

# Evaluation of Surgical Resection for Ampullar Carcinoma at Japanese Single Cancer Institute

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**Aims:** Surgical resection is the only radical treatment option for duodenal ampullar carcinoma (AC) that results in an improved patient prognosis. **Method:** We examined the demographics, surgical records, and outcome in 23 patients with AC undergoing pancreaticoduodenectomy (PD). **Results:** Of 23 patients, 17 underwent pylorus preserving PD (PPPD) and 6 underwent PD, including subtotal stomach-preserving PD in 5. D2 lymphadenectomy was performed in 17 patients and D3 lymphadenectomy was performed in 6. The combined resection of the superior mesenteric vein was performed in 1 patient. Postoperative cancer recurrence was observed in 32%, and 6 patients died of cancer. The 3-year tumor-free survival rates were not different between the final stages ( $p=0.64$ ) and the 5-year cancer-related overall survival rates were not different between stages either ( $p=0.28$ ). Tumor size  $\geq 3$ cm resulted in significantly poorer survival rate compared to smaller tumors ( $p=0.032$ ). Node metastasis at Group 2, and moderately or poorly differentiated adenocarcinoma were significantly associated with poor survival ( $p<0.05$ ); however, cancer infiltration at cut-end margin, degree of node dissection and curability were not associated with overall prognosis. **Conclusions:** Radical surgical resection showed good patient prognosis; however, new adjuvant chemotherapy is a promising modality to improve patient survival in AC patients with poor prognostic factors.

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**Keywords:** Ampullar carcinoma; Pancreaticoduodenectomy; Radical operation

## Introduction

Surgical resection is the only curable treatment for duodenal ampullar carcinomas (AC) and the resection rate is higher than those in other biliary carcinomas at this stage.<sup>1</sup> Pancreaticoduodenectomy (PD) is usually necessary to accomplish complete (R0) resections, which may improve patient prognosis.<sup>1,4</sup> However, on the other hand, physical stress in patients who undergo PD is relatively high and postoperative morbidity is still not low because of the soft architecture of pancreatic tissue.<sup>3,5,6</sup> Advanced ampullar carcinoma (AC) may lead to tumor recurrence and related

poor prognosis. To evaluate the present status regarding surgical treatments for AC at our institute, we examined our series of PC in 23 patients at a Japanese single cancer institute and discuss the clinical significance and problems in the present series.

## Method

### Patients

We experienced 23 patients undergoing surgical resection with AC administrated in the Division of Surgical

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Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences (NUGSBS) between 1994 and 2008. The study design was approved by the Human Ethics Review Board of our institution. Informed consent for data collection was obtained by each patient during this period. Anesthetic and patient data were retrieved in the NUGSBS database. Tumor stage and curability were determined based on the Classification of Biliary Tract Carcinoma in Japan.<sup>7</sup>

### Operative procedures and follow-up

Pancreaticoduodenectomy or pylorus preserving PD (PPPD) is a basic surgical option for AC and lymphadenectomy was performed in Group 2 lymph nodes and lymph nodes at the para-aortic lesion (station number 16a2 and 16b1). Basically, PPPD was selected for AC until 2005 and PD was selected in case that lymph node metastasis was suspected at the peri-pylorus lesion. Since 2006, subtotal stomach-preserving PD (SSPPD) was preferably applied to prevent the postoperative complication of delayed gastric empty. Extrapancreatic nerve plexus was also resected in the right side around the supra-mesenteric artery in case of advanced stage. After PPPD or PD, Child's intestinal reconstruction with end-to-side anastomosis of pancreatojejunostomy was routinely selected. In case of tumor involvement to the portal vein or supra-mesenteric vein (SMV), radical operation was also considered and combined resection of the portal vein accompanied with an end-to-end anastomosis of the vessel was performed. Fibrin glue was sprayed to prevent pancreatic fistula for anastomotic site.

After discharge from the hospital, the patient status, laboratory data, and disease recurrence were carefully checked every 3 months. The minimum follow-up period after operation was 14 months in the present study.

## Results

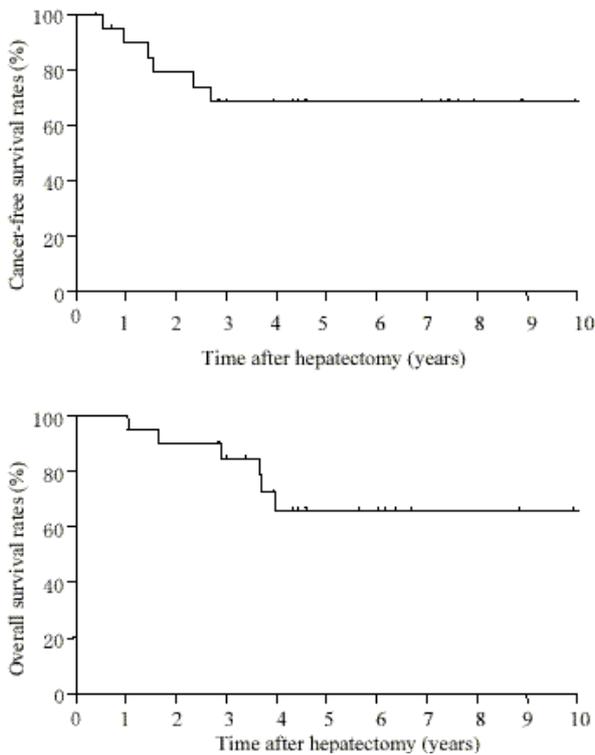
The demographics of AC patients were shown in Table 1. One patient had a rupture of the marginal artery of the stomach caused by pancreatic fistula and interventional radiological embolization was performed. Hospital death was not observed in these patients. Postoperative adjuvant chemotherapy, which was an oral intake of 600 mg daily of tegafur-uracil (Taiho Pharmaceutical. Co. Ltd., Tokyo, Japan), was selected in 3 patients because of highly advanced stage.

Six patients (30%) died of cancer. Figures 1 and 2 show the cancer-free and overall survival after operation. Mean

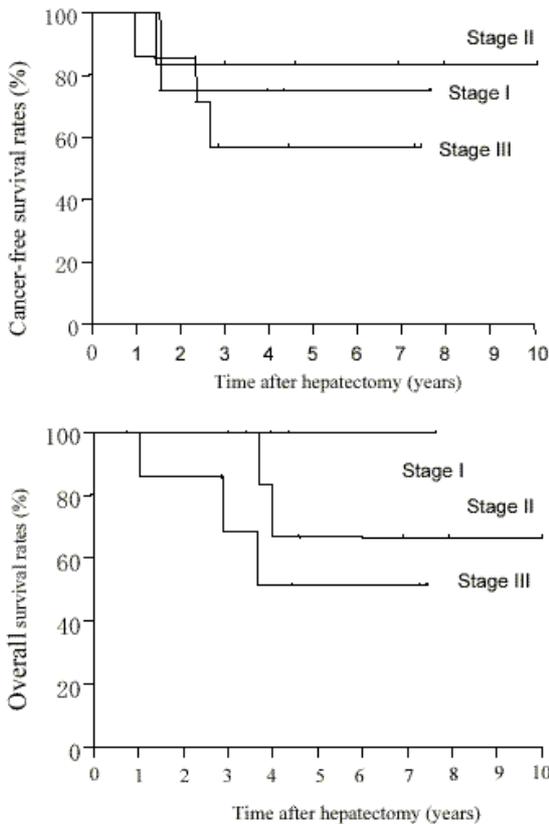
**Table 1.** Clinico-pathological demographics of the ampullar carcinoma patients

Factors	Number
Gender	
Male	14
Female	9
Age (years)	62.0 ± 10.0(range, 38-79)
Operative procedures	
PPPD	17
PD	6
SSPPD	5
Range of lymphadenectomy <sup>#</sup>	
D2	17
D3	6
Combined resection of SMV	1
Postoperative complications	15 (65%)
Pancreatic fistula	3
Delayed gastric empty	12
Macroscopic findings <sup>#</sup>	
Non-exposed protruded type	2
Exposed protruded type	11
Predominant ulcerative type	10
Location of tumor <sup>#</sup>	
Bile duct of the papilla of Vater	12
Common duct into the duodenal lumen	6
Major duodenal papilla	5
Tumor size>3cm	4(17%)
Histological findings of adenocarcinoma <sup>#</sup>	
Papillary	3
Well	5
Moderately	14
Poorly	1
Cancer-stroma relationship <sup>#</sup>	
Intermediate	19
Medullary	1
Scirrhus	3
Vascular invasion <sup>#</sup>	
Lymphatic invasion	17 (74%)
Venous invasion	11 (45%)
Perineural invasion	4 (18%)
Infiltration over Oddi's sphincter <sup>#</sup>	9 (41%)
Pancreatic invasion <sup>#</sup>	3 (13%)
Duodenal invasion <sup>#</sup>	17 (74%)
Node metastasis <sup>#</sup>	5 (22%)
Tumor stage <sup>#</sup>	
1	5
2	9
3	7
4	2
Tumor-node-metastasis (TNM) stage <sup>#</sup>	
I	6
II	9
III	8
Positive cancer margin at the dissected peri-pancreatic tissue margin <sup>#</sup>	3 (9%)
Final curability <sup>#</sup>	
A	19
B	1
C	3
Postoperative cancer recurrence	7 (32%)
Peritonitis carcinomatosa	1
Liver metastasis	4
Local recurrence	3
Lymph node recurrence	2

PPPD; pylorus preserving Pancreaticoduodenectomy (PD), SSPPD; subtotal stomach-preserving PD, SMV; superior mesenteric vein  
#: findings according to the *Classification of Biliary Tract Carcinoma in Japan*<sup>7</sup>



**Figure 1.** Cumulative cancer-free (a) and overall (b) survival after hepatectomy.



**Figure 2.** Comparison between stages of tumor and cumulative cancer-free (a) and overall (b) survival after hepatectomy.

cancer-free survival time was 30 months, and 3-year cancer-free survival rate was 69%. Mean overall survival time was 133 months, and 5-year overall survival rate was 66%. By comparison with tumor stage, 3-year tumor-free survival and mean cancer-free survival periods were not different between stages (75% in I, 83% in II, 57% in III, and 74 months in I, 105 in II and 62 in III, respectively) ( $p=0.64$ ). By comparison with the final stage, 5-year cancer-related overall survival and the mean survival period were not different between stages either (100% in I, 67% in II, 51% in III, and 93 months in I, 98 in II, 62 in III, respectively) ( $p=0.28$ ). Table 2 shows the relationship between overall 5-year survival rate and clinical parameters. Preoperative CA19-9 level, location of tumor and macroscopic type were not associated with overall survival. Tumor size over 3cm showed a significantly poorer survival rate compared to tumors less than 3cm ( $p<0.05$ ). Postoperative adjuvant chemotherapy was not related to patient survival. Table 3 shows the relationship between overall 5-year survival rate and pathological parameters. Node metastasis at Group 2, and moderately or poorly differentiated adenocarcinoma was associated with significantly poorer survival. Cancer infiltration at cut-end margin, degree of node dissection and curability were not associated with overall prognosis.

**Table 2.** Comparison between overall 5-year survival after resection and clinical and macroscopic parameters and postoperative chemotherapy

Parameters	5-year survival(%)	P value
CA19-9(U/ml)		
≤37* (n=18)	56	0.37
>37 (n=5)	83	
Location of carcinoma#		
Portion of the bile duct (n=12)	79	0.80
Portion of the common duct into the duodenal lumen (n=6)	67	
Major duodenal papilla (n=5)	50	
Tumor size		
<3cm (n=19)	71	0.032
≥3cm (n=4)	25	
Macroscopic type#		
Non-exposed protruded type (n=2)	100	0.052
Exposed protruded type (n=11)	100	
Ulcerative type (n=10)	32	
Adjuvant chemotherapy		
No (n=18)	68	0.97
Yes (n=5)	50	

\*; median value

#; findings according to the *Classification of Biliary Tact Carcinoma in Japan*<sup>7</sup>

**Table 3.** Comparison between overall 5-year survival after resection and pathological parameters

Parameters	5-year survival rates (%)	P value
T category <sup>#</sup>		
1 (n=5)	100	0.43
2 (n=9)	58	
3 (n=7)	54	
4 (n=2)	100	
Lymph node metastases <sup>#</sup>		
0 (n=18)	72	0.002
1 (n=3)	100	
2 (n=2)	0	
Histological differentiation or type <sup>#</sup>		
Papillary adenocarcinoma (n=3)	100	0.049
Well differentiated adenocarcinoma (n=5)	100	
Moderately (n=14)	52	
Poorly (n=1)	0	
Cancer-stroma relationship <sup>#</sup>		
Intermediate (n=19)	65	0.69
Medullary (n=1)	100	
Scirrhous (n=3)	50	
Lymphatic invasion <sup>#</sup>		
No (n=6)	67	0.83
Yes (n=17)	65	
Venous invasion <sup>#</sup>		
No (n=12)	65	0.67
Yes (n=11)	67	
Perineural invasion <sup>#</sup>		
No (n=19)	69	0.28
Yes (n=4)	50	
Infiltration to Oddi's sphincter <sup>#</sup>		
Yes (n=14)	59	0.29
Beyond (n=9)	75	
Pancreatic invasion <sup>#</sup>		
No (n=20)	88	0.17
Yes (n=3)	50	
Duodenal invasion <sup>#</sup>		
No (n=6)	100	0.18
Yes (n=17)	58	
Dissected peripancreatic tissue margin <sup>#</sup>		
No (n=20)	64	0.48
Cancer infiltration present (n=3)	100	
Classification of lymph node dissection <sup>#</sup>		
D2 (n=17)	67	0.57
D3 (n=6)	60	
Final curability		
A, B (n=20)	60	0.21
C (n=3)	100	

<sup>#</sup>; findings according to the *Classification of Biliary Tract Carcinoma* in Japan<sup>7</sup>

## Discussion

Surgical exploration is the only curable treatment in patients with AC and survival is relatively better than in other biliary tract carcinomas, even in the advanced stage.<sup>1-5, 8, 9</sup> As the techniques and perioperative management for PD, which is a standard option for AC, have been remarkably improved, we could actively perform complete tumor resections (R0) during the last 15 years, which improved patient prognosis.<sup>1, 3-6</sup>

In our series, the mean age of AC patients tended to be younger than those in bile duct carcinomas.<sup>10</sup> Most patients had no severe accompanying diseases and their general condition was good. Preoperative examinations for AC have not changed dramatically during this 15 years but multi-detector computed tomography (CT) has been applied since 2001 and preoperative diagnosis of lymph nodes seemed to be improved.<sup>11</sup> At our institute, combinations of imaging modalities of CT, magnetic resonance image, etc., have been applied; however, the precise evaluation of cancer extension or node metastasis is still difficult before operation.<sup>12</sup> In the next step, fine needle aspiration or positron emission tomography must be applied to determine the preoperative diagnosis for tumor extension or node metastasis.<sup>13, 14</sup> Resectability of AC was high and only 1 patient was inoperable at the time of laparotomy due to peritoneal carcinomatosis, despite detailed preoperative image examinations in our series. Radical operation by PD or PPPD was performed in the present study because of the lack of a candidate for local resection, which is a standard surgical procedure.<sup>3, 4</sup> Furthermore, most cases underwent D2 lymphadenectomy. Complete lymphadenectomy at station number 162a and 16b1 are considered to be necessary because accurate, preoperative diagnosis is still difficult, as described above.<sup>5, 12</sup> Combined resection of SMV was also aggressively performed to accomplish R0 resection in 1 patient. Eventually, problematic complications such as a pancreatic fistula were observed in 3 patients but 1 had Grade C fistula. Morbidity rate was low as in previous reports<sup>3, 5, 6</sup> and therefore PD or PPPD in AC could be safely selected. Delayed gastric empty is a troublesome complication due to anastomosis by PPPD.<sup>15</sup> We now use subtotal stomach preserving PD to avoid this complication.<sup>16</sup>

Postoperative adjuvant chemotherapy is a recent trend in patients with advanced biliary tract carcinoma due to development of recent chemotherapy using gemcitabine, 5 fluorouracil or S-1 chemotherapy.<sup>17-19</sup> In the present series, we selected S-1 as a promising drug in the future based on results in gastric carcinomas. These 3 patients had no tumor

recurrence during chemotherapy. Lymph node metastasis was histologically observed in 4 patients although T3 or T4 tumor was observed in 41%. Eventually, stage IV tumor was not observed in our series. Surgical curability reflects a good prognosis in AC patients undergoing PD<sup>2,5,6</sup> and we accomplished a high rate of curability A (=best grade of curability). The recurrence rate was relatively lower in comparison with other biliary tract carcinomas<sup>21</sup>; however, tumor recurrence was not rare even in AC in this study. One patient had a liver metastasis at 10 months after primary operation; however, no tumor recurrence was observed for over 3 years after hepatic re-resection with administration of S-1. Lee et al. also reported the survival benefit of hepatectomy for liver metastasis (18). We examined survival results and associated parameters in this study. The 5-year survival in the present study was similar to those in previous reports<sup>3,4,5,8,9</sup> and the mean survival period was over 10 years.

We compared survival rates between stages, and survival rates of stage II and III tended to be lower than that of stage I but no significant difference was observed between stages. Even patients with advanced stage tumor might have long-term survival after operation with or without chemotherapy. By clinico-pathological examinations, serum CA19-9 level, which is a sensitive marker for malignant behavior,<sup>22</sup> did not correlate with patient survival. In recent unpublished data, survival rates were increased according to increased level of CA19-9 in gallbladder carcinomas (not published yet). By comparison with pathological examination, tumor size, node metastasis and histological differentiation were associated parameters with patient prognosis, as well in previous reports.<sup>3,4,6,8,9,23-25</sup> Direct invasion to the pancreas or duodenum, vascular or perineural invasion, number of node metastasis or minute node metastasis detected by only immunohistochemistry were also associated with patient survival.<sup>3,4,8,9,23,24</sup>

Importance of dissected or cut margin was pointed out and presence of residual tumor must be avoided to improve survival. Therefore, extended pancreatectomy is still necessary to improve the patient prognoses.<sup>3-6</sup> In the present results, however, these surgical factors were not significantly associated with prognosis, which might be due to the small number of subjects at this stage. Further long-term follow-up with additional subjects is necessary using promising drugs such as S-1 in high-risk patients with the above predictive parameters.<sup>20</sup>

In conclusion, radical pancreaticoduodenectomy was performed in 23 patients with ampullar carcinomas at a single cancer center over the past 15 years. Radical operation could

be safely performed in most cases. Many patients showed a good prognosis even in the advanced stage. Tumor size, node metastasis and histological differentiation were associated with improved overall survival but not curability. The new and effective adjuvant chemotherapy treatments will be promising to improve patient survival in AC patients with poor prognostic factors.

## References

1. Fischer HP, Zhou H. Pathogenesis of carcinoma of the papilla of Vater. *J Hepatobiliary Pancreat Surg* 11: 301-9, 2004
2. Miyazaki M, Takada T, Miyakawa S, Tsukada K, Nagino M, Kondo S, et al.; Japanese Association of Biliary Surgery; Japanese Society of Hepato-Pancreatic Surgery; Japan Society of Clinical Oncology. Risk factors for biliary tract and ampullary carcinomas and prophylactic surgery for these factors. *J Hepatobiliary Pancreat Surg* 15: 15-24, 2008
3. Shimizu Y, Kimura F, Shimizu H, Yoshidome H, Ohtsuka M, Miyazaki M. The morbidity, mortality, and prognostic factors for ampullary carcinoma and distal cholangiocarcinoma. *Hepatogastroenterology* 55: 699-703, 2008
4. Duffy JP, Hines OJ, Liu JH, Ko CY, Cortina G, Isacoff WH, et al. Improved survival for adenocarcinoma of the ampulla of Vater: fifty-five consecutive resections. *Arch Surg* 138: 941-8, 2003
5. Böttger TC, Boddin J, Heintz A, Junginger T. Clinicopathologic study for the assessment of resection for ampullary carcinoma. *World J Surg* 21: 379-83, 1997
6. Klemptner J, Ridder GJ, Pichlmayr R. Prognostic factors after resection of ampullary carcinoma: multivariate survival analysis in comparison with ductal cancer of the pancreatic head. *Br J Surg* 82: 1686-91, 1995
7. *Japanese Society of Biliary Surgery (JSBS)*. In: Nagakawa T ed. Classification of Biliary Tract Carcinoma. Tokyo: Kanehara & Co., Ltd., 2004, p.11-50
8. Woo SM, Ryu JK, Lee SH, Yoo JW, Park JK, Kim YT, et al. Recurrence and prognostic factors of ampullary carcinoma after radical resection: comparison with distal extrahepatic cholangiocarcinoma. *Ann Surg Oncol* 14: 3195-201, 2007
9. Sakata J, Shirai Y, Wakai T, Yokoyama N, Sakata E, Akazawa K, et al. Number of positive lymph nodes independently affects long-term survival after resection in patients with ampullary carcinoma. *Eur J Surg Oncol* 33: 346-51, 2007
10. Nanashima A, Sumida Y, Tobinaga S, Abo T, Takeshita H, Sawai T, et al. Characteristics of bile duct carcinoma with superficial extension in the epithelium. *World J Surg* 33: 1255-8, 2009
11. Noji T, Kondo S, Hirano S, Tanaka E, Suzuki O, Shichinohe T. Computed tomography evaluation of regional lymph node metastases in patients with biliary cancer. *Br J Surg* 95: 92-6, 2008
12. Nanashima A, Sakamoto I, Hayashi T, Tobinaga S, Araki M, Kunizaki M, et al. Preoperative Diagnosis of Lymph Node Metastasis in Biliary and Pancreatic Carcinomas: Evaluation of the combination of multi-detector CT and serum CA19-9 Level. *Dig Dis Sci* 2010 (in-press)
13. Agarwal B, Gogia S, Eloubeidi MA, Correa AM, Ho L, Collins BT. Malignant mediastinal lymphadenopathy detected by staging EUS in patients with pancreaticobiliary cancer. *Gastrointest Endosc* 61: 849-53, 2005
14. Furukawa H, Ikuma H, Asakura-Yokoe K, Uesaka K. Preoperative staging of biliary carcinoma using 18F-fluorodeoxyglucose PET: prospective comparison with PET+CT, MDCT and histopathology. *Eur Radiol* 8: 2841-7, 2008
15. Paraskevas KI, Avgerinos C, Manes C, Lytras D, Dervenis C. Delayed

- gastric emptying is associated with pylorus-preserving but not classical Whipple pancreaticoduodenectomy: a review of the literature and critical reappraisal of the implicated pathomechanism. *World J Gastroenterol* 12: 5951-8, 2006
16. Akizuki E, Kimura Y, Nobuoka T, Imamura M, Nishidate T, Mizuguchi T, et al. Prospective nonrandomized comparison between pylorus-preserving and subtotal stomach-preserving pancreaticoduodenectomy from the perspectives of DGE occurrence and postoperative digestive functions. *J Gastrointest Surg* 12: 1185-92, 2008
  17. Furuse J, Takada T, Miyazaki M, Miyakawa S, Tsukada K, Nagino M, et al. Japanese Association of Biliary Surgery; Japanese Society of Hepato-Biliary-Pancreatic Surgery; Japan Society of Clinical Oncology: Guidelines for chemotherapy of biliary tract and ampullary carcinomas. *J Hepatobiliary Pancreat Surg* 15: 55-62, 2008
  18. Lee JH, Whittington R, Williams NN, Berry MF, Vaughn DJ, Haller DG, et al. Outcome of pancreaticoduodenectomy and impact of adjuvant therapy for ampullary carcinomas. *Int J Radiat Oncol Biol Phys* 47: 945-53, 2000
  19. Park I, Lee JL, Ryu MH, Kim TW, Chang HM, Lee SS, et al. Efficacy and safety of S-1 monotherapy in patients with advanced biliary tract adenocarcinoma: retrospective analysis of 162 patients. *Oncology* 76: 126-32, 2009
  20. Kubota T. New chemotherapy strategies for gastric cancer. *In Vivo* 22: 273-8, 2008
  21. Berberat PO, Kunzli BM, Gulbinas A, Ramanauskas T, Kleeff J, Muller MW, et al. An audit of outcomes of a series of periampullary carcinomas. *Eur J Surg Oncol* 35: 187-91, 2009
  22. Yamaguchi K, Enjoji M, Nakayama F. Cancer of the extrahepatic bile duct: a clinicopathologic study of immunohistochemistry for CEA, CA19-9, and p21. *World J Surg* 12: 11-7, 1988
  23. Westgaard A, Tafjord S, Farstad IN, Cvancarova M, Eide TJ, Mathisen O, et al. Pancreatobiliary versus intestinal histologic type of differentiation is an independent prognostic factor in resected periampullary adenocarcinoma. *BMC Cancer* 8: 170, 2008
  24. Sakata E, Shirai Y, Yokoyama N, Wakai T, Sakata J, Hatakeyama K. Clinical significance of lymph node micrometastasis in ampullary carcinoma. *World J Surg* 30: 985-91, 2006
  25. Nakai T, Koh K, Kawabe T, Son E, Yoshikawa H, Yasutomi M. Importance of microperineural invasion as a prognostic factor in ampullary carcinoma. *Br J Surg* 84: 1399-401, 1997