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Research Article

Prognostic Factors in Advanced Pancreatic Cancer: Single-Center, Real-World Data

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Abstract

Objectives: Eighty percent of patients with pancreatic cancer present with unresectable/metastatic disease. Although clinical trials evaluating the efficacy of systemic treatments have been conducted in selected patient groups, reported survivals are short. In our study, we aimed to evaluate real-life data and factors affecting survival in patients with unresectable/metastatic pancreatic cancer.

Methods: The files of the patients who were followed up in our outpatient clinic with the diagnosis of pancreatic adenocarcinoma were evaluated retrospectively. A total of 151 patients had de-novo or recurrent, unresectable/metastatic disease. Variables that may affect the survival of these patients were recorded.

Results: The median overall survival (OS) of patients receiving no systemic therapy for unresectable/metastatic disease and patients receiving chemotherapy was 2.4 months(m) and 9.3m, respectively (p <0.001). Patients with unresectable/metastatic disease had a median OS of 11.6 m and 8.9 m (p=0.02) for recurrent disease and de-novo disease, respectively. The median OS of patients with isolated lung metastases and other patients were 15.4m and 7.8m (p=0.02), respectively.

Conclusion: In unresectable/metastatic pancreatic cancer, recurrent disease and isolated lung metastasis are good prognostic factors. These parameters can be used as stratification factors in prospective studies. Real-life survival data are in compliance with the literature. There is a need for new treatments to improve survival in pancreatic cancer, and studies to identify new markers that determine the course of the disease and can create targets in treatment.

Keywords: Chemotherapy, pancreatic cancer, pancreas, recurrence, survival.

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According to 2020 data, pancreatic carcinoma constitutes 2.6% of all newly diagnosed cancers and 4.7% of cancer deaths.[1] It ranks seventh among the causes of death from cancer worldwide.[1] Ninety percent of pancreatic cancers are adenocarcinomas arising from the ductal epithelium.[2] The only curative treatment method is surgical resection. Unfortunately, only 15-20% of patients present with resectable disease. Moreover, 80% of operated patients develop recurrence.[3] Pancreatic cancer continues to be a mortal disease although more effective treatments have been used in both adjuvant and unresectable/metastatic disease in recent years. Phase III studies are performed in selected patient groups with good performance status, no additional comorbidities, and normal visceral functions. We think that the data on real-life findings are important for this reason. In this study, we aimed to evaluate the real-life data of our patients with advanced pancreatic adenocarcinoma followed up from our center and the factors affecting mortality.

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Methods

Patients who applied to our outpatient clinic between January 2012 and September 2020 with the diagnosis of pancreatic adenocarcinoma were retrospectively evaluated. The data of patients were obtained using written patient files and computer records. Patients older than 18 years of age, whose diagnosis of pancreatic adenocarcinoma was confirmed by pathological examination were included in the study. Periampullary tumors and cases without a pathological diagnosis were excluded from the study. The localization of the tumor in the pancreas was recorded as uncinate, head, trunk, and tail. The history of cancer in first- and second-degree relatives was recorded as cancer in the family history. In more than 10% of the patients, involuntary weight loss was recorded in their last 3 months (m). Tumor stages were evaluated according to AJCC 8th edition.[4] Metastatic areas at the date of first metastasis were grouped as lung, liver, lung+liver, peritoneum, liver+peritoneum, lung+liver+peritoneum and local recurrence+lymph nodes in the abdomen.

Statistical analysis was performed using SPSS V.22. Standard descriptive statistics were used to summarize all variables. The Kolmogorov–Smirnov test was used to analyze the normal distribution of data. The chi-square test was used for categorical variables. Kaplan-Meier plots were used to analyze survival data. Multivariate analysis was done by using cox regression. P values <0.05 were accepted as statistically significant. Variables with p <0.15 detected in the univariate analysis were included in the multivariate analysis (cox regression analysis).

Results

The files of 188 patients who were followed up with the diagnosis of a pancreatic tumor in our polyclinic were evaluated. Four patients were removed from the study because they lacked a pathological diagnosis, while three others were removed because they had a periampullary tumor. The baseline clinical characteristics of the patients are summarized in Table 1. The median survivals according to stages I, II, III, IV were 34.3 m, 27.6 m, 11.1 m, and 5.2 m (p<0.001), respectively. The 5-year survival rates for stages I, II, III, IV were 46.7%, 25.4%, 6.8%, 0% (p<0.001), respectively (Fig. 1). The 12-m and 24-m survival rates of stage IV patients were 21% and 5.1%, respectively. According to the location of the primary tumor in the pancreas, the proportion of patients with stage III/IV at diagnosis was 77/117 (65.8%), 11/11 (100%), 29/31 (93.5%), and 17/22 (77.3%) for the head, uncinate, trunk, and tail, respectively (p<0.001). The definitive surgery rates for pancreatic cancer were 65/117 (55.6%), 1/11 (9.7%), 3/31

Table 1. Baseline Characteristics and Treatments for unresectable/metastatic disease

Characteristics	
Age, median, years	64 (40-94)
Sex, n (%)	
male	116 (64.1)
female	65 (35.9)
Smoking history, n (%)	81 (52.6)
Alcohol history, n(%)	15 (9.9)
Cancer in history, n (%)	6 (3.6)
Family history of cancer, n (%)	21 (11.6)
Weight loss, n(%)	77 (45.5)
Primary tumor localization, n (%)	
head	117 (64.6)
uncinate	11 (6.1)
trunk	31 (17.1)
tail	22 (12.2)
Definitive surgery, n (%)	74 (40.1)
Stage, n (%)	
I	20 (11)
II	27 (14.9)
III	53 (29.3)
IV	81 (44.8)
First metastatic areas, n(%)	
Lung	15 (11.3)
Liver	67 (50.4)
Peritoneum	13 (9.8)
Liver+Peritoneum	12 (9)
Lung+Liver	16 (12)
Local recurrence or intraabdominal LAPs	10 (7.5)
First line chemotherapy regimen for metastatic disease, n (%)	
cis/carbo+gemcitabine	24 (23.5)
folfirinox	12 (11.8)
folfox/xelox	22 (21.6)
gem+nabpaklitaxel	8 (7.8)
gemcitabine	33 (32.4)
folfiri	3 (2.9)

n: number; gem: gemcitabine; cis: cisplatin; carbo: carboplatin.

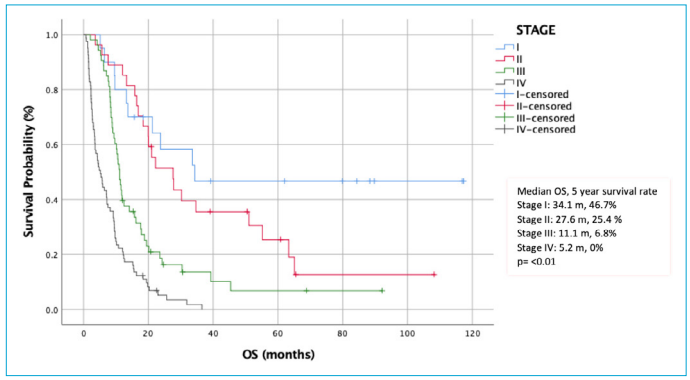

Figure 1. Overall survival according to stages.

OS: overall survival; m: months.

(9.7%), and 6/22 (27.3) for the head, uncinate, trunk, and tail, respectively (p<0.001). Median survivals by location for all patients were 12 m, 8.5 m, 8.9 m, and 8.4 m for head, uncinate, trunk, and tail, respectively (p=0.038). For all patients, gender (p=0.52), presence of weight loss (p=0.096), presence of cancer in the history and family history (p=0.57, p=0.46), history of smoking (p=0.231), history of alcohol use (p=0.323) and tumor grade (p=0.23) had no effect on survival.

Ninety-eight (54.1%) patients had de-novo unresectable/metastatic disease. 53 (71.6%) from 74 of the patients who underwent curative surgery for pancreatic cancer, relapsed as unresectable/metastatic disease at follow-up. Survival data of 151 patients with de-novo or recurrent unresectable/metastatic disease were evaluated. The median survival of these patients from the development of metastatic disease was 7.2 m (5.3 m–9.1 m, 95% CI). Patients with metastatic disease who developed unresectable/metastatic disease with recurrence had a median survival of 9.2 m (5.2 m- 13.2 m, 95% CI), while those with de-novo unresectable/metastatic disease had a median survival of 6.2 m (4.4 m-8 m, 95%CI) (p=0.007). For unresectable/metastatic disease, 106 (66.8%) patients received at least 1 line of systemic chemotherapy. The median survival of patients who received no systemic therapy for unresectable/metastatic disease and patients who received at least 1 line of chemotherapy was 2.4 m (2 m-2.7 m, 95% CI) and 9.3 m (8.6 m-10 m, 95% CI) (p<0.001), respectively. The univariate and multivariate analyzes of the parameters that may affect the survival of patients who have received at least 1 line of chemotherapy for their metastatic disease are summarized in Table 2. There was only 1 patient with lung+liver+peritoneal metastasis among these patients. This patient was included in the lung+liver group and analyzed. Among the patients who received at least 1 line chemotherapy for unresectable/metastatic disease, the median survival of the patients with isolated lung metastasis and the others were 15.4 m (5.8 m-25.1 m) and 7.8 m (5.2 m-10.5 m) (p=0.02), respectively (Fig. 2). In figure 3, the survival data of patients who received at least 1 line of chemotherapy for unresectable/metastatic disease, according to the presence of de-novo or recurrent disease, are summarized.

Discussion

In recent years, with the both targeted therapies and immunotherapy agents, significant improvements in survival have been achieved in many cancer types. In pancreatic cancer, the situation is less optimistic. Despite the use of current chemotherapy combinations, death and recurrence rates are still high.

In almost all clinical studies, evaluation is made in selected patient groups with good performance status, no additional comorbidities, and normal visceral functions. Therefore, we think that reporting the results of real-life data is significant.

As expected, overall survival was significantly different depending on stages in the patients we evaluated in our study. We found that the median survival of patients who were metastatic at baseline is 5.2 m. While the median survival for patients who received no systemic therapy for unresectable/metastatic disease was 2.4 m, it was 9.3 m for patients who received at least 1 line of chemotherapy (p<0.001). We found that almost 1/3 of the patients did not receive any treatment for unresectable/metastatic disease. This was a higher rate than we expected. Patients may not receive treatment due to comorbid diseases, poor performance status, and refusal to receive chemotherapy. On the other hand, some patients may die from acute causes such as disease-related embolism before starting systemic chemotherapy. However, the delay in applying for treatment due to reasons such as the low awareness of the people about the symptoms associated with pancreatic cancer may have contributed to this result. We think that studies are needed to explain this low rate of receiving treatment. In our study, only 66.8% of the patients were able to receive at least 1 line of chemotherapy. The median survival of patients who received no systemic chemotherapy was very short (2.3 m). Since the main patient group to which we can contribute to survival is those who have received chemotherapy, we thought it would be more meaningful to evaluate the parameters affecting survival in these patients. We performed univariate and multivariate survival analyzes in this patient group. In this context, the overall survival was significantly longer in patients who had previously undergone definitive surgery for their primary tumor and subsequently recurrent, compared to patients with de-novo unresectable/metastatic disease (11.6 m vs 8.9 m). Patients with de-novo unresectable/metastatic disease had a 1.88-fold increased risk of death compared to patients with recurrent disease. Recurrent disease was underrepresented in prospective studies which evaluating patients with metastatic pancreatic cancer. We found few studies in the literature comparing the survival data of de-novo and recurrent disease. In a study recently presented at the American Society of Clinical Oncology Congress, it was reported that the survival of patients with recurrent disease is better (10.8 m vs 7.3 m), which is similar to the results in our study.[5] We think that this factor, which has been shown to have an independent effect on prognosis, can be used as a stratification factor in prospective studies.

Another parameter that we evaluated as significant in the

Table 2. Univariate/Multivariate analysis for OS in patients who were given chemotherapy for metastatic disease

	Univariate analysis OS, m (95%CI)	p	Multivariate analysis Adjusted HR (95%CI)	p
Age, years				
>65	9.2 (7-11.4)	0.56		
<65	9.7 (7.8-11.5)			
Sex				
Male	9.3 (8-10.6)	0.63		
Female	9.2 (7-11.4)			
Smoking				
none	9.2 (7.1-11.3)	0.14	0.96 (0.55-1.67)	0.88
present	10 (8.7-10.1)			
Alcohol usage				
none	9.2 (8.3-10.1)	0.68		
present	11.1 (6.5-15.6)			
Metastasis				
de-novo	8.9 (6.8-10.9)	0.02	1.88 (1.1-3.2)	0.02
recurrent	11.6 (10.6-12.6)			
Location of primary tumour				
head	9.5 (7.2-11.8)	1		
uncinate	9.3 (5.1-13.6)	0.25		
trunk	7.1 (2.8-11.4)	0.45		
tail	9.7 (7.6-11.9)	0.97		
Weight loss				
none	9.7 (7.3-12.1)	0.49		
present	9.2 (8.1-10.3)			
Cancer in family history				
none	9.5 (8.6-10.4)	0.52		
present	5.5 (0.3-10.6)			
Cancer in personal history				
none	9.5 (8.6-10.4)	0.04	1.08 (0.20-5.90)	0.93
present	4.7 (2.5-6.8)			
Ca19-9				
>100mg/dl	9.2 (7.4-11)	0.04	0.73 (0.39-1.37)	0.323
<100 mg/dl	9.7 (6.1-13.2)			
First metastatic areas				
Lung	15.4 (5.8-25)	1	1	
Liver	9.2 (8.5-9.9)	0.05	1.75 (0.84-3.6)	0.14
Peritoneum	4.7 (0-10.8)	0.04	2.76 (0.97-7.84)	0.06
Liver+Peritoneum	5.8 (3.1-8.5)	0.01	3.03 (1.15-8.02)	0.03
Lung+Liver	4.3 (4.1-4.5)	<0.01	8.16 (2.66-25.1)	<0.01
Local recurrence or intraabdominal LAPs	19.5 (7.5-11.2)	0.24	1.30 (0.47-3.63)	0.61
Chemotherapy regimen				
cis/carbo+gemcitabine	5.8 (3.2-8.4)	1		
folfirinox	11.5 (10.3-12.7)	0.18		
folfox/xelox	7.8 (1.7-14)	0.59		
gem+nabpaklitaxel	15.5 (0.3-31.8)	0.81		
gemcitabine	9.2 (8-10.4)	0.57		
folfiri	3.1 (2.1-4.2)	0.25		

OS: overall survival; HR: Hazard Ratio; CI: Confidence Interval; m: months; gem: gemcitabine; cis: cisplatin; carbo: carboplatin.

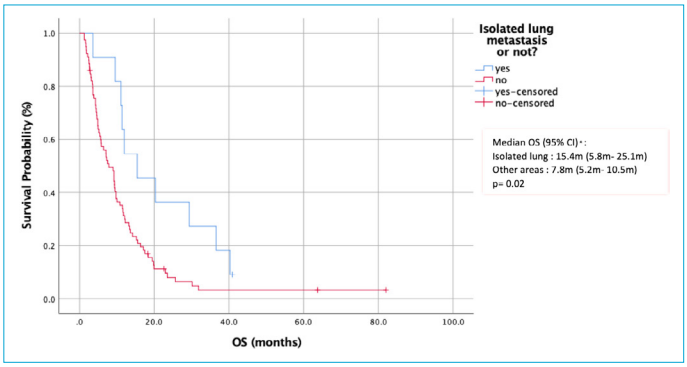

Figure 2. Overall survival according to initial areas of metastasis.

OS: overall survival; m: months.

**In patients who have received chemotherapy for unresectable/metastatic disease.*

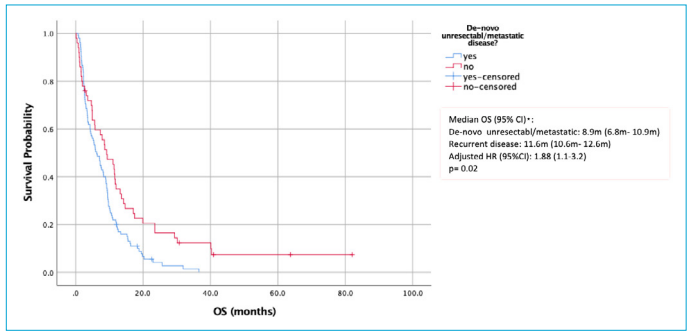

Figure 3. Overall survival according to de-novo or recurrent unresectable/metastatic disease.

OS: Overall Survival; HR: Hazard Ratio; CI: Confidence Interval; m: months.

**In patients who have received chemotherapy for unresectable/metastatic disease.*

multivariate analysis was the area of first metastasis. In our study, lung metastases were present in 31 (23.3%), isolated lung metastases in 15 (11.3%), and liver metastases in 95 (71.4) patients. These rates are similar to those reported in previous studies.[6, 7] The patients who have only lung metastases at the first metastases had a significantly better overall survival than almost all patients with other areas of metastasis. The overall survival of patients who have abdominal lymphadenopathies and/or unresectable local recurrent disease, as the first metastatic area, was similar to patients with metastases to the lung (15.4 m vs. 19.5 m, p=0.61). When compared to those with isolated lung metastases, the risk of death was increased 1.8, 2.8, 3, and 8.2 times in those with liver, peritoneum, liver+peritoneum, and liver+lung metastases, respectively, independent of other factors. Moreover, there are retrospective data reporting that survival can be prolonged to a median of 67.5 m with local treatments for lung metastases (surgical resection/stereotactic radiosurgery).[8, 9] Therefore, we think that local treatments for metastases should be evaluated multidisciplinary in appropriate cases considering that the prognosis is significantly better in patients with isolated lung metastases. In this context, stereotactic radiotherapy or surgical resection of the lung metastases may be a good strategy in patients whose disease is under control after 3-6 m of systemic therapy and have a limited number of metastases, especially in patients who have operated for primary tumor. It would be appropriate to evaluate survival benefit of this approach with prospective studies.

It is possible to obtain better tumor responses and overall survival results with modern chemotherapy combinations than single-agent treatments. In Phase III ACCORD 11 trial, significant improvement in median progression free survival (PFS) (6.4 m vs 3.3 m) and overall survival (11.1 m vs 6.8 m) was demonstrated with the FOLFIRINOX regimen compared to single-agent gemcitabine.[7] A phase II study has shown that with the modified FOLFIRINOX regimen, which is expected to develop less toxicity, an overall survival similar to classic FOLFIRINOX can be achieved.[10] A median overall survival of 7.5 m was reported in a phase II study with FOLFOX, another regimen often preferred in patients who are thought to be unable to tolerate FOLFIRINOX in daily practice. In our study, we found a median overall survival of 11.5 m with FOLFIRINOX and 7.8 m with FOLFOX/XELOX. These data show great similarity with the literature. FOLFOX is a frequently preferred alternative for patients who cannot tolerate FOLFIRINOX in real life. Although we observed better survival in patients receiving FOLFIRINOX compared to patients receiving FOLFOX in our study, we think that this may be due to the patient groups in which two regimens were preferred. We prefer FOLFOX in patients who we think cannot tolerate FOLFIRINOX, such as comorbidities, age, and performance status. Therefore, a prospective study comparing FOLFIRINOX and FOLFOX may be appropriate to evaluate whether irinotecan contributes. In the phase II study that led to Food and Drug Administration approval of gemcitabine+nabpaclitaxel, a median overall survival of 12.2 m was reported.[11] Considering this data, we obtained longer overall survival data than we expected with gemcitabine+nabpaklitaxel in our patients. A total of 8 patients received gemcitabine+nabpaklitaxel in the 1st line treatment. The median PFS achieved with this regimen was actually 3.7 m. Four of the patients received 2nd line chemotherapy. The second line of chemotherapy was XELOX/FOLFOX in all. Moreover, a much longer overall survival (16 m -26 m) was obtained in 3 patients which is more than expected. The patient who had an overall survival of 26 m, was 40 years old. We do not know the breast cancer susceptibility (BRCA) /BRCA-like status in this patient. Perhaps the patient's genomic changes may

have resulted in a better prognosis. Again, the platinum-based treatment they received in the second line (patient received XELOX) may have contributed to their long survival. We think that the low number of patients receiving gemcitabine+nabpaklitaxel and the effectiveness of the second line of treatments may have caused this result.

Pathogenic variants in the BRCA and BRCA-like are present in up to 10% of pancreatic cancers.[12] In germline BRCA-mutated metastatic pancreatic cancers, significant improvement was achieved in disease-free survival (7.4 m vs 3.8 m) with maintenance olaparib after first-line platinum-containing chemotherapy. Similar median overall survival was obtained in patients treated with olaparib (18.9 m vs 18.1 m). In a phase II study with rucaparib, another PARP inhibitor, a median overall survival of 23.5 m was reported after rucaparib maintenance after platinum-based chemotherapy in patients with homologous recombinant repairing (HRR) deficiency. We detected 5.8 m overall survival with platinum+gemcitabine. We think that this combination should not be preferred, except for patients with known BRCA and BRCA-like mutations, based on the findings of our study and literature data.

In a comprehensive meta-analysis, it has been reported that the prognosis of patients with the location of the primary tumor in the head of the pancreas is better than the others. In the subgroup analysis of the same study, it was observed that the location did not have an effect on the prognosis in stage 4 patients.[13] The reason for this was thought to be higher operability rates due to the earlier manifestation of symptoms such as jaundice and steatorrhea in head tumors. In our study, the incidence and operation rates of those with head localization were higher which is in line with the literature. All of the tumors located in the uncinate process appeared at the stage 3-4. We think that this is anatomically due to the close proximity of vessels to this region. However, in our study, we found that the location in the pancreas did not have a prognostic effect in metastatic disease.

Conclusion

Recurrent disease and isolated lung metastasis are good prognostic markers, independent of the other factors for unresectable/metastatic pancreatic cancer. These parameters can be used as stratification factors in prospective studies. Despite combination chemotherapy in metastatic pancreatic cancer, survival is still short. Real-life data are consistent with the literature. Recurrence/metastasis development rates are high in operated patients. There is a need to identify new molecular targets that will increase the efficacy of adjuvant and palliative systemic therapy.

Disclosures

Ethics Committee Approval: The Haydarpasa Numune Training approved this study, and Research Hospital Institutional Review Board (approval no. 2021/243).

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Conflict of Interest: None declared.

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