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Preoperative prognostic factors in patients with ductal adenocarcinoma of the head of the pancreas

Fatores prognósticos pré-operatórios em pacientes com adenocarcinoma ductal da cabeça do pâncreas

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A B S T R A C T

Objective: To identify the preoperative prognostic factors influencing pancreatic cancer survival following curative resection in a single Brazilian institution. **Methods:** From 2005 to 2018, preoperative clinic, demographic and laboratory data were prospectively collected. Survival analysis was performed by the Kaplan-Meier method and the comparison between curves by the log-rank test. For multivariate analysis, the Cox regression model was used. **Results:** advanced age (p = 0.012) and previous history of cancer (p = 0.026) were the preoperative factors, according to the univariate analysis, that significantly impacted survival. Patients with preoperative serum levels of CA 19.9 from 38 to 554 U/mL had a 3.15 times higher chances of death (HR 3.15; 95% CI 1.01-9.82; p = 0.047), whereas patients with the marker above 554 U/mL were 3.96 times more likely than those with the normal level (HR 3.96; 95% CI 1.19-13.10; p = 0.024), by using the multivariate analysis. Patients with previous comorbidities had a 2.90 times higher chance of death than those without associated conditions (HR 2.90; 95% CI 1.10-7.67; p = 0.032). **Conclusion:** Preoperative factors related to the worst prognosis after pancreatic ductal adenocarcinoma resection were advanced age, presence of comorbidities, previous history of cancer and elevated preoperative serum CA 19.9.

Headings: Carcinoma, Pancreatic Ductal. Pancreaticoduodenectomy. Prognosis. Survival Analysis.

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer death in the United States, where the incidence matches mortality[1,2]. In Brazil, it represents 2% of overall cancers and 4% of cancer deaths[3]. The long asymptomatic period contributes to the poor prognosis, which means that the diagnosis is made, in most cases, at an advanced stage. Two-thirds of patients have cancer located in the head of the pancreas, while one third in the body or tail[2].

It predominantly affects individuals between 60 and 80 years of age, it is more frequent in men, and it is related to a component of family origin in about 10% of cases[2,4,5]. In addition to genetic factors, the increased risk among smokers, patients with chronic pancreatitis and type 2 diabetes is well established[6-9].

Only 10% to 20% of patients diagnosed with pancreatic cancer have a locoregional disease, which evolves with a global survival of about 30% in five years[1,2]. 52% of pancreatic neoplasms are diagnosed at an advanced stage and with metastasis and present with a 3% overall five-year survival[1]. The overall survival for all stages of pancreatic cancer is about 8% in five years[1]. Surgical resection is the only therapeutic option with a chance of cure[2].

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Among the periampular carcinomas, the ductal adenocarcinoma of the head of the pancreas (ADCP) has the worst prognosis. The survival of patients undergoing surgical interventions approximates that observed in patients with neoplasia of the papilla or distal choledochus, and belong to the pancreatobiliary subtype[10,11].

When assessing surgical and postoperative data, lymph node involvement, larger lesions, undifferentiated tumors, angiolymphatic and perineural invasion as well as the non-association with adjuvant therapy are well-established predictors of a worse prognosis[12-14]. In order to allow early diagnosis, improve survival and prognosis of patients with pancreatic adenocarcinoma, screening methods are necessary. The identification of specific preoperative prognostic factors in different populations can also lead to improved survival in these patients.

In this regard, this study aims to identify preoperative prognostic factors related to the survival of patients with ADCP undergoing surgical treatment with curative intent, in a single Brazilian institution.

METHODS

This is a retrospective cohort study with data collected prospectively. The Research Ethics Committee of UFMG approved it under the number 23377113100005149. Initially, 116 patients who underwent pancreatectoduodenectomy or cephalic pancreatectomy were selected by the Liver, Bile Ducts, Pancreas and Spleen surgical team, at the Alfa Gastroenterology Institute, Hospital das Clínicas of UFMG, from 2005 to 2018. After fulfilling the inclusion and exclusion criteria, the final sample was 40 patients (Figure 1).

Data were collected by filling in specific protocols, analyzing medical records and clinical follow-up of the patients. Patients with ductal adenocarcinoma of pancreatic origin and cephalic location, who underwent laparotomy via cephalic pancreatectoduodenectomy or cephalic pancreatectomy with pyloric preservation, with curative intent, with or without resection of the superior mesenteric vein, associated with locoregional lymphadenectomy were included. Reconstruction of the transit was done with a single loop, and, in most cases, duct-to-mucosa end-to-side pancreaticojejunostomy, with or without a *stent*, was done. Adjuvant chemotherapy with

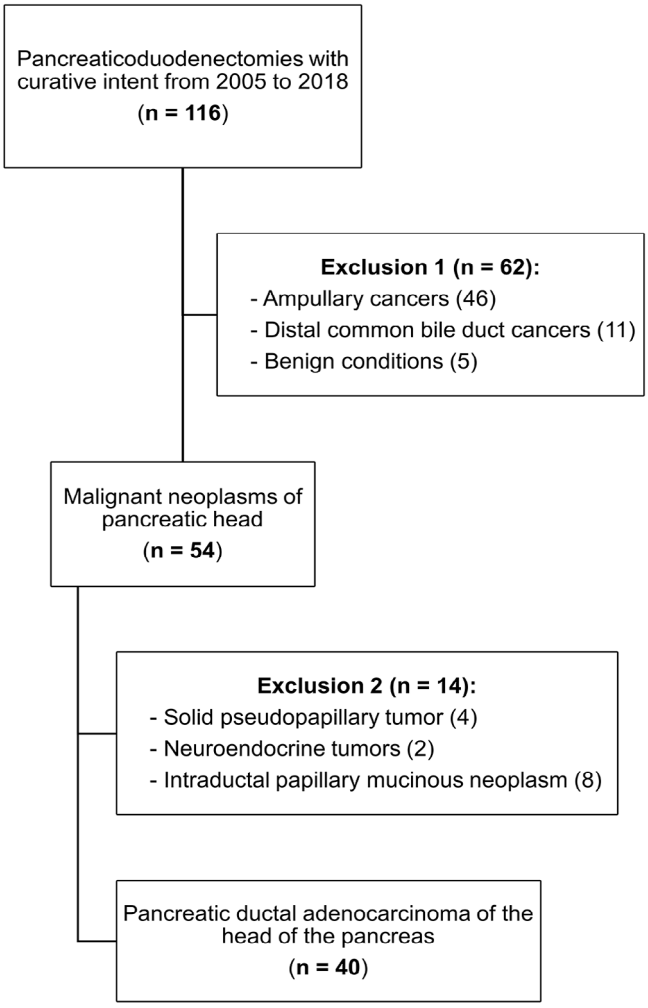

Figure 1. *Patients' distribution, according to the inclusion and exclusion criteria.*

gemcitabine was prescribed for all patients that underwent surgical resection.

The preoperative variables were: sex, age, smoking, alcoholism, previous history of cancer, family history of neoplasms, associated comorbidities and type 2 diabetes. Smokers were patients who reported smoking for ten years or more, and alcoholism was considered when the consumption of more than 30 grams of alcohol per day was informed. Preoperative serum levels of CA 19.9 (U/mL), CEA (ng/mL), total and direct bilirubin (mg/dL), albumin (g/dL), hemoglobin (g/dL), platelets (x10^3/µL) and leukocytes (x10^3/µL). Preoperative biliary drainage was done either by endoscopic biliary prosthesis or percutaneous biliary drainage. Data on survival were obtained either by outpatient follow-up, medical record checking or telephone contact with family members when patients did not attend follow up visits, and there was no notification of death.

Statistical analysis was performed using the *software* Stata® version 12 and IBM SPSS® (Chicago, IL, USA) version 23 for MAC (Macintosh®). Descriptive analysis of the data using measures of central tendency, dispersion and amplitude for continuous variables - mean and standard deviation (SD), median (50th percentile) and interquartile range (25th and 75th percentiles); minimum and maximum values were carried out. The descriptive analysis of categorical variables was performed by distributing the absolute and relative frequencies in each category. In order to test homogeneity, a Chi-square test (n> 4) or Fisher's exact test (n <5) was performed, considering the existence of equality in the categories of variables, as a null hypothesis (H0). Thus, for variables with two categories, the null hypothesis contemplated a proportion (pr) equal to 50% in each category (H0: pr = 0.5); for three categories, H0: pr = 0.33; for four categories, H0: pr = 0.25.

The median survival time and the respective interquartile range (IIQ) were considered for patients in general and according to categories. Survival analysis was done by the Kaplan-Meier method, for which the dependent variable was death, concerning time, in months. In order to assess whether there was a difference between the survival curves, the log-rank test was used. Overall survival was assessed at 12, 18, 24 and 36 months. Deaths that occurred within 30 days of the postoperative period were excluded.

A multivariate regression model was done to assess the relationship between one or more factors of interest and patients' survival. Based on the results of the univariate analysis, variables whose p values were equal to or less than 0.20 (p = 0.20) were selected as candidates for the final multivariate analysis. Cox regression was used to obtain the multivariate model. Survival analysis took into account the risk *ratio* or hazard ratio (HR), which is the chance of death divided by the chance of surviving along the entire spectrum of the survival curve. The level of significance was 5% (p <0.05).

RESULT (S)

Table 1 depicts the clinical and demographic characteristics and the median survival for the variables of interest. There was a predominance of females, with 25 women (62.5%). The patients' age ranged from 34 to 89 years, with a mean of 60.1 years and a median of 59.5 years. Survival was significantly lower in patients aged 70 years or older, with a median of 12 months, while for younger patients, it was 27 months (p = 0.012). Figure 2 depicts the survival curve using the Kaplan-Meier method according to age.

Table 1. *Clinical and demographic variables and median survival of patients with ductal adenocarcinoma of the head of the pancreas undergoing surgical treatment with curative intent.*

Variables	Distribution	P value*	Survival (months) (P25; P75)	P value**
Sex				
Male	15 (37,5%)	0,114	28 (12; 33)	0,493
Female	25 (62,5%)		18 (7; 30)	
Age (years)				
Mean (SD)	60,1 (12,0)	-	-	-
Median (IIQ)	59,5 (20,0)			
Minimum; Maximum	34; 89			
< 60	20 (50,0%)	>0,999	24 (7; 33)	0,993
Greater than or equal to 60	20 (50,0%)		18 (7; 30)	
< 70	29 (72,5%)	0,044	27 (14; 36)	0,012
Greater than or equal to 70	11 (27,5%)		12 (6; 21)	
Smoking				
No	16 (40,0%)	0,206	27 (7; 30)	0,704
Yes	24 (60,0%)		18 (10; 33)	
Alcoholism				
No	22 (55,0%)	0,527	27 (12; 39)	0,158
Yes	18 (45,0%)		18 (6; 33)	
Previous cancer				
No	33 (82,5%)	<0,001	27 (14; 33)	0,026
Yes	7 (17,5%)		10 (5; 12)	
Family history				
No	15 (50,0%)	>0,999	18 (7; 27)	0,997
Yes	15 (50,0%)		30 (12; 30)	
Comorbidities				
No	13 (32,5%)	0,027	30 (14; 40)	0,084
Yes	27 (67,5%)		13 (7; 27)	
Type 2 Diabetes				
No	25 (62,5%)	0,114	27 (12; 30)	0,590
Yes	15 (37,5%)		13 (6; 33)	

*SD = Standard Deviation; IIQ = Interquartile range; * homogeneity test between categories; ** log-rank test for differences between survival curves.*

Smokers predominated (60.0%), while 45.0% of patients reported a history of alcoholism. Of the total number of patients, 27 had associated comorbidities (67.5%) and, despite the discrepancy between median survival (30 months versus 13 months for patients with and without associated conditions, respectively), this was not a statistic prognostic factor (p = 0.084). The most prevalent comorbidity was systemic arterial hypertension (16), followed by type 2 diabetes (15), and seven patients had both comorbidities.

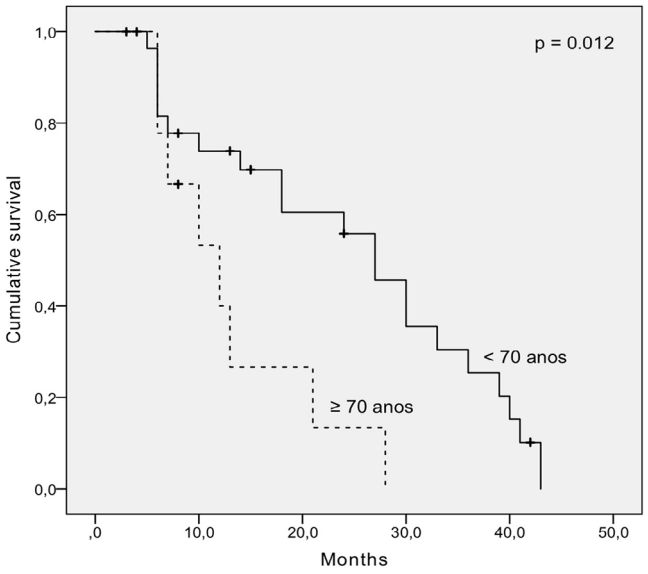

Figure 2. *Kaplan-Meier survival curve in patients that underwent curative surgical treatment for ductal adenocarcinoma of the head of the pancreas, according to age. Curves equality test: log-rank (p = 0.012).*

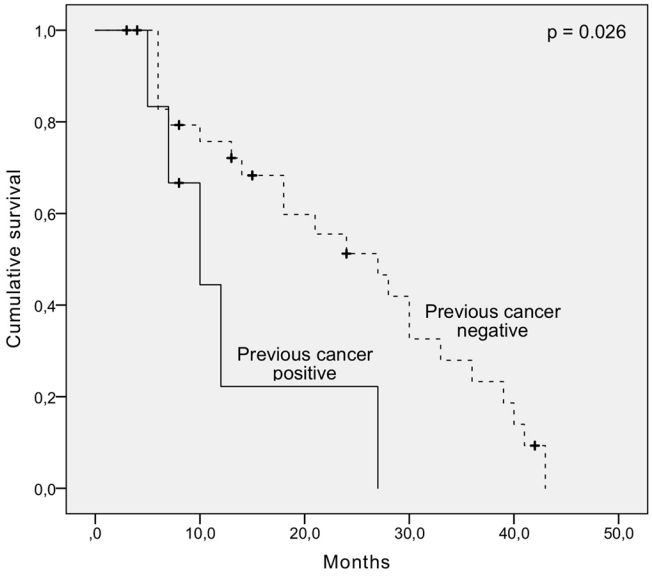

Figure 3. *Kaplan-Meier survival cure in patients who underwent curative surgical treatment for ductal adenocarcinoma of the head of the pancreas, according to the previous history of cancer. Curves equality test: log-rank (p = 0.026).*

Three patients had chronic pancreatitis. All elderly patients had at least one associated comorbidity. Six patients were classified as ASA I (15.0%), the majority as ASA II (31 patients/77.5%) and three ASA III (7.5 %).

Seventy-five percent of patients were able to reply the question regarding a family history of cancer, of which half was positive, two of them with pancreatic cancer. Seven patients (three men and four women) had previously had other types of cancer, and these patients had a median survival of 10 months, while the others, which represented 82.5% of the sample, had significantly higher survival rates, with a median of 27 months (p = 0.026). Figure 3 depicts y the Kaplan-Meier survival curve according to this variable. Among men, prostate cancer predominated (three patients). Among women, previous neoplasms were colorectal cancer, meningioma, gallbladder and breast cancer. Nonetheless, the patient with the longest survival (27 months) was the one with previous breast cancer.

The preoperative laboratory tests and their relationship to median survival are shown in Table 2.

The mean CA 19.9 was 1,186.0 U/mL, with a standard deviation of 2,080.8 U/mL, ranging from 2.0 to 9,760.0 U/mL. The median serum CA 19.9 was 281.0 U/mL, and 25% of the patients were in 25th percentile) with levels below 40.8 U/mL, while 25% (percentile 75) were above 1,532.0 U/mL. 27.2% of the patients had the marker within normal limits.

The mean preoperative CEA was 5.19 ng/mL (SD 4.8 ng/mL), with a median of 3.05 ng/mL. Before the surgical procedure, 80.0% of patients presented a CEA within the reference values. The mean serum albumin was 3.29 g/dL, the median was 3.40 g/dL and just over half of the patients were within the reference values.

Table 2. *Preoperative laboratory tests and median survival in patients who underwent curative surgical treatment for ductal adenocarcinoma of the head of the pancreas.*

Variables	Distribution	P-value*	Survival (months) (P25; P75)	P-value**
CA 19.9 (U/mL)				
Mean (SD)	1186 (2080,8)	-	-	-
Median (IIQ)	281 (1491,2)	-	-	-
Minimum; Maximum	2,0; 9760,0	-	-	-
< 38	9 (27,2%)	0,460	28 (6; 43)	0,170
38 a 554	12 (36,4%)	0,712	14 (6; 33)	
Greater than or equal to 555	12 (36,4%)	0,712	13 (6; 30)	
CEA (ng/mL)				
Mean (SD)	5,19 (4,8)	-	-	-
Median (IIQ)	3,05 (5,2)	-	-	-
Minimum; Maximum	0,80; 19,00	-	-	-
Less than or equal to 5	24 (80,0%)	<0,001	21 (10; 33)	0,110
> 5	6 (20,0%)		10 (6; 13)	
Total bilirubin (mg/dL)				
Mean (SD)	11,92 (9,23)	-	-	-
Median (IIQ)	11,90 (18,30)	-	-	-
Minimum; Maximum	0,50; 32,60	-	-	-
< 20	29 (74,4%)	0,002	24 (10; 30)	0,940
Greater than or equal to 20	10 (25,6%)		21 (5; 40)	
Direct bilirubin (mg/dL)				
Mean (SD)	10,38 (8,27)	-	-	-
Median (IIQ)	10,40 (15,7)	-	-	-
Minimum; Maximum	0,08; 29,70	-	-	-
< 20	32 (82,0%)	<0,001	24 (12; 30)	0,651
Greater than or equal to 20	7 (18,0%)		14 (5; 40)	
Albumin (g/dL)				
Mean (SD)	3,29 (0,67)	-	-	-
Median (IIQ)	3,40 (0,90)	-	-	-
Minimum; Maximum	1,40; 4,40	-	-	-
< 3,5	17 (46,0%)	0,622	14 (6; 27)	0,261
Greater than or equal to 3,5	20 (54,0%)		27 (10; 33)	
Hemoglobin (g/dL)				
Media (SD)	12,23 (1,56)	-	-	-
Median (IIQ)	12,20 (2,00)	-	-	-
Minimum; Maximum	9,10; 16,60	-	-	-
< 13	17 (46,0%)	0,622	21 (6; 28)	0,685
Greater than or equal to 13	20 (54,0%)		18 (10; 36)	

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Variables	Distribution	P-value*	Survival (months) (P25; P75)	P-value**
Platelets (x 10^3/µL)				
Mean (SD)	309,57 (126,69)	-	-	-
Median (IIQ)	274,00 (144,00)	-	-	-
Minimum; Maximum	136,00; 726,00	-	-	-
< 360	29 (76,3%)	0,001	21 (12; 30)	0,888
Greater than or equal to 360	9 (23,7%)		18 (6; 30)	
Leucocytes (x 10^3/µL)				
mean (SD)	8,51 (3,57)	-	-	-
Median (IIQ)	7,76 (4,12)	-	-	-
Minimum; Maximum	2,40; 17,20	-	-	-
4,0 to 11,0	29 (76,3%)	0,001	27 (12; 30)	0,742
> 11,0	9 (23,7%)		7 (6; 40)	

*SD = standard deviation; IIQ = Interquartile range; * homogeneity test between categories; ** log-rank test for differences between survival curves.*

Nine patients (23.7%) underwent preoperative biliary decompression, which did not affect survival (p = 0.398). The mean total preoperative serum bilirubin was 11.92 mg/dL (SD 9.23 mg/dL) and the median was 11.9 mg/dL. 25% of patients in the first quartile had a CEA less than 2.3 mg/dL, while the other 25.0%, in the last quartile, had values higher than 20.6 mg/dL. There was no statistical difference between the groups with and without values above 20.0 mg/dL (p = 0.651). Preoperative hematimetric parameters were not a significant prognostic factor.

According to the multivariate analysis, comorbidities and high preoperative CA 19.9 were the variables that proved to be independent prognostic factors, with statistical significance (Table 3).

Patients with preoperative serum CA 19.9 ranging from 38 to 554 U/mL had 3.15 times greater chance of death than those within the normal range (HR 3.15; 95% CI 1.01-9.82; p = 0.047), while patients with levels over 554 U/mL presented with four times higher risk of death (HR 3.96; 95% CI 1.19-13.10; p = 0.024).

Table 3. *Multivariate and Hazard Ratio (HR) analysis of patients with ductal adenocarcinoma of the head of the pancreas who underwent curative surgical treatment.*

Variables	HR	Confidence interval 95%	p value
CA 19.9 (U/mL)			
< 38	1,00	-	-
38 a 554	3,15	1,01 - 9,82	0,047
Higher than or equal to 555	3,96	1,19 - 13,10	0,024
Comorbidities			
No	1,00	-	-
Yes	2,90	1,10 - 7,67	0,032

Patients with previous comorbidities had a death risk almost three times higher than patients without other associated conditions (HR 2.90; 95% CI 1.10-7.67; p = 0.032).

During the follow-up period, which ranged from three to 43 months, 76.3% of the patients died. The median survival was 18.4 months (SD 12.7 months) and the median survival was 14.5 months (IIQ 7; 28). The overall survival rate at 12, 18, 24 and 36 months was 66.0%, 52.8%, 45.8% and 19.1%, respectively. Figure 4 indicates the overall Kaplan-Meier survival curve.

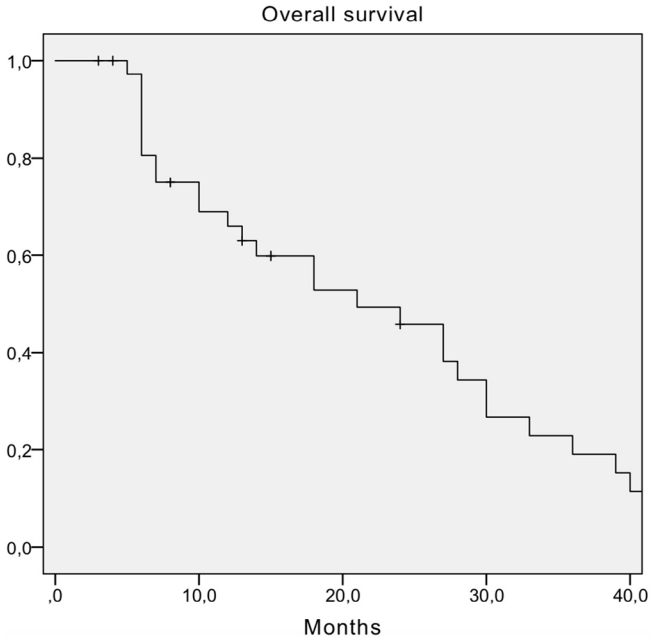

Figure 4. *Global Kaplan-Meier survival curve for patients with ductal adenocarcinoma of the head of the pancreas who underwent curative surgical treatment.*

DISCUSSION

Pancreatic cancer is a tumor with an unfavorable prognosis, being the fourth leading cause of cancer death in the United States[1,2]. In the 70s of the last century, curative intent operations in patients with tumors of the head of the pancreas did not represent a gain in survival compared to the palliative surgical approach, adding, however, postoperative morbidity[15]. Currently, surgical resection represents the only therapeutic option with a chance of cure. However, early diagnosis of a localized and resectable disease occurs in only 10% to 20% of patients[1,2]. The overall five-year survival reaches 32% when patients with pancreatic head cancer are diagnosed and treated at an early stage. When there is regional dissemination, this rate drops to 12%, reaching 3% in five years in patients with distant metastasis at diagnosis[1].

In this study, advanced age was identified as a prognostic factor with a lower survival rate in patients aged 70 years or older. Petrou *et al.*[16] evaluated a total of 101 patients who underwent duodenopancreatectomy due to periampular tumors and indicated that patients older than 65 years were twice as likely to die during follow-up (p = 0.037). However, some authors have not identified age as a prognostic factor[12,17].

The coexistence of comorbidities, found in 67.5% of our sample, was an important prognostic factor, with a significant impact on survival. Patients with associated diseases had an almost three times higher chance of early death than the others. Our sample had a prevalence of comorbidities two to three times higher than that found in the literature, which ranges from 20.0% to 30.0% of patients undergoing pancreatic resection[14,18]. Lim *et al.*[14] allocated operated pancreatic cancer patients into three groups: without comorbidities, one comorbidity and two or more comorbidities. Most patients had no comorbidities (77.0%) and, when comparing the groups, this factor did not significantly affect survival.

Due to the advancement of cancer treatments and improved survival of these patients, the risk of developing second primary neoplasias is increasing[19,20]. These patients are especially susceptible to it due to genetic issues, exposure to common risk factors, as well as the late effect of chemotherapy and radiotherapy treatments[20]. Pancreatic cancer, as the second primary neoplasm, had a more aggressive outcome in our series. The 33 patients who did not have a history of other previous neoplasia had a median survival significantly higher than the others (27 months versus 10 months, respectively, p = 0.026). In a recent Asian study, He *et al.*[21] indicated no significant difference in survival or mortality when comparing patients with pancreatic cancer with and without a previous history of neoplasia.

CA 19.9 is considered the best tumor marker for the evaluation and monitoring of patients with pancreatic ductal adenocarcinoma, with a sensitivity of 70.0% to 90.0% and specificity around 90.0%, being useful as a prognostic factor and tumor recurrence marker[22,23]. Dong *et al.*[24] indicated that patients with serum CA 19.9 equal to or higher than 338.45 U/mL presented with shorter survival compared to the group with lower values (HR 1.96; 95% CI 1.24-3.09; p = 0.004). Another study, with 147 patients, found a preoperative median of 122 U/mL and indicated that patients with serum levels equal to or less than 40 U/mL had a five-time higher chance of survival in five years (OR 5.02; 95% CI 1.68-16.48; p = 0.0036)[25]. In the study by Salmiheimo *et al.*[17], patients with preoperative values of CA 19.9 equal to or higher than 555 U/mL had almost twice the chance of earlier death during follow-up (HR 1.91; 95% CI 1.18-3.08 ; p = 0.008). In our analysis, we used similar cut-off levels, and the chance of death during follow-up was 3.96 times greater than for the patients within the normal range (HR 3, 96; 95% CI 1.19-13.10; p = 0.024).

The type of chemotherapy our patients underwent was similar to what has been recommended: gemcitabine as the first line of treatment. In 2007, after the publication of a relevant randomized clinical trial, it was proven that adjuvant chemotherapy with gemcitabine delays disease recurrence and increases survival when compared to the operation[26]. Ten years later, a new study published by the European pancreatic cancer study group indicated that the combination of gemcitabine and capecitabine, after pancreatic cancer surgical treatment, increased the median survival by 2.5 months compared to gemcitabine alone, suggesting that this should be the ideal adjuvant chemotherapy regimen[27].

The number of patients is a limitation of our study. The sample, which represents the experience of a single institution, may have been responsible for the lack of statistical significance regarding some variables.

CONCLUSION

The prognostic factors related to ductal adenocarcinoma of the head of the pancreas after pancreatectoduodenectomy were older age, previous history of cancer, associated comorbidities and elevated CA 19.9 levels. These factors were associated with decreased overall survival, which

was, for the entire series, 66.0%, 52.8%, 45.8% and 19.1% at 12, 18, 24 and 36 months, respectively. Despite the current advances, the treatment of pancreatic cancer is still a challenge.

R E S U M O

Objetivos: *Identificar fatores prognósticos pré-operatórios relacionados à sobrevida de pacientes com adenocarcinoma ductal da cabeça de pâncreas (ADCP) submetidos a tratamento cirúrgico com intenção curativa em uma única instituição brasileira.* ***Método:*** *No período de 2005 a 2018, dados clinicodemográficos e laboratoriais pré-operatórios foram prospectivamente coletados. A análise de sobrevida foi feita pelo método de Kaplan-Meier e a comparação entre as curvas pelo teste de log-rank. Para a análise multivariada utilizou-se o modelo de regressão de Cox.* ***Resultados:*** *Os fatores pré-operatórios com impacto significativo na sobrevida à análise univariada foram a idade maior ou igual a 70 anos (p=0,012) e história pessoal prévia positiva para câncer (p=0,026). A análise multivariada, pacientes com níveis séricos pré-operatórios de CA 19.9 de 38 a 554 U/ml apresentaram 3,15 vezes maior chance de óbito (HR 3,15; IC 95% 1,01 - 9,82; p=0,047), enquanto que os pacientes com o marcador acima de 554 U/ml evoluíram com chance 3,96 vezes maior de óbito que aqueles com a dosagem normal (HR 3,96; IC 95% 1,19 - 13,10; p=0,024). Pacientes com comorbidades prévias evoluíram com chance 2,90 vezes superior de óbito que doentes sem condições associadas (HR 2,90; IC 95% 1,10 - 7,67; p=0,032).* ***Conclusão:*** *O ADCP mostrou ser doença agressiva para a qual os fatores pré-operatórios de pior prognóstico foram idade avançada, presença de comorbidades, história prévia de câncer e nível sérico de CA 19.9 elevado no pré-operatório.*

Descritores: *Carcinoma Ductal Pancreático. Pancreaticoduodenectomia. Prognóstico. Análise de Sobrevida.*

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