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Original Article

Survival Rate in Curative Resection of Pancreatic Cancer Patients at Maharat Nakhon Ratchasima Hospital

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Abstract

Objective: Pancreatic cancer is difficult to diagnose and treat. Survival rate of pancreatic cancer is also dismal and many clinicopathologic factors are related to survival. The aims of the present study were to determine the 5-year survival rate and prognostic factors associated with survival in pancreatic cancer patients undergoing curative resection.

Patients and Methods: Pancreatic cancer patient data were collected from medical records between January 1, 2009 and June 30, 2012. The primary outcome was overall survival by Kaplan-Meier method. Univariate and multivariate Cox proportional hazard regression analysis was used to determine independent prognostic factors.

Results: Median survival time was 14.3 months and 5-year survival rate was 10.3%. From Cox univariate regression analysis, independent and significant factors predicting the survival of these patients included tumor size, intraoperative blood loss, pathological margin, and lymph node involvement ($p < 0.05$). From Cox multivariate regression analysis only pathological margin, and intraoperative blood loss were significantly associated with survival ($p < 0.05$).

Conclusion: In this study, pathological margin and intraoperative blood loss significantly affected overall survival

Keywords: Pancreatic cancer, Survival rate, Prognostic factors

Introduction

Although the incidence of pancreatic cancer is low, the mortality rate of this lethal disease is high. Because the pancreas is a retroperitoneal organ, it is difficult to make an early diagnosis of pancreatic cancer. The relative incidence of newly diagnosed pancreatic cancer was 2.5% of all cancers. Age-standardized rates (ASRs) per 100,000 person-years was 7.7 in Europe and 7.6 in North America.[1] The Thai National Cancer Institute reported the incidence of pancreatic cancer in 2019 was higher in women. Pancreatic cancer was in the top ten highest ranking causes of cancer-related deaths (8th for males, 9th for females).[2]

Pancreatic cancer is categorized into 2 main types: Pancreatic adenocarcinoma, which is found in 85% of all pancreatic cancer patients, and pancreatic neuroendocrine tumor (PanNET), which is found in less than 5%.[3] There are 4 stages of pancreatic cancer (American Joint Committee on Cancer 7th editon). Curative resection in pancreatic cancer can be performed in all stage 1 and

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some stage 2 patients.[4] Tumors located in the head of pancreas should be be surgically removed by pancreaticoduodenectomy, while cancer located in the body and tail of pancreas is removed by distal pancreatectomy. Only 18 % of pancreatic cancer patients are eligible for curative resection.[5]

Pancreatic cancer has 1-year and 5-year survival rates of 24% and 9%, respectively.[6] In Thailand, 1-year and 3-year survival rates were 24% and 6 %, respectively.[7] From a study of pancreatic cancer survival rates by stage, stages 1 and 2 (localized pancreatic cancer) has a 5-year survival rate of 32% to 39 %. For stage 3 disease (regional pancreatic cancer), the 5-year survival rate was 12% to 13%, and in stage 4 disease (distant metastasis), the 5-year survival rate was 3 %.[8-9]

One study found some clinicopathological factors which may affect survival rates. These include involvement of resection margins, major vascular ingrowth, site of origin, and perioperative blood transfusion.[10] A study reported that, with pancreatic lesions less than 3 cm in size, preoperative EUS -FNA (endoscopic ultrasonography- fine needle aspiration) was able to determine T staging, vascular invasion and resectability with some accuracy.[11] Also, many studies showed that lymph node involvement was related to survival.[12,13] In this study, we aim to determine the survival rates and the clinicopathological factors associated with survival of resectable pancreatic cancer.

Patients and Methods

After approval by the Ethics Committees of the Institute (Document No112/2021), data were collected retrospectively from medical records at Maharat Nakhon Ratchasima Hospital of patients with pancreatic cancer (ICD10 codes: C250, C251, C252, C253) treated between January 1, 2009 to June 30, 2012 (3 years and 6 months). All patients were followed until June 30, 2017. All patients had pathologically confirmed pancreatic adenocarcinoma and all underwent successful curative surgery. Those with recurrent pancreatic cancer or metastatic cancers to the pancreas were excluded.

All statistical analyses were performed with STATA, version 11.0, software (StataCorp LP, College Station, Texas). Histograms, boxplots, and descriptive methods were used to examine data for errors, outliers, and missing values. The primary outcome was overall survival by Kaplan-Meier method, calculated in months from the date of diagnosis to the date of death. Non-deaths or deaths from other causes were censored at the time of the last follow-up. Clinical factors examined included age, gender, tumor size (< 3 cm or ≥ 3 cm),[11] lymph node involvement (negative or positive), pathological margin (positive margin was defined as cancerous cells detected < 1 mm from resection margin; otherwise the margin was negative),[14] and intraoperative blood loss (< 700 mL or ≥ 700 mL).[15]

Comparison of survival curves was done using the log-rank test. Independent prognostic factors were identified using multivariable Cox proportional hazards regression models. In one model, variables with a p-value < 0.1 on univariable analysis were included in analysis, with backward stepwise selection. In another, all variables of a priori interest, which included tumor size, lymph node involvement, pathological margin, and intraoperative blood loss were forced into the model. The results were expressed as hazard ratios with p-values and 95% confidence intervals. A p-value of < 0.05 was considered statistically significant.

Results

There were 177 patients diagnosed with pancreatic cancer in the present study. Only 29 patients (16%) underwent successful curative resection. The mean age was 55.4 years with a range from 40 years to 74 years. There were slightly more men (52%) than women (48%). Classical pancreaticoduodenectomy (38%) was the most common operation, and distal pancreatectomy (35%) was the second most common. Among 29 patients, stage 1a (38%) disease was most commonly found, followed by stage 2b (31%). Median intraoperative blood loss was 750 mL. Ten patients (35%) developed postoperative complications (Table 1). The most common postoperative complication was pancreatic anastomosis leakage seen in 5 patients (17 %), defined as fluid amylase > 3 times the upper limit of serum amylase. Three patients had grade B pancreatic leakage, and 2 patients had grade C leakage based on the 2016 update of the International Study Group (ISGPS).[16] Delayed gastric emptying was seen in 3 patients (10%). Two patients developed wound infection (7%). There were 2 postoperative deaths (7%). Causes of death were sepsis and multiorgan failure following pancreatic anastomosis leakage.

The overall survival is presented in Figure 1. The median survival time was 14.3 months (95% CI: 7.2 to 20 months) and the 5-year survival rate was 10.3%. There was no statistical difference in survival between

Table 1 Clinical and laboratory characteristics of patients.

Characteristics	Summary (N = 29)
Age (year): mean, SD (range)	55.4, 8.9 (40 to 74)
Gender: number (%)	
Male	15 (52)
Female	14 (48)
Operations: number (%)	
Classical pancreaticoduodenectomy	11 (38)
PPPD*	8 (28)
Distal pancreatectomy	10 (34)
Stage: number (%)	
1a	11 (38)
1b	7 (24)
2a	2 (7)
2b	9 (31)
Intraoperative blood loss (mL): median (interquartile range)	750 (500 to 900)
Postoperative complication: number (%)	10 (35)
Postoperative deaths: number (%)	2 (7)
Total bilirubin: number (%)	
< 3 mg/dL	18 (62)
≥ 3 mg/dL	11 (38)
Serum albumin: number (%)	
≤ 3.5 g/dL	17 (59)
> 3.5 g/dL	12 (41)
CEA ≥ 5 ng/mL: number (%)	8 (28)
CA 19-9 ≥ 37 U/mL: number (%)	11 (38)

*PPPD: pylorus-preserving pancreaticoduodenectomy

the pancreatic head resection (combine classical pancreaticoduodenectomy and pylorus-preserving pancreaticoduodenectomy) and distal pancreatectomy ($p = 0.61$), as displayed in Figure 2.

On univariable analysis of clinicopathologic factors in Table 2, tumor size, pathological margins, blood lass and lymph node involvement were significantly related to survival at the 5% level. In particular, the mortality risk was increased for patients with positive pathological margin as compared with patients with negative pathological margin, with a hazard ratio (HR) of 9.5; 95% CI: 3.3 to 27.3; $p < 0.001$. The mortality risk was 6-fold higher in patients with positive lymph node involvement as compared with those with negative lymph node involvement (HR of 6.0; 95% CI: 2.1 to 16.8; $p = 0.001$). In addition, intraoperative blood loss of more than 700 mL increased the mortality risk when compared with intraoperative blood loss of less than 700 mL (HR of 3.7; 95% CI: 1.6 to 8.7; $p = 0.003$). Similarly, the mortality risk of patients who had tumor size greater than 3 cm was 3.2- fold higher than that of patients had tumor size smaller than 3 cm (HR of 3.2, 95% CI: 1.3 to 6.8; $p = 0.01$). Other clinicopathological factors, such as age and gender, had no significant association with survival.

On multivariable Cox regression analysis (Table 3), only pathological margin, and intraoperative blood loss were significantly associated with survival ($p < 0.05$). In detail, positive pathological margin increased 7.4-fold the mortality risk, as compared with negative pathological margin (HR of 7.4; 95% CI: 2.6 to 21.4; $p < 0.001$).

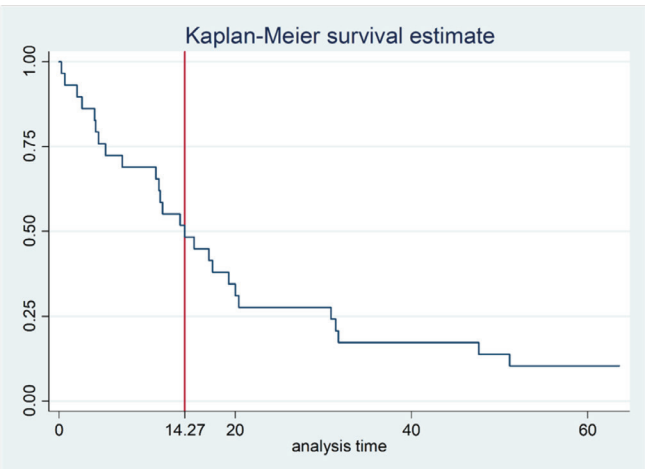

Figure 1 Overall survival of pancreatic cancer patients

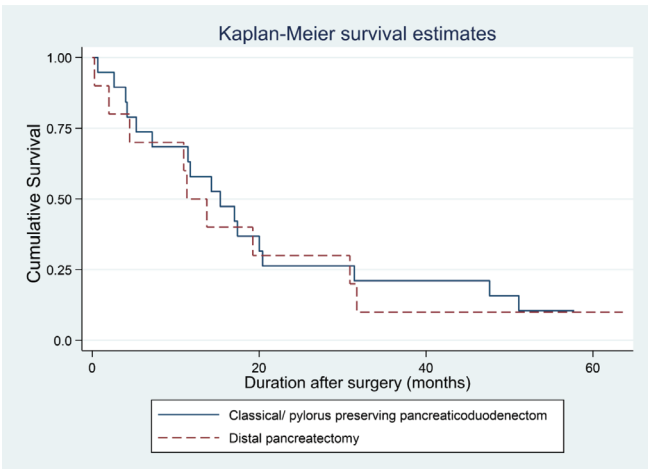

Figure 2 Comparison of survival between pancreatic head resection and distal pancreatectomy (log-rank test $p = 0.61$). See text

Table 2 Univariable Cox regression analysis of clinicopathologic factors

Factors	Number (%) N = 29	Median survival (months)	Time at risk	Incidence rate/100	Crude HR	95% CI	*p*-value
Age (years)						0.8 to 3.9	0.158
< 65	17 (59)	17.40	419.73	3.5	1		
≥ 65	12 (41)	11.33	162.13	6.7	1.8		
Gender						0.2 to 1.1	0.072
Men	15 (52)	13.73	206.33	7.2	1		
Women	14 (48)	17.03	375.53	2.9	0.5		
Tumor size						1.3 to 6.8	0.008
< 3 cm	14 (48)	20.4	404.69	2.9	1		
≥ 3 cm	15 (25)	7.16	177.16	7.9	3.2		
Intraoperative blood loss						1.6 to 8.7	0.003
< 700 mL	15 (52)	20.4	442.09	2.7	1		
≥ 700 mL	14 (48)	7.16	139.76	10.0	3.7		
Pathological margin						3.3 to 27.3	< 0.001
Negative	19 (65)	20	529.36	3.0	1		
Positive	10 (35)	4	52.49	19.0	9.5		
Lymph node involvement						2.1 to 16.8	0.001
Negative	21 (72)	19.23	531.99	3.3	1		
Positive	8 (28)	4.16	49.86	16.0	6.0		

HR: hazard ratio; CI: confidence interval

Table 3 Multivariable Cox regression analysis of clinicopathologic factors

Factors	Crude HR	Adjusted HR* (95% CI)	*p*-value	Adjusted HR* (95% CI)	*p*-value
Gender					
Male	1	-	-	-	-
Female	0.48	-	-	-	-
Tumor size				Ref. 1.64 (0.53 to 5.11)	0.392
< 3 cm	1	-	-		
≥ 3 cm	3.02	-	-		
Intraoperative blood loss		Ref. 2.88 (1.17 to 7.08)		Ref. 3.18 (1.14 to 8.85)	0.027
< 700 cc	1				
≥ 700 cc	3.7		0.023		
Pathological margin		Ref. 7.39 (2.55 to 21.4)		Ref. 6.24 (1.40 to 27.8)	0.016
Negative	1				
Positive	9.48		< 0.001		
Lymph node involvement				Ref. 0.79 (0.17 to 3.66)	0.759
Negative	1	-	-		
Positive	6.01	-	-		

*Each column represents a different cox regression model. Covariates not included in final models are indicated as (-); CI: confidence interval; HR: hazard ratio; Ref.: reference group

Patients with operative blood loss more than 700 mL also had increased mortality risk as compared with patients with operative blood loss less than 700 mL (HR of 2.9; 95% CI 1.2 to 7.1; $p = 0.023$). The result of a model with all *a priori* factors of interest included, also showed that only positive pathological margin and intraoperative blood loss more than 700 mL were significant risk factors, with similar HR's as those in the previous model, while other factors had no significant association with survival.

Discussion

Only 15% to 20% of all pancreatic cancers are resectable. These mostly include stage1 and 2 diseases.[5,17] Our study showed a similar resectability rate (16.4%). To improve resectability, early detection is important. We suggest that patients who have symptoms, including severe weight loss, chronic abdominal pain and jaundice, should be examined by a physician as soon as possible and appropriate investigations be done for detecting early stage pancreatic cancer. A study reported that preoperative EUS- FNA[11] and neoadjuvant chemotherapy may improve resectability.[18]

Operative morbidity and mortality reported in the present study were similar to those of other tertiary centers.[5,19] The 5-year survival rate of patients with resectable pancreatic cancer was comparable to those of some other reports (10% to 31%).[20] However, many recent studies showed better survival.[5,21] We believe that some of these differences may be due to treatment in specialized pancreatic care centers, treated by pancreatic disease specialists, with better treatment options, shorter cancer waiting time, and along with a higher frequency of negative surgical margin, and negative lymph nodes involvement, these can all improve treatment outcomes.

The present study clearly indicated that positive pathological margin was an independent risk factor for cancer-related death. There are 8 pancreatic resection margins: 4 in transection margins that include pancreas cut-end margin, bile duct cut-end margin, proximal gastric or duodenal resection margin, and distal jejunal or enteric margin; 3 in the dissected margins including posterior margin, portal vein (PV) or superior mesenteric vein (SMV) groove margin and superior mesenteric artery (SMA) margin; and the last margin at the anterior surface of the pancreas.[22] Some reports defined the posterior margin as the retroperitoneal margin or the uncinate margin, and the SMA margin as the uncinate margin.[23] One study demonstrated that margin clearance by at least 1.5 mm may improve long-term survival.[23] Another study reported that a margin clearance of 2 mm or greater were associated with increased overall survival.[24] At our Institution, we consider a surgical resection margin negative when at least 1 mm margin clearance is achieved.[14]

Intraoperative blood loss (IBL) is also associated with mortality risk in the present study. A study from Japan reported that operative blood loss was associated with the risk of pancreatic cancer mortality.[25] On the other hand, there are also studies showing that IBL was not an independent risk factor in patients with cancer.[15,26-27] Some studies reported that there was evidence for an association between blood transfusion and increasing risk of infectious complications,[28] and the risk of recurrence.[29] It remains unclear why IBL is associated with morbidity and low survival rate. Data from animal studies found that the activity or cytotoxicity of natural killer cells was depressed after blood loss.[30] In the present study, massive intraoperative blood loss occurred when pancreatic resection was combined with portal vein resection. To prevent massive IBL, we focused on preoperative preparation, especially in jaundice patients. Coagulopathy must be corrected. Moreover, we emphasized good surgical technique, identifying bleeding points and to secure bleeding sites around branches of the portal vein, at blood vessels around the uncinate area, and at the transection margin.

The presence of malignant cells in the lymph node (LN) was a predictor of poor survival in several studies.[12] Some studies demonstrated that patients with one to three involved nodes had better survival when compared with those with four to seven nodes.[31] Other reports also showed that patients with more than three involved LNs had worse survival in relation to those with less than three nodes.[13] Recent studies showed that the lymph node ratio (LNR) may be more useful than involved LN status as a prognostic factor in pancreatic cancer.[32-33] However, one study reported that LNR was not associated with survival.[34] In the present study, lymph node involvement was not associated with cancer-related mortality. This may be due to incomplete lymphadenectomy.

The present study has some limitations. Firstly, it was a retrospective study with a relatively small sample size. Larger-sized studies are needed. Secondly, there was selection bias in that patients who has severe underlying diseases such as severe cardiomyopathy, ischemic

heart disease or of very old age are often not operated on. Surgeons tend to treat these patients conservatively to avoid high operative morbidity and mortality.

Conclusion

In the present study, the 5-year survival rate of patients undergoing curative pancreatic resection for pancreatic cancer was 10.3%. Also, positive pathological margin and intraoperative blood loss of more than 700 mL were the only independent risk factors associated with increased cancer-related mortality. From the present study, we emphasize that patients with positive resection margin must be managed with aggressive treatment.

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บทคัดย่อ **อัตราการรอดชีวิตของผู้ป่วยมะเร็งตับอ่อนที่ได้รับการผ่าตัดหวังผลหายขาด (curative resection) ของโรงพยาบาลมหาราชนครราชสีมา**

กีรศักดิ์ จัตวัฒนกุล, พ.บ.
หน่วยศัลยกรรมทั่วไป กลุ่มงานศัลยกรรม โรงพยาบาลมหาราชนครราชสีมา

ความเป็นมา: มะเร็งตับอ่อนเป็นมะเร็งที่มีการวินิจฉัยได้ยากและมีความเสี่ยงสูงในการผ่าตัดทำให้มีอัตราการรอดชีพที่ต่ำ อีกทั้งยังพบว่ามีปัจจัยเสี่ยงอื่นๆ ต่อการรอดชีพ

วัตถุประสงค์: เพื่อศึกษาอัตราการรอดชีพในระยะเวลา 5 ปี และปัจจัยที่มีผลต่อการรอดชีพของผู้ป่วยมะเร็งตับอ่อนที่ได้รับการผ่าตัดหวังผลหายขาด

วิธีการศึกษา: ศึกษาข้อมูลจากเวชระเบียนย้อนหลังและข้อมูลทะเบียนราษฎร์ของผู้ป่วยมะเร็งตับอ่อนที่ได้รับการผ่าตัดหวังผลหายขาดที่โรงพยาบาลมหาราชนครราชสีมาในช่วงเวลา 1 มกราคม 2552 ถึง 30 มิถุนายน 2555 ศึกษาอัตราการรอดชีพในระยะเวลา 5 ปี โดยวิธี Kaplan-Meier และใช้วิธี Cox proportional hazard regression analysis ในการศึกษาถึงปัจจัยที่มีผลต่อการรอดชีพ

ผลการศึกษา: ผู้ป่วยเพียง 29 ราย (ชาย 15 รายและหญิง 14 ราย) เข้ารับการผ่าตัดหวังผลหายขาด มีอายุเฉลี่ย 55.4 ปี ผู้ป่วย 10 ราย (34.5%) เกิดภาวะแทรกซ้อนหลังผ่าตัด และมีผู้ป่วยเสียชีวิตหลังผ่าตัด 2 ราย (6.9%) พบว่ามีอัตราการรอดชีวิตเฉลี่ยอยู่ที่ 14.27 เดือน และอัตราการรอดชีวิต 5 ปี เท่ากับ 10.3% การวิเคราะห์ Cox univariate regression analysis พบว่าปัจจัยที่มีผลต่อการรอดชีพ ได้แก่ ขนาดของเนื้องอก การสูญเสียเลือดระหว่างการผ่าตัด ขอบพยาธิสภาพ และการมีส่วนร่วมของต่อมน้ำเหลือง ($p < 0.05$) และจากการวิเคราะห์ Cox multivariate regression analysis พบว่ามีเพียงระยะขอบทางพยาธิวิทยา และการสูญเสียเลือดระหว่างการผ่าตัดเท่านั้น มีความสัมพันธ์กับการรอดชีวิตอย่างมีนัยสำคัญ ($p < 0.05$)

สรุปผลการศึกษา: ในการศึกษานี้พบว่ามีอัตราการรอดชีวิตเฉลี่ยอยู่ที่ 14.3 เดือนและอัตราการรอดชีวิต 5 ปี เท่ากับ 12.5% และยังพบว่าระยะขอบทางพยาธิวิทยาและการสูญเสียเลือดระหว่างผ่าตัดมีผลต่อการรอดชีวิตโดยรวมอย่างมีนัยสำคัญ