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Nurmi, Anna Maria

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Research Article

Changes in CRP and CA19-9 during preoperative oncological therapy predict postoperative survival in pancreatic ductal adenocarcinoma

Anna Maria Nurmi[a], Harri Mustonen[a], Caj Haglund[a,b*], Hanna Seppänen[a,b*]

[a] *Department of Surgery, Helsinki University Hospital, University of Helsinki, PO Box 22, 00014 University of Helsinki, Helsinki, Finland*

[b] *Translational Cancer Medicine Research Program, Faculty of Medicine, Haartmaninkatu 8 PO Box 63, 00014 University of Helsinki, Helsinki, Finland*

*Shared last authorship

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Corresponding Author:

Anna Maria Nurmi

Department of Surgery, University of Helsinki, Helsinki University Hospital, Finland

PO Box 22, 00014 University of Helsinki, Finland

Tel: +358504270042

E-mail: anna-maria.nurmi@helsinki.fi

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Abstract

Introduction: Tumor and systemic inflammatory markers predict survival. This retrospective study aimed to explore the changes in CRP, CA19-9, and other routine laboratory tests during preoperative oncological therapy as prognostic factors in pancreatic ductal adenocarcinoma (PDAC).

Methods: Between 2000 and 2016, 68 borderline resectable PDAC patients received preoperative oncological therapy and underwent subsequent surgery at Helsinki University Hospital, Finland. We investigated changes in CRP, CA19-9, CEA, albumin, leukocytes, bilirubin, and platelets and examined the impact on survival.

Results: In the multivariate analysis, CRP remaining at ≥3 mg/l after preoperative oncological therapy predicted a poorer postoperative outcome when compared to CRP decreasing to or remaining at <3 mg/l [HR 2.766, 95% confidence interval (CI) 1.300-5.885, p=0.008]. Furthermore, a CA19-9 decrease >90% during preoperative treatment predicted a favorable postoperative outcome (HR 0.297, 95% CI 0.124-0.708, p=0.006). In the Kaplan-Meier analysis, the median survival for patients with CRP remaining at <3 mg/l was longer than among patients with an increased CRP level at ≥3 mg/l (42 months vs 24 months, p=0.001). Patients with a CA19-9 decrease >90% or level normalization (to ≤37 kU/l) during preoperative treatment exhibited a median survival of 47 months, those with a 50% to 90% decrease 15 months, and those with a <50% decrease 17 months (p<0.001).

Conclusions: Changes in CRP and CA19-9 during preoperative oncological therapy predict postoperative survival.

Introduction

Given the low percentage of resectable patients and the dismal overall survival rate of less than 8%, pancreatic ductal adenocarcinoma (PDAC) represents one of the most fatal malignancies [1]. The only possibility for a cure remains surgery combined with oncological therapy. With preoperative oncological therapy, the number of potentially successful resections increases and borderline resectable patients gain a survival benefit [2,3]. However, routinely administering preoperative oncological therapy to upfront resectable patients remains controversial [4-6].

CA19-9 is a sialylated Lewis blood group antigen, the only guideline-recommended biomarker for pancreatic cancer. However, its clinical utility is impaired since CA19-9 levels can increase in conditions other than cancer, thereby diminishing its specificity. Additionally, 5% to 10% of the Caucasian population cannot produce CA19-9 due to Lewis negativity, further complicating its clinical application [7-9]. However, those with CA19-9 levels below the detection limit appear to survive longer than CA19-9 secretors overall. Furthermore, survival among those with a CA19-9 level below the detection limit exhibit a comparable survival to those with normal levels [9-10]. Previously, it was reported that changes in the CA19-9 level during oncological therapy predicted survival in both resectable and unresectable patients [11-15]. Generally, CA19-9 levels correlate with tumor burden, and an increase in the CA19-9 level signifies disease progression whereas a decrease might reflect treatment response.

Inflammation and carcinogenesis are closely linked. A systemic inflammatory response preoperatively appears to be associated with a worse survival in pancreatic cancer patients [16]. Overall, inflammation has been suggested as promoting tumorigenesis and metastatic potential via different mechanisms [17-21]. Additionally, a high systemic inflammatory response, along with a high CA19-9 level, associate with tumor burden [22]. In esophageal and rectal cancer, the pretreatment CRP level seems to associate with the treatment response [23,24]. In patients with initially unresectable locally advanced pancreatic cancer, a high CRP level following preoperative chemoradiotherapy associated with worse survival [25].

In this study, we examined the changes in CRP and CA19-9 levels along with other routine laboratory tests during preoperative oncological therapy on pancreatic cancer survival in resected patients. We hypothesized that patients with persistent high CRP or CA19-9 levels following preoperative

oncological therapy or those with an increase in the CRP or CA19-9 levels during preoperative treatment would exhibit worse postoperative outcomes.

Materials and Methods

Patients

Between 2000 and 2016, 94 borderline resectable pancreatic cancer patients received preoperative oncological therapy and underwent subsequent surgery at Helsinki University Hospital (HUH), Finland. Patients lacking CRP and CA19-9 results both before and after preoperative oncological therapy (n=15), patients on oral immunosuppressive medication (n=3), patients with an ongoing infection 2 to 4 weeks before preoperative oncological therapy or at the time of surgery (n=6), patients who underwent emergency surgery and those who died from surgery-related complications (n=2) were excluded from further analysis (total n=26). We retrospectively collected patient data from a prospectively maintained database based on patient records and the Finnish Population Registry. PDAC diagnosis was confirmed by an experienced pathologist who re-evaluated all histological tumor samples. The Surgical Ethics Committee of HUH (226/E6/2006, extension 4/17/2013, extension 3/27/2019) and the National Supervisory Authority of Health and Welfare approved this study. Before surgery, all patients signed a written informed consent form allowing their data to be collected for research purposes.

Preoperative oncological therapy

Preoperative oncological therapy consisted of different regimens including FOLFIRINOX, gemcitabine alone or in combination with cisplatin, nab-paclitaxel, or capecitabine. In total, 16 patients (24%) received radiotherapy as a part of their regimen. Preoperative treatment was administered to borderline resectable patients only, defined as superior mesenteric vein, portal vein, or superior mesenteric artery contact upon diagnosis. Supplementary Table 1 summarizes the preoperative oncological therapy regimens administered.

CRP, CA19-9, and other laboratory tests

The laboratory tests examined consisted of routine laboratory tests determined before and after preoperative oncological therapy: CRP (mg/l), CA19-9 (kU/l), albumin (g/l), CEA (μg/l), leukocytes (E9/l), platelets (E9/l), and bilirubin (μmol/l). Samples for laboratory tests were primarily collected

within 2 weeks of initiating preoperative treatment (97%, range: 0-29 days) and 1 to 4 days preoperatively (97%, range: 1-9 days). Table 1 lists the cut-off values for each laboratory test analyzed. We used the manufacturer's recommended cut-off values for CEA, platelets, bilirubin, and leukocytes. The cut-off value for albumin was based on the Glasgow prognostic score [26] and on the literature for CA19-9 [27]. The cut-off value for CRP (3 mg/l) was the cut-off value used in the HUH laboratory at the time of study conduction and mirrors the value used across Finland. The laboratory only determines CRP values ≥3 mg/l numerically, whereby all lower values are classified as <3 mg/l. Hence, we only provide categorical data for CRP here. The decrease in CA19-9 during preoperative oncological therapy was based on the literature [15]: a decrease <50%, a decrease of 50% to 90%, and a decrease >90%. Patients whose CA19-9 level normalized (to ≤37 kU/l) or remained at a normal level were classified as a decrease of >90% due to similar survival patterns and statistical reasons.

Statistical analyses

We used the Kolmogorov-Smirnov test for normality. The Jonckheere-Terpstra test was used to compare clinicopathological characteristics and the change in CA19-9 and CRP. We estimated survival using the Kaplan-Meier method (log-rank test). The primary endpoint was disease-specific survival (DSS) from surgery to cancer-specific death. The secondary endpoint was disease-free survival (DFS) from surgery to the first recorded disease progression or death from PDAC. When assessing pretreatment levels and their association with survival, survival was calculated from the initiation of preoperative oncological therapy, otherwise survival was calculated from the date of surgery. We performed a multivariate analysis using the Cox proportional hazards method based on clinical relevance and the univariate analysis. The multivariate model included age, sex, stage, adjuvant therapy, perivascular invasion, and the change in CEA, CRP, and CA19-9 levels in the models. These variables were considered clinically relevant and, thus included in the model. Due to the small number of patients, two separate multivariate models were used, one with the change in the CRP level and another one with the change in the CA19-9 level. For each variable, the assumption of a constant proportional hazard rate over time was tested using a time-dependent variable; all variables met this assumption. We considered interactions in the multivariate analyses, but detected no significant interactions after correcting for multiple testing using the Bonferroni method. The last day of follow-up was set to 14 January 2020, with a minimum follow-up of 3 years or until death. We

calculated all statistical analyses using SPSS (version 24, IBM, New York, NY, USA), and considered $p<0.05$ as statistically significant. All tests were two-tailed.

Results

After applying the exclusion criteria outlined above, there were 68 eligible patients for the analyses. Out of the 68 patients eligible for analysis, 57 patients (84%) were treated between 2010 and 2016. Median follow-up time was 2.7 years and the median duration of preoperative oncological therapy was 4.4 months (range: 2.4 to 10.8 months). Table 2 summarizes the clinicopathological characteristics of the patients.

Laboratory tests before preoperative oncological therapy and changes during preoperative oncological therapy

The number of patients and the change in CRP, CA19-9, albumin, and CEA are shown in Table 3. During preoperative treatment, there was an increase in the CA19-9 level in 7 patients (10% of patients) (range of increase: 118 to 5456 kU/l); however, these patients already exhibited elevated levels (>37 kU/l) before preoperative oncological therapy. Only 2 patients (3%) exhibited an elevated bilirubin level (>20 μmol/l) following preoperative treatment. The pretreatment levels and change during preoperative treatment for bilirubin, platelets, and leukocytes are shown in Supplementary Table 2. Additionally, changes in the level and their effect on survival are shown in Supplementary Table 2.

The median values before preoperative oncological therapy and changes in each laboratory test with the range for the maximum increase and decrease are shown in Supplementary Table 3. The change in CRP level did not associate with the T or N classification, stage, tumor differentiation, tumor size, perivascular or perineural invasion, the rate of vascular resections, or the rate of radical resections (Shown in Supplementary Table 4). However, the change in the CA19-9 level did associate with tumor size and the T and N classification, and thus, the stage (Shown in Supplementary Table 4). Patients with a decrease in the CA19-9 level of >90% or a normalization had significantly smaller tumors and fewer nodal metastases. Thus, more of these patients had Stage IA or IB disease (Shown in Supplementary Table 4).

Changes in CRP and CA19-9 were additionally tested based on the preoperative treatment regimen used (Shown in Supplementary Table 5). First, patients were grouped into those who received platinum-based preoperative treatment and those who did not. Second, patients were grouped into those who received either platinum-based therapy or radiotherapy and those who received neither of those. Out of 16 patients who were administered radiotherapy, 12 received platinum-based chemotherapy, hence, these patients were grouped together. There were no significant differences between different preoperative regimens and changes in CRP and CA19-9 levels. Furthermore, postoperative median disease-specific survival times did not differ between those who received platinum-based preoperative treatment and those who did not [34 months (95% CI 24-44 months) vs 26 months (95% CI 12-39 months), p=0.780] or between those who received platinum-based treatment or radiotherapy and those who did not [33 months (95% CI 24-42 months) vs 32 months (95% CI 29-34 months), p=0.523].

There were in total 19 patients with preoperative treatment duration >6 months. Out of these patients, seven patients received preoperative treatment for >8 months and two patients for >10 months. Longer treatment periods were due to minimal response after standard preoperative treatment and radiological inoperability. Among these patients 74% had a decrease >90% in CA19-9, 16% a decrease between 50 and 90% and 10% a decrease <50%. Additionally, among those with preoperative treatment >6 months, the CA19-9 level stayed at or decreased to <37kU/l in 42% and stayed at or increased to >37kU/l in 58%. Furthermore, the CRP level stayed at or decreased to <3mg/l in 74% and stayed at or increased to >3mg/l in 26%. All in all, 3 patients out of 11 patients (27%) with both CA19-9 decrease >90% and CRP decrease to <3mg/l were administered preoperative treatment for >6 months. Furthermore, 13 out of 38 patients (34%) with CRP decreasing to or staying at <3mg/l along with CA19-9 decrease >50% had been administered preoperative treatment for >6 months.

Survival and the changes in laboratory tests

The CRP and albumin levels before preoperative treatment did not associate with survival; however, a change in the CRP and albumin levels associated with survival (Shown in Table 3). However, the CA19-9 and CEA levels before preoperative treatment associated with survival (Shown in Table 3). Additionally, a change in the CA19-9 and CEA levels associated with postoperative outcomes.

When examining the prognostic effect of the CRP level, the median survival times were different whether the CRP level remained at <3 mg/l, normalized to <3mg/l, increased to ≥3 mg/l or remained at ≥3 mg/l (DSS p=0.002; DFS p=0.005) (Shown in Fig. 1. a, b and Table 3). The median survival time for patients with an increased CRP level was significantly shorter than for patients with CRP level remaining at <3 mg/ml (median DSS 42 months vs 24 months, p=0.001; median DFS 17 months vs 10 months, p=0.007) (Shown in Fig. 1. a and Table 3). For further analysis, patients were categorized as those whose level remained at or decreased to <3 mg/l and those whose level increased to or remained at ≥3 mg/l (median DSS 47 vs 24 months, p<0.001; median DFS 25 vs 11 months, p=0.001) (Shown in Fig. 1. c, d and Table 3).

A CA19-9 decrease ≤50% resulted in a median DSS of 17 months compared to 15 months among patients with a decrease between 50% and 90% and 47 months among patients with a decrease >90% (p<0.001) (Shown in Fig. 2. a and Table 3). Median DFS reached 7 months, 7 months, and 25 months, respectively (p<0.001) (Shown in Fig. 2. b, Table 3). Among patients with a decrease ≤90%, the 5-year survival rate was <10%, compared to 37% among those whose level decreased >90%. Survival was further analyzed among patients whose level remained at or decreased to ≤37 kU/l and those whose level increased to or remained at >37 kU/l (median DSS 47 vs 18 months, p<0.001; median DFS 31 vs 9 months, p<0.001 (Shown in Fig. 2. c, d and Table 3).

After analyzing CRP and CA19-9 separately, the changes in CRP and CA19-9 levels were combined. (Shown in Supplementary Fig. 1 and Supplementary Table 6). First, a cut-off of 50% was used for CA19-9. Patients whose CRP remained at or decreased to <3 mg/l and CA19-9 decreased >50% (n=38, 56%) had a median DSS of 48 months and a median DFS of 31 months, whereas those whose either CRP remained at or decreased to <3mg/l or CA19-9 decreased by >50% (n=19, 28%) had a median DSS of 24 months and a median DFS of 11 months. Finally, among patients whose CRP was at ≥3 mg/l and the CA19-9 level had decreased by ≤50% following preoperative oncological therapy (n=11, 16%), had a median DSS of 19 months and a median DFS of 9 months (DSS p<0.001, DFS p<0.001) (Shown in Supplementary Fig. 1. a, b and Supplementary Table 6). Next, a cut-off of 90% was used for CA19-9. Among patients whose CA19-9 levels decreased by >90% or normalized levels combined with a CRP level normalizing to <3 following preoperative oncological therapy (n=11, 16%), the median DSS or DFS had not been reached by the end of follow-up. Among those with CA19-9 levels decreasing by >90% or normalized levels and whose CRP level remained at <3 mg/l following preoperative oncological therapy (n=19), median DSS was 47 months and median DFS 20 months.

The remaining patients experienced similar survival patterns, and when analyzed together, had a median DSS of 24 months and a median DFS of 10 months (DSS p<0.001, DFS p<0.001) (Shown in Supplementary Fig. 1. c, d and Supplementary Table 6). Additionally, the 5-year survival rates for each patient group are shown in Supplementary Table 6.

Patients whose albumin levels stayed at or decreased to <35 g/l had significantly shorter median DSS and DFS than those whose levels stayed at or increased to ≥35 g/l (DSS 17 vs 37 months, p=0.019; DFS 5 vs 16 months, p=0.009) (Shown in Fig. 3. a-d and Table 3). The median survival times (DSS) were different whether the CEA level remained ≤5.0 μg/l (median DSS 42 months), decreased to ≤5.0 μg/l (median DSS 34 months), remained at >5.0 μg/l (median DSS 16 months) or increased to >5.0 μg/l mg/l (median DSS 15 months, p=0.017) (Shown in Fig. 3. e and Table 3). Changes in median DFS did not differ significantly (Shown in Fig. 3. f and Table 3).

Univariate and multivariate analysis

Based on the Kaplan-Meier analysis, the change in CEA was grouped as follows: patients whose levels decreased to or stayed at ≤5.0 μg/l and those whose levels increased to or stayed at >5.0 μg/l. For CRP, patients whose levels remained at or decreased to <3 mg/l were analyzed together and compared to those whose levels increased to ≥3 mg/l and those whose levels stayed at ≥3 mg/l. Two multivariate models were constructed due to the small patient number, one model with the change in CRP and the other model with the change in CA19-9.

In the univariate analysis, postoperative adjuvant therapy [hazard ratio (HR) 0.42, p=0.007] and a CA19-9 decreasing by >90% (HR 0.287, p<0.001) predicted a favorable outcome (DSS), whereas perivascular invasion (HR 2.02, p=0.018), an albumin level decreasing to <35 g/l (HR 3.169, p=0.022), a CEA level remaining at or increasing to >5 μg/l (HR 3.935, p=0.004), and a CRP level remaining at ≥3 mg/l (HR 3.95, p=0.004) predicted an unfavorable postoperative outcome (DSS) (Table 4).

In the multivariate analysis, CRP remaining at ≥3 mg/l predicted a worse outcome (DSS) when compared to remaining at or decreasing to <3 mg/l (HR 2.766, p=0.008) (Shown in Table 5). Furthermore, a CA19-9 decrease by >90% predicted a better outcome (DSS) when compared to a decrease <50% (HR 0.297, p=0.006) (Shown in Table 5). CEA, increasing to or staying at >5 μg/l,

associated with a poor postoperative outcome (DSS) in both multivariate models (with CRP HR 3.002, p=0.007; with CA19-9 HR 2.281, p=0.046) (Shown in Table 5). Additionally, postoperative adjuvant therapy predicted better postoperative survival (in multivariate CRP model HR 0.420, p=0.018; in multivariate CA19-9 model HR 0.423, p=0.022) (Shown in Table 5).

Discussion

Here, we show that the CRP level before preoperative oncological therapy did not associate with survival, whereas CRP level normalization did. Furthermore, the CA19-9 level before preoperative treatment and a change in the level were associated with survival. A decrease of >90% or normalization in the CA19-9 level predicted a good postoperative outcome. Additionally, the changes in both CRP and CA19-9 during preoperative treatment were examined together.

The range for survival times among patients with pretreatment CRP levels of ≥3 mg/l was rather vast, ranging from 8 to 121 months, most likely rendering the difference in median survival times insignificant. A better postoperative survival among those whose levels either decreased to <3 mg/l or stayed at <3 mg/l could indicate a good treatment response or reflect systemic effects of the tumor. Previously, a systemic inflammatory response was reported to promote tumor progression and metastatic potential [18-20]. Both an elevated CRP and tumor marker level represent indicators of a poor prognosis in resected PDAC patients [16]. Unlike CA19-9, a change in CRP did not associate with tumor size, pTN classification, or, thus, disease stage. This may indicate that CRP and CA19-9 reflect different aspects of cancer. Furthermore, although the CRP level did not associate with tumor burden, it may predict a better recovery following surgery, a better response to postoperative adjuvant therapy, or other patient-related factors affecting survival.

The decrease in the CA19-9 level during treatment and association with outcome has been studied in both inoperable and resected pancreatic cancer patients [11-13,15]. Among inoperable patients, a decrease from 20% to 75% appears to predict a better survival in patients receiving gemcitabine chemotherapy [11,12]. However, among patients receiving gemcitabine, 5-FU, and radiotherapy, a CA19-9 response >75% in locally advanced patients did not significantly associate with outcome [13]. Boone et al. [15] analyzed the decrease in CA19-9 across three categories: a decrease of <50%, a decrease between 50% and 90%, and a decrease >90%. A decrease >50% associated with a better overall survival (28 months vs 11 months). More than 70% of patients experienced a decrease of >

50% during preoperative oncological therapy. A decrease >50% predicted R0 resection in borderline resectable patients. Interestingly, among those whose level increased, none underwent an R0 resection. A complete pathological response was experienced only among patients with a decrease of > 90% or normalization. In our study, patients with a level decrease of >90% or normalization seemed to survive the longest (47 months) and the 5-year survival rate among those with a CA19-9 level decrease ≤90% was considerably low for resected patients, at only <10%. Median survival times among patients whose level decreased <50% or between 50% to 90% were nearly the same, at 17 and 15 months, respectively. According to Tsai et al. [28], normalizing CA19-9 at <35 kU/l represents a better prognostic factor over the magnitude of change in the CA19-9 level. Those whose level normalized during preoperative oncological therapy, survived significantly longer than those whose did not (46 months vs 23 months, p=0.02) [28]. Interestingly, in our study, all 9 patients with a CA19-9 level ≤37 kU/l before initiating preoperative treatment were all living disease-free at the end of follow-up. However, in our study, these patients were combined with those whose levels decreased >90% or normalized to ≤37 kU/l due to statistical reasons and similar survival patterns.

A decrease in CRP and CA19-9 assessed together predicted postoperative outcome better than assessing them separately. In patients whose CRP level remained at or decreased to <3 mg/l and CA19-9 level decreased >50%, the median DSS reached 48 months. However, if only CRP or CA19-9 decreased, the median DSS was only 24 months, while the 5-year survival rate dropped from 41% to 5%, a considerably low 5-year survival rate for resected patients. Furthermore, if CRP increased to or remained at ≥3 mg/l and CA19-9 decreased <50%, the median DSS was only 19 months. Interestingly, among patients whose CA19-9 level decreased >90% and CRP level decreased from ≥3 to <3 mg/l, median DSS or median DFS were not reached by the end of follow-up. Patients whose CA19-9 level decreased <90% survived significantly shorter despite the CRP change. Additionally, even if the CA19-9 had decreased by >90% and CRP had increased to or remained at ≥3 mg/l, median survival times were significantly shorter than among those with normal CRP levels. Previously, the combined change in CRP and CA19-9 during preoperative oncological therapy has not been studied. However, a prognostic score of preoperative CRP and CA19-9 was previously introduced [29].

Patients whose CRP or CA19-9 levels increased or remained elevated during preoperative oncological therapy exhibited a poor postoperative outcome. Therefore, such patients should be evaluated carefully for any signs of disease progression, metastases, and their performance status for surgery should be considered. Furthermore, other markers, such as weight loss, cachexia, changes in the

albumin level, and other laboratory tests should be taken into account. Among patients with an increase in CRP or CA19-9, the benefits of surgery should be compared to the possible complications and disadvantages of surgery, and clinicians should consider if such patients would rather benefit from continuing oncological therapy. The median survival for patients with locally advanced unresectable disease reached a reported 9-19 months [30-32]. Patients whose CRP increased to or remained at ≥3 mg/l achieved a median survival of 24 months, while those whose CA19-9 increased to or remained at >37 kU/l reached a median survival of 18 months. Also, among patients with locally advanced pancreatic cancer, the increase in CRP and CA19-9 levels previously associated with survival [25]. In a subgroup analysis, those with a weight loss of >5% and skeletal muscle mass reduction of >5% did not benefit from resection [25].

In colorectal cancer, a high systemic inflammatory response before preoperative chemoradiotherapy associates with a poor pathological response [24]. The same has been postulated in esophageal cancer [23]. This does not appear to be the case in pancreatic cancer. In our cohort, patients with an elevated level before preoperative treatment and level normalization during preoperative treatment had the longest median survival. Furthermore, the CRP level before preoperative treatment did not associate with outcome.

We acknowledge several limitations to our study. Our study population is quite small and the multivariate model should, therefore, be interpreted with caution. Additionally, our patients were treated during a period of 17 years, however, due to missing data among patients treated during the early 2000s, majority of the patients eligible for analysis (84%) were treated during 2010-2016 decreasing bias related to changing preoperative treatment regimens. Additionally, the preoperative treatment regimens used were heterogenous. However, platinum-based regimens and radiotherapy were further analyzed separately and no correlation between different regimens and the decrease in CRP and CA19-9 were noted. However, considering the reliable and vast amount of clinical and follow-up data, this study offers additional information on changes in laboratory tests in pancreatic cancer patients. Furthermore, including only surgical patients in our study undoubtedly causes a bias; however, it is important to have available preoperative prognostic factors to be taken into consideration in order to carefully assess patients.

To conclude, in this study, we found that the normalization of the CRP level and a CA19-9 level decreasing by more than 90% or level normalization during preoperative oncological therapy positively associates with postoperative outcomes in borderline resectable PDAC patients.

Statements

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Statement of Ethics

The research was conducted ethically in accordance with the Declaration of Helsinki. The Surgical Ethics Committee of HUH (226/E6/2006, extension 4/17/2013, extension 3/27/2019) and the National Supervisory Authority of Health and Welfare approved this study. Before surgery, all patients signed a written informed consent form allowing their data to be collected for research purposes.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed to the study design and concept. AN, HS, and CH contributed to the data acquisition and material preparation. AN and HM were responsible for the statistical analyses. AN prepared the first draft of the manuscript, which was edited and approved by all authors.

Data Availability Statement

The data that support the findings of this study are not publicly available due to legal reasons but are available upon request from the corresponding author (AN).

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Figure Legends

Fig. 1. a) Change in CRP during preoperative oncological therapy (remained at <3 mg/l, decreased to <3 mg/l, remained at ≥3 mg/l, and increased to ≥3 mg/l). Kaplan-Meier analysis, DSS.

Fig. 1. b) Change in CRP during preoperative oncological therapy (remained at <3 mg/l, decreased to <3 mg/l, remained at ≥3 mg/l, and increased to ≥3 mg/l). Kaplan-Meier analysis, DFS.

Fig. 1. c) CRP level following preoperative oncological therapy (remained at or decreased to <3 mg/l and remained at or increased to ≥3 mg/l). Kaplan-Meier analysis, DSS.

Fig. 1. d) CRP level following preoperative oncological therapy (remained at or decreased to <3 mg/l and remained at or increased to ≥3 mg/l). Kaplan-Meier analysis, DFS.

Fig. 2. a) Decrease in CA19-9 during preoperative oncological therapy (<50%, 50-90%, and >90%). Patients with a CA19-9 decrease of >90% includes patients whose level normalized during preoperative oncological therapy or remained at a normal level (≤37 kU/l). Kaplan-Meier analysis, DSS.

Fig. 2. b) Kaplan-Meier analysis: Decrease in CA19-9 during preoperative oncological therapy (<50%, 50-90%, and >90%). Patients with a CA19-9 decrease of >90% includes patients whose level normalized during preoperative oncological therapy or remained at a normal level (≤37 kU/l). Kaplan-Meier analysis, DFS.

Fig. 2. c) CA19-9 level following preoperative oncological therapy (remained at or decreased to ≤37 kU/l and remained at or increased to >37 kU/l). Kaplan-Meier analysis, DSS.

Fig. 2. d) CA19-9 level following preoperative oncological therapy (remained at or decreased to ≤37 kU/l and remained at or increased to >37 kU/l). Kaplan-Meier analysis, DFS.

Fig. 3. a) Change in albumin during preoperative oncological therapy (remained at <35 g/l, decreased to <35 g/l, remained at ≥35 g/l, and increased to ≥35 g/l. Kaplan-Meier analysis, DSS.

Fig. 3. b) Change in albumin during preoperative oncological therapy (remained at <35 g/l, decreased to <35 g/l, remained at ≥35 g/l, and increased to ≥35 g/l. Kaplan-Meier analysis, DFS.

Fig. 3. c) Change in albumin during preoperative oncological therapy (remained at or decreased to <35 g/l, remained at or increased to ≥35 g/l). Kaplan-Meier analysis, DSS.

Fig. 3. d) Change in albumin during preoperative oncological therapy (remained at or decreased to <35 g/l, remained at or increased to ≥35 g/l) Kaplan-Meier analysis, DFS.

Fig. 3. e) Change in CEA during preoperative oncological therapy (remained at ≤5 µg/l, decreased to ≤5 µg/l, remained at >5 µg/l, and increased to >5 µg/l. Kaplan-Meier analysis, DSS.

Fig. 3. f) Change in CEA during preoperative oncological therapy (remained at ≤5 µg/l, decreased to ≤5 µg/l, remained at >5 µg/l, and increased to >5 µg/l. Kaplan-Meier analysis, DFS.

Supplementary Fig. 1. a) The change in CRP and CA19-9. 1) CRP remained at or decreased to <3 and CA19-9 level decreased >50%, 2) either CRP remained at or decreased to <3 or CA19-9 level decreased >50%, and 3) CRP remained at or increased to ≥3 and CA19-9 decreased ≤50%. Kaplan-Meier analysis, DSS.

Supplementary Fig. 1. b) The change in CRP and CA19-9. 1) CRP remained at or decreased to <3 and CA19-9 level decreased >50%, 2) Either CRP remained at or decreased to <3 or CA19-9 level decreased >50%, and 3) CRP remained at or increased to ≥3 and CA19-9 decreased ≤50%. Kaplan-Meier analysis, DFS.

Supplementary Fig. 1. c) The change in CRP and CA19-9 combined. 1) CRP decreased to <3 and CA19-9 level decreased >90%, 2) CRP remained at <3 and CA19-9 level decreased >90%, and 3) remaining patients. Kaplan-Meier analysis, DSS.

Supplementary Fig. 1. d) The change in CRP and CA19-9 combined. 1) CRP decreased to <3 and CA19-9 level decreased >90%, 2) CRP remained at <3 and CA19-9 level decreased >90%, and 3) remaining patients. Kaplan-Meier analysis, DFS.

Table 1. The cut-off values for each laboratory test.

Laboratory test	**Cut-off values**
CRP	<3 mg/l vs ≥3 mg/l
CA19-9	≤37 kU/l vs >37 kU/l
CEA	≤5 µg/l vs >5 µg/l
Albumin	<35 g/l vs ≥35 g/l
Leukocytes	<3.4 E9/l vs 3.4-8.2 E9/l vs >8.2 E9/l
Bilirubin	≤20 µmol/l vs >20 µmol/l
Platelets	<150 E9/l vs 150-360 E9/l vs >360 E9/l

We used the manufacturer's recommended cut-off values for CRP, CEA, platelets, bilirubin, and leukocytes. The cut-off value for albumin was based on the Glasgow prognostic score[26] and the cut-off value for CA19-9 on the literature[27].

Table 2. Clinicopathological characteristics of the patients.

	Patients (n=68)
Age, median (range)	66 (40-81)
Age, ≥65 years	36 (53%)
Gender, female	36 (53%)
pTN (AJCC 8th edition)	
T0	2 (3%)
T1	15 (22%)
T2	42 (62%)
T3	8 (12%)
T4	1 (1%)
N0	32 (47%)
N1	23 (34%)
N2	13 (19%)
Stage (AJCC 8th edition)	
0	1 (1%)
IA	6 (9%)
IB	22 (32%)
IIA	2 (3%)
IIB	23 (34%)
III	14 (21%)
Pathological tumor size (mm), median (IQR)	26 (22-35)
Grade	
1	13 (19%)
2	38 (56%)
3	13 (25%)
R0 resection margin (>1 mm)	53 (78%)
Vascular resection	41 (60%)
Perineural invasion	49 (72%)
Perivascular invasion	22 (32%)
Postoperative adjuvant therapy	52 (76%)
Discontinuation	15 (22%)
Death, pancreatic cancer	50 (74%)
Other	1 (1%)
Alive	17 (25%)

AJCC=American Joint Committee on Cancer, IQR=interquartile range

Table 3. The Kaplan-Meier analysis according to the levels before preoperative oncological therapy and change in laboratory tests. Both disease-specific and disease-free survival were compared with the Log Rank test.

	n (%)	DSS, months (95% CI)	p-value	p-value (post hoc)	DFS, months (95% CI)	p-value	p-value (post hoc)
CRP before							
<3 mg/l	37 (54%)	36 (33-39)	0.627		18 (14-21)	0.185	
≥3 mg/l	31 (46%)	41 (17-66)			21 (1-41)		
CRP change							
Remained at <3 mg/l	23 (34%)	42 (26-59)	0.002	ref	17 (7-27)	0.005	ref
Decreased to <3 mg/l	18 (26%)	48 (37-60)		0.527*	48 (-)		0.080*
Increased to ≥3 mg/l	14 (21%)	24 (18-30)		0.001*	11 (9-13)		0.007*
Remained at ≥3 mg/l	13 (19%)	25 (1-49)		0.086*	10 (4-16)		0.444*
CRP change							
<3 mg/l (remained at or decreased to)	41 (60%)	47 (39-56)	<0.001		25 (6-45)	0.001	
≥3 mg/l (remained at or increased to)	27 (40%)	24 (16-32)			11 (9-13)		
CA19-9 before							
≤37 kU/l	16 (24%)	53 (-)	0.010		53 (-)	0.003	
>37 kU/l	52 (76%)	30 (24-36)			15 (12-19)		
CA19-9 decrease							
<50% decrease	14 (21%)	17 (14-20)	<0.001	Ref	7 (3-11)	<0.001	Ref
50-90% decrease	14 (21%)	15 (0-35)		0.693**	7 (0-15)		0.871**
>90% decrease	40 (58%)	47 (39-56)		<0.001**	25 (8-41)		<0.001**
CA19-9 change							
≤37 kU/l (remained at or decreased to)	30 (44%)	47 (39-56)	<0.001		31 (3-59)	<0.001	
>37 kU/l (remained at or increased to)	38 (56%)	18 (5-31)			9 (6-12)		
Albumin[1] before							
<35 g/l	23 (34%)	30 (21-40)	0.910		17 (12-21)	0.886	
≥35 g/l	40 (59%)	36 (26-46)			20 (14-27)		
Albumin[1] change							
Remained at <35 g/l	5 (7%)	14 (0-34)	0.103		5 (0-14)	0.058	
Decreased to <35 g/l	5 (7%)	17 (-)			5 (-)		
Increased to ≥35 g/l	18 (26%)	34 (15-52)			13 (10-17)		

Remained at ≥35 g/l	35 (51%)	37 (23-52)			17 (13-20)		
Albumin[1] change							
<35 g/l (remained at or decreased to)	10 (15%)	17 (8-25)	0.019		5 (0-11)	0.009	
≥35 g/l (remained at or increased to)	53 (78%)	37 (27-47)			16 (13-20)		
CEA before							
≤5.0 µg/l	49 (72%)	42 (29-55)	0.049		21 (14-28)	0.271	
>5.0 µg/l	17 (25%)	24 (14-36)			18 (14-22)		
Missing	2 (3%)						
CEA change							
Remained at ≤5.0 µg/l	45 (66%)	42 (31-53)	0.017	ref	17 (8-25)	0.113	
Decreased to ≤5.0 µg/l	11 (16%)	34 (9-58)		0.270*	20 (5-35)		
Remained at >5.0 µg/l	4 (6%)	16 (13-19)		0.001*	6 (0-14)		
Increased to >5.0 µg/l	6 (9%)	15 (2-27)		0.322*	10 (0-22)		
Missing	2 (3%)						

Patients with a CA19-9 decrease above 90% includes patients whose levels normalized during preoperative oncological therapy or remained at normal levels (≤37 kU/l). Kaplan-Meier analysis with Log Rank, survival times are shown in median survival times. DSS=disease-specific survival, DFS=disease-free survival. [1]Missing in 5 patients. Bonferroni correction for multiple comparisons were made in post hoc comparisons by decreasing the decision level to *p<0.017 or **p<0.025.

Table 4. Univariate analysis.

	Univariate	
	HR (95% CI)	**p-value**
Age	1.018 (0.985-1.051)	0.295
Sex, female	1.079 (0.617-1.887)	0.790
Stage, IA-IIA vs IIB-III	0.719 (0.409-1.2649)	0.252
Postoperative adjuvant therapy	0.422 (0.224-0.794)	**0.007**
Perivascular invasion	2.015 (1.126-3.607)	**0.018**
Perineural invasion	1.742 (0.888-3.421)	0.106
Vascular resection	1.060 (0.600-1.873)	0.840
Tumor differentiation, Well	ref	0.287
Moderately	0.884 (0.432-1.783)	0.731
Poorly	1.556 (0.673-3.597)	0.301
Radical resection	0.611 (0.311-1.200)	0.153
Platelets*, decreased	ref	0.780
Stayed the same	0.778 (0.384-1.577)	0.586
Increased	0.779 (0.265-2.288)	0.650
Leukocytes*, decreased	ref	0.613
Stayed the same	1.060 (0.545-2.060	0.865
Increased	0.517 (0.115-2.328)	0.390
Bilirubin, remained at ≤20 μmol/l	ref	0.301
Decreased to ≤20 μmol/l	1.394 (0.790-2.462)	0.252
Remained at >20 μmol/l	-	-
Increased to >20 μmol/l	2.504 (0.585-10.728)	0.216
Albumin, Remained at <35 g/l	1.734 (0.603-4.990)	0.307
Decreased to <35 g/l	3.169 (1.184-8.479)	**0.022**
Increased to ≥35 g/l	0.930 (0.471-1.838)	0.836
Remained at ≥35 g/l	ref	0.092
CEA, remained at or increased to >5 μg/l	2.606 (1.239-5.483)	**0.012**
CA19-9, <50 % decrease	ref	**<0.001**
50-90% decrease	0.805 (0.365-1.777)	0.591
>90% decrease	0.287 (0.143-0.576)	**<0.001**
CRP, remained at or decreased to <3 mg/l	ref	**0.001**
Remained at ≥3 mg/l	3.559 (1.744-7.263)	**<0.001**
Increased to ≥3 mg/l	2.257 (1.076-4.735)	**0.031**

HR=hazards ratio, CI=confidence interval. *Across the reference categories used, listed in Table 1

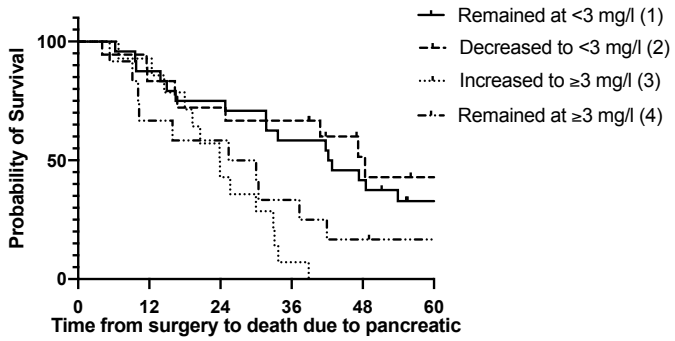
Table 5. Multivariate analysis in two separate models for CRP and CA19-9.

	Multivariate	
	HR (95% CI)	**p-value**
Model 1 (CRP)		
Age	1.011 (0.977-1.046)	0.534
Sex, female	0.872 (0.461-1.646)	0.672
Stage, IA-IIA vs IIB-III	0.805 (0.408-1.589)	0.533
Postoperative adjuvant therapy	0.420 (0.205-0.861)	**0.018**
Perivascular invasion	1.033 (0.485-2.199)	0.934
CEA, increased to or stayed at >5 µg/l	3.002 (1.357-6.642)	**0.007**
CRP, remained at or decreased to <3 mg/l	ref	
Remained at ≥3 mg/l	2.766 (1.300-5.885)	**0.008**
Increased to ≥3 mg/l	1.973 (0.827-4.705)	0.126
Model 2 (CA19-9)		
Age	0.988 (0.952-1.025)	0.517
Sex, female	0.984 (0.525-1.846)	0.960
Stage, IA-IIA vs IIB-III	1.182 (0.541-2.583)	0.675
Postoperative adjuvant therapy	0.423 (0.203-0.881)	**0.022**
Perivascular invasion	1.437 (0.645-3.203)	0.375
CEA, increased to or stayed at >5 µg/l	2.281 (1.015-5.124)	**0.046**
CA19-9 decrease, <50%	ref	
50-90%	0.571 (0.224-1.455)	0.240
>90%	0.297 (0.124-0.708)	**0.006**

Model 1 with CRP and model 2 with CA19-9. HR=Hazards ratio, CI=confidence interval

Figure 1

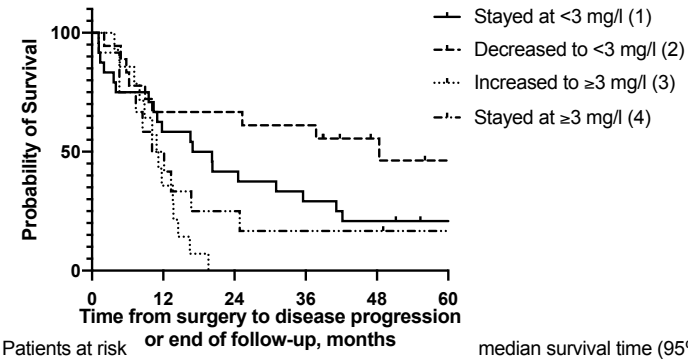
Change in CRP during preoperative treatment therapy, DSS



Patients at risk							median survival time (95% CI)
1	24	22	19	15	11	6	42 months (26-59 months)
2	18	16	14	13	7	5	48 months (37-60 months)
3	14	14	7	2	1	1	24 months (18-30 months)
4	12	9	8	5	3	2	25 months (1-49 months)

p=0.002

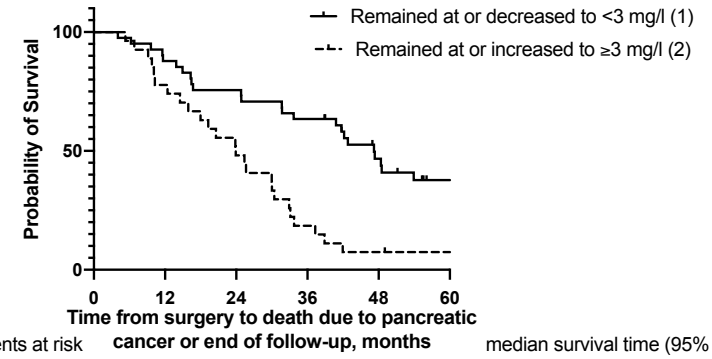
Change in CRP during preoperative treatment, DFS



Patients at risk							median survival time (95% CI)
1	24	15	11	8	6	4	17 months (7-27 months)
2	18	13	13	12	7	5	48 months (-)
3	14	6	1	1	1	1	11 months (9-13 months)
4	12	7	4	3	3	2	10 months (4-16 months)

p=0.005

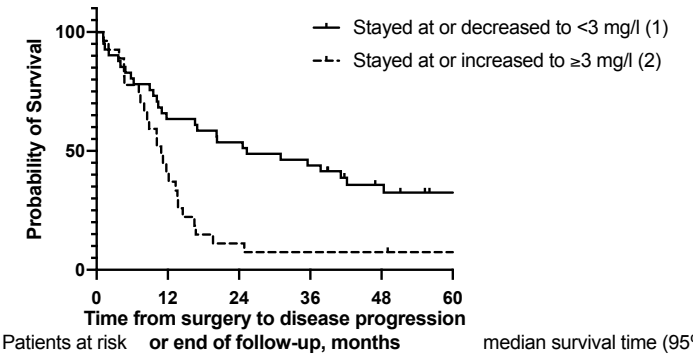
Change in CRP during preoperative treatment, DSS



Patients at risk							median survival time (95% CI)
1	41	37	32	27	17	10	47 months (39-56 months)
2	27	22	14	6	3	1	24 months (16-32 months)

p<0.001

Change in CRP during preoperative treatment, DFS

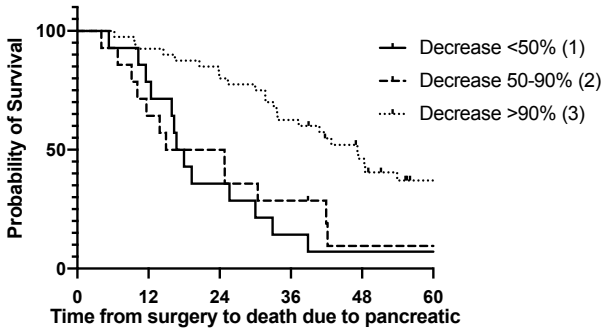


Patients at risk							median survival time (95% CI)
1	41	27	23	19	12	8	25 months (6-45 months)
2	27	12	4	3	3	2	11 months (9-13 months)

p<0.001

Figure 2

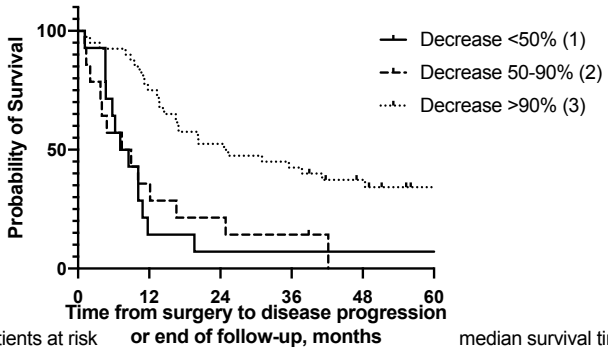
Decrease in CA19-9 during preoperative treatment, DSS



Patients at risk							median survival time (95% CI)
1	14	12	6	3	2	2	17 months (14-20 months)
2	14	10	8	5	2	2	15 months (0-35 months)
3	40	38	33	26	17	9	47 months (39-56 months)

p<0.001

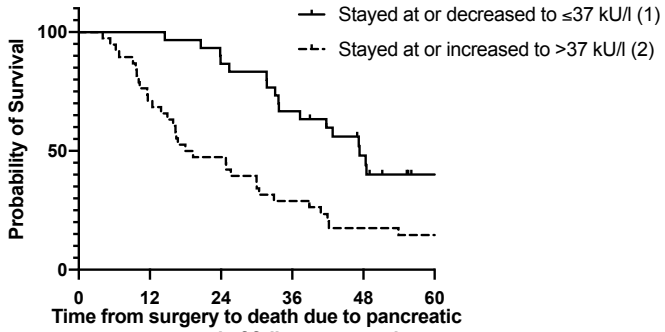
Decrease in CA19-9 during preoperative treatment, DFS



Patients at risk							median survival time (95% CI)
1	14	3	2	2	2	2	7 months (3-11 months)
2	14	6	4	3	1	1	7 months (0-15 months)
3	40	31	22	18	13	8	25 months (8-41 months)

p<0.001

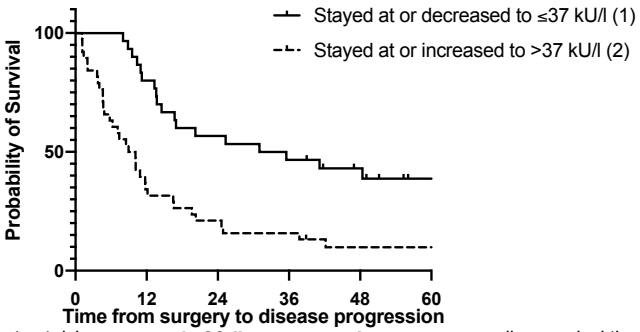
Change in CA19-9 during preoperative treatment, DSS



Patients at risk							median survival time (95% CI)
1	30	30	27	21	13	6	47 months (39-56 months)
2	38	28	19	12	7	6	18 months (5-31 months)

p<0.001

Change in CA19-9 during preoperative treatment, DFS

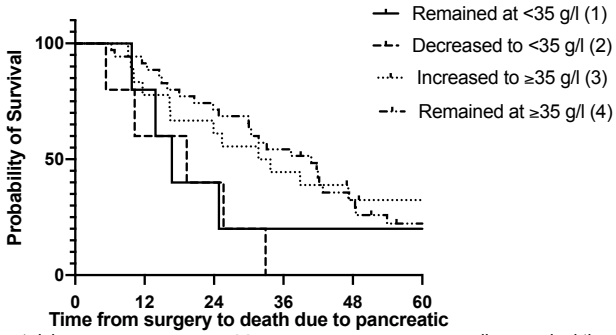


Patients at risk							median survival time (95% CI)
1	30	25	18	15	11	6	31 months (3-59 months)
2	38	14	9	7	4	4	9 months (6-12 months)

p<0.001

Figure 3

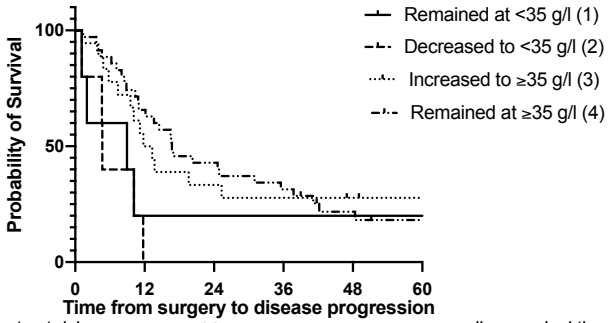
Change in albumin during preoperative treatment, DSS



Patients at risk							median survival time (95% CI)
1	5	5	3	2	2	2	14 months (0-34 months)
2	5	4	3	1	1	1	17 months (-)
3	18	15	12	9	6	5	34 months (15-51 months)
4	35	33	26	20	11	6	37 months (23-52 months)

p=0.103

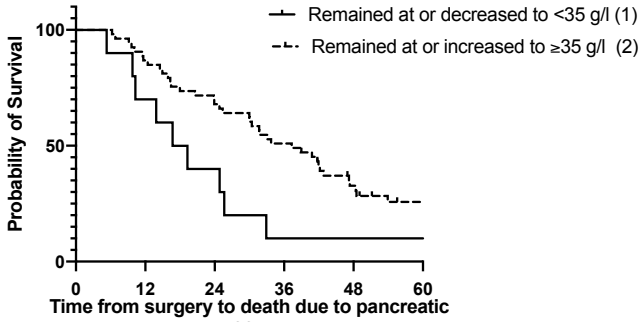
Change in albumin during preoperative treatment, DFS



Patients at risk							median survival time (95% CI)
1	5	2	2	2	2	2	5 months (0-14 months)
2	5	1	1	1	1	1	5 months (-)
3	18	10	7	6	5	4	13 months (10-17 months)
4	35	24	16	12	7	5	17 months (13-20 months)

p=0.058

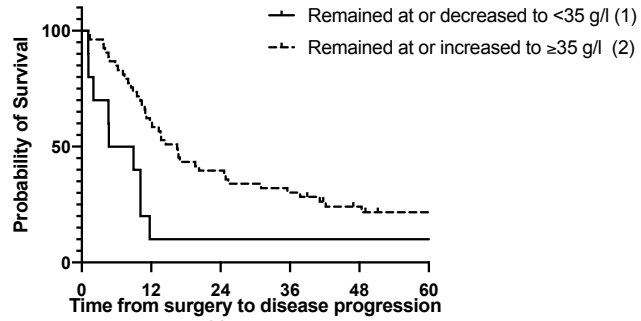
Change in albumin during preoperative treatment, DSS



Patients at risk							median survival time (95% CI)
1	10	8	5	2	2	2	17 months (8-25 months)
2	53	47	37	28	16	10	37 months (27-47 months)

p=0.019

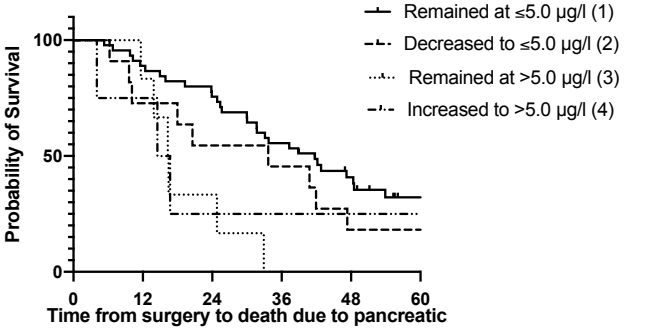
Change in albumin during preoperative treatment, DFS



Patients at risk							median survival time (95% CI)
1	10	2	2	2	2	2	5 months (0-11 months)
2	53	33	22	17	11	8	16 months (13-20 months)

p=0.009

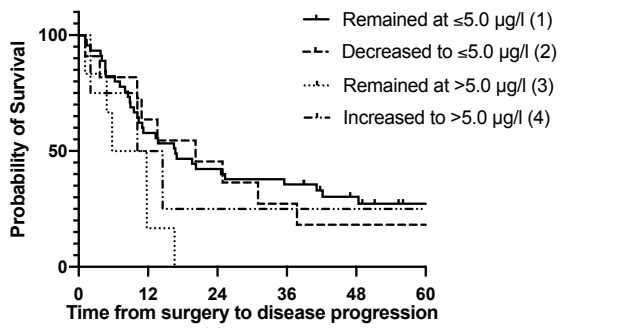
Change in CEA during preoperative treatment, DSS



Patients at risk							median survival time (95% CI)
1	45	41	35	26	16	8	42 months (31-53 months)
2	11	9	7	6	3	3	34 months (9-58 months)
3	6	6	3	1	1	1	16 months (13-19 months)
4	4	4	2	2	2	2	15 months (2-27 months)

p=0.017

Change in CEA during preoperative treatment, DFS



Patients at risk							median survival time (95% CI)
1	45	27	20	17	11	6	17 months (8-25 months)
2	11	8	6	4	3	3	20 months (5-35 months)
3	6	2	1	1	1	1	6 months (0-14 months)
4	4	3	2	2	2	2	10 months (0-22 months)

p=0.113

Supplementary Table 1. Preoperative oncological therapy regimens.

28 x Gemcitabine and cisplatin 3-7 cycles
7 x Gemcitabine 3-8
9 x Folfirinox 5-9 cycles
5 x Gemcitabine and cisplatin 3-6 cycles and gemcitabine chemoradiotherapy 50.4-60 Gy
1 x Gemcitabine and cisplatin 3 cycles, gemcitabine 1 cycle, and gemcitabine chemoradiotherapy 50.4 Gy
4 x Gemcitabine 3-4 cycles and gemcitabine chemoradiotherapy 50.4 Gy
4 x Gemcitabine and cisplatin 3-7 cycles and cabecitabine chemoradiotherapy 50.4 Gy
1 x Gemcitabine chemoradiotherapy 50.4 Gy and gemcitabine and cisplatin 4 cycles
1 x Folfirinox 2 cycles, gemcitabine and cisplatin 2 cycles and gemcitabine chemoradiotherapy 50.4 Gy
3 x Gemcitabine and nab-paclitaxel 3-4 cycles
1 x Gemcitabine and capecitabine 3-5 cycles
2 x Gemcitabine 1-3 cycles and gemcitabine and nab-paclitaxel 2 cycles
1 x Gemcitabine, gemcitabine and cisplatin 7 cycles, and gemcitabine 2 cycles
1 x Folfirinox 3 cycles and gemcitabine and nab-paclitaxel 3 cycles

Supplementary Table 2. Bilirubin, platelets, and leukocytes before and the change in each laboratory test during preoperative oncological therapy. The disease-specific survival (DSS) and disease-free survival (DFS) for each patient group are listed.

	n (%)	DSS, months (95% CI)[1]	p-value	p-value (post hoc)	DFS, months (95% CI)[1]	p-value
Bilirubin before						
≤20 µmol/l	42 (62%)	41 (28-55)	0.284		19 (6-33)	0.041
>20 µmol/l	26 (38%)	35 (28-41)			17 (19-24)	
Bilirubin change						
Remained at ≤20 µmol/l	40 (59%)	37 (25-50)	0.289		15 (1-28)	0.046
Decreased to ≤20 µmol/l	26 (38%)	30 (23-38)			13 (5-21)	
Remained at >20 µmol/l	0	-			-	
Increased to >20 µmol/l	2 (3%)	16 (-)			5 (-)	
Platelets before						
<150 E9/l	2 (3%)	11 (-)	0.048	ref	7 (-)	0.126
150-360 E9/l	58 (85%)	36 (22-49)		0.100**	19 (14-25)	
>360 E9/l	8 (12%)	49 (-)		0.010**	15 (0-59)	
Platelets change*						
Decreased	13 (19%)	25 (17-32)	0.779		11 (5-17)	0.492
Remained the same	48 (71%)	34 (22-45)			15 (10-19)	
Increased	7 (10%)	39 (17-61)			20 (0-39)	
Leukocytes before						
<3.4 E9/l	1 (1%)	-	0.607		-	0.463
3.4-8.2 E9/l	52 (76%)	37 (27-47)			18 (12-24)	
>8.2 E9/l	15 (23%)	35 (26-44)			18 (11-25)	
Leukocytes change*						
Decreased	17 (25%)	24 (3-45)	0.601		11 (5-18)	0.347
Remained the same	46 (68%)	33 (25-41)			14 (8-19)	
Increased	5 (7%)	-			-	

[1]Kaplan-Meier analysis with the Log Rank test. *within the categories outlined before preoperative oncological therapy. Bonferroni correction for multiple comparisons were made in post hoc comparisons by decreasing the decision level to *p<0.017 or **p<0.025.

Supplementary Table 3. Median values before preoperative oncological therapy and changes in laboratory tests during preoperative treatment.

	Median before (IQR)	**Median change (IQR)**	**Mean change (±SD)**	**Range in units**
CA19-9	298 (53-1816)	109 (13 – 890) (decrease)	2349 (71 110)	Maximum increase 5 456 Maximum decrease 41 786
CEA	2.9 (1.7-5.3)	0.3 (-0.2 – 1.6) (decrease)	1.0 (3.6)	Maximum increase 7.1 Maximum decrease 15.8
Albumin	37.0 (32.7-38.5)	2.4 (0.5 – 4.0) (increase)	2.1 (4.2)	Maximum increase 13.9 Maximum decrease 8.7
Leukocytes	6.4 (5.6-8.1)	1.1 (-0.2 – 2.2) (decrease)	1.1 (2.5)	Maximum increase 7.9 Maximum decrease 9.0
Bilirubin	17 (9-28)	8.0 (2 – 19) (decrease)	11 (34.2)	Maximum increase 195 Maximum decrease 148
Platelets	249 (214-306)	38 (3-72) (decrease)	22 (88.2)	Maximum increase 329 Maximum decrease 196

IQR=interquartile range, SD=standard deviation. CA19-9 in kU/l, CEA in µg/l, Albumin in g/l, Leukocytes in E9/l, Bilirubin in µmol/l, Platelets in E9/l.

Supplementary Table 4. Pathological tumor characteristics according to the change in CRP and CA19-9.

	CA19-9 decrease			**CRP**			
	<50% (n=14)	50-90% (n=14)	>90% (n=40)	Remained at <3 (n=24)	Decreased to <3 (n=18)	Remained at ≥3 (n=14)	Increased to ≥3 (n=12)
pTN, T0	**0**	**0**	**2 (5%)**	0	2 (11%)	0	0
T1	**3 (21%)**	**2 (14%)**	**10 (25%)**	4 (17%)	5 (28%)	4 (28%)	2 (17%)
T2	**5 (36%)**	**11 (78%)**	**26 (65%)**	17 (71%)	9 (50%)	7 (51%)	9 (75%)
T3	**6 (43%)**	**1 (8%)**	**1 (2.5%)**	2 (8%)	2 (11%)	3 (21%)	1 (8%)
T4	**0**	**0**	**1 (2.5%)**	1 (4%)	0	0	0
N0	**5 (36%)**	**3 (21%)**	**24 (60%)**	13 (54%)	8 (44%)	9 (64%)	2 (16%)
N1	**4 (28%)**	**7 (51%)**	**12 (30%)**	8 (34%)	6 (33%)	4 (28%)	5 (42%)
N2	**5 (36%)**	**4 (28%)**	**4 (10%)**	3 (12%)	4 (23%)	1 (8%)	5 (42%)
Stage, 0	**0**	**0**	**1 (5%)**	0	1 (6%)	0	0
IA	**2 (14%)**	**0**	**4 (10%)**	2 (8%)	1 (6%)	3 (21%)	0
IB	**1 (8%)**	**3 (21%)**	**18 (45%)**	10 (42%)	5 (28%)	5 (36%)	2 (16%)
IIA	**2 (14%)**	**0**	**0**	0	1 (6%)	1 (7.5%)	0
IIB	**4 (28%)**	**7 (51%)**	**12 (30%)**	8 (33%)	6 (33%)	4 (28%)	5 (42%)
III	**5 (36%)**	**4 (28%)**	**5 (12.5%)**	4 (17%)	4 (23%)	1 (7.5%)	5 (42%)
Grade, 1	3 (21%)	1 (8%)	9 (23%)	5 (21%)	1 (6%)	4 (28%)	3 (25%)
2	5 (36%)	10 (71%)	23 (58%)	16 (67%)	10 (56%)	6 (44%)	6 (50%)
3	6 (43%)	3 (21%)	4 (10%)*	3 (12%)	3 (17%)*	4 (28%)	3 (25%)
Tumor size, ≤30mm	**6 (43%)**	**10 (71%)**	**36 (90%)**	18 (75%)	13 (72%)	10 (71%)	9 (75%)
Perivascular invasion	4 (28%)	8 (57%)	10 (25%)	6 (25%)	5 (28%)	5 (36%)	6 (50%)
Perineural invasion	12 (86%)	12 (86%)	25 (63%)	17 (71%)	13 (72%)	9 (64%)	10 (83%)
Vascular resection	8 (57%)	10 (71%)	23 (58%)	13 (54%)	14 (78%)	6 (43%)	8 (67%)
Radical resection	8 (57%)**	11 (78%)	34 (85%)	20 (83%)	14 (78%)	10 (71%)**	9 (75%)

p-values: CA19-9: **T p=0.025, N p=0.014, stage p=0.021**, Gradus p=0.072, **Tumor size p=0.003**, perivascular invasion p=0.524, perineural invasion p=0.066, vascular resection p=0.880, radical resection p=0.091
CRP: T p=0.879, N p=0.101, stage p=0.226, Gradus p=0.799, Tumor size p=1.000, perivascular invasion p=0.163, perineural invasion p=0.718, vascular resection p=0.912, radical resection p=0.594
Linear-by-linear association test. *=4 missing, **=1 missing

Supplementary Table 5. Platinum- and radiation-based preoperative treatment regimens analysed separately in terms of changes in CRP and CA19-9.

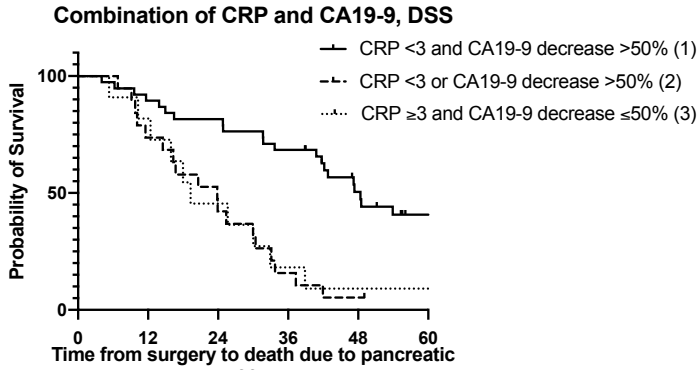
	Sub-analysis 1			**Sub-analysis 2**		
	Platinum-based (n=50)	**Others (n=18)**	**p-value**	**Platinum- and radiation-based (n=54)**	**Others (n=14)**	**p-value**
Pre-oncological therapy CRP						
<3	25 (50%)	12 (67%)	0.276	29 (54%)	8 (57%)	1.000
≥3	25 (50%)	6 (33%)		25 (46%)	6 (43%)	
Post-oncological therapy CRP						
<3	32 (64%)	9 (50%)	0.401	34 (63%)	7 (50%)	0.541
≥3	18 (36%)	9 (50%)		20 (37%)	7 (50%)	
Change in CRP, I						
Stayed at <3	18 (36%)	6 (33%)	0.624	20 (37%)	4 (29%)	0.423
Decreased to <3	15 (30%)	3 (17%)		15 (28%)	3 (21%)	
Increased to ≥3	8 (16%)	6 (33%)		10 (18%)	4 (29%)	
Stayed at ≥3	9 (18%)	3 (17%)		9 (17%)	3 (21%)	
Change in CRP, II						
Stayed at or decreased to <3	32 (64%)	9 (50%)	0.401	34 (63%)	7 (50%)	0.541
Stayed at or increased to ≥3 mg/l	18 (64%)	9 (50%)		20 (37%)	7 (50%)	
Pre-oncological therapy CA19-9						
≤37 kU/l	12 (24%)	4 (22%)	1.000	13 (24%)	3 (21%)	1.000
>37 kU/l	38 (76%)	14 (78%)		41 (76%)	11 (79%)	
Post-oncological therapy CA19-9						
≤37 kU/l	23 (46%)	7 (39%)	0.783	25 (54%)	5 (36%)	0.556
>37 kU/l	27 (54%)	11 (61%)		29 (46%)	9 (64%)	
CA19-9 decrease						
<50%	9 (18%)	5 (28%)	0.126	9 (17%)	5 (36%)	0.062
50-90%	8 (16%)	6 (33%)		10 (18%)	4 (28%)	
>90%	33 (66%)	7 (39%)		35 (65%)	5 (36%)	
CA19-9 change						
Stayed at or decreased to ≤37 kU/l	23 (46%)	7 (39%)	0.783	25 (46%)	5 (36%)	0.556
Stayed at or increased to >37 kU/l	27 (54%)	11 (61%)		29 (54%)	9 (64%)	

Supplementary Table 6. Kaplan-Meier analysis of combination of the change in CRP and CA19-9 during preoperative oncological therapy.

	n	Median DSS, months	Median DFS, months	5-year survival
CRP remained at or decreased to <3 and CA19-9 level decreased >50%	38 (56%)	48 (95% CI 41-56) p-value <0.001 p-value (post hoc) = ref	31 (95%CI 11-51) p-value <0.001 p-value (post hoc) = ref	41%
CRP remained at or decreased to <3 or CA19-9 level decreased >50%	19 (28%)	24 (95% CI 14-34) p-value (post hoc)* <0.001	11 (95% CI 8-14) p-value (post hoc)* = 0.001	5%
CRP remained at or increased to ≥3 and CA19-9 decreased ≤50%	11 (16%)	19 (95% CI 9-30 p-value (post hoc)* = 0.001	9 (95% CI 3-14) p-value (post hoc)* = 0.004	9%
-	-	-	-	-
CRP decreased to <3 and CA19-9 decrease >90%	11 (16%)	Median not reached yet p-value <0.001 p-value (post hoc) = ref	Median not reached yet p-value <0.001 p-value (post hoc) = ref	64%
CRP remained at <3 and CA19-9 decrease >90%	19 (28%)	47 (95% CI 38-57) p-value (post hoc)* = 0.077	20 (95% CI 9-31) p-value (post hoc)* = 0.008	36%
Remaining patients **	38 (56%)	24 (95% CI 16-32) p-value (post hoc)* <0.001	10 (95% CI 8-12) p-value (post hoc)* <0.001	10%

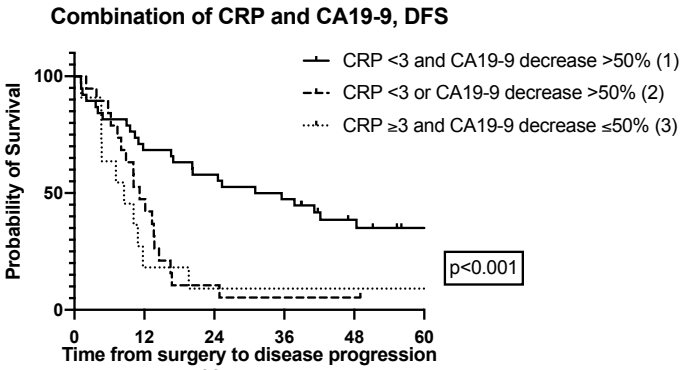
Bonferroni correction for multiple comparisons were made in post hoc comparisons by decreasing the decision level to *p<0.017. Units: CRP mg/l, CA19-9 kU/l. **These patients exhibited similar survival patterns and median survival times, hence, were analysed together

Supplementary Figure 1



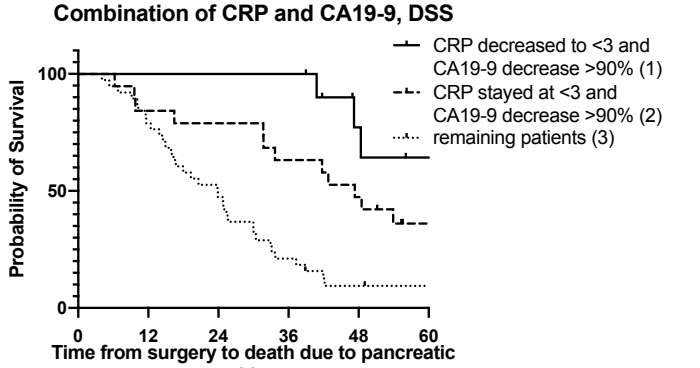
Patients at risk							median survival time (95% CI)
1	38	35	32	27	17	10	48 months (41-56 months)
2	19	15	9	4	2	1	24 months (14-34 months)
3	11	10	6	3	2	2	19 months (9-30 months)

p<0.001



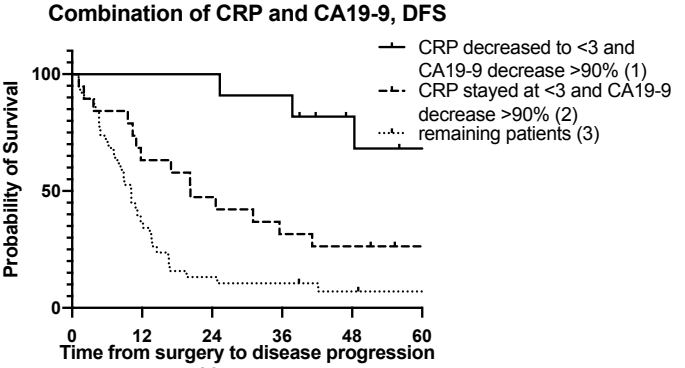
Patients at risk							median survival time (95% CI)
1	38	27	23	19	12	8	31 months (11-51 months)
2	19	10	3	2	2	1	11 months (8-14 months)
3	11	3	2	2	2	2	9 months (3-14 months)

p<0.001



Patients at risk							median survival time (95% CI)
1	11	11	11	11	7	5	not reached yet
2	19	17	16	13	10	5	47 months (38-57 months)
3	38	31	19	9	4	3	24 months (16-32 months)

p<0.001



Patients at risk							median survival time (95% CI)
1	11	11	11	11	7	5	not reached yet
2	19	13	10	7	6	4	20 months (9-31 months)
3	38	15	6	5	3	2	10 months (8-12 months)

p<0.001