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ORIGINAL ARTICLE

Retrospective Study

Outcomes and prognostic factors of patients with stage ⅠB and ⅡA pancreatic cancer according to the 8th edition American Joint Committee on Cancer criteria

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Author contributions: Tang CG, Cao WY and Qu GF designed the research and critically revised the manuscript for important intellectual content; Li Y and Zhao Y performed the research, analyzed the data and wrote the paper.

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Abstract

AIM

To evaluate the changes in the 8th edition American Joint Committee on Cancer (AJCC) for defining stage ⅠB and ⅡA pancreatic cancer and identify their prognostic factors.

METHODS

Pancreatic cancer patients were selected from the Surveillance Epidemiology and End Results database (1973-2013). The enrolled patients were divided into ⅠB and ⅡA groups based on tumor size according to the 8th edition AJCC criteria. Clinical characteristics, including age, gender, race, tumor size, primary site, and grade were summarized. Univariate and multivariate analyses were performed to explore the prognostic factors of the ⅠB and ⅡA stages of pancreatic cancer under new criteria.

RESULTS

A total of 1349 pancreatic cancer patients were included. More patients had stage ⅠB rather than stage ⅡA. Stage ⅠB tumors (54.85%) were mainly

located in the head of the pancreas, while stage ⅡA tumors were more often located in the tail and head of the pancreas (35.21% and 31.75%, respectively). The survival time of stage ⅠB and ⅡA patients had no significant difference. Univariate and multivariate analyses indicated that the prognostic factors of survival for stage ⅠB and ⅡA patients were different. For stage ⅠB patients, age and primary site were the independent prognostic factors; for stage ⅡA patients, age and grade were the independent prognostic factors. The risk of death was lower among patients aged ⩽ 65 years than those aged > 65 years.

CONCLUSION

The prognostic factors for stage ⅠB and ⅡA patients are different, but age is the independent prognostic factor for all patients. The survival time of stage ⅠB and ⅡA patients has no significant difference.

Key words: Pancreatic cancer; Prognostic factor; 8th American Joint Committee on Cancer; TNM; Tumor size

Core tip: The 8th edition American Joint Committee on Cancer TNM criteria for pancreatic cancer emphasize the tumor size cutoff point of 4 cm for the first time. Thus we used the Surveillance Epidemiology and End Results database, a population-based database, to evaluate the new changes in pancreatic cancer staging and the prognostic factors of stage ⅠB and ⅡA pancreatic cancer.

Li Y, Tang CG, Zhao Y, Cao WY, Qu GF. Outcomes and prognostic factors of patients with stage ⅠB and ⅡA pancreatic cancer according to the 8th edition American Joint Committee on Cancer criteria. *World J Gastroenterol* 2017; 23(15): 2757-2762 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i15/2757.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i15.2757

INTRODUCTION

Pancreatic cancer is an aggressive and devastating disease, which is characterized by invasiveness, rapid progression, and profound resistance to treatment[1-3]. The incidence of pancreatic cancer in the United States and western Europe is 10/100000 per year and almost approaches mortality[4]. The overall survival rate at 5 years is less than 5%[5,6]. Surgical resection is still the only treatment providing prolonged survival; however, even after a curative resection, the 5-year survival rate remains low[7].

Tumor size is the basis of cancer staging, which is one of the strongest prognostic factors in various cancers, including pancreatic cancer[8-10]. Compared with the 6th and 7th edition of the American Joint Committee on Cancer (AJCC) system for defining stage ⅠB pancreatic cancer (IB: tumor diameter > 2 cm, no regional lymph node metastasis, no distant metastasis)[11], the 8th edition AJCC criteria emphasize the cutoff point of 4 cm (IB: tumor diameter > 2 but ⩽ 4 cm; ⅡA: tumor diameter > 4 cm, both with no regional lymph node metastasis and no distant metastasis)[12,13]. Clinically, the size and location of pancreatic tumor determine the type of surgical resection[14-16], which suggests the important role of tumor size and location. Therefore, the aim of this study was to evaluate the changes in the AJCC system for defining stage ⅠB and ⅡA pancreatic cancer and identify their prognostic factors.

MATERIALS AND METHODS

Patients

The Surveillance Epidemiology and End Results (SEER) database (1973-2013) was used for the study. The National Cancer Institute's SEER*Stat software (Version 8.2.0) was used to identify patients. All patients underwent surgical treatment and had a pathologically confirmed diagnosis of stage ⅠB pancreatic tumor according to the 6th and 7th edition of the AJCC criteria. Patients with unknown tumor size were excluded. Demographics, including age, gender, and race, were retrieved. Tumor variables included location of the primary tumor, tumor size, and grade. Survival data were extracted at 1 mo intervals for a follow-up period between 1 mo and 110 mo.

Statistical analysis

The enrolled patients were divided into two groups based on tumor size according to the 8th edition AJCC criteria (IB: tumor diameter > 2 but ⩽ 4 cm, ⅡA: tumor diameter > 4 cm). The independent *t*-test and the χ^2 test were used for the difference analysis between the two groups. Univariate analysis with the log-rank test and multivariate analysis with the Cox proportional hazards regression model were performed to explore the difference in prognostic factors between the two groups, with P values < 0.05 considered statistically significant. All analyses were performed using SPSS software, version 13.0 for Windows.

RESULTS

A total of 1349 pancreatic cancer patients were selected from the SEER database. The age of the patients ranged from 18 to 90 years, with a median age of 65 years. There were 626 male patients and 723 female patients. The median tumor diameter was 43.4 mm (range, 21-540 mm). The pathological stage was classified as ⅠB in 886 patients and ⅡA in 463 patients, according to the AJCC 8th criteria. The total median survival of these patients was 62 mo, and their 1-, 3-, and 5-year survival rates were 83.8%, 58.9%, and 50.6%, respectively. The patients' clinical characteristics

Table 1 Clinical characteristics of the entire patient cohort[1] *n* (%)

Characteristic	Entire cohort	Stage ⅠB	Stage ⅡA	*P* value
Number of patients	1349	886	463	
Age (yr), median (range)	65 (18-90)	65 (18-90)	63 (18-90)	0.000
Tumor size (mm), mean (range)	43.4 (21-540)	29.5 (21-40)	70.0 (41-540)	0.000
Gender				
Male	626 (46.40)	405 (45.71)	221 (47.73)	0.480
Female	723 (53.60)	481 (54.29)	242 (52.27)	
Primary site				
Head	633 (46.9)	486 (54.85)	147 (31.75)	0.000
Body	165 (12.23)	103 (11.6)	62 (13.39)	
Tail	350 (25.95)	186 (20.99)	164 (35.21)	
Other	201 (14.90)	111 (12.53)	90 (19.44)	
Grade				
Ⅰ	348 (25.80)	221 (24.94)	127 (27.43)	0.006
Ⅱ	484 (35.88)	335 (37.81)	149 (32.18)	
Ⅲ	230 (17.05)	164 (18.52)	66 (14.25)	
Ⅳ	17 (1.26)	10 (1.13)	7 (1.51)	
Unknown	270 (20.01)	156 (17.61)	114 (24.62)	
Race				
White	1060 (78.58)	694 (78.33)	366 (79.05)	0.760
Other	289 (21.42)	192 (21.67)	97 (20.95)	

[1]Factors were compared by independent *t* test and χ^2 test for continuous and categorical variables, respectively.

Table 2 Prognostic significance for overall survival by univariate analysis of variables for stage ⅠB and ⅡA patients[1]

Variable	Stage ⅠB		Stage ⅡA	
	n	Log-rank	*n*	Log-rank
Age (yr)				
≤ 65	444	0.000	270	0.000
> 65	442		193	
Gender				
Male	405	0.162	221	0.002
Female	481		242	
Tumor size (mm)				
21-30	584	0.258		
31-40	302			
41-70			332	0.013
> 70			131	
Primary site				
Head	486	0.000	147	0.004
Body	103		62	
Tail	186		164	
Other	111		90	
Grade				
Ⅰ	221	0.000	127	0.000
Ⅱ	335		149	
Ⅲ	164		66	
Ⅳ	10		7	
Unknown	156		114	
Race				
White	694	0.148	366	0.685
Other	192		97	

[1]Univariate analysis was done by Kaplan-Meier method.

are presented in Table 1.

Under the new criteria, the median tumor diameter of stage ⅠB patients was 29.5 mm, while the median tumor diameter of stage ⅡA patients was 70.0 mm. The primary site of 54.85% of stage ⅠB tumors was the head of the pancreas, while the primary site of stage ⅡA tumors was mainly the tail and head of the pancreas (35.21% and 31.75%, respectively). Among both stage ⅠB and ⅡA patients, the majority (approximately 60%) were in grade Ⅰ and Ⅱ.

Univariate survival analysis of clinical characteristics was evaluated with a log-rank test (Table 2). Age, grade and primary site were significantly associated with the overall survival of stage ⅠB patients ($P < 0.05$), while gender and race showed no significant association with survival ($P > 0.05$). For stage ⅡA patients, age, gender, grade, and primary site were significantly associated with overall survival ($P < 0.05$), but race showed no significant association with survival ($P > 0.05$). Multivariate analyses for stage ⅠB and ⅡA patients were performed with the Cox regression model (Table 3). The results indicated that for stage ⅠB patients, age and primary site were the independent prognostic factors; for stage ⅡA patients, age and grade were the independent prognostic factors ($P < 0.05$). Overall, the survival time of stage ⅠB and ⅡA patients had no significant difference (Figure 1A); whereas, for both stage ⅠB and ⅡA, the risk of death was lower for patients aged ≤ 65 years than those aged > 65 years (Figure 1B).

DISCUSSION

As one of the most lethal human cancers, pancreatic cancer staging is of important significance clinically. Regardless of how the AJCC definitions of pancreatic cancer staging change, the diameter of the tumor has been shown to be a strong predictor of prognosis. The current cutoff points of > 2 but ≤ 4 and > 4 cm have been proposed to be the sole factor governing the ⅠB and ⅡA stages in pancreatic cancer. However, the

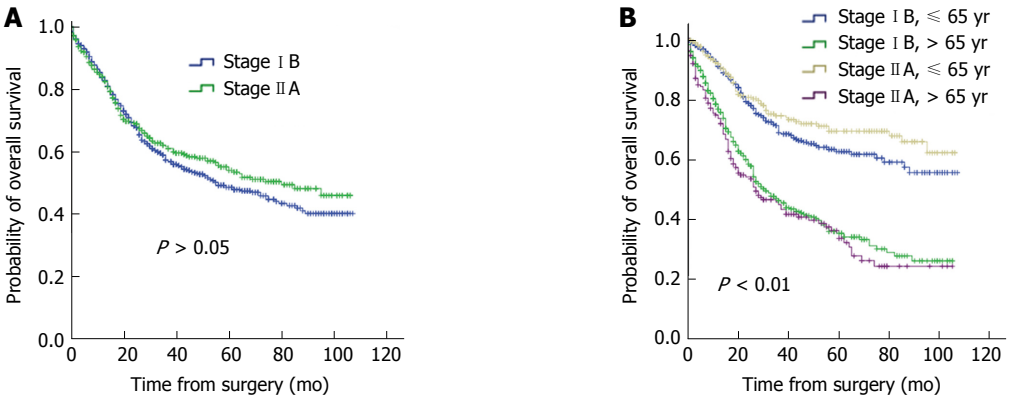

Figure 1 Kaplan-Meier analysis of overall survival. A: Among 1349 patients, the survival time of stage ⅠB and ⅡA patients had no significant difference ($P > 0.05$); B: For both stage ⅠB and ⅡA, death risk was lower in patients aged ≤ 65 yr than those aged > 65 yr.

Table 3 Prognostic significance for overall survival by multivariate analysis of variables for stage ⅠB and ⅡA patients[1]

Variable	Stage ⅠB			Stage ⅡA		
	RR	95%CI	*P* value	RR	95%CI	*P* value
Age	1.037	1.025-1.049	0.000	1.045	1.029-1.062	0.000
Gender (male *vs* female)	1.128	0.887-1.434	0.327	1.235	0.852-1.790	0.265
Tumor size	1.018	0.996-1.039	0.000	1.003	0.999-1.008	0.173
Primary site (head *vs* body-tail)	1.734	1.311-2.294	0.000	1.197	0.825-1.736	0.345
Grade (Ⅰ + Ⅱ *vs* Ⅲ + Ⅳ)	0.570	0.443-0.734	0.104	0.490	0.333-0.721	0.000

[1]Multivariate analysis was done with Cox proportional hazard regression model.

results from the current study suggest that they are not statistically sound, since the patients with stage ⅠB and ⅡA cancer had similar outcomes ($P > 0.05$). The findings reported by Burcu[17] contradicts our findings. Thus, further studies or more clinical data are required to evaluate the cutoff point of 4 cm tumor diameter.

In addition, moving to a different staging system has implications and comes with its challenges, such as hampered comparison with earlier data. In this study, all patients were pathologically diagnosed with stage ⅠB pancreatic tumor according to the 6th and 7th edition AJCC criteria, which means the data were discrete over past decades. Therefore, further work needs to be done to evaluate the quality of the data.

Pancreatic cancer can be divided into head and body/tail cancers according to the anatomy. In this study, we found that stage ⅠB tumors were mainly located in the head of the pancreas, while stage ⅡA tumors were more often located in both the tail and head of the pancreas (35.21% and 31.75%, respectively). Generally, pancreatic development begins with the formation of a ventral and a dorsal bud, which become the ventral head (lower head and uncinate process) and dorsal pancreas (upper head, body, and tail), respectively. This difference in ontogeny leads to significant differences in cell composition, blood supply, lymphatic and venous backflow, and innervations between the head and body/tail of the pancreas[18]. For instance, the number of islets of Langerhans is greater in the body and tail. There have been some reports showing the significance of tumor location in terms of the prognosis of pancreatic tumor. For example, in pancreatic serous cystic neoplasms and intraductal papillary mucinous neoplasms, tumor location in the head of the pancreas was independently associated with local invasiveness and recurrence[19,20], while in pancreatic neuroendocrine tumors, tumors located at the body/tail of the pancreas were more likely to be associated with shorter progression-free survival[21]. Our analysis indicates that tumor location has a correlation with the prognosis in stage ⅠB pancreatic cancer patients.

Prognostic factors combining clinical and laboratory variables with physician's estimates have been developed in recent years[22]. However, in this study, we just selected patients from the SEER database to analyze the prognostic factors. It is necessary for us to include more variables using our own patient database to verify the new TNM staging system.

In conclusion, our analysis demonstrates that more patients tend to be stage ⅠB rather than stage ⅡA when they are diagnosed. Overall survival is mainly associated with age and primary site for stage ⅠB patients, while for stage ⅡA patients, age and grade are the independent prognostic factors. The common independent prognostic factor for both patient groups is age. However, the survival time of stage ⅠB and ⅡA patients has no significant difference. The results suggest that the new AJCC criteria need further evaluation.

COMMENTS

Background

Compared with the 6th and 7th edition American Joint Committee on Cancer (AJCC) system for TNM staging of pancreatic cancer, the 8th edition AJCC criteria emphasize the cutoff point of 4 cm.

Research frontiers

AJCC TNM staging of pancreatic cancer has just been updated to the 8th edition. The aim of our study was to evaluate the changes in the AJCC system for defining stage ⅠB and ⅡA pancreatic cancer - the cutoff point of 4 cm and to identify their prognostic factors.

Innovations and breakthroughs

The prognostic factors for stage ⅠB and ⅡA patients are different, and age is the common factor. But the survival time of stage ⅠB and ⅡA patients has no significant difference.

Applications

The new AJCC criteria need further evaluation.

Peer-review

This is a large retrospective study of patients undergoing resection for pancreatic cancer. The authors have chosen to look at tumor size as an absolute value for determining survival in patients having resection for pancreatic cancer. The manuscript is succinct and reasonably well written. The figures and tables are appropriate.

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