



Upfront Treatment Modality May Have Prognostic Significance in Patients with Local/Locally Advanced Stage Pancreatic Cancer

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Abstract

Background: Cancer of the exocrine pancreas is highly lethal malignancy and the fourth leading cause of cancer related death in the worldwide. Systemic chemotherapy, radiation therapy and concomitant chemoradiotherapy are used as adjuvant treatment following surgical resection and provide survival benefit. The aim our study is to evaluate the prognostic significance of treatment options/sequences and clinical features in patients with local/locally advanced stage pancreatic cancer.

Material and Methods: In this study we retrospectively evaluated the prognostic significance of treatment modalities in local/locally advanced stage pancreatic cancer. A total of 64 patients have been treated in Baskent University Adana Research and Training Hospital between 2007 and 2018 included into our study.

Results: The median age of the patients was 61 (range 31 to 81) years and 42 (65.6%) of patients were male. The median follow-up time was 16 months and 46 (71.9%) of patients were died during follow-up. Disease-Free Survival (DFS) and Overall Survival (OS) were founded as 8, 18 months, respectively. Fifty-one (79.7%) of patients' disease recurrence after treatment. There were statistically significant differences in median OS and DFS between T stages ($p=0.001$ and $p=0.002$, respectively). Patients who underwent surgery had better OS and DFS than those did not go surgery ($p=0.000$ and $p=0.000$, respectively). The best survival results were founded in the group treated with "surgery + CRT + CT" sequence.

Conclusion: In our study, we showed that treatment modalities, basal CA19.9 levels and T stage of tumor may have prognostic significance in patients with local/locally advanced stage pancreatic cancer.

Keywords: Pancreatic cancer; Prognosis; Treatment sequences

Introduction

Pancreatic adenocarcinoma is the 12th most common cancer in the worldwide, but the 4th most frequent cause of cancer-related death [1]. Only 15% to 20% of patients have resectable tumors and approximately 20% of them have long-term survival. 50% of patients have diagnosed at local/locally advanced disease. Surgical resection is the only potentially curative treatment option. The prognosis of pancreatic cancer is poor even in those patients with potentially resectable disease, and despite of progress in surgical techniques and adjuvant treatment options. Recurrence rates after surgical treatment are approximately 80% for these patients and median overall survival is reported as 18 months to 24 months [2]. The optimal management of locally advanced stage patients is controversial, and best of our knowledge, there is no standard treatment modality is reported in the literature. Therapeutic options in this stage of patients include Radiation Therapy (RT), Chemoradiotherapy (CRT) and Chemotherapy (CT) [3].

The aim of our study is to evaluate the prognostic role of treatment sequences and clinical features in local/locally advanced stage pancreatic cancer patients.

Material and Methods

In this study we retrospectively evaluated the prognostic significance of treatment modalities in

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local/locally advanced stage pancreatic cancer. A total of 64 patients have been treated in Baskent University Adana Research and Training Hospital between 2007 and 2018 included into our study. Treatment options and demographic data were collected, together with the outcome of treatments. Kaplan-Meier survival analyses were used to examine the effects of parameters on overall survival and disease-free survival.

Statistical analysis

All results were presented as the rate for categorical values or mean and median for continuous variables. Clinical and statistically significant correlation between continuous variables was calculated by Spearman's rank correlation test; rs (spearman's correlation coefficient) and p value (2-tailed) were noted. Overall Survival (OS) was defined by the time from the date of death and last control minus the first day of the chemotherapy. Survival curves were estimated according to the Kaplan-Meier method, and log-rank tests were used for univariate statistical comparisons. Adjusted Hazard Ratio (HR) and 95% Confidence Interval (95% CIs) were used for estimation. All statistical data were analyzed using the SPSS version 17.0 and a p value of <0.05 was considered statistically significant.

Results

Study patients

Patient demographic characteristics and disease features are shown in Table 1. The median age of the patients was 61 (range 31 to 81) years and 42 (65.6%) of patients were male. 89.1% (n:57) of patients were localized to the head of the pancreas. 42.2% (n:27) of patients had T3 tumor and 39.1% (n:25) of patients had T2 tumor. 68.8% (n:44) of patients had locoregional Lymph Node (LN) metastasis. 27 patients (42.2%) were presented with jaundice at initial diagnosis. Majority of patients had European Cooperative Oncology Group (ECOG) performance score 0 and 1 (n=13, 20.3% and n=49, 76.6% respectively), small percentage of patients (n=2, 3.1%) had ECOG performance score 2. All patients had adenocarcinoma histology. Preoperative serum CA 19.9 levels of 44 (68.8%) patients were higher than Upper Limit of Normal (ULN) levels. 42 (65.6%) of patients underwent surgery after diagnosis. After surgery, concomitant Chemoradiotherapy (CRT) and/or Chemotherapy (CT) were given as adjuvant treatment for the majority of patients (n=53, 82.8% and n=62, 96.9% respectively). The most used agent for adjuvant chemotherapy agent was gemcitabine (n:52, 81.3%). Treatment modalities and sequences were shown in Table 2. The rates of surgical treatment according to patients' T, N stages and CA 19.9 levels are shown in Table 3.

Treatment and outcomes

The median follow-up time was 16 months and 46 (71.9%) of patients were died during follow-up. Disease-Free Survival (DFS) and Overall Survival (OS) were estimated as 8 (6 to 9.9, 95% CI) and 18 (13.7 to 22.3, 95% CI) months, respectively (Figures 1 and 2). 51 (79.7%) of patients had disease recurrence after initial treatment. 13 (20.3%) of patients had not recurrent disease during follow-up.

There was statistically significant difference in median OS between T stages of patients (p=0.001) and all patients who had T4 tumors were died (Figure 3). There was no statistically significant difference in median OS between patients with lymph node metastasis or not (18 months vs. 20 months respectively and p=0.86). Patients with normal serum CA 19.9 level had better overall survival than those had higher values CA 19.9 level (23 vs. 15 months respectively and

Table 1: Patient and tumor characteristics.

Characteristics	n (%)
Median age	61 (31-81) years old
Gender	
Men	42 (65.6)
Women	22 (34.4)
ECOG Status	
0	13 (20.3)
1	49 (76.6)
2	2 (3.1)
Tumor localization	
Head	57 (89.1)
Body	6 (9.4)
Tail	1 (1.6)
T Stages	
T1	3 (4.7)
T2	25 (39.1)
T3	27 (42.2)
T4	9 (14.1)
LN Metastases	
Yes	44 (68.8)
No	20 (31.2)
Jaundice	
Yes	27 (42.2)
No	37 (57.8)
Final Status	
Died	46 (71.9)
Alive	18 (28.1)

Table 2: Treatment Modalities.

Characteristics	n (%)
Surgical Treatment	
Yes	42 (65.6)
No	22 (34.4)
Chemoradiotherapy	
Yes	53 (82.8)
No	11 (17.2)
Chemotherapy	
Gemcitabine	52 (81.3)
5FU	4 (6.3)
Capecitabine	3 (4.7)
FOLFOXIRI	3 (4.7)
No	2 (3)
Treatment Sequences	
Surgery + CRT + CT	34 (53.1)
CRT+CT	19 (29.7)
Surgery+ CT	8 (12.5)
RT+CT	2 (3.1)
RT	1 (1.6)

Table 3: The rates of surgical treatment according to patients' T, N stages and CA 19.9 levels.

Characteristics	Surgical Treatment (n)	No Surgical Treatment (n)
T Stages		
T1	3	0
T2	20	5
T3	16	11
T4	3	6
LN Metastasis		
Yes	30	14
No	12	8
CA 19.9 Levels		
High	24	20
Normal	18	2

Table 4: Comparison of Survival Parameters and Treatment Modalities.

Treatment Modalities	DFS			OS		
	Event (n)	Median (Months)	p	Event (n)	Median Months	p
Surgery+CRT+CT	24	11	0.000	21	24	0
CRT+CT	17	7		16	11	
Surgery+ CT	7	10		6	13	
RT+CT	2	3		2	3	
RT	1	2		1	2	

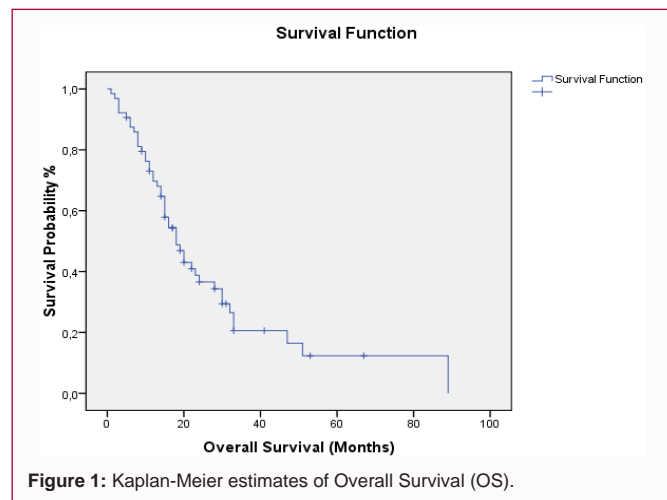


Figure 1: Kaplan-Meier estimates of Overall Survival (OS).

p=0.03). Patients who underwent surgery had better overall survival than those did not go surgery (24 vs. 11 months respectively and p=0,000) (Figure 4). Patients who received chemoradiotherapy had longer survival time but it's not statistically significant (19 months vs. 13 months respectively and p=0.24). The best survival results (median OS was 24 months, p=0.000 and median DFS was 11 months, p=0.000) were founded in the group treated with "surgery + CRT + CT" sequence and these results are shown comparatively with other groups in Table 4.

There was statistically significant difference in median DFS between T stages of patients (p=0.002) (Figure 5). Patients with LN metastasis had worse DFS than those who had no (7 months vs. 10

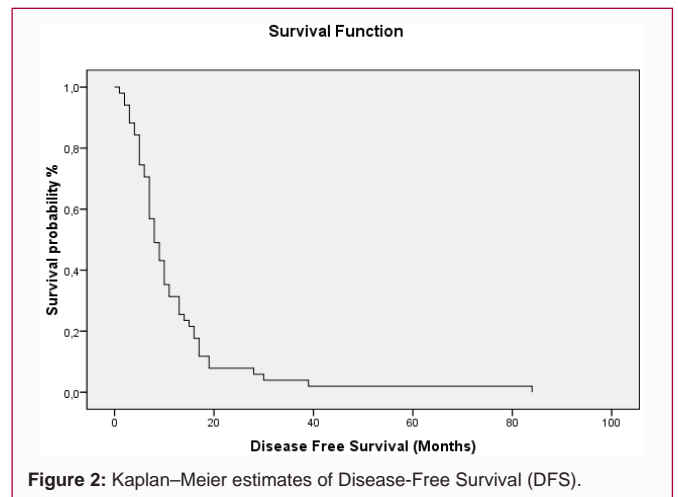


Figure 2: Kaplan-Meier estimates of Disease-Free Survival (DFS).

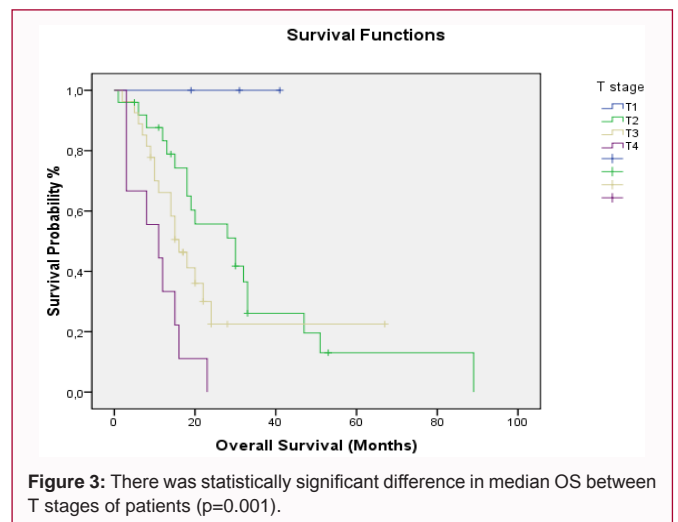


Figure 3: There was statistically significant difference in median OS between T stages of patients (p=0.001).

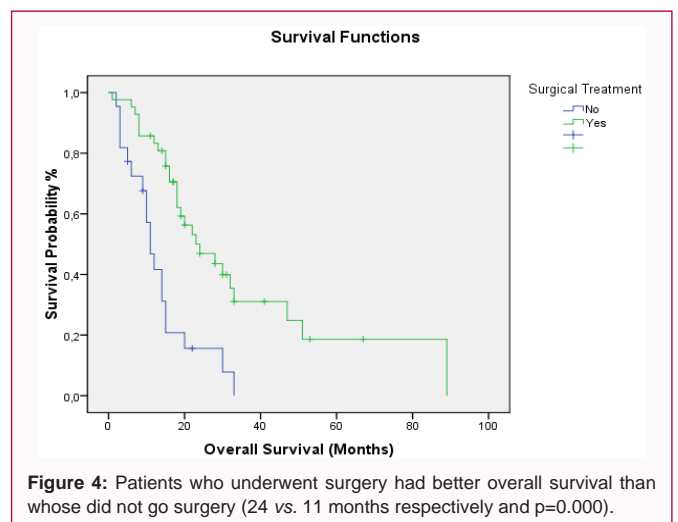


Figure 4: Patients who underwent surgery had better overall survival than those did not go surgery (24 vs. 11 months respectively and p=0.000).

months respectively and p=0.03) (Figure 6). There was no statistically significant relationship between DFS and CA 19.9 levels (p=0.50). Patients who underwent surgery had better DFS than those did not (11 months vs. 7 months respectively and p=0.000) (Figure 7). The effect of chemoradiotherapy on DFS was no statistically significant (p=0.92).

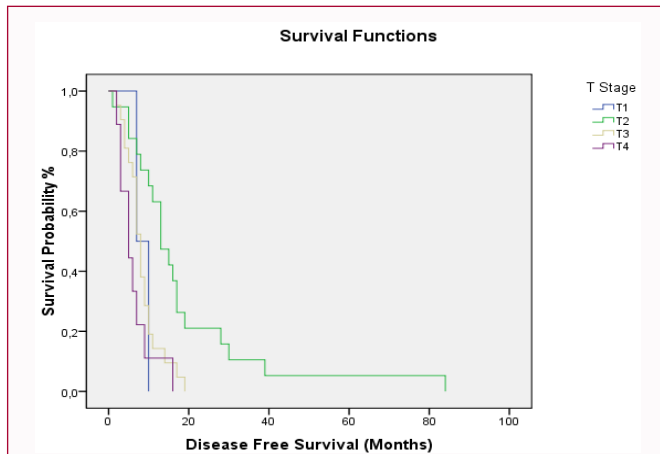


Figure 5: There was statistically significant difference in median DFS between T stages of patients ($p=0.002$).

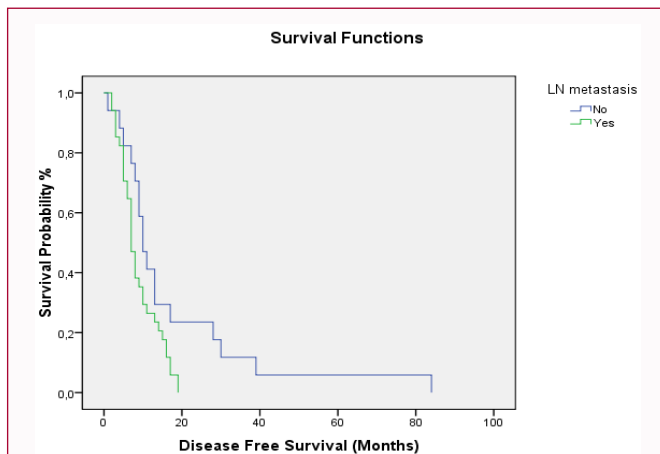


Figure 6: Patients with LN metastasis had worse DFS than those who had no (7 vs. 10 months respectively and $p=0.03$).

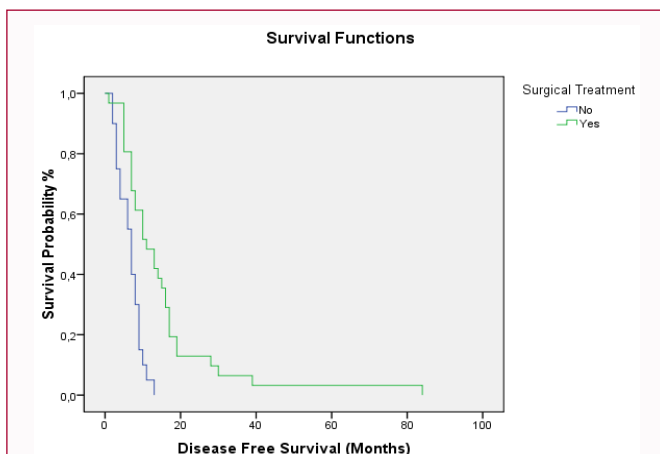


Figure 7: Patients who underwent surgery had better DFS than those who did not (11 vs. 7 months respectively and $p=0.000$).

Discussion

In our study, T stages and CA 19.9 levels had positive effect on survival. Surgical treatment had significant survival benefit in these patients. But chemoradiotherapy did not provide any survival advantage without surgery. The best survival time was obtained by surgical treatment with adjuvant CRT and CT combination (Surgery

+ CRT + CT).

Surgical resection offers the only chance of cure for non-metastatic exocrine pancreatic cancer. However, only 15% to 20% of patients have potentially resectable disease at diagnosis. But, 80% of patients relapse within 12 months after surgical treatment [4]. Therefore, adjuvant therapy is necessary and important for all patients underwent surgical treatment. Adjuvant treatment should be started within 8 to 12 weeks after the surgery. To the best of our knowledge, there is no standard treatment modality for adjuvant setting. Most European clinicians advocate chemotherapy alone (ESPAC-1 and CONCO 001 trials) and chemoradiotherapy is used more prevalent in USA (GITSG trial). Various studies were conducted to investigate the activities of adjuvant chemotherapy and chemoradiotherapy. Furthermore, the efficacy of different chemotherapy regimens was also investigated in these trails.

GIST (Gastrointestinal Tumor Study Group) trial in 1985, the first randomized trial to investigate adjuvant treatment efficacy. In this trial, 5 FU based CRT and observation arms were compared between 43 patients with operated pancreatic cancer and It has been shown that CRT results provide survival advantage (median survival 21 months and 11 months, respectively $p=0.03$) [5]. The EORTC study, which was conducted in 1999 and included 114 patients, compared the 5 FU based CRT and observation and no statistically significant difference was found [6]. These two studies examined the effectiveness of adjuvant CRT and the results were contradictory. In our study, the effect of only chemoradiotherapy without surgery on survival parameters was no statistically significant. The role of CRT is not clear in adjuvant setting for pancreas cancer patients.

In the ESPAC-1 study conducted in 2001, adjuvant CRT and adjuvant CT were evaluated and patients who received chemotherapy had better overall survival than those who did not receive chemotherapy (25.5 months vs. 15.5 months respectively and $p=0.009$). But there was no statistically significant effect of chemoradiotherapy on OS (15.5 months vs. 17.9 months respectively) [7]. In the CONKO 001 trial, adjuvant gemcitabine regimen was compared with observation and the results suggest that significant survival benefit with gemcitabine (median OS 22.8 months vs. 20.2 months respectively, HR 0.76) [8]. In ESPAC 3 trial, gemcitabine and FUFA were compared and no statistically significant difference was observed on overall survival (median OS 23.6 months vs. 23 months, respectively, $p=0.39$) [9]. Gemcitabine was compared with gemcitabine capecitabine combination in the ESPAC-4 study with the participation of 730 patients and significant survival benefit was obtained in the combination arm (median OS 28 months vs. 25.5 months, respectively) [10]. In our study; the best survival results were founded in the group treated with combined treatment modality/ "surgery + CRT + CT" sequence).

Most acceptable strategies are chemotherapy alone or chemoradiation plus chemotherapy [11]. Several studies showed that clear efficacy of adjuvant chemotherapy, but adjuvant chemoradiation is remaining an unanswered important question. The best results in our study were obtained combined group (surgery + CRT + CT). But despite of these findings we found that treatment modalities, basal CA 19.9 levels and T stage of tumor may have prognostic significance in patients with local/locally advanced stage pancreatic cancer. Main restrictions of our study are retrospectively designed in a single center with low volume patients. In conclusion, combined treatment modality was related with good outcomes and we believe that this

approach may have positive effects on overall survival with these patients.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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