

Higher overall survival in metastatic pancreatic cancer: the impact of where and how treatment is delivered

Maior sobrevida global em pacientes com câncer pancreático metastático: o impacto de onde e como o tratamento é realizado

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ABSTRACT

Objective: To determine the overall survival of patients with advanced pancreatic cancer and evaluate factors that impact prognosis in a private cancer center. **Methods:** Data from the Hospital Cancer Registry at *Hospital Israelita Albert Einstein* were retrospectively collected. The patients enrolled had metastatic cancer at diagnosis or earlier staging and subsequent recurrence. Cases of neuroendocrine tumors were excluded. **Results:** A total of 65 patients were evaluated, including 63 with adenocarcinoma. The median overall survival for patients in all stages was 20.7 months (95%CI: 15.6-25.7), while the overall survival of metastatic disease was 13.3 months. Among the 33 cases with stage IV cancer, there was no evidence of a statistically significant association between median survival and CA19-9 dosage ($p=0.212$), tumor location ($p=0.482$), first treatment performed ($p=0.337$), lymphovascular invasion ($p=0.286$), and age ($p=0.152$). However, the number of lines of chemotherapy was significantly associated with survival (\log -rank $p=0.013$), with an estimated median survival of 10.2 months for patients who received up to two lines of treatment and 23.5 months for those receiving more than two lines of chemotherapy. **Conclusion:** The survival of patients treated was longer than that reported in the literature. The only statistically significant factor related to increased survival was higher number of lines of chemotherapy received. We believe that the higher socioeconomic status of patients surveyed in this study, as well as their greater access to treatment options, may have influenced their overall survival.

Keywords: Adenocarcinoma/drug therapy; Pancreatic neoplasms; Survivorship (Public Health)

RESUMO

Objetivo: Determinar a sobrevida global dos pacientes com câncer pancreático avançado e avaliar fatores com impacto prognóstico em um centro de câncer privado. **Métodos:** Foram coletados retrospectivamente os dados do Registro de Câncer do Hospital Israelita Albert Einstein. Os pacientes incluídos apresentaram câncer metastático ao diagnóstico ou em estágio mais precoce com recorrência subsequente. Os casos de tumores neuroendócrinos foram excluídos. **Resultados:** Foram avaliados 65 pacientes, incluindo 63 com adenocarcinoma. A sobrevida global mediana dos pacientes em todos os estádios foi 20,7 meses (IC95%: 15,6-25,7), enquanto a sobrevida global de doença metastática foi de 13,3 meses. Entre os 33 casos com câncer em estágio IV, não houve evidência de associação estatisticamente significativa entre a sobrevida mediana e CA19-9 ao diagnóstico ($p=0,212$), localização do tumor ($p=0,482$), primeiro tratamento realizado ($p=0,337$), invasão vasculo-linfática ($p=0,286$) e idade ($p=0,152$). No entanto, o número de linhas de quimioterapia foi significativamente associado com a sobrevida (\log -rank $p=0,013$), com uma sobrevida mediana estimada de 10,2 meses para os pacientes que receberam até duas linhas de tratamento e de 23,5 meses para os que receberam mais de duas linhas. **Conclusão:** A sobrevida dos pacientes tratados foi maior do que o relatado na literatura. O único fator estatisticamente significativo relacionado à maior sobrevida foi maior número de linhas de quimioterapia recebidas. Acreditamos que o nível socioeconômico dos pacientes pesquisados neste estudo, assim como seu maior acesso a opções de tratamento, pode ter influenciado em sua sobrevivência global.

Descritores: Adenocarcinoma/quimioterapia; Neoplasias pancreáticas; Sobrevida (Saúde Pública)

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INTRODUCTION

Pancreatic cancer is one of the most lethal malignancies worldwide, and ranks fourth in the total number of deaths related to cancer in patients of both genders. In 2013, the United States registered about 45 thousand new cases, and reported that the number of expected deaths was very similar to the number of new cases. The median overall survival at 5 years is between 2 and 6%.⁽¹⁾

Adenocarcinoma of the pancreas is the most common type of pancreatic neoplasm, with all of its subtypes accounting for 85% of cases.⁽¹⁾

Currently, curative treatment is only possible in cases of resectable disease and during the initial stages.⁽²⁾ Although complete surgical resection is the only potential curative approach of this disease, it can only be performed in 10 to 20% of patients, since most individuals present with advanced disease upon diagnosis.^(2,3) After surgical resection, 7 to 25% of patients have a 5-year survival rate,⁽²⁾ with better results in individuals who undergo curative resection (R0).⁽⁴⁾

Several factors are associated with poor prognosis after surgery with complete resection, such as levels of carbohydrate antigen 19-9 (CA19-9) at diagnosis, perineural invasion and tumor size.⁽⁵⁾

The median survival of patients with locally advanced disease is approximately 6 to 11 months.⁽²⁾ In cases of metastatic disease, chemotherapy increases overall survival and improves symptoms.⁽⁶⁻⁸⁾ The longest gain in median overall survival reported in the metastatic setting was 11.1 months, which was achieved with the combination of fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) treatment.⁽⁹⁾

Currently, easy access to all treatment modalities and to new combinations of chemotherapeutic drugs is considered an important factor that interferes in patient survival. Therefore, differences across services often lead to diverse prognoses for this disease.

OBJECTIVE

This study aimed to determine the overall survival of patients with advanced pancreatic cancer in *Hospital Israelita Albert Einstein*, and evaluate possible factors that impact the prognosis of the disease.

METHODS

Data were retrospectively collected from the Hospital Cancer Registry at *Hospital Israelita Albert Einstein* from the period between January 2007 and December 2013. Staging was determined based on the American

Joint Committee on Cancer (AJCC)⁽¹⁰⁾ classification. Age, sex, tumor location, histopathological features, first treatment, surgery, date and site of recurrence or progression in case of metastatic disease, proposed treatment at relapse and number of lines of treatment received were obtained from patient's medical records. The site of recurrence was obtained by imaging method chosen by the professional who attended the patient. The median survival was calculated for the period between the time of diagnosis and February 12, 2014, according to cancer stage. Finally, we calculated the median survival according to tumor location, lymphovascular and perineural invasion, level of CA19-9 marker at diagnosis, and number of lines of treatment, among others.

The median survival was estimated using the Kaplan-Meier method. The analysis of factors associated with survival of stage-IV patients was made by means of analysis of variance with log-rank tests and a Cox proportional hazards model.

Analyses were performed with the Statistical Package for the Social Science (SPSS) software version 17.0, and a 95% confidence interval (95%CI) and a 5% significance level were determined.

The study was approved by the Research Ethics Committee under register no. 687.990 and CAAE: 32349914.2.0000.0071

RESULTS

A total of 146 cases of pancreatic cancer were identified, and patients in stages I, II and III who did not have tumor recurrences were excluded. Those suffering from neuroendocrine tumors were also excluded. Therefore, our final group consisted of 65 patients in all stages, including metastatic (stage IV). The final analysis included 43 deaths. The median age for all patients was 66 years and most were males (62%). The most common histological type was adenocarcinoma, representing 97% of cases. Half of the patients were stage IV at diagnosis and the majority had high CA19-9; only 15% of patients had CA19-9 within the normal range at diagnosis. As expected, the liver was the organ most frequently affected by metastasis among these patients. Chemotherapy alone was used as an initial treatment regimen in 50% of patients and most patients underwent only the first-line of treatment (53%), while another 12% underwent more than three lines of chemotherapy. Radiotherapy was used in 14% of cases with recurrence (nine patients). Other patient characteristics can be found in appendix 1.

Median overall survival for patients in all stages was 20.7 months (95%CI: 15.6-25.7) (Table 1).

We found no evidence of an association between patient death and serum CA19.9 ($p=0.212$), tumor

location ($p=0.482$), first treatment performed ($p=0.337$), site of metastasis ($p=0.197$), lymphovascular invasion ($p=0.286$), age ($p=0.152$) and number of metastases ($p=0.961$). We were unable to evaluate the relationship between survival and stromal reaction, since no stage-IV patient in our group had this condition (Table 2).

The only variable associated with survival in our group of patients was the number of lines of chemotherapy taken: the median survival was 10.2 months among patients with up to two lines of treatment and 23.5 months for patients with more than two lines of chemotherapy (log-rank $p=0.013$).

Relative to patients who underwent more than two lines of chemotherapy, the risk ratio estimated with the Cox model was 4.42 (95%CI: 1.25-15.55).

Table 1. Survival according to cancer staging

Stage	n	Events (n)	Censored patients n (%)	Median survival (months)	95%CI	
					Lower limit	Upper limit
II	23	10	13 (56.5)	31.3	1.7	61.0
III	9	5	4 (44.4)	25.7	15.6	35.8
IV	33	28	5 (15.2)	13.3	6.3	20.2
Total	65	43	22 (33.8)	20.7	15.6	25.7

95%CI: 95% confidence interval.

Table 2. Analysis of factors associated with death

	n	Events (n)	Censored patients n (%)	Median survival (months)	95%CI		Log-rank p
					Lower limit	Upper limit	
Level of carbohydrate antigen 19-9							
<59 x ULN	13	11	2 (15.4)	17.5	7.2	27.8	0.212
≥59 x ULN	10	9	1 (10.0)	6.8	1.1	12.5	
Normal	10	8	2 (20.0)	13.3	6.1	20.4	
Pancreatic tumor site							
Head	19	15	4 (21.1)	15.6	6.1	25.0	0.482
Body	6	5	1 (16.7)	7.6	0.0	22.1	
Tail	8	8	0	10.2	9.2	11.3	
First treatment							
Surgery	2	2	0	7.6	--	--	0.337
Chemotherapy	30	25	5 (16.7)	15.6	4.0	27.1	
Chemo + radiotherapy	1	1	0	9.6	--	--	
Site of metastasis							
Liver	20	18	2 (10)	10.2	7.2	13.2	0.197
Other	13	10	3 (23.1)	15.6	6.1	25.0	
Lymphovascular invasion							
Yes	2	2	0	7.6	--	--	0.286
No	31	26	5 (16.1)	15.6	6.3	24.8	
Stromal reaction							
No	33	28	5 (15.2)	13.3	6.3	20.2	--
Number of chemotherapy lines							
Up to 2	26	22	4 (15.4)	10.2	6.2	14.2	0.013
More than 2	7	6	1 (14.3)	23.5	10.8	36.2	
Age							
<65	12	8	4 (33.3)	20.4	0.0	44.5	0.152
≥65	21	20	1 (4.8)	11.0	6.4	15.5	
Number of metastases							
Up to 2	28	23	5 (17.9)	11.0	6.2	15.8	0.961
More than 2	5	5	0	17.9	1.3	34.5	

95%CI: confidence interval 95%CI; ULN: upper limit of the normal range.

DISCUSSION

The overall median survival of patients surveyed in this review was 20.7 months, which included patients in all stages of pancreatic cancer. The overall median survival for stage IV patients (metastatic disease at diagnosis) was 13.3 months.

According to the data validation of the 6th edition of staging of the AJCC, the median survival of patients in all stages of pancreatic adenocarcinoma (including patients undergoing pancreatectomy) was 12.6 months.⁽¹⁰⁾ In cases of stage IV at diagnosis, median survival was 2.5 months.

This difference in median survival may be related to many factors. It is known that treatment outcome in pancreatic cancer does not only depend on the chemotherapy regimen used, but also on the nature of the primary tumor and the surgery performed.⁽²⁾ In addition, most patients have multiple comorbidities that are also related to the epidemiology of cancer itself, such as smoking, obesity, diabetes and older age.^(11,12)

Other variables known to influence treatment outcome include socioeconomic and performance status. A survey of more than 20 thousand cases of pancreatic cancer, conducted in California, revealed that race and socioeconomic background were related to differences in treatment and survival, with less favored economic groups having lower survival rates.⁽¹³⁾

The cases surveyed in our study were being treated in a private oncology referral center, with full access to modern chemotherapy regimens and procedures, such as prosthetics and surgery, and this may partly explain the difference in the results obtained.

Performance status is also a limiting factor for the onset and maintenance of systemic treatment. The vast majority of studies using first-line chemotherapy include only patients with good functional status, *i.e.*, an Eastern Cooperative Oncology Group (ECOG) performance status 0-1 and a Karnofsky performance scale (KPS) >70.^(7,9,14)

The only factor associated with better survival in our analysis was the number of lines of chemotherapy used, in which using more than two lines was associated with significantly better survival (23.5 months *versus* 10.2 months; $p=0.013$). We cannot exclude the possibility that patients who underwent more lines of treatment had better functional status at diagnosis.

The CA19-9 levels at diagnosis were used as an independent factor of poor prognosis in pancreatic cancer in several studies.⁽¹⁵⁻¹⁷⁾ However, in our study, we did not observe this pattern of association.

The same poor prognosis was associated with lymphovascular^(18,19) and perineural invasion,⁽²⁰⁻²²⁾ but we

were not able to collect enough pathological data from our patients to evaluate these variables.

CONCLUSION

In the group of patients studied at our private institution, we found better overall survival in patients with advanced scenario that reported in the literature. We did not find associations between prognosis and several variables that have previously been reported. One possible explanation could be the greater amount of resources available to these patients relative to the general population.

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Appendix 1. Demographic characteristics of patients

Characteristic	n=66	Stage, n (%)	
Age, years		IB	1 (2.0)
Median	66	IIA	10 (15.0)
Range	29-85	IIB	12 (18.0)
Age, n (%)		III	8 (12.0)
≥65	37 (56.0)	IV	33 (50.0)
<65	29 (44.0)	Unknown	2 (3.0)
Sex, n (%)		Primary therapy, n (%)	
Male	41 (62.0)	Chemotherapy	33 (50.0)
Female	25 (38.0)	Chemotherapy and radiotherapy	4 (6.0)
Pancreatic tumor location, n (%)		Radiotherapy	2 (3.0)
Head	37 (56.0)	Surgery	27 (41.0)
Body	11 (17.0)	Measurable metastatic sites, n patients/total - (%)	
Tail	12 (18.0)	Liver	31/71 (44.0)
Unknown	6 (9.0)	Peritoneal	25/71 (35.0)
Level of carbohydrate antigen 19-9, n (%)		Lung	4/71 (06.0)
Normal:	10 (15.0)	Other	11/71 (15.0)
Elevated, <59 x ULN	34 (52.0)	Metastatic sites involved, n (%)	
Elevated, ≥59 x ULN	12 (18.0)	0	9 (14.0)
Unknown	10 (15.0)	1	45 (68.0)
Histologic type, n (%)		2	11 (17.0)
Adenocarcinoma	64 (97.0)	≥3	1 (1.0)
Anaplastic	2 (3.0)	Lines of chemotherapy, n (%)	
Histopathological characteristics, n (%)		≤1	35 (53.0)
Perineural invasion	22 (33.0)	2-3	23 (35.0)
Vascular invasion	16 (24.0)	≥3	8 (12.0)
Stromal reaction	11 (16.0)		

ULN: Upper limit of the normalcy.