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CONTENT

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SERUM CA 19-9 IN PANCREATIC ADENOCARCINOMA: CORRELATION WITH HYSTOPATHOLOGYCAL CHARACTERISTICS AND A PROGNOSTIC MARKER FOR SURVIVAL AFTER CURATIVE RESECTION

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ABSTRACT

Pancreatic cancer is the EU's third biggest cancer killer, despite being the seventh most common cancer, with the extremely poor outlook for patients. CA19-9 serum levels was evaluated as a screening tool in asymptomatic individuals and in patients with symptoms related to pancreatic cancer. The aim of the study was to correlate CA19-9 serum level in patients with pancreatic adenocarcinoma with gender, age, grade of differentiation, tumor size and tumor stage. Also, CA19-9 serum level and survival rate was determinate for the period of one year. The study included 62 patients, 40 male and 22 female with pancreatic cancer, diagnosis confirmed by histopathological examination after surgical treatment. CA19-9 measurements were carried out at certified laboratories. The normal level of CA19-9 was 37U/ml. The patients were divided into 2 groups: the first group with increased CA19-9 level under 100U/ml and the second group with CA19-9 level over 100U/ml. Correlation between histological tumor characteristics including: tumor size, tumor stage and cell differentiation, as well as CA19-9 serum levels, revealed insignificant results. However, patients with elevated CA19-9 values higher than 100U/ml were more frequently measured in patients with larger tumors, advanced III stage of tumor and poorly differentiated tumors. Our study revealed significant correlation between CA19-9 levels and patients' gender (more in female patients than in male, 90.9% vs 62.5%), age of the patients (older patients) and survival in patients with pancreatic cancer (p=0.022).

Introduction

Pancreatic cancer (PC), as one of the most devastating and lethal malignant diseases, is mostly diagnosed at advanced-stage disease. The new cases of pancreatic cancer in Europe for 2020 are 495,773, and the number of mortalities is 466,003. Higher incidence of PC has population in the United States compared, and in the general population is nearly 8/100,000 persons (1). PC has extremely poor prognosis and 5-years survival rate of less than 10% (2,3,4).

Carbohydrate antigen (CA 19-9) discovered in the year 1979 is the most used tumor marker for pancreatic cancer diagnosis (5,6,7). Furthermore, CA19-9 serum levels were evaluated as a

screening tool in asymptomatic individuals and in patients with symptoms related to pancreatic cancer (8). Numerous studies have reported the utility of preoperative CA19-9 level, as a useful marker for predicting prognosis of pancreatic cancer (9,10). In addition, despite of levels of serum CA19 – 9, novel genetic and epigenetic biomarkers are required for early diagnosis of PC. Elevated CA19-9 serum levels might be associated to other pancreatic diseases such as chronic pancreatitis, hereditary pancreatic lesions and are appropriate with other biomarkers to improve the accuracy of diagnosis (11,12,13,14).

Deficiency of CA19-9 expression is found in about 5% of the population, while an elevation can be observed in other diseases including chronic pancreatitis and obstructive jaundice. The sensitivity and specificity of CA19-9 is a variable, approximately 85% for the detection of PC. This biomarker is not applicable as a screening method, and is not relevant for confirmatory or differential diagnosis (15,16,17). The utility of CA19-9 as a serum biomarker is widely used for detection of tumor recurrence after surgical resection (18,19,20).

Material and Methods

The study included 62 patients, 40 male and 22 female with pancreatic cancer, diagnosis confirmed by histopathological examination after surgical treatment. CA19-9 measurements were carried out at certified laboratories. The normal level of CA19.9 was 37U/ml. The patients were divided into 2 groups: the first group with increased CA19-9 level under 100U/ml and the second group with CA19-9 level over 100U/ml.

The aim of the study was to correlate CA19-9 serum level in patients with pancreatic adenocarcinoma with gender, age, grade of differentiation, tumor size and tumor stage. Also, CA19-9 serum level and survival rate was determinate for the period of one year.

Results

Tumor marker CA19-9 presented values higher than 100U/ml significantly more frequently in female patients than in male patients – 20 (90.9%) vs 25 (62.5%).

Patients with serum CA19-9 level of 100U/ml or lower were significantly older than the patients with CA19-9 level higher than 100U/ml. Patients with a serum CA19-9 level of 100U/ml or lower were aged 56 to 78 years (average of 69.8 ± 6.9 years), while patients aged 42 to 76 years (average of 61.3 ± 7.5 years) showed higher CA19-9 level of >100U/ml. The results revealed that age of the patients with pancreatic cancer had a significant effect on CA19-9 levels ($p=0.00015$).

Correlation between histological tumor characteristics including: tumor size, tumor stage, and cell differentiation and CA19-9 serum levels, revealed insignificant results. However, patients with elevated CA19-9 values higher than 100U/ml were more frequently measured in patients with larger tumors in 66.7%, than small tumors less than 2 cm in size, without statistical significance ($p=0.31$). Similarly, CA19-9 values higher than 100U/ml were found in tumors diagnosed

at an advanced stage, but without statistical significance (p=0.087). 18 (40%) patients were diagnosed with stage III tumor.

Concerning tumor cell differentiation, poorly differentiated tumors were more frequently associated to CA19-9 levels higher than 100U/ml. Correlation of tumor cell differentiation and CA19-9 serum levels were not sufficient for statistical significance (p = 0.55). Summarized results are presented in Table 1.

Table 1. *Correlation of CA 19-9 level with tumor size, stage, and cell differentiation*

Variable	Sizes	CA 19-9 (U/ml)		p value
		≤ 100 n (%)	>100 n (%)	
Tumor size	<2cm	4 (23.53)	3 (6.67)	Fisher exact
	2-4 cm	10 (58.82)	30 (66.67)	p=0.31 ns
	> 4 cm	3 (17.65)	11 (24.44)	
	in the celiac plexus	0	1 (2.22)	
Stage	IA	4 (23.53)	3 (6.67)	Fisher exact
	IB	4 (23.53)	4 (8.89)	p=0.087 ns
	IIA	4 (23.53)	9 (20)	
	IIB	2 (11.76)	11 (24.44)	
	III	3 (17.65)	18 (40)	
Differentiation	Well	0	1 (2.22)	Fisher exact
	Moderately differentiated	13 (70.59)	24 (53.33)	p=0.55 ns
	Poor	5 (29.41)	20 (44.44)	

Patients treated surgically were followed-up for a period of 12 months and there were 5 (29.4%) patients with increased values of CA19-9 up to 100U/ml, and 31 (68.9%) with increased values above 100U/ml.

The 6 and 12-months survival rates were 88.2% and 70.6% respectively in the group of patients with CA19-9 values up to 100U/ml, and 68.9% and 31.1% consistently in the group of patients with CA19-9 more than 100U/ml.

A significant difference in survival time was found between patients in group with CA19-9 above 100U/ml and group two with values up to 100U/ml. (p = 0.012), Table 2.

Table 2. *Total survival time depending on CA 19-9 levels*

CA 19-9 Increased values	Total (n)	Exitus N of events n (%)	cumulative survival % (Std. Error)	
			6 months	12 months
Up to 100	17	5 (29.41)	88.2 (0.045)	70.6 (0.111)
More than 100	45	31 (68.89)	68.9 (0.069)	31.1 (0.069)

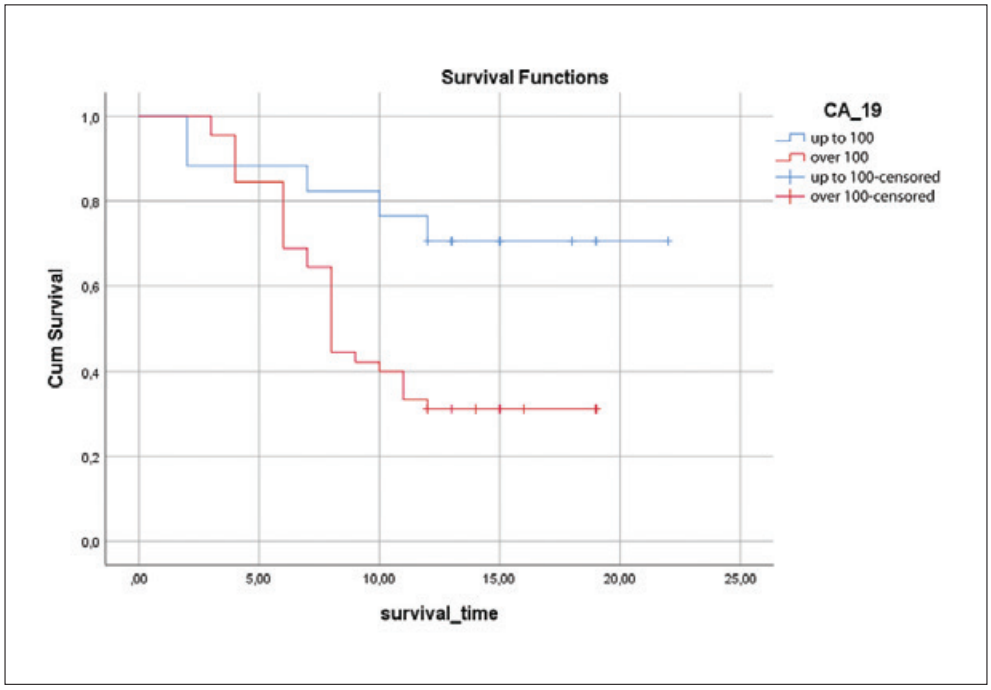
Log Rank (Mantel-Cox) =6.4, p=0.012 sig

The results showed that mean survival rate was 17.5 months in patients with CA19-9 values up to 100U/ml, and 10.8 months in patients with values higher than 100U/ml. The median survival time in the first group with CA19-9 up to 100U/ml is not defined, as more than 50% of these patients were alive after 12 months, and in the second group with CA19 – 9 levels higher than 100U/ml, the median survival time was 8 months, Table 3, Graph 1.

Table 3. *Average and median survival time depending on CA19-9*

CA19-9	Mean and Medians for Survival time							
	mean	Std. Error	95% CI	median	Std. Error	95% CI	75.0% percentile	Std. Error
≤ 100	17.47	1.8	13.97 – 20.97				12.0	
>100	10.76	0.9	9.03 – 12.48	8.0	0.37	7.27 – 8.73	6.0	0.89

Graph 1. *Survival curve depending on serum values of CA19-9*



Tumor marker CA19-9 levels were confirmed as a significant predictor of survival rate in patients with pancreatic cancer (p=0.022). Patients with CA19-9 values above 100U/ml compared to patients with values up to 100U/ml had about 3 times significantly higher risk of lethal outcome (3,026, 95% CI1.171 – 7,822), Table 4.

Table 4. *Univariate Cox regression analysis / CA 19-9*

CA 19-9	P	Exp (B)	95% CI for Exp (B)
Referent category – to 100			
over 100	0.022	3.026	1.171 – 7.822

Statistical Analysis

The continuous variables such as age, serum CA19-9 and follow-up periods were expressed as medians with ranges. The comparisons between clinicopathological characteristics and the CA19-9 values were performed with a Mann-Whitney *U* test or a Kruskal-Wallis *H* test if the grouping variables were more than two. Overall survival (OS) was defined as the time from the date of the surgery to either the date of death from any cause or the date of the last follow-up visit. The survival rate was estimated and calculated using the Kaplan-Meier survival curve. The strongest univariate predictor among the categorized serum CA19-9 measurements was chosen. The multivariate Cox proportional hazards model (forward) was fitted using all of the clinical and pathological variables, which included age, gender, tumor size, tumor cell differentiation, surgical margins, pT category, pN category, pTNM category, and CA19-9 with the optimal cutoff value. The corresponding hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Two-sided *P* values less than 0.05 were considered to be statistically significant.

Discussion

Firstly, numerous studies have investigated the usefulness of CA19-9 serum levels as a screening tool for pancreatic cancer in asymptomatic individuals and population with symptoms that might be related to pancreatic cancer.

Therefore, diagnostic value of tumor marker CA19-9 is limited by non-specific expression in several benign and malignant diseases, false negative results in patients with the presence of obstructive jaundice (10-60%) (21,22). However, serum level of CA19-9 is widely used biomarker for the diagnosis and/ or monitoring of the pancreatic adenocarcinoma, with a sensitivity of 70-95% and a specificity of 70-90% (Ballehaninna and Chamberlain, 2012; Scara et al., 2015).

In our study, the serum value of CA19-9 was elevated in all 62 patients and according to the level of increased value, patients were divided into two groups. The first group had CA19-9 values up to 100U/ml (17 patients) and the second group had values above 100U/ml (45 patients).

Correlation between CA19-9 levels and patients gender revealed values higher than 100U/ml of CA19-9 significantly more in female patients than in male, 90.9% vs 62.5%. The age of patients with pancreatic cancer had a significant effect on CA19-9 levels. Patients with a serum CA19-9 level of 100U/ml or lower were significantly older than patients with CA19-9 higher than 100U/ml. Patients with CA19-9 level of 100U/ml or lower had an average age of 69.8 ± 6.9 years, while the average age of patients with CA19-9 higher than 100U/ml was 61.3 ± 7.5 years.

Correlation between serum level of CA19-9 value and pathohistological tumor characteristic including: tumor size, stage, tumor differentiation, revealed statistically insignificant results.

CA19-9 level higher than 100U/ml were more frequently measured in patients with larger tumors, T2 in 30 (66.67%) and T3 in 11 (24.44%) patients; in patients diagnosed at a more advanced stage, III stage in 18 (40%) patients; and in patients with poorly differentiated tumors, 20 (44.4%) patients and moderately differentiated tumors in 24 (53.3%) patients. The results of a study by Distler M et al. (166) showed that serum levels of tumor markers CEA, CA19-9 and the degree of tumor cell differentiation were important predictors for shorter survival in 195 patients with pancreatoduodenectomy due to adenocarcinoma of the head of the pancreas.

This study revealed that serum marker CA19-9 level has significant prognostic value in patients with pancreatic adenocarcinoma. Survival time for a period of 12 months after the operation in correlation with CA19-9 levels was 29.4% for the patients with CA19-9 less than 100U/ml, and 68.9% for the patients with CA19-9 above 100U/ml. Patients with higher CA19-9 tumor marker values above 100U/ml had shorter, 6 and 12 months, survival time. The median survival time in the group with CA19 – 9 up to 100U/ml was not defined, as more than 50% of these patients were alive after 12 months. The second group with CA 19-9 values higher than 100U/ml, the median survival time was 8 months. The tumor marker CA19-9 was confirmed as a significant predictor of survival in patients with pancreatic cancer (p=0.022). The results of our study showed that increased serum CA19-9 levels more than 100U/ml significantly correlated with gender, age and survival rate. Insignificant correlation, but more frequently increased CA19-9 levels were found in more advanced stage of disease and poorly differentiated tumors. These findings were consistent with several other published studies (23).

CA19-9 values above 100U/ml compared to patients with values up to 100U/ml had about three times significantly higher risk of lethal outcome (3.026, 95% CI1.171-7.822). CA19-9 serum levels can provide important information in regards to prognosis, overall survival, and can predict post-operative recurrence (24).

Despite recent advances in understanding the genetic and cellular basis of the pancreatic adenocarcinoma progression, examinations, and knowledge of histopathological parameters such as tumor differentiation and pancreatic tumor fibrosis, may contribute for improved assessing the prognosis and predicting early recurrence and overall survival.

Conclusion

The results of our study showed that correlation between serum level of CA19-9 value and pathohistological tumor characteristic including: tumor size, stage, tumor differentiation, revealed more frequency, but statistically insignificant results in patients with more elevated tumor marker.

Correlation between CA19-9 levels and patients' gender revealed values higher than 100U/ml of CA19-9 significantly more in female patients than in male, 90.9% vs 62.5%. The age also was determined as a remarkable predictor on CA19-9 levels. The tumor marker CA19-9 was confirmed as a significant predictor of survival in patients with pancreatic cancer (p=0.022).

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