Pancreatic cancer in Saudi patients treated at tertiary institution

Ten years retrospective study

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ABSTRACT

الأهداف: وصف ظهور والسيطرة والنتائج وتحديد العوامل المنذرة لسرطان البنكرياس.

الطريقة: أجريت دراسة استعادية للمرضى الذين تم تشخيصهم بسرطان البنكرياس في مدينة الملك عبدالعزيز، الرياض، المملكة العربية السعودية خلال الفترة من يناير 2000م حتى ديسمبر 2010م. أجري اختبارات وصفية على البيانات وتقدير البقاء كما أجري تحليل الانحدار المتعدد والمفرد.

النتائج: تمت مراجعة السجلات الطبية لعدد 179 مريض. بلغ وسيط العمر 63 عام من 96–15 عام وبلغ عدد الذكور 116 (64%) من المرضى. كان البقاء للعام الأول 39% ولخمسة أعوام بلغ 10%. والوسيط العام للبقاء كان 6.9 شهر. أما التنبؤات المهمة فاشتملت على مايلي: العمر عند التشخيص، والدرجة، والمرحلة T،N، M ، TNM، والمرحلة المجتمعة، ومكان الورم، ومضاد السرطان المضغي، ومضاد الكربوهيدرات، والجراحة، والعلاج الجراحي والكيماوي وذلك في تحليل خطورة انحدار كوكس الجزئي الأحادي. واشتمل نموذج الانحدار المتعدد على جميع التنبؤات المهمة. والعوامل المهمة فهي العمر عند التشخيص ومرحلة M.

خاتمة: تم تشخيص مرضانا بعمر مبكر وكان فترة البقاء لمدة 5 أعوام أعلى من الدول الأخرى الأمر الذي يستحق المزيد من الدراسات. يعد العمر ومرحلة المرض عوامل مستقلة للعيش لدى مرضانا.

Objectives: To describe presentation, management, and outcome, and determine prognostic factors for pancreatic cancer patients.

Methods: A retrospective review of patients diagnosed with pancreatic cancer at King Abdulaziz Medical City, Riyadh, Saudi Arabia during the period from January 2000 to December 2010. Descriptive statistics were conducted on the collected data and survival was estimated using the Kaplan Meier estimate. Univariate and multiple regression analyses were carried out.

Results: The medical records of 179 patients were reviewed. The patients' median age was 63 years ranging from 15-96 years, and 116 (64.8%) of them were male. The one-year survival rate was 39% and the 5-year survival was 10%. The median overall survival (OS) was 6.9 months. Age at diagnosis, grade, T stage, N stage, M stage, TNM stage group, and the combined stage group (stage III/IV versus others), site of distant metastasis, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9, surgery and chemotherapy were significant predictors for OS on an univariate Cox proportional hazards regression analysis. A multiple regression model including all the significant predictors was conducted. Age at the time of diagnosis and M stage were significant variables.

Conclusion: Our patients present at a younger age and have better 5-year survival compared with the United States Surveillance Epidemiology and End Results data, which deserves further evaluation. Age and disease stage were identified as independent prognostic factors for survival in this patient population.

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Carcinoma of the pancreas is a fatal gastrointestinal cancer as it is the fourth leading cause of cancer deaths in the United States of America (USA).[1] In 2012, estimated 43,920 new patients will develop pancreatic cancer in USA and it is estimated to cause 37,390 deaths accounting 6% of cancer deaths in men and 7% of cancer deaths in women.[1] Incidence of pancreatic cancer is 12% in USA,[2] and has been increasing by 0.8% per year in men and by 1% per year in women since 1998.[3] The survival of patients with pancreatic cancer depends on several factors, but it is improving over time.[1] For all stages combined the one and 5-year relative survival rates are 26% and 6%, respectively.[3] Prognostic factors should be considered in management and discussion on the outcome of the disease.[4] Many studies were conducted to identify the prognostic factors of pancreatic cancer with different stages and treatment strategies, which has shown variable results, and factors.[4-6] In Saudi Arabia, pancreatic cancer represents 1.75% of all cancers with 1585 registered cases from 1994 to 2007 accounting 2.5% for males and 1.1% for females of all types of cancer[7] and it is the fifth most prevalent gastrointestinal cancer among Saudis.[8] There is a lack of studies on the presentation and survival of patients with pancreatic cancer in Saudi Arabia. This study aims to describe the demographics, tumor characteristics and treatment modalities and to assess the outcome and the prognostic factors for patients with pancreatic cancer treated at tertiary cancer center in Saudi Arabia.

Methods. A retrospective study was conducted at King Abdulaziz Medical City in Riyadh, Saudi Arabia in 2011. The Cancer Center at King Abdulaziz Medical City is a tertiary care center providing multidisciplinary care to cancer patients from all over Saudi Arabia. Medical records of all patients who were diagnosed with pancreatic cancer from January 2000 to December 2010, and treated at King Abdulaziz Medical City were reviewed. Patients who were treated outside the center were excluded. Data was collected using custom designed data abstraction forms. Data collected included demographic data (age, gender, nationality, and address), disease characteristics (including medical history, features of the disease at the time of presentation, histological and radiological features of the tumor including AJCC cancer stage[9] and grade of the tumor), laboratory results at baseline, treatment strategies, disease outcome using revised response evaluation criteria in solid tumors (RECIST) guideline (Version 1.1),[10] and vital status of the patient. Overall survival (OS) was calculated from the date of initial diagnosis to date of death for any cause or date of last contact. Patients who were alive at the last contact were censored at the last contact date. Analysis was carried out using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Descriptive analyses such as demographics and the disease characteristics were carried out and presented as frequency counts and percentages. The survival analysis was carried out using the Kaplan-Meier survival estimate. Several potential predictors for OS based on the literature review of MEDLINE database and available data were obtained and their association with the OS of the patients was tested using univariate Cox proportional hazards regression models and reported as Hazard ratio (HR) with 95% confidence interval (CI). Predictors found to be significant in the univariate models were tested in a multiple regression analysis model to determine their association with OS. A P value of ≤0.05 was considered statistically significant in this study.

This study was approved by the Institutional Review Board at King Abdullah International Medical Research Center in Riyadh and confidentiality of data was maintained throughout the study.

Results. One hundred and seventy-nine patients (n=179) with pancreatic cancer were included in the study with median age 63 years (range 15-96 years). Other demographic characteristics of patients are shown in **Table 1**. Disease features and treatment modalities are shown in **Table 2 and Table 3**.

Chemotherapy was administered to approximately 33% of the patients. Gemcitabine was the most commonly used agent (59%) followed by capecitabine (12%) and cisplatin (8%). Out of the 106 patients who did not take chemotherapy, it was contraindicated in 22% due to presence of other patient risk factors such as co-morbid conditions and advanced age. Other noted reasons for not taking chemotherapy included patient refusal and patient death before planned chemotherapy. The 1-year survival rate was 39% and the 5-year survival was 10%. Median OS since diagnosis was 6.9 months [95% CI, 4.6-9.7 months] **Figure 1**.

The results of the univariate Cox proportional hazards analysis using OS as the outcome are shown in **Table 4**. A multiple regression model incorporating all

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Table 1 - Demographic characteristics of patients with pancreatic cancer with median age of 63 years (N=179).

Characteristic	Frequency	(%)
Gender		
Male	116	(64.8)
Female	63	(35.2)
Smoking history		
Never	124	(69.3)
Current or former	29	(16.2)
Unknown	26	(14.5)
Alcohol history		
Never	142	(79.3)
Current or former	2	(1.1)
Unknown	35	(19.6)
Family history of cancer		
Yes	2	(1.1)
No	89	(49.7)
Unknown	88	(49.2)
History of diabetes mellitus		
Yes	103	(57.5)
No	73	(40.8)
Unknown	3	(1.7)
History of pancreatitis		
Yes	15	(8.4)
No	136	(76.0)
Unknown	28	(15.6)

the significant predictors was conducted and the results are shown in **Table 5**.

Discussion. Al-Radi et al[8] have reported the presentation of patients with pancreatic cancer in western region of Saudi Arabia at mean age 62±14 years. Similar to the data from Saudi Cancer Registry,[7] which has shown that pancreatic cancer in Saudi Arabia has the highest incidence at the age from 60-74 years and ranks the 8th most incident cancer in males at this age group. These figures are similar to the age figure in our study. Compared to the median age of 72 years in United State,[2] our patients present at approximately 9 years younger median age. This may be attributed to overall younger population pool in Kingdom of Saudi Arabia or may be due to different biology of the cancer. The younger age presentation is not exclusive for pancreatic cancer in Saudi Arabia but is similar to other cancers such as colorectal cancer[11] and breast cancer[12] which are the most prevalent cancers in males and females respectively.[7] This is an intriguing finding that warrants further exploration.

Most of our patients present with abdominal pain at diagnosis. Only 16 % present with jaundice, which may prolong the interval between the onset of symptoms and the treatment as reported in the literature.[13] The delay in presentation may result in more advanced stage at diagnosis. Most of our patients present at advanced stage. Sixty-six percent of our patients present with distant metastasis compared to 53% in United State of America.[3] Considering that most of our patients present with distant metastasis, approximately 37% of them underwent surgical resection which is greater than other international numbers where only less than 20% undergo surgical treatment.[14] On the other hand, 45% of patients underwent palliation with biliary stent placement, which is the main goal of treatment at this stage.[15] Despite the advanced presentation, our patients have a better 1 and 5 years survival compared to United State which are 26% and 6%, respectively[3] which may be explained by the younger age of our patients or the

Table 2 - Presentation and tumor characteristics.

Variable	Frequency	(%)
Symptoms at presentation		
Abdominal pain	70	(39.1)
Jaundice	28	(15.6)
Weight loss	29	(16.2)
Ascites	1	(0.6)
Other	28	(15.6)
Unknown	23	(12.9)
Site of primary tumor		
Head of pancreas	122	(68.2)
Body of pancreas	27	(15.1)
Tail of pancreas	14	(7.8)
Unknown	16	(8.9)
Histopathology		
Adenocarcinoma	120	(67.0)
Adenosquamous carcinoma	1	(0.6)
Mucinous carcinoma	10	(5.6)
Acinar cell adenocarcinoma	1	(0.6)
Neuroendocrine tumor	12	(6.7)
Other	4	(2.2)
Unknown	31	(17.3)
Grade		
Well	20	(11.2)
Moderate	47	(26.3)
Poor	21	(11.7)
Unknown	91	(50.8)
T stage		
Tx	29	(16.2)
T0	0	(0.0)
Tis	0	(0.0)
T1	9	(5.0)
T2	31	(17.3)
T3	46	(25.2)
T4	64	(35.8)
N Stage		
Nx	46	(25.7)
N0	31	(17.3)
N1	102	(57.0)
M Stage		
Mx	1	(0.6)
M0	60	(33.5)
M1	118	(65.9)
TNM stage		
Stage 0	0	(0.0)
Stage IA	5	(2.8)
Stage IB	11	(6.2)
Stage IIA	8	(4.5)
Stage IIB	17	(9.5)
Stage III	16	(8.9)
Stage IV	118	(65.9)
Unknown	4	(2.2)
Combined stage group		
<Stage III	41	(22.9)
Stage III/IV	134	(74.7)
Unknown	4	(2.2)

TNM - classification of malignant tumors

Table 3 - Treatment modalities.

Modality	Frequency	(%)
Biliary stent placement		
Yes	80	(44.7)
No	86	(48.0)
Unknown	13	(7.3)
Surgery		
Yes	67	(37.4)
No	112	(62.6)
Radiation		
Yes	9	(5.0)
No	167	(93.3)
Unknown	3	(1.7)
Chemotherapy		
Yes	59	(30.0)
No	106	(59.2)
Unknown	14	(7.8)

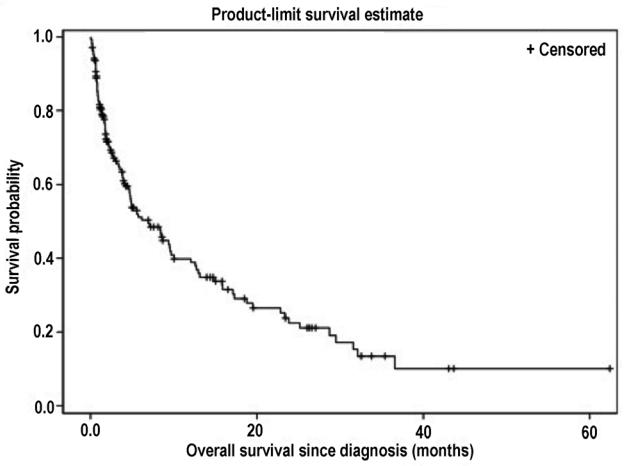

Figure 1 - Median overall survival since diagnosis was 6.9 months (95% confidence interval, 4.6-9.7 months).

different disease biology. Similar to other studies,[5,16] we found that age and tumor characteristics affect the survival. Specifically, we found that advancing of the age, advancing of the grade (differentiation), abdominal lymph node and liver metastasis were all associated with poorer survival. High laboratory levels of tumor markers CA19-9 and CEA were also significantly associated with poorer survival. We also found that survival was significantly poorer in patients who did not receive surgery or chemotherapy treatment, which may reflect the poor condition of the patients at presentation. Early individual T, N and M stages, and combined TNM stage groups were all associated with better survival compared to advanced stages. Unlike other studies which reported laboratory markers such as CA19-9[16,17] and medical and surgical treatment[4,5,16] to be independent prognostic factors, we only found that age at time of diagnosis and disease stage to be the only

Table 4 - Univariate analysis of overall survival.

Univariate analysis	Hazard ratio	95% confidence interval	*P*-value
Age at time of diagnosis	1.03	1.01-1.04	0.0015
Grade			
Moderate versus well differentiated	2.17	1.07-4.41	0.0319
Poor versus well differentiated	2.84	1.28-6.31	0.0104
T stage			
T1 versus TX	0.20	0.06-0.69	0.0108
T2 versus TX	0.28	0.14-0.57	0.0004
T3 versus TX	0.48	0.27-0.84	0.0110
T4 versus TX	0.41	0.24-0.71	0.0013
N stage			
N0 versus NX	0.19	0.09-0.38	<0.0001
N1 versus NX	0.49	0.32-0.77	0.0019
M stage			
M0 versus M1	0.42	0.27-0.65	0.0001
TNM stage			
IA versus IV	0.13	0.02-0.93	0.0422
IB versus IV	0.26	0.10-0.66	0.0044
III versus IV	0.43	0.21-0.87	0.0182
Combined stages groups			
<III/IV versus Stage III/IV	0.48	0.29-0.78	0.0031
Site of distant metastasis			
Liver versus Others	3.19	1.96-5.19	<0.0001
Abdominal lymph nodes versus Others	5.95	1.99-17.8	0.0014
Carcinoembryonic antigen			
≥75th percentile versus <75th percentile	2.52	1.32-4.79	0.0051
Carbohydrate antigen 19-9			
≥75th percentile versus 75th percentile	2.64	1.36-5.14	0.0043
Surgery			
No versus Yes	2.53	1.65-3.88	<0.0001
Chemotherapy			
No versus Yes	1.971	1.227-3.17	0.0051

Table 5 - Final Cox proportional hazards model predicting overall survival.

Variables	Hazard ratio	95% Confidence Interval	*P*-value
Age at time of diagnosis			
Old versus Young	1.051	1.007-1.097	0.0241
Stage			
≤Stage III versus Stage IV	0.004	0.000-0.181	0.0043

independent prognostic factors for overall survival in our study, which is supported by other similar studies.[4,6]

This study was limited by being a retrospective in nature, including a relatively small number of subjects and representing the experience of a single cancer institution. Further larger scale prospective studies are recommended to study the epidemiology and the genetic basis of this disease in the region.

In conclusion, our patients present at younger age compared to the United States Surveillance

Epidemiology and End Results (SEER) data (72 years), similar to other cancers in the region, which warrants further exploration. Furthermore, our patients have better 5-years survival compared to (U.S. SEER) data (5.6%), which may be a result of younger age of our patients' population or different tumor biology. Age and disease stage were identified as independent prognostic factors for overall survival in patients with pancreatic cancer.

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