Retrospective cohort of pancreatic and Vater ampullary adenocarcinoma from a reference center in Mexico

Jorge Sánchez-García[a], Fernando Candanedo-González[b], Anna Karen Félix-Félix[e],
Damián Sánchez-Ramírez[a], Rafael Medrano-Guzmán[c], Miguel Quintana-Quintana[d],
Yair Benjamín Baas-Cabrera[d], Eugenia Flores-Figueroa[a],*

[a] Oncology Research Unit, Mexico
[b] Pathology Service, Mexico
[c] Sarcomas Service, Mexico
[d] Medical Oncology Service, Oncology Hospital, National Medical Center Century XXI, Instituto Mexicano del Seguro Social (IMSS), Mexico City, Mexico
[e] West Medical Center, IMSS, Guadalajara, Mexico

ABSTRACT

Introduction: Pancreatic ductal adenocarcinoma (PDAC) and ampulla of Vater adenocarcinomas (AVAC) are periampullary tumors. These tumors have overlapping symptoms and a common treatment, but present differences in their survival and biology. No recent studies in Mexico have been published that describe the clinicopathological characteristics of these tumors. Therefore, the aim of this study was to describe the clinicopathological characteristics of PDAC and AVAC in patients at a reference center in Mexico.
Methods: A retrospective cohort of patients with PDAC or AVAC was analyzed at our institution (July 2007 to June 2016). Inferential analysis of the clinical data was performed with Student's t-test or a χ^2 test with odds ratios (OR) and confidence intervals (CI), depending on the variables. Overall survival was compared using Kaplan-Meier curves with log-rank p values.
Results: Forty patients with PDAC and 76 with AVAC were analyzed, including 77 females and 39 males with a mean age of 60.6 years and a mean evolution time of 5.7 months. PDAC patients had more abdominal pain, a larger tumor size and more advanced stages than AVAC patients. In contrast, AVAC patients had more jaundice, a higher percentage of complete resections and higher overall survival. Up to 70% of patients were overweight. PDAC cohort included a higher proportion of smokers.
Conclusions: Our cohort was slightly younger, had a larger percentage of females, and a greater percentage of obese patients than those in many international reports. A high proportion of PDAC patients are diagnosed in advanced stages and have a low likelihood of resectability.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) and ampulla of Vater adenocarcinomas (AVAC) are, along with biliary and duodenal cancers, a group of periampullary tumors. These tumors progress share overlapping symptoms and a common treatment (pancreaticoduodenectomy). However, they present significant differences in their survival, and accumulating evidence displays differences in their biology, including their molecular profiles [1].

PDAC is the most common periampullary adenocarcinoma [2], and fewer than 20% of cases are candidates for surgery as a potentially curative treatment; thus, PDAC has the fourth highest cancer-related death rate worldwide, with a five-year survival rate of < 6% [3];

additionally, due to the high fatality index of this disease, the medical treatment costs are estimated to be more than USD$65,500 per patient in the first year after diagnosis [4,5].

AVAC usually presents early symptoms due to biliary outflow obstruction. This malignancy is believed to arise from pancreatobiliary or duodenal epithelia. The former has a worse prognosis than the latter [6,7] with a 25–40% five-year survival rate [8].

Obesity is a modifiable risk factor for PDAC [9,10] and a controversial risk factor for AVAC [11]. Mexico ranks among the top five obese countries in the world [12,13]. By 2030, PDAC is projected to be the second leading cause of cancer-related death and it is projected that the number of overweight/obese patients worldwide will double [3,14]. It is important to identify this risk factor and implement

national public health strategies to reduce morbidity and mortality rates related to these cancers. The aim of this study is to describe the clinicopathological characteristics of PDAC and AVAC patients from a Mexican referral center and to compare it against international reports.

2. Materials and methods

2.1. Study population

In this retrospective study, we identified potentially resectable or borderline resectable patients according to the NCCN guidelines and the institutional guidelines with PDAC (http://www.cenetec.salud.gob.mx/descargas/gpc/CatalogoMaestro/324_IMSS_10_Adenocarcinoma_pancreas/EyR_IMSS_324_10.pdf) or AVAC diagnosis at the Oncology Hospital, National Medical Center Century XXI at the Mexican Institute of Social Security (IMSS) in Mexico City, from July 2007 to June 2016. The IMSS is a public hospital that has 40% of the Mexican population affiliated to it. The project was approved by the local ethics committee (R-2014-3602-23) and it was registered at www.researchregistry.com (researchregistry2562). The paper has been reported in line with the STROCSS criteria [15]. The characteristics that were registered for the study were obtained from clinical records and included age, gender, presenting symptoms, presence of comorbidities, Tumor marker, histopathological data, type of treatment, tumor location, tumor size, depth of invasion (pT stage), lymph node status (pN), distant metastasis (M), stage, margin status, and follow-up data. The clinical data were collected and reviewed by at least three independent observers. We include potentially resectable patients from the surgery records. The archival hematoxylin and eosin–stained slides from all cases were reviewed. Histological assessment for both groups was done based on the 2010 World Health Organization classification. The pathologic stage grouping was determined according to the AJCC Staging Manual, Seventh Edition [16] Patients without complete clinical records or histological confirmation (biopsy or surgery) were excluded.

2.2. Statistical analysis

Demographic data, tumor characteristics and treatments were summarized with descriptive statistics. Continuous variables from PDAC and AVAC patients were compared using Student's t-test. Categorical variables were compared using the χ^2 test. Odds ratios (ORs) and their corresponding 95% confidence intervals were estimated by logistic regression models. The overall survival (OS) was measured from the date of diagnosis to the last medical appointment; patients who did not complete the five-year follow-up and went more than seven months without a follow-up visit were assumed dead and compared using Kaplan-Meier curves (with log-rank p values). Two-tailed probability values were calculated; p values < 0.05 were considered to indicate statistical significance. The analysis was conducted using Prism 6 software.

3. Results

3.1. Clinicopathological features of PDAC and AVAC patients

A total of 116 patients met the selections criteria from an original database of 244 patients. Two-thirds of the patients were female, and one-third were male and the mean age was 60.6 (range 31–86) years. Thirty-four percent of patients had a PDAC diagnosis, and 66% patients had an AVAC diagnosis, with median ages of 62.6 (range 41–86) and 59.5 (range 31–79) years, respectively. Although these groups were similar with regard to sex, mean age and some risk factors, the percentage of smokers in the PDAC group was two times that in the AVAC group (p = 0.008; OR 2.9, 1.2–6.6) (Table 1). The mean body mass index (BMI) of the cohort was 28.6 (range 18.8–45), and 71% were overweight or obese, with no differences between groups.

The evolution time was 5.7 (range 1–84) months, and the principal symptoms were jaundice, weight loss and/or abdominal pain (80%, 74.8% and 63.6%, respectively). Between groups, jaundice was predominant in AVAC patients (p = 0.0068; OR 0.2, 95% CI 0.1–0.7). Abdominal pain was predominant in PDAC patients (p = 0.04; OR 2.4, 95% CI 1.0–5.8).

Tumor marker evaluation showed that 50% of patients had a carbohydrate antigen (Ca) 19.9 level that was greater than the upper limit reference value (27 U/ml), but only 31% of patients had a level higher than 100 U/ml, with a mean of 406.1 U/ml; the values were more than six times higher in PDAC than in AVAC patients (p = 0.024). Carcinoembryonic antigen (CEA) levels higher than the upper limit reference value (4.3 mcg/l) were only identified 22% of patients, but only 15% of patients had levels higher than 10 mcg/l, with a mean of 6.3 (range 0.2–60) mcg/l, with no differences between the groups (Table 1).

3.2. Histopathological features

The median tumor size of the cohort was 3.4 ± 2.9 cm. Tumors in PDAC patients were twice as large as those in AVAC patients (p < 0.0001). In the AVAC group, 55.6% of tumors were classified as the intestinal subtype, 38.1% were pancreatobiliary and 17 (22.3%) were not determined.

Additionally, 41 (35.3%) patients had positive lymph nodes. Regarding the histological grade, 81 (78.6%) tumors were G2. The PDAC group had a G3 ratio 2.5 times that of the AVAC group, which resulted in a statistically significant trend (p = 0.051). More than twice the number of AVAC patients underwent complete resection (R0) compared to PDAC patients (p < 0.0001; OR 22.5, 95% CI 7.3–69.0). In addition, 55% of patients were classified as stages I-II and 45% were stages III-IV; 58% of the patients in stages III-IV were PDAC (p = 0.038; OR 2.2, 95% CI 1.0–5.0) (Table 1).

3.3. Treatment and follow-up

The cohort comprised potentially resectable patients, as expected 81% of patients underwent surgery. Most of resectable patients did not receive adjuvant treatment (51.7%). Chemotherapy was the most frequent adjuvant treatment. Gemcitabine was the most common agent used (54.2% of patients), followed by GEMOX or XELOX in 16.7% of patients, Capecitabine in 12.4% of patients, and FOLFIRINOX in 6.3% of the patients. None of the patients received palliative radiotherapy (Table 1).

The mean disease-free survival time was 31.6 ± 28.2 months, with a mean time of 10.8 months for PDAC patients and 40.0 months for AVAC patients (p < 0.0001). The mean OS was 33.7 ± 26.7 months, with a mean of 13.8 months for PDAC patients and 43.6 months for AVAC patients (p < 0.0001). Kaplan-Meier curves indicated an OS rate of 11% in PDAC patients and 62% in AVAC patients (p < 0.0001) (Table 1 and Fig. 1).

4. Discussion

The Oncology Hospital at the National Medical Center (IMSS) in Mexico City is a referral center for affiliated patients from 7 states of central Mexico. During a period of 7 years (2005–2012), the hospital received 77,402 new patients, where pancreas tumors accounted for 2.1% of the total of cases [17]. In the present study, we included only patients classified as potentially surgical, that might account for less than 15% of all pancreatic and periampullary tumors. It is necessary to conduct prospective studies to included advanced cases.

We described a cohort of potentially resectable patients from a referral center in Mexico City. The study cohort comprised younger and predominantly female PDAC and AVAC patients. Up to 70% of patients were overweight; being overweight is one of the known risk factors for

Table 1
Clinicopathological features.

Variable	PDAC 40 (%/range)	AVAC 76 (%/range)	Total 116 (%/range)	p < 0.05	OR (95% CI)
Gender					
● Male	14 (35)	25 (33)	39 (34)	NS	NS
● Female	26 (65)	51 (67)	77 (66)	NS	NS
Age (years)	62.6 ± 10.1 (41–86)	59.5 ± 10.6 (31–79)	60.6 ± 10.5 (31–86)	NS	NS
Risk factors					
● Smoker*	20 (50)	19 (26)	39 (35)	0.008	2.9 (1.2–6.6)
● Alcoholism	14 (36)	20 (28)	34 (31)	NS	NS
● DM2	11 (28)	17 (24)	28 (25)	NS	NS
● Pancreatitis	2 (5)	3 (4)	5 (5)	NS	NS
● B\MI	28.4 (22.3–36)	28.6 (18.8–45)	28.6 (18.8–45)	NS	NS
● Overweight/Obesity	14 (74)	41 (71)	55 (71)	NS	NS
Evolution time Symptoms and signs	6.1 (1–84)	5.5 (1–20)	5.7 (1–84)	NS	NS
● Jaundice*	25 (66)	63 (88)	88 (80)	0.0068	0.2 (0.1–0.7)
● Weight loss	28 (72)	55 (77)	83 (75)	NS	NS
● Abdominal Pain*	29 (76)	41 (57)	70 (64)	0.044	2.4 (1.0–5.8)
Laboratory					
● Ca 19.9*	954.7 (< 2.5–10001)	150.9 (< 2.5–2115)	406.1 (< 2.5–10001)	0.024	
● CEA	7.7 (1.5–31.8)	5.7 (0.5–60)	6.3 (0.5–60)	NS	
Tumor size*	5.7 (2–20)	2.4 (0.4–11)	3.4 (0.4–20)	< 0.0001	
Histological diagnosis	Adenocarcinoma 40 (100)	Intestinal 35 (46)	NA	NA	NA
		Pancreatobiliary 24 (32)	NA		
		ND 17 (22)	NA		
Positive lymph nodes	12 (30)	29 (45)	41 (35)	NS	NS
Histology grade					
● G3	9 (25)	7 (10)	16 (16)	0.051	NA
● G2	26 (72.2)	55 (82)	81 (79)		
● G1	1 (3)	5 (8)	6 (6)		
R0*	18 (40)	63 (93)	81 (70)	< 0.0001	22.5 (7.3–69.0)
Stage*					
● I-II	17 (42)	44 (63)	61 (55)	0.038	2.2 (1.0–5.0)
● III-IV	23 (58)	26 (37)	49 (45)		
Treatment					
● Surgery	16 (43)	44 (60)	60 (52)	NS	NS
● Surg/Chem	8 (22)	22 (30)	30 (26)	NS	NS
● Surg/Rad	2 (5)	1 (1)	3 (3)	NS	NS
● Chemotherapy*	7 (19)	4 (6)	11 (10)	0.026	4.0 (1.0–14.7)
● Chem/Rad	1 (3)	8 (11)	9 (8)	NS	NS
DFS (months)*	10.8 (1–99)	40.0 (1–91)	31.6 (1–99)	< 0.0001	NA
Overall survival*	13.8 (1–100)	43.6 (1–93)	33.7 (1–100)	< 0.0001	NA

*P level significance tested < 0.05. NS. Not significant. NA. not analyzed.

PDAC and was equally present in AVAC patients. The PDAC cohort included a higher proportion of smokers. Despite the higher proportion of obese patients, only 25% had type 2 diabetes mellitus. As expected, jaundice was the principal sign in AVAC, and abdominal pain was the principal symptom in PDAC.

Although we did not find differences in the evolution time, PDAC patients arrived at the hospital in a more advanced stage, with larger tumors (which was correlated with higher serum concentrations of Ca19.9) and a lower probability to complete surgical resection. Although the cohort comprised patients selected for surgery, almost 20% of PDAC patients could not undergo surgery and received chemotherapy only. In contrast, 91% of AVAC patients underwent surgical treatment, and 93% had R0 resections. The disease-free survival and OS of PDAC patients were lower than those of AVAC patients.

In this study, we reported that PDAC patients were predominantly female (65%), and the mean age was 62.6 years. Another Mexican report by Chan et al. included 30% female patients with a mean age of 57 years [18]; however a recent paper from this group reported 51.7% female patients and a mean age of 57.9 years. Although this study reports the results of pancreaticoduodenectomies, patients were not selected by tumor, and the proportion of females is similar to that of our study [19]. Our results are not comparable with international reports. Risch et al. (USA group) [20], Lakatos et al. (Hungarian group) [21], and Ruiz-Tovar et al. (Spanish group) [21] reported 44.7% (42.8%–46.6%) of female patients, with variable mean ages of 68.5 years, 65.2 years and 63.7 years, respectively [22]. Our cohort presented a higher prevalence of PDAC in females and a slightly younger mean age than other studies (Table 2). The high incidence of obesity in our cohort may be associated with an early diagnosis.

In the PDAC patient group, 50% of the patients were smokers, and 74% of patients were overweight or obese with a mean BMI of 28.4. A meta-analysis identified that smoking and a high BMI (overweight/obesity) are risk factors for PDAC [10]. These results are comparable with a study by Risch et al. that found that 69% of patients were smokers and 24.8% were obese with a mean BMI of 27 [20]. Lakatos et al. identified that 28.5% of patients were smokers and 42.3% were overweight or obese [21], and Ruiz-Tovar found that 37.3% of patients were smokers and 3.4% were obese [22]. We only identified 28% of
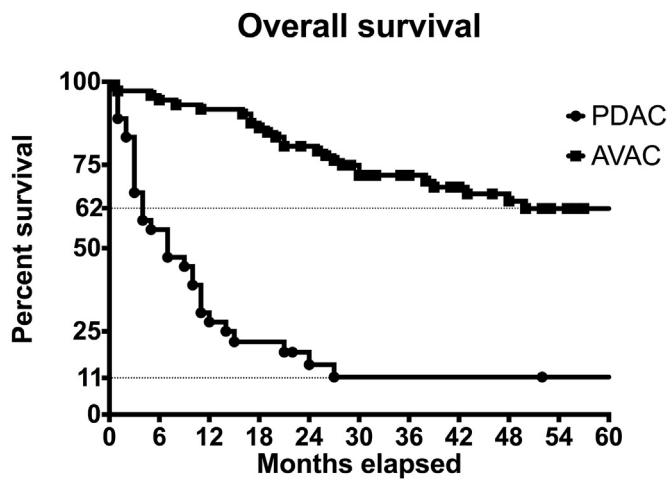
Overall survival

Fig. 1. Kaplan-Meier *curve* analysis for overall survival of Pancreatic ductal adenocarcinoma (PDAC) and Vater ampullary adenocarcinoma (AVAC) patients.

patients with type 2 diabetes mellitus, a well-known risk factor for PDAC [10]. Risch et al. found that 29% of their patients had type 2 diabetes mellitus, while 33.7% and 22% of patients in studies by Lakatos et al. and Ruiz-Tovar et al., respectively, had type 2 diabetes mellitus [20–22]; however, this data may be underestimated. Roeyen

(OGTT) and glycated hemoglobin (HbA1c) assessment. The results were interpreted according to the American Diabetes Association criteria and showed a prevalence of 75.5% of patients with a history of diabetes mellitus, newly diagnosed diabetes mellitus or prediabetes in the oncologic group [23]. We suggest that performing diagnostic tests for type 2 diabetes mellitus or prediabetes could have resulted in obtaining better data for this risk factor in our cohort.

Clinically, we found that 76% of PDAC patients had abdominal pain and 66% had jaundice; only 42% had jaundice with abdominal pain, and 63% of these patients exhibited advanced disease stages. Previous studies have reported that almost 50% of patients with jaundice and pain have advanced disease, but we observed a higher proportion of these patients [24]. In addition, we observed a higher Ca19.9 serum concentration in PDAC patients, with 58% of patients in advanced disease stages.

Finally, it is important to note that the five-year OS was 11%. Although this result is representative of worldwide OS reports in PDAC patients, it should be noted that our cohort only included patients with potentially resectable tumors. Most likely, these five-year OS rates would have decreased if we had included non-resectable patients as well. In addition, our five-year OS rate was similar to that of other cohorts, including that of Ruiz-Tovar et al., who reported a five-year OS rate of 12% [22], and Riall et al., who reported a rate of 17% [2]. A recent study of six Latin European countries reported a five-year OS rate of 6–10% [25]. The limitation of our study is that we did not include most of PDAC patients with advanced stages that were only candidates for palliative treatment.

Table 2
Comparison of different PDAC cohorts.

Variable	Sánchez et al.	Chan et al. [14]	Chan et al. [12]	Risch et al. [15]	Lakatos et al. [16]	Ruiz-Tovar et al. [17]
Gender						
● Male	14 (35)	14 (70)	59 (48.3)	207 (57.2)	189 (53.4)	32 (55.2)
● Female	26 (65)	6 (30)	63 (51.7)	155 (42.8)	165 (46.6)	27 (44.8)
Age (years)	62.6 ± 10.1 (41–86)	57 ± 10	57.9 (17–87)	68.5 (37.5–85.7)	65.2 ± 11.5 (23–88)	63.7 ± 11.03
Risk factors						
● Smoker	20 (50)	NA	NA	250 (69)	101 (28.5)	22 (37.3)
● Alcoholism	14 (36)			NA	97 (27.4)	9 (15.3)
● DM2	11 (28)			105 (29)	119 (33.7)	13 (22.0)
● Pancreatitis	2 (5)			31 (8.6)	8 (2.3)	NA
● BMI	28.4 (22.3–36)			NA	NA	
● Overweight/ Obesity	14 (74)			BMI (> 30) 90 (5.1)	126 (35.6)	> 30 2 (3.4)
Tumor size	5.7 (2–20)	3.5 ± 1.5	2.87	NA	NA	3.59 ± 2.26.
Positive lymph nodes	12 (30)	10 (50)	81 (66)			NA
Histology grade						
● G3	9 (25)	3 (17)	22 (18)	NA	NA	16 (27.1)
● G2	26 (72.2)	7 (35)	87 (71)			17 (28.8)
● G1	1 (3)	10 (50)	14 (11)			23 (39)
R0*	18 (40)	18 (90)	57 (47)	NA	50 (83.3)	39 (97.5)
Treatment						
● Surgery	16 (43)	NA	NA	NA	79 (22.3)	40 (67.8)
● Surg/Chem	8 (22)	1 (5)			9 (2.5)	27 (48.5)
● Surg/Rad	2 (5)	NA			NA	18 (30.5)
● Chemotherapy	7 (19)	NA			33 (9.3)	NA
● Chem/Rad	1 (3)	7 (37)			NA	NA
DFS (months)	10.8 (1–99)	NA	NA	NA	NA	19.29 ± 33.31 (0–110)
Overall survival	13.8 (1–100)	9	22.6	NA	9.97 ± 1.77	25.08 ± 28.91 (1–110)

et al. questioned all patients referred for pancreatic surgery about a diabetes mellitus history; those without a history of diabetes mellitus underwent a fasting plasma glucose test, an oral glucose tolerance test

The AVAC group included 67% females, and the mean age was 59.5 years; these values were similar to a previous report of the Mexican population by Tocay-Ajcuc, who reported 57.5% females and a mean

age of 58.5 years [26]. Bourgouin et al. reported 55% females and a mean age of 66 years [27], and Chang et al. reported 88 (42.3%) fe-

4.1. Perspective

Table 3
Comparison of different AVAC cohorts.

Variable	Sánchez et al.	Tocay-Ajcuc et al. [21]	Chang et al. [7]			Bourgouin et al. [23]
Gender						
• Male	25 (33)	45 (42.5)	42 (58.3)	53 (58.9)	25 (54.3)	25 (45)
• Female	51 (67)	61 (57.5)	30 (41.7)	37 (41.1)	21 (45.7)	62 (46)
Age (years)	59.5 ± 10.6 (31–79)	58.5 ± 14.1	66.1 (34–88)	63.5 (37.7–77.5)	62.9 (38–79)	66 (28–81)
Clinical data						
• Jaundice	25 (66)	96 (91)	NA			62 (46)
• Weight loss	28 (72)	75 (71)				11 (20)
• Abdominal Pain	29 (76)	NA				NA
Tumor size	2.4 (0.4–11)	2.4 ± 1.5 (1–10)	NA	NA	NA	2 (1–7)
Intestinal subtype	35 (46)	NA	41 (56.9)	44 (48.9)	20 (43.5)	
PB subtype	24 (32)	NA	26 (36.1)	41 (45.6)	22 (47.8)	
Not determined	17 (22)	NA	5 (6.9)	5 (5.6)	4 (8.7)	
Histology grade						
• G3	7 (10)	16 (16.3)	NA			NA
• G2	55 (82)	52 (53)				NA
• G1	5 (8)	25 (30.1)				76 (56)
R0*	63 (93)	NA	68 (94.4)	61 (67.8)	40 (87)	122 (90)
Treatment						
• Surgery	44 (60)	69 (65.1)	NA	NA	NA	NA
• Surg/Chem	22 (30)	NA	17 (27.4)	21 (23.3)	26 (56.6)	
• Surg/Rad	1 (1)	NA	NA	NA	NA	
• Chemotherapy*	4 (6)	30 (28.3)	45 (72.6)	69 (76.7)	20 (43.4)	
• Chem/Rad	8 (11)	NA	NA	NA	NA	
5-y survival	62%	NA				50%

males, with a mean age of 64.2 years [7].

We identified 41 (87%) patients who were overweight or obese with a mean BMI of 28.6. Although obesity has not been associated with AVAC, more studies are required to clarify a possible association between obesity and AVAC [11,28].

Clinically, jaundice was the most frequent sign in patients (88%), similar to the study by Tocay-Ajcuc et al. (91%) [26]; this is a higher percentage than found in the Bourgouin cohort, where 47% of patients presented this symptom [27].

Additionally, the mean tumor size in our study was 2.4 (0.4–11) cm, similar to both the Chan and Bourgouin cohorts, in which the mean tumor sizes were 2.27 and 2 cm, respectively [19,27].

The five-year OS for AVAC patients in our study was 62%, while the Bourgouin cohort exhibited a five-year OS rate of 50% [27]; therefore treatment of this tumor results in an OS rate that is similar to that observed internationally (Table 3).

In conclusion, our cohort of PDAC and AVAC patients is similar to those in international reports, although our results suggest that these tumors may be more frequent in females and slightly younger patients in the Mexican population. As expected, we identified a high prevalence of overweight/obesity; this modifiable risk is one of the most important public health issues and is expected to double by 2030 [14]. It is important to conduct effective public health programs to decrease modifiable risk factors not only for these tumors but also for related comorbidities and mortalities [12,13,29].

In our opinion, intensified preventive medicine and health education programs are required to decrease modifiable risk factors such as obesity and smoking. We suggest that biochemical diagnosis of type 2 diabetes mellitus in PDAC patients is required for multidisciplinary pretreatment planning.

We currently do not have a marker that is specific and sensitive for the diagnosis of PDAC or AVAC, we suggest that obese and diabetic patients and those who smoke should be monitored to identify the development of PDAC in early stages.

Ethical approval

The project was approved by the Oncology Hospital local ethics committee (R-2011-3602-20).

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Author contribution

1 Sánchez-García Jorge: conception, design and execution of the work. Final approval of the version to be published.
2 Candanedo-González Fernando: conception, design and execution of the work.Final approval of the version to be published.
3 Félix-Félix Anna Karen: conception, design and execution of the

work. Final approval of the version to be published.

4 Sánchez-Ramírez Damián: Execution of the work. Final approval of the version to be published.

5 Medrano-Guzmán Rafael: critical revision for important intellectual content. Final approval of the version to be published.

6 Quintana-Quintana Miguel: critical revision for important intellectual content. Final approval of the version to be published

7 Baas-Cabrera Yair Benjamín: Execution of the work. Final approval of the version to be published.

8 Flores-Figueroa Eugenia: conception, design, writing of the article and correspondent author.

Conflicts of interest

None.

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Eugenia Flores Figueroa

Consent

The ethical committee consider there was no need for written consent as this is a retrospective cohort.

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