ORIGINAL ARTICLE

Survival Analysis of Palliative Surgery of Advanced Stage Periampullary Cancer

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ABSTRACT

Context Surgery is the main palliative treatment of advanced periampullary cancer; however, it has high number of post-operative complication, disease recurrence, and mortality.

Objective: The objective of the current study was to examine survival rate and prognostic factors of palliative surgery of advanced-stage periampullary cancer.

Methods This was a retrospective cohort study. Patients included in study underwent hepaticojejunostomy and gastrojejunostomy palliative surgery in Cipto Mangunkusumo Hospital. Demographic data, pre-operative laboratory and clinical parameter, cancer spread, histopathological type, and post-operative outcome were collected from medical records from January 2015 until December 2017. One year and 30-day survival rate were analyzed with Kaplan-Meier method. One-year survival comparison, bivariate, and multivariate analysis based on patients' characteristics was done.

Results One-year survival rate of palliative surgery patients is 19 percent with median (min-max) survival 159 (2-365) days. The 30-day survival rate is 88 percent. Based on variables grouping, hemoglobin (p=0.013) and American Society of Anesthesiologists Classification (ASA classification) (p=0.001) showed significant different of survival estimation statistically.

Conclusions One-year survival rate of palliative surgery of advanced stage periampullary cancer patients was low and associated with hemoglobin value and ASA classification. The 30-day mortality rate of palliative surgery was low, it indicates that palliative surgery is a safe procedure.

INTRODUCTION

Periampullary cancer has high mortality and low survival rate until now. Annually, there are 331,000 deaths among 338,000 pancreatic head cancer worldwide. The overall five-year survival rate of pancreatic cancer is less than five percent. In the United States, more than 30,000 cancer mortality is caused by periampullary cancer per year; with incidence are approximately 10 cases per 100,000. A center in Indonesia found the incidence of pancreatic cancer was 79 from 2015-2017, constitutes 1.4% of all cancer cases. Exaggerating this condition, about eighty percent of periampullary cancer cases are inoperable because many of the cases were diagnosed in already advanced stage, either distant metastatic or locally advanced [1, 2, 3, 4, 5, 6].

Surgery remains the main modality of advanced periampullary cancer palliative therapy. However, periampullary cancer surgery is radical with a high number of post-operative complication, disease recurrence, and mortality. Only ten to twenty percent cases are resectable after diagnosis, with an overall five-year survival rate less than ten percent [7].

Data on survival and prognostic factors of hepaticojejunostomy and gastrojejunostomy surgery are scarce or inconsistent. A study found that the pooled median survival of pancreatic cancer bypass surgery was 6.7 months [8]. Another study found the mortality and morbidity of bypass surgery was 6.5% and 29% each and the median survival was six months. A study conducted in Cipto Mangunkusumo Hospital from 2010 until 2015 found that one-year survival of hepaticojejunostomy and gastrojejunostomy patients was 94 days (3 months) [9]. A univariate analysis showed several factors that affect morbidity and mortality of pancreatic cancer: older age,

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Abbreviations ASA American Society of Anesthesiologists; AST Aspartate Aminotransferase; ALT Alanine Aminotransferase; IRB Institutional Review Board; ROC Receiver Operating Characteristic; SPSS Statistical Package for the Social Science; SMA Superior Mesenteric Artery; SMV Superior Mesenteric Vein
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preoperative laboratory values (albumin, hematocrit, creatinine, CA19-9), American Society of Anesthesiologists (ASA) Physical classification, and metastatic diseases [10].

Few studies have focused on periampullary cancer survival. In this study, we conducted a restropective investigation to examine survival rate and prognostic factors of hepaticojejunostomy and gastrojejunostomy palliative surgery of advanced-stage periampullary cancer in Indonesia.

MATERIALS AND METHODS

This was a retrospective cohort study involving hepaticojejunostomy and gastrojejunostomy palliative surgery patient in Cipto Mangunkusumo Hospital from January 2015 until December 2017. This study has been granted an ethical approval from the Institutional Review Board (IRB) of the Faculty of Medicine Universitas Indonesia. Due to small incidence of pancreatic and periampullary cancer (0.01 %) in the previous study [11], total sampling was conducted in our study, so all data which met inclusion and exclusion criteria were analyzed. Data were collected from monthly patient registration of Digestive Surgery Division of Cipto Mangunkusumo Hospital and medical records. To analyze one-year survival, we followed up the patients up to one year after surgery. If there were missing data within one year after surgery, we contacted the patients or their relatives to complete the data.

We did descriptive analysis of demographic and laboratory data from the patients. We assessed gender, age, hemoglobin level, hematocrit level, albumin level, total bilirubin level, creatinine level, CA19-9 level, aspartate aminotransferase (AST) level, alanine aminotransferase (ALT) level, ASA classification, cancer spread, histopathological type, length of preoperative hospitalization, and mortality. Afterward, we analyzed one year and 30-day survival rate with Kaplan-Meier method. We also assessed survival estimation based on variables grouping. We determined survival cut off day by ROC curve analysis prior to final bivariate and multivariate analysis. Normally distributed numerical data was presented as mean (standard deviation) and non-normally distributed data was presented as median (range). Log rank test was used to determine the significant differences between groups. The obtained data was statistically analyzed by Statistical Package for the Social Science (SPSS) version 18.0 for Windows (IBM, Chicago, IL, USA). $P<0.05$ was considered as statistically significant.

RESULTS

Patient Characteristics

There were 58 hepaticojejunostomy and gastrojejunostomy palliative surgery patients included in the study. Mean age of the patients was 49.64 years old. There were more male patients than female. Median hemoglobin, hematocrit, albumin, total bilirubin, and creatinine were 10.5 mg/dL, 31.4 mg/dL, 3 mg/dL, 1.43 mg/dL, and 0.7 mg/dL respectively. Patients usually presented with high CA 19-9, AST and ALT. More patients had ASA Physical classification system score 2. Most of the patients were diagnosed with pancreatic head involvement. About half of the patients had liver metastasis cases. There were five categories of locally advanced case (superior mesenteric artery (SMA) infiltration, superior mesenteric vein (SMV)>180 infiltration, truncus celiacus infiltration, inferior vena cava infiltration, portal vein infiltration), with SMA infiltration dominated the category. More than half of the patients' histopathological type was well-differentiated adenocarcinoma. Median pre-operative length of stay was 20 days. Median mortality of patients was 94.5 days **(Table 1)**.

Survival Analysis

In this study, we analysed one year and 30-day survival rate by Kaplan Meier method. **Figure 1** shows one year survival rate of palliative surgery patients was 19%, with median survival 159 days (95% CI=94.79-223.21) and survival range was 2-365 days. The data suggest 30-day survival rate of the patients was 88% **(Figure 2)**.

Table 2 shows survival estimation based on patients characteristics. Older and male patients had shorter survival estimation. This result also found among patients with lower hemoglobin, hematocrit, and albumin, ASA 3, and metastasis case. Patients with higher total bilirubin and creatinine have shorter survival estimation. Interestingly, patients with higher CA19-9, AST, and ALT have longer survival estimation. Among locally advanced cases, portal vein infiltration and SMA infiltration showed the highest and lowest survival estimation respectively. Survival estimation of well and poorly-differentiated adenocarcinoma was similar and nearly half of the median value of moderately-differentiated adenocarcinoma. Lymphoma cases had the lowest survival estimation among histopathological types. However, survival estimation difference that reaches statistical significance only found between hemoglobin level and ASA variables.

Bivariate and Multivariate Analysis

From ROC curve analysis, we chose 282 days as survival duration cut off that had specificity 91.7%, sensitivity 26.7%, likelihood ratio +3.22, accuracy 59.2%, and post-test probability 76.3%. From the bivariate analysis, there are no factors that effected survival **(Table 3)**. We found that bivariate analysis result was not strong enough to predict association of variables and survival. Consequently, we analysed variables with $P<0.25$ by multivariate analysis. From multivariate analysis final model we also conclude that the variables were not significantly related to one-year survival so that we cannot trust the variables as prognostic factors **(Table 4)**.

DISCUSSION

Patient Characteristics

Our study included 58 patients with advanced-stage periampullary cancer who underwent palliative surgery

Table 1. Descriptive Characteristics of Palliative Surgery Patients.

Characteristics	Frequency (n = 58)
Age	49.64 (12.57)†
≥ 60 years old	12
<60 years old	46
Sex	
Male	34
Female	24
Hemoglobin	10.5 (6.5 – 15.0)‡
≥ 11 mg/dL	37
<11 mg/dL	21
Hematocrit	31.4 (20.3 – 44.9) ‡
≥ 30%	37
<30%	21
Albumin	3.0 (2.2 – 4.3) ‡
≥ 3 mg/dL	29
< 3 mg/dL	29
Total Bilirubin	1.43 (0.3 – 17.1) ‡
≥ 10 mg/dL	11
<10 mg /dL	47
Creatinine	0.7 (0.3 – 4.9) ‡
≥ 1.6 mg/dL	2
<1.6 mg/dL	56
CA19-9	520.0 (0.6 – 1.000) ‡
≥ 300 U/mL	40
<300 U/mL	18
AST	48.00 (10 – 275) ‡
≥ 45 mg/dL	30
<45 mg/dL	28
ALT	40 (4 – 243) ‡
≥ 35 mg/dL	33
<35 mg/dL	25
ASA	
2	37
3	21
Organ involvement	
Pancreatic head	25
Papilla of Vater	13
Duodenum	17
Distal common bile duct	3
Cancer spread	
SMA infiltration	12
SMV>180 infiltration	4
Truncus celiacus infiltration	5
Inferior vena cava infiltration	2
Portal vein infiltration	5
Liver metastasis	30
Histopathological type	
Well-differentiated adenocarcinoma	38
Moderately-differentiated adenocarcinoma	8
Poorly-differentiated adenocarcinoma	11
Lymphoma	1
Pre-operative length of stay (days)	20 (1-57) ‡
Mortality (days)	94.50 (2 – 365) ‡

Note: †Age variable is expressed as mean (standard deviation). ‡Other variables are expressed as median (range)

Abbreviation: AST = aspartate aminotransferase, ALT = alanine aminotransferase, ASA = American Society of Anesthesiologists (ASA) Physical classification system, SMA = superior mesenteric artery, SMV = superior mesenteric vein

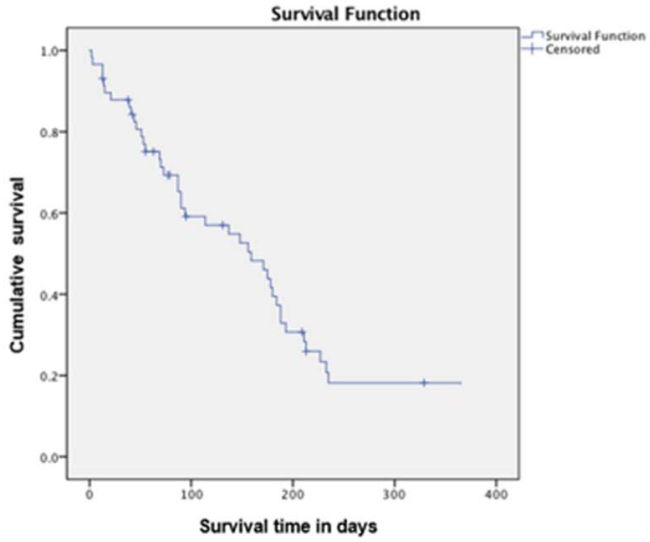

Figure 1. One year survival plot of study group.

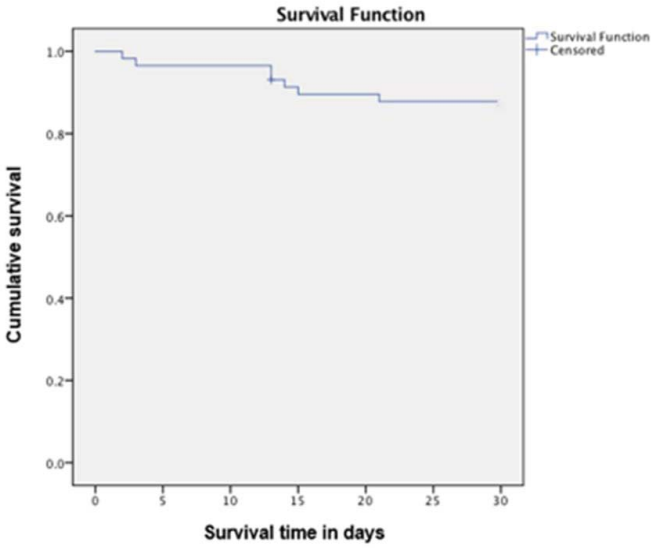

Figure 2. 30-days survival plot of study group.

in Cipto Mangunkusumo Hospital from the year 2015 until 2017. More than half of the patients were males and under 60 years old. We found a balance proportion of locally advanced and metastatic cases among patients. The number of patients included in our study was much less than other similar study conducted in Johns Hopkins Hospital, in which 42 palliative surgeries were conducted annually for the last 14 years. We found similarity with the study that most of the patients were men and half of the cases were metastatic disease [5].

A study based on American College of Surgeons National Surgical Quality Improvement Program database had sample which was dominated by patients under 70 years old. The difference of that age cut off with our study is associated with life expectancy difference among countries where the studies carried out. However, our studies share similarities of laboratory results that most of the patients had hematocrit above 30% and creatinine under 1.6 mg/dL in both studies [9].

Most of the periampullary cancer cases managed in our study is either locally advanced or metastatic cases.

Table 2. Survival Estimation Based on Patients Characteristics, median (range).

Characteristic	Survival Estimation (days)	p-value
Age		0.768
≥ 60 years old	149 (78.13-220.65)	
<60 years old	166 (130-203.24)	
Sex		0.095
Male	127 (89.61-165.46)	
Female	166 (143.73-241.87)	
Hemoglobin		0.013*
≥ 11 mg/dL	166 (155.21-275.51)	
<11 mg/dL	132 (97.12-168.7)	
Hematocrit		0.345
≥ 30%	171 (129.73-214.15)	
<30%	144 (93-195.4)	
Albumin		0.222
≥ 3 mg/dL	178 (133.79 – 221.36)	
<3 mg/dL	146 (99.3 – 194.4)	
Total Bilirubin		0.37
≥ 10 mg/dL	141 (72.42 – 209.70)	
<10 mg/dL	167 (130.469 – 204.86)	
Creatinine		0.135
≥ 1.6 mg/dL	81.5 (66.5 – 211.84)	
<1.6 mg/dL	165 (132.29– 199.42)	
CA19-9		0.327
≥ 300 U/mL	178.6 (120.9 – 236.2)	
<300 U/mL	156.9 (117.14 – 196.60)	
AST		0.862
≥ 45 mg/dL	165 (112.9 – 217.59)	
<45 mg/dL	161 (117.83 – 204.72)	
ALT		0.056
≥ 35 mg/dL	193 (141.29 – 217.59)	
<35 mg/dL	130 (91.56 – 169.02)	
ASA		0.001*
2	197 (155.3 – 239.46)	
3	103 (62.12 – 144.3)	
Cancer spread		
SMA infiltration	55 (0-111.01)	0.762
SMV>180 infiltration	159 (66.88-251.12)	
Truncus celiacus infiltration	171 (0-390)	
Inferior vena cava infiltration	76	
Portal vein infiltration	209 (0-543.94)	
Liver metastasis	90 (46.08-133.92)	
Histopathological type		
Well-differentiated adenocarcinoma	90 (67.04-112.96)	0.564
Moderately-differentiated adenocarcinoma	171 (105.86-236.14)	
Poorly-differentiated adenocarcinoma	90 (26.34-153.66)	
Lymphoma	51	

Note: *p<0.05, log rank test

Abbreviation: AST = aspartate aminotransferase, ALT = alanine aminotransferase, ASA = American Society of Anesthesiologists (ASA) Physical classification system, SMA = superior mesenteric artery, SMV = superior mesenteric vein

Table 3. Factors Associated with One Year Survival by Bivariate Analysis.

Variable	p-value
Age	0.299
Gender	0.759
Hemoglobin	0.728
Hematocrit	0.805
Albumin	0.372
Total Bilirubin	0.178
Creatinine	0.113
CA19-9	0.665
AST	0.489
ALT	0.11
ASA	0.403
Cancer Spread	0.423
Pre-operative Length of Stay	0.904

Abbreviation: AST = aspartate aminotransferase, ALT = alanine aminotransferase, ASA = American Society of Anesthesiologists (ASA) Physical classification system

Table 4. Factors Associated with One Year Survival by Reduced Multivariate Analysis.

Variable	Initial model			Final model		
	HR	p-value	95%CI	HR	p-value	95%CI
Gender	6.46	0.22	0.18-3.43	3.91	0.25	0.38–40.21
Albumin	0.12	0.13	0.17-3.01	0.4	0.35	0.06–2.70
AST	23.12	0.07	0.74-60.89	5.11	0.13	0.61–42.92
ALT	0.05	0.19	0.03-2.933	0.05	0.28	0.01–0.73

Abbreviation: HR = hazard ratio, CI = confidence interval, AST = aspartate aminotransferase, ALT = alanine aminotransferase

Therefore, palliative approach is conducted for each patient to alleviate sign and symptoms. Three main objectives of palliative surgery are reducing pain, preventing upper gastrointestinal tract obstruction, and prevent biliary duct obstruction.

One Year Survival Rate

We found that the overall one-year survival rate of palliative surgery patients was 19% with median survival 159 days and range 2-365 days. This result is slightly less than other study that found one-year survival rate of pancreatic cancer palliative surgery was 6 months **(Figure 1)**[5,9].

However, our study showed an increase of one-year survival rate with previous study in the same hospital. One-year survival of palliative surgery patients in the previous study was 94 days [11]. We analyze this number was increasing because there were more periampullary cancer cases that were managed in the hospital. In addition, the multidisciplinary team conduct routine meeting to analyze periampullary cancer cases. This step supports the treatment of periampullary cancer to be more comprehensive, prompter, more effective and more efficient.

30-day Survival Rate

From the analysis, 30-day survival rate of the subject in our study is 88 percent. This data is similar to other study that showed one-month survival rate of 87% [5]. The low 30-day mortality in our study is estimated due to optimization of patient selection and pre-operative preparation. The optimization includes nutritional support, pre-operative stenting, and comorbidity correction. Our findings suggest that hepaticojejunostomy and gastrojejunostomy palliative surgery is a safe procedure for advanced stage periampullary tumor. This is supported with other study that palliative surgery survival (192 days, $p<0.05$) is superior to biliary stent survival (116 days, $p<0.05$) in icteric cases. In advanced periampullary tumor with gastric outlet obstruction cases, palliative surgery survival (2.6 months) is better than duodenal stent procedure (1.9 months) [10].

Association of Patient Characteristic and One Year Survival Rate We found that hemoglobin (p=0.013) and ASA classification (p=0.001) have significant difference of survival estimation statistically. There is no similar previous study that compares survival based on variables. However, this data can be compared with Kneuertz et al. [5] study that found ASA classification 3-4 (p=0.04) is associated with worse mortality.

From the initial model of multivariate analysis, gender (p=0.25) and preoperative laboratory values (albumin (p=0.35), AST (p=0.13) and ALT (p=0.28) correlated with worse survival rate. This findings differ from multivariate analysis of other similar study [5] that found CA 19-9 level ≥ 350 U/mL (p=0,003) and metastatic disease (p=0.02) are associated with worse survival.

From our study, woman had worse survival than man. This result is supported with Kreiger et al. [12] study that suggested estrogen is one of the pancreatic cancer risk factors. Likewise, experimental studies showed anti-estrogen agent such as tamoxifen, when combined with other chemotherapeutics, has inhibitory effect toward carcinogenesis in the pancreas in phase II trials [13, 14].

We found that a high level of AST is 5.11 times more harmful to affect the patient's survival than normal AST level. Prior research suggests several mechanisms that are consistent with our results. Liver injury, which is in part marked by AST level, will cause many complications that worsens patients outcome. Periampullary cancer is one of structural cause of cholestatic liver disease. Disturbance of bile production and excretion in the hepatobiliary system will lead to hyperbilirubinemia and liver injury. As a response of liver injury, mature cholangiocytes and hepatocytes proliferate, causing periductal fibrosis, biliary fibrosis, and cirrhosis that worsen patient's survival [15].

The interesting result from this study is that low preoperative albumin (HR=0.4) and high ALT (HR=0.05) are protective factors for palliative surgery patient. This result differ with other studies that concludes low preoperative albumin level (<2.5 g/dL) is associated with worse outcome [16]. However, the mechanism of how these parameters affect patient survival remains unclear.

Limitation of the Study

These findings must be interpreted with caution, since the magnitude of the sample was small. The significance value measured from the analysis has not represented the actual significance value.

CONCLUSION

One-year survival rate of hepaticojejunostomy and gastrojejunostomy palliative surgery of advanced stage periampullary cancer patients was low. Factors associated with one-year survival rate were hemoglobin value and ASA classification. The 30-day mortality rate of palliative surgery in this study was low; it indicates that palliative surgery is a safe procedure.

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Conflicts of Interest

All named authors hereby declare that they have no conflicts of interest to disclose.

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