Clinicopathological Findings and Imaging Features of Intraductal Papillary Neoplasm of the Bile Ducts

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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. The median survival time of malignant IPMN-B patients was 40.6±3.0 months, yet median survival time of benign IPMN-B patients was not reached (P=0.19). The one-year survival rate and three-year survival rate of benign IPMN-B were 84% and 74% respectively. The one-year survival rate and three-year survival rate of malignant IPMN-B were 88% and 64% respectively.

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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Abstract

31   **Background.** Intraductal papillary mucinous neoplasm of the bile duct (IPMN-B) is considered

32   an uncommon tumor, and there is limited understanding of IPMN-B. This study aimed to

33   investigate the prognosis and influential factors of the IPMN-B from 58 cases.

34   **Methods.** The clinical data of 58 patients with pathologically confirmed IPMN-B admitted to our

35   hospital from January 1, 2012 to August 2017 were collected and analyzed. The patients were

36   followed up by outpatient or telephone until January 1, 2019. SPSS19.0 software was applied for

37   data analysis. Survival analysis was performed using Kaplan-Meier method and parallel Log-rank

38   test. Prognostic factors were analyzed by univariate analysis and multiple Cox regression model.

39   **Results.** Among of all the patients, 26 cases were benign tumors and 32 cases were malignant

40   tumors. The preoperative tumor markers CA242 and CEA of malignant IPNM-B patients were

41   significantly higher than those in benign tumors (P <0.05). Survival analysis showed that patients

42   with malignant tumors had a worse prognosis. The median survival time of malignant IPMN-B

43   patients was 40.6±3.0 months, yet median survival time of benign IPMN-B patients was not

44   reached (P=0.19). The one-year survival rate and three-year survival rate of benign IPMN-B were

45   84% and 74% respectively. The one-year survival rate and three-year survival rate of malignant

46 IPMN-B   were   88%   and   64%   respectively.

47 Univariate analysis showed that combined lymph node metastasis, surgical method, and

48 differentiation degree could affect patients' prognosis (P <0.05). Multivariate analysis showed

49 differentiation degree was an independent risk factor affecting prognosis (OR = 0.06, 95%

50 confidence interval: 0.007 ~ 0.486, P <0.05).

51 **Conclusion.** The levels of CEA and CA242 were helpful to identify benign and malignant of

52 IPNM-B. Moreover, radical surgical resection could prolong patients' survival. Finally,

53 differentiation degree was an independent risk factor affecting malignant IPNM-B prognosis.

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

55 Introduction

56 Intraductal papillary mucinous neoplasm of the bile duct (IPMN-B) is considered an uncommon

57 tumor, which secretes a large amount of mucus to cause significant expansion and obstruction of

58 the bile ducts. Kim HJ, et al. described nine cases of bile duct tumors secreting a large amount of

59 mucus and concluded that their clinical, imaging and pathological features were similar to those

60 of papillary mucinous tumors in the pancreatic duct in 2000(*Kim HJ et al., 2000*). In 2008, the

61 concept of IPMN-B was first proposed to summarize such diseases (*Paik KY et al., 2008*). There

62 is limited understanding of IPMN-B, which are mostly case reports, and lack of large-scale clinical

63 research (*Nakanuma Y et al.,2016*; *Hokuto D et al., 2017*). This study retrospectively analyzed 58

64 patients with IPMN-B admitted in our hospital from January 2012 to August 2017. Clinical and

65 pathological data were collected and explored to identify the prognosis and influencing factors of

66 IPMN-B in order to provide basis for the clinical diagnosis and treatment of IPMN-B.

67 Materials & Methods

68 **Clinical manifestations**

69 The clinical data of 58 patients with postoperative pathological diagnosis of IPMN-B were

70 collected, including 24 males and 34 females; the median age was 61 years (41-85 years). The

71 clinical manifestations were mainly pain in the right upper abdomen with jaundice. Abdominal

72 ultrasound, CT, or MRI examinations were performed before surgery. Typical imaging findings

73 were local or intrahepatic and extrahepatic bile duct dilatation, thickening of the bile duct wall

74 with nodular tissue protrusions. Jelly-like bile was seen on duodenoscope examination in some

75 patients. The study was approved by the Ethics Committee of Hunan Provincial People's

76 Hospital/The First Affiliated Hospital of Hunan Normal University (Number: 2020-11), and all

77 clinical samples were used in accordance with institutional guidelines and the Declaration of

78 Helsinki after obtaining signed informed consent from all participants.

79 **Surgical methods**

80 Preoperative auxiliary examinations were performed to evaluate important organ functions, liver

81 reserve functions, and resectability of liver. Pathological histological examinations were

82 performed during and after surgery. According to the results of pathological histological

83 examinations and the degree of tumor invasion, they were divided into three subgroups: atypical

84 hyperplasia, adenoma and adenocarcinoma (including cancerous changes). The first two groups

85 belonged to benign tumors. The surgical method was hepatic resection or combined tail resection

86 according to the tumor location, and the intraoperative pathological results. The malignant tumors

87 were routinely dissected with lymph nodes in groups 8, 12, 13a. Patients with multiple intrahepatic

88 bile duct tumors by intraoperative choledochoscopy underwent hepatobiliary reconstruction, bile-

89 gut drainage, and T-tube drainage. The specimens submitted including resected liver specimen,

90 resection margins and lymph nodes.

91 **Follow up**

92 The patients' gender, age, jaundice, biliary stones, previous biliary surgery, tumor markers (CA19-

93 9, CA242, CEA), histological characteristics, lymph node metastasis, resection margins, etc. were

94 followed up in outpatient and telephone visits after the operation. Recurrence was defined as both

95 the recurrence of jaundice and new lesions on imaging. The end point of follow-up was the death

96 of patients or the follow-up time until January 1, 2019, and those who died for other reasons but

97 not IPMN-B were excluded.

98 **Statistical methods**

99 SPSS19.0 software was applied for data analysis. Categorical data was compared using

100 frequencies expressed as percentages, and compared with chi-squared testing. Tumor markers

101 were analyzed by variance among subgroups. Overall survival analysis was performed using

102 Kaplan-Meier method and parallel Log-rank test. Prognostic factors were analyzed by univariate

103 analysis and multiple Cox regression model. P <0.05 was considered statistically significant.

104 # Results

105 **Clinicopathological parameters of IPNM-B patients**

106 45 patients (77.6%) had bile duct stones, 35 patients (60.3%) had previous biliary surgery, and 38

107 patients (65.5%) had jaundice. Six of these 38 patients underwent percutaneous liver puncture of

108 the biliary tract to remove jelly-like bile. The pathological results showed 14 cases (24.1%) were

109 atypical hyperplasia, 12 cases (20.7%) were adenoma, and 32 cases (55.2%) were adenocarcinoma

110 (including canceration). Lymph node metastasis did not occur in benign tumors, and lymph node

111 metastasis occurred in 6 cases (18.8%) of malignant tumors. Radical resection was performed in

112 46 cases (79.3%), and palliative resection was performed in 12 cases (20.7%). Malignant tumor

113 differentiation grade: 17 cases with high differentiation (53.1%), 9 cases with high-medium

114 differentiation or middle differentiation (28.1%), 6 cases with medium-low differentiation or poor

115 differentiation (18.8%). It was reported that CA19-9, CA242 and CEA were three recognized

116 plasma tumor markers of cholangiocarcinoma (*Wongkham S et al., 2012*). In this study, all of the

117 three biomarkers in adenocarcinoma group were higher than the other two groups (P <0.05). See

118 Table 1 for details. Moreover, CA242 and CEA were more valuable in the diagnosis of

119 cholangiocarcinoma (*Ni XG et al.,2005*). In this study, the area under the CA242 curve was 0.781,

120 meanwhile, the area under the CEA curve was 0.728 (P >0.05). It seemed that CA242 was more

121 sensitive and specific than CEA in diagnosing malignant IPMN-B from the ROC curve (Figure 1).

122 All patients in this study underwent radical or palliative surgical treatment. Among them, 13

123 patients who underwent T-tube drainage and palliative intestinal drainage due to acute obstructive

124 suppurative cholangitis (AOSC) or multiple tumors had a shorter survival time than those who

125 underwent liver resection (p <0.05). The median survival time of patients who achieved R0

126 resection was significantly longer than those of R1, R2 resection, meanwhile the recurrence rate

127 of patients with R1, R2 resection was significantly higher than that of R0 resection (R0 is complete

128 microscopic resection, R1 is residual microscopic disease and R2 is residual macroscopic disease).

129 **Imaging of IPNM-B**

130 In this study, massive jelly-like mucus could be seen in the bile duct drainage of most patients.

131 Typical CT manifestations showed obvious cystic dilatation of the intrahepatic bile duct, a small

132 spot-shaped high-density lesion in the bile duct of the right hepatic lobe (Figure 2A). T2 magnetic

133 resonance imaging showed a clear soft vine-like expansion of the intrahepatic bile duct, and a

134 small nodular T2 signal foci in the bile duct (Figure 2B). The duodenoscopy showed that a

135 duodenal fistula with a diameter of 1.0 cm above the nipple which is filled with jelly-like slime

136 (Figure 2C).

137 **Survival analysis**

138   51 cases (87.9%) were followed up to the endpoint, no perioperative deaths,the average follow-

139   up time of these patients was 30.0 ± 3.2 months. Four patients with benign tumors died, of which

140   two elderly patients survived 3.7 months and 8.7 months, respectively; two patients survived 7.5

141   months and 35.2 months due to multiple intrahepatic and extrahepatic bile ducts lesions,

142   respectively. The overall mean survival time of this group was 56.4 ± 6.0 months. 10 patients with

143   malignant tumors died, the median overall survival time was 41.4 ± 6.1 months. Kaplan-Meier

144   survival curves of two groups were shown in Figure 3. Log-rank test= 1.65, P = 0.19. The one-

145   year survival rate and three-year survival rate of benign IPMN-B were 84% and 74% respectively.

146   The one-year survival rate and three-year survival rate of malignant IPMN-B were 88% and 64%

147   respectively. Univariate Cox proportional hazard regression analyses showed that lymph node

148   metastasis, surgical method, and degree of differentiation were prognostic factors of malignant

149   IPNM-B (P <0.05). See Table 2 for details. Including lymph node metastasis, surgical method, and

150   degree of differentiation into the COX model and performing multivariate analysis showed that

151   differentiation degree (OR = 0.06, 95% confidence interval: 0.007-0.486, P <0.05) was an

152   independent factor affecting prognosis.

153   **Discussion**

154   IPMN-B is one of intraductal papillary neoplasm of the bile duct. It secretes a large amount of

155   mucus to block the bile duct and causes obstructive jaundice. Histopathology of IPMN-B is similar

156   to intraductal papillary mucinous neoplasm of the pancreas (IPMN-P) (*Nakanuma Y et al., 2017*;

157   *Fukumura Y et al., 2017*). However, it is also found that IPNB arising in intrahepatic catheters is

158   the biliary counterpart of IPMN, while IPNB arising in extrahepatic catheters is different from

159   typical IPMN (*Yasuni Nakanuma et al., 2019*). Most patients experienced preoperative ultrasound

160   examination showed significant bile duct dilatation, hypoechoic flocculent light masses in the bile

161   duct, and obvious space occupying. Typical CT or MRI imaging features were soft vine-like

162   dilatation of the bile ducts inside and outside the liver, and multiple nodules in the bile duct wall.

163   Previous studies have suggested that CT play an important role in identifying benign and malignant

164   diseases of IPMN-B (*Oki H et al., 2011*; *Paik KY et al., 2008*). It is reported that "floating sign" in

165   the bile duct of MRI imaging is a typical manifestation of IPMN-B (*Ying SH et al., 2015*). In

166   general, the imaging characteristics of IPMN-B patients in this study were basically consistent

167   with the reported imaging characteristics.

168   The tumor markers CA242 and CEA of most patients were significantly increased before surgery,

169   and they were helpful to distinguish benign from malignant diseases. It seemed that CA242 was

170   more sensitive and specific than CEA in diagnosing malignant IPMN-B in this study, however,

171   this conclusion needed more samples to verify. It is more credible that combination all the three

172   biomarkers to assess the benign and malignant disease.

173   IPMN-B often presents with multiple lesions. Intrahepatic bile duct is the most common site and

174   accounts for about 84% of all the IPMN-B. When intrahepatic and extrahepatic bile duct tumors

175   invaded to the hilar region often indicated an enhancement of tumor infiltration. Although the

176   progress of bile duct and pancreatic papillary adenomas is relatively slow, the prognosis is often

177   poor when multiple infiltrates appear (*Luvira V et al., 2016*).

178   Radical surgical resection is considered the only way to cure bile duct malignancies. Even the

179   addition of EGFR-mAbs to gemcitabine-based first-line chemotherapy dose not significantly

180   improve neither overall survival nor progression-free survival (*Rizzo A et al., 2020*). All patients

181   in this study underwent radical or palliative surgical treatment.

182   The original cells of IPNB are considered to be bile duct gland cells, which are distributed along

183   the intrahepatic bile duct and extrahepatic bile ducts, showing a slow transition from adenoma to

184 adenocarcinoma with fewer lymph nodes or distant metastases. The prognosis of IPMN-B is

185 significantly better than any other types of cholangiocarcinoma (*Schlitter AM et al., 2014*; *Gordon*

186 *Weeks AN et al., 2016*). In this study, IPMN-B often accompanied by biliary stones and it

187 progressed slowly, but once jaundice appeared, it was easy to induce AOSC. So it is necessary for

188 patients with stones or previous history of biliary surgery to perform routine physical examination.

189 Radical surgery could effectively improve the survival rate of patients with IPMN-B. The role of

190 adjuvant treatment for IPMN-B is yet to be established (*Yeh TS et al., 2006*). Therefore, it is

191 particularly essential to take the optimal surgical method. For multiple tumors involving the hilar

192 area, in order to avoid the occurrence of biliary obstruction, bile-intestinal drainage may be

193 necessary to increase the diameter of bile outflow channels.

194 In this study, there was different of the cumulative survival rate between benign IPMN-B patients

195 and malignant IPMN-B patients. The median survival time of malignant IPMN-B patients was

196 40.6±3.0 months, yet median survival time of benign IPMN-B patients was not reached (P=0.19),

197 the survival of patients in the malignant group was worse than that of the benign group, which was

198 consistent with the previous studies of IPMN-B survival time (*Wang X et al., 2015*; *Luvira V et*

199 *al., 2017*). But the difference between the two groups is not significant. It is considered that the

200 number of cases in this study is small and the survival time of two older patients in the benign

201 group is particularly short. In the future, we will continue to follow up patients with this disease in

202 order to obtain more convincing data to gain a deeper understanding of IPMN.

203 **Conclusions**

204 In short, preoperative CT and MRI is helpful to improve the detection rate of IPMN-B. Meanwhile,

205 the levels of CEA and CA242 are helpful to identify benign and malignant of IPNM-B. Moreover,

206 radical surgical resection could prolong patients' survival, when radical surgery is not available,

207 unobstructed drainage is necessary. Finally, more data should be collected from more patients of

208 IPMN-B and long-term survival follow-up to improve the diagnosis and treatment of IPMN-B.

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215 **Conflict of interest**

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

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281

282 **Figure legend**

283 Figure 1 ROC curve of CA242 and CEA

284 Figure 2 Imaging of IPNM-B: (A)Typical CT manifestations showed obvious cystic dilatation of

285 the intrahepatic bile duct, a small spot-shaped high-density lesion in the bile duct of the right

286 hepatic lobe. (B) T2 magnetic resonance imaging showed a clear soft vine-like expansion of the

287 intrahepatic bile duct, and a small nodular T2 signal foci in the bile duct. (C)The duodenoscopy

288 showed a common bile duct duodenal fistula by below the duodenum above the duodenal papilla,

289 about 1.0 cm in diameter, full filled with full of jelly-like Slime.

290 Figure 3 The cumulative survival of patients with benign IPNM-B patients and malignant IPNM-

291 B patients was determined by the Kaplan-Meier method.

Figure 1

Figure 1

ROC curve of CA242 and CEA
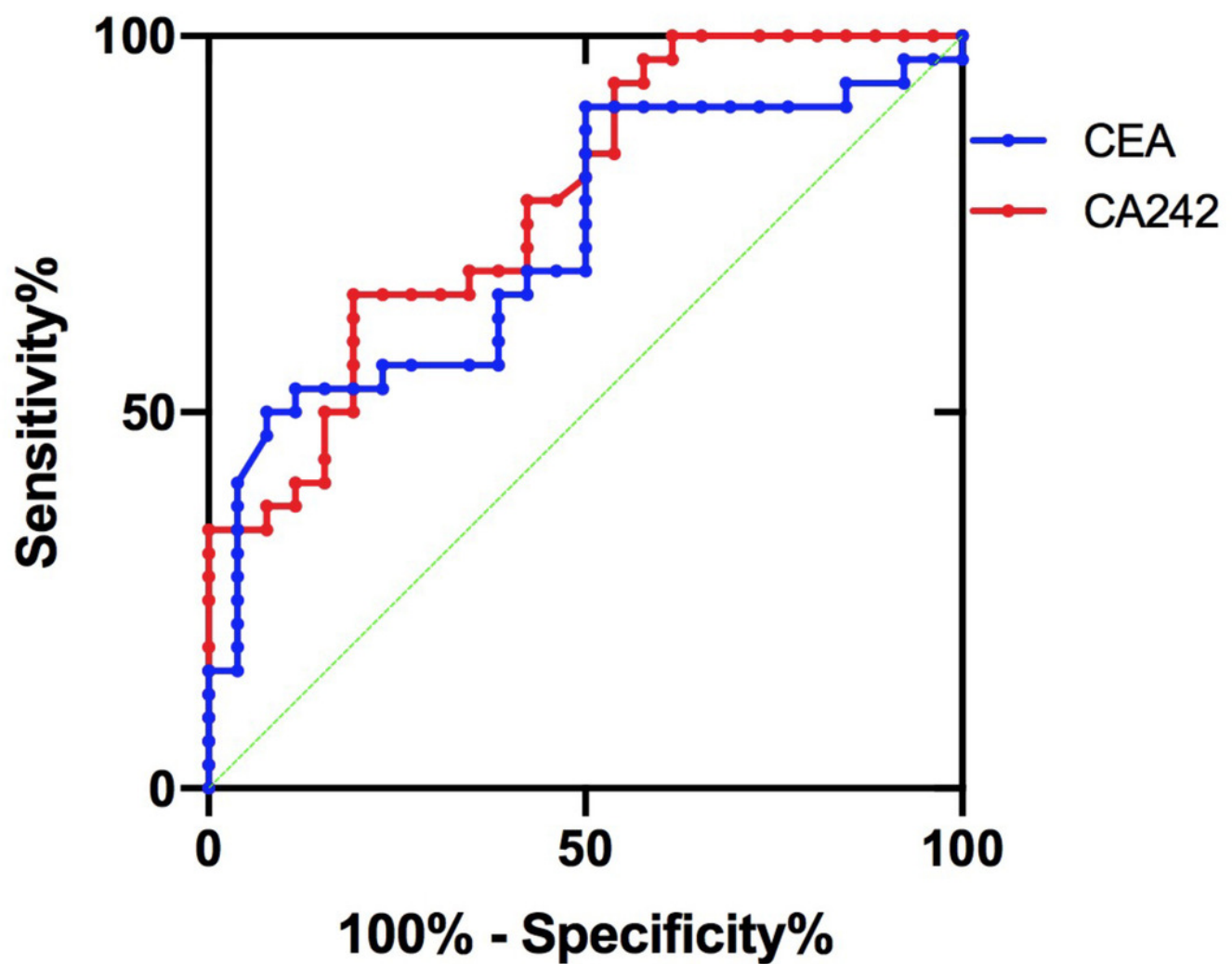
Figure 2

Figure 2

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 duodenoscopy 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.
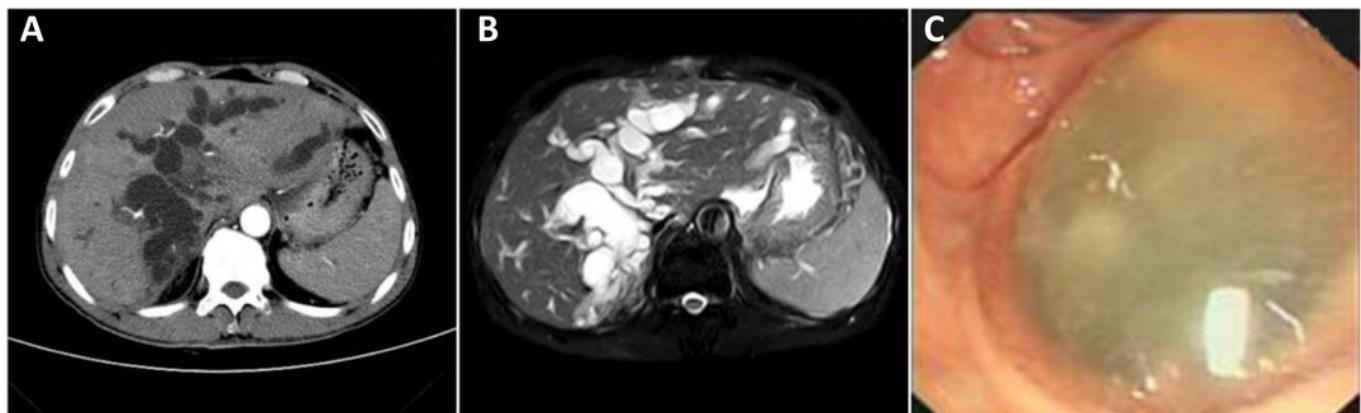
Figure 3

Figure 3

Figure 3 The cumulative survival of patients with benign IPNM-B patients and malignant IPNM-B patients was determined by the Kaplan-Meier method.
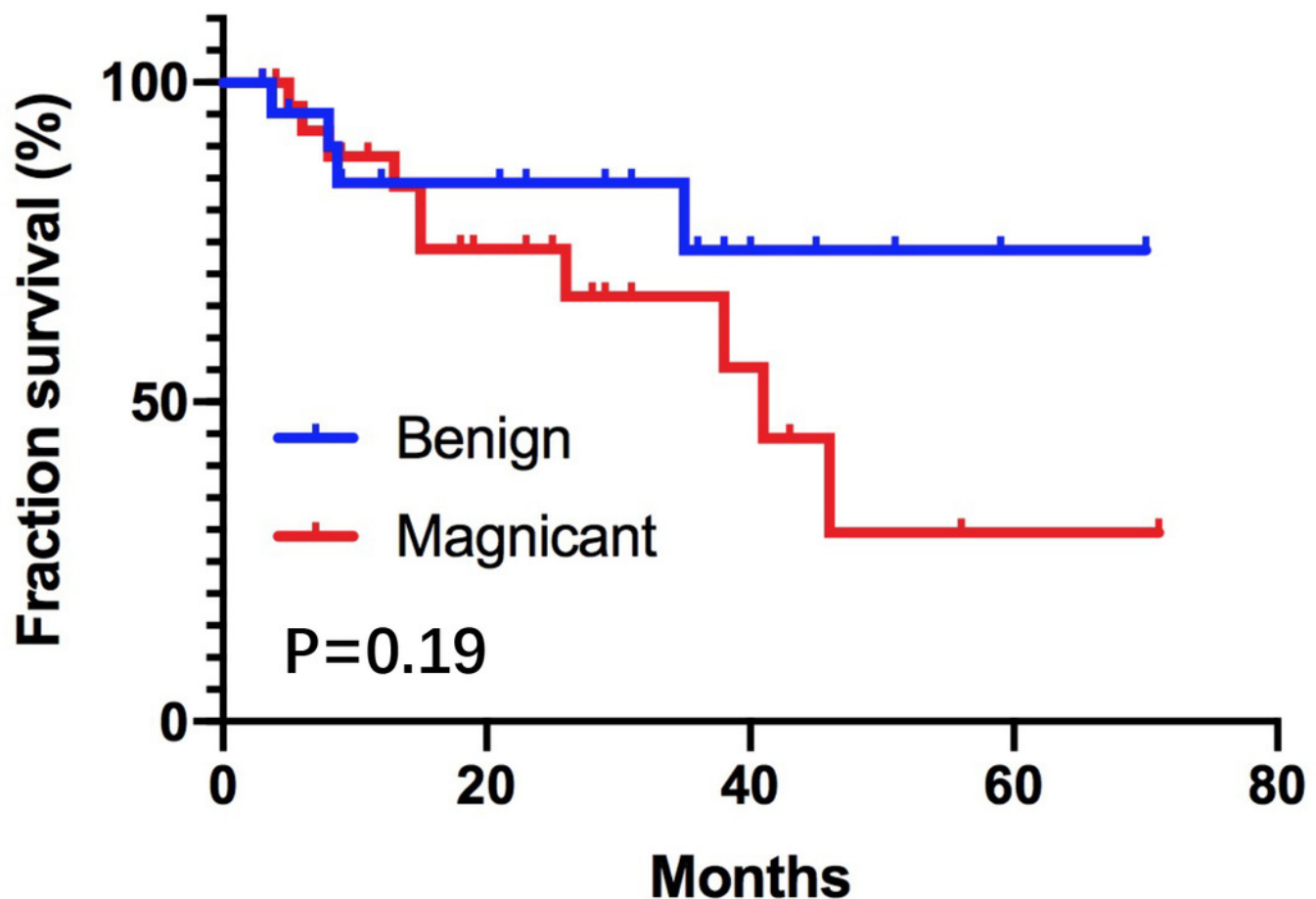
Table 1 Clinicopathological parameters of 58 IPNM-B patients

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Clinical Features	Benign		Malignant		χ2	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

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

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2   in 29 malignant IPNM-B patients

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

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

4   included in the survival analysis.

5   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.