Survival analysis and factors affecting survival in patients with pancreatic cancer

Özgür Önal[1]*, Servet Derya Yılmaz[1], Hande Nur Eroğlu[1], İsmet Eroğlu[2], Murat Koçer[3]

Abstract

Objective: The study aims to investigate the effects of clinicopathological characteristics and laboratory data at the time of diagnosis and of the administered treatments on survival in patients with pancreatic cancer.

Material and Methods: In this retrospective cohort study, we included the patients who presented to the Medical Oncology Outpatient Clinic of Isparta Süleyman Demirel University Medical Faculty Hospital and were diagnosed with pancreatic cancer between January 1, 2010 and December 31, 2017.

Results: A total of 124 patients were examined. The median survival time was 6.97 (%95 CI:4.663-9.270) months, and the 5-year survival rate was 8%. The survival time was shorter in patients diagnosed with adenocarcinoma (HR: 5.350), history of alcohol use (HR: 2.195), an Eastern Cooperative Oncology Group (ECOG) performance score of >2 (HR:2.763), Ca 19-9 value >400 (HR:1.790). Stages 2, 3 and 4 posed 2.034, 3.175 and 6.023 times higher risk of death than stage 1, respectively. Considering the adjuvant chemotherapy group as reference, risk of death was 1.250 times higher for those who received palliative chemotherapy and 2.314 times higher for those who did not receive chemotherapy.

Conclusion: In conclusion, history of alcohol use, Ca 19-9 level, ECOG performance status, disease stage, histopathological subtype of the disease, and whether the patient received chemotherapy or radiotherapy affect survival in patients with pancreatic cancer.

Key words: Cancer, Pancreatic Cancer, Survival, Prognostic Factors

Introduction

The incidence and mortality rates of cancer are rapidly increasing throughout the world, making it an important public health concern. Cancer is the cause of death in 1 of 6 deaths (1); it is estimated to be responsible for 10 million deaths in 2020 (2).

Globally, pancreatic cancer is the 11th most prevalent cancer with 338,000 new cases diagnosed each year, and with more than 334,000 deaths, it is the 7th leading cause of cancer-related deaths. The incidence of pancreatic cancer is increasing by 0.5%–1% each year. The lifetime risk of pancreatic cancer is about 1.6%. Pancreatic cancer has the worst survival rate among all cancers, with a 5-year survival rate of 3% in 1975 and approximately 8.2% today. It is the third leading cause of cancer-related deaths in the USA with more than 53,000 patients diagnosed and more than 43,000 deaths each year. It is estimated to be the 2nd leading cause of cancer-related deaths by 2030. Pancreatic cancer is more common in patients at an advanced age, especially those aged 65–74 years, and it is more prevalent in males than females (3).

According to the 2015 cancer statistics in Turkey, the incidence of pancreatic cancer is 5.6 per 100,000 for men and 3.3 per 100,000 for women (4).

Patients with pancreatic cancer usually present with epigastric pain and jaundice or weight loss without jaundice (3). Approximately 60%, 15%, and 5% tumors are localized in the head, body, and tail of the pancreas, respectively, whereas the remaining 20% are diffuse within the pancreas (5). Smoking, history of diabetes, high body mass index, excessive alcohol use, family history of pancreatic cancer are some important risk factors (6). Only 10%–20% patients present with resectable pancreatic cancer (3).

Thus, we investigated the effects of clinicopathological characteristics and laboratory data at the time of diagnosis and of the treatments administered during follow-up on survival in patients with pancreatic cancer. The results of the study help in appropriate patient management.

Material and Methods

The study was conducted between 2018 and 2019. Ethics Committee of the Isparta Süleyman Demirel University Medical Faculty approved the study (Approval no: 213, dated December 13, 2018).

In this retrospective cohort study, we included the patients who presented to the Medical Oncology Outpatient Clinic of Isparta Süleyman Demirel University and were diagnosed with pancreatic cancer between January 1, 2010 and December 31, 2017. A total of 124 patients were included. Patient information was obtained from the archive files and information system of the hospital. Patient deaths were updated after verifying the same with the system on December 20, 2018. Mean follow-up time and survival time were calculated. Survival time was defined as the duration of time (months) until death for deceased patients and as the duration of time (months) since the diagnosis for living patients.

We recorded the patients' gender, age at diagnosis, presence of abdominal pain and jaundice as presenting symptoms, history of weight loss of >10% in the last 6 months, personal–family medical histories, Eastern Cooperative Oncology Group (ECOG) performance scores, CA 19-9 and CEA levels, treatment history, latest follow-up date, and time of death, if the patient was deceased. The presence of diabetes was particularly investigated in pancreatic cancer cases. A cutoff value of 400 for Ca19-9 level was used in the analyses (7); this value corresponded to the 66th percentile for Ca 19-9. The performance scoring used by the ECOG was employed to identify the performance status of the patients (8).

Data such as tumor localization, TNM stage, site of metastasis (if any), date of pathological diagnosis, and histopathological subtype were obtained from the patient files. In terms of tumor localization, pancreatic cancer was classified as cancer localized in the head, body, and tail and diffused cancer within the pancreas. Because non-adenocarcinoma cases were limited, they were combined with other adenocarcinomas cases for evaluation. AJCC Version 8 TNM staging system was used for staging (9).

Patients who presented to the Oncology Outpatient Clinic of Süleyman Demirel University Hospital and were histopathologically diagnosed with pancreatic cancer between 2010 and 2017 were included.

The data was evaluated using descriptive statistics (number, percentage, mean, median, and standard deviation), Kaplan–Meier analysis, and Cox regression analysis using a statistical software package. Significant variables and variables that were not found to be significant with p values below 0.250 in univariate analyses were used in Cox regression analysis. $P<0.05$ was considered statistically significant.

Results

Overall 124 patients diagnosed with pancreatic cancer between 2010 and 2017 were examined. The mean age of the patients at diagnosis was 62.8 ± 11.6 years, 56.5% (n = 70) patients aged $\geqslant 60$ years at diagnosis, and 64.5% (n = 80) patients were male. Patients with a history of smoking constituted 36.3% (n = 45) of the group, and 6.5% (n = 8) were alcohol users. At admission, 71.8%, 27.4%, 29.1%, and 35.5% (n = 89, 34, 36, and 44) patients stated that they had abdominal pain, jaundice, weight loss in the last 6 months, and a history of diabetes, respectively (Table 1).

Table 1. Demographic and clinical data of patients

		n(%)	Median survival time±SE	p
Age	(Mean ± SD)	62.8±11.6		
	< 60	54 (% 43.5)	9.73±1.67	0.015
	≥ 60	70 (% 56.5)	5.20±0.91	
Gender	Female	44 (% 35.5)	9.73±3.08	0.063
	Male	80 (% 64.5)	6.57±1.23	
Smoking history	Absent	79 (% 63.7)	6.97±1.53	0.793
	Present	45 (% 36.3)		
	< 40 py	30 (% 24.2)	6.93±3.40	
	≥ 40 py	15 (% 12.1)	8.80±2.02	
Alchol history	Present	8 (% 6.5)	4.53±1.79	0.174
	Absent	116 (% 93.5)	7.70±1.22	
Abdominal pain	Present	89 (% 71.8)	6.30±1.29	0.134
	Absent	35 (% 28.2)	10.07±2.94	
Jaundice	Present	34 (% 27.4)	8.80±2.84	0.322
	Absent	90 (% 72.6)	6.40±1.53	
Weight loss (6 months)	Absent	88 (% 70.9)	8.60±1.49	0.584
	Present	36 (% 29.1)		
	< %10	24 (% 19.4)	5.50±1.51	
	≥ %10	12 (% 9.7)	6.30±3.35	
Comorbidities	Diabetes Mellitus	44 (% 35.5)	5.50±0.98	0.189
	Other comorbidities	24 (% 19.4)	7.83±2.45	
	Absent	56 (% 45.1)	9.23±1.66	
Total		124 (100.0)	6.97±1.18 (median±SE) 15.93±2.09 (mean±SE)	

P: log rank (mantel-cox

413

The distribution of histopathological diagnosis was as follows: 92.8%, 4.8%, 1.6%, and 0.8% (n = 115, 6, 2, and 1) of adenocarcinomas, neuroendocrine tumors, acinar cell carcinomas, and sarcomatoid carcinoma, respectively. Because non-adenocarcinoma cases were limited, they were combined with other adenocarcinoma cases for evaluation. Cancer stage at diagnosis was recorded. AJCC Version 8 TNM staging system was used for staging. A total of 4, 12, 40, and 68 (3.2%, 9.7%, 32.3%, and 54.8%) patients had stage 1, 2, 3, and 4 cancer, respectively (Figure 1). Furthermore, 46 (67.6%) patients with stage 4 cancer had single organ metastasis, whereas 22 (32.3%) had multiple metastases. The tumor was localized in the head, body, and tail in 66.9%, 14.5%, and 13.8% patients, respectively, whereas 4.8% had diffuse cancer within the pancreas. In addition, performance status according to the ECOG performance scale was >2 in 31 (25.0%) patients (Figure 2).

CEA values were not available in the file or in the system for 31 (25.0%) patients, whereas 51 (41.1%) had CEA values above 4. Moreover, Ca 19-9 values were not available in the file or in the system for 23 (18.6%) patients, whereas 35 (28.2%) had Ca 19-9 values above 400.

Mean follow-up time was 9.7 ± 13.9 (min: 0.0; max: 81.7) months. Treatments administered during follow-up were as follows: 57, 40, and 17 (46.0%, 32.3%, and 13.7%) patients underwent surgery, radical surgery, and palliative surgery, respectively. Additionally, 67 (54.0%) received systemic chemotherapy; of these, 24 (19.3%) received adjuvant therapy, 43 (34.7%) received palliative treatment, and 2 who received adjuvant therapy were also administered neoadjuvant therapy (Table 2).

Table 2: Clinical-laboratory-pathology data and treatment details at the time of diagnosis of patients

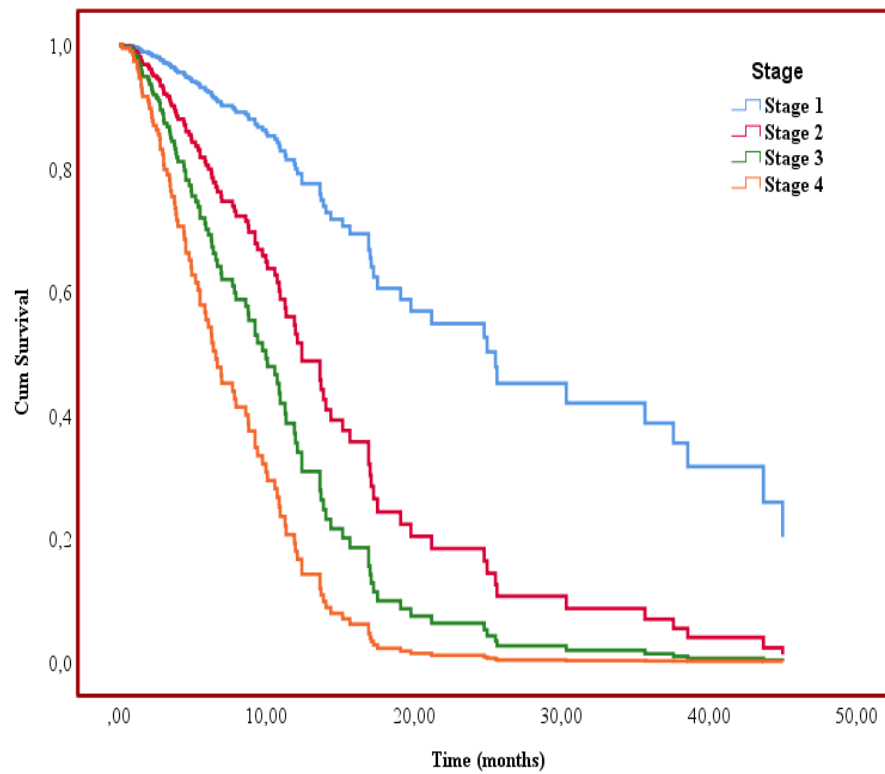|		n(%)	Median survival time±SE	p
ECOG	≤ 2	93 (% 75.0)	10.57±1.25	<0.001
	> 2	31 (% 25.0)	2.80±0.41	
CEA	≤ 4	42 (% 33.9)	11.33±1.65	0.005[1]
	> 4	51 (% 41.1)	4.53±1.07	
	Unknown	31 (% 25.0)	6.30±1.61	
Ca 19-9	≤ 400	66 (% 53.2)	9.40±1.64	0.001[2]
	> 400	35 (% 28.2)	3.90±0.48	
	Unknown	23 (% 18.6)	7.83±1.97	
Stage	1	4 (% 3.2)	35.67±14.31	<0.001[3]
	2	12 (% 9.7)	19.80±6.44	
	3	40 (% 32.3)	10.57±1.27	
	4	68 (% 54.8)	4.00±0.40	
Number of metastases	Single	46 (% 67.7)	4.53±1.11	0.780
	Multiple (≥ 2)	22 (% 32.3)	3.77±0.27	
Histopathological subtype*	Adenocarcinoma	115 (% 92.8)	12.96±1.78**	<0.001
	Other subtype*	9 (%7.2)	53.53±11.17	
Tumor localization (pancreas)	Head	83 (% 66.9)	7.70±1.52	0.510
	Corpus	18 (% 14.5)	7.83±2.23	
	Tail	17 (% 13.8)	6.40±3.77	
	Common	6 (% 4.8)	4.40±2.51	
Operation	Present	57 (% 46.0)		
	Radical	40 (% 32.3)	16.93±1.79	<0.001[4]
	Paliative	17 (% 13.7)	6.40±2.68	
	Absent	67 (% 54.0)	4.43±0.53	
Chemotherapy	Present	67 (% 54.0)		
	Adjuvant	24 (% 19.3)	15.67±1.84	0.001[5]
	Paliative	43 (% 34.7)	6.40±1.22	
	Absent	57 (% 46.0)	4.77±1.04	
Radiotherapy	Present	14 (% 11.3)		
	Adjuvant	12 (% 9.7)	42.18±9.39**	0.004[6]
	Paliative	2 (% 1.6)	9.58±1.75	
	Absent	110 (% 88.7)	12.85±1.84	
Chemoradyotherapy	Present	7 (% 5.6)	6.93±1.88	0.490
	Absent	117 (% 94.4)	7.70±1.22	
	Total	124 (100.0)	6.97±1.18 (median±SE)	
			15.93±2.09 (mean±SE)	

*Neuroendocrine tumor; 6(% 4,8), Acinar cell carcinoma; 2 (% 1,6),Spindle cell carcinoma; 1 (% 0,8)

**calculate mean 1 : The difference is due to CEA ≤ 4 ones. 2 : The difference is between Ca19-9 ≤400 and >400.
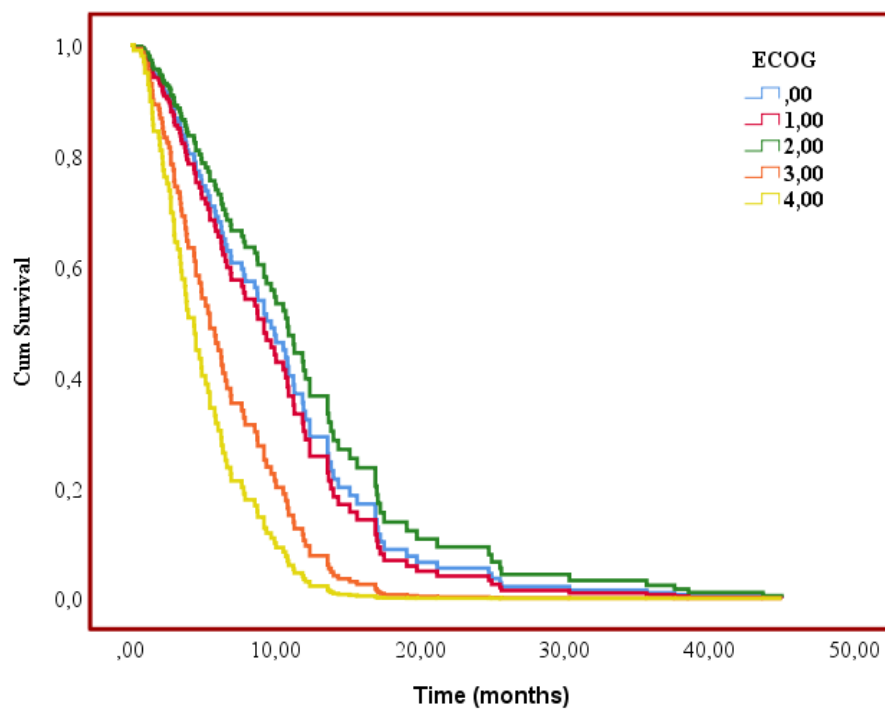
3 :lineer4 : The difference stems from the group undergoing radical operation.

5 : The difference arises from the group receiving adjuvant chemotherapy.

6 : The difference arises from the group receiving adjuvant radiotherapy.

Figure 1. Survival curves according to stages

Figure 2. Survival curves according to ECOG performance status

Univariate Survival Analysis

The median survival was 6.97 (%95 CI:4.663-9.270) months, and the 5-year survival rate was 8%. Mean survival time was 12.96 ± 1.78 months for patients with adenocarcinoma and 53.53 ± 11.17 months for those with non-adenocarcinoma. This difference was statistically significant (p < 0.001). Median survival time for those aged ≥60 years at diagnosis was significantly shorter than that for patients aged <60 years at diagnosis (p = 0.015). Gender, history of smoking and alcohol use, symptoms at presentation, and presence of chronic diseases did not significantly affect survival. Patients with an ECOG performance score of >2, CEA values above 4, and Ca 19-9 values above 400 had significantly short median survival time (p < 0.001, p = 0.005, and p = 0.001, respectively). Survival time significantly decreased with advancing stage of the disease (p < 0.001). Tumor localization or the presence of single metastasis or multiple metastases did not significantly affect survival time. Patients who underwent radical surgery, received adjuvant chemotherapy, or radiotherapy had significantly long median survival time (p< 0.001, p= 0.001, and p= 0.004, respectively). Chemoradiotherapy had no significant effect on survival (Table 3).

Multivariate Survival Analysis

History of alcohol use (HR: 2.195; 95%CI: 1.036–4.649), an ECOG performance score of >2 (2.763, 95%CI: 1.569–4.866), and Ca 19-9 value over 400 (1.790, 95%CI: 1.134–2.824) were the factors that led to short survival time. Stages 2, 3 and 4 posed 2.034 (95%CI: 0.429–9.643), 3.175 (95%CI: 0.727–13.863), and 6.023 (95%CI: 1.333–27.222) times higher risk of death than stage 1, respectively. In terms of the histopathological subtypes, survival time was shorter for patients with adenocarcinoma (HR: 5.350, 95%CI: 1.775–16.120) than that for patients with other subtypes. Considering the adjuvant chemotherapy group as reference, risk of death was 1.250 (95%CI: 0.684–2.285) times higher for those who received palliative chemotherapy and 2.314 (95%CI: 1.252–4.277) times higher for those who did not receive chemotherapy.

Considering the adjuvant radiotherapy group as reference, risk of death was 1.282 (95%CI: 0.234–7.036) times higher for those who received palliative radiotherapy and 3.506 (95%CI: 1.421–8.651) times higher for those who did not receive radiotherapy (Table 3).

Table 3. Multivariate analysis of overall survival (Cox regression-backward-LR).

	Covariates	Multivariate survival analysis	
		Hazard Ratio (95% CI)	P-value
Alchol History	Absent	1	
	Present	2.195 (1.036-4.649)	**0.040**
ECOG	ECOG 1-2	1	
	ECOG 3-4	2.763 (1.569-4.866)	**<0.001**
Ca 19-9	Ca 19-9 ≤ 400	1	
	Ca 19-9 > 400	1.790 (1.134-2.824)	**0.012**
Stage	Stage 1	1	
	Stage 2	2.034 (0.429-9.643)	0.371
	Stage 3	3.175 (0.727-13.863)	0.124
	Stage 4	6.023 (1.333-27.222)	**0.020**
Histopathological subtype	Other subtype	1	
	Adenocarcinoma	5.350 (1.775-16.120)	**0.003**
Chemotherapy	Adjuvant	1	
	Paliative	1.250 (0.684-2.285)	0.469
	Absent	2.314 (1.252-4.277)	**0.007**
Radiotherapy	Adjuvant	1	
	Paliative	1.282 (0.234-7.036)	0.775
	Absent	3.506 (1.421-8.651)	**0.006**

Discussion

According to 2001–2010 data from Surveillance, Epidemiology and End Results, median survival time for pancreatic cancer is 7 months (10). Similarly, the median survival time was 6.97 ± 1.18 months in the present study. History of alcohol use, Ca 19-9 level, ECOG performance status, disease stage, histopathological subtype of the disease, and whether the patient received chemotherapy or radiotherapy were found to affect survival in patients with pancreatic cancer.

Furthermore, 90% pancreatic cancers are exocrine pancreatic ductal adenocarcinomas (11), and 92.8% patients in our study group had adenocarcinoma. Studies that involve ductal adenocarcinoma cases constitute a considerable part of the pancreatic cancer literature. In the present study, survival times were shorter in patients with adenocarcinoma (HR: 5.350; 95%CI: 1.775–16.120) than in those with other subtypes. The mean survival time was 12.96 ± 1.78 for patients with adenocarcinoma and 53.3 ± 11.17 in the other group.

Because neuroendocrine tumors were also included in the present study, the mean survival time was higher in this group. In a study by Nitschke et al. including exocrine pancreatic cancer cases and comparing ductal adenocarcinoma and other exocrine pancreatic cancers, the risk of death from ductal adenocarcinoma was 2.519-fold high (12).

In the present study, risk of death was 2.195 (95%CI: 1.036–4.649) times higher in patients with a history of alcohol use. Although there are no consistent results regarding the relationship between alcohol use and pancreatic cancer, there are several large-scale studies demonstrating that heavy drinking increases the risk of pancreatic cancer (13,14). Although 6.5% of our patients had a history of alcohol use, there was no information regarding the amount of alcohol consumption in these patients.

Moreover, the patients with ECOG performance scores of >2 had lower survival rates and 2.763-fold (95%CI: 1.569–4.866) increased risk of death. Other studies have shown that ECOG performance status is an important determinant of survival in pancreatic cancer patients, and increased performance score leads to shorter survival (15–17).

In the present study, another prognostic factor was the disease stage. Stage 4 posed 6.023 (95%CI: 1.333–27.222) times higher risk of death than stage 1. A study by Malwinder et al. showed that stage 3 and 4 increased the risk of death by 3.8- and 5.7-fold, respectively, compared to stage 1 (17). Pancreatic cancers have the worst survival rates among all cancers, and one of the most important reasons for this is the fact that most of the patients are already at an advanced stage at diagnosis. Stage 4 patients constituted 54.8% of our study group.

Although the Ca19-9 biomarker cannot be used for the early diagnosis of pancreatic cancer, it is the most commonly used marker to monitor the therapeutic progress (18). Elevated Ca 19-9 values were among the factors that decreased survival time in the present study.

Patients who received adjuvant chemotherapy or radiotherapy had significantly high survival, which is also supported by other studies (19,20). Considering that only 10%–20% patients have resectable pancreatic cancer at diagnosis, radiotherapy and chemotherapy have an important role in the treatment of pancreatic cancers.

Conclusion

In conclusion, the median survival time in pancreatic cancer was found to be 6.97 months. Furthermore, history of alcohol use, Ca 19-9 level, ECOG performance status, disease stage and histopathological subtype of the disease, and whether the patient received chemotherapy or radiotherapy are the factors that affect survival. Knowing the survival rate and the factors affecting survival rate for a cancer will guide physicians in patient management as well as I predicting the prognosis of the disease.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.

2. Cancer Tomorrow [Internet]. [cited 2019 Sep 3]. Available from: https://gco.iarc.fr/tomorrow/graphic-isotype?type=1&population=900&mode=population&sex=0&cancer=39&age_group=value&apc_male=0&apc_female=0

3. Daniel D. Von Hoff. Pancreatic Cancer. In: Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 20th ed. 2018. p. 591–5.

4. Türkyılmaz M, Hacıkamiloğlu E, Deniz EB, Boztaş G, Dündar S, Ergün AK, et al. Turkey Cancer Statistics 2015. Ankara; 2018.

5. Kumar V, Abbas AK, Aster JC. Pancreas. In: Kumar V, Abbas AK, Aster JC, editors. Robbins Basic Pathology. 10th ed. 2018. p. 679–89.

6. Aier I, Semwal R, Sharma A, Varadwaj PK. A systematic assessment of statistics, risk factors, and underlying features involved in pancreatic cancer. Cancer Epidemiol [Internet]. 2019;58(November 2018):104–10. Available from: https://doi.org/10.1016/j.canep.2018.12.001

7. Ünek İT. The Prognostic Factors In Patients With Pancreatic Adenocarcinoma. Dokuz Eylül Üniversitesi; 2010.

8. ECOG Performance Status - ECOG-ACRIN [Internet]. [cited 2018 Nov 15]. Available from: https://ecog-acrin.org/resources/ecog-performance-status

9. NCCN - Evidence-Based Cancer Guidelines, Oncology Drug Compendium, Oncology Continuing Medical Education [Internet]. [cited 2018 Nov 16]. Available from: https://www.nccn.org/

10. Sun H, Ma H, Hong G, Sun H, Wang J. Survival improvement in patients with pancreatic cancer by decade: A period analysis of the SEER database, 1981-2010. Sci Rep. 2014;4:1–10.

11. Chua YJ, Cunningham D. Pancreatic Cancer. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al., editors. Harrison's Principles of Internal Medicine Türkçe. 17th ed. 2013. p. 586–8.

12. Nitschke P, Volk A, Welsch T, Hackl J, Reissfelder C, Rahbari M, et al. Impact of intraoperative re-resection to achieve R0 status on survival in patients with pancreatic cancer: A single-center experience with 483 patients. Ann Surg. 2017;265(6):1219–25.

13. Genkinger JM, Spiegelman D, Anderson KE, Bergkvist L, Bernstein L, Van Den Brandt PA, et al. Alcohol intake and pancreatic cancer risk: A pooled analysis of fourteen cohort studies. Cancer Epidemiol Biomarkers Prev. 2009;18(3):765–76.

14. Tramacere I, Scotti L, Jenab M, Bagnardi V, Bellocco R, Rota M, et al. Alcohol drinking and pancreatic cancer risk: A meta-analysis of the dose-risk relation. Int J Cancer. 2010;126(6):1474–86.

15. Hamada T, Nakai Y, Yasunaga H, Isayama H, Matsui H, Takahara N, et al. Prognostic nomogram for nonresectable pancreatic cancer treated with gemcitabine-based chemotherapy. Br J Cancer [Internet]. 2014;110(8):1943–9. Available from: http://dx.doi.org/10.1038/bjc.2014.131

16. Kou T, Kanai M, Yamamoto M, Xue P, Mori Y, Kudo Y, et al. Prognostic model for survival based on readily available pretreatment factors in patients with advanced pancreatic cancer receiving palliative chemotherapy. Int J Clin Oncol. 2016;21(1):118–25.

17. Malwinder S, Wan Zamaniah Bt WI, Cimmeran K, Phua VCE. Prognostic factors for survival in pancreatic cancer patients from university Malaya medical centre, Malaysia. J Heal Transl Med. 2018;21(1):6–13.

18. Laheru D. Pancreatic Cancer. In: Goldman L, Schafer AI, editors. Goldman-Cecil Medicine. 25th ed. 2016. p. 1332–4.

19. Chang, Kenneth J; Parasher, Gulshan; Christie, Catherine; Largent JHA-C. Risk of Pancreatic Adenocarcinoma Disparity between African Americans and Other Race/Ethnic Groups. Am Cancer Soc. 2005;103(2):349–57.

20. Eloubeidi MA, Desmond RA, Wilcox CM, Wilson RJ, Manchikalapati P, Fouad MM, et al. Prognostic factors for survival in pancreatic cancer: a population-based study. Am J Surg. 2006;192(3):322–9.