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Factors affecting survival in operated pancreatic cancer: Does tumor localization have a significant effect on treatment outcomes?

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ABSTRACT

OBJECTIVE: This study aims to investigate the factors affecting survival in operated pancreatic ductal adenocarcinoma (PDAC) and the possible prognostic effect of primary tumor localization on treatment outcomes.

METHODS: In this study, 98 patients with curatively-operated PDAC, who were followed up and treated for the years 2008 through 2018, were enrolled. Metastatic and locally advanced stages and patients under 18 years of age were excluded from this study. Patients were divided into two groups based on the primary tumor localization as *head or *body/tail.

RESULTS: Sixty-seven (68.3%) patients were male and 31 (31.7%) were female, with a median age of 62 years (range, 35–82 years). The numbers of patients with a primary tumor located in *head vs.*body/tail were 74 (75.4%) vs. 24 (24.6%), respectively. Patients with a primary tumor located in *head vs.*body/tail; median disease-free survival was 16.0 months vs. 13 months (p=0.972), respectively, with corresponding median overall survival was 25 months vs. 33 months (p=0.698). The level of carcinoembryonic antigen(CEA) at diagnosis (Hazard ratio[HR], 1.09 95%CI, 1.01–1.18), stage III disease (HR, 2.09 95%CI, 1.16–4.35), and receiving adjuvant treatment (HR, 0.20 95%CI, 0.09–4.34) were the independent predictors of survival.

CONCLUSION: Our study revealed that high levels of CEA at diagnosis and stage III disease adversely affected the survival in non-metastatic PDAC patients, while receiving adjuvant therapy had a positive effect on survival. The findings suggest that primary tumor localization did not affect survival in operated PC patients. The results on this issue are still inconsistent and under debate in the literature.

Keywords: Pancreas cancer; prognosis; survival; treatment effect; tumor localization.

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Exocrine pancreas cancer (PC) is a highly fatal malignancy, with the fourth leading cause of cancer-related deaths in the United States. Worldwide, PC is the eighth leading cause of cancer mortality in both men and women, with a rapidly increasing incidence after 45 years of age. Incidence and mortality rates vary by gender and race, being more prevalent in males than females (1.3/1) and blacks than whites [1–3].

The most common type of PC is pancreatic ductal adenocarcinoma (PDAC). Surgical resection is the only

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potentially curative treatment strategy in early stage disease. However, only 15–20% of patients are candidates for curative resection because of presenting with late-onset symptoms. The prognosis is poor even after complete resection. The five-year survival rate after surgical resection is approximately 30% for patients with lymph node (LN)-negative disease and only 10% for those with LN-positive disease. In the advanced stage, the 5-year survival rate is 8.5%, with a median overall survival (mOS) of 3–6 months [1, 4].

The symptoms associated with PC vary according to the tumor localization. The primary tumor is located in the *head of the pancreas in about 60–70% of all cases and in *body/tail in the remaining 20–25% of the cases. Patients with a primary tumor located in the *head more frequently present with jaundice, steatorrhea, and weight-loss than those with tumor located in *body/tail [5, 6].

Given the highly aggressive biological behavior and increased mortality rates, PC patients should be classified according to the severity of disease following the initial diagnosis. This classification helps physicians guide selecting the most appropriate treatment for the patients. To date, many prognostic factors, including Tumor-Node-Metastasis (TNM) staging system, biomarkers, such as Carbohydrate antigen 19–9 (CA19-9), genomic analysis, and Eastern Cooperative Oncology Group Performance Status (ECOG PS), have been proposed [7, 8].

For surgeons, localization of the primary tumor in PDAC is very essential to determine the extent of tumor resection. Although previous studies have shown that primary tumor localization may be associated with survival as well as guiding resectability or type of surgery, there are insufficient data in the literature regarding the effects of tumor localization on treatment outcomes and survival in patients with PDAC [9–11].

Herein, we aimed to analyze the factors affecting survival in curatively-operated PDAC and the possible prognostic effect of primary tumor localization on treatment outcomes.

MATERIALS AND METHODS

Study Population

This was a retrospective study. In this study, 98 patients with curatively-operated PDAC, who were followed up and treated for the years 2008 through 2018 in Okmeydani Training and Research Hospital, a major oncology center of Turkey, were enrolled. Inclusion criteria were as follows: Patients equal to or greater than 18 years of age, patients with stage I to III disease who underwent an operation, and those with complete data. PC patients without PDAC histology, the age<18 years, receiving neoadjuvant treatment, inoperable patients or Metastatic stage, unknown primary tumor localization, patients with second primary malignancy, and patients with missing data were excluded from the analysis. Staging procedure and localization of the primary tumor were performed using computed tomography (CT) and/or 18 FDG-positron emission tomography-CT. The laboratory data at initial admission were obtained before treatment.

Ethical Approval

This study was conducted after obtaining the ethics committee approval from the Ethics Committee Board of University of Health Sciences, Okmeydani Training and Research Hospital (48670771-514.10)

Data Collection

The information regarding the clinical and demographic characteristics, including age, gender, ECOG PS, smoking status, alcohol consumption, comorbidities, history of surgery, type of surgery, surgical margin status, primary tumor localization, tumor grade, TNM stage at diagnosis, site of metastasis or recurrence, treatments, laboratory parameters at diagnosis, and patient final status, were obtained from the written archive files.

Statistical Analysis

All the statistical analyses were performed using Statistical Package for the Social Sciences 22.0 for Windows software program (IBM Corp. 2013, USA). Numerical variables between two independent groups were analyzed using student t-test in case of normal distribution and with Mann-Whitney U test if else. The comparison of the rates between the groups was performed by chi-square analysis. Monte Carlo simulation was applied if conditions could not be met. Survival was analyzed with the Kaplan-Meier method. Determinant factors were examined with cox regression analysis. Forward stepwise model was used with parameters having a p-value below 0.200. An overall 5% Type-I error level was used to infer statistical significance. Median disease-free survival (mDFS) was defined as the 'time interval' from the date of diagnosis to the date of recurrence or death from any cause, and mOS was calculated as the 'time' from the date of diagnosis to the date of death or last follow-up.

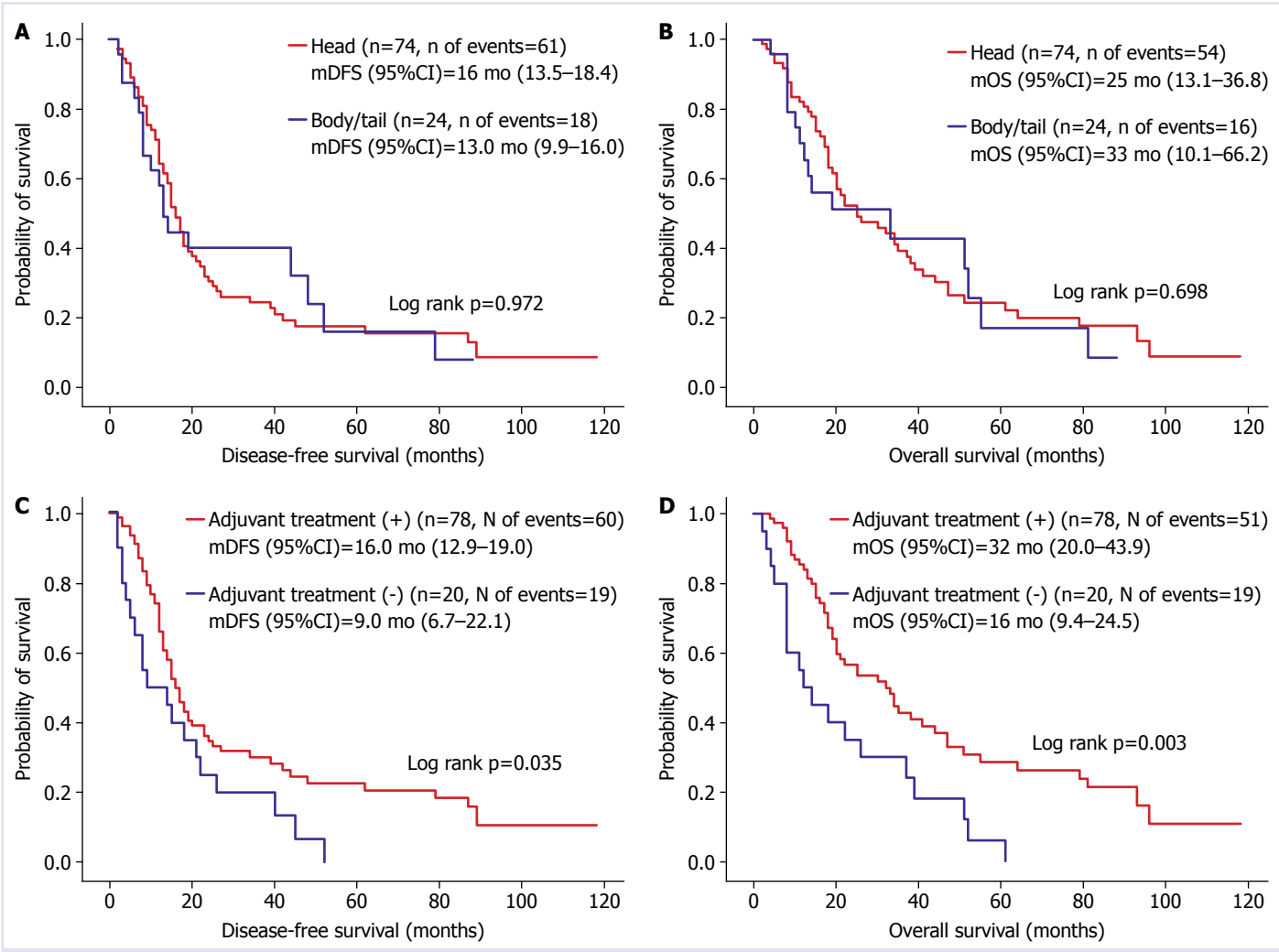

FIGURE 1. **(A)** DFS according to tumor localization. **(B)** OS according to the tumor localization. **(C)** DFS according to adjuvant treatment. **(D)** OS according to adjuvant treatment.

DFS: Disease-free survival; OS: Overall survival.

RESULTS

Sixty-seven (68.3%) patients were male and 31 (31.7%) were female, with a median age of 62 years (range, 35–82 years). The numbers of patients with a primary tumor located in *head vs.*body/tail were 74 (75.4%) vs. 24 (24.6%), respectively. The data of the patients according primary tumor localization are summarized in Table 1. Simply put, there was no statistically significant difference between the primary tumor localization and gender, age, ECOG PS, smoking status, alcohol consumption, comorbidities, surgical margin status, tumor grade, TNM stage at diagnosis, the site of recurrence and the rate of recurrence, and the laboratory data at diagnosis (Table 1).

Patients with a primary tumor located in *head vs. *body/tail, mDFS was 16.0 months (95% CI, 13.5–18.4) vs. 13 months (95% CI, 9.9–16.0), respectively, with corresponding mOS of 25.0 months (95% CI, 13.1–36.8) vs. 33 months (95% CI, 10.1–66.2) (p=0.698) (Fig. 1A, B).

Given the treatment status and regimens, mDFS was 16.0 months (95% CI, 12.9–19.0) in patients receiving adjuvant therapy compared to 9.0 months (95% CI, 6.7–22.1) in patients not receiving adjuvant treatment (Log rank p=0.035), with corresponding mOS of 32.0 months (95% CI, 20.0–43.9) and 16.0 months (95% CI, 9.4–24.5) (Log rank p=0.003) (Fig. 1C, D).

In univariate analysis, Stage, receiving adjuvant treatment and level of CA19-9 at diagnosis were found to be factors related to survival (Table 2). Multivariate analysis

Table 1. Patient data

	Head (n=74)		Body/tail (n=24)		
	n	%	n	%	p
Gender					
Male	54	73.0	13	54.2	0.09
Female	20	27.0	11	45.8	
Age (years), Median (Min.–Max.)	61.0 (35–82)		64.0 (40–81)		0.152
ECOG PS					
0–2	73	98.6	23	95.8	0.397
3–4	1	1.4	1	4.2	
Smoking	49	66.2	13	54.2	0.333
Alcohol usage	6	8.1	1	4.2	0.680
Hypertension	20	27.0	6	25.0	0.85
Diabetes mellitus	19	25.7	4	17.4	0.423
Operation					
Curative	74	100.0	24	100.0	
Palliative					
Surgical margin					
Positive	2	2.7	1	4.2	0.718
Grade					
I	12	16.7	1	4.2	0.240
II	55	76.4	22	91.7	
III	5	6.9	1	4.2	
Stage					
I	14	18.9	5	20.8	0.779
II	43	58.1	12	50.0	
III	17	23.0	7	29.2	
Adjuvant treatment					
CT	59	79.7	19	79.2	0.951
CRT	41	55.4	15	62.5	0.546
CT regimen					
Gemcitabine	54	91.5	14	73.7	0.060
Gemcitabine+capecit-abine	5	8.5	5	26.3	
Recurrence	61	82.4	18	75.0	0.302
The site of recurrence					
Liver	49	80.3	11	64.7	0.161
Peritoneum	3	4.9	2	11.8	
Bone	0	0.0	1	5.9	
Lung	3	4.9	0	0.0	
Locoregional	1	1.6	1	5.9	
Peritoneum+Liver	4	6.6	1	5.9	
Liver+Lung	1	1.6	1	5.9	
CEA (ng/mL), Mean±SD	3.82±3.21		4.22±2.10		0.935
CA19-9 (U/mL), Mean±SD	46.31±69.43		43.98±29.20		0.583
Follow-up duration, Median (Min.–Max.)	20.5 (4–118)		16.5 (4–88)		
Final status					
Dead	54	73.0	16	66.7	0.550
Alive	20	27.0	8	33.3	

CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CRT: Chemoradiotherapy; CT: Chemotherapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; mDFS: Median disease-free survival; mOS: Median overall survival; SD: Standard deviation; Min.: Minimum; Max.: Maximum.

Table 2. Univariate analysis for OS

Characteristic	HR	95.0% CI	p
Gender			
Female vs. male	0.868	0.517–1.457	0.593
Age (years)			
≥65 vs. <65	1.040	0.635–1.700	0.877
ECOG PS			
3–4 vs 0–2	2.378	0.576–9.815	0.231
Smoking			
Yes vs. no	0.882	0.541–1.439	0.616
Alcohol			
Yes vs. no	0.627	0.247–1.588	0.325
HT			
Yes vs. no	1.139	0.668–1.940	0.631
DM			
Yes vs. no	1.211	0.689–2.126	0.506
Grade			
III vs I-II	1.201	0.514–2.808	0.672
Tumor localization			
Body/tail vs. head	1.116	0.636–1.958	0.701
Stage			
III vs I-II	1.605	1.090–2.895	**0.006**
Adjuvant CT			
Yes vs. no	0.448	0.262–0.767	**0.003**
Adjuvant CRT			
Yes vs. no	0.740	0.458–1.195	0.218
CEA (ng/mL)	1.066	0.983–1.555	0.092
CA19-9 (U/mL)	1.005	1.001–1.009	**0.019**

OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HT: Hypertension; DM: Diabetes mellitus; CT: Chemotherapy; CRT: Chemoradiotherapy; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9.

Table 3. Multivariate analysis for OS

Characteristic	HR	95.0% CI	p
CEA (ng/mL)	1.099	1.018–1.186	0.015
Stage			
III vs. I+II	2.092	1.165–4.535	0.021
Adjuvant treatment			
Yes vs. no	0.206	0.098–0.434	<0.001

OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; CEA: Carcinoembryonic antigen.

revealed that the level of CEA at diagnosis (HR, 1.09 95% CI, 1.01–1.18), stage III disease (HR, 2.09 95% CI, 1.16–4.35), and receiving adjuvant treatment (HR, 0.20 95% CI, 0.09–4.34) were the independent predictors of survival (Table 3).

DISCUSSION

The effects of primary tumor localization on treatment outcomes in PDAC are not well-defined. In this study, the possible prognostic role of primary tumor localization was explored in operated PDAC patients; however, it was indicated that primary tumor localization did not affect mDFS and mOS in our study. The level of CEA at diagnosis, disease stage, and receiving adjuvant treatment were the independent factors affecting mOS.

There have been limited numbers of studies performed regarding the prognostic effects of tumor localization on treatment outcomes in PDAC patients, with conflicting findings [7, 9, 11–15]. Lau et al. [9] conducted a study using the Surveillance, Epidemiology, and End Results (SEER) registry data and reported that non-metastatic PC patients with a primary tumor located in *body/tail had higher survival rates than those with tumor located in the *head of pancreas. Winer et al. [12] reported their findings using The National Cancer Database, indicating that tumors located in the *head of pancreas were more amenable to curative resection because of presenting with early-onset symptoms; however, authors also reported that curatively-resected tumors with *head localization were associated with worse mOS compared to *body and *tail tumors. By contrast, in a study of 209 PC patients, the *tail localization was shown to be related to worse survival than head localization [10]. Similarly, another study, including 509 PC patients with stage I to IV disease, reported that patients with tumor located in *body/tail had significantly worse survival than those with tumor located in *head of pancreas (12 months vs. 22.0 months, respectively) [13]. Likewise, another SEER analysis also indicated that patients with PDAC who underwent curative resection for *body/tail-located primary tumor had worse mOS than those with *head-located tumors [11]. However, Dreyer et al. [13] showed that although *body/tail-located tumors were less amenable to resection than *head-located counterparts, they found similar survival durations between different tumor localizations the after resection.

In our study, most of the curatively-resected tumors were located in the *head of the pancreas, supporting the findings of the previous studies that showed higher resectability rates for the *head-located tumors [9, 14]. However, there was no significant difference in mDFS according to tumor localization in curatively-operated patients. Patients with tumor located in *body/tail had longer mOS than those with tumor located in the *head of the pancreas, but this was not statistically significant.

Many clinical studies have shown that receiving adjuvant therapy compared to observation alone improves survival in curatively-operated PDAC patients [16–18]. To illustrate, the CONKO-001 trial demonstrated a survival benefit of adjuvant gemcitabine monotherapy in curatively-operated PDAC patients, with mDFS of 13.4 months in patients receiving adjuvant therapy vs. 6.9 months in observation arm [16]. Later, the ESPAC-4 study showed that adding capecitabine to gemcitabine treatment was superior to single-agent gemcitabine [17]. Recently, the PRODIGE-24 trial reported mDFS of 21.6 months for patients treated with adjuvant FOLFIRINOX regimen vs. 12.8 months for those receiving single-agent gemcitabine in curatively-operated PC patients, with the corresponding mOS of 54.4 months vs. 34.8 months [18]. In our study, the adjuvant therapy significantly prolonged mOS in curatively-operated patients, with most of them receiving single-agent gemcitabine (mDFS; 16 months and mOS; 33 months).

Previous studies have also compared chemoradiation (CRT) to CT in the adjuvant setting of PC [19, 20]. In the ESPAC-1 study, the survival benefit of CRT could not be demonstrated [19]. Another large phase II trial-EORTC-40013-22012/FFCD-9203/GERCOR did not show any survival benefit of CRT [20]. Similarly, the survival benefit of CRT was not demonstrated in our study.

The strength of this study was that it included homogen patients group and the follow-up period was relatively longer in our study than those reported in the literature, and some important demographic features that might affect the results were also available in our database, such as comorbidities, smoking status, and alcohol consumption. It is also an analysis of real-life data. The major limitations of this study were its retrospective nature and small sample size, leading us not to be able to divide the subjects into three subgroups as *head, *body, and *tail. Moreover, some information, such as primary tumor size, number of positive or resected LN, and new molecular markers such as microsatellite instability, RAS and RAF mutation status, was not available.

In conclusion, our study revealed that high levels of CEA at diagnosis and stage III disease adversely affected the survival in non-metastatic PDAC patients while receiving adjuvant therapy had a positive effect on survival. Primary tumor localization did not affect survival in operated PC patients. The results on this issue are still inconsistent and under debate.

Ethics Committee Approval: The Okmeydani Training and Research Hospital Ethics Committee granted approval for this study (date: 25.06.2019, number: 48670771-514.10).

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Authorship Contributions: Concept – AS, SC, AyS, SA; Design – NY, CG, AyS, MMA; Supervision – SC, SS, CD, MMA; Resources – CG, SC, AyS, SA; Materials – AS, NY, SS, CG; Data Collection and/or Processing – AS, SS, NY, CD; Analysis and/or Interpretation – SS, NY, AS, MMA; Literature Search – CD, AS, SC, SS; Writing Manuscript – AS, SS, AyS; Critical Review – SC, CD, SS, SA; Other – CG, AyS, SC, NY.

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