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Factors affecting survival in patients who underwent pancreaticoduodenectomy for periampullary cancers

Temel Deniz Şeren[1], Koray Topgül[2], Bülent Koca[3], Kenan Erzurumlu[4]

ABSTRACT

Objective: The purpose of this study was to determine the factors affecting survival in patients who underwent pancreaticoduodenectomy for periampullary cancers and to discuss the outcomes of our findings.

Material and Methods: This retrospective study included 79 patients who underwent pancreaticoduodenectomy for periampullary cancers between September 1987 and October 2011 in the Department of General Surgery at Ondokuz Mayis University School of Medicine. The factors of age, tumor localization, tumor size, lymphovascular invasion, status of lymph node metastasis, tumor differentiation, preoperative CA 19-9 levels, preoperative total bilirubin levels, preoperative albumin levels, and preoperative biliary drainage were investigated to determine their influence on survival. The survival periods were calculated using the Kaplan-Meier method. The log-rank test was used for comparison of the prognostic factors. The independent prognostic factors affecting survival were determined by Cox hazard regression analysis and hazard ratios (HR) and 95% confidence intervals (CI) were calculated. $P<0.05$ was considered as significant.

Results: The following were identified as independent prognostic factors adversely affecting survival: tumor size ≥2 cm (HR: 2.0, 95% CI: 0.27-0.90), lymphovascular invasion (HR: 2.9, 95% CI: 0.18-0.60), CA 19-9 levels ≥100 U/mL (HR: 2.0, 95% CI: 0.26-0.90), and albumin levels <2.5 mg/dL (HR: 2.7, 95% CI: 1.14-6.66).

Conclusion: The independent prognostic factors identified in this study can be used for selection of patients for whom pancreaticoduodenectomy should be applied for periampullary cancers. These factors could help us to estimate survival rates.

Keywords: Periampullary tumors, pancreatic carcinoma, pancreaticoduodenectomy, prognostic factor

INTRODUCTION

Periampullary cancers include tumors originating within 2cm of the major papilla (1). These tumors are, in order of decreasing incidence, pancreatic head, ampulla Vateri, distal common bile duct and duodenal cancers (1, 2). Although their biological behavior and prognosis are different, they show similar clinical features and the origin of the tumor usually cannot be differentiated with preoperative imaging, and even with surgery. However, the only curative treatment known today in all these types is pancreaticoduodenectomy (PD) (3). The main issues in PD are the complexity of the surgery and the high morbidity and mortality rates related to the procedure. In the 1960s, most surgeons reported the surgical mortality rate as 20-40%. These results led to doubts that surgery is worse than the disease itself, along with the low long-term survival rates (4). Recently, surgery-related mortality is reported as 5% (5, 6).

Selection of suitable patients with periampullary cancer for surgery is of utmost importance due to the high morbidity and mortality rates after PD, and the low survival rates of PD patients. Thus, identifying patients with longer survival is important. We aimed to identify independent prognostic factors that influence survival and report results of our series of patients who underwent PD due to periampullary malignant tumors.

MATERIAL AND METHODS

Medical records of 85 patients who underwent PD for periampullary malignancy, were histologically diagnosed with adenocarcinoma, and had resectable disease between September 1987 and October 2011 in Ondokuz Mayıs University General Surgery Department were reviewed. Five patients whose files could not be reached and one patient who died due to acute myocardial infarction at 5 months after surgery were excluded from the study, with 79 patients being included in the study. In the retrospective study, age (<65, ≥65), localization (pancreas, non-pancreatic), tumor size (<2 cm, ≥2 cm), lymphovascular invasion (LVI), lymph node metastasis, tumor differentiation (well, moderate-poor), CA 19-9 level (<100 U/mL, ≥100 U/mL), preoperative total bilirubin level (<5 mg/dL, ≥5 mg/dL), preoperative albumin level (<2.5 g/ dL, ≥2.5 g/dL) and presence of preoperative biliary drainage (diagnostic and / or therapeu-

[1]Clinic of General Surgery, Çankırı State Hospital, Çankırı, Turkey
[2]Department of General Surgery, İstanbul Kemerburgaz University Faculty of Medicine, İstanbul, Turkey
[3]Clinic of General Surgery, Korgan State Hospital, Ordu, Turkey
[4]Department of General Surgery, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey

Address for Correspondence
Temel Deniz Şeren
Çankırı Devlet Hastanesi, Genel Cerrahi Kliniği, Çankırı, Türkiye
Phone: +90 376 213 27 27
e-mail: tdenizseren@gmail.com

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Table 1. Patient characteristics and 3-year survival rates

	Patient number (n=79) and percentage (%)	3-year survival (%)	p
Age			
<65	39 (49)	28.1	0.118
≥65	40 (51)	20.1	
Location			
Pancreas head	28 (35)	9	
Non-pancreatic periampullary cancer	51 (65)	42.2	0.02
-Ampulla Vateri	41 (52)		
-Distal common bile duct	7 (9)		
-Duodenum	3 (4)		
Size			
<2 cm	35 (44)	42.9	0.042
≥2 cm	44 (56)	25.8	
LVI			
Present	31 (39)	20.1	<0.001
Absent	48 (61)	39.3	
Lymph node metastasis			
Present	36 (45)	35	0.375
Absent	43 (55)	41.5	
Differentiation			
Well	38 (48)	37.1	0.245
Moderate or poor	41 (52)	25.4	
Preoperative CA 19-9			
<100	35 (44)	41.9	0.013
≥100	44 (56)	22.3	
Preoperative total bilirubin			
<5	31 (39)	43.6	0.031
≥5	48 (61)	23.8	
Preoperative albumin (g/dL)			
<2.5	7 (9)	0	<0.001
≥2.5	72 (91)	34.1	
Preoperative intervention (ERCP and/or PTC)			
Present	42 (53)	31.2	0.737
Absent	37 (47)	30.3	

LVI: Lymphovascular invasion; CA: carbohydrate antigen; ERCP: endoscopic retrograde cholangiopancreatography; PTC: percutaneous transhepatic cholangiography

tic for hyperbilirubinemia) (ERCP and / or PTC) were identified as factors to be investigated for impact on survival.

Statistical Analysis

Statistical analysis were performed with Statistical Program for Social Sciences (SPSS Inc., Chicago, IL, USA) 15.0. Survival rate was calculated by Kaplan-Meier method. Comparison of prognostic factors was performed using the log-rank test, and independent prognostic factors affecting survival were determined by Cox hazard regression test. P<0.05 was considered significant.

RESULTS

The study included 79 patients with periampullary tumors, who were histologically diagnosed as adenocarcinoma, were resectable and underwent PD. The mean age of the patients was 63.7 (range 37-85). General characteristics of the patients are shown in Table 1.

The mean follow-up period was 22.3 (range: 1-84) months. Evaluation of surgeries according to years showed that three patients had been operated during 1987-1997 without hospital mortality, 32 patients underwent surgery between 1998-2007, covering a ten-year period, with six hospital mortalities, whereas in the last period of four years, 2008-2011, 44 patients underwent surgery and hospital mortality was observed in three patients.

Nine patients died within the first 30 days postoperatively. While in the first two decades, peri-operative mortality was seen in six patients, in the last four years the number of mortal surgeries was three. Overall postoperative in-hospital mortality was11.3%. Within the last four years, including 44 patients, there were three postoperative hospital mortalities yielding a hospital mortality rate of 6.8%.

The 5-year survival in non-pancreatic periampullary tumors undergoing PD was estimated as 33%. The three-year survival rate was 42.2%. Since there were no survivors at 5-years in pancreatic cancer patients undergoing PD, we were unable to calculate five-year survival, the three-year survival in this group of patients was 9%. The overall 5-year survival in patients with PD performed by our group was found to be 24% (Figure 1).

The log-rank analysis revealed that being younger or older than 65 years of age did not have a significant effect on survival (p=0.118). The 3-year survival rates of patients younger than 65 were 28.1%, and that of older than 65 years was 20.1%.

In 28 patients (35%) the tumor originated from the pancreatic head, and in 51 (65%) it was located in the non-pancreatic periampullary region. Of the non-pancreatic tumors, three were duodenal tumors, 7 distal common bile duct tumors, and 41 ampulla Vateri tumors. On univariate analysis, the survival in non-pancreatic periampullary cancers after PD was significantly better as compared to pancreatic cancer (p=0.02). In patients with tumors of the pancreas, the 3-year survival was 9%, while this rate was 42.2% in non-pancreatic periampullary cancer patients.

In the study, the mean tumor size was 2.1 cm (range: 0.7 to 8 cm). In 35 patients the tumor size was <2 cm, while the tumor size was ≥2 cm in 44 patients. The log-rank analysis showed

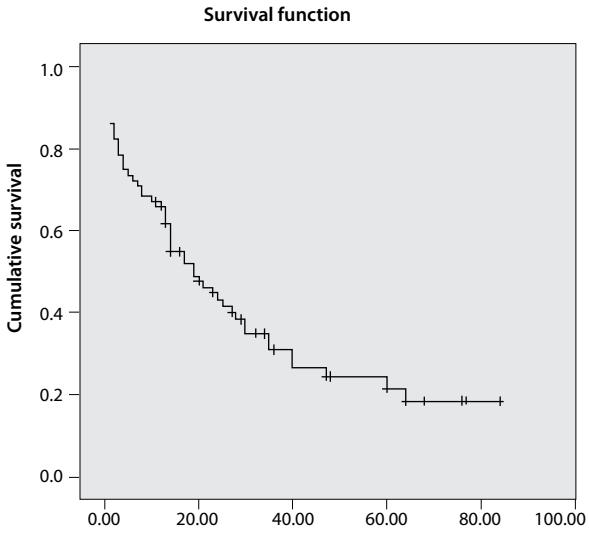

Figure 1. Survival plot of study group

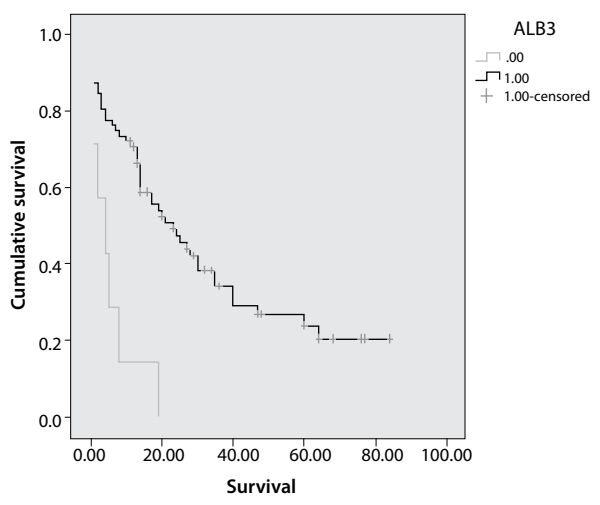

Figure 2. Survival plot according to preoperative albumin level (p<0.001)

that survival was shorter in patients with tumor size ≥2 cm (p=0.042). The 3-year survival rate for patients with tumor size over two cm was found to be 25.8%. In patients with tumor size below 2 cm, the 3-year survival rate was 42.9%.

In the statistical evaluation, it was found that LVI had a significant impact on survival (p<0.001). Survival of patients with positive LVI was found to be worse. The 3-year survival rate in patients with LVI was 20.1%, while the rate in LVI negative patients was calculated as 39.3%.

Lymph node metastasis was present in 36 patients. Forty-three patients had no evidence of lymph node metastasis. There was no significant effect of lymph node metastasis on survival in statistical analysis (p=0.375). The 3-year survival rate was 35% in patients with lymph node metastasis. This rate was 41.5% in patients without lymph node metastasis.

Tumor differentiation of patients included in the study was classified into two groups, well and moderate or poorly differentiated. 38 patients had well-differentiated tumors, and 41 showed moderate or poorly differentiated tumors. It was determined that tumor differentiation did not have a statistically significant effect on survival (p=0.245). The 3-year survival rate was 37.1% in well-differentiated tumors, and in the moderate-poorly differentiated group, this rate was calculated as 25.4%.

The CA 19-9 level was less than 100 U/mL in 35 patients, and 44 patients had a level equal to or higher than 100 U/mL. The statistical analysis showed that preoperative CA19-9 value of ≥100 U/mL had a significantly negative effect on survival (p=0.013). The 3-year survival rate was 22.3% in patients with CA 19-9 levels ≥100 U/mL. The 3-year survival rate in the group of patients with CA 19-9 <100 U/mL was found to be 41.9%.

In our study, total bilirubin levels of 31 patients were below 5 mg/dL, and 48 patients had a level equal to or higher than 5 mg/dL. The mean preoperative total bilirubin was 13.2 mg/dL (range: 0.3 to 34.6 mg/dL). It was detected that total bilirubin levels greater than 5 mg/dL significantly increased mortality (p=0.031). The 3-year survival rate of patients with preoperative total bilirubin level less than 5 mg/dL was 43.6%, while it was 23.8% in patients with preoperative total bilirubin ≥5 mg/dL.

The preoperative albumin level was found to be below 2.5 g/dL in seven patients. The remaining 72 patients had a preoperative albumin level equal to or higher than 2.5 g/dL. The mean albumin level was 3.3 g/dL (range: 1.75 to 4.85 g/dL). Univariate analysis indicated that preoperative albumin levels higher than 2.5 g/dL had a significant impact on survival (p<0.001). Preoperative albumin levels less than 2.5 g/dL had a worse survival rate (Figure 2). There were no survivors on the third year within the group of patients with an albumin value less than 2.5 g/dL, while the 3-year survival rate of patients with a higher level was found to be 34.1%.

The effect of preoperative biliary drainage in patients enrolled in the study (ERCP and/or PTC) on survival was statistically analyzed. 42 patients underwent preoperative ERCP and/or PTC. 37 patients did not receive any preoperative intervention. It was determined that preoperative interventions had no significant effect on survival (p=0.737) (Figure 3). The 3-year survival rate in patients undergoing preoperative interventional procedures was 31.2%. This rate was 30.3% for patients without such procedures.

Univariate analysis revealed tumor location, tumor size, LVI, pre-operative CA 19-9, bilirubin and albumin levels to be significant. The Cox hazard regression test that was performed based on these findings identified tumor size ≥2 cm (HR 2.0, 95% CI: 0.27 to 0.90), presence of LVI (HR 2.9, 95% CI: 0.18 to 0.60), preoperative CA 19-9 level higher than 100 U/mL (HR 2.0, 95% CI: 0.26 to 0.90) and preoperative albumin level <2.5 mg/dL (HR 2.7, 95% CI: 1.14 to 6.66) as independent prognostic factors that negatively affect survival (Table 2).

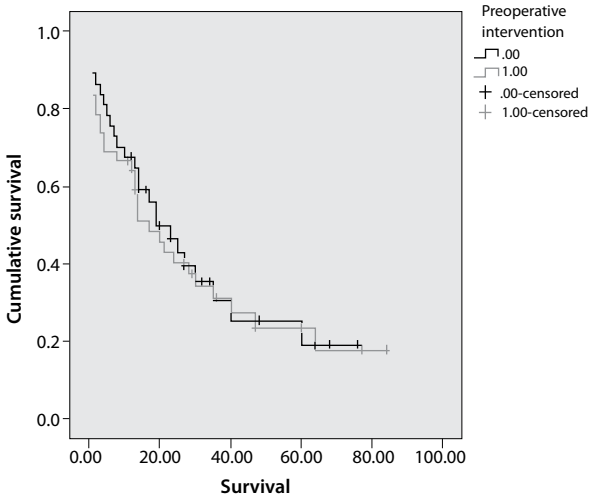

Figure 3. Survival plot according to preoperative biliary drainage status (p=0.737).

Table 2. Cox hazard regression test results

	Risk ratio (RR)	95% confidence interval (CI)	p value
Size	2	0.27-0.9	0.022
LVI	2.9	0.18-0.6	<0.001
CA 19-9	2	0.26-0.9	0.022
Albumin	2.7	1.14-6.66	0.024

LVI: lymphovascular invasion; CA: carbohydrate antigen

DISCUSSION

Periampullary tumor incidence increases with age, and has a high mortality and morbidity rate. The most common gastrointestinal tumor in the fifth decade is periampullary tumors (7). Nuzzo (8) reported a mean age of 67.4 years. Kim et al. (3) found the average age to be 61.5 years. From Turkey, Mersin et al. (9) reported the median age as 53 years. In our study, the mean age was 63.7 years.

Periampullary cancer is more common in men. Kim et al. (3) identified the male/female ratio as 1.5. In our study, male/female ratio was found to be 1.2.

Pancreaticoduodenectomy is currently the only curative treatment for periampullary tumors (3). The main issues in PD are the complexity of the surgery and the high morbidity and mortality rates related to the procedure. In 1970s, postoperative hospital mortality was reported to be over 25% in several series (10-16). Since the 1980s, there has been a dramatic reduction in postoperative hospital mortality, and rates less than 5% have been reported (5, 6). Selection of appropriate patients and surgical technique, postoperative care, high-level support of interventional radiology have contributed in reducing both mortality and morbidity. In their study on 915 patients with periampullary adenocarcinoma between 1970-1999, Riall et al. (17) reported hospital mortality rate as 30% in 1970s, as 3.6% in 1980s, while in the nineties it has been reported as 2.3%. Hatzaras et al. (18) identified perioperative mortality as 4.6% in their series of 398 periampullary cancer patients with PD. Sosa et al. (19) grouped hospitals by the number of pancreatic resection as low volume (<5 operations / year), moderate (5-19 operations / year) and high-volume (>20 operations/year). In this study, hospital mortality rates for low-volume, moderate and high-volume hospitals were reported to be 18.8%, 6.9% and 0.9%, respectively. In our study, nine patients died during the postoperative period and our hospital mortality was 11.3%. The number of annual operations was 3.2, parallel to the Sosa study. Although according to our annual case number we are within the low-volume hospital group, according to the number of cases per year we are involved in the group of medium-sized hospitals based on the last four-year period. Three PDs were performed during the first decade with 32 patients in the second decade, yielding just 35 cases in twenty years. In contrast, the number of operations we performed over the last 4 years was 44, which makes us a medium-sized hospital with an annual average of 11 surgeries. The hospital mortality rate for low-volume hospitals was reported as 18.8% by Sosa. The rate for medium-sized hospitals was reported as 6.9%. During the first twenty-year period, we had five mortalities, thus, a 17.1% mortality rate. However, for a 24-year period our mortality rate was 11.3%, which is a good rate for low-volume hospitals, although still far from acceptable levels. In contrast, in the last four years that we can be accepted as a medium-sized hospital, there were only three deaths in the group of 44 patients with a mortality rate of 6.8%. Today, centers with less than 5% hospital mortality rate are considered as eligible for PD. Our mortality rate of 6.8% is consistent with the literature for medium-sized hospitals, and is an acceptable mortality rate. Mortality rates are positively affected from increased expertise. As Sosa (19) indicated while the sheer number of cases carried out results in a decrease in mortality rates, the treatment and care done by an experienced team is also of great importance in reducing this rate in high-volume centers.

Identification of factors that affect life expectancy and quality of life, and determination of appropriate patients to undergo PD are very important for periampullary tumors due to its high mortality and morbidity as well as low survival rates. There are previous studies on this issue.

The long-term life expectancy is unfortunately low after PD, which can be perfromed in many high-volume centers with acceptable mortality and morbidity rates (5, 6, 20). Andersen et al. (21) reported the postoperative 5-year survival as 15% in117 patients with periampullary tumor. In another study published in 2006, Cameron et al. (22) reported the 5-year survival as 18%, in a series of 1000 consecutive PDs. In our study, the 5-year survival in patients undergoing PD was found to be 24%. Our 3-year survival rate was 9% for pancreatic head cancer, and 42.2% for periampullary tumors other than the head of the pancreas (ampulla Vateri, distal common bile duct and duodenum). When considered along with the literature, it can be said that our 5-year survival rate is satisfactory. We believe that the higher 5-year survival rate

in our study was related to the proportionally more ampulla Vateri tumors in our series.

Hatzaras et al. (18) identified that tumor origin (pancreas), positive surgical margins, presence of lymph node metastasis, LVI and perineural invasion negatively affect survival in periampullary cancer patients according to univariate analysis. The Cox hazard test identified only the presence of neural invasion and lymph node metastasis as negative factors on survival. Yoon et al. (23) found bilirubin level of >7 mg/dL and preoperative CA 19-9 level of 37 U/mL as negative prognostic factors that affect survival on multivariate analysis of 176 surgically treated pancreatic cancer patients. In a similar study by Kim et al. (2) tumors originating from the pancreas, tumor size greater than 2 cm, lymph node positivity and classic PD were reported as poor prognostic factors on univariate analysis. In the multivariate analysis performed in the same study, originating from pancreas and lymph node involvement has been reported as independent prognostic factors for poor prognosis. In our study, on univariate analysis, age (<65 or ≥65), lymph node metastasis, differentiation status (well or moderate-poor) and presence of preoperative biliary drainage (PTC and/or ERCP) did not affect prognosis. The negative factors affecting prognosis in univariate analysis were identified as tumor size ≥2 cm, pancreatic tumor origin, LVI positivity, preoperative CA19-9 level greater than 100 U/mL, preoperative albumin level <2.5 g/dL, and preoperative serum bilirubin value of ≥5 mg/dL. In multivariate analysis that were conducted with significant variables on univariate analysis; tumor size ≥2 cm, presence of LVI, preoperative albumin level <2.5 g/dL, and preoperative CA19-9 levels ≥100 U/mL were identified as independent prognostic factors with a negative impact on survival.

CONCLUSION

Lymphovascular invasion is not a prognostic factor that can be used in the selection of appropriate patients in the preoperative period, since it is a postoperative finding. Tumor size, CA 19-9 and albumin levels were identified as independent prognostic factors that can be used in the selection of patients with periampullary cancer for PD. Albumin level is a factor that can be corrected with proper nutritional support and preoperative albumin replacement. We may use these prognostic factors to select patients for PD and to predict postoperative survival rates.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ondokuz Mayıs University Faculty of Medicine (30.11.2012).

Informed Consent: We only considered the ethical committe approval due to retrospective characteristic of the research. No written informed consent was obtained.

Peer-review: Externally peer-reviewed.

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