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ORIGINAL ARTICLE

Performance status of patients is the major prognostic factor at all stages of pancreatic cancer

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Abstract
Background The aim of this study was to identify and evaluate the clinicopathologic factors and to elucidate the clinical importance of performance status on the outcome of patients with pancreatic cancer.
Materials and method The data of 335 patients with histologically confirmed diagnosis of pancreatic cancer who were treated and followed up between 2000 and 2010 were recorded from medical charts.
Results The median age of the patients was 59 years (range 25–88 years) and 226 (67.5 %) were male. The study group comprised localized disease (18 %), locally advanced disease (36 %) and metastatic disease (46 %). The median survival of all patients was 280 days and the 4-year survival rate was 5 %. Univariate analysis indicated that initial poor performance status of patients (PS 2–4) was significantly associated with shorter survival in localized ($p = 0.015$), locally advanced ($p = 0.01$), metastatic stage ($p < 0.001$) and in the whole group ($p < 0.001$). Multivariate analyses also showed the same findings except in local disease ($p = 0.04$ for locally advanced disease, $p = 0.002$ for metastatic stage, and $p < 0.001$ for all stages). In patients with poor performance status, severe weight loss (>10 %) ($p = 0.007$), large tumor diameter (>3 cm) ($p = 0.046$), and especially metastatic disease ($p < 0.001$) were associated with significantly shorter overall survival.
Conclusions The performance status of a patient is the major prognostic factor predicting overall survival for all stages of pancreatic cancer. Severe weight loss, large tumor, and metastatic disease were found to be unfavorable prognostic factors in patients with poor performance status.

Keywords Pancreatic cancer · Performance status · Prognosis · Survival

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Introduction

The majority (85–90 %) of pancreatic cancer patients present with advanced disease [1]. Despite a 5-year survival rate for patients who undergo curative surgery of approximately 80 %, the 1-year survival rate for patients with advanced disease does not exceed 11–25 % [2, 3]. Because of high rate of local progression and distant metastatic ability, localized but unresectable disease cannot be cured with systemic chemotherapy or radiotherapy without surgery [4, 5].

Non-surgical treatment options such as chemotherapy or targeted therapy have been investigated to see whether they prolong the overall survival of pancreatic cancer patients [6]. Due to moderate progress provided by chemotherapeutics, recent studies evaluated if subgroups of patients can be identified who could benefit most from specific treatment strategies [7]. This would lead to improvement in the selection of patients with a poor prognosis to be treated only with supportive care and thereby avoiding unnecessary adverse effects and complications associated with systemic chemotherapy.

Pretreatment serum hemoglobin levels, age, initial serum carbohydrate antigen (CA) 19-9 level, carcinoembryonic antigen (CEA) level and lactate dehydrogenase (LDH) have been reported to be significant prognostic factors in different stages of pancreatic cancer [8–15]. In

addition, several studies demonstrated that baseline performance status is an important independent prognostic factor for survival [5]. Moreover, patients with poor performance status usually do not benefit from combination or intensified chemotherapy regimens.

In a previous study, we studied immediate and long-term outcome in a limited number of patients with pancreatic cancer and evaluated the possible impact of different clinicopathologic factors on survival in Turkey, as a developing country [8]. Here, we aim to identify and evaluate the same clinicopathologic factors in a larger cohort and to elucidate the clinical importance of Eastern Cooperative Oncology Group (ECOG) performance status for the outcome of pancreatic cancer.

Materials and methods

Data of 335 patients with histologically confirmed diagnosis of pancreatic adenocarcinoma, treated and followed up in our clinic were recorded from medical charts. The localization of tumor was determined either surgically, endoscopically or radiologically. Pathologic confirmation of pancreatic cancer was obtained by surgery or fine-needle aspiration biopsy. Patients who underwent surgery were staged pathologically, whereas staging of initially inoperable patients was performed using various imaging modalities such as computed tomography (CT), magnetic resonance imaging, and positron emission tomography/CT scan. Patients were staged according to the International Union Against Cancer TNM classification [16].

Treatment choices of patients with localized resectable disease were either the Whippple procedure ($n = 34$) or pancreatectomy ($n = 33$). The type of surgery was determined according to the localization and extent of the tumor. Adjuvant chemotherapy was given to the majority of patients (75 %) and started within 3–6 weeks after surgery. A total of 50 Gy radiotherapy was administered in 25 fractions concomitantly with continous infusional fluorouracil (5-FU) or intravenous bolus 5-FU plus folinic acid. Patients without metastatic disease in whom curative surgery could not be performed due to an inoperable or unresectable tumor and in those with residual tunors after primary surgery were treated with same chemotherapy regimens that were given to patients with metastatic disease; the radiation dose was 60 Gy/30 fractions in these patients. Palliative surgery was performed on 33 patients.

Patients with locally advanced unresectable disease or metastatic disease were treated with the same chemotherapy regimens. Drug schemes were applied as follows: gemcitabine alone in 171 patients, combination of gemcitabine with platinum in 28 patients or with capesitabine in 4 patients or 5-FU in 3 patients and combination 5-FU with folinic acid in 1 patient. Response to chemotherapy was evaluated radiologically after 2–3 cycles of chemotherapy according to international criteria. Chemotherapy was continued until disease progression or unacceptable toxicity.

Possible prognostic variables were selected based on those identified in previous studies [8, 10–12]. Serum CEA and CA 19-9 levels were determined by microparticle enzyme immunoassay (Abbott Diagnostics, Chicago, IL, USA). Serum LDH levels, albumin, and hemoglobin were measured at presentation in our biochemical laboratory. Serum LDH activity was determined immediately after collection by the kinetic method on a Targa-3000 autoanalyzer (Pointe Scientific Inc., Lincoln Park, MI, USA) at 37 °C.

Statistical analysis

SPSS software (SPSS 16, Chicago, IL, USA) was used for statistical analysis. Quantitative analyses were summarized by median, minimum and maximum, and qualitative analyses were presented as frequencies and percentages. The chi-squared test was used to assess the difference in the distribution of the clinicopathologic parameters in the localized, locally advanced and metastatic subgroups.

Overall survival was determined as the time elapsed between the time of histologic diagnosis and the date of death or the date of last follow-up visit or the date of point of study if the patient was still alive at this time. Time-dependent variables and overall survivals were estimated by using Kaplan–Meier method; their differences were evaluated by the log-rank test. Multivariate analysis (Cox proportional hazards) was used to determine which variables had an independent effect on survival. All deaths were considered as events, regardless of their cause. A level of $p \leq 0.05$ was considered as statistically significant.

Results

Demographic, laboratory and clinicopathologic features of patients are presented in Table 1. The majority of patients were male (68 %) and young (<60 years old) (54 %). Aproximately half (53 %) of the whole group presented with jaundice and 64 % of all patients had weight loss during initial diagnosis. In contrast, only 24 % of patients had poor performance status (PS 2–4).

Distribution of prognostic factors including performance status among stages

Age and gender of patients in addition to serum hemoglobin, leukocyte, platelet, albumin and LDH levels were

Table 1 Distribution of prognostic factors between stages of disease

Characteristics	All patients (stages I–IV) %	Local (L) (stages I + II) %	Locally advanced (LA) (stage III) %	Metastatic (M) (stage IV) %	*p* value
Age (older; >60 years)	46	48	56	55	NS
Sex (male)	68	70	68	66	NS
Performance status (ECOG), poor (2–4)	24	11	18	34	<0.001
					L vs LA; p = NS
					L vs M; $p = 0.001$
					LA vs M; $p = 0.004$
Weight loss (yes; >10 %)	64	52	58	74	0.031
					L vs LA; p = NS
					L vs M; $p = 0.022$
					LA vs M; $p = 0.033$
Jaundice (yes)	53	73	58	42	0.001
					L vs LA; $p = 0.074$
					L vs M; $p < 0.001$
					LA vs M; $p = 0.016$
Localization (head)	64	86	69	50	<0.001
					L vs LA; $p = 0.024$
					L vs M; $p < 0.001$
					LA vs M; $p = 0.003$
Diameter (large; >3 cm)	70	47	85	75	<0.001
					L vs LA; $p < 0.001$
					L vs M; $p = 0.001$
					LA vs M; p = NS
Hemoglobin (anemia; <12 g/dl)	42	55	42	38	NS
WBC (leucocytosis; >10,000)	27	24	24	31	NS
Platelets (thrombocytosis; >450,000)	11	17	9	10	NS
Albumin (hypoalbuminemia; <4 g/dl)	56	46	63	54	NS
LDH (elevated; >450 U/l)	26	27	23	29	NS
CEA (elevated; >4 ng/ml)	50.9	21	40	66	<0.001
					L vs LA; p = NS
					L vs M; $p < 0.001$
					LA vs M; $p = 0.002$
CA 19-9 (elevated; >37 IU/ml)	80	58	82	85	0.008
					L vs LA; $p = 0.013$
					L vs M; $p = 0.003$
					LA vs M; p = NS
Response (complete + partial)	22	–	20	23	NS

distributed equally among the three groups (Table 1). However, performance status of patients, weight loss, jaundice, localization of tumor, tumor diameter, and serum levels of CEA and CA 19-9 were significantly different between groups. The proportion of patients with poor performance status was higher for metastatic disease (34 %) than localized (11 %) and locally advanced (18 %) disease ($p = 0.001$ for between locally vs metastatic disease; $p = 0.004$ for local advanced vs metastatic disease; $p > 0.05$ for locally vs local advanced disease, and $p < 0.001$ for non-metastatic vs metastatic disease).

Prognosis on survival

Localized disease

Fifty-nine (18 %) patients had localized disease (stage I or II). Table 2 summarizes the results of evaluation of

Table 2 Statistically significant ($p < 0.05$) prognostic factors predicting overall survival in non-metastatic, metastatic and whole groups

Stage	Univariate analysis	p	Multivariate analysis	p
Local disease (stages I–II)	Albumin level (normal vs low)	0.004		
	WBC (normal vs high)	0.010		
	Performance status (0–1 vs 2–4)	0.015		
	LDH (normal vs high)	0.022		
	CA 19-9 (normal vs high)	0.056		
Locally advanced disease (stage III)	LDH (normal vs high)	0.003	Performance status (0–1 vs 2–4)	0.040
	Performance status (0–1 vs 2–4)	0.010	Platelet (normal vs high)	0.048
	Platelet (normal vs high)	0.020		
	Response to chemotherapy (yes vs no)	0.045		
Metastatic disease (stage IV)	Performance status (0–1 vs 2–4)	<0.001	Performance status (0–1 vs 2–4)	0.002
	CA 19-9 (normal vs high)	<0.001	Tumor site (head vs others)	0.019
	CEA (normal vs high)	0.001	CA 19-9 (normal vs high)	0.034
	Jaundice (yes vs no)	0.004	CEA (normal vs high)	0.034
	Response to chemotherapy (yes vs no)	0.030	Jaundice (yes vs no)	0.043
	WBC (normal vs high)	0.035	Response to chemotherapy (yes vs no)	0.047
	Age (older vs younger)	0.040	Age (older vs younger)	0.048
All diseases (stages I–IV)	Performance status (0–1 vs 2–4)	<0.001	Performance status (0–1 vs 2–4)	<0.001
	Stage (non-metastatic vs metastatic)	<0.001	Stage (non-metastatic vs metastatic)	<0.001
	CA 19-9 (normal vs high)	<0.001	CA 19-9 (normal vs high)	0.001
	CEA (normal vs high)	<0.001	Tumor diameter (small vs large)	0.018
	Platelet (normal vs high)	0.012		
	Tumor diameter (small vs large)	0.020		
	LDH (normal vs high)	0.022		
	WBC (normal vs high)	0.049		

prognostic factors associated with overall survival. The median survival duration of the patients with localized disease was 664 days, and the survival rates at 1 year and 5 years were 41 % and 5 %, respectively. As expected, these patients were associated with improved survival compared with the locally advanced or metastatic disease patients ($p < 0.001$). Univariate analysis showed that in addition to decreased albumin level, increased leukocyte count, increased LDH level, and elevated CA 19-9, patients with poor performance status were associated with poor outcome compared to those with good performance status as seen in patients with localized disease (371 vs 705 days, $p = 0.015$) (Fig. 1a). However, multivariate analysis did not reveal any statistically significant variable which can predict the outcome (Table 2).

Locally advanced disease

Of the 122 (36 %) patients with local advanced disease (stage III), the median survival duration was 309 days, and the 1-year survival rate was 13 %. Similar to patients with elevated LDH levels, thrombocytosis, and unresponsiveness to chemotherapy, patients with poor performance status had a shorter survival outcome compared to those with normal values (Table 2). Median survival of patients with good and poor performance status was 322 and 138 days, respectively ($p = 0.01$) (Fig. 1b). When using the Cox model, poor performance status ($p = 0.04$, 95 % CI 0.288–0.958) was found to be an independent unfavorable prognostic factor in patients with locally advanced disease.

Metastatic disease

The median survival time of 154 (46 %) patients with metastatic disease (stage IV) was 179 days, and the 1-year survival rate was 7 %. In univariate analyses, patients with poor performance status had a poorer outcome than those with good performance status (93 vs 223 days, $p < 0.001$) (Table 2; Fig. 1c). Additionally, high CA 19-9 level, high CEA level, presence of jaundice, leukocytosis, old age, and unresponsiveness to chemotherapy were associated with shorter survival. Multivariate analysis revealed that poor performance status similar to other variables, including tumor localization at head of pancreas, high CA 19-9 and CEA levels, presence of jaundice, response to chemotherapy, and age >60 years was found to be a statistically significant parameter on outcome ($p = 0.002$, 95 % CI 0–0.18).

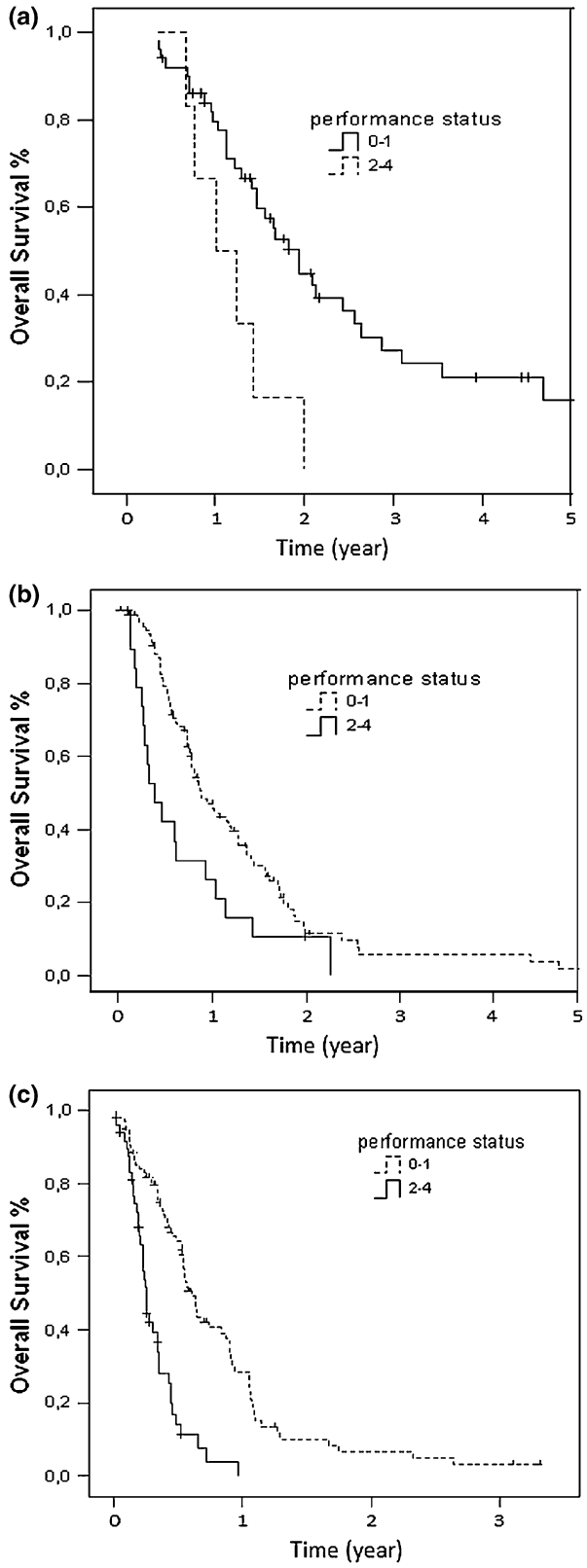

Fig. 1 Overall survival of patients with **a** localized ($p = 0.015$), **b** locally advanced ($p = 0.01$), or **c** metastatic disease ($p < 0.001$) according to performance status

All patients

At the time of analysis, 74 (21 %) patients were alive, 261 (75 %) patients had died and 14 (4 %) patients were lost-to-follow-up. The median time of follow-up was 290 days (range 1–78 months) for all patients. The median survival time was 280 ± 23 days. Univariate analysis revealed that advanced disease, high CA 19-9 level, high CEA level, thrombocytosis, large tumor diameter, high LDH level and leukocytosis were associated with poor outcome in all patients (Table 2). Patients with poor performance status also had shorter overall survival than those with good performance status ($p < 0.001$) (Fig. 2a). However, only performance status in addition to stage of disease, serum CA 19-9 level and tumor diameter were found to be independent prognostic factors in multivariate analyses ($p < 0.001$) (Fig. 2a, b).

Association between performance status and various clinical factors

Table 3 summarizes the analyses of the association of initial ECOG performance status and various clinical features and laboratory findings. Patients with poor performance status had some unfavorable clinical prognostic factors including age of patients, stage of disease, presence of jaundice and response to chemotherapy compared with those who had good performance status. Anemia, thrombocytosis, and elevated CEA levels were more common in patients with poor performance status than those with good performance status (Table 3).

Overall survival according to performance status

In the poor performance status group, univariate analysis showed that patients with severe weight loss ($p = 0.007$), large tumor diameter ($p = 0.046$), and especially metastatic disease ($p < 0.001$) had a significantly shorter overall survival than those without the above-mentioned parameters (Table 4). However, in multivariate analysis, we could not find any statistically significant variable that could predict overall survival of patients with poor performance status.

Discussion

Pancreatic cancer patients usually have a poor prognosis [17]. There are several studies which investigated clinicopathologic and laboratory variables which can predict the outcome in pancreatic cancer [18–21]. The evaluation of initial clinical and laboratory features could enable

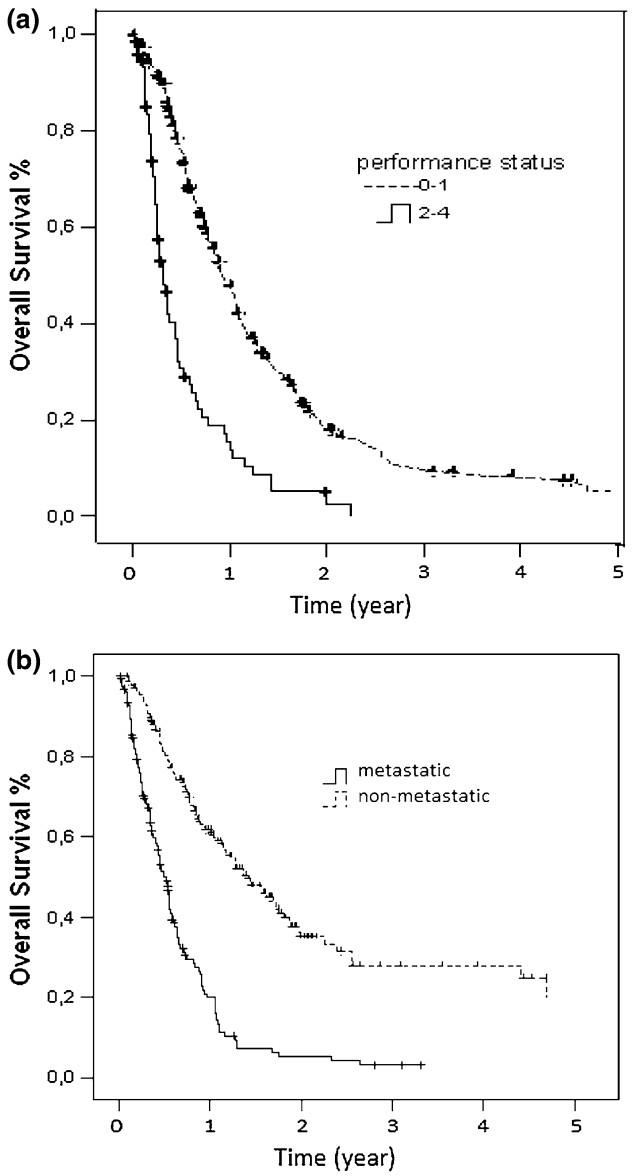

Fig. 2 Overall survival of **a** all patients according to performance status ($p < 0.001$) or **b** whole group according to stage of disease ($p < 0.001$)

physicians to identify individuals with a potentially better prognosis. This will result in improved management of patients and increased overall survival in pancreatic cancer. The current retrospective study was also designed to analyze prognostic factors for overall survival in pancreatic cancer patients in Turkey, as a developing country.

Performance status has been a recognized prognostic factor in multiple cancers treated with definitive intent. In pancreatic cancer patients who have been definitively treated, performance status is consistently shown to influence overall survival [9, 18, 19]. This study also suggests that ECOG performance status is a major independent prognostic factor for overall survival at all stages of pancreatic cancer even in early localized disease. This may be due to the increased percentage of patients with older age, jaundice, anemia and/or decreased chemotherapy response in patients with poor performance status. The inability and/or decreased compliance of these patients to administered therapies are possible co-factors which cause a worse outcome.

Table 3 Distribution of prognostic factors between good and poor performance status groups

Characteristics	PS 0–1 %	PS 2–4 %	*p*
Age (older)	42	58	**0.018**
Sex (male)	67	74	0.89
Disease stage [advanced (III–IV)]	79	90	**<0.001**
Weight loss (yes)	65	68	0.74
Jaundice (yes)	49	68	**0.008**
Tumor site (head)	66	57	0.21
Tumor diameter (large)	68	71	0.73
Hemoglobin (anemia)	39	55	**0.031**
WBC (elevated)	24	33	0.19
Platelet (elevated)	13	4	**0.05**
Albumin (low)	56	63	0.52
LDH (elevated)	28	29	0.90
CEA (elevated)	47	65	**0.055**
CA 19-9 (elevated)	80	84	0.55
Response to chemotherapy (yes)	25	0	**0.02**

Bold *p* values are statistically significant ($p < 0.05$ and $p = 0.005$)

Once performance status is defined as a clinically relevant prognostic factor for patient outcome, the question needs to be asked if performance status can also be used to guide adequate treatment selection. Several recently published randomized trials comparing gemcitabine with gemcitabine plus cisplatin or oxaliplatin or tipifarnib showed that baseline performance status and disease stage were independent prognostic factors for survival in pancreatic cancer [22–24]. Additionally, Storniolo et al. [25] reported that the benefit from single agent gemcitabine is very low if patients with a Karnofsky performance status <70 % were treated. If chemotherapy is planned to be administered to a patient, the next question should be whether combination or single agent chemotherapy is optimal. The relevance of performance status with regard to this particular question was evaluated based on a randomized trial comparing a combination of gemcitabine/cisplatin with gemcitabine alone [22]. Patients with poor performance status usually do not benefit from combination or intensified chemotherapy regimens and the outcome of patients with a poor performance status status was not affected by the choice of treatment. Further phase III trials supported these findings [26]. A significant superiority of combination chemotherapy for the whole study population

Table 4 Statistically significant prognostic variables for survival according to performance status

Performance status	Univariate analysis	*p*	Multivariate analysis	*p*
Good (PS 0–1)	Stage (non-metastatic vs metastatic)	<0.001		
	CA 19-9 (normal vs high)	<0.001	CA 19-9 (normal vs high)	0.03
	CEA (normal vs high)	0.005	Diameter of tumor (small vs large)	
	LDH (normal vs high)	0.016		0.055
	Platelets (normal vs high)	0.021		
	Response to chemotherapy (yes vs no)	0.022		
	Diameter (small vs large)	0.044		
Poor (PS 2–4)	Stage (non-metastatic vs metastatic)	<0.001		
	Weight loss (yes vs no)	0.007		
	Diameter (small vs large)	0.046		

could not be demonstrated in any of these studies, whereas patients with good performance status could have a significant clinical benefit [26].

Our analyses revealed that patients with weight loss, metastatic disease and large primary tumor were found to have a worse prognosis by univarite analysis. Moreover, patients with a good performance status had a clear benefit from combination chemotherapy with regard to survival, similar to the literature [22]. Despite sensitivity to chemotherapy being similar between patients with poor and good performance status, poor performance status affects the outcome of patients undergoing chemotherapy which is why patients with poor performance status have a worse prognosis.

Our results also demonstrated that higher levels of serum CA 19-9 and older age may predict a poor outcome for survival in patients with metastatic pancreatic cancer [14, 15]. Presence of jaundice, unresponsiveness to chemotherapy and primary tumor localization at the head of the pancreas were other independent prognostic factors in our patients with metastatic disease. The importance of hemoglobin level at any stage of pancreatic cancer could not be demonstrated in this analysis in contast to previous reports [9].

In conclusion, the majority of pancreatic cancer patients still have a poor prognosis. Therefore, establishing clear prognostic variables during initial diagnosis may help physicians to decide which patients should be considered for supportive care only, single agent chemotherapy, combination chemotherapies or multimodality treatment options. In this study, we demonstrated that the ECOG performance status is one of the major prognostic factor influencing survival at all stages of pancreatic cancer. Additionally, patients with poor performance status may be recommended for different treatment options if patients do not lose weight, have non-metastatic disease and have small diameter primary tumors.

Conflict of interest None.

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