RESEARCH ARTICLE

Evaluation of Prognostic Factors and Survival Results in Pancreatic Carcinomas in Turkey

Emine Canyilmaz[1]*, Lasif Serdar[1], Gonca Hanedan Uslu[2], Gulsen Soydemir[1], Zumrut Bahat[1], Adnan Yoney[1]

Abstract

Background: The goal of this retrospective study was to evaluate patient characteristics, treatment modalities and prognostic factors in Turkish patients with pancreatic cancer. Materials and Methods: Between January 1997 and December 2012, 64 patients who presented to the Department of Radiation Oncology, Karadeniz Technical University, Faculty of Medicine with a diagnosis of pancreatic cancer were evaluated. The E/K ratio of the cases was 2.4/1 and the median age was 59.6 (32-80) years, respectively. Some 11 cases (18%) were stage 1, 21 (34.4%) were stage 2, 10 (16.4%) were stage 3, and 19 (31.1%) were metastatic. Results: The mean follow-up time was 15.7 months (0.7-117.5) and loco-regional recurrence was noted in 11 (40.7%) who underwent surgery while metastases were observed in 41 patients (66.1%). The median overall survival (OS) was 11.2 months and the 1, 3 and 5-year OS rates were 41.7%, 9.9% and 7.9% respectively. The median disease-free survival (DFS) was 5.2 month and the1, 2 and 5 year DFS were 22.6%, 7.6% and 3.8% respectively. On univariate analysis, prognostic factors affecting OS included status of the operation (p<0.001), tumor stage (p=0.008), ECOG performance status (p=0.005) and CEA level (p=0.017).On multivariate analysis, prognostic factors affecting survival included status of the operation (p=0.033) and age (p= 0.023). Conclusions: In the current study, age and operation status were independent prognostic factors for overall survival with pancreatic patients. Thus, the patients early diagnosis and treatment ars essential. However, prospective studies with more patients are needed for confirmation.

Keywords: Pancreatic cancer - radiotherapy - chemotherapy - CEA

Asian Pac J Cancer Prev, **14 (11)**, 6573-6578

Introduction

Pancreatic cancer is an extremely aggressive malignancy, and is the fourth most common cause of cancer-related death in the Western world. Surgical resection is the only curative option. Only 20% of patients with pancreatic cancer present at a resectable stage, 50% of these are metastatic, and 30% are at a locally advanced stage. When all stages are taken into consideration, the median survival is 5-8 months, and the 5-year survival rate is less than 5% (Barreto et al., 2007; 2010). Poor prognosis is related to delayed diagnosis of the disease, a highly malignant potential, high rate of metastases, and high resistance to anti-tumor agents (Bayraktar et al., 2010).

In recent years, studies have shown that the addition of chemotherapy has contributed insignificantly to survival. This has led to the investigation of new therapeutic modalities (Bramhall et al., 1995; Boeck et al., 2007; Berhard et al., 2010). Among these new approaches, radiation therapy (RT) following systemic chemotherapy (CT) appears to be potentially useful as a treatment method (Brennan et al., 2004). Although new developments in the radiotherapy improve local control rates, systemic failure continues to be a major obstacle in improving survival (Burris et al., 1997).

In this study, patients who presented to the Department of Radiation Oncology, Karadeniz Technical University, Faculty of Medicine between January 1997 and December 2012 with a diagnosis of pancreatic cancer were studied. Treatment results and prognostic factors affecting survival were evaluated.

Materials and Methods

Patients:

In this study, 64 patients who presented to the Department of Radiation Oncology, Karadeniz Technical University, Faculty of Medicine between January 1997 and December 2012 with the diagnosis of pancreatic cancer were evaluated retrospectively. Patient information was obtained through files, conversations with patients or their relatives directly and/or by phone calls. Two patients were lost to follow-up, and one patient could not be reached. Thus, the assessment of survival was performed on 61 patients.

*Department of Radiation Oncology, [1]Faculty of Medicine, Karadeniz Technical University, [2]Kanuni Research and Education Hospital, Trabzon, Turkey *For correspondence: dremocan@yahoo.com*

Staging of patients was performed in accordance with the American Joint Committee on Cancer staging system, 7th edition, 2010 TNM staging system. Performance evaluation was performed according to the Eastern Cooperative Oncology Group (ECOG).

Treatment

RT was performed between January 1997-June 2011 in a two-dimensional planning system via the Co60 and/or linear accelerator (6-10 MV), and after June 2011 via the Linear accelerator (6-18 MV) apparatus with the three-dimensional planning system. Until June 2011, anterior or posterior RT, or multi-field RT was performed at fractions of 1.8-2 Gy daily for a total of 45-50.4 Gy. After June 2011, three-dimensional conformal RT, or the Intensity-Modulated Radiation Therapy technique was performed at the same dose and fraction. Except for patients who were treated with palliation, the area for radiotherapy was planned to include tumor and lymphatic regions, and after exclusion of lymphatic regions over 45 Gy, 5-14.4 Gy additional doses were administered to the tumor area. CT was then added to the treatment in various doses prior to and after radiotherapy.

Endpoints

Overall survival was defined as the duration from diagnosis to the last follow-up or date of death. Disease-free survival was defined as the duration from the operation to recurrence or metastasis, and for inoperable patients from the date of diagnosis to metastasis.

Statistical analysis

Statistical analysis was performed with the SPSS version13 software. In order to examine the distribution of survival times, Kaplan-Meier survival analysis was used. To examine the difference in survival between groups, the log-rank test was used, and the Bonferroni correction was used to make comparisons among groups. On multivariate analysis, independent factors predicting survival were analyzed using the Cox regression analysis. A Type-1 error level of less than 5% was considered significant.

Results

Patient characteristics

Curative surgery was performed in 27 patients (43.5%) with the diagnosis of pancreatic cancer. In the study group, 35 (56.5%) patients were considered inoperable for T4 disease, metastatic involvement and poor performance status. The Whipple procedure was performed in 23 patients (85.2%) and total excision was perfomed in 4 patients (14.8%).The surgical margin was positive in 9 cases (33.3%) and negative in 17 (63%). The information about the status of surgical margins of 1 case (3.7%) could not be obtained. Patient characteristics are summarized in Table 1.

Treatment facilities

Prior to RT, 26 (41.9%) patients underwent CT. Of these, 15 patients were (57.7%) inoperable, and 11 (42.3%) were operable. For chemotherapeutic regimens, gemcitabine was administered to 10 (38.5%) patients, while gemcitabine with cisplatin was administered to 10 (38.5%) patients, 5 FU+folinic acid was administered to 4 (15.4%) patients, and other CT regimens were administered to 2 (7.7%) patients. The number of patients who were cured from CT prior to RT was 4.35 (1-12). RT treatment was administered as part of chemoradiotherapy (CRT) in 27 of 60 patients (45%), while 8 (13.3%) underwent radical RT without CT and palliative RT was administered to 25 (41.7%) patients.

In 17 of 27 (63%) patients who underwent CRT with gemcitabine, 10 patients (37%) received 5-FU+folinic acid-based CT regimens. In patients who underwent RT, 1.8-2 Gy/day to a total 45-50.4 Gy was administered. While 21.6 Gy was given to 1 patient who subsequently died, 9 Gy was administered to 1 patient due to the deterioration of the general condition of the patient, and 36 Gy RT was administered to 1 patient due to renal toxicity. Only 15 patients (55.6%) were administered RT at 50.4 Gy. The average dose of RT in patients who underwent CRT was 45.9 Gy (9-50.4). Without addition of CT, treatment at the same dose and fraction was planned in 8 patients who underwent RT. Any patient with impaired general condition was administered 30 Gy RT. The average dose of RT in patients receiving curative RT was 47.4 (30-59.4) Gy.

With palliative RT at a fraction of 3 Gy/day, a total of 30 Gy was administered. RT was directed to the pancreatic

Table 1. Patient characteristics

Characteristics		Value
Age (year)	Median (range)	62 (32-80%)
Gender	Male	44 (71.0%)
	Female	18 (29.0%)
ECOG performance status	0-1	48 (77.4%)
	2-3	11 (17.7%)
Operation Status	Operated	27 (43.5%)
	Not operated	35 (56.5%)
Location of primary tumor	Head	39 (62.9%)
	Body	6 (9.7%)
	Tail	10 (16.1%)
	Head-Body	2 (3.2%)
	Body-Tail	4 (6.5%)
Stage	I	11 (18.0%)
	II	21 (34.4%)
	III	10 (16.4%)
	IV	19 (31.1%)
Histologic grade	G1	11 (17.7%)
	G2	7 (11.3%)
	G3	8 (12.9%)
	Unknown	36 (58.1%)
Pre-treatment CA 19-9	Normal	10 (16.1%)
	High	26 (41.9%)
	Unknown	26 (41.9%)
Pre-treatment CEA	Normal	15 (24.2%)
	High	17 (27.4%)
	Unknown	30 (48.4%)
Treatment	Surgery+RT+CT	28 (45.2%)
	RT+CT	21 (33.9%)
	RT	13 (21.0%)
Radiotherapy type	CRT	27 (45.0%)
	Radical RT	8 (13.3%)
	Pallliative RT	25 (41.7%)

Table 2. Results of log-rank univariate analysis for overall survival

Variable		n	Median Survival (months) (95% CI)	1-y OS (%) (±SE)	2-y OS (%) (±SE)	3-y OS (%) (±SE)	5-y OS (%) (±SE)	p
Age (year)	≤60	29	12.0 (8.7-15.3)	48.3 (±0.09)	24.1 (±0.08)	10.3 (±0.06)	10.3 (±0.06)	0.220
	>60	32	8.8 (4.5-13.2)	35.7 (±0.09)	10.7 (±0.07)	10.7 (±0.07)	5.4 (±0.05)	
Gender	Male	43	10.4 (7.7-13.1)	34.0 (±0.07)	16.0 (±0.06)	8.0 (±0.04)	5.3 (±0.04)	0.283
	Female	18	14.7 (10.0-19.3)	60.6 (±0.12)	22.7 (±0.11)	15.2 (±0.09)	15.2 (±0.09)	
ECOG performance status	0-1	47	12.0 (9.9-14.2)	48.4 (±0.07)	22.9 (±0.06)	2.7 (±0.05)	10.2 (±0.05)	0.005
	2-Mar	11	6.3 (0.8-11.8)	18.2 (±0.12)	-	-	-	
Operation Status	Operable	27	16.5 (10.6-22.4)	66.3 (±0.09)	37.8 (±0.09)	23.6 (±0.09)	18.9 (±0.08)	<0.001
	Inoperable	34	7.8 (5.3-10.4)	22.1 (±0.07)	3.2 (±0.03)	-	-	
Location of primary tumor	Head	41	11.2 (8.5-13.9)	43.3 (±0.08)	18.8 (±0.06)	12.5 (±0.06)	12.5 (±0.06)	0.406
	Body/Tail	20	10.4 (4.6-16.2)	38.5 (±0.11)	16.5 (±0.09)	5.5 (±0.05)	-	
Surgical margin status	Negative	17	17.5 (12.5-22.6)	70.1 (±0.11)	44.6 (±0.12)	25.5 (±0.11)	25.5 (±0.11)	0.165
	Positive	9	12.5 (6.4-18.5)	55.6 (±0.17)	-	-	-	
Stage	I-II	32	12.5 (10.8-14.2)	52.6 (±0.09)	28.1 (±0.08)	16.0 (±0.07)	16.0 (±0.07)	0.008
	III	10	11.2 (8.6-13.8)	46.7 (±0.17)	-	-	-	
	IV	18	5.6 (0.0-13.5)	16.7 (±0.09)	5.6 (±0.05)	-	-	
Histologic grade	G1-G2	18	12.5 (9.8-15.2)	54.5 (±0.12)	24.2 (±0.11)	12.1 (±0.08)	12.1 (±0.08)	0.608
	G3	8	6.3 (0.0-18.6)	37.5 (±0.17)	18.8 (±0.16)	18.8 (±0.16)	18.8 (±0.16)	
Pre-treatment CA 19-9	Normal	10	8.8 (2.6-15.0)	50.0 (±0.16)	25.0 (±0.15)	12.5 (±0.12)	12.5 (±0.12)	0.457
	High	26	9.8 (7.1-12.5)	26.9 (±0.09)	11.5 (±0.06)	3.8 (±0.04)	3.8 (±0.04)	
Pre-treatment CEA	Normal	15	12.5 (9.0-16.0)	51.3 (±0.13)	29.3 (±0.12)	14.7 (±0.10)	14.7 (±0.10)	0.017
	High	17	7.6 (3.7-11.4)	17.6 (±0.09)	5.9 (±0.06)	-	-	

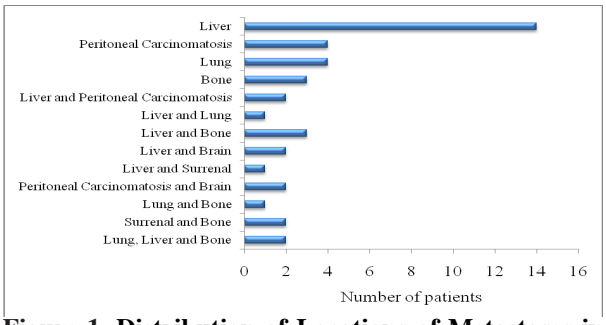

Figure 1. Distribution of Locations of Metastases in Patients with Pancreatic Cancer

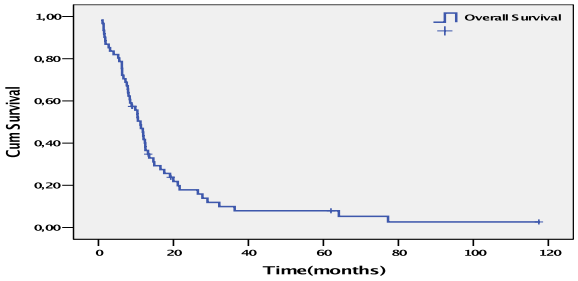

Figure 2. Overall Survival

bed in 11 (44%) patients undergoing palliative RT, in 8 patients (32%) to the involved bones, in 4 (16%) patients to the cranium, and in 2 (8%) patients, it was directed to lung metastases. The average dose of RT in patients receiving palliative RT was 26.8 (5.4-30) Gy.

After treatment with RT, 29 (46.8%) patients received chemotherapy. 17 (58.6%) patients received gemcitabine, 6 (20.7%) patients received gemcitabine with cisplatin, 2 (6.9%) patients received 5-FU+folic acid, and 4 (13.7%) patients received other chemotherapy regimens. The average number of patients who were cured was 5.17 (1-12).

Relapsing features

The average duration of follow-up was 15.7 months (range 0.7-117.5). In 11 (40.7%) patients who underwent surgery during follow-up, local-regional recurrence was observed, and when the whole group was taken into consideration, metastases were observed in 41 (66.1%) patients. In 5 patients, (8.1%), both metastasis and recurrence were noted. The distribution of metastatic regions included the liver in 25 (60.9%) patients, bone in 11 (26.8%) patients, peritoneal carcinomatosis in 8 patients (19.5%), lung in 8 patients (19.5%), brain in 4 (9.7%) patients, and adrenal metastases in 3 (7.3%) patients (Figure 1).

During follow-up, 56 (90.3%) patients died. The observation and treatment of 6 (9.7%)patients who survived is ongoing.

Survival

Median overall survival (OS) 11.2 months and (95%GI:9-13 .3) 1, 3 and 5 year GS are respectively, 41.7%(SE±0.064), 9.9% (SE±0.041) and 7.9% (SE±0.037) (Figure 2).

On univariate analysis, age (≤60 and>60), status at operation (operated with inoperable), stage (1-2, 3 and 4), gender, ECOG (0-1 and 2-3),CEA level before treatment (normal to high), CA 19-9 level before treatment (normal to high), tumor size (≤4 and >4cm), tumor location (the head-to-tail and the body), tumor grade (good, moderate and bad), nodal involvement, surgical margin status and radiation therapy (CRT with radical RT) were investigated as prognostic factors that could affect OS. Of these, operative status, stage, ECOG performance status, pre-operative CEA level were statistically significant. The results of univariate analysis are summarized in Table 2.

On multivariate analysis, age (≤60 and >60), operative status (operated with inoperable), stage (1-2, 3 and 4), gender, ECOG (0-1 and 2-3), CEA level before treatment (normal to high) were investigated as prognostic factors that could affect survival. Among these variables, the operation status [HZ: 2.4 (95%CI:1.07-5.5 GI)] (p=0.033) and age [HZ:2.6 (95%CI:1.1-6.3GI)] (p=0.023) were found to be significant. The results of multivariate analysis

Table 3. Results of multivariate analysis for overall survival by Cox proportional hazard model

Variable	Variable classification	Hazard Ratio (95% CI)	p
Age (year)	≤60 >60	2.7 (1.15-6.32)	0.023
Operation status	Opere Inop	2.4 (1.07-5.53)	0.033
Stage	I-II III-IV	1.26 (0.41-3.90)	0.686
ECOG performance status	0-1 2-3	1.60 (0.54-4.74)	0.392
Pre-treatment CEA	Normal High	1.31 (0.56-3.04)	0.531

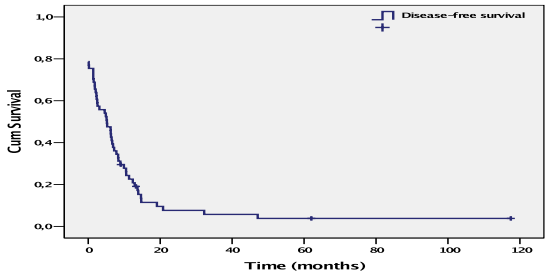

Figure 3. Disease-Free Survival

are summarized in Table 3.

The median disease-free survival was (HS) 5.2 months (95%CI: 1.7-8 .6 GI) and the 1-2 and 5-year survival are 22.6% (SE±0.05). 7.6% (SE±0.04), and 3.8% (SE±0.03) respectively (Figure 3).

In patients who underwent surgery, while the HS median was 8.9 months (95%GI: 2.9-15.0) in 40.1%, the 1-2 and 5-year HS was (SE±0.10), 18.1% (SE±0.08) and 9% (SE± 0.06) respectively. In inoperable patients, while the HS median was 1.5 months (95%GI: 0.0-3.9), the 1-year HS was 8.8% (SE±0.05). On univariate analysis, a statistically significant relationship (p<0.001) was found between operation status and disease-free survival. The time to recurrence and/or metastasis on average was 5.6 months (range 0-47.1).

Discussion

There is a marked increase in the incidence of pancreatic cancer (Barreto et al., 2007). Patients with pancreatic cancer have a very poor prognosis. Although rates of 10-15% have been reported, the 5-year survival rates after resection in many centers is exceptional (Charles et al., 2005; Barreto et al., 2007). In a review by Gudjonsson (Conlon et al., 1996), the OS rate was reported as <0.4%, with the best overall survival rate in surgical trials being only 3.6%. However, despite high recurrence rates, surgery was identified as a factor that increased survival significantly. Other published results of the 5-year survival ranged from 5-40%, and less than 3% of patients were cured. With such a poor prognosis, it has been difficult to assess the effectiveness of therapeutic advances (Foo et al., 1993). In our study, while the median OS was 11.2 months, the 1-2-3 and 5-year OS were found to be 41.7%, 17.8%, 9.9% and 7.9% respectively, and these rates are consistent with the literature.

Pancreatic cancer is rarely seen before the age of 45 years, and approximately 80% of the cases occur between the ages of 60 and 80 years (Garcea et al., 2008). In our study, the median age of patients was 62 years (32-80), and this is consistent with the literature. Vainshtein et al. (Vainshtein et al., 2012) found that age was predictive of overall survival. In our study, age was found to be a prognostic factor associated with OS (p=0.023). The risk of death in patients over 60 years old was 2.6 times greater.

Worldwide, pancreatic cancer is seen more commonly in men than in women with a male/female ratio ranging from 1.5-2. However the data from England also shows that the male predominance has fallen to 1.25: 1 over the last 20 years (Bramhall et al., 1995). In our study, the male/female ratio was 2.4/1. As stated in several studies, performance status is a well-known prognostic factor (Boeck et al., 2007; Bernhard et al., 2010). In our study, a statistically significant difference between ECOG 0-1 and ECOG 2-3 in terms of survival (p=0.005) was noted, which is compatible with the literature.

Among pancreatic cancers, 60- 70% occur at the head of the pancreas, 15-20% in the body of the pancreas, and 5-10% at the tail of the pancreas. In 16-30% of pancreatic cancers, multifocal disease is noted (Charles et al., 2005). In our study, in 62.9% of patients, the tumor was located at the head of the pancreas, in 9.7% at the body of the pancreas, in 16.1% at the tail, and 9.7% of patients presented with multifocal disease. Although ductal epithelial cells consist of lower than 5% of pancreatic tissue, more than 90% of exocrine pancreatic cancers are adenocarcinomas originating from the ductal epithelium (Charles et al., 2005). In our study, the histopathologic diagnosis was adenocarcinoma in 72.6% of patients.

Among other prognostic factors affecting survival in pancreatic cancer, tumor resectability, surgical margin status, and tumor stage are considered important (Evans et al., 2001; Lim et al., 2003; Brennan et al., 2004). In our study, on univariate and multivariate analysis, a statistically significant relationship (p<0.001) was found between OS and the tumor resectability. While the median survival was 16.5 months in patients who underwent surgery, it was 7.8 months in patients who were inoperable. When the surgical margin status was assessed, it was found that the median OS in patients who had undergone surgery with positive surgical margins was 12.5 months, while the median OS was 17.5 months in those with negative surgical margins. The survival time was significantly lower in the group with positive surgical margins, although it did not reach statistically significance due to the small sample size.

The 5-year survival rates in the literature have been reported to be 31.4% at stage IA, 27.2% at stage IB, 15.7% at stage IIA, 7.7% at stage IIB, 6.8% at stage III and 2.8% at stage IV (Herreros-Villanueva et al., 2012). While the median survival of patients with locally advanced pancreatic cancer was 6-10 months, in metastatic pancreatic cancer, the survival rate was only 3-6 months (Moertel et al., 1969; Burris et al., 1997). In our study, the median survival was 12.5 months in patients who presented at stage 1-2, 11.2 months in patients who presented at stage 3, and 5.6 months in patients who

presented at stage 4. While the 5-year survival rate for stages I-II was 16%, there were no survivors at 5 years at stages III and IV. On univariate analysis, a statistically significant relationship was found between stage and survival (p=0.008). On linear analysis, a linear relationship between stage and OS was observed (p=0.033). As the stage increased, the OS worsened. This result is consistent with the literature.

The use of CEA as a biomarker for pancreatic adenocarcinoma was investigated, but compared to CA 19-9, it was found to be less sensitive and specific for pancreatic cancer (Winter et al., 2013). A study by Ishii et al. (1996) showed that performance status, CEA levels <10 ng/mL, and absence of distant metastases before treatment were statistically significant prognostic factors that affected survival. In this study a statistically significant relationship was found between CEA levels and survival (p=0.017).

CA 19-9 is a unique tumor marker approved by the FDA for pancreatic adenocarcinoma. It is used to determine prognosis and tumor burden (recurrence or progression) (Winter et al., 2013). In many studies, the CA 19-9 level was included among well-known prognostic factors (Boeck et al., 2007; Bernhard et al., 2010). However, in our study, no significant relationship between CA 19-9 levels and survival was found. The main reason for this may be low number of patients who did not undergo CA 19-9 testing.

Existing studies report local recurrence at a rate of 50-86%, and distant metastases at a rate of 40-90% after surgery (Ozaki et al., 1992; Klinkenbijl et al., 1999). In a literature review by Garcea et al. (2008) even in the most positive subgroup with 10-15% of patients with newly diagnosed pancreatic cancer, a loco-regional recurrence rate of 50-80% and systematic failure rate of 70% has been reported. The European Study Group for Pancreatic Cancer" (ESPAC) -1 reported a local recurrence rate of 63% (Neoptolemos et al., 2004). In a study conducted by Yovino et al. (2012) in patients with pancreatic cancer, a recurrence rate of 69% was reported in a 2-year follow-up period with the most common site of recurrence being the liver in 49% of patients. When the areas of treatment failure in patients with pancreatic cancer were studied, the liver and peritoneal bed after resection were the most common locations. In our study, 40.7% of patients who underwent surgery during follow-up were noted to have loco-regional recurrence. When the whole group was evaluated, the rate of metastasis was 66.1%. The most common site of metastasis was the liver in 60.9% of patients. The other metastatic sites were bone in 26.8% of patients, peritoneal carcinomatosis in 19.5%, and the lung in 19.5% of patients.

In studies involving patients who underwent curative surgery, postoperative RT and CT, a median survival of 10.9-22.7 months was reported. The 2-year survival was reported to be 18-50% (Gastrointestinal Tumor Study Group et al., 1988; Foo et al., 1993). In patients who were inoperable and underwent RT and CT, the median survival increased from 3-6 months to 9-13 months, and the 2-year survival rates increased from 0-5% to 10-20%. In one study, while the median survival in patients who received only RT was 6 months, the survival in patients who underwent RT with 5FU chemotherapy increased to 10 months (Herreros-Villanueva et al., 2012). Sultana et al. (2007) in their systematic review, which included a meta-analysis, showed that in locally advanced pancreatic cancer, CRT and survival increased only when compared with RT, and the risk of death was reduced by 32%. In this study, in patients who were operable and treated with CRT, the median survival was 12.5 months, while the 2-year survival was 34.4%. In patients who were operated and treated with curative RT, the median survival was 19.1 months while the 2-year survival was 50%. The median survival in patients who were inoperable and treated with CRT was 11.3 months, while the 1-year survival was 33.3%. When taking into consideration the entire sample of patients, in patients treated with CRT, the median OS was 12.4 months, and in patients receiving curative RT, the median survival was 19.1 months. The difference between the two groups was not statistically significant.

Krishnan et al. (2006) reported in their study that in patients with unresectable locally advanced pancreatic cancer, the median disease-free survival was 4.2 months, and the overall survival was 8.5 months after CRT. In our study, the median HS in the whole group was 5.2 months, and the 1-2 and 5 year HS was 22.6%, 7.6% and 3.8%, respectively. On univariate analysis, a statistically significant relationship was found between operation status and disease-free survival (p<0.001).

In conclusion, over the past two decades, although several efforts have been made to study the treatment of pancreatic cancer, little benefit in survival has been achieved. After the radical resection of early-stage disease, a high rate of metastatic recurrence indicates that pancreatic cancer is a systematic disease in most patients. In the current study, age and operation status was an independent prognosis factor for overall survival with pancreatic patients. Thus, the patients early diagnosis and treatment is essential. However, due to a retrospective study, prospective studies with more patients are needed.

Furthermore, as conventional treatments have shown only a lowest impact on disease course, development of new therapeutic strategies based on the molecular biology of pancreatic cancer must be a high priority.

References

Bayraktar S, Bayraktar UD, Rocha-Lima CM (2010). Recent developments in palliative chemotherapy for locally advanced and metastatic pancreas cancer. *World J Gastroenterol*, **16**, 673-82.

Bernhard J, Dietrich D, Glimelius B, et al (2010). Estimating prognosis and palliation based on tumour marker CA 19-9 and quality of life indicators in patients with advanced pancreatic cancer receiving chemotherapy. *Br J Cancer*, **103**, 1318-24.

Boeck S, Hinke A, Wilkowsky R, et al (2007). Heinemann V. Importance of performance status for treatment outcome in advanced pancreatic cancer. *World J Gastroenterol*, **13**, 224-7.

Bramhall SR, Allum WH, Jones AG, et al (1995). Treatment and survival in 13,560 patients with pancreatic cancer, and incidence of the disease, in the West Midlands: an epidemiological study. *Br J Surg*, **82**, 111-5.

Brennan MF, Kattan M, Klimstra D, et al (2004). Prognostic nomogram for patients undergoing resection for adenocarcinoma of the pancreas. *Ann Surg*, **240**, 293-8.

Burris HA, Moore MJ, Andersen J, et al (1997). Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*, **15**, 2403-13.

Conlon KC, Klimstra DS, Brennan MF (1996). Long-term survival after curative resection for pancreatic ductal adenocarcinoma. Clinicopathologic analysis of 5-year survivors. *Ann Surg*, **223**, 273-9.

Evans D, Abbruzzese J, Willett C (2001). Cancer of the pancreas, 6th ed. Philadelphia: Lippincott Williams and Wilkins,

Foo ML, Gunderson LL, Nagorney DM, et al (1993). Paterns of failure in grossly resected pancreatic ductal adenocarcinoma treated with adjuvant irradiation +/- 5 fluorourasil. *Int J Radiat Oncol Biol Phys*, **26**, 483-9.

Garcea G, Dennison AR, Pattenden CJ, et al (2008): Survival following curative resection for pancreatic ductal adenocarcinoma. A systematic review of the literature. *JOP,* **9**, 99-132.

Gudjonsson B (1995). Carcinoma of the pancreas: critical analysis of costs, results of resections, and the need for standardized reporting. *J Am Coll Surg*, **181**, 483-503.

Gastrointestinal Tumor Study Group (1985). Radiation therapy combined with Adriamycin or 5-fluorourasil for the treatment of locally unresectable pancreatic carcinoma. *Cancer*, **56**, 2563-8.

Gastrointestinal Tumor Study Group (1979). A multi-institutional comparative trial of radiation therapy alone and in combination with 5-fluorouracil for locally unresectable pancreatic carcinoma. *Ann Surg*, **189**, 205-8.

Heinemann V, Boeck S, Hinke A, et al (2008). Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer*, **8**, 82

Huguet F, Andre T, Hammel P, et al (2007). Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol*, **25**, 326-31.

Iacobuzio-Donahue CA, Fu B, et al (2009). DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. *J Clin Oncol*, **27**, 1806-13.

Ishii H, Okada S, Nose H, et al (1996). Prognostic factors in patients with advanced pancreatic cancer treated with systemic chemotherapy. *Pancreas*, **12**, 267-71.

Jemal A, Siegel R, Ward E, et al (2009). Cancer statistics, 2009. *CA Cancer J Clin*, **59**, 225-49.

Klaassen DJ, Maclntyre JM, Catton GE, et al (1985). Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorourasil alone with radiation plus concurrent and maintenance 5-fluorourasil- an Eastern Cooperative Oncology Group study. *J Clin Oncol*, **3**, 373-8.

Kindler HL, Niedzwiecki D, Sutherland S, et al (2010). Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol*, **28**, 3617-22.

Krishnan S, Rana V, Janjan NA, et al (2006). Prognostic factors in patients with unresectable locally advanced pancreatic adenocarcinoma treated with chemoradiation. *Cancer*, **107**, 2589-96.

Lim JE, Chien MW, Earle CC (2003). Prognostic factors following curative resection for pancreatic adenocarcinoma: a population based, linked database analysis of 396 patients. *Ann Surg*, **237**, 74-85.

Malik NK, May KS, Chandrasekhar R, et al (2012). Treatment of locally advanced unresectable pancreatic cancer: a 10-year experience. *J Gastrointest Oncol*, **3**, 326-34.

Moertel CG, Childs DS Jr, Reitemeier RJ, et al (1969). Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. *Lancet*, **2**, 865-7.

Mullinax JE, Hernandez JM, Toomey P, et al (2012). Survival after pancreatectomy for pancreatic adenocarcinoma is not impacted by performance status. *Am J Surg*, **204**, 704-8.

Neoptolemos JP, Stocken DD, Friess H, et al (2004). A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med*, **350**, 1200-10.

Ozaki H (1992). Improvement of pancreatic cancer treatment from the Japanese experience in the 1980s. *Int J Pancreatol*, **12**, 5-9.

Philip A, Mooney M, Jaffe D, et al (2009). Consensus report of the National Cancer Institute Clinical Trials Planning Meeting on pancreas cancer treatment. *J Clin Oncol*, **27**, 5660-9.

Sultana A, Tudur Smith C, Cunningham D, et al (2007). Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. *Br J Cancer*, **96**, 1183-90.

Vainshtein JM, Schipper M, Zalupski MM, et al (2012). Prognostic significance of carbohydrate antigen 19-9 in unresectable locally advanced pancreatic cancer treated with dose-escalated intensity modulated radiation therapy and concurrent full-dose gemcitabine: analysis of a prospective phase 1/2 dose escalation study. *Int J Radiat Oncol Biol Phys*, **86**, 96-101

Winter JM, Yeo CJ, Brody JR (2013). Diagnostic, prognostic, and predictive biomarkers in pancreatic cancer. *J Surg Oncol*, **7**, 15-22.

Yeo CJ, Yeo TP, Hruban RH, et al (2005). Cancer of the Pancreas. In: Devita, Vincent T.; Hellman, Samuel; Rosenberg, Steven A. Cancer: Principles and Practice of Oncology, 7th Edition, Lippincott Williams and Wilkins, 947-50 (Beyza-15).

Yovino S, Maidment BW 3rd, Herman JM, et al (2012). Analysis of local control in patients receiving IMRT for resected pancreatic cancers. *Int J Radiat Oncol Biol Phys*, **83**, 916-20.