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Prognostic value of CA 19-9 level in resectable pancreatic adenocarcinoma

J. Rudnicki[1], A.K. Agrawal[2], Z. Grzebieniak[2], P. Żukrowski[2], D. Zyśko[4], M. Jelen[3], W. Kielan[2], M. Sebastian[1], J. Słonina[5], G. Marek[2], Ł. Duda-Barcik[2]

[1]Department of Minimally Invasive Surgery and Proctology, Wroclaw Medical University, Poland
[2]2nd Department of General and Oncological Surgery, Wroclaw Medical University, Poland
[3]Department of Pathology, Wroclaw Medical University, Poland
[4]Teaching Department for Emergency Medical Services, Wroclaw Medical University, Poland
[5]Department of Radiology, Wroclaw Medical University, Poland

Abstract: The prognosis in patients with pancreatic cancer is poor and some authors describe it as a lethal disease. At the time of diagnosis only 14% of patients could be surgically treated and up to 30% of them die within 12 months. Therefore, further clinical investigations on preoperative patient qualification are needed. A total of 81 patients were included into the study. The CA 19-9 concentration was measured before surgery by an automated, commercially available enzyme immunoassay in Axsym analyzer (Abott Diagnostics Laboratory). A value of 37 U/ml was used as the upper limit of normal levels. Tumors were staged according to the Union Against Cancer (UICC) of 2004 and graded during the histological evaluation according to the G0-G4 scale. All patients were monitored every three month via outpatient clinic visits. In the case of missing visit we contacted the families to establish the cause. We assessed perioperative, 12 month, 2 year and 5 year survival. Twelve moth, 2 year and 5 year survival were assessed in the whole studied population and in the group of patients with the exception of these who died during the perioperative period. The total five year survival was 6%. The median time of survival was 467 days (range: 163 – 586 days). The perioperative period was survived by 91.4% patients, 12 months were survived by 71.6% patients, 2 years were survived by 35.8% patients, 5 years were survived by 6.2% patients. The serum Ca 19-9 level was above the normal limit in 80.5% patients. ROC curve analysis revealed that CA 19-9 level of more than 106 U/ml was linked to 2 year survival with 79.3% sensitivity and 74.5% specificity. Preoperative level of CA 19-9 below 106U/ml represents a predictive factor of 2- and 5-year survival, independent of other factors, such as lower size of the tumor, absence of metastases to lymph nodes, female gender of patients.After exclusion of the patients who died in the perioperative period, no relationship could have been disclosed between preoperative CA 19-9 levels and one year survival. The observation points to the chance that patients with higher levels of CA 19-9 harbour micrometastases, the development of which is sufficiently slow to allow for a one-year survival of the patients but which increase the risk of death after two and five years

Keywords: pancreatic cancer, serum tumor marker, CA 19-9

Introduction

The prognosis in patients with pancreatic cancer is poor and some authors describe it as a lethal disease. At the time of diagnosis only 14% of patients could be surgically treated and up to 30% of them die within 12 months [1]. Therefore, further clinical investigations on preoperative patient qualification are needed.

Correspondence: J. Rudnicki, Department of Minimally Invasive Surgery and Proctology, Wroclaw Medical University, Borowska Str. 213, 50-556 Wroclaw, Poland;
tel.: (+4871) 7343000, fax: (+4871) 7828834,
e-mail: jrudnicki@op.pl

Serum carbohydrate antigen 19-9, the sialylated Lewis blood group antigen defined by the monoclonal antibody 1116 NS 19-9 (2), is a tumor-associated antigen synthesized by normal pancreatic and ductal cells, present in large quantities in normal pancreatic juice [3]. CA 19-9 is considered to be the best serum marker of pancreatic cancer due to its high sensitivity of 70-90% and specificity of around 90% [4].

In the patients with pancreatic cancer, CA19-9 level may depend on the increased production by pancreatic cancer cells or by other cells of the affected region. The concentration of the tumor marker CA 19-9 is influenced by the patient's secretor status and Lewis

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genotype [5]. Therefore, the predictive value of CA 19-9 may differ among different populations. Little is known about the predictive value of the preoperative serum CA 19-9 levels in patients with pancreatic cancer.

The aim of the study was to assess the value of the preoperative plasma CA 19-9 level in determining prognosis of the patients with pancreatic cancer, treated with a radical pancreatectomy.

Material and methods

Patients. Between 2000 and 2006, 92 patients with pancreatic cancer underwent radical resection at the 2nd Department of General and Oncological Surgery at Wroclaw Medical University in Poland. The inclusion criteria to the study were the planned radical surgical removal of the pancreatic tumor and absence of other malignancies. The exclusion criteria included absence of histopathological confirmation of the pancreatic tumor, presence of distant metastases confirmed during operation, palliative surgery and absence of 5 year follow-up after operation or follow-up until patient's death.

A total of 81 patients were included into the study. The profile of study group is presented in Table 1.

The plasma CA 19-9 and bilirubin concentrations were measured before surgery by an automated, commercially available enzyme immunoassay in Axsym analyzer (Abott Diagnostics Laboratory). A value of 37 U/ml was used as the upper limit of normal levels.

Tumors were staged according to the Union Against Cancer (UICC) of 2004 and graded during the histological evaluation according to the G0-G4 scale.

Surgical treatment. The kind of surgical treatment depended on location of the tumor. Whipple pancreatoduodenectomy in Traverso-Longmire modification was performed for adenocarcinoma located in pancreatic head. Distal pancreatoduodenectomy was performed for tumors located in the body and tail of the pancreas. Resectability was defined as tumor limited to the pancreas with no invasion of the superior mesenteric vein and artery, portal vein and absence of metastases (to coeliac lymph nodes, peritoneum or liver).

Adjuvant therapy. Adjuvant therapy was used in 70 patients (chemotherapy in 63 and radiotherapy in 13 patients). The chemotherapy protocols which were used are listed below:

- Regimen A – gemcitabine 1000 mg/m^2 iv on days 1, 8, 15; rest period of 28 days between the cycles,
- Regimen B – gemcitabine 1000 mg/m^2 iv on days 1, 8, 15 + cisplatin 25 mg/m^2 iv. on days 1, 8, 15; rest period of 28 days between the cycles,
- Regimen C – calcium folinate 20 mg/m2 iv on days 1 – 5 + fluorouracil 300 mg/m^2 iv. on days 1 – 5 (continuous infusion) + cisplatin 20 mg/m^2 iv. on days 1 – 5 (continuous infusion); rest period of 28 days between the cycles,
- Regimen D- fluorouracil 500 mg/m^2 iv on days 1 – 5; rest period of 28 days between the cycles.

The type of protocol, in each patient ,was assigned by the oncologist on the basis of individual assessment.

Follow-up. All patients were monitored every three month via outpatient clinic visits. In the case of missing visit we contacted the families to establish the cause.

The patients were divided into groups according to their outcome: death during the perioperative period, death in postoperative period till 12 months follow up, survival longer than 12 months.

Survival analysis.

We assessed perioperative, 12 month, 2 year and 5 year survival.

Table 1. Characteristics of the studied group of patients.

Trait	Values
Gender	Females – 36 (44.4%) Males – 45 (55.6%)
Age (mean)	63.6 years
Location of the tumour	Pancreatic head – 65 (80.2%) Pancreatic body / tail – 16 (19.8%)
Size of the tumour (T)	T1 – 15 (18.5%) T2 – 35 (43.2%) T3 – 31 (38.3%)
Metastases to draining lymph nodes (N)	N0 – 45 (55.6%) N1 – 36 (44.4%)
Distant metastases (M)	M0 – 81 (100%) M1 – 0 (0%)
Advancement acc. to UICC	1A – 9 (11.1%) 1B – 22 (27.2%) 2A – 14 (17.3%) 2B – 36 (44.4%)
Grade of tumour differentiation	Anaplastic – 10 (12.3%) Low differentiation – 23 (28.4%) Moderate differentiation – 28 (34.6%) High differentiation– 20 (24.7%)
Serum CA 19-9 before operation (mean)	281.0 U/l

Twelve moth, 2 year and 5 year survival were assessed in the whole studied population and in the group of patients with the exception of these who died during the perioperative period.

Statistical analysis.

Continuous variables were presented as means and their standard deviation or median and interquartile range, according to their distribution.

Categorical variables were presented as numbers and percentages.

All continuous data were dichotomized around the median value or according to significant cut-off points.

We performed ROC curve analyses to find the serum CA19-9 levels which could have predicted survival to hospital discharge, 12 month survival, 2 year survival

Preoperative CA 19-9 concentrations were dichotomized according the value calculated by means of ROC curve analyses.

For the purposes of statistical analyses the categorical variables, such as tumor size, grade, location were linked to obtain two categories of patients in respect to a given parameter on the basis of the comparison of their distribution in studied groups.

For 12 month and 2 year survival we also performed analysis after excluding the patients who died during perioperative period because their survival could be related to other factors than pancreatic cancer.

Statistical analysis. Survival probability was estimated according to Kaplan-Meier method, the log rank test was used to compare survival in different subgroups. Multivariate analyses were performed using Cox's proportional hazard model or logistic regression analysis. P values less than 0.05 were considered significant.

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Table 2. Demographics, histological characteristics and biochemical data in studied population divided into groups of various survival time.

	Perioperative death (PD)	Early death (ED)	1-year survivors (1Y-S)
No. of patients n (%)	7 (8.6)	16 (19.8)	58 (71.6)
Age (years)			
Average±SD	70.3±4.9	63.1±7.7*	62.5±7.9*
Range	64-78	48-76	45-76
Age ≤ 65 years n (%)	2 (28.6)	10 (62.5)	35 (60.0)
Females n (%)	2 (28.6)	5 (31.3)	29 (50.0)
Site of primary lesion n (%)			
head	6 (85.7)	12 (75.0)	47 (81.0)
body or tail	1 (14.3)	4 (25.0)	11 (19.0)
Tumour stage			
1	1 (14.3)	3 (18.8)	11 (19.0)
2	2 (28.6)	4 (25.0)	29 (50.0)
3	4 (57.1)	9 (56.3)	18 (31.0)
Nodal status			
0	3 (42.9)	4 (25.0)	38 (65.5)$^{\#\#}$
1	4 (57.1)	12 (75.0)	20 (34.5)$^{\#\#}$
Grade			
0	0 (0)	2 (12.5)	8 (13.8)
1	2 (28.6)	3 (18.8)	18 (31.0)
2	3 (42.9)	3 (18.8)	22 (37.9)
3	2 (28.6)	8 (50.0)	10 (17.2) $^{\#\#\text{-A}}$
Clinical stage n (%)			
IA	0 (0)	1 (6.3)	8 (13.8)
IIA	2 (28.6)	2 (12.5)	10 (17.2)
IB	1 (14.3)	1 (6.3)	20 (34.5)
IIB	4 (57.1)	12 (75)	20 (34.5) $^{\#\#\text{-B}}$
bilirubin level (mg%) mean ±SD	12.5 ±5.1	9.8 ±6.9	7.8±5.6*
bulirubin level normal n (%)	0 (0)	1 (6.3)	2 (3.4)
bilirubin level ≤12.1mg% n (%)	2 (28.6)	11 (68.5)*	46 (79.3)*
CA 19-9 level median (range) (U/ml)	329 (105-1067)	185 (21-1270)	112.5 (45-278)* $^{\#}$
CA 19-9 level normal n (%)	0 (0)	2 (12.5)	14 (24.1)
CA 19-9 level ≤ 106 U/ml n (%)	2 (28.6)	5 (31.2)	29 (50.0)

ED or 1Y-S vs PD *p<0.05 1Y-S vs ED: # p<0.05 $^{\#\#\text{-A}}$-p<0.01 T1+T2+T3 vs T4 $^{\#\#\text{-B}}$-p<0.01 IA+IIA+IB vs IIB p<0.01

Results

Overall survival

The total five year survival was 6%. The median time of survival was 467 days (range: 163 – 586 days). The perioperative period was survived by 91.4% patients, 12 months were survived by 71.6% patients, 2 years were survived by 35.8% patients, 5 years were survived by 6.2% patients.

Out of the 45 men and 36 women included into the analyses 7 patients (5 men and 2 women) died during the perioperative period (perioperative death – PD).

Out of the 40 men and 34 women who were discharged alive from hospital, 16 patients (11 men, 5 women) died during the 12 month follow-up after the surgery (early death – ED).

Out of the remaining 58 patients (29 men and 29 women), 5 patients (3 men, 2 women) survived 5-year follow-up and 53 patients (26 men, 27 women) died during the follow-up.

The clinical, histopathological and biochemical characteristics of the patients divided into groups according to the time of survival are shown in Table 2 and 3.

Table 3. Demographics, histological characteristics and biochemical data in studied patients who survived for more than 12 months

	Survival >12 months up to 2 years	Survival >2 years	P
No. of patients (%)	29 (50)	29 (50)	NS
Age Mean ±SD Range	 62.3±7.8 45-78	 62.7±8.0 45-74	NS
Age ≤ 65 years n (%)	20 (69.0)	15 (51.7)	NS
Females n (%)	10 (34.5)	19 (65.5)	<0.05
Site of primary lesion n (%) head body or tail	 24 (82.8) 5 (17.2)	 23 (79.3) 6 (20.7)	NS
Tumour stage 1 2 3	 4 (13.8) 12 (41.4) 13 (44.8)	 7 (24.1) 17 (58.6) 5 (17.2)	p<0.03 tumour stage I+II *vs* III
Nodal status 0 1	 14 (48.3) 15 (51.7)	 24 (82.8) 5 (17.2)	p<0.01
Grade 0 1 2 3	 2 (6.9) 7 (24.1) 11 (37.9) 9 (31.0)	 6 (20.7) 11 (37.9) 11 (37.9) 1 (3.4)	p<0.05 grade 0+1 *vs* grade 2+3
Clinical stage n (%) IA IIA IB IIB	 1 (3.4) 6 (20.7) 7 (24.1) 15 (51.7)	 7 (24.1) 4 (13.8) 13 (44.8) 5 (17.2)	p<0.01 IA+IB+IIA *vs* IIB
bilirubin level (mg%) mean±SD	8.6 (5.9)	7.0 (5.2)	NS
bulirubin level normal n (%)	0 (0)	2 (6.9)	NS
bilirubin level ≤12.1mg% n(%)	20 (69.0)	26 (89.7)	<0.001
CA 19-9 level, median (range) (U/ml)	242 (153-492)	57 (29-97)	<0.001
CA 19-9 level normal n (%)	4 (13.8)	10 (34.5)	NS
CA 19-9 level ≤ 106 U/ml n (%)	6 (20.7)	23 (79.3)	<0.001

Serum CA 19-9 level

The serum Ca 19-9 level was above the normal limit in 80.5% patients.

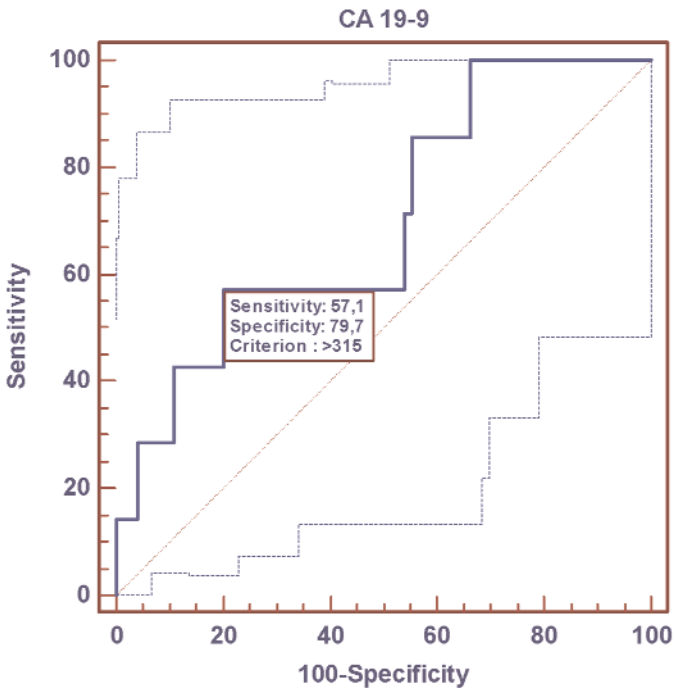
ROC curve analysis revealed that CA 19-9 level of more than 106 U/ml was linked to 2 year survival with 79.3% sensitivity and 74.5% specificity. Twelve month survival and survival to hospital discharge could not be predicted by CA 19-9 level (Tables 1, 2, 3).

CA 19-9 level, both as a continuous variable and dichotomized, as at least 106 U/ml or more than 106 U/ml, was an independent predictor of overall survival, 2 year survival but it was not related to perioperative death (Table 4-11). Survival analysis during the first 12 months showed that the higher level of CA 19-9 was linked to the higher risk of death in the whole analyzed group, but such a relationship could not be detected when the subgroup of patients who died during the perioperative period was excluded (Table 7-12).

In the Fig. 1-3 the results of ROC curve analysis of the serum CA 19-9 in prediction of the perioperative, 12 month and 2 years survival were presented.

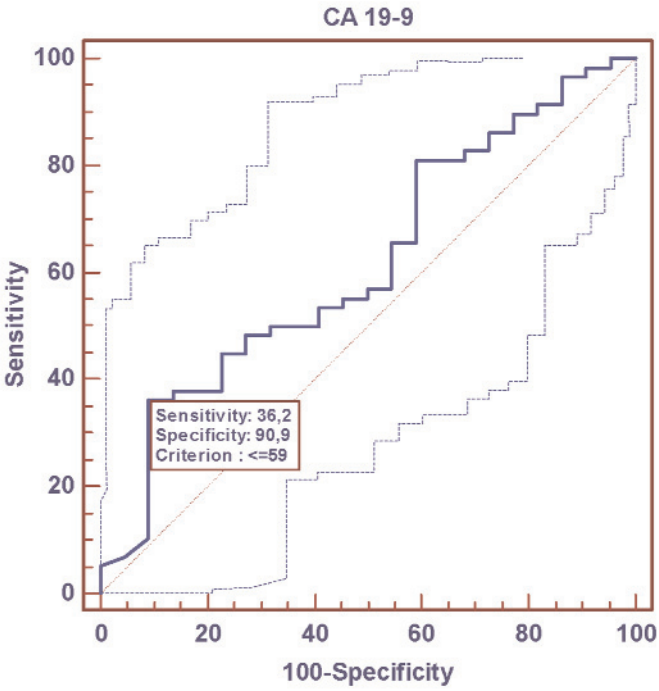
Bilirubin

Serum bilirubin did not correlate with CA 19-9 level but it was significantly higher in patients with higher T, N stages, G grades.



Area under the ROC curve (AUC)	0,699
Standard error	0,115
95% Confidence interval	0,587 to 0,796
z statistic	1,733
Significance level p (Area=0.5)	0,0832

Fig. 1. ROC curve analysis of preoperative Ca 19-9 level for the prediction death before hospital discharge.



Area under the ROC curve (AUC)	0,617
Standard error	0,0727
95% Confidence interval	0,502 to 0,724
z statistic	1,611
Significance level p (Area=0.5)	0,1072

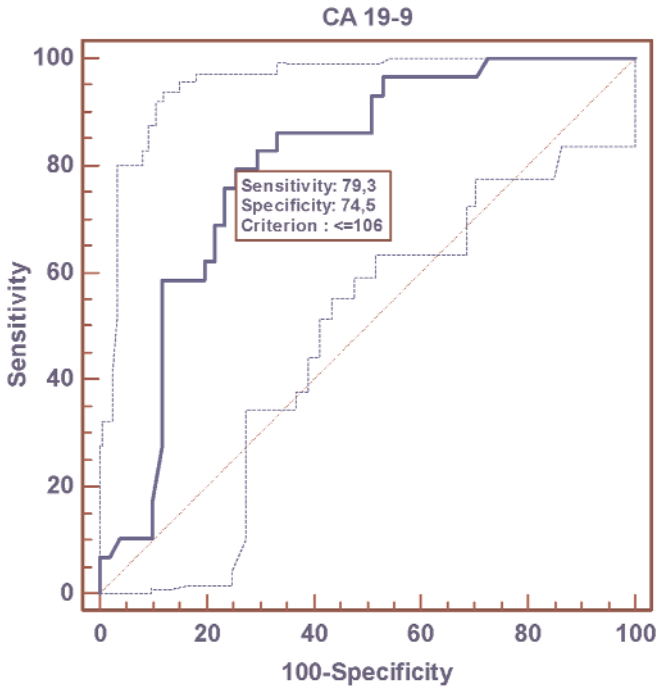
Fig. 2. ROC curve analysis of preoperative Ca 19-9 level for the prediction 12 month survival.

Serum bilirubin of no more than 12.1mg% could predict 2 year survival with low sensitivity and a relatively high specificity (Fig. 4, Table 4).

The ROC analysis showed no relationship between the level of bilirubin and the perioperative and 12-month period deaths. Thus, for further analysis the dichotomized variable of bilirubin level was used, higher or lower than that obtained for 2 year survival. Serum bilirubin as a continuous variable was not independently related to overall survival, 2 year survival, 12 month survival (Table 7-12) but when dichotomized its higher level was related to death during the perioperative period (OR 8.3, CI 1.5- 48.4; p<0.001).

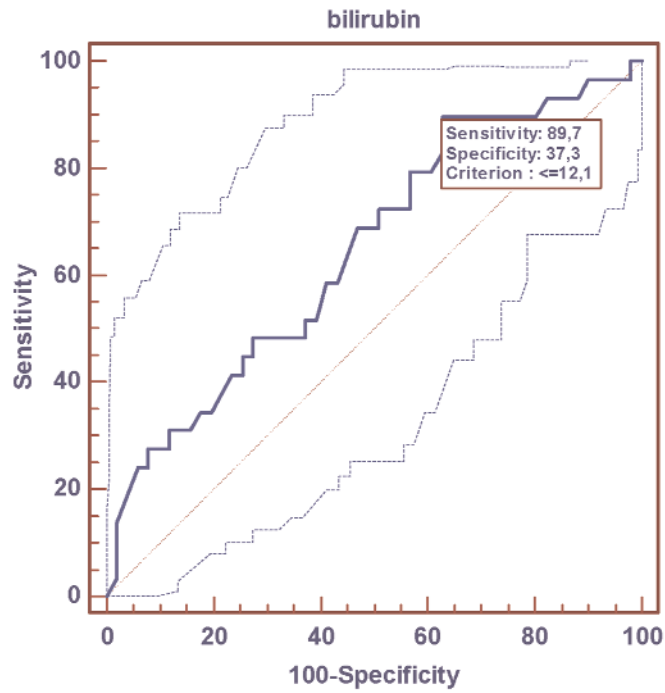
Adjuvant therapy

In 63 patients chemotherapy and in 13 patients radiotherapy was used as the adjuvant therapy. Both the



Area under the ROC curve (AUC)	0,798
Standard error	0,0488
95% Confidence interval	0,694 to 0,880
z statistic	6,116
Significance level p (Area=0.5)	0,0001

Fig. 3. ROC curve analysis of preoperative Ca 19-9 level for the prediction 2 year survival.



Area under the ROC curve (AUC)	0,647
Standard error	0,0622
95% Confidence interval	0,532 to 0,750
z statistic	2,359
Significance level p (Area=0.5)	0,0183

Fig. 4. ROC curve analysis of plasma bilirubin level in predicting 2 year survival.

Table 4. Logistic regression analysis, prognostic factors associated with perioperative death.

		Hazard ratio	95% CI	P value
Age	patient older by 1 year	1.20	1.02-1.42	<0.05
bilirubin	≤12mg% >12mg%	1 42.1	3.9- 451.4	<0.02

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Table 5. Multiple logistic regression analysis, prognostic factors significantly associated with 12-month mortality in the group of patients who were discharged alive from hospital.

		Hazard ratio	95% CI	P value
N	0 1	1 5.7	1.6-20.4	<0.01

methods were used post-operatively, hence in 7 patients who died in the peri-operative period no adjuvant therapy was used. From among the 74 patients who survived to hospital discharge in 4 patients no adjuvant therapy was used due to lack of approval by the oncologist or patient's refusal.

Table 6. Multiple logistic regression analysis, prognostic factors significantly associated with 2-year mortality in the group of patients who were discharged alive from hospital.

		Hazard ratio	95% CI	P value
Gender	female male	1 54.4	4.4-674.6	<0.002
CA 19-9	≤106U/ml >106ml	1 42.1	3.9- 451.4	<0.02
T	T1 or T2 T3	1 14.9	1.3-168.5	<0.02
G	G0 or G1 or G2 G3	1 56.1	2.2-1446.5	<0.02
age	≤65 years >65years	1 32.5	2.6-399.8	<0.01

Table 7. Cox's proportional hazard model prognostic factors related to 12 month survival.

	Beta	Standard error	T	Beta exponent	Wald's statistics	P
Female gender	-0.792	0.470	-1.69	0.453	2.843	0.092
N 1	1.075	0.555	1.94	2.930	3.753	0.053
CA 19-9	0.001	0.000	2.44	1.001	5.973	0.015
T 3	0.412	0.469	0.88	1.510	0.771	0.380
G 3	-0.112	0.500	-0.22	0.894	0.050	0.823
Age	0.061	0.034	1.79	1.063	3.198	0.074
Bilirubin	0.028	0.041	0.68	1.028	0.457	0.499
Localisation in head	0.263	0.543	0.48	1.301	0.235	0.628

Table 8. Cox's proportional hazard model: prognostic factors related to 12 month survival in the studied population following exclusion of patients who died in periprocedural period.

	Beta	Standard error	T	Beta exponent	Wald's statistics	P
Female gender	-0,769	0,588	-1,31	0,463	1,712	0,191
N 1	1,313	0,700	1,87	3,718	3,515	0,061
CA 19-9	0,001	0,001	0,73	1,001	0,528	0,468
T 3	1,034	0,712	1,45	2,813	2,112	0,146
G 3	0,374	0,617	0,61	1,454	0,368	0,544
Age	0,016	0,037	0,44	1,016	0,191	0,662
Bilirubin	-0,007	0,053	-0,13	0,993	0,018	0,894
Localisation in head	0,447	0,628	0,71	1,564	0,507	0,476
Radiotherapy	0,943	0,920	1,03	2,566	1,051	0,305
Chemotherapy	-0,756	0,882	-0,86	0,470	0,734	0,391

Table 9. Cox's proportional hazard model, prognostic factors related to 2 year survival.

	Beta	Standard error	T	Beta exponent	Wald's statistics	P
Female gender	-0.983	0.313	-3.14	0.374	9.85	0.002
N 1	0.971	0.376	2.58	2.640	6.68	0.010
CA 19-9	0.001	0.000	3.75	1.001	14.09	0.000
T 3	0.359	0.305	1.17	1.431	1.38	0.240
G 3	0.228	0.364	0.63	1.256	0.39	0.531
Age	0.011	0.021	0.49	1.011	0.24	0.623
Bilirubin	-0.008	0.028	-0.28	0.992	0.08	0.777
Localisation in head	0.323	0.387	0.83	1.381	0.70	0.404

Table 10. Cox's proportional hazard model, prognostic factors related with 2 year survival in the studied population following exclusion of the patients who died in periprocedural period.

	Beta	Standard error	t	Beta exponent	Wald's statistics	p
Female gender	-1,024	0,340	-3,008	0,359	9,051	0,003
N 1	1,071	0,409	2,616	2,918	6,846	0,009
CA 19-9	0,001	0,000	2,793	1,001	7,801	0,005
T 3	0,583	0,365	1,596	1,791	2,546	0,111
G 3	0,406	0,403	1,008	1,501	1,016	0,313
Age	-0,009	0,023	-0,412	0,991	0,169	0,681
Bilirubin	-0,028	0,032	-0,876	0,973	0,768	0,381
Localisation in head	0,353	0,422	0,835	1,423	0,698	0,403
Radiotherapy	0,431	0,524	0,823	1,540	0,678	0,410
Chemotherapy	-0,329	0,533	-0,616	0,720	0,380	0,538

Table 11. Cox's proportional hazard model, prognostic factors related to 5 year survival.

	Beta	Standard error	T	Beta exponent	Wald's statistics	P
Female gender	-0.514	0.249	-2.07	0.598	4.28	0.039
N 1	1.004	0.317	3.17	2.730	10.06	0.002
CA 19-9	0.001	0.000	3.55	1.001	12.61	0.000
T 3	0.498	0.275	1.81	1.645	3.27	0.070
G 3	-0.022	0.330	-0.07	0.978	0.00	0.946
Age	0.004	0.017	0.25	1.004	0.06	0.806
Bilirubin	0.007	0.025	0.26	1.007	0.07	0.793
Localisation in head	0.139	0.338	0.41	1.149	0.17	0.682

Patients who underwent chemotherapy differed significantly in respect to T stage in comparison to the population in whom no chemotherapy was used.. Chemotherapy was used in 6 patients with T1 stage, in 31 patients with T2 stage and 26 patients with T3 stage cancer; whereas it was not used in 8 patients with T1 stage, 2 patients with T2 and 1 patient with T3 stage ($p<0.001$). Radiotherapy was used in 13 patients among which 11 patients with T1 and 2 patients with T2 and it was not used in 3 patients with T1, 31 patients with T2 and 27 patients with T3 stage. Patients in whom radiotherapy was used differed from those in

Table 12. Cox's proportional hazard model, prognostic factors related to 5 year survival in the studied population following exclusion of patients who died in periprocedural period.

	Beta	Standard error	T	Beta exponent	Wald's statistics	P
Female gender	-0,635	0,274	-2,31	0,530	5,36	0,021
N 1	1,071	0,338	3,17	2,919	10,06	0,002
CA 19-9	0,001	0,000	2,50	1,001	6,26	0,012
T 3	0,633	0,309	2,05	1,883	4,19	0,041
G 3	0,105	0,365	0,29	1,110	0,08	0,775
Age	-0,017	0,019	-0,91	0,983	0,83	0,361
Bilirubin	-0,008	0,027	-0,32	0,992	0,10	0,752
Localisation in head	0,202	0,371	0,54	1,224	0,30	0,586
Radiotherapy	0,541	0,399	1,36	1,717	1,84	0,175
Chemotherapy	0,573	0,459	1,25	1,774	1,56	0,212

Table 13. Results of till now published studies on CA 19-9 level in groups of specific advancement in pancreatic neoplasia.

Study, year	Groups	Number of pts	CA 19-9 (median) (U/ml)
Kiliç *et al*. 2004 [9]	resectable unresectable inoperable (metastatic)	18 15 18	19.3 302 500
Barugola *et al*. 2009 [1]	1- resected 2- locally advanced 3- metastasized	1- 228 2+3- 906	100 261 809
Fujioka *et al*. 2007 [10]	pancreatic operation, curative pancreatic operation, noncurative unexpected metastasis or locally advanced disease	93 66 85	78 155 326

whom radiotherapy was not used in respect to T stage distribution ($p<0.001$)

Four methods of chemotherapy were used as described above: regimen A in 17 patients, regimen B in 13 patients, regimen C in 10 patients and regimen D in 23 patients.

Analysis of survival

Overall mortality was independently related to N1, male gender, CA 19-9 level (Tables 11, 12).

After exclusion of the PD group, five year survival was related to N1, male gender, CA 19-9 level and also to T3 (Tables 10, 11).

In patients who survived till the hospital discharge, two year mortality was independently related to CA 19-9 level above 106 mU/ml, T3, G3, age above 65 years, male gender (Tables 8, 9).

In patients who survived till the hospital discharge twelve month mortality was related only to N1. (Table 7-8)

Perioperative death was related to bilirubin level and older age of the patients (Table 4).

Overall survival in the group according to the CA 19-9 level was presented in the Fig. 5.

The influence of the adjuvant therapy on the long term survival was assessed only in patients who survived to hospital discharge after surgery. Overall survival in groups treated and no treated with chemotherapy and radiotherapy were presented in Fig. 6 and 7.

In univariate and multivariate Cox proportional hazards regression both chemotherapy and radiotherapy were not independent factors affecting 12 months survival, 2 years survival and 5 year survival. (Figs 6, 7, Tables 8, 10, 12) Additionally, no relation was found with the chemotherapy regimen.

Discussion

The overall prognosis associated with carcinoma of the pancreas has not improved over the last 20 years, even if new diagnostic and therapeutic strategies have

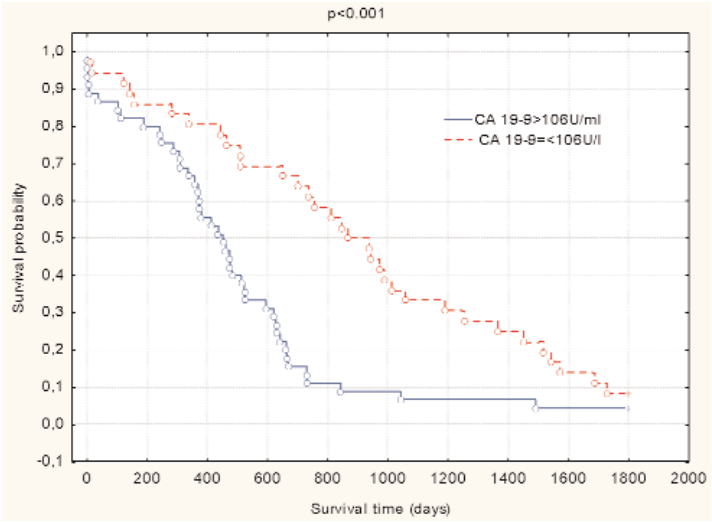

Fig. 5. Overall survival in the group according to the CA 19-9 level.

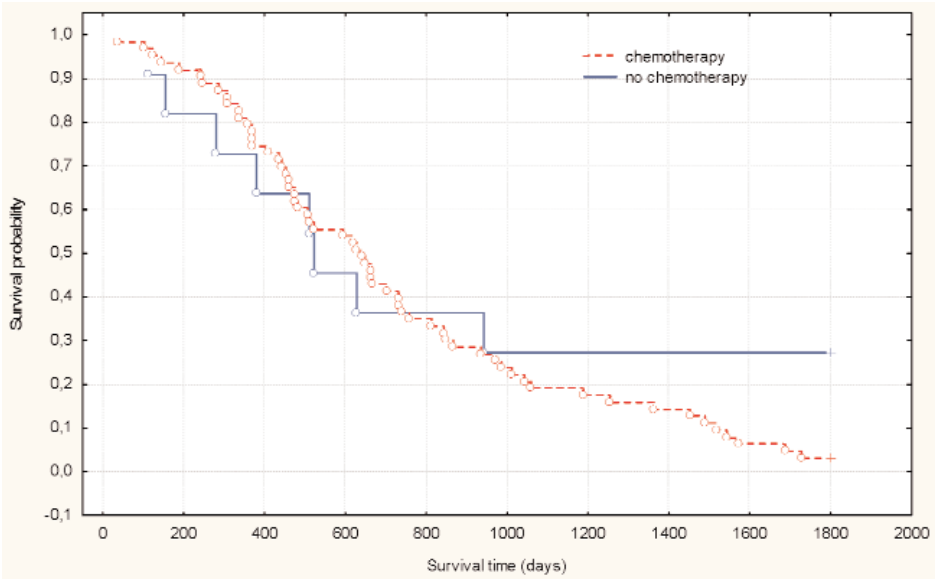

Fig. 6. Overall survival in the group according to chemotherapy using (p=NS).

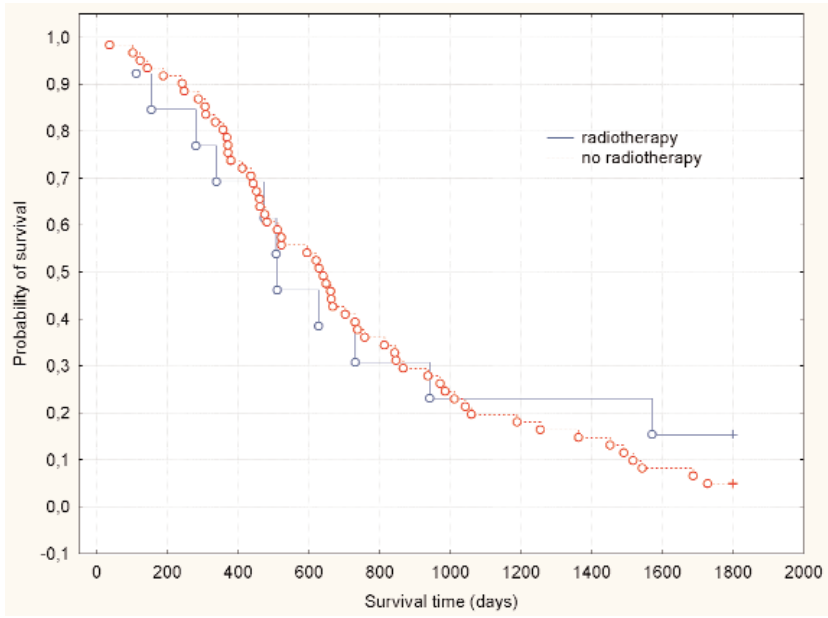

Fig. 7. Overall survival in the group according to radiotherapy using (p=NS).

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Table 14. Results of till now performed studies on predictive significance of CA 19-9 level in patients with pancreatic carcinoma.

Study, year	CA 19-9 levels (U/ml)	Number of patients	Median survival (months)	Predictors of survival on multivariate analysis	5 year survival (%)
Takai *et al*. 2003 [11]	<100 ≥100	46 42	12 10 p=NS	-	-
Schmidt *et al* 2004 [12]	-	-	-	CA 19-9 level does not predict survival on multivariate analysis	-
Berger *et al*. 2004 [13]	Undetectable >37 38-200 >200	7 21 44 57	32 33 22 16 p<0.01	-	20 34 11 2
Shimada *et al*. 2006 [14]	<143 ≥143		31 20 p=0.04	CA 19-9 was not an independent predictor	-
Ferrone *et al* 2006 [15]	<1000 >1000	90 21	28 12 p=0.01	-	-
Hernandez *et al*. 2008 [16]	-	96	-	Negative correlation between CA 19-9 level and survival time	-
Sandblom *et al*. 2008 [17]	-	-	marker level was not a predictor of survival	-	-
Smith *et al*. 2008 [18]	≤150 >150	64 45	22.1 10.4 p<0.012	CA 19-9>150, lymph node ratio	-
Turrini *et al*. 2009 [19]	<37 400-900 >900	50 27 26	22 15 p=0.02	-	-
Ueda *et al*. 2009 [20]	<100 >100	-	-	Ca 19-9>100 HR 1.94 (CI 1.21-5.11)	-
Barugola *et al*. 2009 [1]	≤200 >200	-	-	CA 19.9>200, G3, R2, symptoms duration>40days	-
Katz *et al*. 2010 [21]	Analysed using 4 cut-off points: 37, 149, 200, 1000	-	in resected patients p=NS	-	-

appeared [6,7]. Radical pancreatectomy is the only method which enables long term survival but quite often in cases of potentially operable pancreatic tumor the cancer has already spread outside of the pancreas and long-term survival is impossible. Surgical treatment may be a risky procedure, it worsens the quality of life and may shorten the life expectancy. Thus, investigations on predictive factors in pancreatic cancer are needed. These factors should have predictive value in relation to longer survival after surgery than after palliative treatment. Tumor characteristics (tumor size, lymph node metastases, histologic differentiation) and post-surgery blood transfusion are the established predictors of survival [8]. The value of CA 19-9

levels as a prognostic factor in pancreatic cancer has not been established yet. Higher levels of CA 19-9 have been found to be associated with more advanced cancer, as expressed by tumor size and lymph node, peritoneal and liver metastases (Table 13). According to other studies, lower CA 19-9 levels have been found to be associated with longer survival (Table 14) but no unambiguous cut-off value of CA19-9 has been established for presence or absence of the long-term risk, ranging in various studies between 37 U/ml and 1000 U/ml.

We have found that CA 19-9 serum level before surgery could have been taken as a prognostic factor for 2 and 5 year survival, independent from other factors like tumor size, lymph node metastasis, age. Our results are consistent with other publications on this topic (Table 14).

The main result of our study is that CA19-9 level not higher than 106 U/ml is connected with survival of at least 2 years with relatively high specificity and sensitivity in patients with pancreatic cancer treated with radical pancreatectomy, chemotherapy and radiotherapy. In other publications on this topic, longer survival was connected with higher CA 19-9 levels, but the cut-off point was established arbitrarily or on the level of its median value. In our study, the CA 19-9 level accepted as the cut-off point has been established as a result of statistical analysis of specificity and sensitivity of 2 years survival upon acceptance of different cut-off points using ROC method.

No relationship has been identified between the preoperative CA 19-9 level and deaths in the first year. An elevated CA 19-9 level may be caused by an increased expression of sialyated proteins on cancer cells which may mark their higher metastatic potential and the presence of metastases which have not been identified during routine imaging studies. On the other hand, high CA 19-9 levels may be an unspecific reaction of bile duct cells to cancer or inflammation. Inflammatory response is also activated in pancreatic cancer, thus high platelet and C-reactive protein levels can be observed [22,23]. The lack of relationship between one-year mortality and preoperative CA 19-9 levels argues against the hypothesis that its elevated levels represents an exponent of metastases which have not been identified: if they were present, the survival time would be very short and, thus, one-year mortality should be higher. It cannot, however, be excluded, that an elevated preoperative CA 19-9 level in cases of a resectable tumor reflect presence of micrometastases, which activate the inflammatory response and lead to an increase in CA 19-9 production in non-cancerous bile duct cells.

In our study group the perioperative mortality has amounted to 8.6% and has been similar to observations of other authors. Up to now, in most of the studies the perioperative mortality was related to the course of operation, higher blood loss, longer time of operation. We have found that patients who did not survive the operation had significantly higher CA 19-9 levels than patients who survived at least one year. In ROC analysis we have found that the trend can be noted toward the perioperative deaths upon CA 19-9 levels of at least 315 U/ml.

Our results support the opinion that radiotherapy and chemotherapy has only small effect on the survival in patients with pancreatic cancer and that only an early radical surgery increases the survival time.

Conclusions

Preoperative level of CA 19-9 below 106U/ml represents a predictive factor of 2- and 5-year survival, independent of other factors, such as lower size of the tumor, absence of metastases to lymph nodes, female gender of patients. After exclusion of the patients who died in the perioperative period, no relationship could have been disclosed between preoperative CA 19-9 levels and one year survival. The observation points to the chance that patients with higher levels of CA 19-9 harbour micrometastases, the development of which is sufficiently slow to allow for a one-year survival of the patients but which increase the risk of death after two and five years. A markedly elevated preoperative level of CA 19-9 may point to the local advancement of the neoplastic lesion, making the surgical procedure more difficult and, therefore, increasing periprocedural mortality. The hypothesis requires verification by further investigations.

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