

Clinical Outcome of Exocrine Pancreatic Adenocarcinoma: A Single Center Experience

Suzy F. Gohar¹, Fawzy Megahid², Mahmoud Rizk², Zeinab A. Kasemy³, Tamer Y. Barsoom⁴

¹Clinical Oncology Department, Faculty of Medicine, Menoufia University, Shebin El-Kom, Egypt; ²Internal Medicine Department, Faculty of Medicine, Benha University, Benha, Egypt; ³Public Health and Community Medicine Department, Faculty of Medicine, Menoufia University, Shebin El-Kom, Egypt; ⁴Internal Medicine Department, Benha Teaching Hospital, Benha, Egypt.

Background: Pancreatic carcinoma is an uncommon tumor with a high mortality rate. Because of the late presentation of the disease, only a small percent of patients are candidate for surgery.

Aim: To assess the epidemiology and the clinical outcome of patients diagnosed with pancreatic adenocarcinoma presented to the Clinical Oncology Department at Menoufia University.

Methods: All patients presenting with exocrine pancreatic carcinoma from January 2007 to December 2011 were included. Epidemiological features of patients and their treatment details and outcome were collected retrospectively from the medical records. An equal number of matched controls were interviewed and filled a questionnaire to identify possible risk factors.

Results: Exocrine pancreatic adenocarcinoma represented 1.4 % of all cancer patients treated at our institution. The study included 76 patients and 76 controls. Pancreatic cancer patients were significantly more likely to be overweight when compared to controls (OR= 2.51, 95% CI: 1.04-6.06). Diabetes mellitus and smoking were significantly more prevalent among patients (OR= 2.36, 95% CI: 1.23-4.54; OR= 2, 95% CI: 1.05-3.81; respectively). The median time to progression was 12 weeks (95% CI: 9.46-14.53) and the median overall survival was 16 weeks (95% CI: 12.22-19.78). Patients with earlier tumor stage and those who underwent surgery followed by adjuvant chemotherapy had significantly better overall survival (p=0.02 and <0.001, respectively).

Conclusion: Exocrine pancreatic adenocarcinoma is an uncommon tumor among cancer patients treated at the Clinical Oncology Department of Menoufia University. Diabetes mellitus, higher body mass index and smoking are significantly more prevalent in pancreatic carcinoma patients. Earlier tumor stage and undergoing surgery followed by chemotherapy are associated with statistically significant better overall survival.

Keywords: Pancreatic adenocarcinoma, Epidemiology, Survival

Corresponding author: Suzy Gohar, MD; Clinical Oncology Department, Faculty of medicine, Menoufia University, Shebin El-Kom, Egypt ; Email: Suzygohar@gmail.com

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INTRODUCTION

Ductal adenocarcinoma of the pancreas ranks as the fourth leading cause of cancer related deaths in western countries¹. In Arab countries, the incidence of pancreatic cancer is generally low². It represents the tenth most common cancer in men. It also represents the fourth leading cause of cancer-related deaths in both men and women. Pancreatic adenocarcinoma incidence is higher in men than women and the mean age at diagnosis is 70 years³. Most pancreatic tumors are located in the head of pancreas (47-65%), followed by the body and tail (15-18%)⁴. Tobacco smoking, diabetes mellitus, obesity, heavy alcohol drinking, family history, certain genetic polymorphisms, and chronic pancreatitis have been considered as risk factors for pancreatic adenocarcinoma⁵.

Surgical resection remains the only potentially curative treatment. Unfortunately, < 20% of patients present with resectable disease and 45% present with overtly metastatic disease⁶. Despite the introduction of adjuvant chemotherapy in patients with resectable disease and the development of novel chemotherapeutic agents in patients with advanced disease, prognosis remains poor¹.

Pancreatic carcinoma has one of the highest mortality-to-incidence ratios of any cancer⁷. This is because many patients do not experience symptoms until the disease is in an advanced stage, leading to delay in initiation of treatment⁸. Late presentation, tumor aggressiveness, difficult surgical resection, and availability of few effective systemic therapies contribute to the poor clinical outcome of pancreatic adenocarcinoma⁹.

Egypt, as in many other developing countries, has little countrywide descriptive epidemiology about cancer including exocrine pancreatic adenocarcinoma. The aim of this study was to assess the clinical and epidemiological characteristics of patients diagnosed with pancreatic adenocarcinoma at Menoufia University and to identify possible risk factors for pancreatic cancer.

METHODS

The study was carried out as a part of an institutional project to study the epidemiological and clinical features of cancers of gastrointestinal tract, breast, lung and female genital tract and lymphomas. The first part of the study was a case-control analysis to determine possible risk

factors for pancreatic cancer. The second part described the management and treatment outcome of cases.

We reviewed the medical data of pancreatic cancer patients presented to the Clinical Oncology Department, Faculty of Medicine, Menoufia University, from January 2007 to December 2011. The epidemiological data collected were age, sex, body mass index (BMI), smoking history, family history of cancer, diabetes mellitus, performance status, and presenting complaint. Tumor features were also recorded including site in the pancreas, stage, site and number of metastases, baseline level of tumor markers cancer antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) and treatment given.

To study possible risk factors, an equal number of matched controls from the general population were included in the study. A clear explanation of the research objectives and procedures was provided to controls. After obtaining an oral informed consent, the controls were subjected to a questionnaire that included data about their epidemiological features. This questionnaire was designed by the authors and was reviewed by three professional doctors in the departments of Public health and Community Medicine and Clinical Oncology. Patients having history of other malignancies were excluded. The studied risk factors included age, sex, BMI, smoking,

positive family history of cancer pancreas, positive family history of other tumors, chronic alcoholism and personal history of diabetes mellitus.

Time to progression (TTP) was calculated from the date of starting treatment until disease progression in the form of local recurrence, development of new distant metastases or increase in size and/or number of metastases. Overall survival (OS) was calculated from the date of start of treatment until the date of patient's death. Response to treatment was assessed according to revised Response Evaluation Criteria In Solid Tumors (RECIST) guidelines, version 1.1¹⁰.

The study proposal was approved by the Ethics Committee of the Faculty of Medicine - Menoufia University and the Clinical Oncology Department.

The SPSS 16 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Descriptive statistics were used to present the distribution of demographic and clinical characteristics. The Chi-square and fisher's exact tests were used for qualitative data. *t*, Mann-Whitney and Kruskal-Wallis tests were used to test the difference in quantitative data. The odds ratio (OR) and 95% confidence intervals (CI) were calculated. P value less than 0.05 was considered statistically significant.

Table 1: Epidemiological characteristics of patients and controls

	Patients (n=76)	Controls (n=76)	χ^2	p value	OR (95% CI)
	No (%)	No (%)			
Age					
≤50	17 (22.4)	18(23.7)			Ref
>50	59 (30.3)	58(76.3)	0.04	0.837	1.08 (0.51-2.29)
Sex					
Female	23 (30.3)	26 (34.2)			Ref
Male	53 (69.7)	50 (65.8)	0.27	0.602	1.20 (0.61-2.37)
Body mass index					
Normal	51 (67.1)	64 (84.2)			Ref
Underweight	3 (3.9)	2 (2.6)	0.47	0.656	1.80 (0.30-11.70)
Overweight	18 (23.7)	9 (11.8)	4.36	0.036	2.51 (1.04-6.06)
Obese	4 (5.3)	1 (1.3)	2.45	0.177	5.02 (0.54-46.31)
Smoking					
No	31 (40.8)	44 (57.9)			Ref
Yes	45 (59.2)	32 (42.1)	4.45	0.034	2 (1.05-3.81)
Diabetes mellitus					
No	27 (35.5)	43 (56.6)			Ref
Yes	49 (64.5)	33 (43.4)	6.78	0.009	2.36 (1.23-4.54)
Family history of cancer other than pancreatic					
No	68 (89.5)	69 (90.8)			Ref
Yes	8 (10.5)	7 (9.2)	0.07	0.785	1.16 (0.4-3.37)
Presenting symptom					
Jaundice	16 (21.1)				
Abdominal pain	57 (75)				
Dyspepsia	2 (2.6)				
Vomiting	1 (1.3)				
ECOG* performance scale					
≤2	47 (61.8)				
>2	29 (38.2)				

OR: Odds ratio; ECOG: Eastern Cooperative Oncology Group

RESULTS

Out of 5625 patients treated at the Clinical Oncology Department of Menoufia University, only 76 patients were diagnosed with exocrine pancreatic adenocarcinoma representing 1.35% of the total patients.

Table 1 illustrates the characteristics of cases and controls. The age of patients ranged between 35 and 76 and the mean was 59.27 ± 9.26 . Cases and controls were similar in age and sex. Pancreatic cancer patients were significantly more likely to be overweight, smokers and diabetic. Only 8 (10.5%) patients and seven (9.2 %) controls had positive family history of cancers other than pancreatic adenocarcinoma e.g. breast, colon and lung cancers and lymphoma. Neither patients nor controls had history of chronic alcoholism or family history of cancer pancreas.

Tumor characteristics and treatment delivered are summarized in table 2. Head of pancreas was the most common site of the tumor and patients frequently presented in an advanced stage IV disease. Liver was the most frequent site of metastases in almost two-thirds of patients. The most common presenting symptom was abdominal pain. Patients with an Eastern Cooperative Oncology Group performance status 4 (22.4% of patients) and those who experienced treatment failure were treated by best supportive care. Only 11 (14.5%) patients underwent surgery as the primary treatment modality. Fifty-nine (77.3%) patients received chemotherapy either as an adjuvant (14.5%), palliative (53.9%) or neo-adjuvant (9.2%) treatment. Gemcitabine was used as single agent in 52 (68.4%) patients or in combination with carboplatin in 7 (9.2 %) as neoadjuvant in patients with good performance status. Only 15 (19.7%) patients completed the scheduled chemotherapy regimen (2 neoadjuvant, 7 adjuvant and 6 palliative). Forty-four patients did not complete the scheduled treatment either because of disease progression (29, 38.1%) or severe treatment related toxicity (15, 19.7%) in the form of hematological toxicities or drug induced liver cell failure.

The TTP and OS are shown in tables 3 and 4. The one-year survival rate was 0%. Time to progression correlated significantly with the stage of the disease, number of metastatic sites and treatment modality. Patients with advanced stage, 2 or more metastatic sites and inability to undergo surgery as part of their treatment had shorter TTP. Time to progression according to the treatment modality is illustrated in Figure 1.

Patients with earlier stage non-metastatic disease and those who underwent surgery had significantly better OS than others (table 4). Overall survival according to the treatment modality is illustrated in Figure 2. The longest OS was for patients who underwent surgery followed by adjuvant chemotherapy.

DISCUSSION

Pancreatic adenocarcinoma is a public health problem as it remains a fatal disease with poor prognosis and represents the 4th cause of cancer related deaths worldwide ^{11,12}. Risk factors for pancreatic cancer include older age, tobacco smoking, personal history of chronic

pancreatitis, long-term diabetes mellitus, non-O ABO blood group, obesity, and family history of pancreatic cancer ⁷. Surgery is the only curative treatment for pancreatic cancer. However, unfortunately, the majority of pancreatic cancer patients are diagnosed at an advanced stage where only 10%-15% of them are candidate for curative resection. This is reflected on the OS which is less than 5% ¹¹.

Generally the characteristics of our patients are largely similar to that observed in other studies. The age of pancreatic cancer patients varied between studies. The mean age of our patients was 59 years, which is similar to that reported by Vasen et al and Tas et al (58 years) ^{13, 14}. Other studies reported higher average age, e.g. Liszka et al (67.1 years) and Worni et al (67.4 years) ^{15, 16}.

Table 2: Tumor characteristics and treatment (76 pts)

	No.	%
Site of the tumor within pancreas		
Head	63	82.9
Body	9	11.8
Tail	2	2.6
Head and body	2	2.6
Tumor stage		
I	5	6.6
II	12	15.8
III	8	10.5
IV	51	67.1
Metastases		
Present	51	67.1
Absent	25	32.9
Site of metastases		
Liver	51	67.1
Lung	13	17.1
Bone	9	11.8
Brain	1	1.3
Number of metastases (51 pts)		
1	30	39.5
2	19	37.3
3	2	3.9
CEA		
Normal	61	80.3
Elevated	15	19.7
CA 19-9		
Normal	51	67.1
Elevated	25	32.9
Surgery		
Yes	18	23.3
No	58	76.7
Treatment plan		
Palliative chemotherapy	41	53.9
Best supportive care	17	22.4
Surgery + adjuvant chemotherapy	11	14.5
Neo-adjuvant chemotherapy + surgery	7	9.2
Completed chemotherapy schedule		
Yes	15	19.7
No	44	57.9

Table 3: Time to progression according to patients' and tumor characteristics

	Time to progression in weeks				Log rank	p value
	Mean		Median			
	Estimated	95% CI	Estimated	95% CI		
Overall	16.97	13.53-20.41	12	9.46-14.53		
Age						
≤50	19.05	11.79-26.32	16	9.37-22.62	0.2	0.65
>50	16.37	12.44-20.3	11	8.26-13.73		
Sex						
Male	17.74	13.66-21.82	12	9.97-14.02	0.22	0.63
Female	15.19	8.7-21.69	8	5.65-10.34		
Body mass index						
Underweight	7.66	3.38-11.95	6	4.4-7.6	3.61	0.3
Normal	15.86	11.74-19.97	11	7.82-14.17		
Overweight	21	13.5-28.49	12	3.68-20.31		
Obese	20	0.31-39.68	12	0-24.74		
Site in pancreas						
Head	16.82	12.97-20.67	11	8.4-13.59	2.25	0.52
Body	13.33	4.74-21.92	8	2.15-13.84		
Tail	35	9.52-60.48	22	--		
Head and body	20	12.16-27.84	16	--		
Tumor stage						
I	49.2	42.15-56.24	48	41.55-54.44	23.39	<0.001
II	25.08	14.46-35.7	12	0.96-23.03		
III	10.75	3.24-3.24	6	1.97-10.02		
IV	12.88	9.96-9.96	9	6.45-11.54		
Metastases						
Present	12.88	9.96-15.8	9	6.45-11.54	12.41	<0.001
Absent	25.32	17.65-32.98	22	11.39-32.6		
Number of metastases sites						
0	25.32	17.65-32.98	22	11.39-32.6	14.41	0.002
1	11.25	8.34-14.15	9	6.32-11.67		
2	14.07	7.99-20.16	8	5.89-10.1		
3	26	22.08-29.92	24	--		
CEA						
Normal	17.49	13.47-21.5	12	4.9-14.51	0.55	0.45
Elevated	14.86	8.64-21.09	11	6.26-15.73		
CA-19.9						
Normal	16.56	12.73-20.4	12	9.02-14.97	0.24	0.61
Elevated	17.8	10.76-24.83	11	6.1-15.89		
Surgery						
Yes	31.31	21.78-40.83	40	8.88-71.11	16.71	<0.001
No	13.15	10.27-16.02	9	6.72-11.27		
Treatment						
Best supportive care	19.7	10.08-19.32	12	0-24.1	10.06	0.01
Surgery + adjuvant chemotherapy	29.62	19.35-39.91	40	10.81-60.18		
Palliative chemotherapy	13.19	9.93-16.45	9	6.49-11.5		
Neoadjuvant chemotherapy + surgery	12.57	4.57-20.57	10	0-20.26		

Table 4: Overall survival according to patients' and tumor characteristics

	Overall survival in weeks				Log rank	P value
	Mean		Median			
	Estimated	95% CI	Estimated	95% CI		
Overall	22.49	17.83-27.16	16	12.22-19.78		
Age						
≤50	23.58	15.9-31.27	22	12.31-31.68	0.81	0.36
>50	21.41	16.91-26.64	14	10.52-17.47		
Sex						
Male	23.25	17.72-28.78	16	10.91-21.08	0.3	0.58
Female	18.91	11.91-25.9	12	4.17-19.82		
Body mass index						
Underweight	9.33	5.69-12.97	8	6.4-9.6	4.57	0.2
Normal	20.99	15.65-26.32	16	9.8-22.19		
Overweight	24.94	16.59-33.29	16	4.91-27.08		
Obese	22.5	4.89-40.1	14	0-29.68		
Site in pancreas						
Head	22.25	16.99-27.51	15	11.66-18.33	2.37	0.49
Body	17.27	7.97-26.58	13	1.31-24.68		
Tail	36.5	19.17-53.82	24	--		
Head and body	30	26.08-33.92	28	--		
Tumor stage						
I	53.8	43.81-63.79	not reached		7.05	0.02
II	29.7	18.94-40.47	25	4.63-45.36		
III	16.33	12.91-19.75	13	9.18-16.81		
IV	13.25	4.21-22.28	8	2.63-13.36		
Metastases						
Present	16.33	12.91-19.75	13	9.18-16.81	9.59	0.002
Absent	33.78	23.48-44.07	25	5.41-44.58		
Number of metastases sites						
0	33.78	23.48-44.07	25	5.41-44.58	11.41	0.01
1	29.5	28.52-30.48	29	--		
2	17.68	11.12-24.24	16	6.15-25.84		
3	14.5	10.8-18.19	12	9.87-14.12		
CEA						
Normal	23.41	17.83-28.98	16	11.65-20.34	0.63	0.42
Elevated	18.76	12.25-25.27	16	9.68-22.31		
CA-19.9						
Normal	20.92	16.54-25.29	16	11.33-20.66	0.01	0.9
Elevated	22.34	13.35-31.32	12	7.13-16.86		
Surgery						
Yes	41.9	29.37-54.43	44	6.76-81.24	13.22	<0.001
No	16.56	13.19-19.94	12	7.25-16.74		
Treatment						
Best supportive care	15.28	5.58-24.98	12	1.73-22.26	9.51	0.02
Surgery + adjuvant chemotherapy	35.27	25.27-45.27	44	20.26-67.73		
Palliative chemotherapy	16.73	12.96-20.5	14	10.23-17.76		
Neoadjuvant chemotherapy +	25.44	13.11-37.76	13	0-34.51		

Also, Fest et al who reported in his work a mean age of 77.3 years at diagnosis and Sellam et al reported a mean age of 63.1 years^{17, 18}. Similar to the findings of other studies¹⁶⁻¹⁸, our patients were predominantly males. Other pancreatic malignancies may be more common in females, like mucinous cystadenocarcinoma¹⁹. The most common patients' complaint was abdominal pain (75% of patients) which is comparable to that reported by Lakatos et al²⁰.

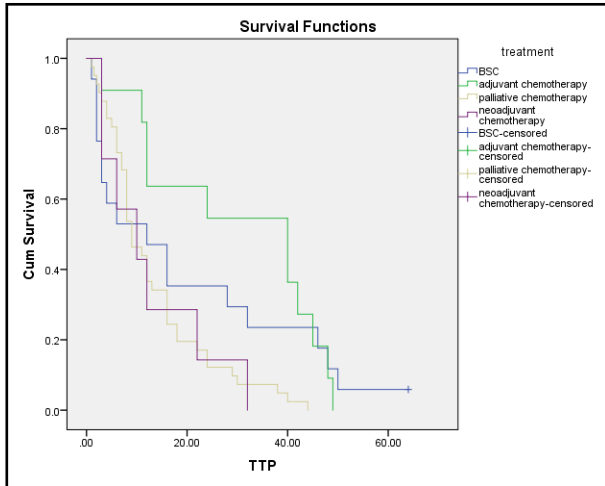


Figure 1: Relation between time to progression and treatment modalities

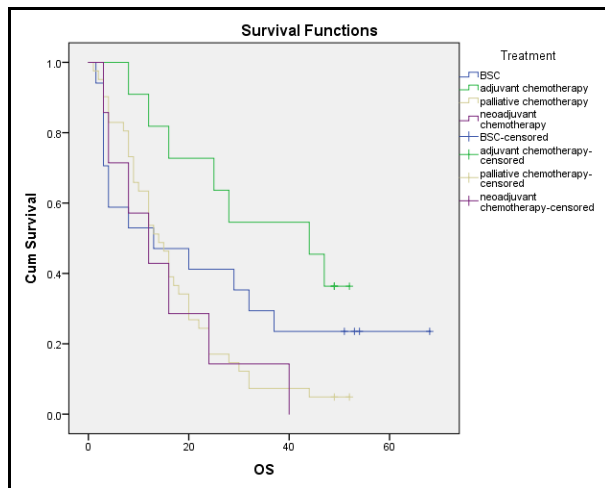


Figure 2: Relation between overall survival and treatment modalities

Stage IV disease was the most common stage representing 67% of patients with the liver being the most common site of metastases. This confirms the late presentation of pancreatic cancer and agrees with the finding of Lakatos et al²⁰. Only 18 (23.3%) patients underwent radical surgery which is explained by late and advanced presentation in most of cases. Furthermore, unfortunately, most (59.7%) of the patients did not complete their planned schedule of chemotherapy especially those with metastatic disease. The cause is not clear as most of these patients died before radiological evaluation is available.

In the current work, median TTP and OS were 12 and 16 weeks, respectively, which is shorter than that reported by the SEER data²². Lakatos et al reported a median

survival of about 8.7 months²⁰. The shorter survival of our patients may be related to a more advanced stage at presentation and a higher incidence of liver involvement with hepatic decompensation. On the other hand, Fest et al reported a median survival of 71 days which is shorter than that reported in our study¹⁷.

There was no statistically significant relation between both age and gender and survival. Mishra et al found that younger age and female gender were associated with better prognosis²³. In contrast to that, Tas et al, Worni et al, Gong et al and Luo et al found that shorter survival was associated with older age at diagnosis and male sex^{14, 16, 24, 25}.

In the current study, base line patient's performance status, tumor site in the pancreas and CA19-9 level did not correlate significantly with survival. However, in other studies, survival differed significantly according to these variables. Krishnan et al and Tas et al reported that patients with bad performance status experienced poor prognosis^{14, 26}. Worni et al and Artinyan et al found that tumor location in the pancreatic body/tail is associated with poor survival^{16, 27}. Tas et al found a statistically significant relation between survival and elevated tumor markers¹⁴.

Time to progression and OS differed significantly according to the tumor stage. This is similar to the results of Mishra et al and Luo et al studies, where earlier stage was associated with better OS^{23, 25}. When we compared between stage IV patients and all other stages together, we found that the presence of metastases has statistically significant relation with both TTP and OS. In contrast to that, Gong et al and Luo et al found that the presence of metastases is correlated with TTP but not OS^{24, 25}. A statistically significant relation between OS and TTP and adjuvant chemotherapy was documented in our study and is similar to the results of Stark et al²⁸.

Conclusion

Exocrine pancreatic adenocarcinoma is an uncommon tumor among cancer patients treated at the Clinical Oncology Department of Menoufia University. The results of the current study confirm that diabetes mellitus, higher body mass index and smoking are risk factors for pancreatic adenocarcinoma. Non-metastatic earlier stage and undergoing surgery followed by chemotherapy are associated with statistically significant better TTP and OS.

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