



# REVISTA DE GASTROENTEROLOGÍA DE MÉXICO

[www.elsevier.es/rgmx](http://www.elsevier.es/rgmx)



## ORIGINAL ARTICLE

# Pancreatic ductal adenocarcinoma: Eleven years of experience at a tertiary care hospital center<sup>☆</sup>



G.E. Sánchez Morales<sup>a</sup>, R.A. Moguel Valladares<sup>a</sup>, J. Flores Maza<sup>a</sup>,  
U. Clemente Gutiérrez<sup>a</sup>, E. Sánchez-García Ramos<sup>a</sup>, I. Domínguez Rosado<sup>b</sup>,  
L.C. Chan Núñez<sup>b,\*</sup>

<sup>a</sup> Departamento de Cirugía General, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Tlalpan, Mexico City, Mexico

<sup>b</sup> Departamento de Cirugía General, Servicio de Cirugía Hepatopancreatobiliar, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Tlalpan, Mexico City, Mexico

Received 14 September 2019; accepted 1 April 2020  
Available online 6 April 2021

### KEYWORDS

Pancreatic cancer;  
Epidemiology;  
Mortality

### Abstract

**Introduction and aim:** Pancreatic cancer is considered one of the most aggressive solid tumors. In Mexico, it is the twelfth cause of cancer, with 4,489 cases diagnosed annually, and accounts for 4.9% of oncologic deaths.

**Aim:** The aim of our study was to describe the clinical and epidemiologic characteristics of the patients diagnosed with pancreatic cancer spanning an 11-year period at the *Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán"*.

**Methods:** A retrospective, cross-sectional study was conducted that included 479 patients diagnosed with pancreatic cancer, within the time frame of 2003–2013. The documented findings were summarized through descriptive statistics.

**Results:** Of the patients with pancreatic ductal adenocarcinoma, 50.9% were women, and the mean patient age at diagnosis was 61.5 years. A total of 48.4% of the cases were diagnosed at clinical stage IV, 12.9% presented with clinical stage III, and 25.0% had localized disease. Surgery was performed on 37.5% of the patients, the most frequent of which was pancreatoduodenectomy. The surgical mortality rate was 5.5%.

<sup>☆</sup> Please cite this article as: Sánchez Morales GE, Moguel Valladares RA, Flores Maza J, Clemente Gutiérrez U, Sánchez-García Ramos E, Domínguez Rosado I, et al. Adenocarcinoma ductal de páncreas. Experiencia de 11 años en un centro de tercer nivel. *Revista de Gastroenterología de México*. 2021;86:118–124.

\* Corresponding author. Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Vasco De Quiroga 15, Tlalpan, Sección XVI, 14000, Mexico City, Mexico, Tel.: 01 (52) 54 87 09 00 ext. 2133.

E-mail address: [carlos.chann@incmsz.mx](mailto:carlos.chann@incmsz.mx) (L.C. Chan Núñez).

**Conclusion:** The clinical characteristics in our study group were similar to those described in the literature. However, the number of candidates for surgical treatment was higher than that reported in other hospitals and the percentage of borderline tumors was lower. Those differences, respectively, are possibly associated with the nature of our referral center and the prolonged intervals between diagnosis and treatment that result in the loss of potential surgical patients.

© 2020 Asociación Mexicana de Gastroenterología. Published by Masson Doyma México S.A. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## PALABRAS CLAVE

Cáncer de páncreas;  
Epidemiología;  
Mortalidad

## Adenocarcinoma ductal de páncreas. Experiencia de 11 años en un centro de tercer nivel

### Resumen

**Introducción y objetivo:** El cáncer de páncreas es considerado uno de los tumores sólidos más agresivos. En México representa la doceava causa de cáncer con 4,489 casos diagnosticados por año y representa el 4.9% de las defunciones oncológicas. El objetivo del estudio es describir las características epidemiológicas y clínicas de los pacientes con diagnóstico de cáncer de páncreas en un periodo de once años del Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán".

**Métodos:** Estudio retrospectivo – transversal que incluyó 479 pacientes con diagnóstico de cáncer de páncreas en el periodo 2003 - 2013. Se incluyó estadística descriptiva para resumir los hallazgos documentados.

**Resultados:** De los pacientes con adenocarcinoma ductal de páncreas el 50.9% fueron mujeres, la edad promedio al diagnóstico fue de 61.5 años. Se diagnosticaron en un estadio clínico IV el 48.4 % de los casos, mientras que el 12.9% se presentaron como estadio clínico III y el 25.0% como enfermedad localizada. El 37.5% de los pacientes fueron sometidos a cirugía, siendo la pancreatoduodenectomía el procedimiento más frecuentemente realizado. La mortalidad quirúrgica fue del 5.5%.

**Conclusión:** Las características clínicas en nuestro grupo de estudio muestran similitud con la literatura, sin embargo, el número de candidatos a un tratamiento quirúrgico fue superior a las cifras reportadas en otros hospitales, no obstante, la cifra de tumores limítrofes fue menor; probablemente asociado con la naturaleza de centro de referencia que representa nuestra institución, así como a la pérdida de pacientes potencialmente quirúrgicos debido a un periodo de ventana prolongado entre diagnóstico y tratamiento.

© 2020 Asociación Mexicana de Gastroenterología. Publicado por Masson Doyma México S.A. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction and aim

Pancreatic cancer is considered one of the most aggressive solid tumors and is one of the main causes of oncologic mortality in Western countries. Pancreatic ductal adenocarcinoma (PDAC) is the most common histologic variant in 85% of cases.<sup>1-3</sup> It frequently presents in patients above 70 years of age as locally advanced or metastatic disease.<sup>4</sup>

According to 2018 data from the World Health Organization, PDAC is the fifteenth cause of cancer worldwide, with an incidence of 4.8 cases per 100,000 inhabitants and a mortality rate of 4.4 cases per 100,000 inhabitants.<sup>5</sup>

In 2018, in the United States, 55,440 new cases were diagnosed, and 43,330 deaths were reported, making it the fourth cause of oncologic mortality in that country.<sup>6</sup> An incidence of 6.9 cases per 100,000 inhabitants has been esti-

mated, according to the latest 2012 data. Incidence has risen, compared with the 6.6 and 5.7 cases per 100,000 inhabitants in 2008 and 1999, respectively. That increase is most likely associated with the risk factors of obesity and population aging. In contrast, there have been no significant changes in the mortality rate over time,<sup>7-9</sup> showing the trend for an increase in frequency of the disease and its poor survival rate. Currently, overall 5-year survival is estimated at less than 5%,<sup>5</sup> which can increase to 15-30% with surgical treatment. However, only 15-20% of patients present with resectable disease at diagnosis, based on the degree of contact between the tumor and certain vessels.<sup>10,11</sup>

In Mexico, PDAC is the twelfth cause of cancer, with 4,489 cases diagnosed annually, and is the cause of 4.9% of oncologic deaths, according to 2015 data from the *Instituto Nacional de Estadística y Geografía (INEGI)*, figures that

demonstrate an area of opportunity in the prevention, diagnosis, and treatment of PDAC.<sup>12</sup>

The aim of the present study was to describe the epidemiologic and clinical characteristics of the patients diagnosed with pancreatic cancer spanning an 11-year period at the *Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán"*.

## Methods

A total of 479 patients were included that had a histopathologic diagnosis of PDAC, documented within the time frame of 2003 and 2013. Electronic and physical case records were reviewed to obtain the clinical and epidemiologic characteristics.

**Statistical analysis.** Through descriptive statistics, the quantitative variables were expressed as mean and range and the qualitative variables as frequency and percentage. Electronic and physical case records were reviewed for the postoperative follow-up. The patients whose records did not contain the information required were called by telephone if a current number was available.

## Ethical considerations

The present study was approved by the research and ethics committee of the *Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán"* and the authors declare that it contains no personal information through which the patients could be identified.

## Results

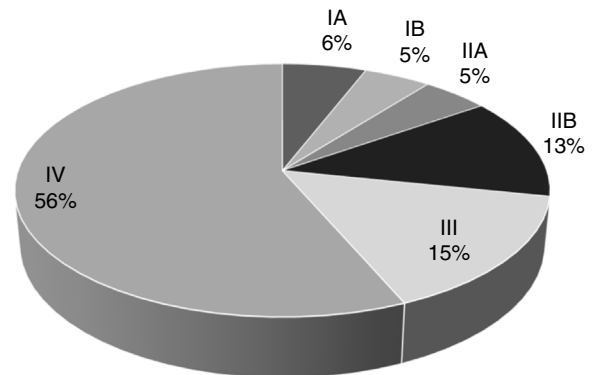
The data from 479 patients with a histopathologic diagnosis of PDAC were obtained. Of those patients, 244 (50.9%) were women, 235 (49.1%) were men, and the mean patient age at diagnosis was 61.5 years (range 27-91). According to age distribution, 53% of the cases were reported in patients above 60 years of age and 16% of the cases were diagnosed in patients under 50 years of age. The most frequent associated comorbidities were smoking (44.8%, with a mean smoking index of 0.45), diabetes mellitus (DM) in 151 cases (31.5), and high blood pressure in 148 (30.8). Abdominal pain was the most frequent symptom in 379 patients (79.1%), followed by weight loss in 313 (65.3%) and jaundice in 232 (59.4% n = 232). Other clinical presentations were inability to tolerate oral intake, acute cholangitis, and recently diagnosed DM (defined as DM diagnosed within the 6 months prior to PDAC diagnosis) (Table 1).

Over the span of the eleven years analyzed, 232 patients (48.4%) were diagnosed with clinical stage IV metastatic disease, 62 cases (12.9%) presented with clinical stage III locally advanced disease, and 121 patients (25.0%) had localized disease, the most favorable scenario. Clinical stage was not determined at diagnosis in 64 cases (14.4%) because those patients were diagnosed outside of our hospital center or their case records contained inaccurately recorded data (Fig. 1).

Regarding tumor characteristics, 353 cases (73.6%) had tumors located at the head of the pancreas, 54 cases (11.2%) at the neck-body of the pancreas, and only 28 cases (5.8%) at

**Table 1** Clinical characteristics of the patients diagnosed with PDAC.

<b>Sex</b>		
Male, n (%)	244	50.9
Female, n (%)	235	40.1
<b>Age at diagnosis, (years) (range)</b>		
Under 50 years of age, n (%)	76	16
50 – 59 years of age, n (%)	128	27
60 – 69 years of age, n (%)	136	28
70 – 79 years of age, n (%)	19	19
Above 79 years of age, n (%)	31	6
Not documented	19	4
<b>Comorbidities</b>		
Smoking, n (%)	214	44.8
Diabetes mellitus, n (%)	151	31.5
High blood pressure, n (%)	148	30.8
Ischemic heart disease, n (%)	41	8.5
Coagulopathy, n (%)	39	8.1
Alcohol use disorder, n (%)	39	8.1
Kidney failure, n (%)	31	6.4
COPD, n (%)	13	2.7
<b>Clinical presentation</b>		
Abdominal pain, n (%)	379	79.1
Weight loss, n (%)	313	65.3
Jaundice, n (%)	232	59.4
Inability to tolerate oral intake, n (%)	167	34.8
Acute cholangitis, n (%)	160	33.4
Recent DM diagnosis, n (%)	33	6.8

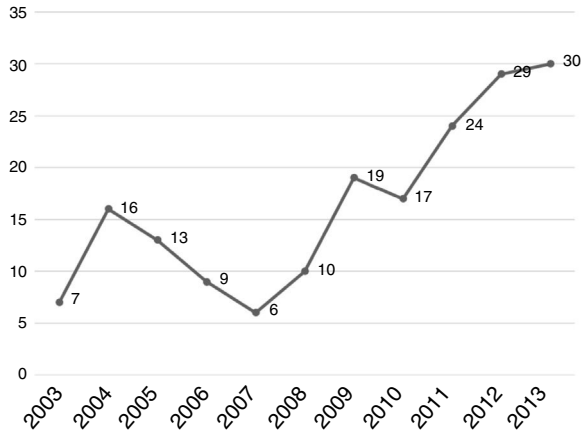


**Figure 1** Clinical stages of the patients diagnosed with PDAC.

the tail of the pancreas. Specific location was not recorded for 44 patients (9.1%). All patients diagnosed at our hospital center were evaluated through tomography, revealing resectable tumor in 178 patients (37.1%). Seven patients (1.6%) had borderline tumors, according to the definition provided by the National Comprehensive Cancer Network and they received neoadjuvant chemotherapy (Table 2). A total of 180 patients (37.5%) underwent surgery: 178 patients with resectable PDAC at diagnosis and 2 patients (28.5%) with borderline PDAC that responded to neoadjuvant chemotherapy. A total of 128 patients (71.1%) received adjuvant chemotherapy. The analysis of the yearly number of cases that were candidates for surgery showed an increase

**Table 2** Patients diagnosed with pancreatic ductal adenocarcinoma that received neoadjuvant chemotherapy.

Sex	Age	Neoadjuvant chemotherapy regimen	Surgical procedure
Male	68	FOLFOX4	None Peritoneal metastases
Male	69	Not specified	Pancreatoduodenectomy
Male	72	Gemcitabine	NoneDBD + gastrojejunal anastomosis
Female	68	Oxaliplatin, irinotecan, 5-FU.	Pancreatoduodenectomy
Female	65	Not specified	None Peritoneal metastases
Female	71	Not specified	None Vascular involvement
Female	69	Not specified	None Not specified



**Figure 2** Number of patients diagnosed with PDAC that underwent surgery.

over time and 2011-2013 was the most representative period of time at our hospital center (Fig. 2).

Two main surgical procedures were carried out. The Whipple procedure (pancreatoduodenectomy) was the most frequent. It was performed on 176 patients (97.7%) and 37 cases (21.0%) required portal vein reconstruction. Distal pancreatectomy was performed on the rest of the patients (2.3%). Mean tumor size was 27.3 × 20.3 mm, the majority of the patients presented with moderately differentiated lesions (56.1%) and the pancreatobiliary subtype (13.3%). The pathologic evaluation, showing other characteristics, as well, is summarized in Table 3.

Abdominal sepsis and pancreatic fistula were among the postoperative complications, presenting in 40 and 25 patients, respectively (22.2 and 13.8%). Less than 10% of the cases presented with postoperative bleeding, bile duct fistula, or surgical site infection. The mortality rate was 5.5% (10 patients), 7 cases of which were secondary to septic shock and 3 to hemorrhagic shock, which presented within the first 24 h after surgery (Table 4).

The mean follow-up for the patients that underwent surgery was 28 months (range 0-137) in 58% of the cases. The remaining 42% were lost to surgical follow-up and could not be reached by telephone. Fifty percent of the cases that underwent surgery (52 patients) had disease recurrence at a mean of 22 months (range 1-114). Recurrence was local in 26.0% (14 patients) and systemic in the

**Table 3** Pathologic characteristics of the patients with pancreatic resection.

Variable	n	%
Mean size (range)(mean)	80 – 5 × 60 – 427.3 × 20.3	
Positive margins	40	22.2
Number of lymph nodes harvested (range)(mean)	59 – 0	12.7
Number of patients with positive lymph nodes	85	47.2
<i>Differentiation grade</i>		
In situ	1	0.5
Well differentiated	13	7.2
Moderately differentiated	101	56.1
Poorly differentiated	55	30.6
Not reported	10	5.6
Vascular invasion	74	41.1
Perineural invasion	104	57.7
Lymphatic invasion	77	42.7
<i>Histologic subtype</i>		
Intestinal	21	11.7
Pancreatobiliary	24	13.3
Mixed	11	6.1
Sarcomatoid	1	0.621
Squamous cell	4	2.2
Mucinous	10	5.5
Foamy cell	2	1.1
Not identified	107	59.5

**Table 4** Surgical characteristics of the patients diagnosed with PDAC.

<i>Procedure performed, n (%)</i>	180	100
Whipple (pancreatoduodenectomy), n (%)	176	97.7
Distal pancreatectomy, n (%)	4	2.3
<i>Vascular reconstruction, n (%)</i>	37	100
Primary anastomosis, n (%)	24	64.8
Venorrhaphy, n (%)	13	35.2
<i>Postoperative complications</i>		
Abdominal sepsis, n (%)	40	22.2
Pancreatic fistula, n (%)	25	13.8
Postoperative bleeding, n (%)	13	7.2
Bile duct fistula, n (%)	9	5
Surgical site infection, n (%)	7	3.8
<i>Mortality, n (%)</i>	10	5.5
Septic shock, n (%)	7	3.8
Hemorrhagic shock, n (%)	3	1.6

remaining 38 patients. Overall postoperative 3-year survival was 13.6%.

## Discussion and conclusion

The *Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán"* is a tertiary care hospital center in Mexico City that focuses on different surgical areas, including hepatopancreatobiliary surgery and pancreatic cancer surgery. The population treated at the center is made up of patients diagnosed there, as well as a majority of patients that are referred there for multidisciplinary treatment. Said population has specific characteristics, given that the hospital is a referral center, and represents a small sample of pancreatic cancer in Mexico. Among the limitations of our study, are those inherent in its retrospective design, which include a lack of data availability, loss of information, and loss of long-term follow-up. Nevertheless, it provides valuable information on the PDAC population at our hospital center.

We know that the incidence of PDAC varies across the globe and that the highest incidence is in developed regions, such as the United States and the European countries. However, there is a worldwide trend toward an increase in the number of cases, associated with a longer-living population and better diagnosis and treatment of oncologic tumors.<sup>13</sup> A higher incidence has also been reported in male patients in certain regions of Armenia, the Czech Republic, and Hungary, but sex distribution is the same in high incidence regions, such as North America and Western Europe.<sup>14</sup> In addition, age at diagnosis in those areas tends to be above 70 years and only 5-10% of the cases present in patients under 50 years of age.<sup>15</sup> Sex distribution was the same in our patients, showing a similar behavior in relation to developed regions. However, the mean age at diagnosis was 61 years, with 16% of the patients under 50 years of age, revealing a younger age at diagnosis. That could be related to the presence of risk factors in our society, such as smoking, obesity, and DM, which are comorbidities that are strongly associated with the development of PDAC.<sup>16-19</sup> In our study patients, 44.8% were smokers and 31.5% presented with DM, but given the limitations of our study, we could not establish a cause-and-effect relationship.

With respect to the clinical stage of presentation, worldwide statistics show that more than 50% of the patients are diagnosed with metastatic disease, whereas 30-35% and 15-20% present with locally advanced disease and localized disease, respectively. An effort has been made to improve those figures through new tools for disease prevention and diagnosis in patients with risk factors.<sup>20-22</sup> Over the 11 years analyzed herein, the percentage of patients with localized disease that were candidates for surgical treatment was 25%, slightly higher than the figures reported by other hospitals, which is most likely associated with the fact that our hospital is a referral center.

The clinical presentation of PDAC varies, depending on its location and the time of disease progression. It tends to manifest nonspecifically, and the most frequent symptoms are

weight loss in 92% of cases, jaundice in 80%, and abdominal pain in 70%, according to reports in the literature.<sup>23,24</sup> Other symptoms are anorexia, choloria, acholia, nausea, vomiting, and weakness. We found similar figures at our hospital center. The most frequent symptom was abdominal pain in 79.1% of the patients, weight loss in 65.3%, and jaundice in 59.4%. Those data were strongly associated with tumor location, with 84.8% at the head of the pancreas and 5.8% at the tail of the pancreas.

Surgery is currently the only curative treatment for PDAC, improving 3-year survival from 5-6% to 35-40% in patients with clinical stage I and from 3-4% to 15-25% in patients with clinical stage II.<sup>20</sup> In the subgroup of patients with borderline disease, response to neoadjuvant treatment enables them to undergo surgical treatment at high-volume centers, with the same survival rates.<sup>25</sup> In our study, 28.3% of the patients were found to have resectable tumors at diagnosis, through tomographic evaluation, compared with the 10-20% reported in the majority of studies in the literature,<sup>26</sup> and 13.9% of the cases fit the criteria for borderline tumor, in contrast to the 30-40% reported in other studies.<sup>26,27</sup> That low figure could be associated with the prolonged time interval between diagnostic suspicion and diagnostic approach, in which patients that are candidates for potentially curative treatment are lost.

A total of one hundred and eighty patients underwent surgery and the Whipple procedure was performed in 97.7%. In the 11-year evaluation, the number of annual cases were shown to increase at our hospital center up to a mean 25-30 cases in recent years. In addition, 21% of the surgical cases required vascular reconstruction, which is a lower percentage than that reported at other hospital centers.<sup>28,29</sup> Those findings are associated with the higher level of experience attained in pancreatic surgery at our hospital, as well as the emergence of greater scientific evidence related to vascular reconstruction techniques. In the postoperative evaluation, abdominal sepsis and the presence of pancreatic fistula were the most common complications, at 22.2 and 13.8%, respectively. The postoperative mortality rate was 5.5%, comparable to that of other high-volume referral centers.<sup>30</sup> Importantly, our hospital center now has the protocols for postoperative serial drain amylase measurement, something that was not adequately established during part of our study period, resulting in bias related to the diagnosis of pancreatic fistulas, especially grade A fistulas ("biochemical leaks").

Mean follow-up was 28.06 months in 58% of the postoperative patients. There was disease recurrence in 50% of the cases at a mean 22.06 months and systemic recurrence was the most frequent. The general 3-year mortality rate was 13.6%, similar to that reported in the literature for patients with clinical stage III, but below that expected for earlier stages.

In conclusion, our study group had clinical characteristics similar to the etiology reported in developed countries, but there was a higher number of patients under 50 years of age. On the other hand, the number of candidates for surgical treatment was higher than the figures described at other hospitals, but the number of borderline tumors was

lower. Respectively, those differences are possibly associated with the fact that our hospital is a referral center, and with the prolonged time interval between diagnostic suspicion and diagnostic approach, resulting in the loss of patients that could have been possible surgical candidates. Despite the limitations inherent in the retrospective design of our study, the data we found show areas of opportunity for improving PDAC statistics in Mexico: establishing measures for improving modifiable risk factors, carrying out opportune screening in high-risk patients, and improving the time intervals involved in the care given patients suspected of PDAC.

## Financial disclosure

No financial support was received in relation to this article.

## Conflict of interest

The authors declare that there is no conflict of interest.

## References

- Ilic M, Ilic I. Epidemiology of pancreatic cancer. *World J Gastroenterol.* 2016;22:9694–705, <http://dx.doi.org/10.3748/wjg.v22.i44.9694>.
- Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015;136:E359–386, <http://dx.doi.org/10.1002/ijc.29210>.
- Yeo TP. Demographics, epidemiology, and inheritance of pancreatic ductal adenocarcinoma. *Semin Oncol.* 2015;42:8–18, <http://dx.doi.org/10.1053/j.seminoncol.2014.12.002>.
- Abrams RA, Lowy AM, O'Reilly EM, et al. Combined modality treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. *Ann Surg Oncol.* 2009;16:1751–6, <http://dx.doi.org/10.1245/s10434-009-0413-9>.
- Gco.iarc.fr [online] Available at: <https://gco.iarc.fr> [Accessed 24 Jan. 2019] Global Cancer Observatory; 2019.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* 2018;68:7–30, <http://dx.doi.org/10.3322/caac.21442>.
- Simard EP, Ward EM, Siegel R, et al. Cancers with increasing incidence trends in the United States: 1999 through 2008. *CA Cancer J Clin.* 2012;62:118–28, <http://dx.doi.org/10.3322/caac.20141>.
- Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol.* 2009;27:2758–65, <http://dx.doi.org/10.1200/JCO.2008.20.8983>.
- StatBite. U.S. pancreatic cancer rates. *J Natl Cancer Inst.* 2010;102:1822, <http://dx.doi.org/10.1093/jnci/djq517>.
- Lillemoe KD, Yeo CJ, Cameron JL. Pancreatic cancer: state-of-the-art care. *CA Cancer J Clin.* 2000;50:241–68, <http://dx.doi.org/10.3322/canjclin.50.4.241>.
- Ducreux M, Cuhna AS, Caramella C, et al. ESMO Guidelines Committee. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2015;26 Suppl 5:v56–68, <http://dx.doi.org/10.1093/annonc/mdv295>.
- INEGI I [online] Inegi.org.mx. Available at: <https://www.inegi.org.mx/default.html> [Accessed 23 January 2019] Instituto Nacional de Estadística y Geografía (INEGI); 2019.
- Ferlay J, Soerjomataram I, Ervik M, et al. Accessed 4 March 2016. Available from: URL: GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013 <http://globocan.iarc.fr>
- Malvezzi M, Carioli G, Bertuccio P, et al. European cancer mortality predictions for the year 2016 with focus on leukaemias. *Ann Oncol.* 2016;27:725–31, <http://dx.doi.org/10.1093/annonc/mdw022>.
- Hidalgo M, Cascinu S, Kleeff J, et al. Addressing the challenges of pancreatic cancer: future directions for improving outcomes. *Pancreatol.* 2013;15:8–18, <http://dx.doi.org/10.1016/j.pan.2014.10.001>.
- Iodice S, Gandini S, Maisonneuve P, et al. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. *Langenbecks Arch Surg.* 2008;393:535–45, <http://dx.doi.org/10.1007/s00423-007-0266-2>.
- Aune D, Greenwood DC, Chan DS, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. *Ann Oncol.* 2012;23:843–52, <http://dx.doi.org/10.1093/annonc/mdr398>.
- Batabyal P, Vander Hoorn S, Christophi C, et al. Association of diabetes mellitus and pancreatic adenocarcinoma: a meta-analysis of 88 studies. *Ann Surg Oncol.* 2014;21:2453–62, <http://dx.doi.org/10.1245/s10434-014-3625-6>.
- Stevens RJ, Roddam AW, Beral V. Pancreatic cancer in type 1 and young-onset diabetes: systematic review and meta-analysis. *Br J Cancer.* 2007;96:507–9, <http://dx.doi.org/10.1038/sj.bjc.6603571>.
- Bilimoria KY, Bentrem DJ, Ko CY, et al. Validation of the 6th edition AJCC pancreatic cancer staging system: Report from the National Cancer Database. *Cancer.* 2007;110:738–44, <http://dx.doi.org/10.1002/cncr.22852>.
- Unger K, Mehta KY, Kaur P, et al. Metabolomics based predictive classifier for early detection of pancreatic ductal adenocarcinoma. *Oncotarget.* 2018;9:23078–90, <http://dx.doi.org/10.18632/oncotarget.25212>.
- Lu C, Xu CF, Wan XY, et al. Screening for pancreatic cancer in familial high-risk individuals: A systematic review. *World J Gastroenterol.* 2015;21:8678–86, <http://dx.doi.org/10.3748/wjg.v21.i28.8678>.
- Wolfgang CL, Herman JM, Laheru DA, et al. Recent progress in pancreatic cancer. *CA Cancer J Clin.* 2013;63:318–48, <http://dx.doi.org/10.3322/caac.21190>.
- De La Cruz MS, Young AP, Ruffin MT. Diagnosis and management of pancreatic cancer. *Am Fam Physician.* 2014;89:626–32.
- Kim HS, Jang JY, Han Y, et al. Survival outcome and prognostic factors of neoadjuvant treatment followed by resection for borderline resectable pancreatic cancer. *Ann Surg Treat Res.* 2017;93:186–94, <http://dx.doi.org/10.4174/astr.2017.93.4.186>.
- Bockhorn M, Uzunoglu FG, Adham M, et al. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery.* 2014;155:977–88, <http://dx.doi.org/10.1016/j.surg.2014.02.001>.
- Hackert T, Ulrich A, Büchler MW. Borderline resectable pancreatic cancer. *Cancer Lett.* 2016;375:231–7, <http://dx.doi.org/10.1016/j.canlet.2016.02.039>.

28. Maley WR, Yeo CJ. Vascular Resections During the Whipple Procedure. *Adv Surg.* 2017;51:41–63, <http://dx.doi.org/10.1016/j.yasu.2017.03.004>.
29. Sgroi MD, Narayan RR, Lane JS, et al. Vascular reconstruction plays an important role in the treatment of pancreatic adenocarcinoma. *J Vasc Surg.* 2015;61:475–80, <http://dx.doi.org/10.1016/j.jvs.2014.09.003>.
30. Hartwig W, et al. Pancreatic cancer surgery in the new millennium: better prediction of outcome. *Ann. Surg.* 2011;254:311–9, <http://dx.doi.org/10.1097/SLA.0b013e31821fd334>.