

Do the Well Known Prognostic Parameters in Pancreatic Ductal Adenocarcinoma Really Reflect Survival?

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ABSTRACT

Objective: Pancreatic ductal adenocarcinoma is an aggressive tumor with short survival. In this study we aimed to investigate the effect of well-known prognostic parameters on survival in these tumors.

Material and Method: A total of 56 pancreatic ductal adenocarcinoma cases diagnosed between 2005 and 2014 were included in the study. Survival data were obtained and histopathological parameters were re-evaluated in each patient.

Results: Tumor size (p=0.029), mitotic count (p=0.030), lymph node metastasis (p=0.003), metastatic lymph node ratio (p<0.001) and ampullary invasion (p=0.044) had a statistically significant relationship with survival. However, there was no relationship between survival and tumor grade, lymphovascular and perineural invasion, and peripancreatic soft tissue invasion.

Conclusion: Our results showed that existent 2010 WHO pancreatic ductal adenocarcinoma grading parameters excluding mitotic count are subjective and not applicable. Considering that almost all of the tumors in our series were larger than 2 cm, we think that the 2 cm cut-off in tumor size is insufficient to make the tumor stage pT2. Peripancreatic soft tissue invasion, which is a common finding in pancreatic ductal adenocarcinoma, should also not be assessed like adjacent tissue invasion and make the tumor reach pT3 stage independent of tumor size. It is clear that the existent WHO tumor grading and pT staging parameters need to be revised and the mitotic count, which correlates with survival, should be presented in pathology reports.

Key Words: Pancreatic ductal carcinoma, Survival, Mitosis, Grade, Peripancreatic invasion, Tumor size

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC), representing the majority (80-90%) of pancreatic neoplasia, is the fourth leading cause of cancer-related deaths. Unfortunately, these tumors tend to present with non-specific symptoms and generally in advanced stages. High recurrence and metastatic capacity support the aggressiveness and high mortality rates in these tumors (1, 2). The most important prognostic parameter is total resection of the tumor. However, only 10-20% of the patients have surgically resectable tumors at the time of diagnosis (3, 4). Even in patients who undergo total resection, the overall survival only increases from 3-5 months to 10-20 months (3, 5).

It has been shown that tumors smaller than 3 cm and limited to the pancreas have a better prognosis than larger or extensive tumors (6-8). Tumor size and extension beyond the pancreas already constitute the basic parameters of the existing pT stage (1). Another basic factor for PDAC prognosis is lymph node metastasis which constitutes pN staging. Most of the studies about lymph node metastasis

(Turk Patoloji Derg 2018, 34:127-133) Received: 10.01.2017 Accepted: 31.07.2017 in PDACs have reported that the metastatic lymph node ratio is more important than the presence of lymph node metastasis regarding the prognosis (9-15).

Although not taking part in pT or pN staging, it has been indicated that tumor grade, histologic subtype, mitotic count, vascular invasion, and perineural invasion also affect survival in PDACs (5, 16-21).

In our study, we investigated the effects of histologic and staging parameters on survival in PDACs. We aimed to show how these parameters reflect survival in these aggressive tumors.

METHODS

Patient and Specimen Characteristics

A total of 56 pancreatic ductal adenocarcinoma cases that were diagnosed between 2005 and 2014 at the Ankara University Pathology Department were evaluated. Pancreatectomy specimens were either Whipple or distal pancreatectomy materials. Ethical approval was obtained from the institute's ethics committee (Ref No. 18-766-14).

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Clinical data including age, gender, additional therapy and overall survival were obtained from the hospital's database system. In each case, Formalin-fixed, paraffinembedded (FFPE) tissues representing the whole tumor were sectioned into 4µm thick slices and H&E stained in order to re-evaluate the pathological data as tumor grade, mitotic activity, lymphovascular and perineural invasion, lymph node metastasis and resection margin status.

Grading the Tumors

All the tumors were re-evaluated according to the WHO 2010 PDAC grading criteria shown in the Table I (1).

Statistics

'SPSS for Windows 11.5' was used for data collection and statistical analysis. The Kaplan-Meier survival curve was estimated and the log-rank test was used to compare the survival. A p-value <0.05 was considered statistically significant.

RESULTS

Patients, Operations and Follow-Up

A total of 108 patients received a PDAC diagnosis between 2005 and 2014 at our department. Treatment and survival



Figure 1: The distribution of the tumors according to the tumor size.

mucoepidermoid and pleomorphic structures

Table I: Grading criteria's in PDACs						
Tumor grade	Glandular differentiation	Mucin production	Mitosis (per 10HPF)	Nuclear features		
Grade I	Well-differentiated	Intensive	≤5	Little polymorphism, pola arrangement		
Grade II	Moderately differentiated duct-like structures and tubular glands	Irregular	6-10	Moderate polymorphism		
Grade III	Poorly differentiated glands, abortive	Abortive	>10	Marked polymorphism and		

Tab

data were obtained from 60 of them. Four patients who died due to surgical complications were excluded from the group and 56 patients were included in the study. The mean age was 63.9 years (range 44-83 years) and the patients had a male predominance with a ratio of 1.9:1 (male, n=37; female, n=19). The majority of the patients (66.1%) had undergone the Whipple operation and more than half of the tumors (53.5%) were localized in the pancreatic head. The ratio of patients treated with adjuvant chemotherapy was 80.3% while 48.2% received radiotherapy. Three liver metastases and one omentum metastasis were proven by histopathological examinations. 42.9% of the patients had radiologically diagnosed metastasis and the liver constituted the majority of the suspected areas (28.5%). During the study, 48 patients died and the mean overall survival was 15.7 months (range 1-49 months) (Table II).

The mean tumor size was 4.4 cm (range 2-8.5 cm) and the distribution was as follows: 78.6% had a diameter >3 cm. 16.1% 2-3 cm and 5.3% ≤ 2 cm (Figure 1). The majority of the tumors (69.6%) were Grade II, 28.6% were Grade III and only 1.8% were Grade I (Figure 2-4). The mitotic rate was $\leq 5/\text{HPF}$ (x400 magnification) in 51.8% of the tumors, 6-10/HPF in 32.1% and >10/HPF in 16.1% (Figure 5).



Figure 2: The distribution of tumors according to the tumor grade.

increased size

The number of mitoses showed a more balanced distribution than the tumor grade. Among the cases, 91.1% of the tumors had perineural and 39.3% had lymphovascular invasions. The average number of dissected lymph nodes was 10.53 and 10% were metastatic.

Among the operation materials, 32% (n=18) had pancreatic resection margin, 86% (n=48) had pancreatic soft tissue and, 25% (n=14) had retroperitoneal margin positivity. Furthermore, 2% (n=1) of the Whipple operation materials

Table II:	The	features	of the	patients
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Features of the patients (n=56)	Frequency n (%)
Age (year)	63.9 (44-83)
Gender	
Female	19 (33.9)
Male	37 (66.1)
Operation type	
Whipple	37 (66.1)
Distal pancreatectomy	19 (33.9)
Tumor localization	
Head	30(53.5)
Body	24(42.8)
Tail	2(3.5)
Adjuvant chemotherapy	
Present	45 (80.3)
Absent	11 (19.6)
Radiotherapy	
Present	27 (48.2)
Absent	29 (51.7)
Radiologically diagnosed metastasis	24 (42.9)
Liver	16 (28.5)
Lung	5 (8.9)
Bone	3 (5.3)
Brain	1 (1.8)
Omentum	1 (1.8)
Overall survival (min-max) (months)	15.7 (1-49)

had choleduct margin positivity. The frequencies of adjacent tissue invasions were as follows: choleduct invasion 21% (n=12), ampullary invasion 7% (n=4) and duodenum invasion 23% (n=13). The average survival of the 48 patients was 15.7 months (Figure 6).

Relation Between Clinicopathological Parameters and Survival

As shown in the Table III, tumor size (p=0.029), mitotic count (p=0.030), lymph node metastasis (p=0.003) and ampullary invasion (p=0.044) had a significant positive correlation with survival. The increase in metastatic lymph node ratio and survival had a significant negative correlation (p<0.001). Tumor grade was correlated neither with mitotic count (p=0.846) nor with survival (p=0.309). Therapy status, lymphovascular invasion, perineural invasion, margin positivities and adjacent tissue invasions excluding ampullary invasion had no relation with overall survival.

DISCUSSION

PDACs which have high capacity of invasion and metastasis are generally diagnosed in advanced stages. These tumors are the fourth leading cause of death among all cancers in the United States. 5 year survival rates raise from 3-5% to 15-25% only after complete resection (1). The percentage of male patients in our group was 66.1% and the average age 63.9 years. Nearly half of the tumors (53.5%) were localized in the pancreatic head. The average tumor size was 4.4 cm and the majority of them (78.5%) were larger than 3 cm in diameter. Perineural invasion was a common finding (91.1%). Average number of dissected lymph nodes was 10.5 and the metastatic rate was 10%. Peripancreatic soft tissue invasion (86%) was the most commonly observed adjacent tissue invasion in our series. Mean survival was 15.7 months. There was a remarkable fall in survival after first year. All these findings were parallel with the literature and prior studies (1, 3, 5, 6, 11).



Figure 3: A,B) Grade II tumor (H&E; x200 & x400).

Tumor grade is one of the commonly accepted prognostic factors in PDAC. However, we could not find any statistically significant relationship between the tumor grade and survival in our series. Moreover, there was no homogeneous distribution among tumor grade groups in our series. On the other hand, a statistically significant correlation between the mitotic count and the survival was found (p=0.030). Except for mitotic count, WHO tumor grading parameters of PDACs such as mucin production, glandular differentiation, and nuclear features are subjective. Therefore, grading these tumors with these parameters is not applicable and causes interobserver variability. Conflicting results have been reported about the relation between tumor grade and survival in various studies. Some studies reported that tumor grade was significantly related to survival (9, 22, 23) whereas some studies declared that existent grading parameters cause interobserver variability (24, 25). Therefore, tumor grading parameters in PDACs must be revised and mitotic count which has significant correlation with survival should be specified in the pathology reports (as <5, 6-10, >10).

After grouping the tumors according to the tumor size (≤ 3 cm and >3 cm), shorter survival was found in tumors >3 cm (p=0.029). Tumor size is already one of the parameters in existent pT staging. Tumors greater than 2 cm are assessed in pT2 stage for tumors limited to the pancreas (1). However, tumors tend to have larger sizes and 2 cm cut-off is not sufficient in pT staging in these tumors. Even in our series, there was no tumor smaller than 2 cm. This problem would be solved by the recently published AJCC Cancer Staging Manual 8th edition which recommends discriminating pT2 (2-4 cm) and pT3 (>4 cm) with the tumor size (26). The effects of new cut-offs on survival would be investigated in new studies with large series.

In our series, peripancreatic soft tissue invasion had no relationship with survival. However, in the 2010 WHO TNM classification, all tumors showing peripancreatic soft tissue invasion are evaluated in the pT3 stage, independent of tumor size. The fact that the pancreas is located in fatty tissue without a capsule makes it difficult to distinguish the peripancreatic soft tissue border. Moreover, similar to



Figure 4: A,B) Grade III tumor (H&E; x50 & x400).



Figure 5: The distribution of tumors according to the mitotic count.



Figure 6: Overall survival-time graphics in PDAC patients.

Feature	n	Median overall survival (months)	p value
Tumor size(cm)			0.029
≤3	12	28	
>3	44	14	
Tumor grade			0.309
Low grade (Grade I and II)	40	16	
High grade (Grade III)	16	12	
Mitotic count			0.030
≤5	29	19	
6-10	18	15	
>10	9	8	
Lymph node metastasis			0.003
Present	34	8	
Absent	22	28	
Lymphovascular invasion			0.719
Present	22	14	
Absent	34	16	
Perineural invasion			0.492
Present	51	16	
Absent	5	14	
Retroperitoneal margin			0.164
Positive	14	7	
Negative	31	19	
Peripancreatic soft tissue			0.696
Positive	48	15	
Negative	8	18	
Choledochal invasion			0.605
Present	12	19	
Absent	25	18	
Duodenum invasion			0.398
Present	13	16	
Absent	24	18	
Ampullary invasion			0.044
Present	4	6	
Absent	33	18	
Radiologically diagnosed metastasis			0.360
Present	24	14	
Absent	32	18	
Treatment			0.129
Surgery	11	5	

18

27

13

18

Table III: Relation of clinicopathological parameters and survival

Surgery and chemotherapy

Surgery, chemotherapy and radiotherapy

our findings, peripancreatic soft tissue invasions have been usually observed in PDACs even in the early stages (27). Also, the superiority of tumor size to peripancreatic soft tissue invasion as a prognostic factor has been shown in various studies (28, 29). Recently, extrapancreatic extension is no longer a part of pT3 definition in AJCC Cancer Staging Manual 8th. edition (26).

Existence of lymph node metastasis (p=0.003) and metastatic lymph node ratio (p<0,001) had a statistically significant relationship with survival in our study. Existence of lymph node metastasis, independent from metastatic lymph node number is sufficient to indicate pN stage pN1 (1). In some studies, it has been reported that metastatic lymph node ratio is more important than only the presence of lymph node metastasis on survival (9, 11, 12, 30, 31). There are also important changes regarding the pN stage in the recently published AJCC Cancer Staging Manuel 8th edition. In this edition, the N stage is subdivided into N1 (\leq 3) and N2 (> 3) groups according to the number of metastatic lymph nodes (26).

In conclusion, our study showed that well known prognostic parameters like tumor grade and peripancreatic soft tissue invasion did not have any significant relationship with survival. As mitotic count showed a statistically significant correlation with survival, it should be presented in pathology reports. Most of the problematic issues (tumor size, peripancreatic soft tissue invasion and pN stage) we discussed in this study already underwent fundamental changes with the recently published AJCC Cancer Staging Manual 8th edition. We look forward to hearing changes about tumor grading parameters that can make the grading of PDACs more relevant.

CONFLICT of INTEREST

The authors declare no conflict of interest.

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