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The Current Status of Pancreatic Cancer in Tunisia

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Abstract

Background: Few studies have investigated pancreatic cancer in Tunisia and there are no reported survival data. The aim of this study was to analyze the epidemiologic profile, treatment modalities, and survival and prognostic factors of patients with pancreatic cancer in Tunisia.

Method: In this retrospective study, we included patients treated between 2001 and 2016 for a histologically proven pancreatic cancer in the Department of Medical Oncology in Tunisia.

Results: We examined 130 patients with a median age of 58.7 years and a sex ratio of 1.8. Thirty percent had surgery for a localized disease. Among resected patients, 14% received adjuvant chemotherapy. 14.5% of the patients with borderline resectable tumors underwent induction chemotherapy without leading to surgery. Palliative chemotherapy was administrated for unresectable locally advanced (14%) and metastatic (41.5%) tumors. Median overall survival for localized, locally advanced, and metastatic disease was 20.5, 10.4, and 6.3 months, respectively. Independent prognostic factors were female gender, performance status, tumor localization, and chemotherapy.

Conclusions: Unlike what was published in the literature, patients in our study were younger and there was a male predominance. Survival rates were low even for localized stages. Treatment strategy, chemotherapy protocols, survival, and prognostic factors were in line with the literature.

Keywords: Pancreatic neoplasms, Epidemiology, Therapeutics, Prognosis

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Introduction

Pancreatic cancers are among the most important unsolved health problems worldwide;[1] they are the fourth cause of cancer-related death in both sexes,[2,3] and rank eleventh in incidence.[4-6] In developed countries, pancreatic cancer is also one of the leading causes of cancer mortality.[7] Prognosis is very poor. The estimated five-year survival rate for pancreatic cancer is 5-9%.[4,8,9]

With a life expectancy of ~5% at five years, the prognosis of this cancer has not improved over the past 20 years, and incidence and mortality rates are very similar. Surgical resection is the only potentially curative treatment of pancreatic adenocarcinoma. However, at diagnosis, less than 20% of patients have a resectable tumor. Among the validated drugs for pancreatic cancer, there is currently no relevant biomarker used in medical decision-making and none should be employed in clinical practice. Few studies have investigated pancreatic cancer in Tunisia and there are no reported survival data.

The objective of our study was to report the epidemiologic profile of patients with pancreatic cancer in Tunisia in order to analyze treatment modalities and identify prognostic factors in Tunisian patients.

Materials and Methods

This is a retrospective study conducted from January 2001 to December 2016 in the Department of Medical Oncology in Farhat Hached University Hospital in Tunisia. We included all patients with localized, locally advanced, and metastatic histologically proven pancreatic cancer.

The following characteristics or results were

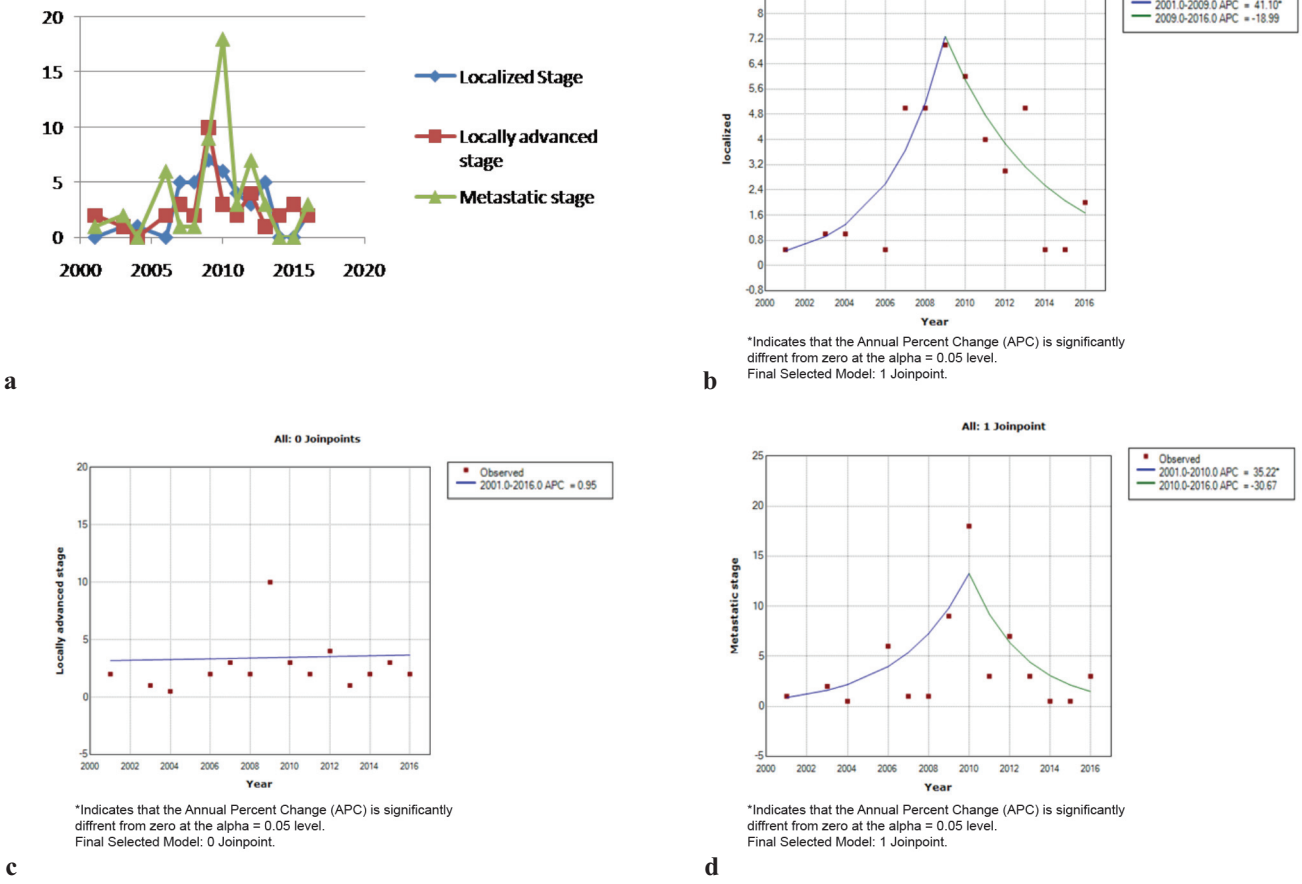

Figure 1. The time trend of pancreatic cancer in our center according to the stage of the disease (a) and for localized stage (b), locally advanced stage (c), and metastatic stage (d), separately.

recorded for each patient: medical history, physical examination, and computed tomography of the thorax, abdomen, and pelvic cavity. We further recorded the treatment modality of each patient and calculated the overall survival (OS) from the date of diagnosis.

We estimated OS using the Kaplan–Meier method. The effects of different variables on OS were assessed by a univariate analysis using the log-rank test and a multivariate analysis using a Cox proportional hazards model. The statistical level of significance was defined as *P* less than 0.05.

For the trend study, we used the Joinpoint software version 4.7.0.0. This software offers the closest possible regression model related to different points and gives an annual percentage change (APC) with a 95% confidence interval.

Results

Epidemiological and anatomoclinical characteristics

From January 2001 to December 2016, 130 patients were treated for pancreatic cancer in the Department of Medical Oncology in Tunisia. There was an increase of the incidence of pancreatic cancer in our center. The annual change percentage was 2.31(*P*=0.7). Table 1 summarizes the characteristics of patients and tumor.

Mean age at diagnosis was 58.7 years with extremes ranging from 32 to 81 years. There was a male predominance (85 men and 45 women) with a sex ratio of 1.8.

A family history of cancer was observed in 4% of the patients. 38.5% of patients had diabetes, 10% were obese, and 2% had a chronic pancreatitis. Smoking and alcohol consumption were noted in 39% and 20% of patients, respectively.

In our series, the most common complaints at diagnosis were abdominal pain (38%) and jaundice (33%). Tumors were mainly located in the head of the pancreas (59%). 30 % of the patients had a localized tumor, 28.5% patients had a locally advanced disease, and 41.5% were metastatic at diagnosis. The liver was the main site of metastases (64%).

The study of the trend (Figure 1) showed that between 2001 and 2016, the incidence trend of localized and metastatic stages was significantly upward from 2001 to 2009 (*P*<0.05), and then, downward from 2009 to 2016 (*P*=0.1). Concerning locally advanced stages, the trend was stable from 2001 to 2016 (APC=0.9, [-10.9;11.4], *P*=0.9).

Table 1. Characteristics of patients with pancreatic cancer in the Department of Medical) oncology in Tunisia

Characteristics	Number of patients (%)
Risk factors studied	
Family history of cancer	5(4)
Diabetes	50(38.5)
Obesity	13(10)
Chronic pancreatitis	3(2)
Smoking	51(39)
Alcohol consumption	26(20)
Clinical complaints	
Abdominal pain	49(38)
Jaundice	43(33)
Epigastric pain	23(17)
General state alteration	14(11)
Fortuitous discovery by imagery	1(1)
Tumour localization	
Head	77(59)
Body	31(24)
Tail	22(17)
Stage	
Localized	39(30)
Locally advanced	37(28.5)
Borderline resectable	19
Unresectable	18
Metastatic	54(41.5)
Metastatic sites	
Hepatic	36(64)
Pulmonary	4(7)
Peritonea	3(5)
Hepatic and peritonea	6(11)
Hepatic and pulmonary	6(11)
Others	2(7)

Treatment modalities, survival, and prognostic factors

39 patients (30%) underwent surgery. Among these patients, 14% (n=18) had curative surgery with adjuvant chemotherapy and 16% (n=21) had only surgery. We performed complete resection R0 in 30 cases (23%).

Table 2. First line chemotherapy protocols and the response rate of pancreatic cancer patients in Tunisia

First line chemotherapy protocols	Number of patients (%)
Gemcitabine monotherapy	45 (54)
Gemcitabince –Cisplatin	19 (23)
5FU-Leucovorin-Cisplatin	15 (18)
Oxaliplatine based protocols (Gemcitabine-Oxaliplatine , Capeciabine-Oxaliplatine , FOLFOX)	4 (5)
Type of response following first line chemotherapy	**Number of patients (%)**
Stability	13 (16)
Partial Response	12 (14)
Progression	58 (70)

The most commonly used protocol at the adjuvant setting was 5FU-leucovorin (57%) followed by gemcitabine monotherapy (19%).

Relapse rate following curative surgery was 27 % with a mean relapse time of 12.6 months.

19 patients (15%) with borderline resectable tumors underwent induction chemotherapy. None of these patients was made resectable. Gemcitabine-Cisplatin was the main protocol of induction chemotherapy in our patients (85%).

We found locally advanced unresectable tumors in 14% (n=18) and metastatic disease in 41.5% (n= 54) cases. 52% of cases (n=68) had palliative chemotherapy, while 11 patients were unfit for chemotherapy and only received best supportive care.

Table 2 summarizes the chemotherapy protocols used in the palliative setting and the type of response.

Response rates after first- and second-line chemotherapy were 14% and 11 %, respectively (Table 3).

Median OS was 6 months (figure 2a) and median progression-free survival (PFS) was 4 months (Figure 2b).

Five-year survival rate was 10%. Median OS of localized, locally advanced, and metastatic disease were 20.5, 10.4, and 6.3 months, respectively.

In univariate analysis, prognostic factors significantly related to better survival rates (Table

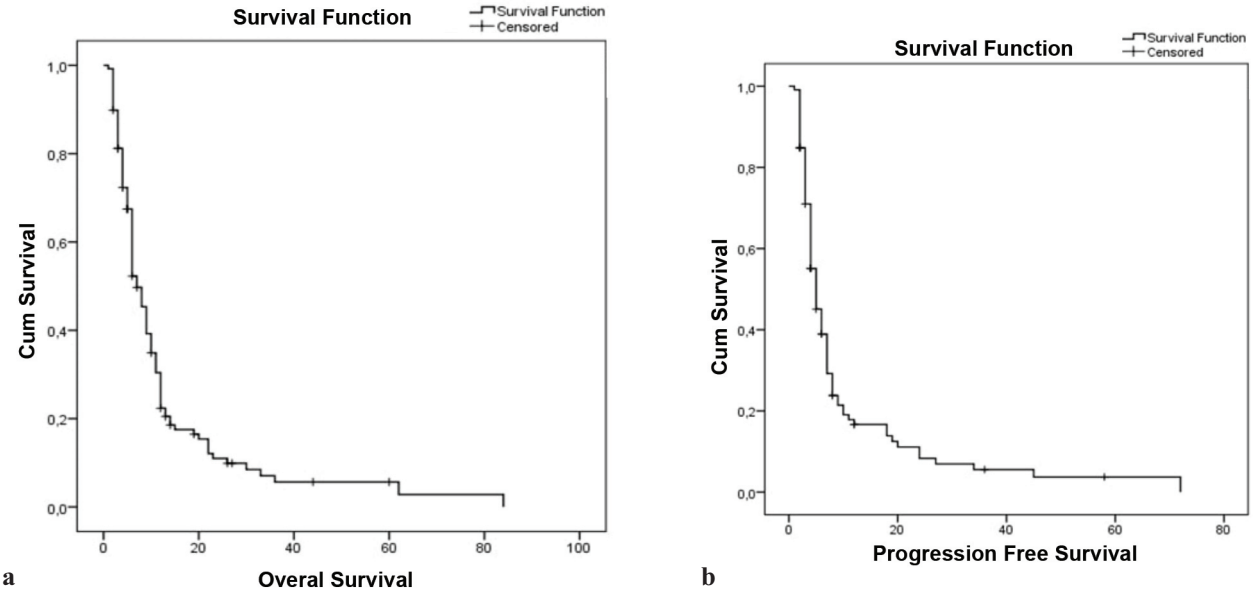

Figure 2. (a) Overall survival of 130 patients with pancreatic cancer i the department of medical oncology in Tunisi, (b) The progression free survival of 130 patients with pancreatic cancer in the department of medical oncology in Tunisia.

Table 3. Second-line chemotherapy protocols and the response rate of pancreatic cancer patients in Tunisia

Second line chemotherapy protocols	Number of patients (%)
Gemcitabine monotherapy	4(22)
5FU-Leucovorin	4(22)
5FU-Leucovorin-Cisplatin	4(22)
FOLFOX	3(17)
Other protocol (FOLFIRI- Capecitabine)	3(17)
Type of response after second line chemotherapy	**Number of patients (%)**
Stability	5(28)
Partial Response	2(11)
Progression	11(61)

4) were: female gender (P=0.013), performance status ECOG (0-1) (P<0.0001), location of tumor in the head of the pancreas (P=0.054), localized stage at diagnosis (P<0.0001), curative surgery (P<0.0001), adjuvant chemotherapy (P<0.0001), and palliative chemotherapy (P<0.0001).

Prognostic factors significantly related to better survival rates with multivariate analysis (Figure 3) were: female gender (P=0.008), performance status ECOG (0-1) (P=0.001), localization of tumor (P<0.001), and chemotherapy (P<0.001).

Discussion

Epidemiological and anatomoclinical characteristics

We observed well-known risk factors for pancreatic cancer (smoking, diabetes) in almost half of our patients, while pancreatitis existed in only 2% of the cases.[10-13]

Pancreatic cancers rarely occur prior to 40 years of age; over 80% of these cancers develop between the ages of 60 and 80 years.[12] Patients in our series were younger than what was published in the literature (mean age of 58.7 years) and other countries of northern Africa.[14,15]

There was a male predominance in our patients; whereas, in the literature, pancreatic cancer equally affected men and women.[14]

Almost all pancreatic cancers are adenocarcinomas of the ductal epithelium and symptoms are usually caused by mass effect. The clinical features are dependent on the size, location, and metastases of the tumor.[15] As in our patients, jaundice and abdominal pains are the most prevalent symptoms of pancreatic cancer.

Treatment and outcome

Surgical resection is the only potentially curative treatment of pancreatic adenocarcinoma. However, at diagnosis, less than 20% of patients have a resectable tumor.[16] The main goal of surgery is to achieve negative (R0) resection margins. Patients with borderline resectable tumors have a high probability of R1 resection and, as such, should not be considered as good candidates for upfront surgery.[17] Patients with locally advanced or metastatic disease are to be considered as having unresectable tumors.[17]

Adjuvant chemotherapy with gemcitabine or 5 FU has enhanced the OS of patients with resectable pancreatic cancer. In 2017, a phase III ESPAC-4 study showed an increase in OS at 28 months versus 25.5 months with gemcitabine plus capecitabine versus gemcitabine alone.[18] A phase III study PRODIGE 24 compared gemcitabine to modified FOLFIRINOX (FFX) for six months and reported improvement in PFS (median: 21.6 vs. 12.8 months) and OS (median: 54.4 vs. 35 months) in good performance status patients ECOG(0-1) without diarrhea or cardiac contraindication to 5-FU.[19]

Regarding borderline resectable tumors, chemotherapy with G nab-paclitaxel (G-nab) and FFX were effective treatments in the phase III trial of Junko Tahara et al. with a disease control rate of 86.7% in the G-nab group and 75% in the FFX group. 20 Median OS time was 8.9 months in the FFX group and 11.8 months in the G-nab

group.

It is not a rule to conduct secondary resection for locally advanced pancreatic cancer following "induction" chemotherapy; however, it may be considered in certain favorable cases.

Data has shown that single-agent chemotherapy with gemcitabine is the reference for locally advanced and metastatic tumors;[17] moreover, it was the most commonly used protocol in our patients.

In palliative settings, the use of gemcitabine at first-line therapy has a 12-month survival advantage and improves or stabilizes pain, performance status, and weight compared with fluorouracil monotherapy.[21]

In 2011, a phase III PRODIGE-4 / ACCORD-11 study demonstrated the superiority of FFX regimen compared to gemcitabine (median OS: 11.1 vs 6.8 months) in patients under 75 years old with performance status ECOG(0-1) and bilirubin upper 1.5 limit of normal.[22] More adverse events were observed in the FFX group, with 5.4% of patients developing neutropenia with fever. The modified FFX appears to result in a better tolerant profile and efficacy in view of retrospective studies.[23]

In the present study, we employed gemcitabine in 54% of the patients, but progression was noted in 70%.

Following progression under a first line of chemotherapy, about half of the patients with metastatic pancreatic cancer were fit to receive one or more line(s) of palliative chemotherapy.[24]

After progression with gemcitabine, the

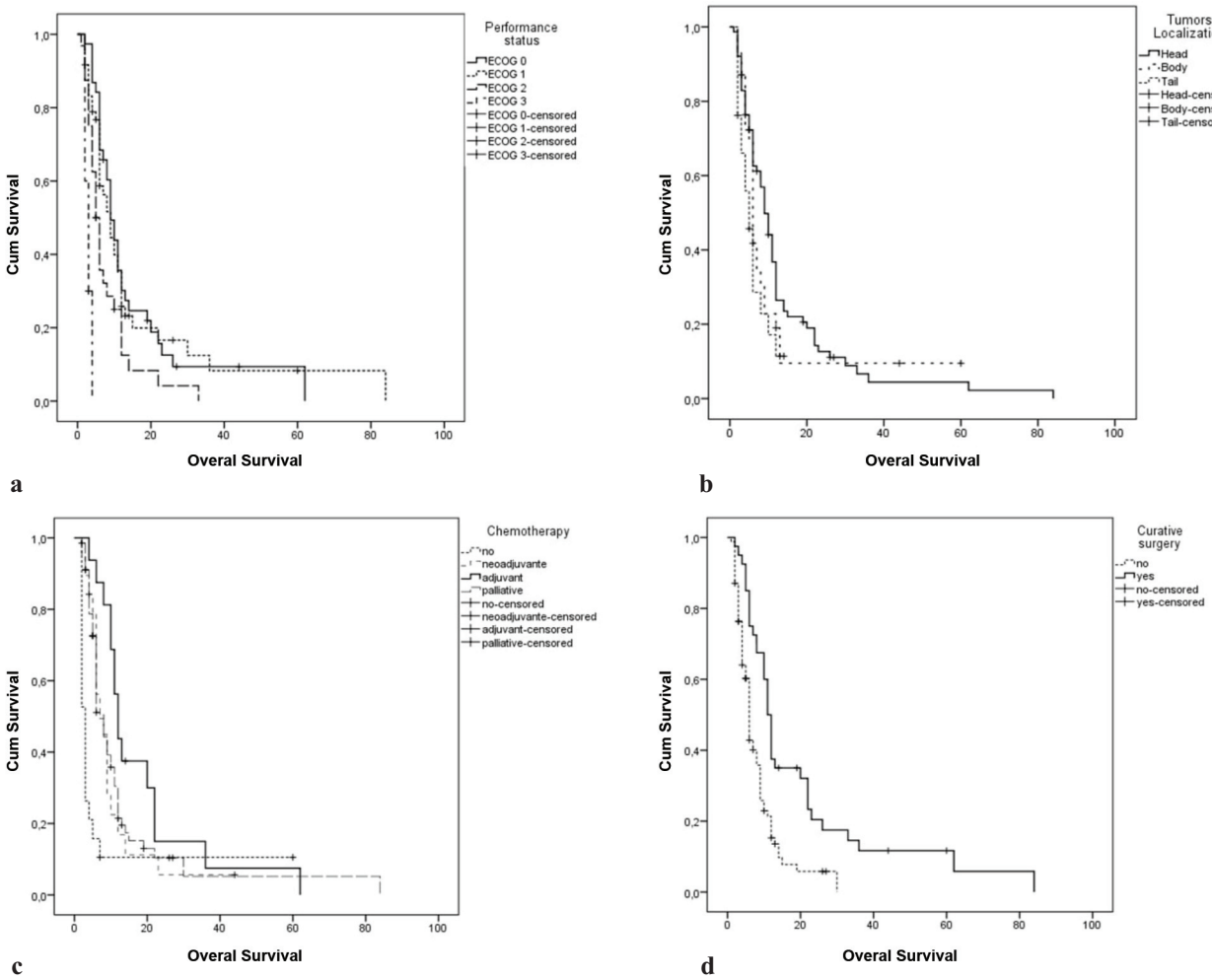

Figure 3. The overall survival of the 130 patients with pancreatic cancer according to independent prognostic factors: performance status (a), tumor localization (b), chemotherapy (c), and curative surgery (d).

Table 4. Univariate and multivariate analysis of prognostic factors related to pancreatic cancer patients in Tunisia

Univariate analysis of prognostic factors	***P***
Female gender	0.013
WHO (0-1)	<0.000
Localization of tumor in the head of the pancreas	0.054
Localized stage at diagnosis	<0.0001
Curative surgery	<0.0001
Adjuvant chemotherapy	<0.0001
Palliative chemotherapy	<0.0001
Multivariate analysis of prognostic factors	
Female gender	0.008
WHO (0-1)	0.001
Localization of tumor	<0.001
Chemotherapy	<0.001

combinations of 5-FU with platinum (oxaliplatin or cisplatin) or irinotecan (standard or nanoliposomal (Nal-IRI) form) were mainly studied.

The combination of nal-IRI (MM-398) with 5-FU and folic acid(AF) showed enhancement in OS (median: 6.1 vs. 4.2 months, *P*= 0.012) compared with 5- FU / AF alone in a phase III study (NAPOLI-1).[25] In our series, in second-line chemotherapy, patients mainly received gemcitabine, 5FU-leucovorin, and 5FU-leucovorin-cisplatin with a median OS of six months.

Five-year OS of our patients is in line with the literature. A retrospective cohort study in the AC Camargo Cancer Center showed higher median OS: 35.4, 14.1, and 9.3 months for resectable, unresectable locally advanced, and metastatic pancreatic cancer, respectively.[26]

As observed in the present study, advanced stage is an important prognostic factor in patients with pancreatic cancer.[27-30] Lymph node invasion also influenced patient survival.[2,27]

Contrary to the study done by Renata D'Alpino Peixoto et al., female gender was correlated with a significantly better OS in our study.[33]

Furthermore, tumor localization was an independent prognostic factor in the present research. Few studies have investigated the prognostic significance of tumor localization in pancreatic cancer patients with no current consensus.[32,34]

Sezgin et al. demonstrated that performance status was the only independent prognostic factor for OS in patients with advanced pancreatic cancer. [35] A good performance status ECOG (0-1) was a prognostic factor associated with better survival in our study.

Park et al. analysed 340 patients with pancreatic cancer: 141 were in stage III and 199 were in stage IV.[31] In line with the present study, a univariate analysis showed that chemotherapy was a significant prognostic indicator for OS in stage III patients compared to patients only receiving supportive care.

Conclusion

Pancreatic cancer is still one of the deadliest tumors. Our study showed that smoking, diabetes, obesity, alcohol consumption, and chronic pancreatitis might be associated with an increased risk of pancreatic cancer. Contrary to what was published in the literature, patients in the current study were younger and there was a male predominance. Treatment strategy, chemotherapy protocols, and survival and prognostic factors were consistent with the literature. Progress in the management of pancreatic cancer has been limited to multiagent chemotherapy regimens offering a relatively short survival advantage. Accordingly, there is an urgent need for innovative research to improve survival.

Conflict of Interest

None declared.

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