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Written Report

Degree Project Medicine Programme Uppsala University (30 hp)

Prognostic value of peritoneal metastasis localization of colorectal origin

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List of abbreviations

CRS – Cytoreductive surgery

PCI – Peritoneal Cancer Index, is calculated by adding the LS-score of the 13 regions (0-12).

LS – Lesion Size Score, the surgeons evaluation of how much cancer is present in a region.

PSDSS – Peritoneal Surface Disease Severity Score, a combination of PCI, scored symptoms and histology.

UU – Uppsala University

UAS – Uppsala Akademiska Hospital

Abstract

Introduction

Peritoneal metastases of colorectal origin is a severe disease manifestation which can affect virtually the entire abdomen. However, little is yet know about the significance of localization of metastases and no study has previously been published describing any possible association to survival time.

Objective

To ascertain if the localization of metastases in the abdomen is of prognostic value in peritoneally metastasized colorectal cancer.

Method

In retrospective cohort study based on data collected from the department of surgical sciences of Uppsala University, we analyzed a possible association between location of metastases to survival time.

Result

41 patients were included in one set including only patients with colon cancer. 73 patients with colon and rectal cancer were also analyzed as another cohort. No significant association between metastasis location and survival time was found.

Conclusion

Based on this preliminary study, there is no significant association between metastasis location and survival time in colon and rectal cancer. Several possible improvements to the study were identified and suggestions made for further studies.

Populärvetenskaplig sammanfattning

Tjock- och ändtarmscancer behandlas primärt med kirurgi, ibland med tillägg av cellgifter och strålning. För att veta vilken behandling eller kombination av behandlingar som passar bäst för varje patient har man utvecklat olika system för att bedöma sjukdomen. Om cancern har spridit sig och bildat dottertumörer i bukhålan, som ibland är fallet, används ofta PCI, peritoneal cancer index för att bedöma sjukdomsutbredning. Skalan bygger på mätning av metastasernas storlek som påvisas i buken. Skalan väger dock alla områden i buken lika och hittills har ingen studie publicerats som beskriver skillnader i prognos baserat på var dessa dottertumörer sitter. I den här studien analyseras ett retrospektivt material från institutionen för kirurgiska vetenskaper vid Uppsala Universitet för att se om lokalisation av dottertumörer kan användas som prognostisk faktor. Det resultat vi fann var att lokalisationen av dottertumörer inte signifikant påverkade prognosen. Vi fann dock att total mängd dottertumörmassa hade en signifikant påverkan på prognosen, vilket tidigare var känt.

Background

Cancer

Cancer is the second most common cause of death in Sweden, being responsible for 26% of all deaths [1]. Cancer is a large group of diseases caused by uncontrolled, increased division of the body's cells. Depending on the tissue origins, cancers can either be solid or non-solid. Non-solid tumors are called that because they do not present themselves as a coherent mass, rather they are dispersed within the body. Leukemia and lymphoma are two examples of non-solid cancers. Solid tumor cancers are masses of dividing cells forming tumor deposits within the body. These cancers can however metastasize, that is they can release daughter tumors via either the blood, the lymphatic system or by movements of peritoneal fluid. Because of the exponential increase in tumor mass due to the constant division of cancer cells, the host will inevitably develop symptoms and finally expire, given the absence of treatment and given enough time to progress.

Colorectal cancer

Colorectal cancer is the third most common type of cancer in Sweden. It represents roughly 7 percent of all types of cancer reported. The average 10-year survival rate for colon cancer was roughly 60 percent as of 2016 [2]. This relatively high survival rate is due to continued advances in diagnosis, surgical and medical treatment that has been achieved during the past decades. In 1980 the average 10-year survival rate for colorectal cancer in Sweden was below 50 percent [3]. With a prevalence of more than 30'000 affected Swedes, a 10 percent increase of 10-year survival can be seen as a great step forward.

Peritoneal carcinomatosis

About 30% of colon cancer patients will develop peritoneal metastases [4]. That is, the cancer will metastasize to the peritoneum. This signifies a significant worsening of the disease, complicating treatment and reducing the chance of cure and long-term survival. Historically this diagnosis was viewed as a terminal condition with palliative care as the only option [5]. In 1979 the first intraperitoneal hyper thermic chemoperfusion, HIPEC (then called TIFS), was performed [6]. Ever since then the treatment has been refined and new studies have paved the way for improvement. In a study from Washington Cancer Institute, the median survival time for peritoneal cancer of colonic origin studied during 1990-2015 was 20,6 and 23,1 months for men and women, respectively [7].

HIPEC

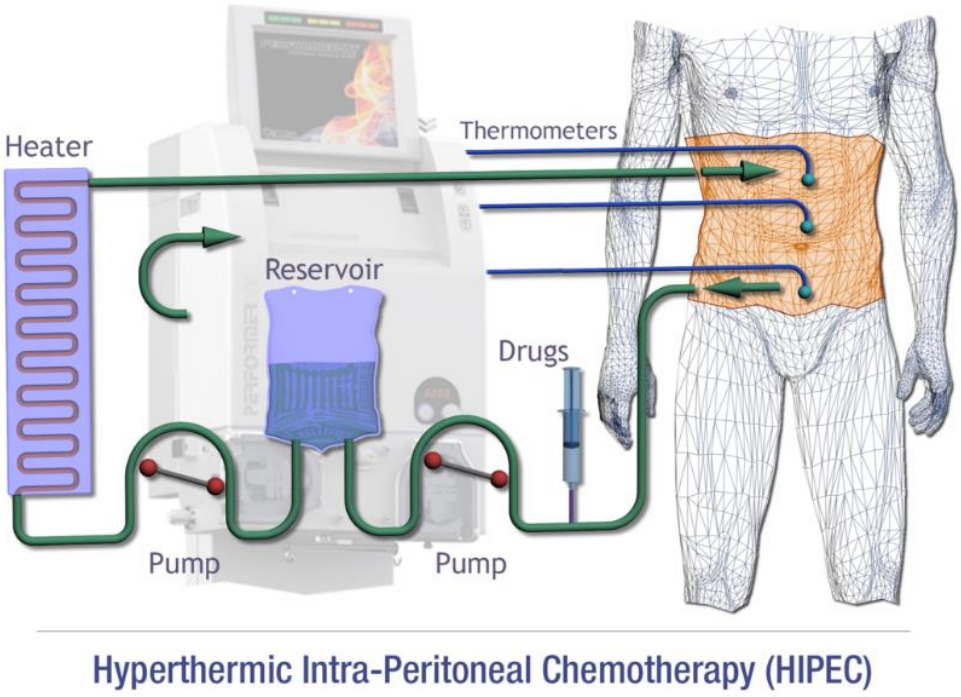


Figure 2: A schematic drawing of a HIPEC setup.

https://upload.wikimedia.org/wikipedia/commons/thumb/0/09/Schema_HIPEC.png/1200px-Schema_HIPEC.png

CRS+HIPEC is a combination of surgery and heated chemotherapy that intends to relieve or cure peritoneal metastases with suitable tumor biology. These operations usually take a long time to preform and they consist of several phases. The initial goal is to access the extent of cancer in the abdomen, this is done though either laparoscopy or by open surgery. The surgeon will then classify the amount of cancer according to a predefined score. The most commonly used is the PCI-score, peritoneal cancer index score (see next paragraph). Once the extent of the cancer, the tumor lesions, have been established the surgical team will make a decision on whether the patent will benefit from the treatment or not. An aggressive cancer with high PCI-score can sometimes be deemed impossible to cure and the side-effects of the proposed surgery and chemotherapy may sometimes outweigh any potential benefit. Tumors that are located in areas where they are impossible to remove, for example due to being connected to large blood vessels or growing in hard-to-reach areas might also be a reason to halt the procedure since incomplete surgical removal of tumor mass will render the treatment ineffective. If the treatment is decided to be continued, the next step is to surgically remove all macroscopic tumor lesions. This can involve the removal of parts of, or entire organs.

Once the surgery is finished the abdomen is perfused with chemotherapy agents which are heated to 41-42 C. The heat is believed to increase the effect of the chemotherapy and improve drug uptake. Since the abdomen is to be treated and chemotherapy is administered directly into the abdomen, the concentration and thereby the effect can be heightened, compared to intravenous chemotherapy [8, 9].

PCI

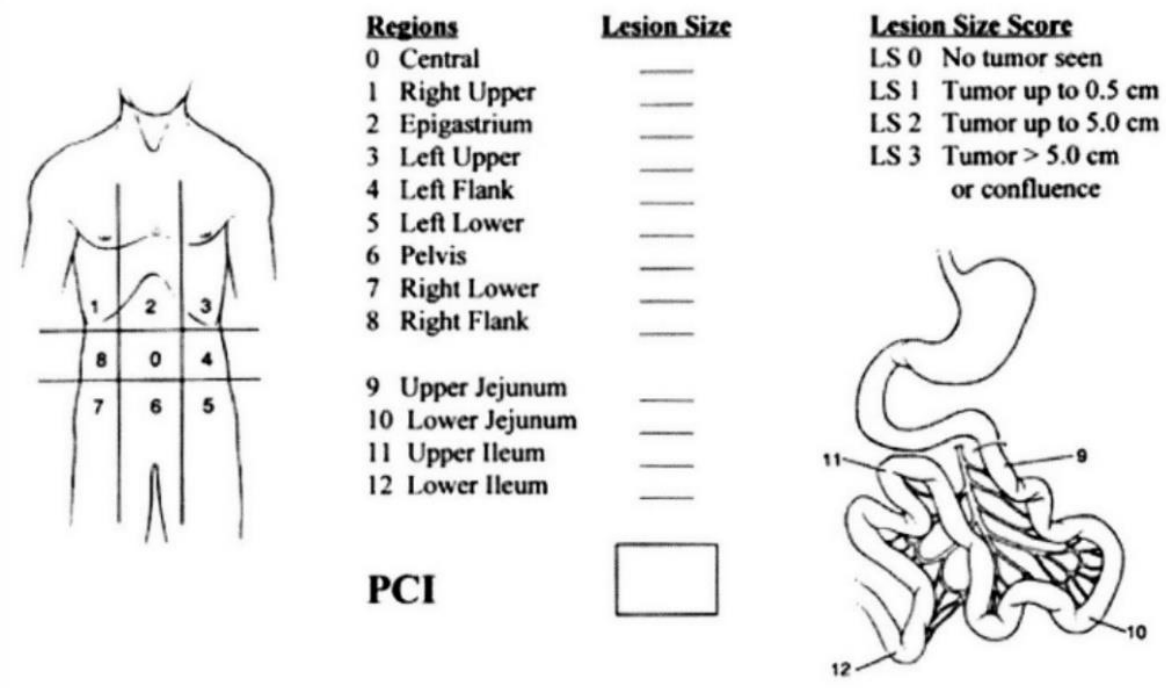


Figure 3: PCI table used to fill out the score during or after surgery.

http://www.hipec.com/wp-content/uploads/2014/07/PCI-e1422275096101.jpg

In order to compare and stratify patients with peritoneal cancer, several indexes and scoring systems have been invented. Today one of the most widespread and used index is the Peritoneal Cancer Index (PCI). PCI is a score ranging from 0 to a maximum of 39. The score is calculated by adding up Lesion Size Score (LS) from 13 different regions in the abdomen. LS is defined by tumor size LS 0 representing no tumor in the region, LS 1 a tumor <0,5cm, LS 2 a tumor 0,5<5 cm, LS 3 a tumor >5cm or a confluence of tumors [10]. (figure 3) PCI was invented in 1999 [11] and is generally considered a good indicator of prognosis, but since it involved the entire abdomen it serves as a relatively imprecise indicator.

Previous Studies

Some suggestions with different amount of bearing and practical use have been proposed as a refined index or score. Peritoneal surface disease severity score (PSDSS) is combining PCI,

patient symptoms and histology to stage the disease in a severity grading from 1-4 [12]. Other studies have been focusing on the localization of tumor burden in the abdomen, several studies have found that primary tumor localization in the right side of the colon is an independent negative predictor [13,14]. A large American study from 2019 found that patients with right sided tumors were more likely to be older, male, have higher PCI and more likely to have a perforated tumor in addition to validating that right-sided localization of the primary tumor is in itself a negative predictor [13].

This study

There have not yet been any articles describing the importance of distribution of PCI/LS within the abdomen in colon cancer peritoneal metastases. Therefore the exact role of tumor localization within the abdomen has not been established. This study aims to shed light on whether or not the distribution of PCI can be used as a prognostic factor.

Method

Design

This study is designed as a retrospective cohort study. All data for the study was obtained through the department of surgical sciences of Uppsala University. Data was processed using Excel and Statistica. The purpose of the study was to identify any prognostic differences in peritoneal cancer of colorectal origin dependent on differences in tumor burden in the lateral and cranio-caudal regions of the abdomen.

Initial research

Information about the research field was collected primarily through other published articles. These were obtained before and during the time for this study through PubMed and Google Scholar. Search terms included *colon cancer, survival, metastasis, prognosis, colorectal cancer, cytoreduction, peritonectomy, hipec, hyperthermic intraperitoneal chemotherapy.* The search terms were used in different combinations in order to improve the search results and find more articles. In addition to this, the website hipec.com was used for initial research.

Data collection

Anonymized datasets were collected for use in the study through the department of surgical sciences of Uppsala university (UU). Patients that had undergone surgery for peritoneal cancer between 2009-08 and 2017-12 at Uppsala Akademiska Hospital (UAS) were included. Data was collected from handwritten reports that the surgeon had filled out postoperatively as well as from the department's datasets regarding patient outcome. All patient identifiers had been removed and replaced with an arbitrary number, only linking the postoperative reports to the outcome datasets. Unfortunately, considerably less PCI-reports from prior surgery were available than was initially expected.

Study population and Inclusion criteria

This study was designed to meet the recommendations from Uppsala University regarding data protection. Because of this all data had been anonymized before the analysis.

For inclusion in the study the data had to include all variables needed for data processing and analysis. Diagnosis, date of surgery, survival, survival days, PCI-score and LS-score distribution were all obligatory items for dataset inclusion, see figure 4.

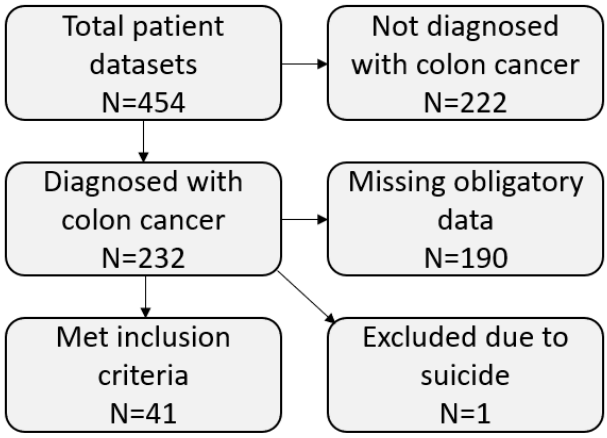


Figure 4: A flowchart of patient inclusion.

Statistical analysis

Statistical significance was defined as $p \leq 0{,}05$

Four groups were constructed based on tumor localization, see figure 5.

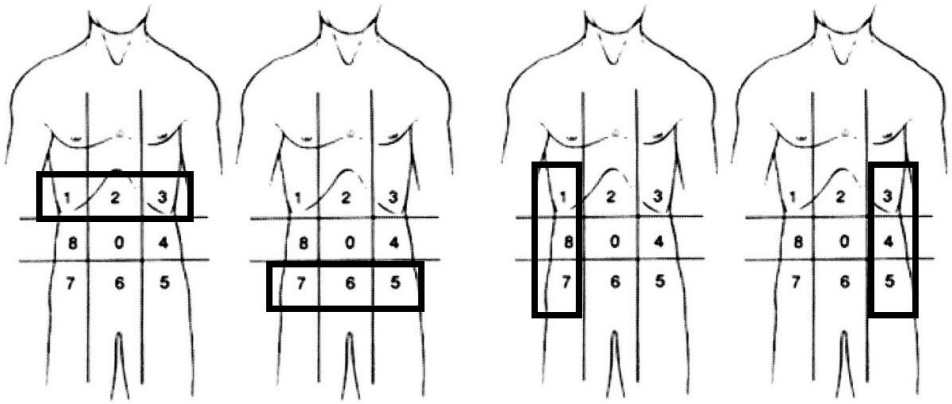


Figure 5: Image representation of the studied regions.

http://www.hipec.com/wp-content/uploads/2014/07/PCI-e1422275096101.jpg

1. Tumor burden in any of locations 1, 2, 3 equal to or in excess of an LS-score of 1 was compared regarding survival time to all patients with no tumor burden in the area.
2. Tumor burden in any of locations 7, 6, 5 equal to or in excess of an LS-score of 1 was compared regarding survival time to all patients with no tumor burden in the area.
3. Tumor burden in any of locations 1, 8, 7 equal to or in excess of an LS-score of 1 was compared regarding survival time to all patients with no tumor burden in the area.
4. Tumor burden in any of locations 3, 4, 5 equal to or in excess of an LS-score of 1 was compared regarding survival time to all patients with no tumor burden in the area.

All results were visualized using Kaplan-Meier curves and differences between the curves assessed using Log-rank tests. The PCI-score for the two groups in each four sets of tests were compared using Mann-Whitney U-tests. This was done to visualize discrepancies regarding PCI-score between the two groups.

A PCI-scatterplot was constructed from all available diseased patients with peritoneal metastasized colon cancer. This was done in order to validate the datasets - a shorter survival time should be seen with an increase in PCI-score. Note that this was done using more datasets than the other statistics due to it only requiring PCI-score and survival status, thus allowing more incomplete datasets to be included.

Ethical Approval

Since no identifiable data was accessible to the student, no ethical approval was necessary for this study.

Additional Analysis

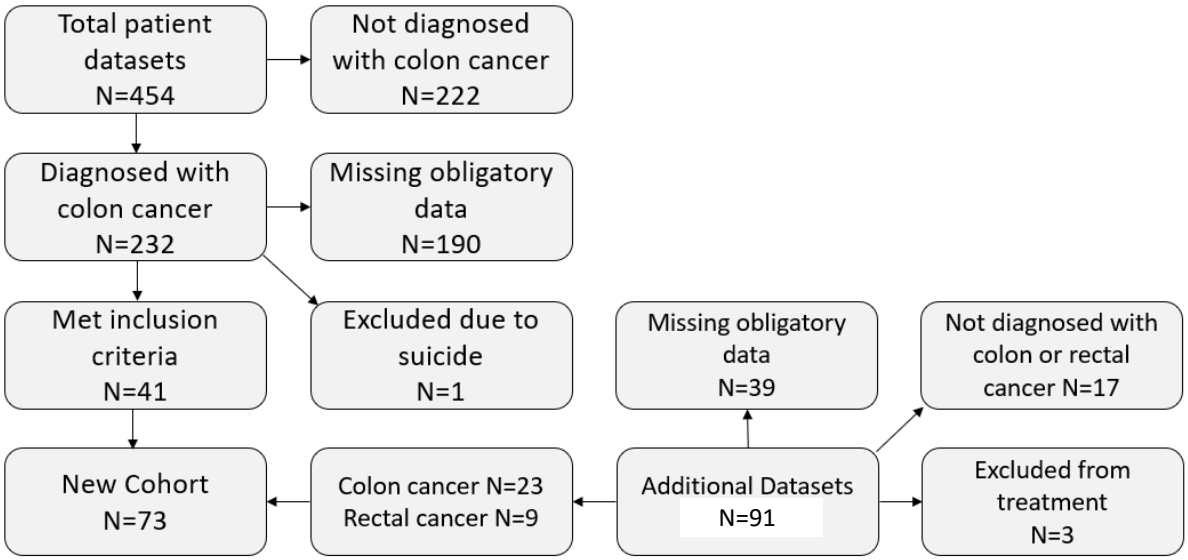


Figure 6: A flowchart of patient inclusion.

In an effort to improve the power of the study and in order to eliminate the confounding effect of higher PCI in all groups of LS-score of $\geq$1, improvements were carried out at the later stages of the study. Patients with rectal cancer were included, as well as additional datasets of patients with colon cancer as well as rectal cancer. This resulted in an additional 32 datasets being included, increasing the number of included patients to 73.

Kaplan-Meier and Log-Rank tests were carried out for this new cohort in the same manner as described in ‘’Statistical Analysis’’.

The large increase in the number of included patient datasets enabled additional statistics to be carried out with higher reliability. A Cox Regression analysis was run for each group and sub-group (PCI 0-12) in order to quantify the hazard ratio and power for both increased PCI as well as LS-score $\geq$1 in the respective groups.

Result

Worsened prognosis in the terms of lessened survival time for patients with PCI >1 in the respective regions was demonstrated for all abdominal regions. None of the results met the required p-value of 0,95 and hence none of the results were statistically significant. PCI-score was higher for group 1 in all sets.

Result PCI Region 1-3

Group 1 with a PCI-score in region 1,2,3 of $\geq$1 consisted of 24 patients. Group 0, with a PCI-score in region 1,2,3 of 0 in total consisted of 17 patients. Lessened survival time was demonstrated for group 1 with a log-rank p-value of 0,11.(figure 7) Mean PCI in group 0 was 6,76 and mean PCI in group 1 was 19,08.(figure 8)

Result PCI Region 5-7

Group 1 with a PCI-score in region 5,6,7 of $\geq$1 consisted of 36 patients. Group 0, with a PCI-score in region 5,6,7 of 0 in total consisted of 5 patients. Lessened survival time was demonstrated for group 1 with a log-rank p-value of 0,48.(figure 9) Mean PCI in group 0 was 7,40 and mean PCI in group 1 was 14,89.(figure 10)

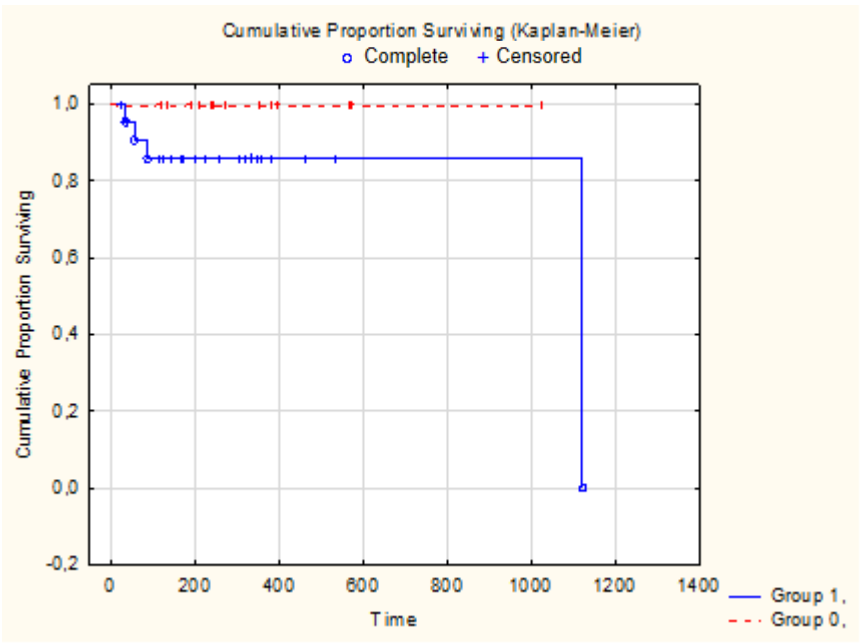
Result PCI Region 1,7-8

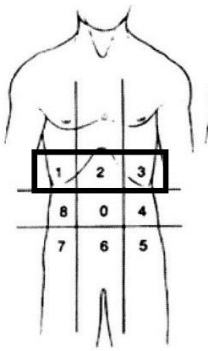
Group 1 with a PCI-score in region 1,7,8 of $\geq$1 consisted of 33 patients. Group 0, with a PCI-score in region 1,7,8 of 0 in total consisted of 8 patients. Lessened survival time was demonstrated for group 1 with a log-rank p-value of 0,41.(figure 11) Mean PCI in group 0 was 6,50 and mean PCI in group 1 was 15,79.(figure 12)

Result PCI Region 3-5

Group 1 with a PCI-score in region 3,4,5 of $\geq$1 consisted of 27 patients. Group 0, with a PCI-score in region 3,4,5 of 0 in total consisted of 14 patients. Lessened survival time was demonstrated for group 1 with a log-rank p-value of 0,17.(figure 13) Mean PCI in group 0 was 6,43 and mean PCI in group 1 was 17,89.(figure 14)

Graphs and Tables PCI Region 1-3





Total number of valid observations: 41
uncensored: 4 (9,76%) censored: 37 (90,24%)
Valid observations: Group 1: 24 Group 0: 17
Uncensored: 4 (16,67%) 0 (0,00%)
Censored: 20 (83,33%) 17 (100,00%)
Log-Rank Test: p = ,10857

Figure 7: Kaplan-Meier Chart and Log-Rank results from region 1-3

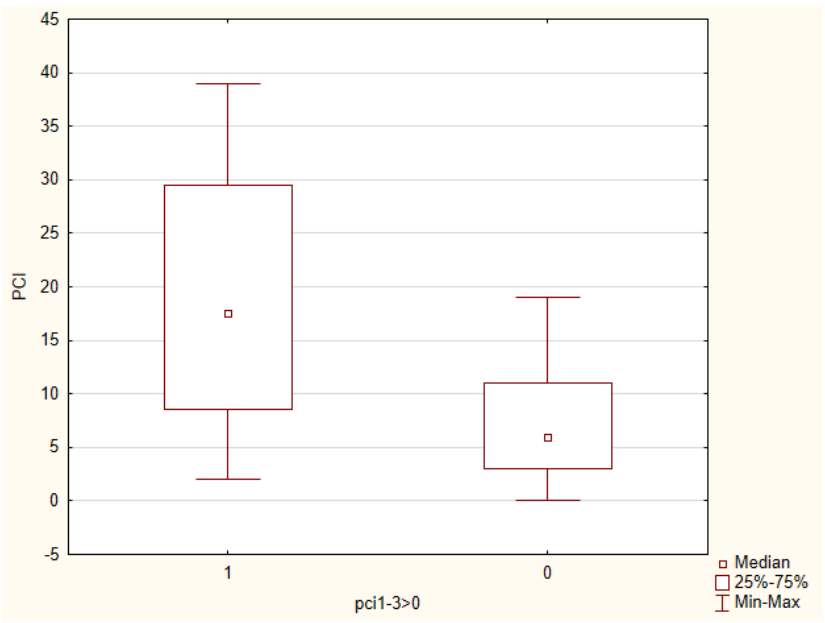
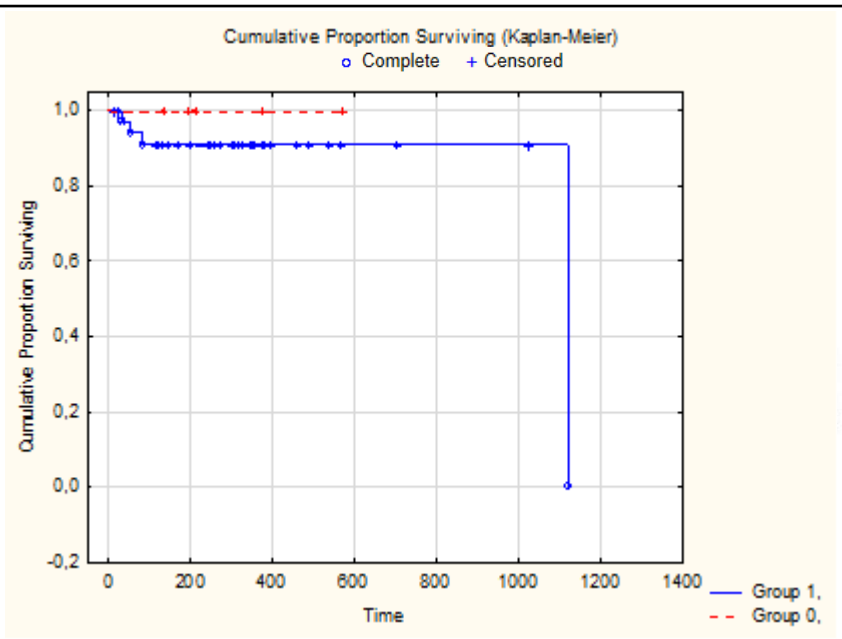
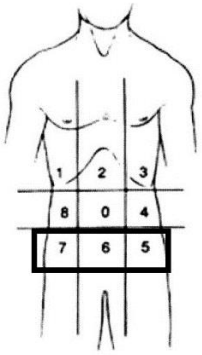


Figure 8: Boxplot of Mann-Whitney U describing the PCI scores of group 1 and 0 respectively in region 1-3

Graphs and Tables PCI Region 5-7





Total number of valid observations: 41
uncensored: 4 (9,76%) censored: 37 (90,24%)
Valid observations: Group 1: 36 Group 0: 5
Uncensored: 4 (11,11%) 0 (0,00%)
Censored: 32 (88,89%) 5 (100,00%)
Log-Rank Test: p = ,47736

Figure 9: Kaplan-Meier Chart and Log-Rank results from region 5-7

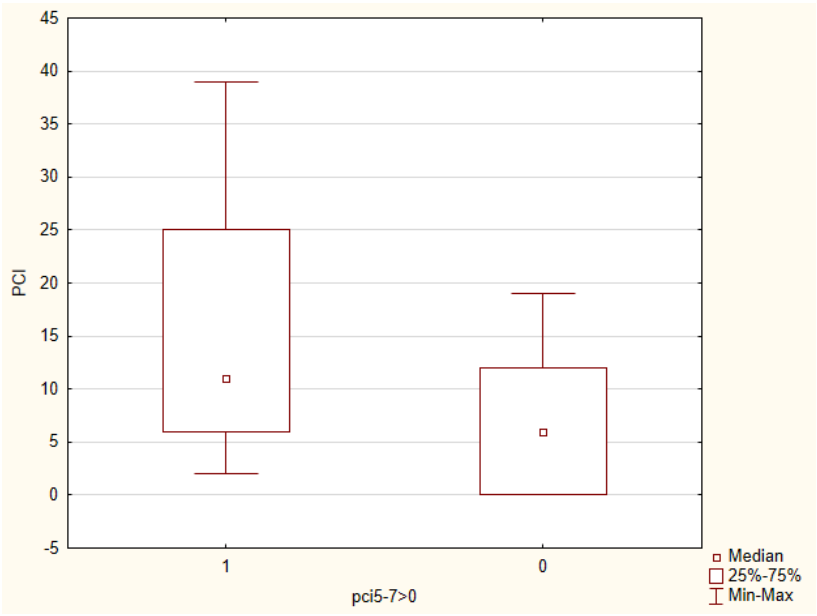
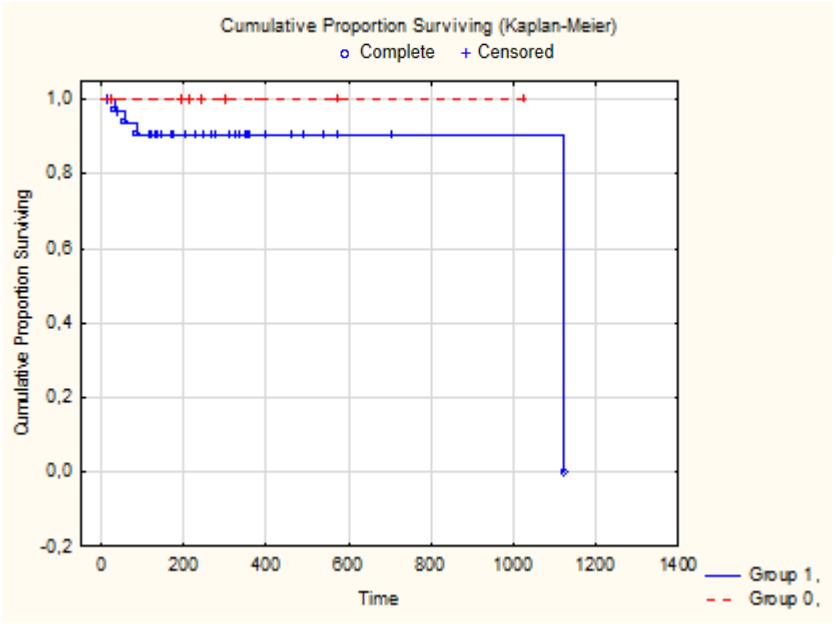
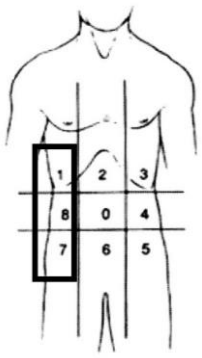


Figure 10: Boxplot of Mann-Whitney U describing the PCI scores of group 1 and 0 respectively in region 5-7

Graphs and Tables PCI Region 1,7-8





Total number of valid observations: 41
uncensored: 4 (9,76%) censored: 37 (90,24%)
Valid observations: Group 1: 33 Group 0: 8
Uncensored: 4 (12,12%) 0 (0,00%)
Censored: 29 (87,88%) 8 (100,00%)
Log-Rank Test: p = ,41141

Figure 11: Kaplan-Meier Chart and Log-Rank results from region 1,7-8

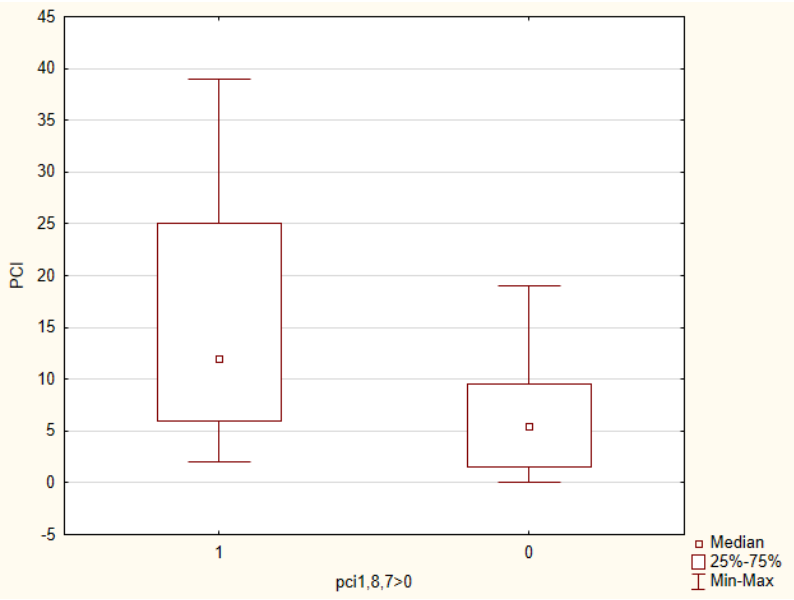
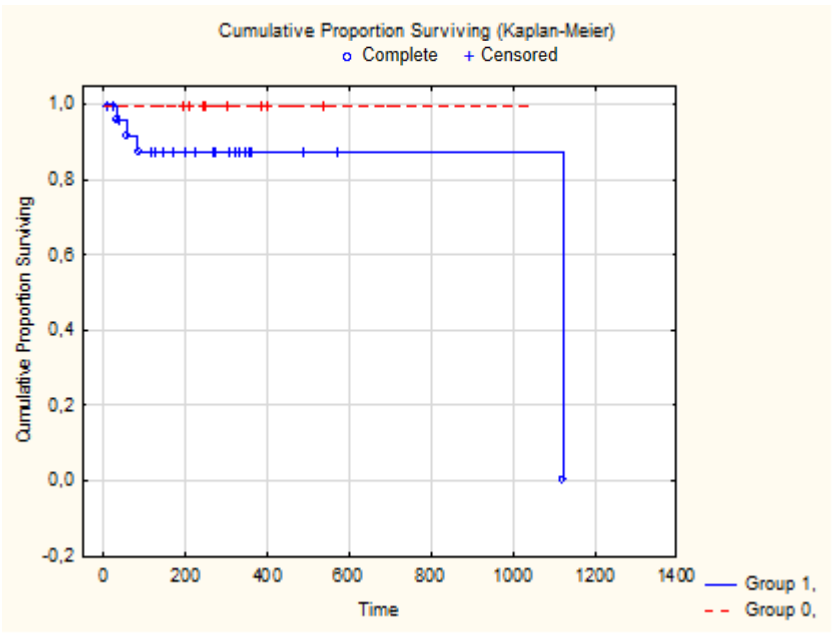
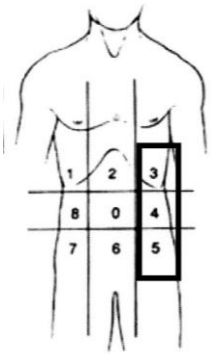


Figure 12: Boxplot of Mann-Whitney U describing the PCI scores of group 1 and 0 respectively in region 1,7-8

Graphs and Tables PCI Region 3-5





Total number of valid observations: 41
uncensored: 4 (9,76%) censored: 37 (90,24%)
Valid observations: Group 1: 27 Group 0: 14
Uncensored: 4 (14,81%) 0 (0,00%)
Censored: 23 (85,19%) 14 (100,00%)
Log-Rank Test: p = ,16977

Figure 13: Kaplan-Meier Chart and Log-Rank results from region 3-5

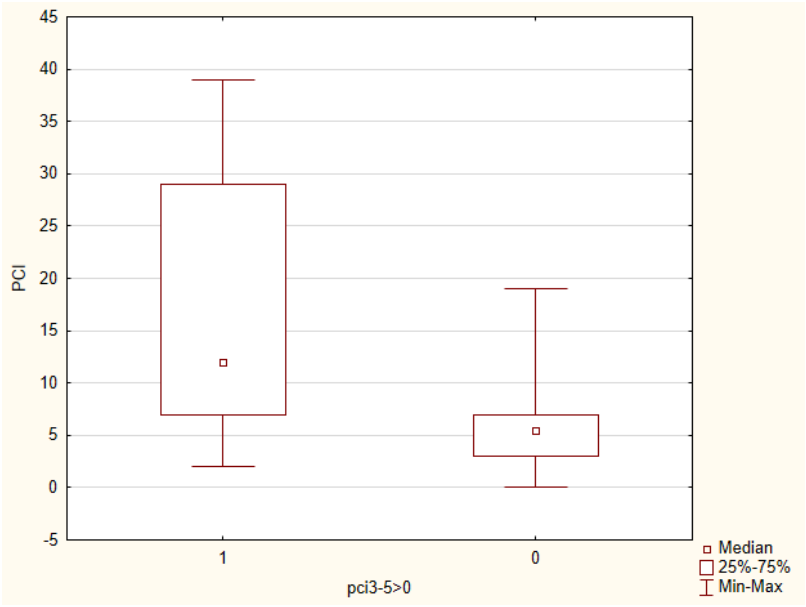


Figure 14: Boxplot of Mann-Whitney U describing the PCI scores of group 1 and 0 respectively in region 1,7-8

Scatterplot of all non-Surviving Patients

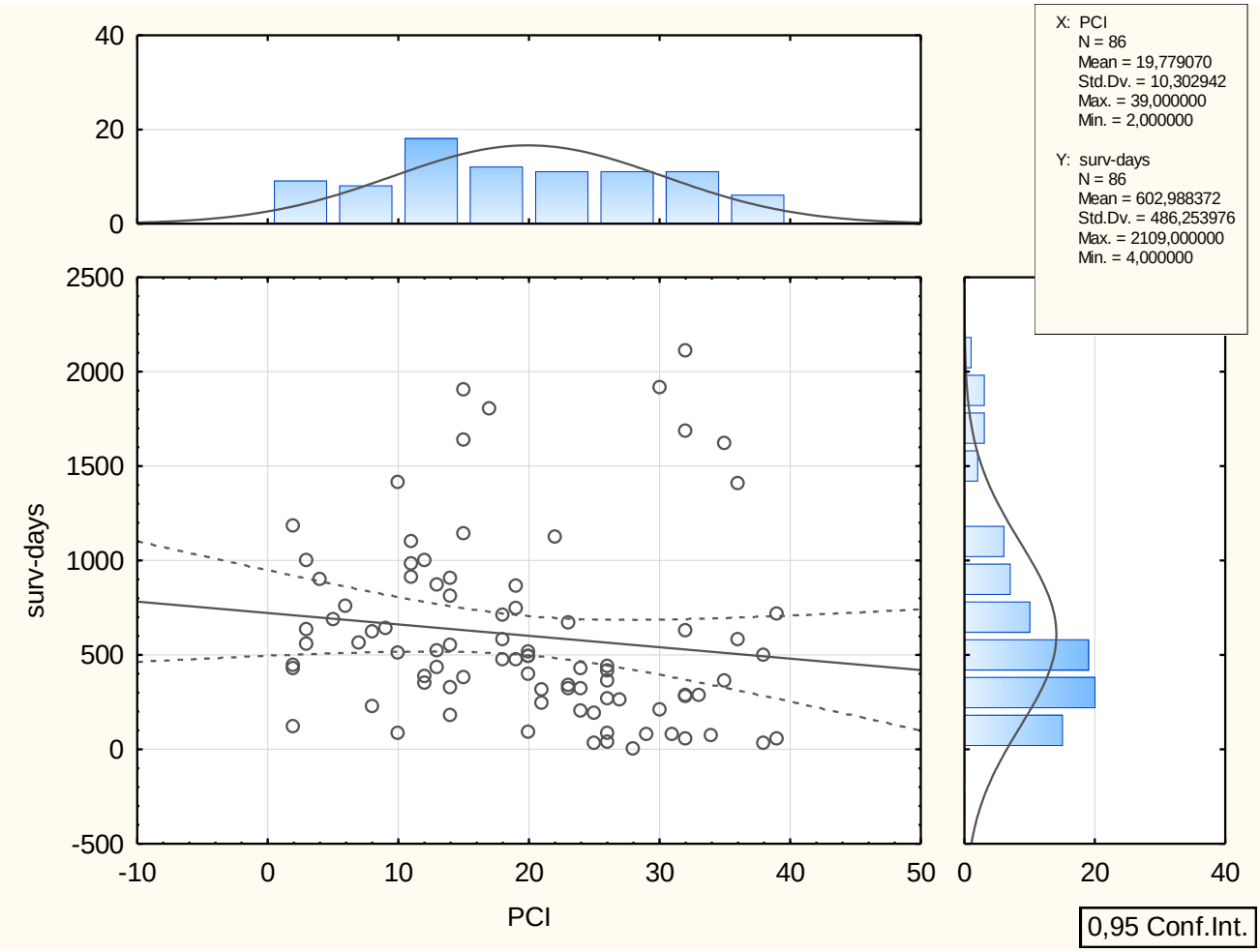


Figure 15: A scatterplot describing survival time in all diseased patients from the obtained datasets

This scatterplot shows the survival time for all deceased patients. Since PCI-distribution/LS-score was not necessary for the creation of this graph, n=86 and not 41. The scatterplot indicate an association between PCI level and overall survival at a level of p>0,05 as indicated by the dotted lines.

Additional Analysis – Kaplan Meier, Log-Rank - Overview

Worsened prognosis in the terms of lessened survival time for patients with PCI $\geq$1 in the respective regions was demonstrated for all test sets. None of the results met the required p-value of 0,05 and hence none of the results were statistically significant. PCI-score was higher for group 1 in all sets.

Additional Analysis – Result PCI Region 1-3

Group 1 with a PCI-score in region 1,2,3 of $\geq$1 consisted of 47 patients. Group 0, with a PCI-score in region 1,2,3 of 0 in total consisted of 26 patients. Lessened survival time was demonstrated for group 1 with a log-rank p-value of 0,56.(figure 16) Mean PCI was lower in group 0 compared to group 1.(figure 17)

Additional Analysis – Result PCI Region 5-7

Group 1 with a PCI-score in region 5,6,7 of $\geq$1 consisted of 62 patients. Group 0, with a PCI-score in region 5,6,7 of 0 in total consisted of 11 patients. Lessened survival time was demonstrated for group 1 with a log-rank p-value of 0,31.(figure 18) Mean PCI was lower in group 0 compared to group 1.(figure 19)

Additional Analysis – Result PCI Region 1,7-8

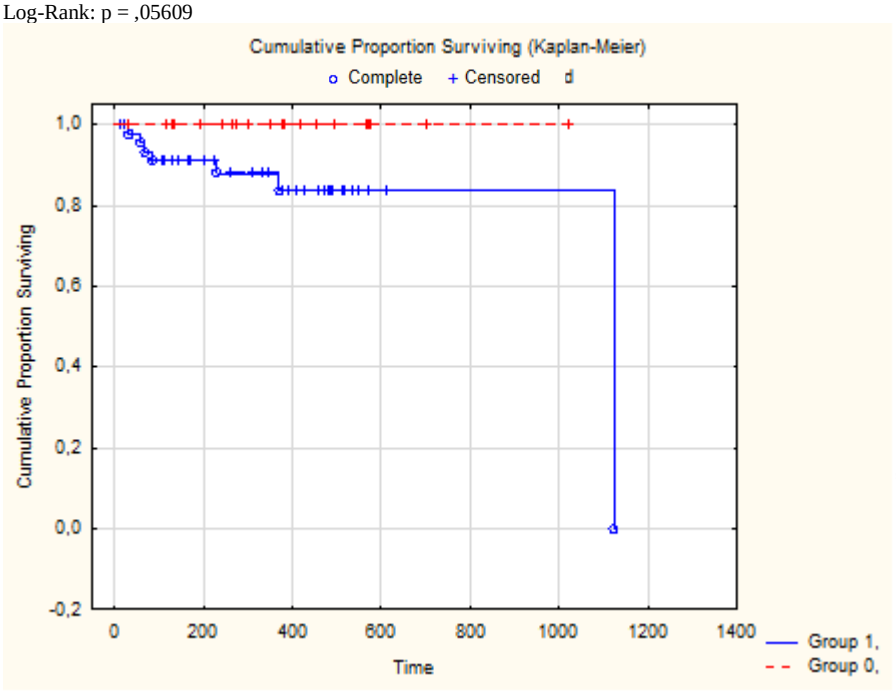
Group 1 with a PCI-score in region 1,7,8 of $\geq$1 consisted of 57 patients. Group 0, with a PCI-score in region 1,7,8 of 0 in total consisted of 16 patients. Lessened survival time was demonstrated for group 1 with a log-rank p-value of 0,21.(figure 20) Mean PCI was lower in group 0 compared to group 1.(figure 21)

Additional Analysis – Result PCI Region 3-5

Group 1 with a PCI-score in region 3,4,5 of $\geq$1 consisted of 51 patients. Group 0, with a PCI-score in region 3,4,5 of 0 in total consisted of 16 patients. Lessened survival time was demonstrated for group 1 with a log-rank p-value of 0,21.(figure 22) Mean PCI was lower in group 0 compared to group 1.(figure 23)

Additional Analysis – Kaplan Meier, Log-Rank – Region 1-3

Total number of valid observations: 73
uncensored: 7 (9,59%) censored: 66 (90,41%)
Valid observations: Group 1: 47 Group 0: 26
Uncensored: 7 (14,89%) 0 (0,00%)
Censored: 40 (85,11%) 26 (100,00%)
Log-Rank: p = ,05609



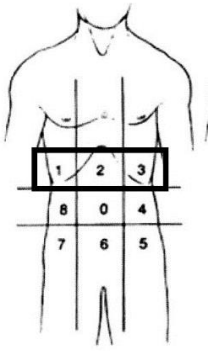


Figure 16: Kaplan-Meier Chart and Log-Rank results from region 1-3

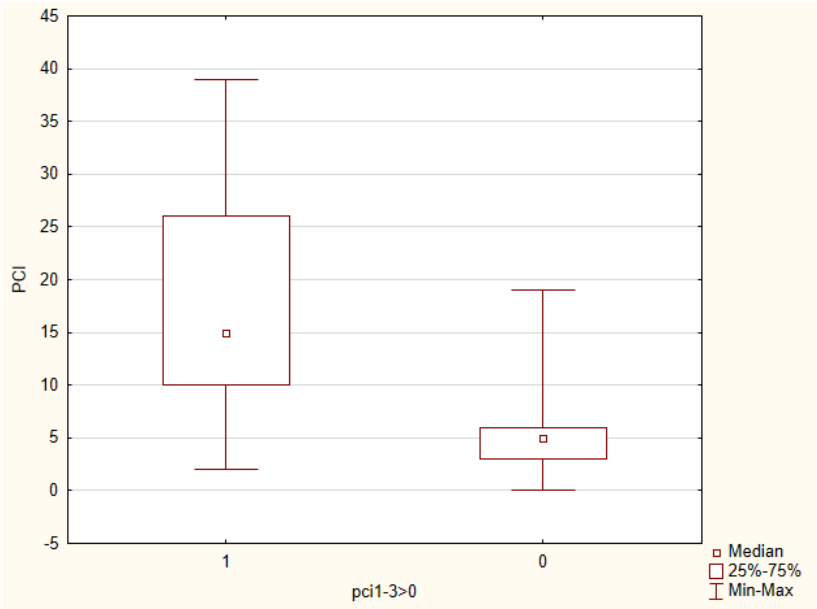
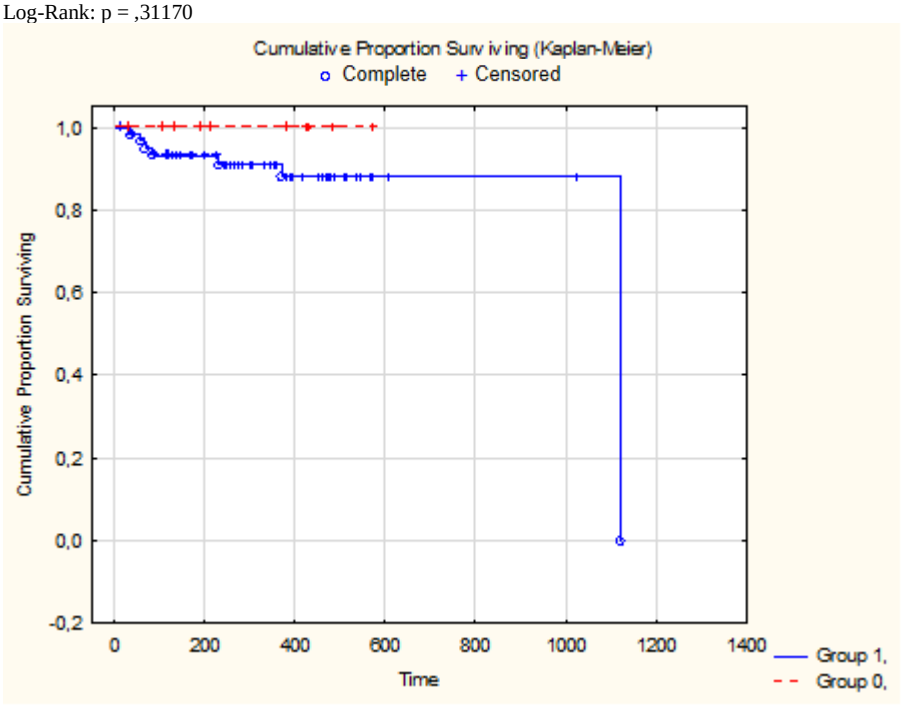


Figure 17: Boxplot of Mann-Whitney U describing the PCI scores of group 1 and 0 respectively in region 1-3

Additional Analysis – Kaplan Meier, Log-Rank - Region 5-7

Total number of valid observations: 73
uncensored: 7 (9,59%) censored: 66 (90,41%)
Valid observations: Group 1: 62 Group 0: 11
Uncensored: 7 (11,29%) 0 (0,00%)
Censored: 55 (88,71%) 11 (100,00%)
Log-Rank: p = ,31170



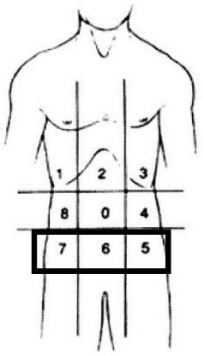


Figure 18: Kaplan-Meier Chart and Log-Rank results from region 5-7

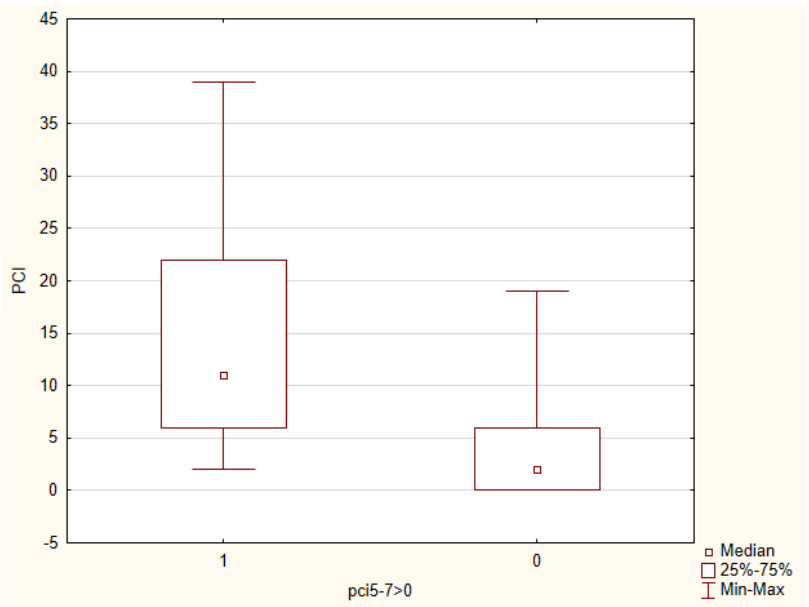
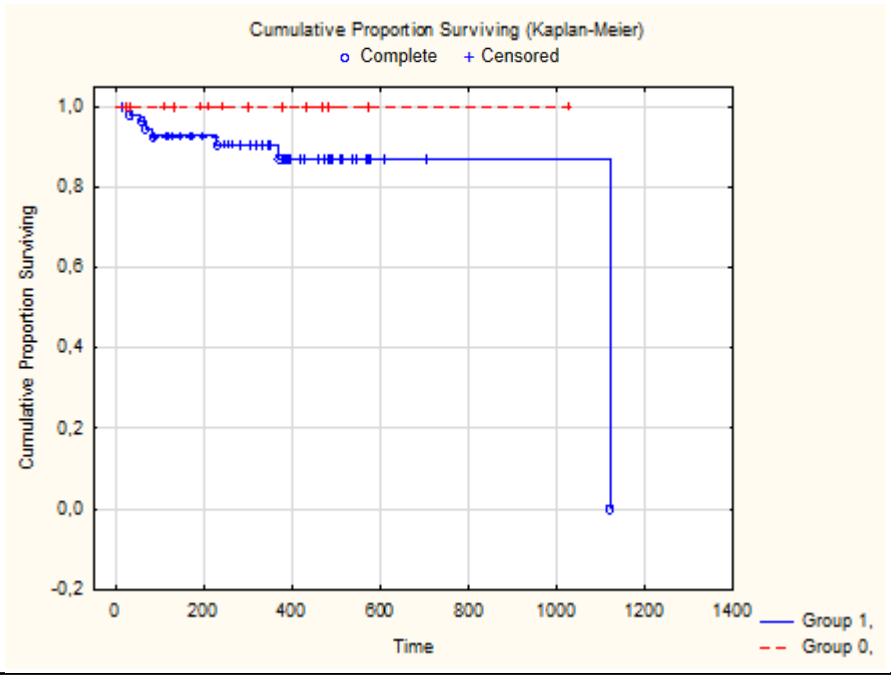


Figure 19: Boxplot of Mann-Whitney U describing the PCI scores of group 1 and 0 respectively in region 5-7

Additional Analysis – Kaplan Meier, Log-Rank - Region 1,8,7

Total number of valid observations: 73
uncensored: 7 (9,59%) censored: 66 (90,41%)
Valid observations: Group 1: 57 Group 0: 16
Uncensored: 7 (12,28%) 0 (0,00%)
Censored: 50 (87,72%) 16 (100,00%)
Log-Rank: p = ,21285



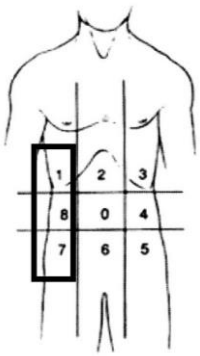


Figure 20: Kaplan-Meier Chart and Log-Rank results from region 1,8,7

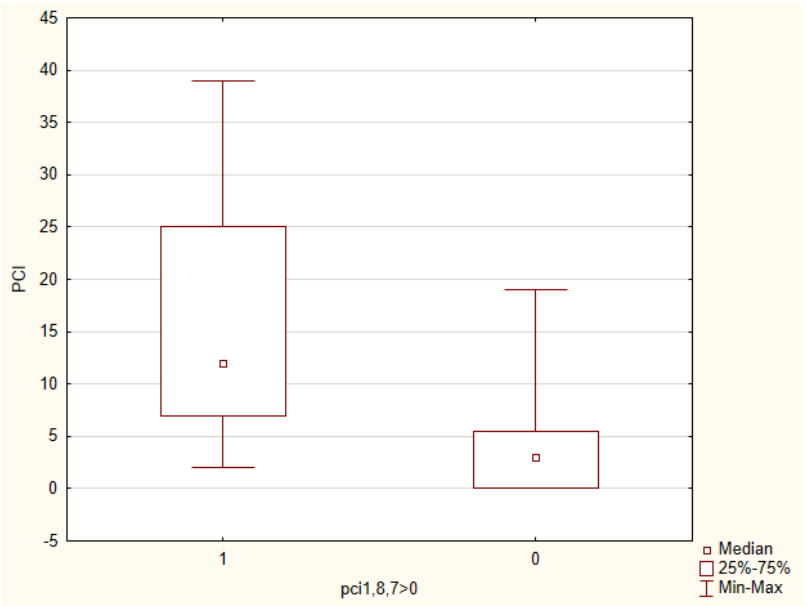
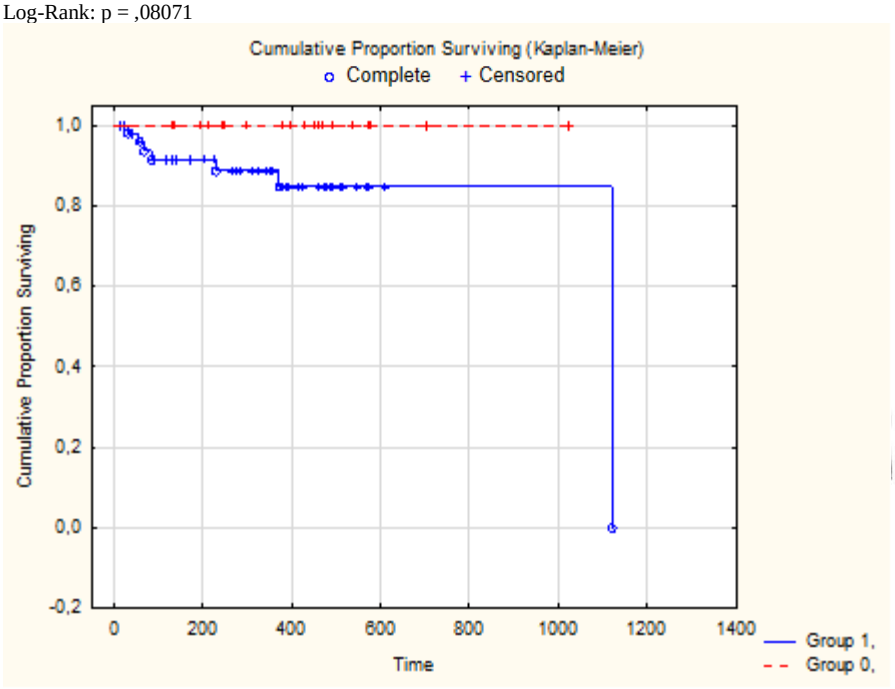


Figure 21: Boxplot of Mann-Whitney U describing the PCI scores of group 1 and 0 respectively in region 1,8,7

Additional Analysis – Kaplan Meier, Log-Rank - Region 3-5

Total number of valid observations: 73
uncensored: 7 (9,59%) censored: 66 (90,41%)
Valid observations: Group 1: 51 Group 0: 22
Uncensored: 7 (13,73%) 0 (0,00%)
Censored: 44 (86,27%) 22 (100,00%)
Log-Rank: p = ,08071



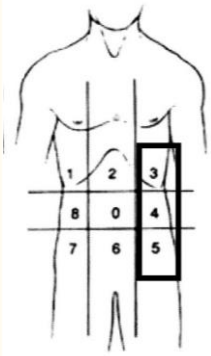


Figure 22: Kaplan-Meier Chart and Log-Rank results from region 3-5

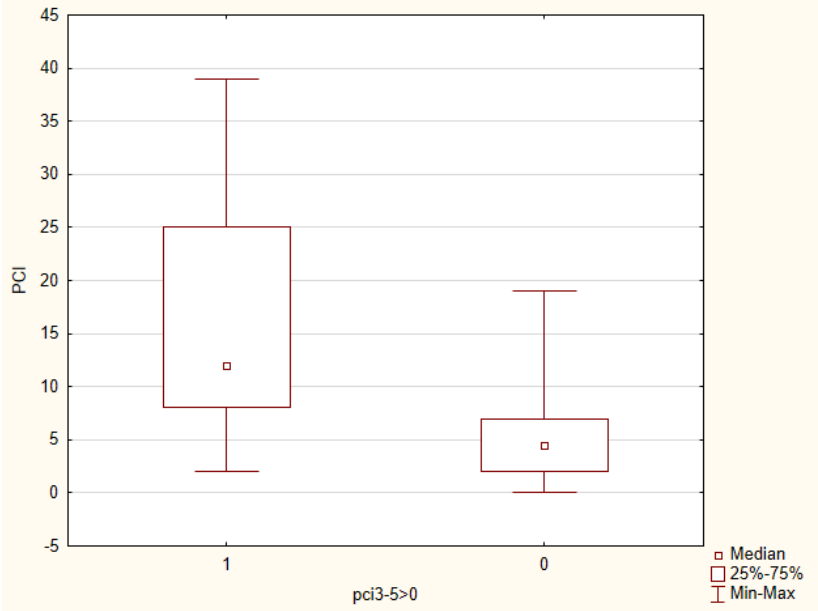


Figure 23: Boxplot of Mann-Whitney U describing the PCI scores of group 1 and 0 respectively in region 3-5

Additional Analysis – Cox Regression – All regions

A significant increase in hazard was demonstrated for all regions for total PCI. No significant increase was found for any region or subregion (PCI 0-12) for tumor burden >0.

Table 1: Cox Regression Analysis, Parameter estimates region 1-3

	p-value	95% Lower Cl	95% Upper CL	Hazard ratio	95% Hazard Ratio Lower CL	98% Hazard Ration Upper CL
Total PCI	0,037350	0,01	0,178	1,096134	1,005391	1,195067
PCI 1-3>0	0,995915	-3085,78	3069,704	0,000000	0,000000	

Table 2: Cox Regression Analysis, Parameter estimates region 5-7

	p-value	95% Lower Cl	95% Upper CL	Hazard ratio	95% Hazard Ratio Lower CL	98% Hazard Ration Upper CL
Total PCI	0,009831	0,03	0,189	1,113711	1,026276	1,208594
PCI 5-7>0	0,995767	-2675,91	2661,464	0,000001	0,000000	

Table 3: Cox Regression Analysis, Parameter estimates region 3-5

	p-value	95% Lower Cl	95% Upper CL	Hazard ratio	95% Hazard Ratio Lower CL	98% Hazard Ration Upper CL
Total PCI	0,026307	0,01	0,180	1,100544	1,011349	1,197606
PCI 3-5>0	0,996027	-3148,73	3132,77	0,000000	0,000000	

Table 4: Cox Regression Analysis, Parameter estimates region 1,8,7

	p-value	95% Lower Cl	95% Upper CL	Hazard ratio	95% Hazard Ratio Lower CL	98% Hazard Ration Upper CL
Total PCI	0,013777	0,02	0,187	1,109952	1,021535	1,206022
PCI1,8,7>0	0,995165	-2367,88	2353,279	0,000000	0,000000	

Discussion

Initial Analysis

The purpose of this study was to find out if localization of tumor burden in peritoneally metastasized colon cancer had an effect on the prognosis in terms of overall survival. Previous research has indicated that primary tumor localization is of predictive value. A recent study[13], described how primary tumors located to the right in abdomen was associated with reduced survival time. If a predictive marker such as a certain negative or positive localization of peritoneal metastasis could be clearly identified and quantified in its effect, this could be used to select patients for more individualized treatment.

All sets of Log-Rank tests in this study concluded that survival time was reduced with the occurrence of tumor burden in the studied locals. All sets of Mann-Whitney U-tests showed a higher mean PCI-score associated with the inclusion in group 1 (PCI $x+y+z>0$) as compared to group 0 (PCI $x+y+z=0$).

This study found that tumor burden in all studied localizations was correlated to shorter survival time. This could be interpreted as cohesive study result. However, the fact that tumor burden in all locals lessened survival time should rather be seen as indication of flaws in the study. If the localization of the tumor burden was the main reason of lessened survival time, it could be anticipated that some tumor localization would be more favorable and thus result in longer survival time than the average. The fact that no such result can be seen in this study could point towards some other confounding factor being the reason that the survival time is reduced. The most probable confounding factor would be a higher PCI-score within group 1 than in group 0, which was observed in all sets of tests.

Since this study is composed of such a limited number of patients, it is possible for a small number of outliers to affect the study quite severely. This might be one reason that all p-values obtained were insignificant ($p>0,05$). In addition to this, the small numbers in itself predispose to non-significant results, rendering results harder to interpret. Even if a study such as this one would yield a significant result, it is possible that a large number of patients that qualify to a given 1-group due to tumor localization would inevitably also be valid for other 1-groups. As is the risk that patients with low PCI-score would qualify for several 0-groups. Thus, the analysis would not yield results depending on the tumor localization but rather solely on the severity of tumor burden and random chance. This flaw would not lessen

with an increase in the patient dataset number, however it would be easier to possible to better adapt the analysis used in order to lessen this effect.

Validity of Patient Selection

The scatterplot of all non-surviving patients (figure 15) shows a reduced survival time with higher PCI-score. This is consistent with results from clinical knowledge. Even if there is not a significant difference even between the highest and lowest PCI, this is still somewhat indicative that the patient selection for the study is to some degree representative of the patient spectra in peritoneally metastasized colon cancer.

The large majority of the patient datasets that were collected for this study were incomplete and thus could not be used for the study. (Figure 4) The study would have been bigger and thus more reliable if these could have been included. The removal of large amounts of data from any study should generally be seen as negative for study credibility. Since all but one patient dataset that met the inclusion criteria was used, it is unlikely that patient exclusion would skew the results in any significant way.

Additional possible confounders

Since strict anonymity had to be upheld in this study, the included patients could not be screened or studied for any possible confounders. This is negative for the credibility of the study results. There are many of these possible confounders that could affect this study. Patient age could affect the survival, both since a higher age is associated with a lessened chance of survival [15], as well as that there is a possibility that an older patient would not qualify for specific treatments. Patients could also be suffering other illnesses, possibly affecting survival, as well as choice of treatment. Other malignancies could also be present. Gender, race and BMI are additional examples of possible confounders that were not analyzed in this study. A possible heterogeneity between the groups could severely affect the results. However, eligibility for treatment with cancer reduction surgery and HUPEC include acceptable performance and absence of severe comorbidity.

Possible Study Improvements

The main way to improve this study would be an increase of the number of patient datasets included. A higher number of datasets would increase the power of all results. With a larger patient size other advantages would come as well. It would enable the use of stratified log-rank that could be used to compare local differences in tumor burden in a given PCI-score selection. This would enable the analysis to only compare groups of patients with the same

amount of total tumor burden but with different localization. This would improve the probability that any difference in result between the groups actually is caused by a difference in localization. Since this would involve analyzing many subgroups individually, this study would not benefit from this, but a larger study could benefit tremendously.

If possible, it would be better to include all patients admitted for surgery within a given timespan. This would require that complete datasets would be collected from all patients, this method of patient selection would limit the possible effect of accidental or malicious selective patient selection, something that could not be ruled out in this study due to the selection being carried out before the author gained access to the data.

Another way to improve the reliability of the study would be to grant the author access to the patient's medical history, sex, BMI, treatment, previous and ongoing malignancies and all other applicable data. This would enable the ability to compare groups to each other, as well as to other study populations in order to identify or disprove potential confounders.

Additional Analysis

In order to remedy flaws in the initial study and enable the use of better methods of analysis, being that stratified Log-Rank was no longer an option do to the low number of included datasets, improvements were made. Firstly, additional patient datasets were obtained and added to the study cohort in an additional analysis. In order to enlarge the cohort patients with rectal cancer were included, in addition to some additional colon cancer patients. Secondly, an alternative statistical method, Cox-regression, was used. This resulted in a larger and in many ways better cohort and test. The inclusion of additional datasets improved the main flaw in the study, the small number of included datasets. This however introduced a new possible confounder, being that two different types of cancer patients were included. Rectal cancer with peritoneal metastasis is however known to present itself similarly to colon cancer with peritoneal metastasis. The result from the Kaplan-Meier and Log-Rank test are in line with the first test in this study, suggesting that the larger cohort is similar in composition to the smaller, original one. The Cox-Regression analysis clearly showed a significant association between PCI and survival time. No association was found between tumor burden in any of the analyzed locals and survival time when corrected for the increased PCI, suggesting that tumor location has marginal impact on survival time.

Conclusion

The purpose of this study was to analyze the significance of tumor localization for survival prognosis for patients suffering peritoneally metastasized colon cancer. Some early results in this study alluded to localization having some effect on survival time. However, when adjusted for the increase in PCI seen in all groups with tumor burden, there was no association. No association was found between tumor burden in any of the analyzed locals and survival time when corrected for the increased PCI, suggesting that tumor burden localization has little or no impact on survival time.

Recognitions

Many thanks to professor Wilhelm Graf for overseeing and helping out with this study, making it possible.

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