



RESEARCH

IS THE WHIPPLE PROCEDURE SAFE AND FEASIBLE IN ELDERLY PATIENTS?

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ABSTRACT

Introduction: The world population is getting older due to increasing life expectancy. Deciding to perform surgery for pancreatic cancer in elderly patients has been difficult due to high comorbidities and limited survival. This study aimed to compare the results of the Whipple procedure performed in elderly patients with non-elderly patients to demonstrate the safety and feasibility of the Whipple procedure.

Materials and Methods: Patients underwent the Whipple procedure for pancreatic adenocarcinoma between January 2010 and December 2019 were retrospectively analyzed. Patients were classified into two groups as, Group I (<65 years) and Group II (≥65 years), and compared.

Results: 178 patients were included, with 97 (54.5%) in group I and 81 (45.5%) in group II. The mean age of the patients was 63.48±12.95 years, while 65.2% were male and 34.8% were female. Gender distribution, preoperative hyperbilirubinemia, The American Society of Anesthesiologists score, and endoscopic retrograde cholangiopancreatography status were found to be statistically similar between the groups. Group II had more comorbid disease (p=0.002), longer hospital stay duration (p<0.001), and more intensive care unit admission (p=0.001). There was no statistical difference between the groups regarding postoperative complications, pancreatic cancer stage, and R0 resection rate. There was no difference between the groups regarding survival (p=0.11).

Conclusion: The Whipple procedure is an operation with a high complication rate regardless of age. The most adverse factor affecting survival is the aggressive nature of the disease rather than older age. Therefore, the Whipple procedure is safe and feasible in elderly patients.

Keywords: Aged; Pancreatic Neoplasms; Survival; Pancreaticoduodenectomy.



INTRODUCTION

The world population is aging due to increasing life expectancy. Thus, the number of elderly cancer patients has increased worldwide (1). As a result, healthcare systems have seen the beginnings of the “silver tsunami” with the increasing proportion of the population defined as geriatric (2). However, old age is not considered a contraindication for surgical treatment, and many studies have supported that older patients should undergo surgical treatment as the younger patients should (3,4).

The Whipple procedure (WP), also known as pancreaticoduodenectomy, is the most common curative resection performed for pancreatic adenocarcinoma confined to the head of the pancreas, including ampullary cancers. In this procedure, the head of the pancreas, the first and second portions of the duodenum, distal stomach, proximal jejunum, a portion of the common bile duct, the gallbladder, and the surrounding lymph nodes are removed. The reconstruction for gastrointestinal continuity includes connecting the jejunum to the remaining pancreatic duct with pancreaticojejunostomy, the bile duct with hepaticojejunostomy, and the stomach with gastrojejunostomy. WP complication rate is high and is a highly invasive operation. Despite improvements in surgical techniques, chemotherapy, and follow-up methodology, pancreatic tumors remain a fatal disease, with a five-year survival rate of less than 10% (1). The majority of patients present with locally advanced or metastatic disease, and less than 20% of patients are fit for resection at the time of diagnosis (5). Ampullary tumors are rarer than pancreatic tumors. The one-year survival rate and three-year survival rate are 60.5% and 27.7% (6). Surgical resection is still considered the only potentially curative treatment.

In this study, we aimed to compare elderly patients who underwent WP for pancreatic adenocarcinoma with nonelderly patients and investigate the

factors affecting morbidity and mortality in patients in the postoperative period and the effects of age on prognosis and survival.

METHODS

Study Design

Data of patients who underwent PD for pancreatic adenocarcinoma in our clinic between January 2010 and December 2019 were retrospectively analyzed by reviewing the hospital database system. Combined visceral resection with PD or total pancreatectomy patients were excluded from the study. Additionally, patients who had missing data files were excluded from the study. Demographic characteristics, pancreatic cancer stage, comorbid diseases, The American Society of Anesthesiologists (ASA) score, endoscopic retrograde cholangiopancreatography (ERCP) status, operation time, intensive care unit (ICU) admission status, length of hospital stay, postoperative complications, perioperative mortality rates, and survival were recorded. Data from 178 patients were included. Patients were analyzed in two groups according to their age: group I (<65 years) and group II (≥65 years).

Surgical intervention and risks were explained to all patients, and informed consent was obtained before surgery.

Statistical analyses

In the analysis of the data, the mean and standard deviation, the minimum and maximum values of the features, frequency, and percentage values were used when defining the categorical variables while performing the statistics of the continuous data on the scales. Student's t-test was used to compare the means of two independent groups. Chi-square test statistics were used to evaluate the relationship between categorical variables. To evaluate the relationship between age and clinical outcomes, logistic regression analysis was performed using backward and enter methods with statistically

significant variables. The results were accepted as a 95% confidence interval, and the statistical error margin was 0.05. The cumulative survival rate was calculated using Kaplan-Meier survival analysis, and the difference between groups was evaluated using the log-rank test. The statistical significance level of the data was taken as $p < 0.05$. In evaluating the data, www.e-picos.com New York software and the MedCalc statistical package program were used.

RESULTS

A total of 178 patients were included in the study, with 97 (54.5%) in group I and 81 (45.5%) in group II. The mean age of the patients was 63.48 ± 12.95 years, while 65.2% were male and 34.8% were female.

The demographic and clinical characteristics of the patients are summarized in Table 1. Gender distribution, preoperative hyperbilirubinemia, and ERCP status were found to be statistically similar between the groups. In total, 64.9% and 85.2% of the patients in group I and group II, respectively, had comorbid disease ($p = 0.002$). ASA score was found to be similar in statistical evaluation ($p = 0.15$). Hospital stay duration was found statistically longer in group II with 13.09 ± 1.61 days, while it was 11.67 ± 1.92 days in group I ($p < 0.001$).

Thirty-three (34.0%) patients in group I were admitted to the postoperative ICU, while 47 (58.0%) patients were in group II. There was a statistical difference in ICU admission between the groups ($p = 0.001$). The reason for ICU admission in group I was preoperative high-risk stratification due to comorbidities with major surgery, The reasons for ICU admission in group 1 were preoperative high-risk stratification due to multiple comorbidities with major surgery in 17 patients, hemorrhage to cause hypotension in 6 patients, cardiac causes in 5 patients, respiratory insufficiency in 3 patients and other reasons in 2 patients. The reasons for ICU admission in group 2 were preoperative high-risk stratification

due to multiple comorbidities with major surgery in 22 patients, cardiac causes in 9 patients, hemorrhage to cause hypotension in 8 patients, respiratory insufficiency in 4 patients, and other reasons in 4 patients. While blood transfusion was given to 25 (25.8%) patients in group I, 33 (40.7%) patients in group II received a blood transfusion. There was a statistical difference in blood transfusion between the groups ($p = 0.03$). There were 4 (4.1%) biliary fistula and 27 (27.8%) pancreatic fistula in group 1 while there were 2 (2.5%) biliary fistula and 19 (23.5%) pancreatic fistula in group 2. There was no statistical difference between the groups' postoperative complications, biliary fistula, and pancreatic fistula without grade classification. However, when pancreatic fistula grade classification was considered, there was a statistically significant difference between the groups ($p = 0.03$). Grade a pancreatic fistula developed in 26 patients and grade b pancreatic fistula in 1 patient in group 1, grade a fistula developed in 13 patients in group 2, and grade b fistula in 6 patients. There was no statistical difference between the groups' pancreatic cancer staging according to The American Joint Committee on Cancer (AJCC) 8th classification and R0 resection rate.

The relationship between age and clinical outcomes with multivariate analyses is summarised in Table 2. With a 95% confidence interval, preoperative blood transfusion and postoperative ICU admission were found to be related to the age of patients (OR 10.28, 95% CI 5.11-20.67 $p < 0.05$; OR 2.68, 95% CI 1.48-4.93 $p < 0.05$ respectively). Conversely, multivariate analysis found that postoperative blood transfusion, complications, pancreatic fistula, and biliary fistula were unrelated to age with a 95% confidence interval.

The geriatric age patient group was re-evaluated by dividing them into subgroups in decades to examine in more detail. There were 47 patients in age between 65-74, 24 patients in age between 75-84, and 10 patients over 85 years. There were no statistical differences between these groups at hos-

**Table 1.** Demographic and Clinical characteristics according to age groups

	All (n=178)	Group I (n=97)	Group II (n=81)	p-value
	x±SD	x±SD	x±SD	
Age	63.48±12.95	53.85±5.49	75.01±8.42	<0.001
Gender	n (%)	n (%)	n (%)	
Male	116 (65.2)	62 (62.9)	54 (66.7)	0.71
Female	62 (34.8)	35 (36.1)	27 (33.3)	
Comorbid Disease	132 (74.2)	63 (64.9)	69 (85.2)	0.002
Preop Hiperbilirubinemia	97 (54.5)	51 (52.6)	46 (56.8)	0.57
ERCP	116 (65.2)	60 (61.9)	56 (69.1)	0.31
Preop Anemia	90 (50.6)	26 (26.8)	64 (79.0)	<0.001
ASA Score				
I	20 (11.2)	14 (14.4)	6 (7.4)	0.15
II	58 (32.6)	46 (47.4)	33(40.7)	
III	69 (38.8)	35 (36.1)	37 (45.7)	
IV	31 (17.4)	2 (2.1)	5 (6.2)	
Hospital Stay (days)	12.33±1.91	11.67±1.92	13.09±1.61	<0.001
ICU Admission	80 (44.9)	33 (34)	47 (58)	0.001
Blood Transfusion	58 (32.6)	25 (25.8)	33 (40.7)	0.03
Postop Complication	91 (51.1)	47 (48.5)	44 (54.3)	0.44
Biliary Fistule	6 (3.4)	4 (4.1)	2 (2.5)	0.54
Pancreatic Fistule	46 (25.8)	27 (27.8)	19 (23.5)	0.51
Pancreatic Fistule Grade				
Grade A	40 (86.9)	26 (96.3)	13 (64.4)	0.03
Grade B	6 (13.1)	1 (3.7)	6 (35.6)	
Grade C	-	-	-	
Pancreatic Cancer Stage (AJCC 8th)				
Stage I	53 (29.8)	30 (30.9)	23 (28.4)	0.58
Stage II	64 (36)	37 (38.2)	27 (33.3)	
Stage III	61 (34.2)	30 (30.9)	31 (38.3)	
Stage IV	-	-	-	
R0 Resection	144(80.9)	80(82.4)	64(79.0)	0.56

ERCP: endoscopic retrograde cholangiopancreatography, ASA: The American Society of Anesthesiologists score, ICU: intensive care unit, AJCC: The American Joint Committee on Cancer.

Table 2. The relationship between multivariate analysis of group 2 (age \geq 65 years) compared to group 1 (age $<$ 65 years), age, and clinical outcomes

	OR (Odds ratio)	95% CI (Confidence interval)	p-value
Preop blood transfusion	10.28	5.11 – 20.67	<0.05
Postop ICU admission	2.68	1.48 – 4.93	<0.05
Postop blood transfusion	1.98	1.00 – 1.94	>0.05
Postop complication	1.27	0.70 – 2.29	>0.05
Pancreatic fistula	0.99	0.50 – 1.98	>0.05
Biliary Fistula	0.59	0.11 – 3.29	>0.05

ICU: intensive care unit

Table 3. Subgroup analyses of patients over 65 years

Age	65-74 (n=47)	75-84 (n=24)	>85 (n=10)	p-value
	x\pmSD	x\pmSD	x\pmSD	
Hospital Stay (days)	12.84 \pm 2.05	13.56 \pm 2.73	14.11 \pm 2.32	0.19
ICU Admission	n (%)	n (%)	n (%)	
Blood Transfusion	26 (55.3)	15 (62.5)	6 (60)	0.84
Postop Complication	16 (34)	11 (45.8)	6 (60)	0.26
Biliary Fistule	28 (59.6)	11 (45.8)	5 (50)	0.52
Pancreatic Fistule	12 (25.5)	5 (20.8)	2 (20)	0.87
Pancreatic Fistule Grade	1 (2.1)	1 (4.2)	-	0.76
Grade A				
Grade B	9 (75)	4 (80)	1 (50)	0.71
Grade C	3 (25)	1 (20)	1 (50)	
Pancreatic Cancer Stage (AJCC 8th)	-	-	-	
Stage I				
Stage II	10 (21.3)	8 (33.3)	5 (50)	0.39
Stage III	17 (36.2)	7 (29.2)	3 (30)	
Stage IV	20 (42.6)	9 (37.5)	2 (20)	

ICU: intensive care unit, AJCC: The American Joint Committee on Cancer



pital stay, ICU admission, blood transfusion, postop complication, biliary fistule, pancreatic fistule, and Pancreatic Cancer Stage. Statistical analyses between the groups were summarized in Table 3.

The mean survival was 14.71 months in group I and 13.17 months in group II (Table 4). In addition, there was no statistical difference between the survival of the groups ($p=0.11$). In the survival analysis performed by dividing geriatric patients into subgroups, the mean survival was 14.71 months in patients under 65 years of age, 13.55 months in patients aged 65-74 years, 11.48 months in patients aged 75-84 years, and 11.51 months in patients over 85 years of age. There was no statistical difference between the survival of the groups ($p=0.23$).

DISCUSSION

Pancreatic cancer is the 14th most common cancer with 495,773 (2.6% of all new cancer cases) new cases and the 7th leading cause of cancer-related death with 466,003 (4.2% of all cancer-related deaths) patients in 2020 (7). Pancreatic cancer arises from the exocrine or endocrine systems of the pancreas. The most common form of pancreatic cancer is ductal adenocarcinoma. More than half of

patients diagnosed with pancreatic cancer are diagnosed at an advanced age. (8). Surgical resection is the only way to offer a potential cure. Once advanced age was a relative contraindication for surgery and chemotherapy, the usage areas of these applications are gradually expanding. The increasing elderly population reveals the need to recognize the specific risks associated with surgery being applied to elderly patients. Unfortunately, there is no consensus on the age limit in the definition of the elderly individuals worldwide. Traditionally, the United Nations has used measures and indicators of population ageing primarily or entirely based on people's chronological age, defining older persons as those aged 60 or 65 years or over (9). This provides a simple, clear, and easily reproducible way to measure and monitor various indicators of population aging. Therefore, in designing our study, we accepted the age threshold as 65.

The preoperative hyperbilirubinemia status and the need for ERCP were similar between the groups in the setting of preoperative assessment of the groups. In addition, the distribution of pancreatic cancer staging according to the AJCC 8th classification and ASA Score was comparable between the two groups. Gastinger et al. found a perioperative

Table 4. Survival Analyses of the Groups

	Mean (Months)	%95 CI (Confidence interval)	p-value
Overall	14.10	12.96 – 15.04	
Group 1 (<65 years)	14.71	13.28 – 16.13	0.11
Group 2 (>65 years)	13.17	11.64 – 14.69	
	Mean (Months)	%95 CI (Confidence interval)	p-value
<65	14.71	13.28 – 16.13	0.23
65-74	13.55	11.84 – 15.23	
75-84	11.48	8.49 – 14.47	
>85	11.51	9.41 – 13.59	

mortality of 2.1% in patients with an ASA score of 1 or 2 who underwent pancreatic surgery and 5.4% in patients with an ASA score of 3 or 4 (10). Moreover, all malignant and benign pancreatic surgeries were included in this multicenter study, which included 2003 patients. The similar ASA score distribution in our study is because patients with high ASA scores rejected surgery due to high mortality expectations.

PD morbidities range from 41% to 62% in the reported literature (11-13). In this study, postoperative complications were found 54.3% of the elderly and 48.5% of nonelderly patients. Despite the presence of more comorbid diseases in the elderly group, the postoperative complication rate was statistically similar to that in the non-elderly group. Biliary fistula and pancreatic fistula are complications specific to PD. Reported literature reveals that age does not affect their development (8,14). In this study, complications specific to PD were found to be similar between the groups, consistent with the published literature. The International Study Group of Pancreatic Fistula (ISGPS) developed a definition and grading of postoperative pancreatic fistula in 2005 and redefined their grading in 2016 (15). In our study, there was no statistical difference in the presence of a pancreatic fistula. However, in the evaluation of the grading in the subgroup analysis in terms of pancreatic fistula, it was observed that the grade of the pancreatic fistula was higher in the elderly. This may be because leaks from the more fragile pancreatic tissue with advanced age take longer, or tissue healing due to advanced age is prolonged. Nevertheless, binary logistic regression analysis showed that postoperative complications and pancreatic and biliary fistula were not correlated with age.

Cameron et al. reported that patients' hospital stay at Johns Hopkins Medical Center decreased from 21 days to 10 days over decades (16). In our study, the median hospital stay was significantly longer in the elderly (13.09 ± 1.61 days) than in the nonelderly (11.67 ± 1.92 days), which may be due to the higher admission rate to the ICU in the elderly

group. The ICU admission delayed early mobilization, resulting in a prolonged hospital stay. In the reported literature, elderly patients were far more likely to be discharged to a rehabilitation facility than home (11,17). In our study, most elderly patients were discharged to home rather than a facility on the contrary.

Anemia is common in geriatric patients, and its prevalence increases with age after 65 years of age (18). In our study, preoperative anemia was seen at a higher rate in the elderly group, thus leading to more postoperative blood transfusions in the elderly group. Abitagaoglu et al. found ICU admission rates to be higher with aging (19). Consistent with the published literature, in our study, binary logistic regression analysis showed that preoperative blood transfusion and postoperative ICU admission were significantly associated with older age.

In survival comparison, some studies have found lower survival rates for PD performed for pancreatic cancer in the elderly than in the nonelderly (11,20). Conversely, the literature finds comparable survival between the elderly and the nonelderly (4,21). In our study, the overall survival was similar between the elderly and nonelderly groups, which was related to the fact that pancreatic cancer is a highly morbid disease regardless of age (Figure 1). Even when geriatric patients were divided into subgroups, no statistically significant difference was observed in terms of survival (Figure 2).

Our study has several limitations. Firstly, it was a retrospective study with a single center design leads to a small number of patients. Retrospective design leads to the inability to use a scoring system other than ASA in the preoperative evaluation due to missing data. Possible selection bias that may occur in retrospective studies and the incompleteness of the data may reveal possible relationships rather than causal relationships. Therefore, multicenter prospective studies are needed to reveal the causal relationships. Despite these limitations, our study will contribute to the known literature. There are a



Figure 1. Kaplan Meier Survival Curve of the groups.

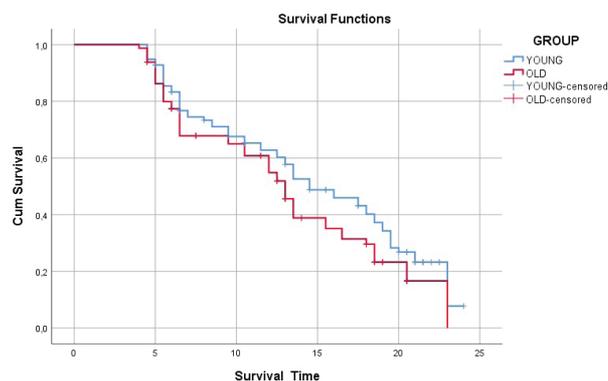
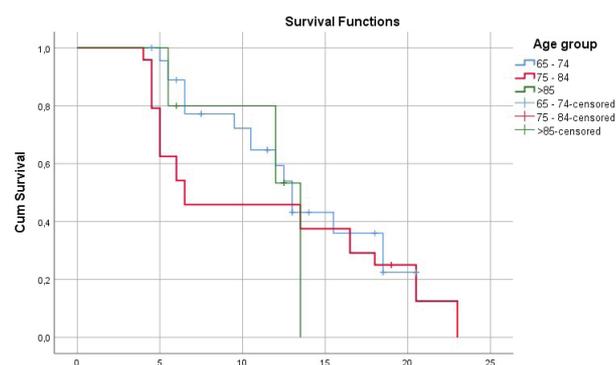


Figure 2. Kaplan Meier Survival Curve of under 65 age patients and subgroup geriatric patients.



limited number of studies examining the relationship between pancreaticoduodenectomy and age in the current literature, and also this study differs from them by re-examining geriatric age groups with subgroups according to decades.

CONCLUSION

PD is an operation with a high complication rate regardless of age, and the most adverse factor affecting survival is the aggressive nature of the disease rather than older age. Therefore, PD for pancreatic adenocarcinoma is a safe and feasible treatment in elderly patients, and surgeons should apply the same procedures and strive to achieve the same goal as younger patients.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants performed by the author. However, ethical approval was obtained from the Mersin University Clinical Research Ethics Committee for this study with the date 05/02/2020 and the number 2020/100.

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