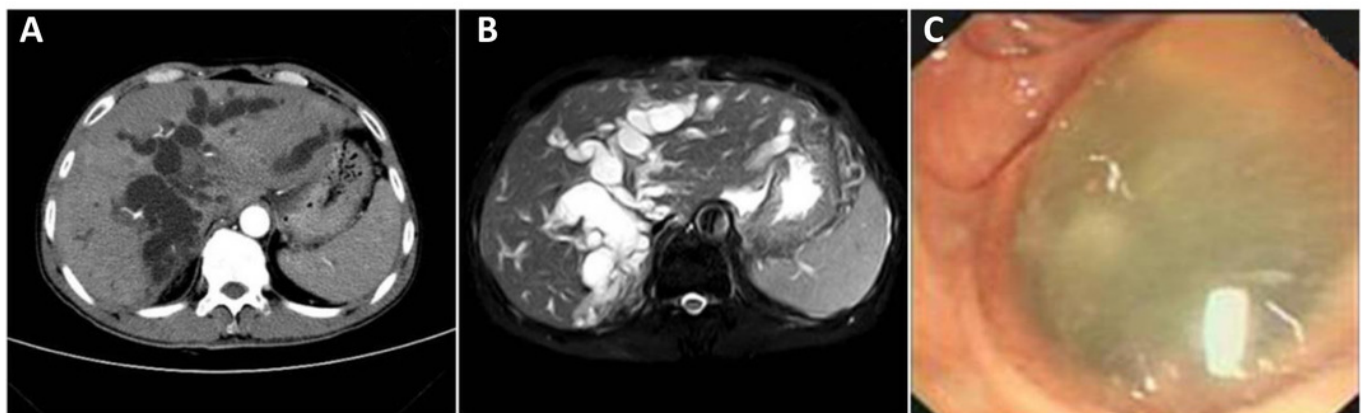
6 was considered significant. *Italic* indicates significant P values.

7 CI, confidence interval.

# Figure 1

Figure 1

Figure 1 Imaging of IPNM-B: (A) Typical CT manifestations showed obvious cystic dilatation of the intrahepatic bile duct, a small spot-shaped high-density lesion in the bile duct of the right hepatic lobe. (B) T2 magnetic resonance imaging showed a clear soft vine-like expansion of the intrahepatic bile duct, and a small nodular T2 signal foci in the bile duct. (C) The electronic duodenum showed a common bile duct duodenal fistula by below the duodenum above the duodenal papilla, about 1.0 cm in diameter, full filled with full of jelly-like Slime.



# Figure 2

Figure 2

Figure 2 The cumulative survival of patients with benign IPNM-B patients and malignant IPNM-B patients was determined by the Kaplan-Meier method.

