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Original Article

Results and Predictive Factors for Survival of Periampullary Cancer Patients at Uttaradit Hospital

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Abstract

Introduction: **Periampullary cancer is one of the major health concerns worldwide. Even though there are some attempts to work the disease out, the prognosis of periampullary cancer remains poor.**

Objective: **To study results and predictive factors for survival of periampullary cancer patients at Uttaradit Hospital.**

Patients and Methods: **A long-term observational analytic study was done. Information of 82 patients diagnosed with periampullary cancer who received treatment at Uttaradit Hospital from October 2007 to October 2012 was gathered from the database of Department of Surgery, Uttaradit Hospital. The patients' final status had been followed until September 2015. Descriptive statistics, Kaplan-Meier method and a Log-rank test were applied to analyze the information.**

Results: **Patients had an average age of 64.99 years and 52.44% of them were male. All patients had primary tumors located in places as follows: 56.09% at the head of pancreas and 39.02% at the ampulla of Vater. Pancreaticoduodenectomy (PD) was performed in 48.78% of the patients. The overall mortality rate was 53.66%. The median survival time was 2.75 years. The predictive factors were chronic alcohol drinking ($p < 0.01$) and PD operation ($p < 0.05$).**

Conclusion: **Chronic alcohol drinking and a PD operation have significant contribution to the survival of periampullary cancer patients.**

Keywords: **Periampullary cancer, result, predictive factor, survival**

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Introduction

Periampullary cancer is a group of cancers located in pancreatic tissue, distal bile duct, ampulla of Vater, and duodenum. Despite their difference in origins, these cancers are categorized together because of their anatomical proximity, common clinical presentation with signs and symptoms of obstructive jaundice and surgical treatment requiring pancreaticoduodenectomy (PD). Pancreatic ductal adenocarcinoma is the most common cancer in the group, found in nearly 85% of patients, followed by cholangiocarcinoma, adenocarcinoma of the ampulla of Vater, and duodenal adenocarcinoma, respectively. In the United States, the disease emerges at rate of 60,000 per year[1]. Pancreatic cancer was the 9th most common type of cancer diagnosed and the 4th most common cause of cancer-related death each year[2,3].

Long term survival varies widely depending on the tissue of tumor origin, stage at diagnosis, degree of differentiation, ability to perform a complete resection (R0)[4], age, chronic alcohol drinking, smoking, chronic illnesses[5-7]. A treatment that is effective and beneficial to patients is removing the cancer by surgery. Uttaradit Hospital is a tertiary care center with 620 beds. From 2007-2012, there were 92 periampullary cancer patients. There has been no follow-up study of the result of periampullary cancer patients. The authors aimed to study the efficiency of treatments and predictors of survival of periampullary cancer patients.

Objective

To study results and predictive factors for survival of periampullary cancer patients at Uttaradit Hospital.

Patients and Methods

The retrospective cohort study was performed. A total of periampullary cancer patient is 92 but there were 82 patients who had been diagnosed with periampullary cancer and were treated at Uttaradit Hospital from October 2007 to October 2012 and followed until September 2015. Exclusion criteria is the patient who has more than one primary cancer.

Medical records with demographic data, cancer related data, treatment, and patients' current status were obtained from the hospital-based registry of Uttaradit Hospital.

The demographic data was analyzed using descriptive statistics and expressed as percentage, mean, median, and standard deviation. Factors related to patients' survival were analyzed using Kaplan-Meier method, log-rank test and Cox regression.

Results

Periampullary cancer patients were those eligible for this study, numbering 82 cases and representing 89.13% of patients. They were 52.44% male, whose age average was 64.99, 37.80% had a history of chronic drinking, 31.71% had a history of smoking, 24.39% had diabetes and 34.15% had hypertension, as shown in Table 1.

Table 1 Demographic data of periampullary cancer patients

Data	Pancreas, n (%)	Ampulla, n (%)	Distal bile duct, n (%)	Total, n (%)
N	46 (56.10)	32 (39.02)	4 (4.88)	82 (100.00)
Male	26 (56.52)	17 (53.13)	0 (0.00)	43 (52.44)
Age>60 years	36 (78.30)	16 (50.00)	3 (100.00)	55 (67.07)
Average age	68.33 (10.07)	59.63 (13.95)	69.50 (15.29)	64.99 (12.58)
Chronic alcohol drinking	17 (36.96)	13 (40.63)	1 (33.33)	31 (37.80)
Smoking	17 (36.96)	7 (21.88)	2 (66.67)	26 (31.71)
Diabetes	13 (28.26)	7 (21.88)	0 (0.00)	20 (24.39)
Hypertension	12 (26.09)	14 (43.75)	2 (66.67)	28 (34.15)

The pathological staging was made according to AJCC Cancer Staging Manual 7th edition[8]. Stage IIA (45.65%) was the most common stage followed by stage IB (19.57%) and stage IIB cancer (17.39%). The spread of cancer to the liver was 6.07%, followed by peritoneum (3.65 %) as shown in Table 2.

For the treatment, 37.80% of the patient underwent preoperative biliary drainage with stent, 56.09% underwent surgery, 80.49% received chemotherapy, 10.98% received supportive care alone. For the patient who underwent surgery, curative intent resection was performed with PD in 86.96 and palliative bypass was performed in 13.04% of surgical procedure (Table 3).

Table 2 Signs/symptoms and stage of periampullary cancer

Data	Pancreas, n (%)	Ampulla, n (%)	Distal bile duct, n (%)	Total, n (%)
Signs and symptoms				
Jaundice	35 (76.09)	26 (81.25)	2 (50.00)	63 (76.83)
Flatulence	26 (56.52)	25 (78.13)	3 (75.00)	54 (65.85)
Abdominal mass	15 (32.61)	10 (31.25)	1 (25.00)	26 (31.70)
Nausea/Vomiting	14 (30.43)	14 (43.75)	0 (0.00)	28 (34.15)
Anorexia	31 (67.39)	24 (75.00)	3 (75.00)	58 (70.73)
Pathologic staging				
IA	1 (4.55)	0 (0.00)	1 (33.33)	2 (4.35)
IB	3 (13.63)	6 (27.27)	0 (0.00)	9 (19.57)
IIA	11 (50.00)	9 (40.91)	1 (33.33)	21 (45.65)
IIB	2 (9.09)	5 (22.73)	1 (33.33)	8 (17.39)
III	3 (13.64)	0 (0.00)	0 (0.00)	3 (6.52)
IV	2 (9.09)	1 (4.55)	0 (0.00)	3 (6.52)
Location of metastasis				
Bone	1 (2.17)	1 (3.15)	0 (0.00)	2 (2.43)
Liver	3 (6.52)	1 (3.15)	1 (33.33)	5 (6.07)
Brain	1 (2.17)	1 (3.15)	0 (0.00)	2 (2.43)
Peritoneum	2 (4.34)	0 (0.00)	1 (33.33)	3 (3.65)
Lung	0 (0.00)	2 (6.25)	0 (0.00)	2 (2.43)

Table 3 Treatment of periampullary cancer

Treatment	Pancreas, n (%)	Ampulla, n (%)	Distal bile duct, n (%)	Total, n (%)
Supportive	5 (10.87)	3 (9.38)	1 (33.33)	9 (10.98)
Biliary stent	5 (10.87)	2 (6.25)	0 (0.00)	7 (8.54)
Biliary stent with surgery	12 (26.08)	18 (56.25)	1 (33.33)	31 (37.80)
Chemotherapy	38 (82.61)	27 (84.38)	1 (25.00)	66 (80.49)
Chemotherapy after surgery	21 (45.65)	21 (65.63)	0 (0.00)	42 (51.22)
Surgery	22 (26.83)	21 (25.61)	3 (3.65)	46 (56.09)
PD	17 (77.77)	20 (95.24)	3 (33.33)	40 (86.96)
Palliative bypass	5 (22.72)	1 (4.76)	0 (0.00)	6 (13.04)
Postoperative complication				
Delay gastric emptying	2 (6.45)	2 (7.41)	0 (0.00)	4 (8.69)
Postoperative hemorrhage	1 (3.23)	0 (0.00)	0 (0.00)	1 (2.17)
Wound infection	2 (6.45)	2 (7.41)	0 (0.00)	4 (8.69)
Anastomotic leak	1 (3.23)	0 (0.00)	0 (0.00)	1 (2.17)

Table 4 Mortality rate and 5-year survival of periampullary cancer patients

	Pancreas	Ampulla	Distal bile duct	Total
Mortality rate, n (%)	23 (45.62)	17 (46.88)	4 (100.00)	44 (53.66)
5-year survival, years (95%CI)	3.23 (1.65-4.25)	3.02 (1.74-4.20)	0.31 (0.11-0.52)	2.75 (1.65-3.39)

The mortality rate was 53.66% and median survival was 2.75 years (95% CI=1.65-3.39). The patients with distal bile duct cancer had a mortality rate of 100% and their median survival was 0.31 years (95%CI=0.11-0.52), as shown in Table 4.

Periampullary cancer among the patients under and over the age of 60 years; patients under the age of 60 years had a median survival of 3.12 years (95% CI=1.71-4.53) and a 5-year survival rate of 40.00% and patients over the age of 60 years had a median survival of 2.95 years (95% CI=0.08-5.81) and a 5-year survival rate of 0.00% (Figure 1).

Male and female patients; male patients had a median survival of 2.08 years (95% CI=0.26-3.88) and a 5-year survival rate of 0.00% and female patients had a median survival of 3.12 years (95% CI=2.02-3.12) and a 5-year survival rate of 45.00% (Figure 2).

Patients with and without chronic alcohol drinking; patients with chronic alcohol drinking had a median survival of 2.26 years (95% CI=0.16-4.36) and a 5-year survival rate of 45.00% and patients without chronic alcohol drinking had a median survival of 3.57 years (95% CI=2.14-5.00) and a 5-year survival rate of 0.00% (Figure 3).

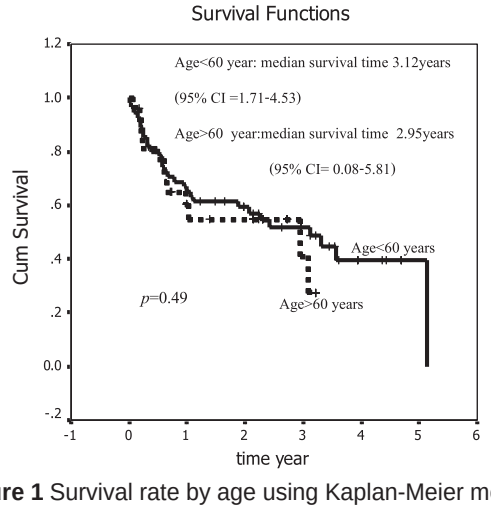

Figure 1 Survival rate by age using Kaplan-Meier method

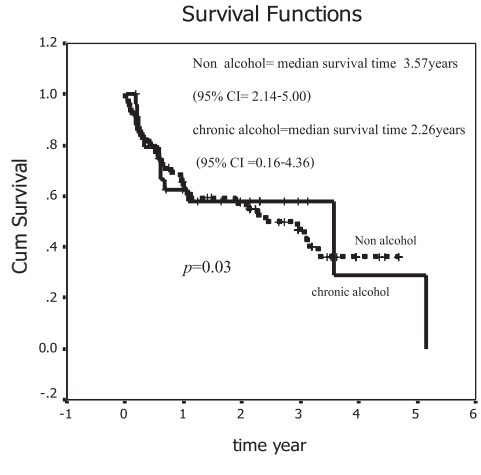

Figure 3 Survival rate by alcohol drinking with Kaplan-Meier method

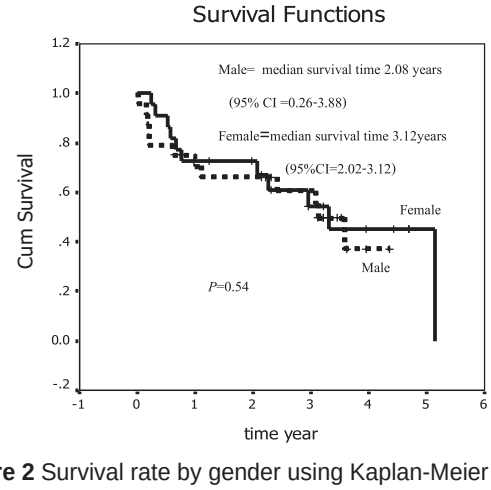

Figure 2 Survival rate by gender using Kaplan-Meier method

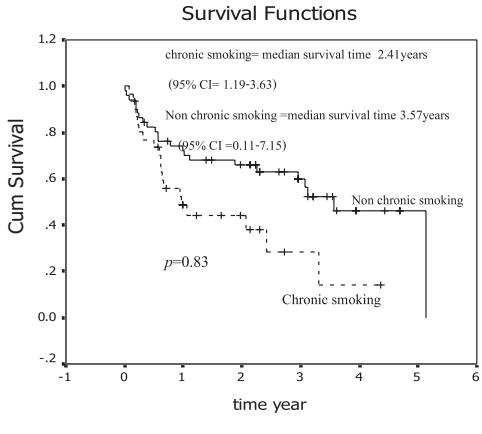

Figure 4 Survival rate by smoking with Kaplan-Meier method

Patients who smoked and those who did not; patients who smoked had a median survival of 2.41 years (95% CI=0.19-3.63) and a 5-year survival rate of 0.00% and patients who did not smoke had a median survival of 3.57 years (95% CI=0.11-7.15) and a 5-year survival rate of 28.00% (Figure 4).

Patients with and without diabetes; patients without diabetes had a median survival of 2.95 years (95% CI=2.14-5.01) and a 5-year survival rate of 25.00% and patients with diabetes had a median survival rate of 2.84 years (95% CI=1.93-3.73) and a 5-year survival rate of 0.00% (Figure 5).

Patients with and without hypertension; patients without hypertension had a median survival of 3.07 years (95% CI=1.77-4.34) and a 5-year survival rate of 40.00% and patients with hypertension had a median survival of 2.95 years (95% CI=1.29-4.62) and a 5-year survival rate of 0.00% (Figure 6).

Patients with pancreatic, ampullary and distal bile duct cancer; Patients with pancreatic cancer had a median survival of 3.30 years (95% CI=1.85-4.75) and a 5-year survival rate of 0.00%, patients with ampullary cancer had a median survival of 3.07 years (95% CI=1.74-4.40) and a 5-year survival rate of 0.00% and patients with distal bile duct cancer had a median survival of 0.32 years (95% CI=0.11-1.52) and a 5-year survival rate of 0.00% (Figure 7).

Patients with stage IA, stage IB, stage IIA, stage IIB, stage III and stage IV cancer; patients with stage IA cancer had a median survival of 0.52 years (95% CI=0.00-0.19), patients with stage IB cancer had a median survival of 3.26 years (95% CI=2.14-4.37), patients with stage IIA cancer had a median survival of 2.26 years (95% CI=1.46-3.06), patients with stage IIB cancer had a median survival of 2.35 years (95% CI=1.36-3.33), patients with stage III cancer had a

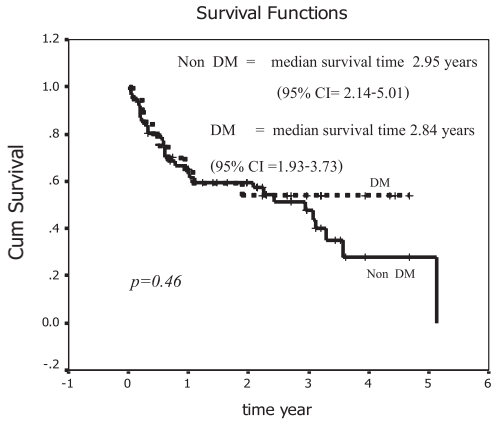

Figure 5 Survival rate by diabetes with Kaplan-Meier method

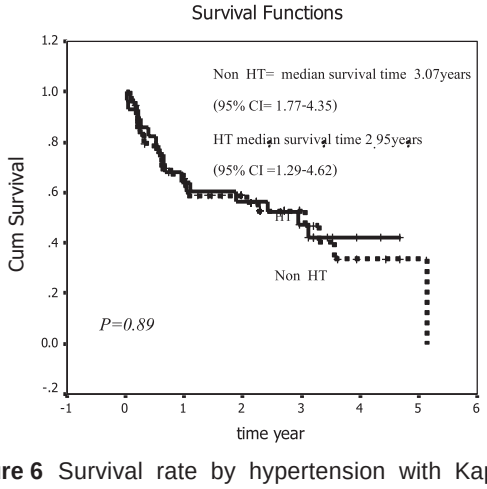

Figure 6 Survival rate by hypertension with Kaplan-Meier method

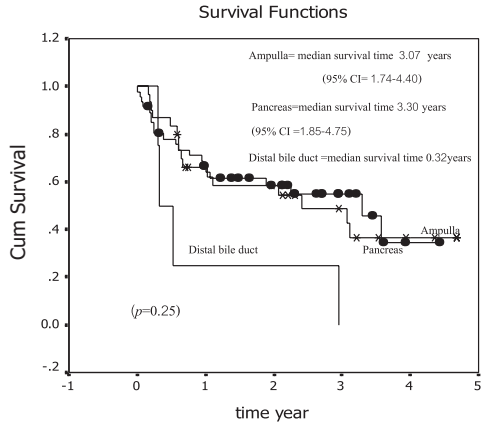

Figure 7 Survival rate by type of cancer with Kaplan-Meier method

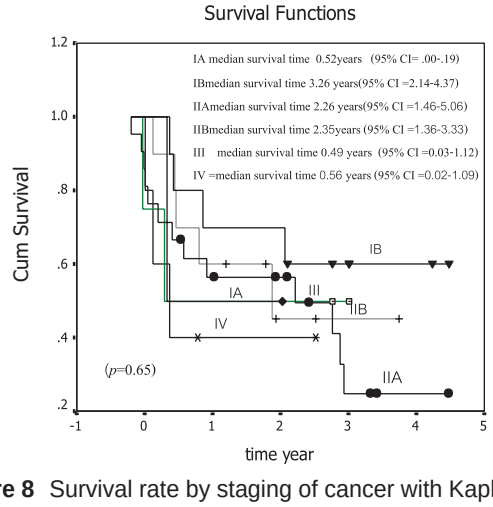

Figure 8 Survival rate by staging of cancer with Kaplan-Meier method

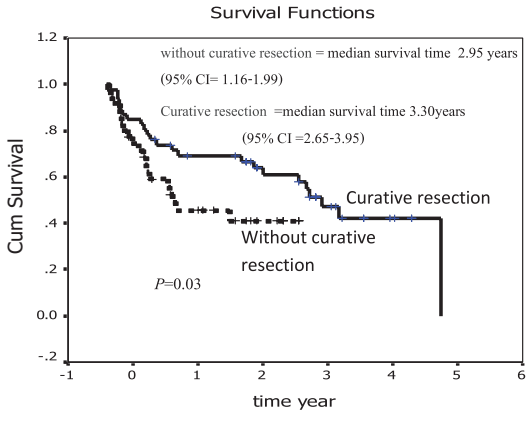

Figure 9 Survival rate by curative resection with Kaplan-Meier method

Table 5 Analyzed 5-year predictors of survival in multivariate analysis of periampullary cancer with Cox-regression

Factor	HR	(95% CI)	*p*-value
Age	1.67	0.60-2.98	0.47
Male	1.48	0.57-2.27	0.72
Smoking	0.32	0.42-1.92	0.79
Chronic Alcohol drinking	0.38	1.05-4.26	0.04
Diabetes	0.76	0.59-3.20	0.49
Hypertension	0.66	0.40-2.11	0.84
Type of cancer	1.49	0.89-3.37	0.11
Stage of cancer	1.25	0.94-1.78	0.76
Curative resection	1.13	0.60-2.14	0.03

median survival of 0.49 years (95% CI=0.03-1.12), patients with stage IV cancer had a median survival of 0.56 years (95% CI=0.02-1.09). Every patient, despite different stage of the cancer, had the same 5-year survival rate which is 0.00% (Figure 8).

Patients who received curative surgery and those who did not; patients who did not receive curative surgery had a median survival of 2.95 years (95%CI= 1.16-1.99) and a 5-year survival rate of 0.00% and patients who received curative surgery had a median survival of 3.30 years (95%CI=2.65-3.95) and a 5-year survival rate of 40.00% (Figure 9).

The predictors of survival in multivariate analysis with Cox-regression revealed that chronic alcoholic drinking (p=0.04) and curative resection (p=0.03) were the factors related to 5-year survival rate as shown in Table 5.

Discussion

This study attempts to determine results and predictive factors for periampullary cancer survival by collecting the data of treatment at Uttaradit Hospital from October 2007 to October 2012. The population was 92 patients but 10 patients were excluded due to missing criteria. There were 82 periampullary cancer patients (89.13%), 46 had pancreatic head cancer (56.10%), 32 had ampullary cancer (39.02%), and 4 had distal bile duct cancer (4.88%). No duodenal cancer was found. It is different from America that distal bile duct cancer is the second most common cancer in group run after pancreatic cancer[1]. Periampullary cancer patients were admitted with jaundice (76.83%) consistent with Fischer (2015)[10], flatulence (65.85%), nausea and vomiting (34.15%), and abdominal mass (31.70%). Diagnosis of cancer was not pathologically confirmed in all patients. Many patients were diagnosed with imaging study and tumor markers. The metastasis of cancer spread to liver (6.07%) and peritoneum (3.65%); consistent with Jagannath, Shrikhande (2003)[9].

During 2007 and 2012 at Uttaradit Hospital, surgeons took the responsibility for the entire treatment of solid cancer patients except radiation therapy. In this study of 82 patients' treatments, 10.98% were supportive, 8.54% underwent biliary stenting as palliative treatment, 37.80% underwent preoperative biliary stenting and surgery, and 56.09% underwent surgery, of which 86.96% was PD and the other (13.04%) was palliative bypass. Preoperative biliary drainage in resectable cancer patient was controversy. A prospective randomized trial in patients with pancreatic cancer found that routine preoperative stenting was associated with an increase in serious septic complication with no change in mortality and morbidity[2]. Endoscopic retrograde cholangiopancreatography (ERCP) directly visualized the ampullary region and provided an opportunity to relieve biliary obstruction while obtaining a provisional diagnosis. Duodenal and ampullary cancer may present themselves for immediate biopsy. ERCP in distal bile duct cancer, attempts at brushing of duct or intraductal biopsy may provide a cytology/pathology diagnosis. Biliary stenting at the time of ERCP provides immediate relief from biliary obstruction and allows the patient's symptom to improve in cholangitis, intractable pruritus, significant malnutrition, coagulopathy. It is a palliative

treatment for patient presented with metastatic/locally advanced cancer.

PD is the preferred operation for potentially curable periampullary cancer. In this study, the authors performed pylorus-preserving PD in all resectable cancer patients.

After tumor specimen was removed, the authors performed reconstruction in the operation. The divided jejunum was pulled through the ligament of Treitz in the proper orientation under the root of mesentery to lay in the right upper quadrant as an upside-down "J". The end-to-side invaginated duct-to-mucosa pancreaticojejunostomy is fashioned in two layers, with a 4-0 braided polyglactin interrupted suture used on the mucosa and a 3-0 silk interrupted suture used on the serosa and pancreatic capsule to buttress the pancreas against the jejunum.

There are more than 70 technical variations for pancreatic anastomosis, and all have equivalent results. The choice of techniques usually depends on the surgeon's personal experience[10].

The end-to-side hepaticodochojejunostomy is constructed 5-10 cm away from the pancreaticojejunostomy. One layer (mucosa to mucosa) is fashioned using a 3-0 braided polyglactin interrupted suture.

The duodenojejunostomy is preferred in antecolic fashion 15-20 cm downstream from the hepaticodochojejunostomy.

Mortality and morbidity showed no significant differences between classic Whipple and pylorus-preserving approach, operating time and intraoperative blood loss were significant reduced in the pylorus-preserving approach[11].

There was no trial to suggest the superiority of a pylorus-preserving over classic Whipple procedure[2]. PD is an acceptable alternative to the classic Whipple's[3].

Postoperative complications; the authors found no mortality in this study. Postoperative mortality in high-volume center (>5 pancreatectomy/year) is low (0-3%)[1] and less than 5%[10]. There was delay gastric emptying time in 8.69%, wound infection in 8.69%, postoperative hemorrhage in 2.17%, and anastomotic leakage in 2.17%. These findings seem to be less than in other literatures. Yeo et al. (1997)[12] found delayed gastric emptying 23%, pancreatic fistula 17%, and wound infection 9%. A review by Edil (2014) 1 showed delayed gastric emptying 15-40%, pancreatic anastomotic leakage 10-20%, intraabdominal abscess 8-10% and postoperative hemorrhage 1-8%. The high variability in complication rate between studies can partially be attributed to lack of standardized reporting of postoperative adverse events.

Curative resections are related to increased survival[13] and also the main treatment of periampullary cancer. Following surgical resection for pancreatic cancer, the median survival is approximately 22 months[10], with 5-year survival of 15-20%. In the absence of surgical resection, those with locally advanced disease who received palliative chemotherapy may survive 10-12 months, whereas those with metastases rarely survive beyond 6 months[1]. This study has established that having curative resection can cause the survival rate to be significantly different. The patients who did not undergo curative resection had a median survival rate of 2.95 years (95% CI 1.16-1.99) and a 5-year survival rate of 0.00%. On the other hand, the patients who underwent curative resection had a median survival rate of 3.30 years (95% CI 2.65-3.95) and a 5-year survival rate of 40.00%. Some studies reported less benefit of surgery. Zerbi[14] et al. found that without PD, a median survival was 15 months, compared with 17 months in the patients who underwent PD.

A curative intent resection provides the only potential chance for cure or long term survival. On the other hand, up to 80% of the patients had disease recurrence following PD. This finding argues against surgery alone being an adequate treatment modality. Adjuvant chemotherapy likely increases the chance of survival, although the benefit is on the order of months rather than years. In this study, most patients received chemotherapy (80.49%) as adjuvant therapy or palliative therapy. The role of radiation therapy is even more controversial. In this study, no patients with curative intent resection cancer received adjuvant radiation therapy.

Large European multicenter trial concluded that there was no value of chemoradiotherapy. The study suggested that chemotherapy alone might have survival benefit in resectable pancreatic cancer[15].

When the patients' current vital status was reviewed and followed up, statistical analysis demonstrated that periampullary cancer patients' median survival was 2.75 years (95%CI= 1.89-4.01) and mortality rate 53.66%. 0.31 year with distal bile duct cancer, 3.02 years with ampullary cancer, 3.23 years with pancreatic head cancer. Median survival for resected pancreatic

cancer is less than 24 months[2], 5-year survival of resected pancreatic cancer, distal bile duct cancer, ampullary cancer, duodenal cancer at about 15-25%, 16-52%, 35-55%, and 40-60%, respectively[1,3].

In this study, ampullary cancer tended to have more biologic aggressiveness than pancreatic cancer. The study did not separate type of ampullary cancer (intestinal subtype vs pancreaticobiliary subtype). Ampullary cancer in this study may be pancreaticobiliary subtype that has worse survival[10].

This study suggests that the factors related to survival were not age, sex, smoking, chronic diseases, diabetes or hypertension as they did not provide significant results. However, chronic alcohol drinking did effect the result significantly (p=0.03). This finding is consistent with the studies by Chernrungroj, 2000, Honjo et al., 2005; Songserm, 2011 which reported that chronic alcohol drinking increases the risk of death.

The limitation of this study was the inability to collect other factors that might have contributed to the results, such as tumor size, lymph node status, free resection margins, tumor DNA, genetic alteration, tumor type in nonoperable patient, vascular invasion, intraoperative blood loss, blood transfusion, chemotherapeutic agents, postoperative hospital stay, tumor marker. (Yeo, Sohn, Cameron, Hruban, Uiemoe, and Pitt, 1997, Van Roest et al., 2008).

Suggestions

1. Further study should be performed with a bigger population, multi-institution.

2. Confirm type of cancer with pathologic results in all patients. Develop capability of nonoperative tissue diagnosis: endoscopic ultrasonography-fine needle aspiration biopsy/core needle biopsy, ERCP-peroral cholangioscopy.

3. Develop a hospital-based registry of cancer patients for easier and more efficient access to the data.

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บทคัดย่อ **ผลลัพธ์และปัจจัยพยากรณ์การรอดชีวิตของผู้ป่วยมะเร็ง Periampullary ที่รักษาในโรงพยาบาลอุตรดิตถ์**

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บทนำ: ผู้ป่วยมะเร็ง periampullary เป็นปัญหาสุขภาพที่สำคัญทั่วโลก ถึงแม้ว่าจะมีความพยายามในการบริหารจัดการโรค แต่ยังพบว่าการพยากรณ์โรคของมะเร็ง periampullary ไม่ดี

ระเบียบวิธีวิจัย: เป็นการวิจัยเชิงวิเคราะห์แบบการศึกษาระยะยาว มีวัตถุประสงค์เพื่อศึกษาผลลัพธ์และปัจจัยพยากรณ์การรอดชีวิตของผู้ป่วยมะเร็ง periampullary ที่รักษาในโรงพยาบาลอุตรดิตถ์ โดยการเก็บรวบรวมข้อมูลผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นมะเร็ง periampullary และได้รับการรักษาที่โรงพยาบาลอุตรดิตถ์ ระหว่างวันที่ 1 ตุลาคม 2550 ถึง 30 กันยายน 2555 มีจำนวน 82 คน ติดตามสถานะสุดท้ายของผู้ป่วย จนถึงวันที่ 30 กันยายน 2558 โดยรวบรวมข้อมูลผู้ป่วยจากฐานข้อมูลหน่วยทะเบียนมะเร็ง ฐานข้อมูลการตายของสำนักทะเบียนราษฎร์ วิเคราะห์ข้อมูล โดยใช้สถิติพรรณนา วิธีของแคปลานและไมย์เออร์ สถิติและทดสอบลอกแรง

ผลการวิจัย: ผู้ป่วยมีอายุเฉลี่ย 64.99 ปี เป็นเพศชาย ร้อยละ 52.44 เป็นมะเร็งส่วนหัวของตับอ่อน ร้อยละ 56.09 ส่วนแอมพูลา ร้อยละ 39.02 ผู้ป่วยได้รับการผ่าตัด PD ร้อยละ 48.78 อัตราการเสียชีวิตภาพรวม ร้อยละ 53.66 มีค่ามัธยฐานระยะเวลารอดชีวิต เท่ากับ 2.75 ปี ปัจจัยพยากรณ์การรอดชีวิตของผู้ป่วยมะเร็ง คือ การดื่มแอลกอฮอล์เรื้อรัง ($p < 0.01$) และการผ่าตัด PD ($p < 0.05$)

สรุป: การดื่มแอลกอฮอล์เรื้อรังและการรักษาด้วยการผ่าตัด PD มีความสำคัญต่อผลลัพธ์การรักษาและการพยากรณ์การรอดชีวิตของผู้ป่วยมะเร็ง periampullary