Journal of Gastroenterology Research and Practice

www.jjgastro.com

Research Article

Open Access, Volume 4

Survival of periampullary adenocarcinoma post curative resection: A tertiary academic center experience

Abdullah M Oraini[1]*; Sulaiman A Shammari[1]; Razan N Rabah[2]; Amirah M Zahrani[2]; Mohammed A Swayyed[3]; Mazen M Hassanain[4]; Faisal A Saif[1]

[1]Department of Surgery, College of Medicine, King Saud University, Riyadh, Saudi Arabia.

[2]College of Medicine, King Saud University, Riyadh, Saudi Arabia.

[3]Department of Pathology and Laboratory Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia.

[4]Department of Medical Oncology, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia.

***Corresponding Author: Abdullah M Oraini**

Department of Surgery, College of Medicine, King Saud University, Riyadh, Saudi Arabia.

Email: abdaloraini@ksu.edu.sa

Received: Jun 09, 2024

Accepted: Jul 04, 2024

Published: Jul 11, 2024

Archived: www.jjgastro.com

Keywords: Oncological outcomes; Overall survival; Periampullary tumors; Prognostic variables.

Abstract

Introduction: Periampullary adenocarcinoma is one of the most aggressive malignancies, with biological behavior as its most significant predictor of survival. Curative surgical resection is the main contributing factor in the management. Yet, no oncological data exist for patients who underwent curative resection locally in Saudi Arabia. The study aimed to identify the oncological outcomes of curatively resected periampullary adenocarcinoma and the prognostic factors toward survival.

Methods: All patients who underwent surgical intervention for periampullary adenocarcinoma in a single institution between November 2015 to August 2022 were retrospectively reviewed and analyzed. Only patients who underwent curative resection were included for oncological outcomes.

Results: A total of 58 patients underwent surgical intervention for periampullary adenocarcinoma. Of them, 51 patients underwent curative surgical resection. The most common adenocarcinoma origin was ductal (57%), followed by pancreaticobiliary (16%), ampullary (16%), intestinal (10%), and lastly mixed (2%). The distant metastasis rate was 37.3%, with a mean disease-free interval of 15.8 months (SD 18.1). The median overall survival for all patients who underwent curative surgical resection was 44.07 months (95% CI, 19.54-68.59), while the disease-free survival was 24.67 months (95% CI, 15.77-33.56). The predictors of survival on univariate analysis were female gender (P=0.02) and ASA score IV (P=0.01). However, no variables were significant in the multivariate analysis.

Conclusion: Periampullary adenocarcinoma remains to have aggressive behavior despite optimal surgical resection and appropriate adjuvant therapy. As it tends to metastasize systematically with short disease-free intervals. Pancreatic adenocarcinoma is the highest mortality rate among our patients. There is a need for referral centers to increase the volume and improve the outcomes.

Introduction

The Periampullary region comprises several organs packed nearby the [1]. Adenocarcinoma of this region includes adenocarcinoma of the pancreatic head, distal common bile duct, ampulla of Vater, and duodenum [2]. Therefore, it might be challenging to determine the primary tumor site in some cases [1]. Epidemiologically, pancreatic cancer is the third leading cause of death in the United States, with a 5-year survival rate of 11% [3]. In addition, the 5-year survival rate for duodenal and ampullary adenocarcinoma is 53% and 38%, respectively [4]. Lastly, the 5-year survival rate of extrahepatic bile duct cancer is 17.6% [5]. The prevalence of periampullary adenocarcinoma increases with age, and risk factors include smoking, alcohol consumption, a history of diabetes, and chronic pancreatitis [6].

Surgical resection is the only potential cure and long-term survival for patients with periampullary tumors [7]. The standard treatment for periampullary tumors consists of either a classic Whipple's procedure (pancreaticoduodenectomy) or a pylorus-preserving Pancreaticoduodenectomy (PD) [8]. In contrast to the improvement in survival rate post-curative resection, the recurrence rate remained high [9]. Unfortunately, in most patients, the diagnosis is made at a stage where surgical treatment is not curable, and limited effect is provided by other therapies such as chemotherapy and radiation therapy [10].

Factors reported in the literature that influences better prognosis and long-term survival in patients with periampullary adenocarcinomas; degree of differentiation, stage I or II, small tumor size (<3 cm), no lymph node metastases, negative resection margins, completion adjuvant chemoradiation therapy, low preoperative and post-operative CA19-9 levels, and low Albumin bilirubin ratio [10-14].

Despite the recent advancements in diagnosis, early detection, and therapeutic modalities, the death rate due to periampullary adenocarcinoma has shown minimal improvement [15]. In Saudi Arabia, the incidence of pancreatic cancer showed a 4-fold increase from 1990 to 2016, with the highest incidence in patients above 70 years, with rates significantly higher among males [16,17]. Therefore, this study aims to identify the oncological outcomes of periampullary adenocarcinoma in patients who underwent curative resection.

Materials and methods

Following the approval of the Institutional Review Board (IRB) at King Saud University, we retrospectively collected and reviewed the electronic medical records of all patients with periampullary adenocarcinoma who underwent surgical resection for curative intent from November 2015 to August 2022 at King Saud University Medical City (KSUMC), an academic medical institution in Riyadh, Saudi Arabia.

Periampullary adenocarcinoma was defined as adenocarcinoma of the pancreatic head, distal common bile duct, ampulla of Vater, or duodenum. We included only patients who underwent curative resection with no distant metastasis upon initial presentation. Patients with benign disease, malignancies other than adenocarcinoma, and patients who did not undergo surgical intervention were excluded.

All patients with periampullary carcinoma were admitted to the hepatobiliary surgery unit for workup and therapy. All cases were discussed in the multidisciplinary tumor board meeting. The tumor board members included specialized radiologists, pathologists, surgical oncologists, hepatobiliary surgeons, and medical and radiation oncologists. Qualified specialized hepatobiliary surgeons operated on all cases.

Data collected included baseline demographic, oncological parameters, surgical intervention, histopathological characteristics, neo-adjuvant and adjuvant therapy, tumor board reports, and clinical follow-up reports. Regression test was used to assess prognostic factors toward survival.

Statistical analysis: Data were analyzed using Statistical Package for Social Studies (SPSS 22; IBM Corp., New York, NY, USA). Continuous variables were expressed as mean ± standard deviation when normally distributed, and categorical variables were expressed as percentages. The t-test was used for continuous variables, and the chi-square test was used for categorical variables. Cox proportional hazards regression was performed to estimate Hazard Ratios (HR) (95% CI). Survival curves were estimated by the Kaplan–Meier method. A p-value <0.05 was considered statistically significant.

Results

Between November 2015 to August 2022, fifty-eight patients with periampullary adenocarcinoma underwent surgical intervention. Seven patients who had aborted surgery due to intraoperative findings of unrespectability or the presence of distant metastasis were excluded from the survival analysis. Patients were followed up for a mean of 15.27 months (±14.13).

The demographics, baseline characteristics, preoperative parameters, and oncological outcomes are presented in Table 1. The mean age of the 58 patients was 60 years (range 33 to 84), with 40 patients being males (69%). The most common presenting signs and symptoms were jaundice (82%), followed by abdominal pain (70%), and weight loss (63%). Preoperative ERCP with stent placement was performed in 62% of the patients. The radiological staging was defined as resectable in 48 of our patients (83%), eight as borderline (14%), and two were unresectable (3%).

Surgical parameters, histopathological characteristics, and adjuvant therapy of fifty-one patients who underwent curative resection are shown in Table 2. All our patients who underwent surgical resection had an open surgery approach. The portal vein was reconstructed in 5 patients (10%). The most common adenocarcinoma origin was ductal (57%), followed by pancreaticobiliary (16%), ampullary (16%), intestinal (10%), and lastly mixed (2%). Moderately differentiated tumors were the most common type (59%). Thirty-six patients had positive lymph nodes (71%) with a lymph node ratio of 0.22. Furthermore, five patients had a positive resected margin (10%). Out of which, two patients received post-op radiation therapy. Twenty-five patients (50%) received adjuvant therapy with a mean initiation duration of 7.76 weeks. Of them, only seven patients received adjuvant therapy within 6 weeks of curative surgery. Additionally, only two patients received and completed neo-adjuvant therapy (4%).

Oncological outcomes are shown in Table 3. Four patients

(8%) had a local recurrence, and nineteen had distant metastasis (37%). The overall mortality rate was 26%. Figure 1 shows the cumulative Kaplan Meier 5-year survival curve, the median of overall survival for all patients who underwent curative surgical resection was 44.07 months (95% CI, 19.54-68.59). In respect of the median of disease-free survival was 24.67 months (95% CI, 15.77-33.56) which is shown in Figure 2.

Survival rate correlated significantly with age, gender, and ASA score, as shown in Table 4. In addition, receiving less than four cycles of adjuvant therapy was marginally significant for survival (*P*=0.05). Moreover, seven patients received adjuvant chemotherapy within six weeks, and all survived (*P*=0.10). We observed survival difference in the interval between curative resection and local recurrence in deceased patients compared to alive patients, but it was not statistically significant (312.5 vs. 959 days, *P*=0.46).

On univariate analysis, several significant factors associated with survival were identified (Table 5). These variables included female gender (*P*=0.02), and ASA score IV (*P*=0.01). However, on multivariate analysis, no variables were significant.

Table 2: Surgical intervention and oncological parameters (n=51).

Variable		n(%)
Type of Surgery	Classic Whipple	42(82.35)
	Pylorus preserving	8(15.69)
	Total pancreatectomy	1(1.96)
Portal vein reconstruction		5(9.80)
Adenocarcinoma origin	Ductal	29(56.86)
	Pancreaticobiliary	8(15.69)
	Ampullary	8(15.69)
	Intestinal	5(9.80)
	Mixed	1(1.96)
Differentiation	Well	9(18.00)
	Moderate	30(58.80)
	Poor	11(21.60)
Greater dimension (cm)†		2.83(1.31)
Lymph node dissected†		13.02(8.44)
Patient with positive nodes		36(70.59)
Lymph node ratio†		0.22(0.24)
Positive margin		5(9.80)
Lymphovascular invasion		34(66.67)
Perineural invasion		34(66.67)
Mucinous component		2(3.92)
Signet ring cell		1(1.96)
Adjuvant therapy		25(49.02)
Number of cycles	≤4.0	5(20.0)
	>4.0	20(80.0)
Initiation of adjuvant therapy within 6 weeks of surgery		7(13.73)
Type of chemotherapy	Gemcitibine/Capecitabine	13(52.0)
	Gemcitibine	5(20.0)
	mFOLFIRIONOX	3(12.0)
	FOLFERNIOX	2(8.0)
	FOLFOX	1(4.0)
Tolerance of chemotherapy	Completed	11(44.0)

Data are expressed as numbers (percentages) except †mean (standard deviation). *P* values <0.05 were considered statistically significant.

Table 1: Baseline demographics and preoperative clinical characteristics (n=58).

Variable		n(%)
Age†		60.62(12.71)
Male		40(68.97)
BMI†		26.28(6.28)
Smoking		8(13.79)
Ex-smoker		5(8.62)
Personal history of cancer		5(8.62)
Comorbidities	Diabetes mellitus	31(53.45)
	Hypertension	26(44.83)
	Cardiomyopathy/Heart failure	3(5.17)
	Ischemic heart disease	3(5.17)
	Dyslipidemia	14(24.14)
	Asthma	2(3.45)
ASA Score	I	1(1.72)
	II	31(53.45)
	III	22(37.93)
	IV	3(5.17)
	V	1(1.72)
Symptoms	Jaundice	47(82.46)
	Abdominal pain	40(70.18)
	Weight loss	36(63.16)
	Loss of appetite	31(54.39)
	Gastric outlet obstruction	1(1.75)
CEA†		70.84(373.41)
CA 19-9†		1594.98(4325.36)
Albumin (gm/L)†		27.25(6.31)
Total Bilirubin (mcmol/L)†		74.10(94.91)
Preoperative interventions	ERCP with Stent	36(62.07)
	ERCP Diagnostic	2(3.45)
	Failed ERCP	1(1.72)
	PTC	1(1.72)
Radiological staging	Resectable	48(82.76)
	Borderline	8(13.79)
	Unresectable	2(3.45)
Distant metastasis upon presentation		6(10.34)
Site of metastasis	Liver	2(3.45)
	Peritoneum	2(3.45)
	Extra regional lymph nodes	2(3.45)
	Adnexa	1(1.72)
	Retroperitoneal soft tissue	1(1.72)

Data are expressed as numbers (percentages) except †mean (standard deviation). *P* values <0.05 were considered statistically significant. ASA: American Society of Anesthesiologists; BMI: Body Mass Index; CA 19-9: Carbohydrate Antigen; CEA: Carcinoembryonic Antigen; ERCP: Endoscopic retrograde cholangiopancreatography; PTC: Percutaneous Transhepatic Cholangiography.

Table 3: Oncological outcomes (n=51).

Variable		n(%)
Local recurrence		4(7.8)
Distant metastasis		19(37.3)
Site of distant metastasis	Lung	8(42.1)
	Liver	8(42.1)
	Lymph nodes	6(31.6)
	Peritoneum	2(10.5)
	Bone	1(5.3)
	Retroperitoneal lesions	2(10.5)
Interval between curative resection to local recurrence, in months†		21.19(23.22)
Interval between curative resection to Distant metastasis, in months†		15.78(18.06)
Mortality rate		13(25.5)
Interval between curative resection to mortality, in months†		11.09(13.93)

Data are expressed as numbers (percentages) except †mean (standard deviation). *P* values <0.05 were considered statistically significant.

Table 4: Prognostic variables toward survival.

		Death (n=13)	Alive (n=38)	Pvalue
Variable		**n(%)**	**n(%)**	
Age†		66.58(11.95)	58.83(11.93)	**0.049***
Gender	Male	5(38.46)	30(78.95)	**0.007***
	Female	8(61.54)	8(21.05)	
ASA Score	I		1(2.63)	**0.021***
	II	8(61.54)	20(52.63)	
	III	2(15.38)	16(42.11)	
	IV	3(23.08)	1(2.63)	
CEA†		6.37(7.06)	99.72(447.13)	0.649
CA 19-9†		2204.06(4209.44)	1535.24(4702.14)	0.674
Resectable		11(84.62)	33(86.84)	0.581
Borderline		1(7.69)	4(10.53)	0.622
Unresectable		1(7.69)	1(2.63)	0.449
Preoperative intervention		9(69.23)	26(68.42)	0.813
Surgery	Classic Whipple	11(84.62)	31(81.58)	0.838
	Pylorus preserving	2(15.38)	6(15.79)	
	Total pancreatectomy		1(2.63)	
Differentiation	Well	1(7.69)	8(21.62)	0.413
	Moderate	9(69.23)	21(56.76)	
	Poor	3(23.08)	8(21.05)	
Adenocarcinoma origin	Ductal	10(76.92)	19(50.00)	0.604
	Pancreaticobiliary	2(15.38)	6(15.79)	
	Ampullary	1(7.69)	7(18.42)	
	Intestinal		5(13.16)	
	Mixed		1(2.63)	
Site of adenocarcinoma	Pancreas	10(76.92)	19(50.00)	0.211
	Ampulla of Vater	2(15.38)	16(42.11)	
	CBD	1(7.69)	1(2.63)	
	Duodenum		2(5.26)	
Greater dimension (cm)†		3.14(0.77)	2.73(1.45)	0.333

Number of pts with positive node		8(61.5)	28(73.7)	0.407
Positive nodes†		2.77(3.47)	2.61(2.66)	0.860
Positive margin		1(7.69)	4(10.53)	0.622
Lymphovascular invasion		8(61.54)	26(68.42)	0.650
Perineural invasion		10(76.92)	24(63.16)	0.290
Mucinous component			2(5.26)	0.551
Signet ring cell		1(7.69)		0.255
Neo-adjuvant therapy		1(7.69)	1(2.63)	0.449
Adjuvant therapy		4(30.8)	21(55.3)	0.114
Incomplete adjuvant therapy		2(50.0)	12(57.1)	0.604
Patients with less than 4 adjuvant therapy		2(50.0)	1(4.8)	0.057
Recurrence rate		7(53.8)	12(31.6)	0.136
Interval between curative resection to local recurrence, in days		312.50(306.18)	959.00(971.56)	0.464
Interval between curative resection to Distant metastasis, in days		407.86(446.87)	546.33(611.53)	0.609
Initiation of adjuvant therapy within 6 weeks of surgery		0(0.00)	7(18.42)	0.109

Data are expressed as numbers (percentages) except †mean (standard deviation). *P* values <0.05 were considered statistically significant. ASA: American Society of Anesthesiologists; CA 19-9: Carbohydrate Antigen; CBD: Common Bile Duct; CEA: Carcinoembryonic Antigen.

Table 5: Cox proportional-hazards analysis of prognostic factors toward survival.

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age	1.04	(0.99-1.09)	0.083			
Female gender	3.63	(1.18-11.20)	**0.025***	2.97	(0.89-9.93)	0.077
ASA Score						
II‡	1.00			1.00		
III	0.35	(0.07-1.66)	0.186	0.60	(0.12-3.11)	0.541
IV	6.31	(1.52-26.21)	**0.011***	5.48	(0.86-35.04)	0.072

Data are expressed as numbers. *P* values <0.05 were considered statistically significant. ‡Used as a reference.

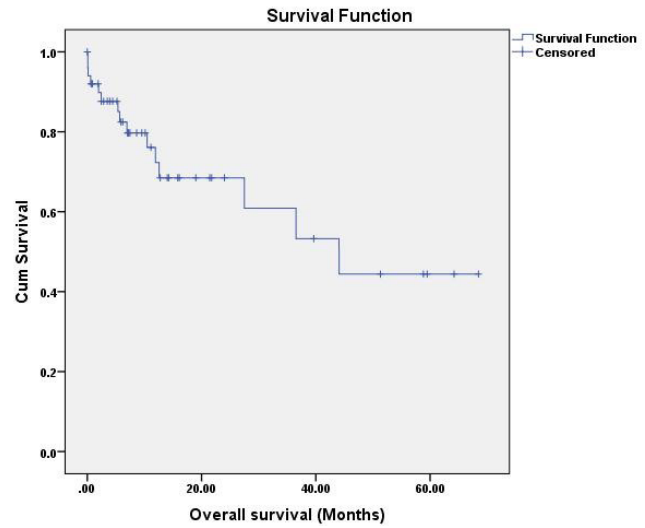

Figure 1: Shows the cumulative Kaplan Meier survival curve. The cumulative survival rate was 0.4 and the Overall survival, Median, 95% CI, Months was 44(19.5-68.5).

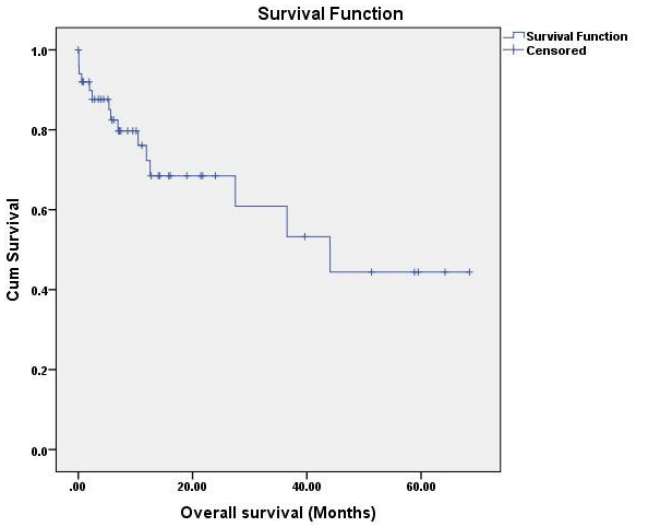

Figure 2: Shows the cumulative Kaplan Meier Disease free survival curve. The cumulative Disease-free survival rate was 0.1 and the Disease-free survival, Median, 95% CI, Months was 24.6(15.7-33.5).

Discussion

Periampullary adenocarcinoma is one of the worst survival rates among gastrointestinal malignancies [18]. Curative resection is the main factor in achieving better oncological outcomes [7,19]. There is no published data on periampullary adenocarcinoma in Saudi Arabia after curative resection. The primary goal of this study is to identify the oncological outcomes of periampullary adenocarcinoma post-curative resection.

Several studies showed that adenocarcinoma originating from the intestine has the best survival outcomes, followed by ampullary, biliary, and ductal in patients who underwent curative resection [18,20,21]. Hester et al. reported 5-year survival

rates of 50% for duodenal, 45% for ampullary, 31% for distal bile duct, and 18% for pancreatic head. He et al. showed that the overall estimated 5-year median survival for periampullary adenocarcinoma was 22 months; pancreatic cancer had the worst survival (median survival 19 months), followed by bile duct cancer (median survival 23 months), ampullary cancer (median survival 47 months) and duodenal cancer (median survival 54 months) [18]. Similarly, in a study by Hatzaras et al., pancreatic cancer histology correlated with the shortest median survival (17.1 months), followed by cholangiocarcinoma (17.9 months) and ampullary carcinoma (44.3 months) [22]. In this study, the median overall survival for all patients who underwent curative surgical resection was 44.07 months (95% CI, 19.54-68.59). The mortality rate based on the adenocarcinoma site was pancreas at 34.48%, followed by cholangiocarcinoma, in which we had two patients, and one is deceased. Then, the ampullary adenocarcinoma mortality rate was 11%. Lastly, we had two patients with duodenum cancer, and both are alive. This finding is interesting since periampullary adenocarcinomas are tissues that are packed nearby, sharing the same venous and lymphatic drainage.

In some cases, it's challenging to differentiate between them on a gross and histological level, yet they have different outcomes [18]. Thus, each type's "biological behavior" is one of the most important prognostic factors [22]. With the advancement in medicine and more understanding of the histomolecular basis of these tumors, each periampullary adenocarcinoma needs to be recognized as a distinct entity which will enable us to treat each type as a unique entity for a better outcome [23].

Prognostic variables have been investigated in several studies [10-12,20,22,24,25]. Favorable prognostic variables toward survival were well-differentiated histology, duodenal or ampullary adenocarcinoma, early stage, tumor diameter <2 cm, negative margins, receipt of chemotherapy, and absence of lymph node metastases, perineural or vascular invasion. Interestingly, this study's demographic factors, such as age, gender, and ASA score, and on univariate analysis, female gender (P=0.02) and ASA score IV (P=0.01) were significantly associated with survival, in contrast to other studies, which showed no relation [24]. None of the pathological factors reached statistical significance, which the small sample size can justify in our study.

Furthermore, supporting that surgical resection is the only potential for cure, a study showed that the median survival was 20.4 months for resectable patients versus 4.5 months for unresectable patients with periampullary adenocarcinoma [24]. Nevertheless, no statistically significant differences were observed between patients who underwent classic Whipple's or total pancreatectomy nor for those in whom a pylorus-preserving PD was performed. Similar results were documented elsewhere [24,26].

Patients who underwent only surgical resection experienced a 30-50% recurrence rate [27]. Therefore, surgery alone is not enough. Ongoing studies are evaluating the role of neoadjuvant therapy in patients with resectable periampullary tumors. Whereas a few studies have supported its use in the management of pancreatic adenocarcinoma and cholangiocarcinoma with evidence of improved overall survival [28,29]. In this study, only two patients received and completed neo-adjuvant therapy, which limits the interpretation of its effect on oncological outcomes.

Adjuvant therapy mirrors improving survival and reducing recurrence in surgically resected patients, which could represent a superior efficacy of multimodal treatment with combined chemotherapy [20,30-32]. Although not statistically significant, those who received incomplete adjuvant therapy or less than four cycles had 60% and 20% recurrence, respectively. Additionally, out of twenty-five patients who received adjuvant therapy, twenty-one patients survived (55.3%), but this did not yield any statistical significance. While all patients who received adjuvant chemotherapy within six weeks survived, no statistical significance was observed. Justifiably, the small sample size did not allow proper statistical analysis denoting the need for referral centers to increase the volumes and improve outcomes.

As reported in the literature, the most common site of distant metastasis was the liver, regional lymph node, lungs, and peritoneum [19,33]. In this study, the most common site of metastasis was the liver 42.1%, lung 42.1%, and regional lymph node 31.6%.

This study has several limitations. One of these limitations is that this study is a retrospective cohort study; thus, potential bias exists. Another limitation, the sample size is small, which might contribute to the statistical insignificance of different variables. Therefore, multi-center studies with larger sample sizes are warranted to confirm the results.

Conclusion

Periampullary adenocarcinoma remains to have aggressive behavior despite optimal surgical resection and appropriate adjuvant therapy, as it tends to metastasize systematically with short disease-free intervals. However, there is a significant variation in survival based on biological behavior, with pancreatic and common bile duct tumors associated with the worst survival rates. This is evident in our study, as patients with pancreatic adenocarcinoma have the highest mortality rate.

Conflicting interest: The authors have no conflict of interest to disclose.

Acknowledgment: The authors thank Ahmad H. Al-Sharqawi for his statistical analysis.

References

1. Komine R, et al. Recognition and pathological features of periampullary region adenocarcinoma with an indeterminable origin. Cancer Med. 2021; 10(11): 3499-3510.
2. Braasch JW, SJ Camer. Periampullary carcinoma. Med Clin North Am. 1975; 59(2): 309-14.
3. Siegel RL, et al. Cancer statistics, 2022. CA Cancer J Clin. 2022; 72(1): 7-33.
4. Sohn TA, et al. Adenocarcinoma of the duodenum: Factors influencing long-term survival. J Gastrointest Surg. 1998; 2(1): 79-87.
5. Jang JY, et al. Actual long-term outcome of extrahepatic bile duct cancer after surgical resection. Ann Surg. 2005; 241(1): 77-84.
6. Hidalgo M. Pancreatic cancer. N Engl J Med. 2010; 362(17): 1605-17.
7. Surgical Treatment: Evidence-Based and Problem-Oriented, in Surgical Treatment: Evidence-Based and Problem-Oriented, R.G. Holzheimer and J.A. Mannick, Editors. Zuckschwerdt Copyright © 2001, W. Zuckschwerdt Verlag GmbH.: Munich. 2021.
8. Diener MK, et al. Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic Whipple) for surgical treatment of periampullary and pancreatic car-

cinoma. Cochrane Database of Systematic Reviews, 2014.

9. Nakeeb, A.E., et al. Trends and outcomes of pancreaticoduodenectomy for periampullary tumors: A 25-year single-center study of 1000 consecutive cases. World Journal of Gastroenterology, 2017. 23(38): p. 7025-7036.

10. Yeo, C.J. and J.L. Cameron, Prognostic factors in ductal pancreatic cancer. Langenbecks Arch Surg, 1998. 383(2): p. 129-33.

11. Nakagawa, K., et al. Prognostic factors for actual long-term survival in the era of multidisciplinary treatment for pancreatic ductal adenocarcinoma. Langenbecks Arch Surg, 2018. 403(6): p. 693-700.

12. Kondo N, et al. Prognostic impact of perioperative serum CA 19-9 levels in patients with resectable pancreatic cancer. Ann Surg Oncol. 2010; 17(9): 2321-9.

13. Saraee A, et al. Whipple procedure: A review of a 7-year clinical experience in a referral center for hepatobiliary and pancreas diseases. World J Surg Oncol. 2015; 13: 98.

14. Zhang TN, RH Yin, LW Wang. The prognostic and predictive value of the albumin-bilirubin score in advanced pancreatic cancer. Medicine (Baltimore). 2020; 99(28): e20654.

15. Jemal A, et al. Global cancer statistics. CA Cancer J Clin. 2011; 61(2): 69-90.

16. Althubiti MA, MM Nour Eldein. Trends in the incidence and mortality of cancer in Saudi Arabia. Saudi Med J. 2018; 39(12): 1259-1262.

17. Alghamdi IG, et al. Epidemiology of Pancreatic Cancer in Saudi Arabia: A Retrospective Analysis of Pancreatic Cancer Diagnosed in Saudi Arabia Between 2004 and 2015. Clin Exp Gastroenterol. 2021; 14: 45-57.

18. He J, et al. 2564 resected periampullary adenocarcinomas at a single institution: trends over three decades. HPB (Oxford). 2014; 16(1): 83-90.

19. Al-Hawary MM, RK Kaza, IR Francis. Optimal Imaging Modalities for the Diagnosis and Staging of Periampullary Masses. Surg Oncol Clin N Am. 2016; 25(2): 239-53.

20. Hester CA, et al. Incidence and comparative outcomes of periampullary cancer: A population-based analysis demonstrating improved outcomes and increased use of adjuvant therapy from 2004 to 2012. J Surg Oncol. 2019; 119(3): 303-317.

21. Riall TS, et al. Resected periampullary adenocarcinoma: 5-year survivors and their 6- to 10-year follow-up. Surgery. 2006; 140(5): 764-72.

22. Hatzaras I, et al. Predictors of survival in periampullary cancers following pancreaticoduodenectomy. Ann Surg Oncol. 2010; 17(4): 991-7.

23. Chandrasegaram MD, et al. Distribution and pathological features of pancreatic, ampullary, biliary and duodenal cancers resected with pancreaticoduodenectomy. World J Surg Oncol. 2015; 13: 85.

24. Bouvet M, Factors Influencing Survival after Resection for Periampullary Neoplasms. THE AMERICAN JOURNAL OF SURGERY®. 2000; 180.

25. Berberat PO, et al. An audit of outcomes of a series of periampullary carcinomas. Eur J Surg Oncol. 2009; 35(2): 187-91.

26. Grace PA, et al. Decreased morbidity and mortality after pancreatoduodenectomy. Am J Surg. 1986; 151(1): 141-9.

27. Zhou YM, et al. Prognostic factors and benefits of adjuvant therapy for ampullary cancer following pancreatoduodenectomy: A systematic review and meta-analysis. Asian J Surg. 2020; 43(12): 1133-1141.

28. Adam MA, et al. Neoadjuvant Therapy Versus Upfront Resection for Nonpancreatic Periampullary Adenocarcinoma. Ann Surg Oncol. 2023; 30(1): 165-174.

29. Christians KK, et al. Survival of patients with resectable pancreatic cancer who received neoadjuvant therapy. Surgery. 2016; 159(3): 893-900.

30. Kim SM, JR Eads. Adjuvant and Neoadjuvant Therapy for Resectable Pancreatic and Periampullary Cancer. Surg Clin North Am. 2016; 96(6): 1287-1300.

31. Ostwal V, et al. Role of adjuvant chemotherapy in T2N0M0 periampullary cancers. Asia Pac J Clin Oncol. 2017; 13(5): e298-e303.

32. Neoptolemos JP, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): A multicentre, open-label, randomised, phase 3 trial. Lancet. 2017; 389(10073): 1011-1024.

33. Kim JH, et al. Adjuvant Chemotherapy for Resected Ampulla of Vater Carcinoma: Retrospective Analysis of 646 Patients. Cancer Res Treat. 2021; 53(2): 424-435.