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Higher Tumor Cellularity in Resected Pancreatic Ductal Adenocarcinoma Is a Negative Prognostic Indicator

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Background/Aims: Desmoplasia is a prominent feature of pancreatic ductal adenocarcinoma (PDA). Stromal desmoplasia reflects the low cellularity that is characteristic of PDA, and it may play a role in PDA chemoresistance. In this retrospective study, we evaluated the relationship between tumor cellularity in resected PDA specimens and long-term patient outcomes. **Methods:** We retrospectively reviewed the data from 175 patients who underwent PDA resection between January 2010 and December 2015 at Seoul National University Bundang Hospital, and analyzed their clinicopathological features and the relationship between tumor cellularity (high vs low based on a cutoff of 30% cellularity) and patient outcomes. **Results:** The high-cellularity group had significantly shorter overall survival (OS) (18.7 months vs 26.6 months, p=0.006) and disease-free survival (11.0 months vs 16.9 months, p=0.031) than the low-cellularity group. Multivariate analysis revealed that high tumor cellularity was an independent risk factor for poor OS (hazard ratio, 2.008; 95% confidence interval, 1.361 to 2.962; p<0.001). Adjuvant therapy improved OS in the low-cellularity group (16.3 months vs 41.3 months, p=0.001) but not in the high-cellularity group (15.9 months vs 24.4 months, p=0.107). **Conclusions:** Tumor cellularity in PDA specimens may be a prognostic and predictive biomarker that could aid in identifying patients who would benefit from adjuvant therapy for PDA. **(Gut Liver 2020;14:521-528)**

Key Words: Tumor cellularity; Biomarker; Carcinoma, pancreatic ductal; Prognosis; Chemotherapy, adjuvant

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDA) is the fourth leading cause of cancer-related deaths and has a 5-year survival of 8% in Western countries.[1,2] The prognosis for patients with PDA remains dismal despite recent modest improvements that have resulted from the optimized use of systemic chemotherapy.[3,4] The only curative treatment for PDA is complete resection, which is only possible in 10% to 20% of patients.[2,5,6] Even after potentially curative resection, locoregional recurrences and distant metastases are common, and the 5-year survival rates remain poor.[7-11]

The histological characteristics of PDA often include abundant desmoplastic stroma with low tumor cellularity.[12,13] There is increasing evidence that the stromal desmoplasia of PDA helps impair drug delivery to tumor cells and increases resistance to chemotherapy.[14-17] A recent clinical trial has also demonstrated that targeting the stromal compartment in pancreatic cancer may have antitumor effects and enhance the sensitivity to chemotherapy.[18] Although few studies have evaluated the clinical implications of tumor cellularity in PDA, this parameter is a significant prognostic indicator in other solid tumors, such as gastrointestinal stromal tumors[19] and breast cancers.[20] Therefore, this retrospective study aimed to explore whether tumor cellularity could predict prognosis and response to adjuvant therapy among PDA patients.

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MATERIALS AND METHODS

1. Patients and clinicopathological variables

The study's retrospective protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB number: SNUBH B-1804/463-104) and informed consent was waived. Clinicopathological data were retrieved for all 225 patients who underwent surgical resection of PDA between January 2010 and December 2015 at our center. Patients were excluded from the analysis if they received neoadjuvant treatment, did not have histological confirmation of the PDA diagnosis, had a macroscopically positive resection (R2), or died within 30 days after surgery (Fig. 1). Thus, 175 patients who underwent potentially curative resection were included in the present study.

2. Assessment of tumor cellularity

Hematoxylin and eosin stained histology slides from all resected cases were retrieved from the archives of the Seoul National University Bundang Hospital, Department of Pathology, and assessed by two pathologists with expertise in pancreaticobiliary pathology (H.K. and S.A.). For all cases, the entire tumor was submitted for histological evaluation, which is the routine practice of the institution. One representative microscopic slide containing the highest cellularity was selected for each case, and after examining the entire slide at scanning power (×10) microscopy, one most representative area containing the highest cellularity was selected for tumor cellularity assessment. In order to reduce intra- and inter-observer variability in estimating tumor cellularity, five random cases were initially evaluated using a quantitative approach (Supplementary Fig. 1). Briefly, ×100 magnification fields were captured on an Olympus BX50 microscope (Tokyo, Japan), and the photomicrograph images were analyzed using ImageJ analysis software version 1.47 (National Institutes of Health, Bethesda, MD, USA; downloaded from imagej.nih.gov/ij). Tumor cellularity was defined as the total area occupied by tumor cells divided by the area of the entire ×100 field, expressed as a percentage. Using the captured images and corresponding morphometric analyses for guidance, the tumor cellularity of the remaining cases was estimated independently by two pathologists, both blinded to the other's cellularity score, the patient identification and outcome status. The intraclass correlation score and the Pearson correlation coefficient between the two pathologists were 0.650 (95% confidence interval [CI], 0.475 to 0.766) and r=0.789 (p<0.001), respectively. For discrepant cases, a consensus was arrived at using a multiheaded microscope.

3. Adjuvant therapy and outcomes

Adequate adjuvant therapy was defined as receiving ≥4 cycles of chemotherapy with or without radiation. Chemotherapeutic regimens included gemcitabine monotherapy (intravenous gemcitabine at 1,000 mg/m^2 over 30 minutes on days 1, 8, and 15, followed by 1-week rest), gemcitabine plus erlotinib (intravenous gemcitabine at 1,000 mg/m^2 over 30 minutes on days 1, 8, and 15, plus oral erlotinib at 100 mg daily for 28 days), and 5-fluorouracil plus leucovorin (bolus intravenous leucovorin at 20 mg/m^2 followed by bolus intravenous 5-fluorouracil at 425 mg/m^2 on days 1–5 every 4 weeks). The outcomes were defined as disease-free survival (DFS; time from surgery to the first instance of recurrence or the date of last follow-up) and overall survival (OS; time from diagnosis to death or the date of last follow-up).

4. Statistical analysis

All statistical analyses were performed using STATA/SE soft-

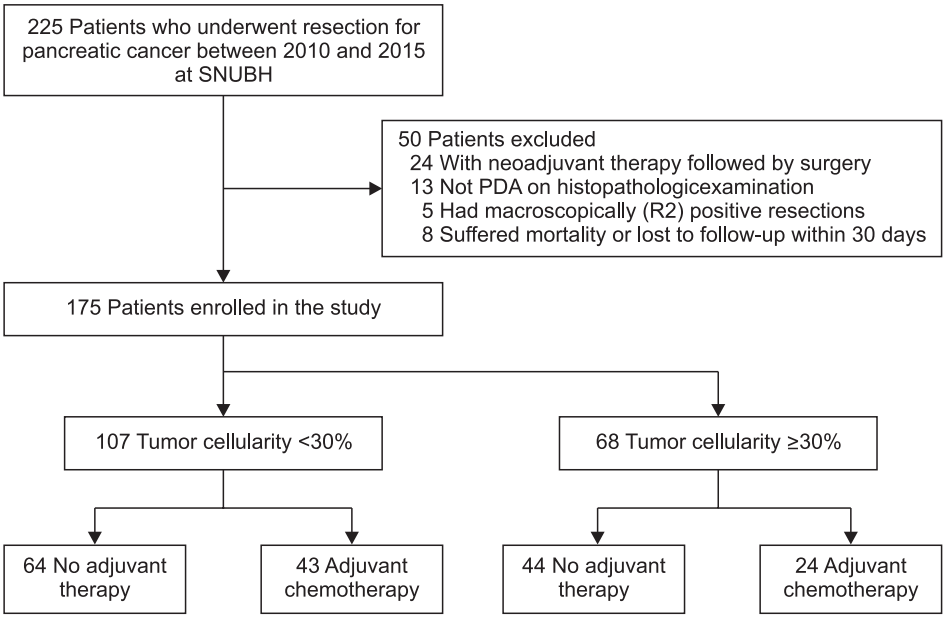

Fig. 1. Flowchart illustrating inclusion/exclusion criteria of the study. SNUBH, Seoul National University Bundang Hospital; PDA, pancreatic ductal adenocarcinoma.

ware version 14.0 (STATA Corp., College Station, TX, USA). The chi-square test or Fisher exact test was used to analyze categorical variables. The optimal cutoff value for defining low or high tumor cellularity was determined using receiver operating characteristic curve analysis. Univariate analyses of DFS were performed using the Kaplan-Meier method and the log-rank test. Significant variables from the univariate analyses, and those that met the proportional hazard assumptions were also analyzed in a multivariate Cox proportional hazard model. Differences were considered statistically significant at p-values <0.05.

RESULTS

1. Baseline characteristics

The patient and disease characteristics are summarized in Table 1. The median age was 66.2 years (range, 35.7 to 88.3 years) and 59.4% of patients were men. The majority of the PDAs (68.0%) were located in the head of the pancreas. The median tumor size was 3.0 cm (range, 1.2 to 9.5 cm). Lymph node metastasis was identified in 110 cases (62.9%). The histological classifications were: well differentiated in 18 cases (10.3%), moderately differentiated in 138 cases (78.9%), and poorly differentiated in 19 cases (10.8%). Angiolymphatic invasion was present in 100 cases (57.1%), venous invasion was present in 80 cases (45.7%), and perineural invasion was present in 153 cases (87.4%). Microscopically negative margins (R0 resection) were achieved in 140 patients (80.0%). The median preoperative serum CA19-9 level was 128.0 U/mL (range, 0.1 to 6,500.0 U/mL). Among the 175 cases, adjuvant chemotherapy was provided to 108 patients (61.7%) and adequate adjuvant chemotherapy was identified for 67 patients (38.3%).

2. Clinicopathological characteristics of PDA according to tumor cellularity

The median tumor cellularity percentage was 25.9% (range, 10% to 90%). The receiver operating characteristic curve analysis revealed that the optimal cutoff value for cellularity was 30%, which provided an area under the receiver operating characteristic curve of 0.655 (95% CI, 0.572 to 0.738). Thus, patients were classified into a low-cellularity group (<30%, 107 patients) and a high-cellularity group (≥30%, 68 patients). The high-cellularity group had a significantly higher prevalence of poor histological differentiation (p<0.001) (Table 2).

3. Survival analysis according to tumor cellularity

The median OS was 22.6 months (95% CI, 18.1 to 26.5 months), and the high-cellularity group had a significantly shorter median OS than the low-cellularity group (18.7 months [95% CI, 15.8 to 22.7 months] vs 26.6 months [95% CI, 18.5 to 33.3 months]: hazard ratio [HR], 1.674; 95% CI, 1.159 to 2.418; p=0.006) (Fig. 2A). The univariate analyses revealed that shorter median OS was associated with older age (HR, 1.643; 95% CI, 1.127 to 2.396; p=0.01), tumor size >3 cm (HR, 1.758; 95% CI, 1.217 to 2.539; p=0.003), lymph node involvement (HR, 2.160; 95% CI, 1.438 to 3.245; p<0.001), angiolymphatic invasion (HR, 1.747; 95% CI, 1.198 to 2.548; p=0.004), venous invasion (HR, 1.858; 95% CI, 1.287 to 2.684; p=0.001), not adequate adjuvant therapy (HR, 2.207; 95% CI, 1.477 to 3.297; p<0.001),

Table 1. Patient Characteristics

Characteristics	No. (%)
Age, yr	
<65	71 (40.6)
≥65	104 (59.4)
Sex	
Male	104 (59.4)
Female	71 (40.6)
Tumor location	
Head	119 (68.0)
Body/tail/others	56 (32.0)
Median tumor size, cm	
<3	75 (42.9)
≥3	100 (57.1)
Lymph node involvement	
Absent	65 (37.1)
Present	110 (62.9)
Histology (differentiation)	
Well	18 (10.3)
Moderate	138 (78.9)
Poor	19 (10.8)
Angiolymphatic invasion	
Absent	75 (42.9)
Present	100 (57.1)
Venous invasion	
Absent	95 (54.3)
Present	80 (45.7)
Perineural invasion	
Absent	22 (12.6)
Present	153 (87.4)
Resection margin	
R0	140 (80.0)
R1	35 (20.0)
Median preoperative CA19-9, U/mL	
<128	87 (49.7)
≥128	88 (50.3)
Adequate adjuvant therapy	
Yes	67 (38.3)
No	108 (61.7)

R0, no residual tumor; R1, microscopic residual tumor (corresponds to positive resection margins); CA19-9, carbohydrate antigen 19-9.

Table 2. Correlation between Tumor Cellularity and the Clinicopathological Characteristics of Pancreatic Ductal Adenocarcinoma

Characteristics	Tumor cellularity <30% (n=107)	Tumor cellularity ≥30% (n=68)	p-value
Age, yr			0.656
<65	42 (59.1)	29 (40.9)	
≥65	65 (62.5)	39 (37.5)	
Sex			0.257
Male	60 (57.7)	44 (42.3)	
Female	47 (66.2)	24 (33.8)	
Tumor location			0.055
Head	67 (56.3)	52 (43.7)	
Body/tail/others	40 (71.4)	16 (28.6)	
Median tumor size, cm			0.371
<3	43 (57.3)	32 (42.7)	
≥3	64 (64.0)	36 (36.0)	
Lymph node involvement			0.687
Absent	41 (63.1)	24 (36.9)	
Present	66 (60.0)	44 (40.0)	
Histology (differentiation)			<0.001
Well	16 (88.9)	2 (11.1)	
Moderate	86 (62.3)	52 (37.7)	
Poor	5 (26.3)	14 (73.7)	
Angiolymphatic invasion			0.227
Absent	42 (56.0)	33 (44.0)	
Present	65 (65.0)	35 (35.0)	
Venous invasion			0.735
Absent	57 (60.0)	38 (40.0)	
Present	50 (62.5)	30 (37.5)	
Perineural invasion			0.497
Absent	12 (54.5)	10 (45.5)	
Present	95 (62.1)	58 (37.9)	
Resection margin			0.816
R0	85 (60.7)	55 (39.3)	
R1	22 (62.9)	13 (37.1)	
Median preoperative CA19-9, U/mL			0.131
<128	58 (66.7)	29 (33.3)	
≥128	49 (55.7)	39 (44.3)	
Adequate adjuvant therapy			0.516
Yes	43 (64.2)	24 (35.8)	
No	64 (59.3)	44 (40.7)	

Data are presented as number (%).
R0, no residual tumor; R1, microscopic residual tumor (corresponds to positive resection margins); CA19-9, carbohydrate antigen 19-9.

and tumor cellularity ≥30% (HR, 1.674; 95% CI, 1.159 to 2.418; p=0.006) (Table 3). According to the multivariate analysis, independent predictors of poor survival included tumor cellularity ≥30% (HR, 2.008; 95% CI, 1.361 to 2.962; p<0.001), older age (HR, 1.476; 95% CI, 1.004 to 2.170; p=0.048), tumor size >3 cm (HR, 1.723; 95% CI, 1.171 to 2.535; p=0.006), lymph node involvement (HR, 1.716; 95% CI, 1.093 to 2.692; p=0.014), venous invasion (HR, 1.755; 95% CI, 1.196 to 2.574; p=0.004), and not adequate adjuvant therapy (HR, 2.064; 95% CI, 1.371 to 3.109; p=0.001) (Table 3). The median DFS was 12.9 months (95% CI, 9.8 to 16.9 months). Relative to the low-cellularity group, the high-cellularity group had a significantly shorter median DFS

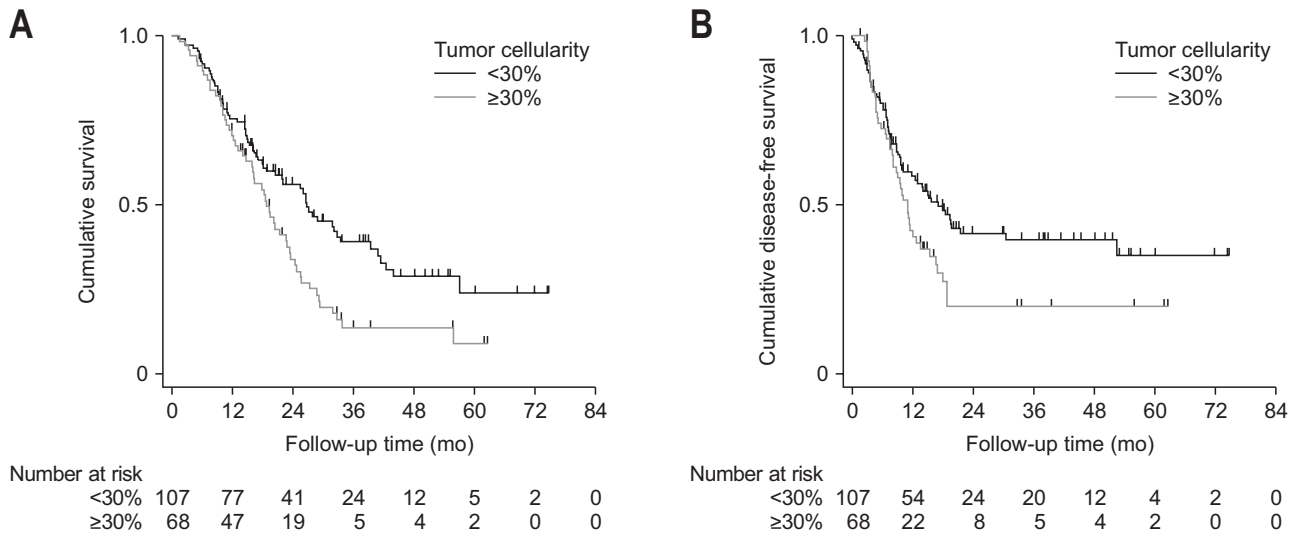

Fig. 2. Kaplan-Meier estimates for (A) overall survival (HR, 1.674; 95% CI, 1.159–2.418; p=0.006) and (B) disease-free survival (HR, 1.536; 95% CI, 1.039–2.270; p=0.031) for patients stratified by tumor cellularity in of pancreatic ductal adenocarcinoma.
HR, hazard ratio; CI, confidence interval.

(11.0 months [95% CI, 8.0 to 13.5 months] vs 16.9 months [95% CI, 10.0 to 30.3 months]: HR, 1.536; 95% CI, 1.039 to 2.270; p=0.031) (Fig. 2B).

4. Survival benefit of adjuvant therapy according to tumor cellularity

The median OS were 16.0 months in the no adjuvant therapy subgroup and 31.8 months in the adjuvant therapy subgroup (HR, 0.453; 95% CI, 0.303 to 0.676; p<0.001). In the low-cellularity group, patients who received adjuvant therapy had a much longer median OS than those who did not (41.3 months vs 16.3 months: HR, 0.380; 95% CI, 0.218 to 0.659; p=0.001). However, in the high-cellularity group, adjuvant therapy provided only a small, non-significant increase in OS (24.4 months vs 15.9 months: HR, 0.616; 95% CI, 0.342 to 1.110; p=0.107) (Fig. 3).

DISCUSSION

Our results indicate that high PDA tumor cellularity was associated with poorer histological differentiation and worse survival and that the benefit of adjuvant therapy on OS was significantly diminished in the high-cellularity group relative to the low-cellularity group. Therefore, tumor cellularity can serve as a potential predictive biomarker for adjuvant therapy in PDA patients.

Although surgery is the only treatment that can potentially provide long-term survival in PDA cases, only a small subset of patients is eligible for surgery at the time of diagnosis because of invasive nature of the disease and the high recurrence rate.[21] Therefore, chemotherapy remains an important treatment modality for PDA patients, and it is important to identify biomarkers that can predict the response to chemotherapy and subsequent survival outcomes.

Relative to other epithelial malignancies, the general histological features of PDA are abundant desmoplastic stroma and relatively sparse tumor cellularity, with the stromal compartment often exceeding 80% of the tumor volume.[12,22] However, there are limited clinicopathological data regarding the relationship between PDA tumor cellularity and patient outcomes, which prompted us to perform this analysis of tumor cellularity in resected PDA specimens from 175 consecutive patients, as well as the relationship of tumor cellularity with survival and adjuvant chemotherapy response.

Our findings agree with those of Heid *et al*.,[23] who recently demonstrated that high preoperative tumor cellularity was a negative prognostic factor for PDA. In that study, the researchers evaluated tumor cellularity based on the apparent diffusion coefficient parameter from diffusion-weighted magnetic resonance imaging, and suggested that subgroups of PDA with high tumor cellularity could be identified non-invasively.[23] Our data provide histological confirmation that PDA tumor cellularity is a strong independent predictor of survival outcomes, and also indicate that adjuvant chemotherapy may provide significant benefits to PDA patients with low cellularity. Thus, including tumor cellularity assessments in pathology reports may help guide the selection of adjuvant treatment regimens. It may also be possible to assess tumor cellularity using small specimens from endoscopic ultrasound-guided fine needle aspiration biopsies, although prospective studies are needed to determine whether this approach could be used to guide the management of advanced stage PDA.

Tumor cellularity is relatively sparse in PDA (median proportion, 25.9% in the present study), and these tumors

Table 3. Prognostic Factors for Survival Identified by Univariate and Multivariate Analyses

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age, yr				
<65	Reference		Reference	
≥65	1.643 (1.127–2.396)	0.010	1.476 (1.004–2.170)	0.048
Sex				
Male	Reference			
Female	0.741 (0.507–1.081)	0.120		
Tumor location				
Head	Reference			
Body/tail/others	1.073 (0.727–1.584)	0.721		
Median tumor size, cm				
≤3	Reference		Reference	
>3	1.758 (1.217–2.539)	0.003	1.723 (1.171–2.535)	0.006
Lymph node involvement				
Absent	Reference		Reference	
Present	2.160 (1.438–3.245)	<0.001	1.716 (1.093–2.692)	0.014
Angiolymphatic invasion				
Absent	Reference		Reference	
Present	1.747 (1.198–2.548)	0.004	1.208 (0.792–1.841)	0.380
Venous invasion				
Absent	Reference		Reference	
Present	1.858 (1.287–2.684)	0.001	1.755 (1.196–2.574)	0.004
Perineural invasion				
Absent	Reference			
Present	1.811 (0.993–3.302)	0.052		
Resection margin				
R0	Reference			
R1	1.484 (0.962–2.290)	0.074		
Median preoperative CA19-9, U/mL				
<128	Reference			
≥128	1.253 (0.864–1.818)	0.233		
Adequate adjuvant therapy				
Yes	Reference		Reference	
No	2.207 (1.477–3.297)	<0.001	2.064 (1.371–3.109)	0.001
Tumor cellularity, %				
<30	Reference		Reference	
≥30	1.674 (1.159–2.418)	0.006	2.008 (1.361–2.962)	<0.001

HR, hazard ratio; CI, confidence interval; R0, no residual tumor; R1, microscopic residual tumor (corresponds to positive resection margins); CA19–9, carbohydrate antigen 19–9.

typically have abundant desmoplastic stroma that accounts for most of the tumor volume. There are limited data regarding the clinicopathological significance of desmoplastic stroma in human malignancies, and research has recently focused on the roles that the tumor stroma play in tumor initiation, progression, and resistance to chemotherapy and radiotherapy.[24,25] A study of resected PDAs has also indicated that high stromal content was associated with poor long-term outcomes.[26] In contrast, our previous study of a subset of PDA cases revealed that high cancer-associated fibroblast (CAF) counts were associated with

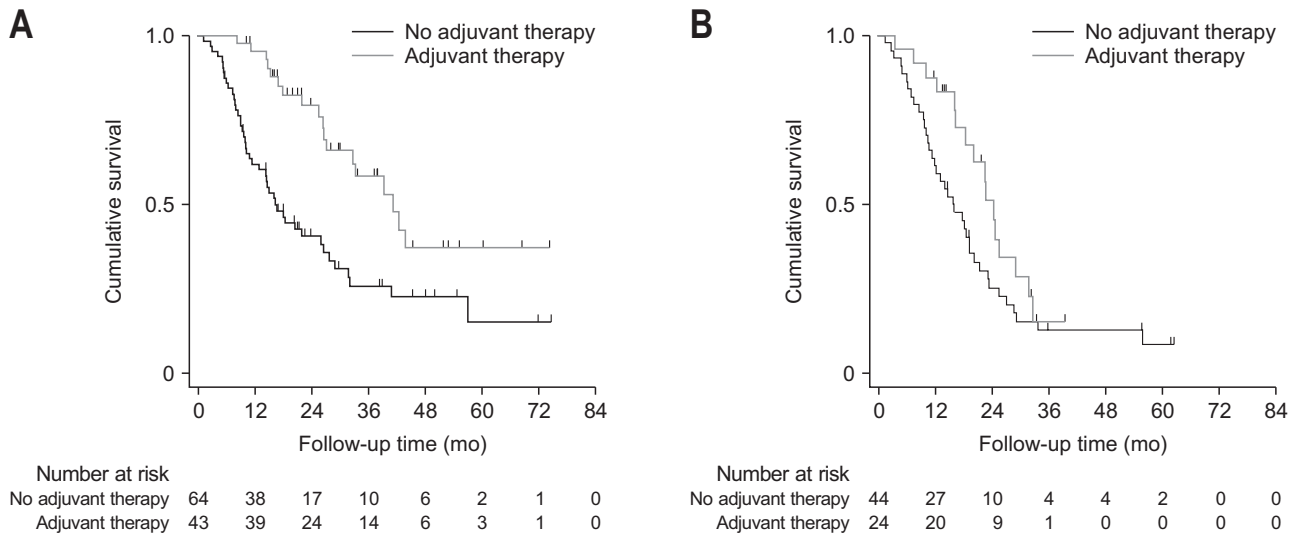

Fig. 3. Kaplan-Meier estimates of overall survival by the receipt of adjuvant therapy in the (A) low-cellularity group (HR, 0.380; 95% CI, 0.218–0.659; p=0.001) and (B) high-cellularity group (HR, 0.616; 95% CI, 0.342–1.110; p=0.107).
HR, hazard ratio; CI, confidence interval.

significantly better survival outcomes, which supports recent experimental findings that the tumor stroma may have a protective role rather than an enhancing role for any aggressive behavior.[27-30] Because the influence of PDA tumor cellularity on patient survival and response to chemotherapy is unclear, the present study focused on the epithelial cell compartment of PDA. However, we did not find significant inverse correlations between the expression of CAF-related markers and tumor cellularity (data not shown), which is unsurprising because the tumor microenvironment is a complex network of many cell types (e.g., fibroblasts, endothelial cells, and inflammatory cells) interacting with the extracellular matrix.[24]

The mechanism behind the relationships between high tumor cellularity and poor patient outcomes and PDA chemoresistance remains unclear. It is possible that tumors with high cellularity have relatively sparse amounts of CAFs, which could result in accelerated tumor growth, invasiveness, and chemoresistance. For example, Rhim *et al*.[30] reported that reducing the amount of stromal content by genetically deleting sonic hedgehog in a mouse model of PDA resulted in more aggressive behavior, undifferentiated histology, increased angiogenesis, and accelerated cellular proliferation. Furthermore, depletion of stromal myofibroblasts in another mouse model of PDA resulted in enhanced tumor aggressiveness and shorter survival.[29] However, *in vitro* studies have revealed increased invasiveness and migration of PDA cancer cells when they are co-cultured with pancreatic stellate cells, as well as CAFs, protecting the cancer cells from the effects of chemoradiation therapy.[31]

The present study has two important limitations. First, this retrospective, single-center study focused on surgically resected PDAs, which led to the exclusion of patients with advanced PDA. Thus, validation is needed in further prospective studies of independent cohorts, preferably with the addition of preoperative biopsy findings. Second, patients who received neoadjuvant treatment were excluded to eliminate any effects of preoperative treatment on tumor cellularity. Therefore, a separate study is needed to determine whether cellularity assessments provide clinical value for patients who receive neoadjuvant therapy.

In conclusion, the present study revealed that tumor cellularity significantly and independently predicted OS and DFS after potentially curative resection of PDA. In addition, adjuvant therapy was more effective for patients with low tumor cellularity, which suggests that assessing tumor cellularity may help guide the post-operative management of PDA patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Study design: J.H.H., J.K. Sample preparation: J.C.L., J.L. Data analysis: I.K.C., S.A., H.P. Interpretation of the results: I.K.C., J.H.H. Writing - original draft: I.K.C., H.K. Writing - review and editing: J.H.H., J.K. All authors provided critical feedback and helped shape the research, analysis and manuscript.

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