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Original Article

Serum CA125 levels change during intensity-modulated radiation therapy in prediction of prognosis in locally pancreatic ductal adenocarcinoma

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Abstract: We analyzed the capability of serum CA125 levels change during intensity-modulated radiation therapy (IMRT) for predicting survival in locally pancreatic ductal adenocarcinoma (PDA). A total of 118 locally advanced PDA patients who underwent intensity modulated radiation therapy (IMRT) with or without chemotherapy were enrolled in this study. Patients were categorized into two groups according to their serum CA125 levels change prior to IMRT and on the third day after radiotherapy: group A = serum CA-125 levels increasing during treatment, group B = serum CA-125 levels decreasing during treatment. There was significant difference between the group A and B with regard to treatment response (P=0.004). The clinical benefit rate was significantly higher for group B than for group A (95.7% vs. 4.3%, P=0.004). The 1 year cumulative overall survival (OS) rates for group A and group B were 32.7% and 51.5%, respectively. On multivariate analysis, the serum CA125 levels change group was a significant predictor for overall survival (HR=1.82, P=0.035). The serum CA125 levels change was a useful prognostic indicator to predict for overall survival in locally advanced PDA underwent IMRT.

Keywords: Pancreatic ductal adenocarcinoma, CA125, IMRT, prognosis

Introduction

The prognosis of advanced pancreatic ductal adenocarcinoma (PDA) remains poor and the purpose of treatment remains palliative [1, 2]. Gemcitabine based chemoradiotherapy is the main treatment for advanced pancreatic ductal adenocarcinoma. A reliable evaluation of tumor response to chemoradiation assumes a crucial role in making the treatment decisions in order to obtain the maximum treatment benefits. Although the pathologic tumor-node-metastasis (TNM) stage system can provide the best prognostic information, the outcome of patients with same stage varies widely, especially in advanced PDA [3]. Additionally, among the available tools for tumor response evaluation, even with newer imaging techniques, is considered unreliable because of the inflammation and fibrosis, within and around the tumor, and regional lymph node micrometastasis [4, 5]. To identify the subgroup of patients with high risk of relapse, several molecular and biological markers were investigated their roles in predicting tumor response and patients' prognosis [6-9]. However, the validity of those markers is still controversial and the clinical application is not widely available [10, 11].

The serum CA-125 is well-established and widely used tumor marker for monitoring the treatment response of ovarian cancer [12] and PDA [13]. There have been several retrospective studies that elevated pretreatment serum CA-125 levels are associated with an increased risk of recurrence and poor prognosis [13, 14]. However, less study has been performed to evaluate the prognostic significance of CA-125 change during the chemoradiotherapy. Therefore, the objective of the current study was to assess the prognostic value in CA-125 levels change two weeks after radiotherapy in a cohort of locally advanced PDA patients treated with IMRT.

Methods

A total of 118 patients with locally advanced PDA who underwent IMRT with or without che-

Table 1. Relationship between clinicopathologic features and CA125 group in 118 locally advanced pancreatic ductal adenocarcinoma

Variables	Total (n)	Group A (n=20)	Group B (n=98)	P
Age, median ± SD	118	62.5±9.82	60.5±9.54	0.773
Sex				
Female	46	8 (17.4)	38 (82.6)	0.918
Male	72	12 (16.7)	60 (83.3)	
Tumor location				
Head	53	9 (17.0)	44 (83.0)	0.993
Body and tail	65	11 (16.9)	54 (83.1)	
Chemotherpy				
No	44	9 (20.5)	35 (79.5)	0.434
Yes	74	11 (14.9)	63 (85.1)	
Tumor size				
≤4 cm	62	11 (17.7)	51 (82.3)	0.809
>4 cm	56	9 (16.1)	47 (83.9)	
T stage				
T_{1-2}	32	4 (12.5)	28 (87.5)	0.432
T_{3-4}	86	16 (18.6)	70 (81.4)	
N stage				
N_0	53	10 (18.9)	43 (81.1)	0.616
N_+	65	10 (15.4)	55 (84.6)	
Pretreatment serum CA125 levels				
<35 U/ml	43	14 (32.6)	29 (67.4)	0.001
≥35 U/ml	75	6 (8.0)	69 (92.0)	
Treatment response				
CR+PR	46	2 (4.3)	44 (95.7)	0.004
SD+PD	72	18 (25.0)	54 (75.0)	

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease Group A: serum CA-125 levels increasing during treatment, Group B = serum CA-125 levels decreasing during treatment.

motherapy from January 2011 to December 2014 at Zhejiang Cancer Hospital. All patients were newly confirmed to have pancreatic adenocarcinoma and had not received treatment previously. Patients with other malignancies were excluded from this study. All patients provided written informed consent before treatment. Each case was reassigned for tumor, node and metastases (TNM stage) classification and clinical stage according to the American Joint Committee on Cancer (AJCC) staging system. The following detail clinical information was retrospectively collected and analyzed for each case: gender, age at treatment, smoking status, tumor location, clinical TNM stage, treatment response and overall survival (OS) after IMRT. Overall survival was calculated as the time from radiotherapy to death or last follow-up.

Serum CA-125 levels were measured prior to IMRT and after radiotherapy. For the present analysis, serum CA-125 levels on the third day after radiotherapy was considered the last measurement of CA-125 levels over the treatment period. Serum CA-125 levels were analyzed using immunoenzymometric assays (Immuno 1, Bayer, Tarrytown, N.Y., USA). The cut-off value for diagnostic purpose was 35 UmL for CA-125, consistent with the definition of CA-125 normalization commonly used in clinical practice.

Patients were categorized into two groups according to their serum CA-125 levels' variation before and after IMRT: group A = serum CA-125 levels increasing during treatment, group B = serum CA-125 levels decreasing during treatment.

The median delivered dose of IMRT was 50 Gy (ranged: 44.0-55.8 Gy). The area of solid macroscopic tumors in pancreas, the surrounding tissue infiltrated and the regional lymph node metastasis were defined as the gross tumor volume (GTV). The GTV plus a margin of at least 5 mm, including any areas of microscopic spread and the regional lymph nodes (peripancreatic, celiac, superior mesenteric, portal hepatic, retroperitoneal), was defied as the clinical target volume (CTV). The plan target volume (PTV) was defined as the CTV plus 0.5-1.0 cm to account for the daily setup variation and respiratory movement. Seventy-four patients received two cycles of gemcitabine or S-1 based concurrent chemotherapy.

The CR (complete response), PR (partial response), SD (stable disease) and PD (progressive disease) were assessed at an interval of at least 4 weeks to confirm the objective response. All patients received standardized follow-up,

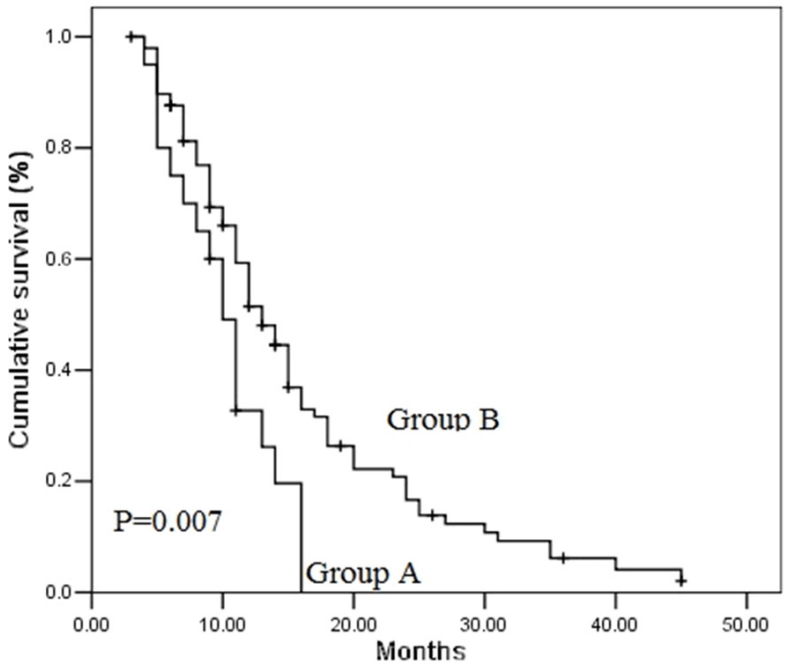

Figure 1. Kaplan-Meier overall survival curves of the patients with group A (n=20) and group B (n=98). All patients underwent IMRT (P=0.007, log-rank test).

occurring at 3 months interval for two years, 6 months interval the third year, and yearly thereafter. Evaluations comprised a physical examination, complete blood count, liver and kidney function tests, abdominal ultrasound or CT, chest radiography and pelvic CT.

Statistical analyses were performed by using SPSS version 13.0 for Windows (SPSS, Inc., Chicago, IL). The chi-square test was performed to evaluate the association between the clinicopathological variables and peritreatment change of serum CA125 levels. Survival curves were estimated by the univariate Kaplan-Meier method. The log-rank test was applied to check the significant differences in the curves among groups. Furthermore, we used the Cox proportional hazards model with the backward selection method for multivariate analysis. All statistical calculations were performed with SPSS 13.0 for Windows (Chicago, IL). Two-sides *P* values of < 0.05 were considered statistical significance.

Results

Relationship between serum CA-125 levels change and clinicopathological parameters

The clincopathological characteristics of two groups categorized by serum CA-125 levels change during treatment were summarized in **Table 1**. A total of 118 locally advanced PDA were enrolled in this study. The analysis was performed on January 2015, when 99 0f 118 patients (83.9%) had died and only 19 patients who still alive. The overall follow-up durations ranged from 3 to 45 months (median, 13.0 months). The patient distribution in the groups was 20 patients in group A, 98 in group B. Serum CA-125 levels were decreased after IMRT. There were no significant differences between the groups with regard to age, sex, tumor location, tumor size and regional lymph node status (P>0.05). There was also no significant difference in adjuvant chemotherapy between these two groups (P>0.05). The median serum CA-125 levels were 3.67 U/ml. Serum CA-125 levels change was related with pretreatment serum CA-125 levels (P=0.001).

After IMRT, Eleven patients (9.3%) achieved a complete response (CR) as the best response post-treatment. The median overall survival time was 35 months. Thirty-five patients had a partial response (PR) with median overall survival time 15.0 months. The clinical benefit rate, calculated as CR+PR, was 39.0%. 67 patients (56.8%) had stable disease (SD). The median overall survival time was 10.0 months. Progressive disease (PD) was observed in 5 patients (4.2%). The median overall survival time was only 7 months. There was significant difference between the group A and B with regard to treatment response (P=0.004). The clinical benefit rate was significantly higher for group B than for group A (95.7% vs. 4.3%, P=0.004).

Serum CA-125 levels change and patients' prognosis with univariable and multivariable analysis

The 1-year cumulative overall survival (OS) rates for group A and group B were 32.7% and 51.5%, respectively. The median overall surviv-

Table 2. Univariate and multivariate analysis of prognostic factor for overall survival

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Sex				
Female	1		1	
Male	0.95 (0.63-1.43)	0.801	1.01 (0.65-1.57)	0.963
Age, years				
≤60	1		1	
>60	1.01 (0.68-1.52)	0.927	1.06 (0.69-1.62)	0.786
Tumor location				
Head	1		1	
Body and tail	1.19 (0.80-1.77)	0.401	1.20 (0.78-1.85)	0.415
Chemotherpy				
No	1		1	
Yes	0.82 (0.54-1.24)	0.334	0.84 (0.53-1.31)	0.433
Tumor size				
≤4 cm	1		1	
>4 cm	1.09 (0.73-1.64)	0.668	1.13 (0.73-1.74)	0.587
T stage				
T_{1-2}	1		1	
T_{3-4}	1.04 (0.67-1.62)	0.854	1.03 (0.63-1.68)	0.902
N stage				
N_0	1		1	
N_+	1.35 (0.91-2.01)	0.134	1.38 (0.88-2.15)	0.158
Pretreatment serum CA125 levels				
<35 U/ml	1			
≥35 U/ml	1.21 (0.80-1.81)	0.365	1.10 (0.71-1.69)	0.675
CA125 group				
Group B	1		1	
Group A	2.00 (1.17-3.39)	0.011	1.82 (1.04-3.19)	0.035

HR, hazard ratio; CI, confidence interval. Group A: serum CA-125 levels increasing during treatment, Group B = serum CA-125 levels decreasing during treatment.

al time was 10.0 months for patients in group A and 13.0 months for group B. A significant difference in OS was observed between Groups A and B (**Figure 1**, P=0.007).

We performed univariate analysis for serum CA-125 levels change and other 8 clinicopathological variables **Table 2**, (including sex, age, tumor location, T stage, lymph node metastasis, tumor size, pretreatment serum CA-125 levels and chemotherapy) to find useful prognostic factors for locally advanced PDA. Serum CA-125 levels change was as independent significant prognostic factor (P=0.011). The hazard ratio (HR) of group A compared with group B was 2.00 (95% CI: 1.17-3.39), indicating that group A had 2.36-fold higher risk for cancer-related death. We then performed multivariate analysis for all eight variables. Patients in group A had a 1.82-fold increased risk of death compared to those in group B.

Discussion

In the present study, serum CA125 levels change during IMRT could predict indicators of tumor response and overall survival in locally advanced PDA. The patients with increased serum CA125 levels during IMRT showed less frequently effective tumor response and worse overall survival rates than that with decreased serum CA125 levels (median overall survival time: 10.0 months vs. 13.0 months). By multivariate analysis, serum CA125 levels change is an independent prognostic factor for overall survival, adjusted for patient age, sex, chemo-

therapy, disease stage, tumor size and pretreatment serum CA125 levels. Patients with increased serum CA125 levels during IMRT had 1.82 times the risk of death compared with those with decreased serum CA125 levels during treatment.

The locoregional extent and distant metastasis of tumor are the useful measurement of predicting survival in PDA. However, some patients with similar clinical stage have remarkably different survival prognosis [15]. Numerous previous studies report that serum CA125 levels can be used as a potential surrogate marker of treatment efficacy and predicting overall survival [14, 16, 17]. Most of these studies about the role of CA125 in PDA focused on the preoperative serum CA125 levels. Recently, Zhou et al [18] performed measurement of serum CA125 before and one month after cryosurgery in 37 pancreatic cancer patients. Preoperative serum CA125 levels are related with tumor size, clinical stage, tumor cell differentiation, regional lymph node metastasis and liver metastasis. Serum CA125 levels one month after treatment was significantly lower than levels before treatment. However, the prognostic role of serum CA125 change peri-treatment was not investigated extensively. Another limitation of this study that cryosurgery is not standard treatment in pancreatic cancer. Furthermore, the small sample size also can not reflect the response to the treatment.

In our current study, serum CA125 change during IMRT was classified into two groups: group A including patients with serum CA-125 levels increasing during treatment and group B including patients with serum CA-125 levels decreasing during treatment. This study was performed in only one hospital and all the samples were measured using the same device. Therefore, the bias induced by different definition of serum CA125 levels can be avoided. According to the result, serum CA-125 levels change was significantly related with tumor response and overall survival. However, the major limitation in this study is that the information on post-treatment local recurrence or metastasis was insufficient. One of the least convincing things in this study is lack the data of disease free survival, although overall survival is the standard indicator in the cancer prognosis study. Second, this retrospective study is relatively small sample size. A prospective study is required to determine the prognostic value of serum CA125 levels change.

In summary, change in serum CA 125 levels may be a useful tool for predicting of tumor response after chemoradiotherapy and overall survival in locally advanced PDA. The results also provided that by this tool may be useful in clinical practice to make treatment decisions in critical situations.

Disclosure of conflict of interest

None.

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