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The role of clinicopathological features in the prognosis of resected pancreatic ductal adenocarcinoma: a retrospective study

Masoomeh Safaei[1], Nima Taghizadeh Mortezaei[2], Farid Azmoudeh-Ardalan[3], Ali Jafarian[4], Elham Ebrahimi Niyari[5], Behnaz Bouzari[6*]

[1]Department of Pathology, Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
[2]School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[3]Department of Pathology, Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
[4]Department of General Surgery, Liver Transplantation Research Center Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
[5]School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[6]Department of Pathology, School of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran

***Correspondence to**
Behnaz Bouzari, Email: behnaz.boozari@gmail.com

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Abstract

Introduction: Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive and lethal malignancies, with a poor overall prognosis and low survival rates. Despite advances in treatment, the five-year survival rate remains dismally low, particularly for patients with advanced disease. Several clinicopathological factors have been associated with survival outcomes; however, their prognostic significance remains debated.

Objectives: This study aims to investigate the survival rates of patients with resected PDAC and evaluate the association between clinicopathological characteristics and patient survival outcomes.

Patients and Methods: The data of patients diagnosed with PDAC who underwent surgical resection at Tehran Cancer Institute between 2013 and 2019 were retrospectively analyzed. Demographic, clinical, and histopathological characteristics were extracted from medical records and pathology reviews. Patients were followed up to assess their 1- and 3-year survival. Survival analysis was conducted using the Kaplan-Meier method, with comparisons made via the Log Rank test. Cox regression was used for multivariate analysis to assess the association between clinicopathological factors and survival.

Results: Thirty-seven patients (56.8% female) with PDAC were included in this study, with a mean age of 59.57 ± 9.24 years. The average tumor size was 3.42 ± 1.19 cm, and 67.5% of tumors were located in the pancreatic head. Lymph node involvement was observed in 67.6% of cases, with vascular and perineural invasion present in 91.9% and 94.6% of patients, respectively. The overall median survival was 15.16 months, with 1-year and 3-year survival rates of 56.8% and 27%, respectively. Univariate analysis showed that diabetes was significantly associated with reduced survival, while multivariate analysis indicated that male gender (hazard ratio [HR] =2.44, 95% confidence interval [CI] = 1.04 to 5.74, *P*=0.04), underlying diseases (HR =3.54, 95% CI = 1.26 to 9.97, *P*=0.01), and perineural invasion (HR=34.63, 95% CI =1.04 to 1154.8, *P*=0.04) were linked to a worse prognosis.

Conclusion: In our study, we found that underlying diseases, particularly diabetes, male gender, and perineural invasion, were significantly associated with worse survival in PDAC patients. Despite surgical resection, the median survival was 18 months, with only 1/4 of patients alive at three years. These findings highlight the need for further studies to identify prognostic markers and develop more effective treatment strategies.

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Introduction

According to the American Cancer Society's 2021 cancer statistics, approximately 60 430 new cases and 48 220 deaths from pancreatic cancer were reported in the United States, placing it as the third leading cause after lung and colorectal cancers (1). A 2017 systematic analysis on the global burden of disease showed that the number of new cases and deaths from pancreatic cancer increased from 195 000 cases and 196 000 deaths in 1990 to 448 000 cases and 441 000 deaths in 2017, representing a two to three-fold increase (2). Global cancer statistics in 2020 revealed 495 773 new cases and 466 003 deaths from pancreatic cancer worldwide, indicating similar incidence and mortality rates (3). These findings demonstrate a gradual increase in the number of cases and deaths due to pancreatic cancer.

Pancreatic ductal adenocarcinoma (PDAC) is the most common pancreatic malignancy. It is currently the sixth leading cause of cancer death worldwide and the fourth leading cause of cancer death in the United States (4). The incidence of PDAC is increasing, and a

Key point

- In pancreatic ductal adenocarcinoma patients, diabetes was associated with decreased survival rates, while multiple factors like being male, having underlying diseases, and perineural invasion were linked to poorer prognosis.

- The study highlights the significance of identifying prognostic indicators and developing improved treatment strategies for pancreatic ductal adenocarcinoma patients, as even after surgery, the survival rates remain relatively low.

doubling of cases and deaths is estimated in European and American countries over the next 10 years. Based on advances in knowledge about potential risk factors for pancreatic cancer and new tools available for early diagnosis of the disease, it is estimated that the incidence of the disease will increase in the coming decades and will reach 355 317 new cases in 2040 (3,5).

Pancreatic adenocarcinoma has a very poor prognosis, with only 24% of patients surviving 1 year after diagnosis and a 5-year survival rate of 12.8% (6). In fact, pancreatic cancer remains one of the deadliest cancers with a dismal prognosis and a mortality-to-incidence ratio of 94%. More than half of pancreatic cancer deaths occur in developed countries. Pancreatic cancer mortality rates increase with age in both sexes, and approximately 90% of all deaths occur after age 55 (3,5). 24% of patients have unresectable tumors due to advanced stage at diagnosis. In fact, more than 80% of patients diagnosed with pancreatic carcinoma are not suitable for surgical treatment due to the presence of local or distant metastases (7). This is especially true for adenocarcinoma, which is diagnosed in over 90% of cases (8). In addition, the current chemotherapy regimen available for stage III or IV disease is often limited and ineffective (9,10). Even with radical resection, tumor recurrence or metastasis will occur in most cases within 1-2 years, and the median overall survival (OS) after surgery is only 20-25 months (11). Therefore, early diagnosis can be the key to reducing mortality and may be supported by screening and prevention of the disease.

Several factors have been identified in various studies as being involved in the prognosis and survival of these patients, including age, gender, underlying diseases, clinical stage and tumor grade, tumor size, tumor characteristics including vascular and nerve invasion, lymph node involvement and number of them, tumor margin, and type of treatment performed including chemotherapy before and after surgery to control cancer (12). In Whipple surgery, the most common surgical procedure used for PDAC, the surgical margins include uncinate margin and portal vein groove margin. According to the recommendation of the National Comprehensive Cancer Network (NCCN), a margin is considered positive if the tumor was at a distance of 1 mm or less from the margin and is reported as R1 (presence of microscopic residual disease) or R2 (presence of macroscopic residual disease) (13,14). In the literature, there is disagreement between different studies on the prognostic importance of surgical margins in pancreatic cancer; While several studies have found no association between increased survival and negative margin (R0), other articles have not observed a link between the presence of R1 margins and local recurrence (14).

Pancreatic cancer is a relatively common and highly lethal cancer worldwide, with ductal adenocarcinoma of the pancreas accounting for most cases. According to epidemiological studies, the annual incidence and mortality rates of pancreatic cancer are very close, indicating the high fatality rate of this malignancy. The survival rate of patients with PDAC has not improved significantly in recent decades. In fact, this is likely due to the late diagnosis of patients and the ineffectiveness of current treatment regimens in patients with advanced stages of the disease. Therefore, we decided to conduct a study to determine the overall median survival, one- and three-year survival, and their association with clinicopathological characteristics in patients with PDAC.

Objectives

This study aims to investigate the survival rates of patients with resected PDAC and evaluate the association between clinicopathological characteristics and patient survival outcomes.

Patients and Methods

Study design

The present study is a retrospective cohort study conducted on patients with pancreatic cancer who underwent surgical resection of the tumor at Tehran Cancer Institute between 2013 and 2019. It aims to evaluate their mean survival rate as well as their 1- and 3-year survival rates and the association of these rates with clinicopathological characteristics in these patients.

Study population

The study population included all patients diagnosed with PDAC who underwent surgery at Tehran Cancer Institute between 2013 and 2019. Eligible patients were enrolled in the study using a census method, resulting in a sample size of 37 patients. Patients with incomplete medical records or who could not be contacted by phone were excluded from the study. Patients with unresectable pancreatic tumors were also excluded from the study.

Data collection

Information on patients' age, gender, comorbidities, tumor location, tumor size, and type of treatment before and after surgery was extracted from their medical records in the pathology department archive of Tehran Cancer Institute. The paraffin blocks and H&E-stained slides of the patients were retrieved from the pathology department archive. All slides were reviewed again by two pathologists. In cases where the slides were of inadequate quality, a new section

was prepared from the paraffin block. Histopathological information of the specimens included tumor type, tumor grade, tumor stage, surgical margin status, tumor distance from the margin (less or more than 1 mm), lymph node involvement, Ink, vascular invasion, and perineural invasion were assessed by reviewing the Hematoxylin and Eosin (H&E)-stained slides with a light microscope. Information on patients' 1-year survival, and 3-year survival was also collected by following them up by phone call.

Statistical analysis

The collected data were coded and analyzed using SPSS software version 26 (IBM Inc, Chicago, USA) for statistical analysis of the study data. Quantitative data were reported as mean and standard deviation, and qualitative data were reported as percentages and frequencies. The significance level was set at 0.05. The normality of quantitative data was examined using the Kolmogorov-Smirnov test. For the analysis of normally distributed variables, parametric tests were used, and for the analysis of non-normally distributed variables, non-parametric tests were used. The Kaplan-Meier test was conducted to assess patient survival, and the log rank test was used to compare survival curves between groups. Multivariate analysis using Cox regression was performed to investigate the effect of covariates on survival.

Results

In this study, 37 patients were enrolled, 56.8% of whom were women. The average age of the patients was 59.57 ± 9.24 years. The minimum age was 43 years and the maximum age was 83 years. The mean tumor size was 3.42 ± 1.19 cm, with a range extending from 1.8 cm to 7 cm. The majority of tumors (67.5%) were located in the head of the pancreas. Regional lymph nodes involvement was present in 67.6% of patients, while vascular and perineural invasion were present in 91.9% and 94.6% of cases, respectively.

Positive surgical margins as Ink involvement were observed in 12 samples (32.4 %); however, there were 2 samples with less than 1 mm tumor to margin distance without Ink involvement. The most common margins involved was the uncinate and portal vein groove margins, and the most common histological grade observed was well differentiated (40.5%). Regarding the treatment framework, complete tumor resection was achieved via Whipple surgery in all cases. Furthermore, 32.4% of patients received neoadjuvant chemotherapy, and 83.8% received adjuvant chemotherapy. Additional clinical patient characteristics and histopathological details of the investigated tumors are documented in Tables 1 and 2, respectively.

Survival findings

The maximum follow-up duration for patients in this

Table 1. Clinical characteristics

Variable		No. (%)
Gender	Male	21 (56.8)
	Female	16 (43.2)
Age (y)	≤60	20 (54.1)
	>60	17 (45.9)
Underlying disease	Yes	8 (22.2)
	No	28 (77.8)
Neo-adjuvant chemotherapy	Yes	12 (32.4)
	No	25 (67.6)
Adjuvant chemotherapy	Yes	31 (83.8)
	No	6 (16.2)

Table 2. Histopathological characteristics

Variable		No. (%)
ypTNM stage	pT2	9 (24.3)
	pT2/N1	2 (5.4)
	pT2/N2	1 (2.7)
	pT3	17 (45.9)
	pT3/N1	0 (0.0)
	ypT1	1 (2.7)
	ypT1c/pN1	1 (2.7)
	ypT2	4 (10.8)
	ypT3	2 (5.4)
	ypT4	0 (0.0)
Tumor grading	Well differentiated	15 (40.5)
	Well to moderate differentiated	5 (13.5)
	Moderate differentiated	14 (37.8)
	Moderate to poor differentiated	2 (5.4)
	Poor differentiated	1 (2.7)
Tumor location	Pancreatic head	12 (32.4)
	Pancreatic head and uncinate	13 (35.1)
	Uncinate process	7 (18.9)
	Uncinate process and groove region	1 (2.7)
	Pancreatic body	1 (2.7)
	Pancreatic tail and body	2 (5.4)
	Distal of common bile duct	1 (2.7)
Tumor size (cm)	≤ 4	27 (73)
	> 4	10 (27)
Vascular invasion	Yes	34 (91.9)
	No	3 (8.1)
Perineural invasion	Yes	35 (94.6)
	No	2 (5.4)
Lymph node involvement	Yes	25 (67.6)
	No	12 (32.4)
Surgical margin	Positive	12 (32.4)
	Negative	25 (67.6)

study was 74 months. The mean OS time for the patients was 22.63 ± 18.39 months, with a median survival of 15.16 months. Based on this study's findings, 21 patients were alive at the end of one year, and 10 were alive at the end of three years after surgery. Accordingly, the patients' 1-year and 3-year survival rates were calculated to be 56.8% and 27%, respectively. Figure 1 shows the patients' survival curve during the follow-up period.

The findings of univariate analysis regarding the association between various clinicopathological variables studied and patient survival time revealed that the presence of diabetes is significantly associated with shorter patient survival. Additionally, the demographic analysis demonstrated that OS was shorter in male patients, patients under 60, and patients with underlying disease. Regarding the histopathological characteristics, pancreatic head tumors, lymph node involvement, perineural invasion, positive surgical margin, and no history of adjuvant or neoadjuvant chemotherapy associated with shorter OS; however, these differences were not statistically significant (Table 3).

Through a multivariate analysis of the association between different variables studied and patient survival time, we found a significant reverse relationship between a history of underlying diseases and patient survival time, with a hazard ratio (HR) of 3.54 (95% CI=1.26–9.97, $P=0.01$; Figure 2A). Additionally, male gender had a significantly higher risk of death with an HR of 2.44 (95% CI=1.04–5.74, $P=0.04$; Figure 2B). Analyzing histopathological features revealed that increasing tumor size, lymph node involvement, and positive margin associated with higher HR, suggesting an increased risk of death compared to their counterparts at any given time; however, these varying risks among different subcategories did not encounter statistically significant levels. Similarly, it was demonstrated that patients who undertook neoadjuvant and adjuvant chemotherapy had higher survival rates; however, after adjustments for confounding

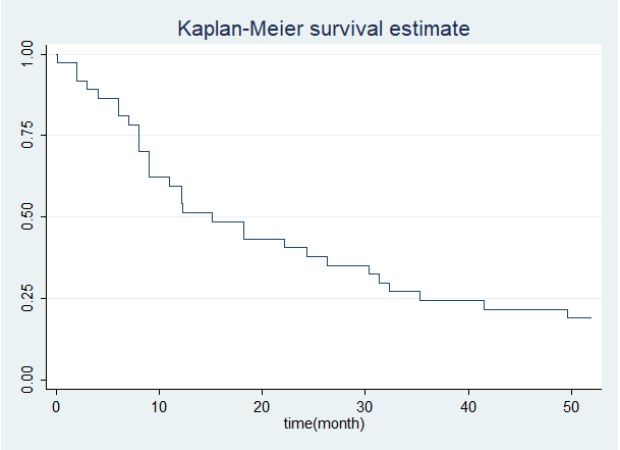

Figure 1. Overall survival in the whole cohort.

Table 3. Univariate analysis of clinicopathological characteristics

Variable		Mean Survival (mon) ± SD	*P* value
Gender	Male	16.23 ± 16.30	0.063
	Female	27.52 ± 18.75	
Age (y)	≤ 60	17.76 ± 14.77	0.090
	> 60	28.37 ± 20.91	
Underlying disease	Yes	13.30 ± 16.06	0.130
	No	24.25 ± 17.99	
Diabetes	Yes	8.07 ± 4.23	**0.000**
	No	24.57 ± 18.42	
HTN	Yes	28.00 ± 33.94	0.068
	No	22.33 ± 17.96	
Tumor stage	pT2	20.65 ± 20.25	0.770
	pT3	22.87 ± 17.12	
Tumor grade	Moderately differentiated	25.69 ± 18.36	0.505
	Well differentiated	21.15 ± 17.86	
Tumor location	Pancreatin head	16.60 ± 15.17	0.183
	Pancreatic head and uncinate	25.56 ± 17.28	
Vascular invasion	Yes	22.69 ± 18.07	0.957
	No	22.08 ± 26.41	
Perineural Invasion	Yes	22.09 ± 18.15	0.461
	No	32.12 ± 28.12	
Lymph node involvement	Yes	21.12 ± 17.23	0.477
	No	25.80 ± 21.06	
Surgical margin	Positive	21.28 ± 17.50	0.760
	Negative	23.29 ± 19.12	
Neoadjuvant chemotherapy	Yes	22.58 ± 22.18	0.991
	No	22.66 ± 16.79	
Adjuvant chemotherapy	Yes	24.03 ± 18.35	0.300
	No	15.42 ± 18.46	

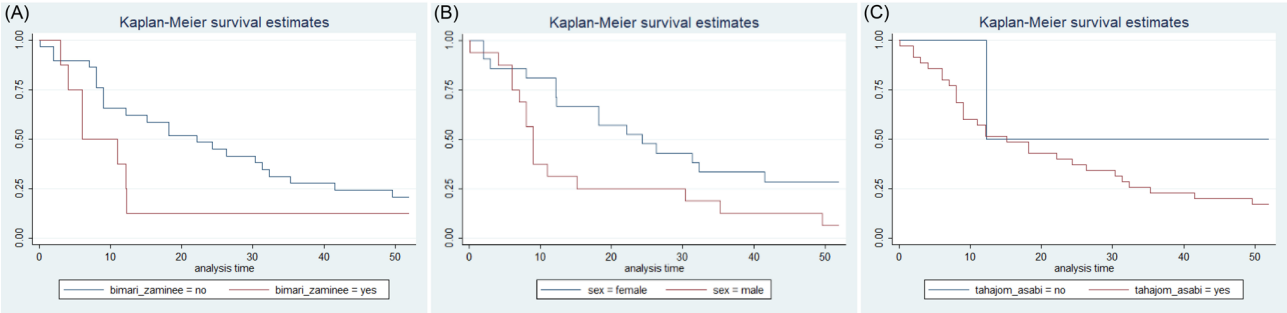

Figure 2. **A:** Overall survival in the patients with and without underlying disease represented by red and blue lines, respectively. **B:** Overall Survival in the male and female patients represented by red and blue lines, respectively. **C:** Overall survival in the patients with and without perineural invasion represented by red and blue lines, respectively.

variables, there was no statistically significant relationship between history of chemotherapy and survival.

Based on the findings of our study, tumors with perineural invasion had a significantly greater HR (34.63, $P=0.04$), indicating worse prognosis and higher risk of death in this subgroup (Figure 2C).

Furthermore, despite the insignificant OS difference between subgroups of tumoral vascular invasion, there was a significant association between this variable and survival in the multivariate analysis (HR = 0.02, 95% CI = 0.00 – 0.37, $P=0.008$). However, due to the small sample size and limited number of cases in our subgroups—only two instances without nerve invasion and three instances without vascular invasion—it was not feasible to conduct a comprehensive statistical analysis of vascular and neural involvement. Notably, there were two patients who was free of both vascular and nerve invasion which one of them died two days after her surgery and the other one was still alive approximately five years post-surgery (Table 4).

Discussion

Despite numerous studies investigating the epidemiology and mortality rate of pancreatic cancer in various countries, the survival rate of these patients and the association between tumor histopathological factors and patient survival have been less explored in previous studies due to the low proportion of patients undergoing surgery. In the present study, the median survival time of patients with PDAC after curative surgery was calculated to be 18 months. The 1-year and 3-year survival rates were 64% and 25%, respectively. Our analysis also revealed that male gender, the presence of comorbidities, and perineural invasion are independent prognostic indicators for survival in this patient population.

Furthermore, it appears that other studies conducted in Iran have reported lower survival rates for patients with pancreatic cancer compared to our study. However, it should be noted that these studies included all patients with pancreatic cancer, including those with unresectable

Table 4. Multivariate analysis of clinicopathological characteristics

Variable		HR	95% CI	*P* value
Gender	Male	2.44	1.04 to 5.74	**0.041**
	Female	Reference	Reference	
Age (y)	Quantitative	0.97	0.93 to 1.01	0.184
Underlying disease	Yes	3.54	1.26 to 9.97	**0.017**
	No	Reference	Reference	
Tumor size	Quantitative	1.09	0.7 to 1.69	0.718
Vascular invasion	Yes	0.02	0.00 to 0.37	**0.008**
	No	Reference	Reference	
Perineural invasion	Yes	34.63	1.04 to 1154.81	**0.048**
	No	Reference	Reference	
Lymph node involvement	Yes	2.67	0.82 to 8.61	0.101
	No	Reference	Reference	
Surgical margin	Positive	1.56	0.56 to 4.34	0.391
	Negative	Reference	Reference	
Neoadjuvant chemotherapy	Yes	1.23	0.46 to 3.29	0.674
	No	Reference	Reference	
Adjuvant chemotherapy	Yes	0.37	0.1 to 1.40	0.145
	No	Reference	Reference	

tumors. This could be a factor contributing to the shorter survival of patients in these studies compared to our study. There were also studies conducted in East and Southeast Asia that demonstrated a broad range of median OS for PDAC patients varying from 8 to 33 months based on the treatment approach (11). A retrospective study utilizing German Cancer Registry Group data assessed 5794 patients diagnosed with primary PDAC as part of the evaluation. The study reported a median OS of 19 months, with corresponding 1- and 3-year survival rates of 66% and 22%, respectively, which are quite comparable to our survival outcomes (15). Khalil et al conducted a retrospective study evaluating and comparing 2430 colloid carcinoma patients with 54416 PDAC patients. They reported varying survival outcomes for patients with PDAC across different stages: from a median survival of 28.7 months, with 1—and 5-year survival rates of 77.1% and 31.1%, respectively, in Stage 1 to a median survival of 3.9 months, with 1—and 5-year survival rates of 18.1% and 1.5% in Stage 4 PDAC (16). The variability and generally suboptimal survival indices across different studies highlight the complexity of the pancreatic tumor microenvironment. This underscores the importance of enhancing current treatment strategies and the need for further investigation into clinicopathological and biochemical predictors to improve long-term survival.

43.2% of the patients were male. We found that male patients had shorter mean OS in comparison to females (16.2 versus 27.5 months) and the analysis revealed that male gender is an independent predictor for OS after surgery (HR = 2.44, CI = 1.04-5.74, $P = 0.04$). In alignment with our findings, various studies found an association between male gender and shorter OS (11,17-20); although, this association did not reach the significance level in some of them (17,18). However, the findings of other studies did not confirm the association between gender of patients with their OS time after pancreatic cancer surgery (21). Additionally, 54.1% of patients were younger than 60 years old. We analyzed age as a quantitative variable; given the HR of 0.97 (95% CI: 0.93–1.01) and a P value of 0.97, our findings suggest that age has no significant effect on OS, indicating a lack of meaningful association between age and OS. Various studies with different cohorts and treatment strategies have similar results to us in terms of age impact on OS (22). However, there are several studies with different results; Pu et al evaluated 1589 PDAC patients and found age as an independent prognostic factors for OS by analyzing their matched dataset. They revealed that patients older than 65 years old had a HR=1.48 (95% CI = 1.25-1.76, $P = 0.001$) (23). Similarly, studies by Bengtsson et al in Sweden (20) and Luo et al in China (19) found that older age were associated with shorter survival times in patients.

Findings of our study showed that there was a statistically significant association between patients' survival time and a history of underlying disease; specifically, diabetes. A meta-analysis showed that diabetic patients with pancreatic carcinoma have shorter survival times and more complications (24). Moreover, Cheon et al reported that patients with pancreatic carcinoma and higher glycosylated hemoglobin levels showed shorter survival times (25). Amaral et al, similarly revealed that PDAC patients with arterial hypertension (HTN) and or history of diabetes had significant shorter survival. They also found that HTN and diabetes are independent prognostic factors for OS after surgery (26). Hank and his colleagues demonstrated that diabetic PDAC patients had a significantly reduced median OS compared to non-diabetic patients (18 versus 34 months), with this difference being even more pronounced in those undergoing neoadjuvant therapy (18 versus 54 months). Furthermore, multivariate analysis identified diabetes as an independent prognostic factor for post-resection survival (22). However, in a single study, Li et al also found no association between diabetes and survival status in patients with pancreatic adenocarcinoma, but HTN and heart disease were significantly associated with increased mortality (27). Jiang et al also found no association between underlying disease and survival indices in PDAC patients (28). Therefore, due to the divergent findings in this field, further studies are recommended to draw more definitive conclusions.

Regarding tumor histopathological features, we found that patients with perineural invasion exhibited a significantly higher hazard ratio than those who did not ($P = 0.048$). A 2017 systematic review and meta-analysis combined HRs from multivariable regression models to assess perineural invasion impact on patient survival. The analysis of 36 studies revealed that perineural invasion is an independent predictor associated with unfavorable OS, with a pooled HR of 1.68 (95% CI: 1.47–1.92; $P < 0.00001$), indicating a significant negative impact on survival outcomes (29). Lee et al and Park et al also found higher HRs with positive perineural invasion; however, the impact was not significant in their studies (18,30). On the other hand, there were other studies with no association between perineural invasion and OS in PDAC patients after surgery (21,28). Regarding the vascular invasion, our analysis demonstrated that HR for the positive vascular invasion was 0.02 with a P value of 0.008, indicating a more favorable survival outcome in this subgroup of patients; however, this finding does not align with the literature findings. In our cohort, there was a patient who was free of both vascular and perineural invasion, who unfortunately died just two days after surgery; however, considering the inclusion criteria, she was not excluded. Therefore, the short survival time of this patient impacts the mean survival and HR of vascular and perineural invasion in the subgroup of patients without these features. Furthermore, given the small sample size of these subgroups (2 patients without perineural invasion and 3 patients without vascular invasion), performing a detailed statistical analysis and

drawing conclusions was not possible. Nevertheless, the other patient, who was free of both vascular and nerve invasion at the time of our follow-up, which was about 5 years after surgery, was still alive and well, suggesting a favorable prognosis in patients without these features. There are several studies that found vascular invasion as a poor prognostic factor for OS (18,30). However, some studies observed no significant association between vascular invasion and OS rate in PDAC patients (21,26).

In evaluating other histopathological characteristics of tumors, our study observed that patients with larger tumor sizes, positive surgical margins (R1), and lymph node involvement had higher hazard ratios; however, none of these associations reached statistical significance. In assessing tumor size as a quantitative factor for OS, the HR was 1.09 (95% CI: 0.7–1.69), with a *P* value of 0.71. This suggests that while there is a slight trend indicating that increasing tumor size may be associated with a higher risk of mortality, the association is not statistically significant. Various studies found similar results to ours, demonstrating a non-significant increasing risk of mortality with increasing tumor size and higher T stages (21,23,26,31). However, Hank and his colleagues evaluated 622 PDAC patients with surgical resection and found increasing tumor size a significant independent prognostic factor for OS (HR = 1.02, 95% CI = 1.01-1.03, $P < 0.001$) (22).

Based on the findings of our study, tumors with surgical margin involvement with a surgical margin distance of less than one millimeter showed lower survival rates than tumors with a margin distance of more than one millimeter, but this difference was not statistically significant. Surgical margin status has been reported to be closely associated with local recurrence and long-term survival for PDAC after surgery (32). In recent years, a 1 mm tumor-to-margin distance has been widely agreed upon to define R0 resection as the absence of cancer cells within 1 mm of the surgical margin (33). Based on our analysis, patients with positive surgical margins (R1) had an HR of 1.56 (95% CI: 0.56–4.34) compared to those with negative margins (R0). However, the association is not statistically significant ($P = 0.391$). Consistent with our findings, Amaral et al (26), Yang et al (17), and Einama et al (31), in three distinct studies, showed a trend towards worse survival rates with positive surgical margins; however, this trend did not reach statistical significance. In contrast, other studies have identified a similar association but reported a significant impact of positive surgical margins on survival (22). A 2020 systematic review and meta-analysis, which included five eligible studies, demonstrated that a resection margin of ≥1 mm was associated with a better prognosis. The pooled multivariable HR was 1.32 (95% CI: 1.03–1.68, $P = 0.03$), indicating a statistically significant benefit for patients with negative surgical margins (34). Similarly, one study found that a margin clearance greater than 2 mm was similarly associated with improved overall patient survival (35), while another reported that a margin clearance of at least 5 mm could enhance long-term survival outcomes (36). Therefore, in most studies, surgical margin involvement has been reported as a significant risk factor for survival in patients with PDAC. In our study, although there was no statistically significant association in this regard, the observed trend towards decreased survival time in patients with microscopically involved margins may be associated with significant results if the sample size is increased.

In our study, 67.6 % of patients had lymph node involvement, which had a non-significant decreased mean survival time compared to those without node involvement (21.1 versus 25.8 months; $P = 0.47$). After adjusting for confounding factors, we found that nodal involvement, compared to no lymph node involvement, had a 2.67-fold risk of death in our cohort; however, the association was insignificant. Different studies employ various approaches to assessing lymph node status in survival analyses. While some focus on positive versus negative LN involvement, others compare outcomes based on the pathological N staging, numbers of involved LN, or the lymph node ratio, defined as the ratio of involved to total resected lymph nodes. Our findings are consistent with several studies that observed an increased risk of death comparing positive to negative LN (lymph node) status (26); however, most of these studies reported a statistically significant association (31). The findings of another study revealed that the HR for surgical resection in patients with involved LN compared to surgical resection in patients without LN involvement equals 1.62 (95% CI=0.77-3.42); however, the association was not significant ($P = 0.206$) (37). Lee and his colleagues revealed that PDAC patients with pathological N stages 1 and 2 had a non-significant higher risk of death compared to N0 status (HR=1.34, 95% CI =0.84-2.13, $P = 0.223$) (18). In contrast, Hank and Pu, in two different studies, demonstrated that N1 and N2 status are significant independent poor prognostic factors for OS in PDAC patients (22,23). Some studies have shown that patients with more than three lymph nodes involvement had worse survival compared to those with less than 3 involved lymph nodes (38,39). Similar to most of these studies, we found that nodal involvement status affects the prognosis; however, possibly due to the small sample size or inadequate lymphadenectomy in our study, we didn't reach the statistical significance.

In terms of the type of treatment received by the patients in our study, neoadjuvant chemotherapy and adjuvant chemotherapy were performed in approximately 32.4% and 83.8% of patients, respectively. The mean survival time of patients who received neoadjuvant chemotherapy was slightly lower than those who did not. In contrast, patients who received adjuvant chemotherapy post-surgery demonstrated a longer mean OS compared to those who did not undergo this treatment. However, in both treatment modalities, the observed differences did

not reach statistical significance. Various studies report differing outcomes regarding the effect of neoadjuvant chemotherapy and chemoradiotherapy on survival in patients with PDAC. While some research indicates that neoadjuvant chemotherapy can inhibit tumor progression and significantly improve postoperative survival (40,41), other studies present conflicting findings (37). Huang et al observed better prognosis in patients receiving neoadjuvant chemotherapy, particularly those with favorable preoperative nutritional status (40). Additionally, Chopra et al demonstrated significantly improved progression-free survival (HR =0.64, 95% CI =0.42–0.96, $P=0.031$) and OS (HR =0.60, 95% CI =0.39–0.93, $P=0.021$) with neoadjuvant therapy in patients with distal PDAC (41). A systematic review and meta-analysis demonstrated a statistically significant increase in the rates of pCR (pathological complete response) and R0 resections among patients receiving neoadjuvant chemoradiotherapy; however, no significant difference was observed in 3-year OS (OR =1.07, 95% CI =0.84–1.36, $P=0.6$) (42). Given these conflicting findings and the lack of thorough criteria for identifying suitable candidates for neoadjuvant therapy, further research is necessary to establish clear guidelines and better understand long-term benefits and risks. Many studies have reported adjuvant chemotherapy as a factor that effectively increases survival time in patients with pancreatic cancer (27). However, the high rate of postoperative complications after pancreatoduodenectomy and the high costs associated with this surgery may reduce the acceptance of patients for adjuvant chemotherapy after surgery. On the other hand, some other single-center studies, such as ours, have not statistically proven a clinically independent association of adjuvant chemotherapy with long-term patient survival (12). The reason for this may be the smaller sample size in single-center studies.

Our findings revealed the relationships between some clinicopathologic factors and survival indices in patients who have undergone resection for PDAC; however, various evidences suggest a complex interaction between risk factors, tumor biology, patient characteristics, and management-related elements (43). Therefore, further studies are necessary to determine the causal factors that influence long-term survival in PDAC and to stratify these results for application to specific clinical populations. Finally, it should be noted that the present study has limitations that should be considered. First, the present study is a single-center retrospective study with a relatively small sample size, which requires further studies to generalize its findings. Second, the present study was only conducted on patients with respectable pancreatic tumors, and physicians may treat some patients with severe underlying diseases or advanced age with conservative treatments to prevent complications and mortality from surgery. In addition, some potentially prognostic factors such as bilirubin, albumin, distant metastasis, and serum levels of carcinoembryonic antigen and carbohydrate antigen 19-9 were not examined in this study.

Conclusion

The median survival of patients with PDAC after surgical resection is 18 months, and the 1-year and 3-year survival rates are approximately 56.8% and 27%, respectively. This indicates that these patients have a poor prognosis even after surgery, one of the reasons for which may be incomplete tumor resection and surgical margin involvement in more than half of cases. In addition, the survival time of patients after surgery is significantly reduced in the presence of male gender, perineural invasion, and underlying diseases such as diabetes. The present study did not confirm an independent association between survival time of pancreatic cancer patients with other clinical and histopathological factors. Therefore, further studies with larger sample sizes are needed to investigate these factors.

Limitations of the study

Considering to limitations of our study, it is suggested that multicenter studies with large sample sizes be conducted to investigate the association between survival of patients with pancreatic cancer and clinical and histopathological factors. Also, it is suggested that studies be conducted to investigate the genetic factors that affect the survival of patients with pancreatic cancer. Furthermore, it is suggested that diagnostic and screening methods for early detection of patients with pancreatic cancer, especially in high-risk groups, be considered.

Authors' contribution

Conceptualization: Behnaz Bouzari.
Data curation: Masoomeh Safaei, Ali Jafarian.
Formal analysis: Ali Jafarian, Farid Azmoudeh-Ardalan.
Funding acquisition: Nima Taghizadeh Mortezaei.
Investigation: Masoomeh Safaei, Nima Taghizadeh Mortezaei.
Methodology: Behnaz Bouzari, Nima Taghizadeh Mortezaei.
Project administration: Behnaz Bouzari.
Resources: Behnaz Bouzari.
Software: Farid Azmoudeh-Ardalan, Masoomeh Safaei.
Supervision: Behnaz Bouzari.
Validation: Masoomeh Safaei, Nima Taghizadeh Mortezaei.
Visualization: Farid Azmoudeh-Ardalan.
Writing–original draft: Ali Jafarian, Farid Azmoudeh-Ardalan.
Writing–review & editing: Behnaz Bouzari.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Tehran University of Medical Sciences (Ethical code #IR.TUMS.IKHC.REC.1399.485) Prior to any intervention, all participants provided written informed consent. The study was extracted from "the role of clinicopathological features in the prognosis of resected pancreatic ductal adenocarcinoma: a retrospective study" thesis in the department of pathology at this university. The study was extracted from residency thesis of Elham Ebrahimi Niyari at this university (Thesis #51358). The authors

have fully complied with ethical issues, such as plagiarism, data fabrication, and double publication.

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