Clinical Epidemiological Profile and Global Survival in Patients with Pancreatic Adenocarcinoma at a Reference Hospital in Oncology

Perfil Clínico-Epidemiológico e Sobrevida Global em Pacientes com Adenocarcinoma de Pâncreas em um Hospital de Referência em Oncologia

Perfil Clínico-Epidemiológico y Supervivencia General en Pacientes com Adenocarcinoma de Páncreas em un Hospital de Referencia em Oncología

Wanessa Cristina Farias da Silva[1]; Ana Gabriela Silva de Lima[2]; Heverton Valentim Colaço da Silva[3]; Rozangela Amorim Santos[4]

ABSTRACT

Introduction: Pancreatic malignant neoplasia represents one of the highest mortality neoplasms worldwide, almost always associated to a dismal prognosis, especially when associated with lymphatic spread and to distant organs. **Objective**: To assess the global survival in patients with pancreatic adenocarcinoma treated at a specialized oncology center. **Method:** From January 2011 to December 2014, 71 medical records were retrospectively evaluated. The data were analyzed using the STATA software version 14, using the Kaplan-Meier curve and the Cox regression. The confidence interval used was 95% (p<0.05). Ethical and confidentiality principles have been secured. **Results:** There was predominance of males, mixed race and over 61 years of age at diagnosis. As for the clinical characteristics, 87.8% of the tumors were located in the head of the pancreas. Abdominal pain (92.7%) was the most frequent symptom, followed by progressive weight loss (79.3%) and jaundice (57.3%). The three-months follow-up survival rate was 48.4%. **Conclusion:** The study shows that pancreatic cancer has an extremely negative repercussion, since most patients are diagnosed in advanced stages of the disease, hindering the possibility of curative treatment.
Key words: Pancreatic Neoplasms/epidemiology; Survival Analysis; Delayed Diagnosis.

RESUMO

Introdução: A neoplasia maligna de pâncreas configura uma das neoplasias de maior mortalidade em todo o mundo, quase sempre atrelada a um prognóstico sombrio, principalmente quando associada à disseminação linfática e para órgãos distantes. **Objetivo**: Avaliar a sobrevida global em pacientes com adenocarcinoma de pâncreas atendidos em um centro especializado em oncologia. **Método:** No período de janeiro de 2011 a dezembro de 2014, foram avaliados retrospectivamente 71 prontuários. Os dados foram analisados pelo *software* STATA versão 14, utilizando análise de Kaplan-Meier e de regressão de Cox. O intervalo de confiança utilizado foi de 95% e considerado significante p<0,05. Foram preservados os princípios éticos e da confidencialidade. **Resultados:** Houve predomínio do sexo masculino, raça parda e com idade superior a 61 anos ao diagnóstico. Quanto às características clínicas, 87,8% dos tumores estavam localizados em cabeça de pâncreas. A dor abdominal (92,7%) foi o sintoma mais frequente, seguida de perda progressiva de peso (79,3%) e icterícia (57,3%). A taxa de sobrevida em três meses de acompanhamento foi de 48,4%. **Conclusão:** O estudo evidencia que o câncer de pâncreas tem uma repercussão extremamente negativa, visto que a maioria dos pacientes recebe o diagnóstico em estágios avançados da doença, dificultando a possibilidade de tratamento curativo.
Palavras-chave: Neoplasias pancreáticas/epidemiologia; Análise de Sobrevida; Diagnóstico Tardio.

RESUMEN

Introducción: La neoplasia maligna pancreática representa una de las neoplasias de mortalidad más altas del mundo, casi siempre vinculada a un pronóstico sombrío, especialmente cuando se asocia con diseminación linfática y órganos distantes. **Objetivo:** Evaluar la supervivencia global en pacientes con adenocarcinoma pancreático tratados en un centro de oncología especializado. **Método:** Desde enero de 2011 hasta diciembre de 2014, se evaluaron retrospectivamente 71 registros médicos. Los datos se analizaron utilizando el *software* STATA versión 14, utilizando la curva de Kaplan-Meier y la regresión de Cox. El intervalo de confianza utilizado fue del 95% (p<0,05). Se han preservado los principios éticos y de confidencialidad. **Resultados:** Predominó el sexo masculino, la raza mixta y los mayores de 61 años en el momento del diagnóstico. En cuanto a las características clínicas, el 87,8% de los tumores se ubicaron en la cabeza del páncreas. El dolor abdominal (92,7%) fue el síntoma más frecuente, seguido de pérdida progresiva de peso (79,3%) e icterícia (57,3%). La tasa de supervivencia de seguimiento a los tres meses fue del 48,4%. **Conclusión:** El estudio muestra que el cáncer de páncreas tiene un impacto extremadamente negativo, ya que la mayoría de los pacientes reciben el diagnóstico en etapas avanzadas, obstaculizando la posibilidad de tratamiento curativo.
Palabras clave: Neoplasias Pancreáticas/epidemiología; Análisis de Supervivencia; Diagnóstico Tardío.

[1,2,4]Cancer Hospital of Pernambuco (HCP). Department of Teaching and Research (DEP). Santo Amaro. Recife (PE), Brazil. E-mails: wanessa_farias@outlook.com; gabriela_27lima@hotmail.com; anjuamorim@yahoo.com. Orcid iD: https://orcid.org/0000-0002-8022-0091; Orcid iD: http://orcid.org/0000-0001-9041-4618; Orcid iD: https://orcid.org/0000-0002-5289-999X
[3]Federal University of Pernambuco (UFPE). Department of Pathology. University City. Recife (PE), Brazil. E-mail: neto_pe6@live.com. Orcid iD: https://orcid.org/0000-0001-7169-4140
Corresponding author: Heverton Valentim Colaço da Silva. Departamento de Patologia da UFPE. Av. Prof. Moraes Rego, 1235 - Cidade Universitária. Recife (PE), Brazil. CEP 50670-420. E-mail: neto_pe6@live.com

INTRODUCTION

Pancreatic cancer is one of the most lethal neoplasms and is the seventh in the number of cancer-related deaths[1]. It is estimated for 2030 that pancreatic cancer will be the second cause of death by cancer in the United States[2] According to the National Cancer Institute José Alencar Gomes da Silva (INCA)[3], it is responsible for nearly 2% of all types of cancer diagnosed and by 4% of total deaths in Brazil.

Approximately 95% of pancreatic malignant tumors are of adenocarcinoma histological type[2]. With only 5-years survival rate, it is one of the malignant neoplasms[4] with worst prognosis.

Regardless of pancreatic cancer affecting both genders, prevalence is higher in males, its small portion of cases occurring within the age-range of 40-50 years old and the rest in older than 65 years, more common in Blacks[5,6]. Population studies suggest that some cases of pancreatic carcinoma can be hereditary reinforcing the hypotheses of genetic predisposition[7]. Nearly 10% of the patients with pancreatic adenocarcinoma have or will have at least one first or second degree relative affected[3,4].

Of difficult detection, INCA has no recommended screening[3]. Its dismal prognosis is associated to rapid spread to the lymphatic system and remote organs and absence of specific symptoms of the disease able to allow early diagnosis[5]. These factors led to an estimate that in 2040, its incidence will increase at world level with 355,317 new cases of pancreatic cancer[8].

At the diagnosis, only 20% of the patients are able to undergo surgical procedures. Surgery is considered the only current curative therapy so far and even though, the survival rate is 12 months in average[9,10] after this procedure.

For unresectable tumors and without evidence of remote metastasis the association of chemotherapy/radiotherapy is recommended for local control of the disease and improvement of quality of life with relative increase of mean survival; however, rare are the cases with long-time survival[11]. For the patients with remote metastasis, palliative chemotherapy with gemcitabine is indicated. The mean survival for metastatic patients is around six to nine months[12].

Therefore, the present study has the objective of describing the main epidemiologic and clinical characteristics related to pancreatic adenocarcinoma and estimate the global survival of patients treated at Pernambuco Cancer Hospital from 2011 to 2015.

METHOD

Retrospective, descriptive, and quantitative study. The main source of the data was the Cancer Hospital Registry of Pernambuco Cancer Hospital and Mortality Information System (SIM) of the state of Pernambuco. Patients with diagnosis of adenocarcinoma from January 1, 2011 to December 31, 2015 were included in the study.

The inclusion criteria were age equal or above 18 years old, pancreatic adenocarcinoma diagnosis and confirmation of the expected outcome (death). The variables analyzed were age, gender, ethnicity, family history, alcohol and tobacco use, current comorbidities, systemic arterial hypertension (SAH), *diabetes mellitus* and obesity, symptoms that motivated the seek for hospital consultation, biopsy, staging, treatment, and death. Patients diagnosed off the study period and who did not present pancreatic adenocarcinoma were excluded. 71 patients met the study criteria and 22 were excluded.

Absolute and relative frequencies distribution was presented to describe the population. Survival analysis was applied for mortality through the Kaplan-Meier curve and the rate of mortality was estimated in deaths per each 100 patients/month with confidence interval of 95%. The study statistical significance was 5% (p<0.05), STATA software version 14 was utilized.

The Institutional Review Board reviewed and approved the study, submitted through "*Plataforma Brasil*", number CAAE 84665418.2.0000.5205.

RESULTS

Of the 71 study patients, 47 (66.19%) were aged between 35 and 64 years. The mean age at the diagnosis was 61 years. Most of the patients were males (n: 40; 56.3%) and approximately 60.56% of the investigated claimed they were Brown. For life habits, nearly 34% (n: 24) of the patients informed they were smokers and alcohol users (35.2%) (Table 1).

In relation to the sites with high frequency, 61 patients (85.9%) had tumors in the head of the pancreas. Among the symptoms that led the patients to seek hospital treatment, the most common were abdominal pain (n: 64; 91.5%) followed by progressive weight loss (n: 46; 64.7%) and jaundice (n: 41; 57.7%). The characteristics of the of tumor are described in Table 2.

Treatment modalities included curative surgery in 17 individuals (23.9%). None of these patients was submitted to pre-surgery treatment modalities. Of the patients submitted to curative surgery, 12 (16.9%) underwent adjuvant chemotherapy. Seven patients were submitted to palliative surgery. The modality of choice was biliary shunt surgery. Only 32 patients of the population were submitted to chemotherapy treatment (Table 3) with curative or palliative intent.

The mortality rate was 1.8 deaths per month for each 100 patients diagnosed (CI95%: 9.4 to 14.9). The mean

Table 1. Characterization of the sample per patients affected by pancreatic adenocarcinoma consulted at Pernambuco Cancer Hospital – January 2011 to December 2015

Factors	Statistics
Age Range	
35 to 50 years	16 (22.5%)
From 51 to 65 years	31 (43.7%)
Older than 65 years	24 (33.8%)
Gender	
Female	31(43.7)
Male	40 (56.3%)
Ethnicity	
Caucasian	9 (12.7%)
Black	19 (26.8%)
Brown	43 (60.5%)
Life habits[a]	
Not reported	22 (30.9%)
Tobacco use	24 (33.8%)
Alcoholism	25(35.2%)
Comorbidities[a]	
No comorbidities	24 (33.8%)
Systemic blood hypertension	23 (32.4%)
Diabetes mellitus	23 (32.4%)
Pancreatitis	1 (1.4%)
Neoplasm family history[a]	
No	52 (73.2%)
Yes	19 (26.8%)

Caption: [a]Non-excluding categories.

time of patients' follow-up was 7.3 months. The main cause of death was sepsis. The probability of death of patients with pancreatic adenocarcinoma in six months after the diagnosis was 62.9%. Based in the data about patients' follow up, it was clear the evolution of the percent of death from 48.4% to 75.2% in the periods of three and 12 months, respectively (Table 4; Figure 1).

DISCUSSSION

The descriptive analysis in the current study found higher prevalence of males because tobacco use is more frequent in men, an important risk factor for neoplasms[10]. Approximately 20% of pancreatic cancer are associated to tobacco use and smokers have increased risk for the development of genetic mutations[5].

A study about the predominance of patients affected in the sixth decade of life was found with patterns compatible with recent data from INCA[3]. The mean age found corroborates the study of Kongkam et al.[13]

Table 2. Characteristics of the tumor of patients affected by pancreatic carcinoma at the Cancer Hospital of Pernambuco from January 2011 to December 2015

Factors	Statistics
Sites affected	
Other Sites	10 (14%)
Pancreas head	61 (86%)
Location of the tumor[a]	
Local	3 (4.2%)
Locally advanced	9 (12.7%)
Metastatic	59 (83.1%)
Lymph node affected	
No	12 (17%)
Yes	59 (83%)
Metastasis	
No	12 (17%)
One site affected	49 (69%)
More than one site affected	10 (14%)
Staging	
IA and IB	9 (12.6%)
IIA and IIB	6 (8.5%)
III	6 (8.5%)
IV	50 (70.4%)

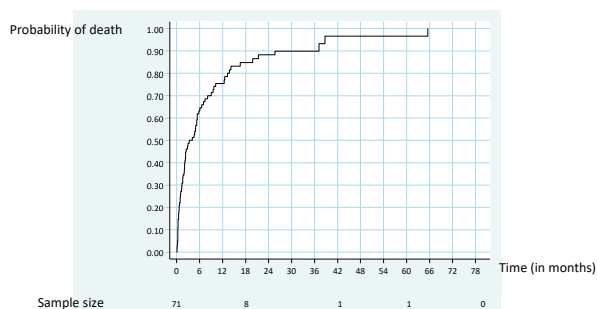**Caption:** [a]Non-excluding categories.

Table 3. Characteristics related to the treatment of patients affected by pancreatic adenocarcinoma treated at Cancer Hospital of Pernambuco from January 2011 to December 2015.

Characteristics	Number (%)
Treatment	
Exclusive palliative	31 (43.6%)
Palliative	23 (32.3%)
Palliative Surgery	7 (9.8%)
Exclusive palliative chemotherapy	16 (22.5%)
Curative surgical[a]	17 (23.9%)
Adjuvant chemotherapy	12(16.9%)
Adjuvant radiotherapy[a]	1(1.4%)
Type of surgery	
Duodenopancreatectomy	7 (9.8%)
Gastroduodenopancreatectomy	10 (14%)
Exclusive derivation	7 (9.8%)
Chemotherapeutic Protocol	
Gemzar	20 (28.1%)
Other	5 (7%)
More than one protocol	7 (7%)

Caption: [a]Procedure with curative intent.

Table 4. Statistics of deaths and description of the follow up

Characteristics	Statistics
Number of deaths	71 deaths
Cause of death	
Sepsis	19 (26.8%)
Renal insufficiency	4 (5.6%)
Respiratory insufficiency	7 (9.9%)
PCR	5 (7.0%)
Neoplastic cachexia	8 (11.3%)
Postoperative complications	7 (9.9%)
Other causes	21 (29.5%)
Time of follow-up	
Mean (minimum - maximum)	7.3 months (3 days – 5.4 years)
Rate of mortality (CI95%)	
Deaths per month at each 100 diagnosed	11.8 (9.4 – 14.9)

Figure 1. Probability of survival of patients affected by pancreas adenocarcinoma treated at Cancer Hospital of Pernambuco from January 2011 to December 2015

which evaluated 100 patients with diagnosis of pancreatic adenocarcinoma and mean age of 62.7 years at the diagnosis.

Regarding race, the study does not concur with the literature which shows pancreatic cancer affecting Blacks more frequently[3,4]. Most of the study patients claimed they were Brown. A hypothesis that attempts to justify this discrepancy is that racial miscegenation is quite common in Brazil.

In the casuistic presented, 26 patients (32.3%) reported *diabetes mellitus*. The literature indicates that the incidence of diabetes is increased in patients with pancreatic cancer, but the connection with cancer is controversial[8]. For Andersen et al.[14], *diabetes mellitus* can be an earlier manifestation of pancreatic cancer and not only a risk factor. Liao et al.[15] concluded that diagnosed diabetic for less than two years have elevated risk for the development of pancreatic cancer. However, patients

with diagnosis above this time interval failed to present significant difference.

Data found in the literature are not fully determined about alcohol use and increase of risk of pancreatic cancer because the current studies have limitations in their correlations[16]. However, the literature associates alcoholism to the development of pancreatic lesions and pancreatitis is considered a risk factor for the development of pancreatic neoplasms[16,17]. Most of the individuals reported alcohol use in the population investigated.

Overall, alcohol abusive users are smokers and tobacco is a risk factor associated to the development of pancreatic cancer[16].

In the current study, abdominal pain, progressive weight loss and jaundice were the most common complaints and quite often, are the first warning signs for investigation and diagnosis. The tumor type and site usually define the initial symptomatology and approximately 70% of pancreatic adenocarcinoma occur in the cephalic area of the organ and because of its proximity with biliary ducts they may present symptoms while still potentially curable[18,19]. Body and tail tumors are habitually asymptomatic in more advanced stages and have worse prognosis[20,21]. The more advanced the tumors, resulting symptomatologies are not limited to the previously quoted ones.

The result of the symptoms described in this analysis is compatible with the study conducted with 50 patients with pancreatic cancer in the Asian population and 72% of the patients investigated reported abdominal pain[22]. In another study conducted in England with 119 patients with pancreatic cancer aged 40 years or older, among the most common symptoms, jaundice (51%) and weight loss (55%) were found, corroborating the findings in the respective study[23]. The findings are consistent also with Reddy et al.[24] study where abdominal pain was the most common symptom, affecting 84% of the individuals investigated[22]. Therefore, based in the results of these studies in individuals aged 40 years or older who complained of abdominal pain, weight progressive loss, signs of jaundice, hereditary risk factors and presence of pancreatic solid mass, suspicion of pancreatic cancer should be investigated.

Staging is an important step in managing the conducts to be followed in relation to the treatment proposed[23]. Therefore, tumors diagnosed in initial stages demand less aggressive treatment and have better outcomes[25]. Currently, surgical resection continues to be the only curative option for pancreatic cancer, however, due to its late presentation, nearly 20% of the patients are eligible to surgical procedure[11]. These data corroborate the results of the current study since only 23.9% of the patients

submitted to surgical procedure with curative intent and 83% of the total already had metastatic disease.

At the diagnosis, several authors consider the stage of the disease a determinant factor for the patient's survival[26]. The late diagnosis can be one of the reasons for high probability of locally advanced or metastatic disease[10]. The restricted access to health and low education are factors that can influence the diagnosis of the disease, making the late discovery to shift from a potentially curable stage to palliative care[27].

For tumors diagnosed at an advanced stage and metastatic the modality of treatment is chemotherapy and/or radiotherapy[11,28]. But due to its high toxicity and incidence of adverse events, the modality is indicated for patients who have clinical conditions and good performance only[28]. In the present study, only one patient (1.4%) was referred to the modality of treatment with chemotherapy associated to radiotherapy.

While analyzing the global survival after three-months follow up, 48.4% evolved to death and in one year from the diagnosis, this probability reached 75.2%. In a comparison with this study, in a Espindola et al.[29] cohort study who evaluated the survival in patients with pancreatic cancer in a two-years period, after five-months follow up, the survival was 47.64% and in one year, 87%. The survival rate encountered in both studies can be used to estimate the efficiency of the health system, which depends of the quality of the care provided and accessibility of the health system.

The respective study shows that the most frequent cause of death was sepsis followed by neoplastic cachexia. It is important to remind that the treatment with antineoplastic chemotherapy, corticoids, radiotherapy and/or surgery predisposes immunosupression[30]. In addition, the recurrence of hospitalizations exposes the patient to invasive devices that increase the risk of infections[31].

Some study limitations need to be acknowledged. In addition to issues inherent to health professionals' wrongful completion of the charts, the non-functional evaluation of the patient's health compromised the analysis of some variables. So far, this is one of the first studies to evaluate the epidemiological and clinical profile and the global survival time in patients diagnosed with pancreatic adenocarcinoma in a reference hospital of Brazil's Northeast region and must be useful to guide the development of health policies for this population.

CONCLUSION

The results showed that the most predominant clinical-epidemiologic characteristics were tobacco and alcohol use, Brown race, *diabetes mellitus*, abdominal pain, progressive weight loss and jaundice. Large part of the population investigated was diagnosed at advanced stages, which hindered the possibility of curative treatment. Pancreatic cancer continues to be a challenging disease to diagnose and treat. This reality shows, therefore, the necessity of new studies in this area, further to new public policies promoting the early diagnosis of this neoplasm that appear to be the most important measure to improve the rates of cure of this infirmity.

CONTRIBUTIONS

All the authors contributed for the study conception and/or design, gathering, analysis and interpretation of the data, wording, critical review and approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

FUNDING SOURCES

None.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA. Cancer J. Clin. 2018;68(6):394-424. doi: https://doi.org/10.3322/caac.21492

2. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74(11):2913-21. doi: https://doi.org/10.1158/0008-5472.CAN-14-0155

3. Instituto Nacional de Câncer José Alencar Gomes da Silva [Internet]. Rio de Janeiro: INCA; [data desconhecida]. Tipos de câncer: câncer de pâncreas; [modificado 2020 abr 4; acesso 2020 abr 4]. Available from: https://www.inca.gov.br/tipos-de-cancer/cancer-de-pancreas

4. Jomrich G, Gruber ES, Winkler D, et al. Systemic Immune-Inflammation Index (SII) predicts poor survival in pancreatic cancer patients undergoing resection. J GastrointestSurg. 2020;24(3):610-18. doi: https://doi.org/10.1007/s11605-019-04187-z

5. Bontempo L, Jácome GC, Bitencourt EL. Perfil epidemiológico do câncer de pâncreas na região Norte do Brasil no período de 2010 a 2018. Rev Patol Tocantins. 2019;6(2):20-5. doi: https://doi.org/10.20873/uft.2446-6492.2019v6n2p20

6. Permuth JB, Clark Daly A, Jeong D, et al. Racial and ethnic disparities in a state- wide registry of patients with pancreatic cancer and an exploratory investigation of cancer cachexia as a contributor to observed inequities. Cancer Med. 2019;8(6):3314-24. doi: https://doi.org/10.1002/cam4.2180

7. Malhotra L, Ahn DH, Bloomston M. The pathogenesis, diagnosis, and management of pancreatic cancer. J Gastrointest Dig Syst. 2015;5(2):1-11. doi: https://doi.org/10.4172/2161-069X.1000278

8. Rawla P, Sunkara T, Gaduputi V. Epidemiology of pancreatic cancer: global trends, etiology and risk factors. World J Oncol. 2019;10(1):10-27. doi: https://doi.org/10.14740/wjon1166

9. Usón Junior PLS, França MS, Rodrigues HV, et al. Maior sobrevida global em pacientes com câncer pancreático metastático: o impacto de onde e como o tratamento é realizado. Einstein. São Paulo. 2015;13(3):347-351. doi: https://doi.org/10.1590/S1679-45082015AO3303

10. Bittencourt CP, Abreu MC, Souza TF, et al. Tabagismo e sua relação com o desenvolvimento de câncer. Rev Cient ITPAC [Internet]. 2017 [acesso 2020 ago 12];10(1):13-18. Available from: https://assets.unitpac.com.br/arquivos/revista/2017-1/Artigo_2.pdf

11. Kamisawa T, Wood LD, Itoi T, et al. Pancreatic cancer. Lancet. 2016;388(10039):73-85. doi: https://doi.org/10.1016/S0140-6736(16)00141-0

12. McGuigan A, Kelly P, Turkington RC, et al. Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol. 2018;24(43):4846-61. doi: https://doi.org/10.3748/wjg.v24.i43.4846

13. Kongkam P, Benjasupattananun P, Taytawat P, et al. Pancreatic cancer in an Asian population. Endosc Ultrasound. 2015;4(1):56-62. doi: https://doi.org/10.4103/2303-9027.151361

14. Andersen DK, Korc M, Petersen GM, et al. Diabetes, pancreatogenic diabetes, and pancreatic cancer. Diabetes. 2017;66(5):1103-10. doi: https://doi.org/10.2337/db16-1477

15. Liao KF, Lai SW, Li CI, et al. Diabetes mellitus correlates with increased risk of pancreatic cancer: a population-based cohort study in Taiwan. J Gastroenterol Hepatol. 2012;27(4):709-13. doi: https://doi.org/10.1111/j.1440-1746.2011.06938.x

16. Korc M, Jeon CY, Edderkaoui M, et al. Tobacco and alcohol as risk factors for pancreatic cancer. Best Pract Res Clin Gastroenterol. 2017;31(5):529-36. doi: https://doi.org/10.1016/j.bpg.2017.09.001

17. Jayasekara H, English DR, Hodge AM, et al. Lifetime alcohol intake and pancreatic cancer incidence and survival: findings from the Melbourne Collaborative Cohort Study. Cancer Causes Control. 2019;30(4):323-31. doi: https://doi.org/10.1007/s10552-019-01146-6

18. Walling A, Freelove R. Pancreatitis and pancreatic cancer. Prim Care. 2017;44(4):609-20. doi: https://doi.org/10.1016/j.pop.2017.07.004

19. Song TJ, Seo DW, Lakhtakia S, et al. Initial experience of EUS-guided radiofrequency ablation of unresectable pancreatic cancer. Gastrointest Endosc. 2016;83(2):440-3. doi: https://doi.org/10.1016/j.gie.2015.08.048

20. Dreyer SB, Jamieson NB, Upstill-Goddard R, et al. Defining the molecular pathology of pancreatic body and tail adenocarcinoma. Br J Surg. 2018;105(2):e183-e191. doi: https://doi.org/10.1002/bjs.10772

21. van Erning FN, Mackay TM, van der Geest LGM, et al. Association of the location of pancreatic ductal adenocarcinoma (head, body, tail) with tumor stage, treatment, and survival: a population-based analysis. Acta Oncol. 2018;57(12):1655-62. doi: https://doi.org/10.1080/0284186X.2018.1518593

22. Kanno A, Masamune A, Hanada K, et al. Multicenter study of early pancreatic cancer in Japan. Pancreatology. 2018;18(1):61-7. doi: https://doi.org/10.1016/j.pan.2017.11.007

23. Walter FM, Mills K, Mendonça SC, et al. Symptoms and patient factors associated with diagnostic intervals for pancreatic cancer (SYMPTOM pancreatic study): a prospective cohort study. Lancet Gastroenterol Hepatol. 2016;1(4):298-306. doi: https://doi.org/10.1016/S2468-1253(16)30079-6

24. Reddy S, Cameron JL, Scudiere J, et al. Surgical Management of Solid-Pseudopapillary Neoplasms of the Pancreas (Franz or Hamoudi Tumors): a large single-institutional series. J Am Coll Surg. 2009;208(5):950-7. doi: https://doi.org/10.1016/j.jamcollsurg.2009.01.044

25. Adamska A, Domenichini A, Falasca M. Pancreatic ductal adenocarcinoma: current and evolving therapies. Int J Mol Sci. 2017;18(7):1338. doi: https://doi.org/10.3390/ijms18071338

26. Zhang Q, Zeng L, Chen Y, et al. Pancreatic cancer epidemiology, detection, and management. Gastroenterol Res Pract. 2016;2016:8962321. doi: https://doi.org/10.1155/2016/8962321

27. Visentin A, Mantovani MF, Kalinke LP, et al. Palliative therapy in adults with cancer: a cross-sectional study. Rev Bras Enferm. 2018;71(2):252-8. doi: https://doi.org/10.1590/0034-7167-2016-0563

28. Kasuga A, Hamamoto Y, Takeuchi A, et al. Positive relationship between subsequent chemotherapy and overall survival in pancreatic cancer: meta-analysis of postprogression survival for first-line chemotherapy. Cancer Chemother Pharmacol. 2017;79(3):595-602. doi: https://doi.org/10.1007/s00280-017-3263-3

29. Espindola LMD, Mota A, Gomes EAP, et al. Sobrevida em dois anos de pacientes acometidos por câncer de pâncreas e os fatores associados. ACM Arq Catarin Med [Internet]. 2013 [acesso 2020 set 14];42(2)62-9.

Available from: http://www.acm.org.br/acm/revista/pdf/artigos/1230.pdf

30. Togashi Y, Shitara K, Nishikawa H. Regulatory T cells in cancer immunosuppression - implications for anticancer therapy. Nat Rev Clin Oncol. 2019;16(16):356-71. doi: https://doi.org/10.1038/s41571-019-0175-7

31. Almeida RVS, Pacheco-JR AM, Silva RA, et al. Angiolymphatic invasion as a prognostic fator in resected N0 pancreatic adenocarcinoma. ABCD Arq Bras Cir Dig. 2017;30(1):42-46. doi: https://doi.org/10.1590/0102-6720201700010012