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Retrospective evaluation of our patients diagnosed with advanced pancreatic cancer

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ABSTRACT

Aims: Pancreatic cancer attracts attention with its increasing frequency among gastrointestinal cancers. It has the worst prognosis of all cancer types. In this study, we aimed to retrospectively evaluate the clinical features and treatment results of our patients with advanced pancreatic cancer.

Methods: In this study, 131 patients diagnosed with advanced pancreatic cancer and admitted to the Ankara Numune Training and Research Hospital Medical Oncology Polyclinic between November 2002 and January 2014 were retrospectively analyzed. Demographic characteristics of the patients, smoking, family history, basal CEA and basal CA 19-9 levels, treatment modalities, metastasis sites, progression-free survival, and overall survival times were evaluated.

Results: The study population consisted of 131 patients, including 94 males and 37 females. Twenty of the patients were in the locally advanced stage, and 111 were in the metastatic stage. The median age of the patients was 60 years. 53.4% of the patients were smokers, and the median amount of smoking was 30 packs/year. Adenocancer was the most common histopathological subtype. The median basal CEA and Ca 19-9 levels were high at the time of diagnosis. Neoadjuvant chemotherapy was given to all locally advanced patients. The most commonly used chemotherapy regimens were single-agent gemcitabine and gemcitabine-cisplatin combination therapies. While 10 of the locally advanced patients received local treatment (chemotherapy or surgery) after neoadjuvant chemotherapy, the remaining 10 patients could not receive local treatment. The median overall and progression-free survival times were found to be significantly longer in patients with locally advanced disease who received local treatment after neoadjuvant chemotherapy [(18 months vs. 6.5 months; p=0.008), (11.3 months vs. 6.4 months; p=0.05)]. The most common site of metastasis in our patients with metastatic pancreatic cancer was the liver (80%). Cisplatin-gemcitabine was preferred as a KT regimen in 63.4% of metastatic cases. The median overall survival time of the patients in the metastatic stage was 8.1 months, and the median progression-free survival time was 5.7 months. The median progression-free survival of all patients included in the study was 6.2 months, while the median overall survival was 8.8 months.

Conclusion: The median overall survival of patients with locally advanced pancreatic cancer was significantly longer compared to metastatic patients (18 months vs. 8.1 months; p=0.028). Progression-free survival and overall survival of patients with locally advanced disease who received or did not receive local treatment after neoadjuvant chemotherapy were found to be significantly longer in patients who received local treatment. (11.3 months vs. 6.4 months; p=0.05) (18 months vs. 6.5 months; p=0.008). Response rates of patients with metastatic pancreatic cancer; It was 49% in the gemcitabine-cisplatin combination arm and 30% in the single-agent gemcitabine arm.

Keywords: Advanced pancreatic cancer, gemcitabine, cisplatin, survival

INTRODUCTION

Pancreatic cancer is one of the most common cancers in the world and is an important cause of cancer-related deaths.[1] It has attracted attention with its increasing frequency among gastrointestinal cancers in recent years.[2] At the time of diagnosis, the disease is usually at an advanced stage, and distant organ metastasis is encountered. Since there are no obvious symptoms in the early stages of the disease, the majority of patients lost the chance of curative resection at the time of diagnosis.[3] Palliative surgeries and systemic or regional treatments are usually applied to these patients who cannot be operated on.

According to the SEER (U.S. Surveillance, Epidemiology, and End Results) database, the 5-year survival rate for localized pancreatic cancer patients is 31.5%, 11.5% for those with regional disease, and 2-5% for patients with advanced metastases.[4] Factors affecting survival include age, gender, comorbidities and habits. However, the most important

factor affecting the outcome is the stage of the tumor at the time of diagnosis.[5] Survival in metastatic patients is around 3-6 months.[5]

The curative treatment of pancreatic cancer is surgical resection.[6] Most patients with pancreatic adenocarcinoma are metastatic at diagnosis. In patients with distant organ metastases and locoregional unresectable tumors, chemotherapy is the primary treatment option.[7]

In this study, we aimed to evaluate the clinicopathological features, prognostic factors, clinical course, treatment modalities, and overall and progression-free survival times of our patients with locally advanced and metastatic pancreatic cancer.

METHODS

This study was produced from the internal medicine specialty thesis titled 'Retrospective Evaluation of Our Patients Diagnosed with Advanced Pancreatic Cancer', conducted in 2015. All procedures were carried out in accordance with the ethical rules and the principles of Helsinki Declaration

Between November 2002 and January 2014, 131 patients with advanced pancreatic cancer (locally advanced and metastatic) who were admitted to the Medical Oncology Outpatient Clinic of Ankara Numune Training and Research Hospital were included in the study. Information about the patients was obtained through the retrospective examination of patient files.

Gender, age at diagnosis, smoking status and amount, family history of cancer, history and duration of diabetes mellitus, tumor stage, baseline CEA and CA 19-9 levels, treatment modalities, chemotherapy protocols, site of metastasis, chemotherapy response rates, last updated status, and last contact dates were recorded. Biopsy types, histopathologic types, and pathologic differentiation grades were analyzed from the patients' files. Progression-free and overall survival rates were determined. The study was approved by the Ankara Numune Training and Research Hospital's Ethics Committee.

RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria were used to evaluate the response to chemotherapy.[8] Complete response was defined as the disappearance of all target lesions; partial response as at least 30% reduction in the sum of the longest diameters of the target lesions; progression as at least 20% increase in the sum of the longest diameters of the target lesions; and stable response as no shrinkage as a partial response and no growth as progressive disease (<30% shrinkage, <20% growth).

Overall survival was calculated as the time from the date of diagnosis until death, and for patients who were still alive at the end of the study, the time from the date of the update of patient information was taken as the basis. Progression-free survival was calculated based on the time from diagnosis to progression. In patients who died before progression evaluation, the date of death was considered the date of progression.

The data obtained were interpreted by descriptive and comparative statistical analysis using the "SPSS for Windows 18" package program in a computer environment. In the study, variables with categorical values were given with numbers and percentages, and measurement variables with continuous values were given with median, minimum, and maximum values. The Kaplan-Meier method was used to construct survival curves, and the Log-rank test was used to compare variables in survival analysis. A value of $p<0.05$ was considered significant in statistical analyses.

RESULTS

Of the patients included in the study, 15% (n=20) were locally advanced and 85% (n=111) were metastatic. 71.8% (n=94) were male and 28.2% (n=37) were female. The male/female ratio was 2.54. The median age of the patients was 60 (28-80) years. The clinical and demographic characteristics of the patients are given in detail in **Table 1**.

Table 1. Clinical and demographic characteristics of the patients (n=131)

	n	%
Stage		
Locally advanced	20	15
Metastatic	111	85
Gender		
Male	94	71.8
Female	37	28.2
Age (years) (median-range)	60 (28-80)	
Cigarette consumption	70	53.4
Cigarette quantity (pack/year) (median-range)	30 (1-100)	
Diabetes mellitus	50	38.1
Diabetes mellitus duration (year) (median-range)	4 (1-15)	
Family history of cancer	27	20.6
Histopathological type		
--Adenocancer	100	76.3
--Malignant epithelial tumor	23	17.6
--Other *	8	6.1
Basal CEA ** (IU/L) (median-range)	6.6 (0-1440)	
Basal Ca 19-9 ***(IU/L) (median-range)	929 (1-120000)	

* Other: Adenosquamous (1), squamous cell (1), anaplastic carcinoma (1), carcinoma (4), neuroendocrine tumor (1)
**CEA: Carcinoembryonic antigen
***CA 19-9: Carbohydrate antigen 19-9

Of the 20 patients in the locally advanced stage, 11 were male and 9 were female. The male/female ratio was 1.22/1. The median age of the patients was 60 (42-78) years. When the patients were analyzed according to smoking characteristics, 35% were smokers, and 43% of them were active smokers at the time of diagnosis. The median amount of smoking was 25 (10-40) pack/year. When the patients were analyzed in terms of comorbid Diabetes Mellitus (DM), it was observed that 40% of the patients had a history of DM. Of the 8 patients with DM, 2 were newly diagnosed DM and 4 were using insulin. When the family history of cancer was investigated, 5 patients had a family history of cancer, but none of them had a family history of pancreatic cancer. When the types of biopsies performed during the pathologic diagnosis were evaluated, 80% of the patients were diagnosed with a tru-cut' biopsy. The histopathologic diagnosis was adenocarcinoma in 80% of the patients. When the baseline CEA and CA19-9 values of the patients were analyzed, the median baseline CEA level was 5 (1.6-72) IU/L and the median baseline CA 19-9 level was 355 (3.4-1200) IU/L. All patients received chemotherapy as neoadjuvant treatment. Of the 20 patients, 12 received cisplatin-gemcitabine combination chemotherapy and 8 received single-agent gemcitabine. Regarding the response

rates after chemotherapy, 12 (60%) patients had a stable response, 4 (20%) had a partial response, and 4 (20%) had progression. Clinical and pathologic characteristics of the patients with locally advanced pancreatic cancer are given in **Table 2**.

Table 2. Clinical and pathological features of locally advanced patients (n=20)

	n (%)
Age (years) (median-range)	60 (42-78)
Gender	
Male	11 (55)
Female	9 45)
Male/Female	1.22
Cigarette consumption	7 (35)
Cigarette quantity (pack/year) (median-range)	25 (10-40)
History of DM	8 (40)
Family history of cancer	5 (25)
Biopsy types	
Tru-cut biopsy	16 (80)
EUS-FNAB	3 (15)
ERCP-brush biopsy	1 (5)
Histopathological types	
Adenocancer	16 (80)
Malignant epithelial tumor	3 (15)
Undifferentiated carcinoma	1 (5)
Differentiation	
Grade 1	2 (10)
Grade 2	1 (5)
Grade 3	1 (5)
Unknown	16 (80)
Basal CEA (IU/L) (median-range)	5 (1.6-72)
Basal CA 19-9 (IU/L) (median-range)	355 (3.4-1200)
CTX Regimes	
Gemcitabine	8 (40)
Gemcitabine-Cisplatin	12 (60)
Treatment response	
Stable response	12 (60)
Partial response	4 (20)
Progression	4 (20)

Of the 20 patients with locally advanced disease who received neoadjuvant chemotherapy (CT), 10 received local treatment (surgery and chemoradiotherapy) after neoadjuvant CT. While 9 of these patients received chemoradiotherapy as local treatment, one of them underwent surgery. The overall survival time of the operating patient was 11.7 months, and the progression-free survival time was 11.3 months. Only one of the 10 patients who could receive local treatment died. That patient had received chemoradiotherapy as a local treatment. Of the remaining 10 patients who did not receive local treatment, 3 died due to disease progression. When the median overall and progression-free survival times of patients with locally advanced disease who received local treatment after neoadjuvant KT and those who did not were compared, they were significantly longer [(18 months vs. 6.5 months; p:0.008), (11.3 months vs. 6.4 months; p:0.05)]. The median overall survival time of all patients with locally advanced pancreatic cancer was 18 months, and the progression-free survival time was 8.7 months.

Of the 131 patients with advanced pancreatic cancer, 111 were metastatic at the time of diagnosis. Of the patients, 83 (74.8%) were male and 28 (25.2%) were female. The male/female ratio was 2.96/1. The median age of the patients was 60 (28-80) years. When the patients were analyzed according to smoking characteristics, 63 (56.7%) had a history of smoking, and 57% were active smokers at the time of diagnosis. The median value of the amount of smoking was 30 (1-100) pack/year. In terms of DM, 42 patients (38%) had a history of DM. The diagnosis of DM was new in 8 of the patients with DM, and 22 of them had a history of insulin use and 8 of them had a history of metformin use. In terms of family history of cancer, 23 (20.7%) patients had a family history of cancer, and 3 of the 23 patients had a family history of pancreatic cancer, unlike patients with locally advanced pancreatic cancer. When the histopathologic diagnosis was analyzed, 84% were diagnosed as adenocarcinoma. Most of the patients whose differentiation was specified in the pathology notes in the patient files were in grade 3. When the baseline tumor markers of the patients were analyzed, the median baseline CEA level was 7.9 (0.2-1140) IU/L and the median baseline Ca 19-9 level was 1000 (0.6- 120000) IU/L. Clinical and pathologic characteristics of the patients with metastatic pancreatic cancer are given in **Table 3**.

Table 3. Clinical and pathological features of metastatic patients (n=111)

	n (%)
Age (years) (median-range)	60 (28-80)
Gender	
Male	83 (74.8)
Female	28 (25.2)
Male/Female	2.96
Cigarette consumption	63 (56.7)
Cigarette quantity (pack/year) (median-range)	30 (1-100)
History of DM	42 (38)
Family history of cancer	23 (20.7)
Biopsy types	
Tru-cut biopsy	102 (91.9)
EUS-FNAB	4 (3.6)
ERCP-brush biopsy	3 (2.7)
Unknown	2 (1.8)
Histopathological types	
Adenocancer	84 (%75.7)
Malignant epithelial tumor	20 (%18)
Others*	7 (%6.3)
Differentiation	
Grade 1	1 (1)
Grade 2	11 (10)
Grade 3	24 (22)
Unknown	75 (67)
Basal CEA (IU/L) (median-range)	7.9 (0.2-1140)
Basal CA 19-9 (IU/L) (median-range)	1000 (0.6-120000)

* Others: Adenosquamous carcinoma (1), Anaplastic carcinoma (1), Carcinoma metastasis (3), Neuroendocrine tumor (1), Squamous cell cancer (1)

The most common site of first metastasis in patients with metastatic pancreatic cancer was the liver (80%), followed by the lung and the liver (11%). First-line CT was given to 93 metastatic patients. The gemcitabine-cisplatin combination was the most preferred regimen (63.4%). The second-most preferred regimen was single-agent gemcitabine (32.2%). The stable response rate was 44%, the progression rate was 34%, the partial response rate was 20.3%, and the complete response rate was 1.7%. The median overall survival time of patients with metastatic cancer was 8.1 months, while the median progression-free survival time was 5.7 months.

The median progression-free survival of patients with advanced pancreatic cancer (locally advanced and metastatic) included in our study was 6.2 months (95% CI: 5.4-6.9) and the median overall survival was 8.8 months (95% CI: 6.3-11.2). Progression-free and overall survival curves of patients with advanced (locally advanced and metastatic) pancreatic cancer are shown in **Figures 1 and 2**.

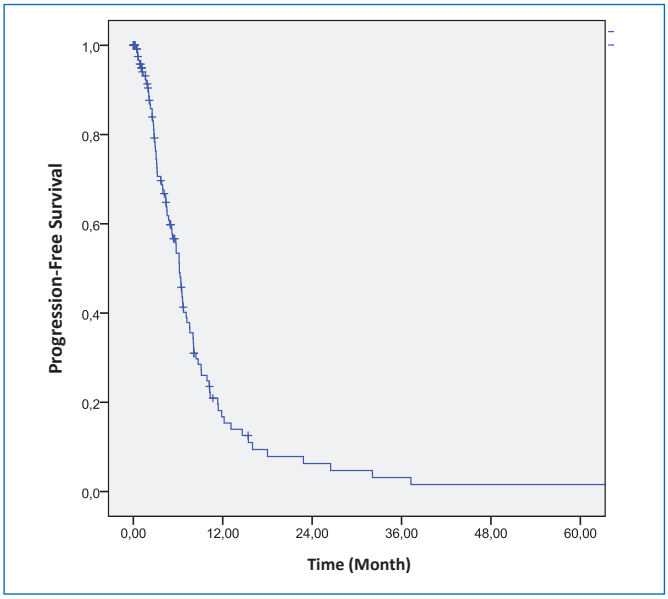

Figure 1. Progression-free survival of patients with advanced (locally advanced and metastatic) pancreatic cancer

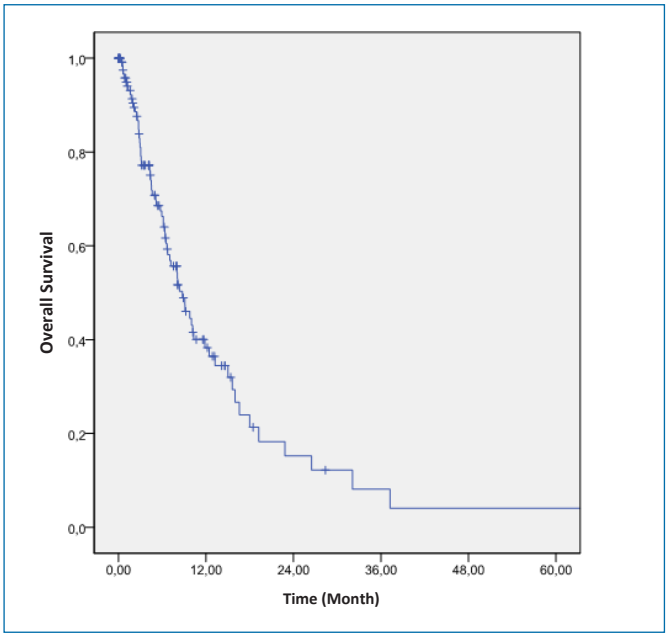

Figure 2. Overall survival of patients with advanced (locally advanced and metastatic) pancreatic cancer

DISCUSSION

Pancreatic cancer is most common in the 7th and 8th decades, and the median age at diagnosis is 60-65 years.[9] It has been reported that the risk of pancreatic cancer increases 2-3 times every decade after the age of 40 years.[10] The median age of the patients in our study was 60 years, similar to the data in the literature. The youngest patient was 28 years old at the time of diagnosis. The incidence of pancreatic cancer in men is higher than in women.[11] In recent years, the relative risk for women has been approaching that of men. The reason for this increase is thought to be the increase in smoking among women.[12] In our study, the male/female ratio was 2.54/1, and the incidence of pancreatic cancer was higher in men. Approximately 85-90% of pancreatic cancers are ductal adenocarcinoma.[13] 76.4% of our patients had an adenocarcinoma histopathologic subtype.

Seventy patients (53.4%) had a smoking history, and the median cigarette consumption was 30 pack/year. It is estimated that smoking contributes to the development of 20-30% of pancreatic cancers.[14] The incidence of pancreatic cancer is 75% higher in smokers. It has been reported that each pack/year of cigarettes consumed increases the risk of developing pancreatic cancer by 2%. As the number of cigarettes smoked increases, the risk of pancreatic cancer increases in parallel .[15]

It has been reported that high insulin concentrations, glucose intolerance, and insulin resistance may play a role in carcinogenesis.[16] Patients with DM for at least 5 years have a 2-fold increased risk of developing pancreatic cancer.[17] 50 (38.4%) of the patients in our study had comorbid DM. The median duration of DM was calculated at 4 years.

In terms of family history of cancer, 20.6% had a family history of cancer. It was observed that 11% of these patients had a family history of pancreatic cancer. All patients with a family history of pancreatic cancer had metastatic pancreatic cancer at the time of diagnosis. A history of pancreatic cancer in one first-degree relative increases the risk of pancreatic cancer 4.5 times; in 2 relatives, the risk increases 8.4 times; and in 3 relatives, the risk increases 32 times.[18] In patients with familial pancreatic cancer, the risk of pancreatic cancer increases, as well as the risk of non-pancreatic cancers (especially breast, ovarian, and biliary tract cancers).[19]

Similar to the literature, the most common metastatic site in our metastatic patients was the liver (80%). The second-most common metastasis was simultaneous liver and lung metastasis. When basal CA 19-9, one of the tumor markers, was analyzed, the median value was 929 IU/ml. It has been reported that pancreatic cancer patients presenting with high basal CA 19-9 levels have a worse prognosis than others.[20] Ni et al.[21] found that high serum CA 19-9 levels were associated with distant metastasis, advanced stage, and a poor prognosis for pancreatic cancer. When the median CA 19-9 levels of our locally advanced and metastatic patients at the time of diagnosis were compared, the CA 19-9 levels of metastatic patients were higher than those of locally advanced patients. In our study, the median CEA level of patients with advanced pancreatic cancer was 6.6 IU/ml, and our results were consistent with the literature.

In a study by Tsavaris et al.[22] it was found that the CEA value increased with increasing tumor mass and was associated with a poor prognosis. In this study, those with a CEA value above 5 IU/ml had a 1.4-fold higher risk of death.In a study by Trikudanathan et al.[23] in patients with pancreatic cancer, 70% had elevated CEA and CA 19-9 .

In the treatment of pancreatic cancer, a triple treatment modality (surgery, RT, and CT) is preferred. The only potentially curative treatment modality in pancreatic cancer is surgery in early-stage disease.[24] In our study, all 20 patients with locally advanced disease received neoadjuvant CT. The preferred combination was gemcitabine-cisplatin (60%) and single-agent gemcitabine (40%). After neoadjuvant CT, 10 patients were able to receive local treatment (CRT or surgery). The median overall survival time and median progression-free survival time of the 10 patients with locally advanced disease who could receive local treatment (CRT or surgery) after neoadjuvant CT (18 months vs. 6.5 months, p:0.008) and the 10 patients who could not receive local treatment (11.3 months vs. 6.4 months, p:0.05) were significantly longer in the locally treated group. The fact that local treatment after neoadjuvant KT increased survival is promising for a cancer with such a poor prognosis.

Invasion of vascular structures in locally advanced pancreatic cancers makes surgical resection difficult. When the chemoradiotherapy outcomes of 323 patients with locally

advanced pancreatic cancer at M.D. Anderson Cancer Center were analyzed, 76 patients who received gemcitabine for 2.5 months before chemoradiotherapy had a longer median overall survival and progression-free survival.[25] In another retrospective series, 181 patients with locally advanced pancreatic cancer were given gemcitabine-containing chemotherapy for 3 months; 72 of the 128 patients who did not progress were continued with chemoradiotherapy, and the remaining 56 received chemotherapy. The median progression-free and overall survival times of patients who continued with chemoradiotherapy (10.8 months and 15 months) were longer than those of patients who continued with chemotherapy (7.4 months and 11.7 months) .[26] Systemic palliative chemotherapy for metastatic pancreatic cancer is primarily aimed at relieving disease-related symptoms.[27] 93 of the 111 metastatic patients included in the study could receive CT. The gemcitabine-Cisplatin combination (63.4%) and single-agent gemcitabine (32.2%) were the most preferred CT regimens.

In studies comparing the efficacy of gemcitabine and cisplatin combination with single agent gemcitabine in the treatment of metastatic pancreatic cancer, the response rate (26% vs. 9%) and median survival time (30 weeks vs. 20 weeks) were reported to be better in the combination arm.[28] In our study, the response rates of metastatic patients after first-line KT were 49% in the combination arm and 30% in the single-agent gemcitabine arm. In a multicenter retrospective study conducted in our country, the efficacy of cisplatin and gemcitabine combination and single agent gemcitabine in locally advanced or metastatic pancreatic cancer was compared, and it was found that the response rate was significantly higher in the combination arm (69% vs. 49.7%), but there was no significant difference between the treatment arms in terms of time to progression (8.9 months vs. 6 months) and overall survival (12 vs. 10.2 months).[29]

CONCLUSION

The results of our study clearly demonstrate the need for new chemotherapy regimens in the treatment of advanced pancreatic cancer. Pancreatic cancer is one of the cancer types with a very poor prognosis. The median time to progression of 6.2 months and median overall survival of 8.8 months in the patients in our study indicate the mortal course of the disease. When patients with locally advanced and metastatic pancreatic cancer were compared in terms of median overall and progression-free survival, median overall survival was longer in patients with locally advanced disease (p:0.028). Although all our patients had advanced disease, survival outcomes were worse in patients with systemic metastases.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was produced from the internal medicine specialty thesis titled 'Retrospective Evaluation of Our Patients Diagnosed with Advanced Pancreatic Cancer', conducted in 2015.

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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