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PhD THESIS

**THE IMPACT OF COVID-19 PANDEMIC ON THE CLINICAL
AND THERAPEUTIC MANAGEMENT OF COLON CANCER**

A B S T R A C T

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ABSTRACT

Introduction

Colon cancer represents the 3rd most common cancer in male patients and the 2nd most common in female patients. With over 600.000 deaths that occur annually, this clinical entity is slowly becoming a public health problem. Healthcare systems around the world have taken multiple approaches in dealing with this clinical entity, including serious screening programs in order to detect colon tumor at an earlier stage. Despite all efforts, the 5-year survival rate in the European Union varies from 28.5% to 60%, proving there is a need to upgrade the clinical and therapeutic management of patients with colon cancer.

Normally, dealing with patients with colon cancer, requires plenty of medical resources both material and human ones alongside with a close long-term monitoring of the patient. These aspects were massively influenced by the Sars CoV-2 generated pandemic, with an important impact on clinical and therapeutic management of these patients, with outcomes that are still unknown for the moment.

First confirmed case of Covid-19 was reported in December 2019 in Wuhan, China, while on 26th of February 2020, the first case of Sars CoV-2 infection was reported in Romania. Due to a fast development of the pandemic, and the impossibility of coping with the daily high number of infections, in October 2021, worldwide there were reported 240.000.000 infected patients and a total number of 5.000.000 deaths.

The First Surgery Clinic of the Pius Brinzeu Clinical Emergency County Hospital in Timisoara, was responsible for treating 289 patients for colon cancer in 2016-2020 period, with all this patients undergoing classic surgery for treatment.

The aim of this study is to emphasize the impact of Covid-19 pandemic on clinical and therapeutic management of colon cancer of patients who were treated in this clinic. In addition to this, management measures for treating the patients with this clinical entity in critical situations such as this pandemic will be presented.

GENERAL PART

The first part of this PhD thesis was divided in 4 chapters. The first chapter was dedicated to the surgical anatomy presentation of the colon. It includes the colon segments, anatomical relationships and the arterial, venous and lymphatic circulation of these segments.

The main focus of the second chapter was represented by colon cancer. There are data regarding the epidemiology, etiopathogenesis, morphopathology, stadializations as well as diagnosis and prognostic elements regarding this clinical entity.

The 3rd chapter was reserved for the presentation of colon cancer treatment. There are presented types of treatments such as: prophylactic, surgical (with various surgical techniques described), as well as the chemotherapies and radiotherapies applied in this pathology.

The last chapter presents a short description of the Sars CoV-2 virus, its specific clinical manifestations and the pandemic generated by it. The impact of this pandemic on clinical and therapeutic management of colon cancer will be presented in the special part of this PhD thesis.

SPECIAL PART

The aim of this thesis was to emphasize the impact of Covid-19 generated pandemic had on the clinical and therapeutic management of patients with colon cancer. This aspect was evaluated by multiple scientific studies realized in the First Surgery Clinic of the Pius Brinzeu Clinical Emergency County Hospital in Timisoara.

Materials and methods

In order to conceive the studies regarding the elective surgical and emergency surgical treatment for patients with colon cancer, as well as the 90 days postoperative mortality rate, data from 289 patients that have been treated in the First Surgery clinic, were taken into consideration. This study investigated the period 26.02.2020-01.10.2021 and the same period of the years 2016-2017 respectively 2018-2019. The patients have been divided in 2 groups. First group contained the

patients that underwent an elective surgery for colon cancer treatment. Data from 147 patients in this group were collected. The second group contained 142 patients who underwent an emergency surgery for colon cancer treatment. The aim of these studies was to evaluate the consequences of Covid-19 pandemic on colon cancer clinical and therapeutic management without studying the effect of Covid-19 infection on these patients.

There were several inclusion and exclusion criteria created, with the most important being the absence of an active Covid-19 infection or an antecedence infection or an infection in the first 90 postoperative days.

Multiple data were taken into consideration (age, gender, tumor location, type of intervention, duration of surgery, duration of hospital stay, etc), with the processing and interpretation of it being realized. Central tendency parameters as well as dispersion parameters were determined for numerical data, as well as the study of statistically significant differences between the 3 periods. Categorical data were analyzed as well by calculating central and dispersion parameters, frequency tables and percentages. Chi square as well as Anova tests were applied, and there were studies regarding the correlation and association between different variables. A p value lower than 0.05 was considered as statistically significant.

1. A study regarding the effect of the pandemic on management of colon cancer patients

This PhD thesis was conceived during the Covid-19 pandemic. There were several aspects that influenced the activity of First Surgery clinic during this period. These aspects have influenced the management of colon cancer patients.

These modifications that occurred during this period represented the starting point of an extensive study of literature realized in order to assess the impact of this pandemic.

Materials and Methods

In order to carry out this study, an extensive search was conducted, using the three most known databases, PubMed/Medline, Scopus, and Web of Science. The selected time period for the published articles was 2020-2021. The aim was to

identify the relevant articles which presented the consequences of Covid-19 pandemic on elective surgery for colon cancer, as well as the duration of hospital stay and data regarding the 30 days postoperative mortality. After matching the inclusion and exclusion criteria a number of 23 studies were found.

Results

The number of elective surgeries for colon cancer have reduced during the pandemic. In Europe, there was a minimum decrease of 11.26% in Austria, and a maximum decrease of 52.51% in University Hospital of Oxford, UK. The average decrease in European countries was 36.93%.

There was a minimum decrease of 34% and a maximum of 64% regarding the number of elective surgeries in Asia.

In a study carried out in our clinic, during the pandemic it was reported a decrease of 42% compared to the previous period.

The duration of hospital stay was also taken into consideration. This duration was reduced during the pandemic in all studies. In University Hospital of Fudan was reported an increase regarding the hospital stay. Our study also presented a shorter hospital stay during the pandemic.

When it comes to the impact of Covid-19 pandemic on the 30 days postoperative mortality, studies have shown an increase regarding this parameter, even though only a small number of studies approached this subject. It must be mentioned that these rates do not include Covid-19 infected patients.

Conclusions

Although this extensive study has shown the presence of several modifications in the management of colon cancer patients during the pandemic, it also presented some strategies and ideas in order to cope with such critical situations.

Firstly, a prioritization of colon cancer diagnosis via colonoscopy and biopsy is recommended, while patients who underwent neoadjuvant chemotherapy and radiotherapy with a higher stage of disease should be prioritized for surgical treatment.

Secondly, a routine testing is recommended for the clinic's staff, and a decrease in the time spent with the patient. The distribution of medical and auxiliary

personal should be done carefully in order not to influence the activity of the surgery clinic. Moreover there is a clear need of protocols in order to stop the virus spread in the clinic and the surgery room. It is recommended a shorting of the hospital stay, without influencing the outcome of the patients, in order to maximize the total number of patients who undergo surgery.

2. The consequences of Covid-19 pandemic on elective surgery for colon cancer

After the extensive literature study, we decided to evaluate the impact of Covid-19 pandemic on patients with colon cancer who underwent elective surgery treatment on the First Surgery Clinic.

The Covid-19 generated pandemic had major consequences on surgery clinic's activity worldwide, and also on the life style of patients with colon cancer. Due to restrictions imposed by authorities, the quarantine, the advice of visiting the hospitals only when severe symptoms occur, as well as patients fear to develop Covid-19, interesting results were obtained after analyzing the data collected and compared it to the previous periods.

Results

From the total of elective surgeries performed in the First Surgery Clinic throughout the 3 periods of time, 19.72% took place during the pandemic, in 2018-2019 there were 46.25% and in the first period of the study 34%.

The average duration of surgical intervention was 230.21 min. during the pandemic, while in 2016-2017 the average was 165.28 min. and in the 2018-2019 period 193.44 min. After applying the Anova test a $p < 0.001$ resulted between the 3 periods.

Regarding the postoperative complications, in the pandemic period they were 6.89% (compared to 10% respectively 19.11% in the other 2 periods), and a frequency of fistula in 3.44% (compared to 4%, respectively 5.88%). This drop in the proportion of complications is justified by an increase in protective stoma realization with a percent of 13.8% during the pandemic period compared cu 10% and 8.82% during the other 2 periods of the study.

While analyzing the proportion of patients who spent minimum a day in intensive care units, Chi square test generated a $p=0.045$, during the pandemic 13.79% of the patients being for at least a day in the intensive care unit.

During the pandemic 37.93% of patients presented severe symptoms at their hospital presentation, after applying the Chi square test a $p=0.02$ resulted.

There was a higher preoperative average hospital stay during the pandemic (4.29 days, compared to 3.82 in 2018-2019), but a shorter average lengths of hospital stay (14.33 days compared to 18.18 and 16.21 days), as well as shorter length of postoperative stay (11.17 days, compared to 12 respectively 14.58 days).

3. The consequences of Covid-19 pandemic of emergency surgery for colon cancer treatment

During the Covid-19 pandemic the colon cancer screening has severely decreased. All elective surgical procedures were postponed during the first phase of the pandemic, only patients who needed an emergency surgery were treated.

Alongside with the restrictions imposed by the authorities, the fear of patients coming in contact with the virus, the above mentioned aspects led to an increase in the number of patients who presented at the hospital with severe symptoms, with an influenced biological, hematological status, parameters that had an impact on the outcome of these patients.

Results

During the 3 periods of time, 142 patients underwent emergency surgery for colon cancer treatment. 24.6% of these interventions took place during the pandemic, while 33.8% in 2016-2017, and 41.5% took place in 2018-2019, after applying the Chi square test a $p=0.028$ resulted.

During the pandemic period, 94.3% patients presented at the hospital with severe symptoms (compared to 66.7% during 2016-2017 and 67.8% during 2018-2019), after applying the Chi square test a $p=0.007$ was obtained.

The protective stoma was realized in 57.1% cases during the pandemic, (39.6% in 2016-2017), and none of the patients developed intestinal fistula in this period.

The average length of the surgery was 217.38 min. during the pandemic (174.77min. and 199.66 min. during the other 2 periods), after applying the Anova tests a $p=0.021$ was obtained between the 3 periods.

The average hospital stay was 12.63 days in 2020-2021, compared to 14.08 days pre-pandemic, and the average postoperative stay decreased from 12.46 to 11.14 days during the pandemic.

After a more advanced statistical analysis a negative correlation was obtained between the age of the patients and the length of surgery ($r=-0.355$, $p=0.039$), as well as a positive correlation between the length of postoperative stay and Charlson index ($r=0.928$, $p<0.001$).

There were also multiple statistical relations between age and the presence of protective stoma, or the necessity of intensive care monitoring. Moreover there was a statistical relation between the postoperative death and the intensive care monitoring and the necessity of receiving erythrocyte concentrate transfusions.

4. The impact of Covid-19 pandemic on the activity of a General Surgery Clinic

The activity of surgery clinics around the world have been massively influenced by the Covid-19 pandemic. At first the authorities have given indications to postpone all elective surgeries, only emergency surgeries being allowed to be performed. Moreover, the distribution of medical resources, both material and human ones in order to cope with the high number of Covid-19 infected patients, led to a lower surgical activity.

Materials and methods

In order to carry out this study, multiple parameters regarding the activity of the First Surgery Clinic of SCJUPB were analyzed. The pandemic period (26.02.2020-31.12.2021) was compared to the same period of 2018-2019. Multiple data regarding the activity of the clinic were collected, such as: total number of patients, number patients who presented via ambulatory, number of patients who presented via emergency service. The number of patients who underwent elective and emergency surgery was analyzed, as well as the monthly average length of

hospital stay, as long as the monthly mortality rate. Moreover the number of rooms, number of beds as well as the number of medical and auxiliary staff that went through a Sars CoV-2 infection were analyzed.

The obtained data was analyzed using the IBM Spss Statistics for Windows, version 21.0 program, for numerical data parameters of central tendency and dispersion being calculated. Statistical tests were applied as well, and a p value lower than 0.05 was considered statistically significant.

Results

During the pandemic period, there were 39.25% less patients admitted in the First Surgery clinic than the previous period.

The clinic's capacity decreased with 56.25% during the pandemic. After the statistical analysis regarding the monthly average of patients admitted via ambulatory and via emergency service, multiple values of $p < 0.001$ were obtained between the 2 periods of time.

Alongside the evolution of the pandemic an increase in the number of the monthly admitted patients was observed. During the first wave of the Covid-19 pandemic, there was an average of 61 patients admitted, this increased to 105 during the 4th wave.

When it came to analyzing the average length of hospital stay as well as the monthly mortality rate, after applying statistical tests, a $p < 0.05$ was obtained.

5. The Covid-19 pandemic influence on 90 days postoperative mortality in patients who underwent elective surgery for treatment of colon cancer

First phase of the Covid-19 pandemic led to the postponement of all elective surgeries, this including the ones made for colon cancer. It is a well known fact that delaying the treatment in patients with colon cancer can lead to unwanted effects on the outcome of the patients. The 90 day postoperative mortality rate is a very important parameter, this study's aim being to emphasize the pandemic influence on this parameter in patients who did not present Covid-19 infection.

Results

From the total number of elective surgeries performed in the First Surgery Clinic throughout the 3 periods of time, 19.72% took place during the pandemic, in 2018-2019 there were 46.25% and in the first period of the study 34%.

The 90 days postoperative mortality rate increased from 4.41% (pre-pandemic) to 13.79% during the pandemic. 71.42% of patients who died being male.

From the patients who presented 90 day postoperative mortality, 50% were presenting severe symptoms at their admission (during the pre-pandemic the rate was 33.3%), and 75% had a stage III or IV disease.

After an extensive statistical analysis, during the pandemic, multiple relations were detected between the variables of the study. The presence of 90 days postoperative mortality was associated with the presence of severe symptoms ($p=0.039$). Moreover an association between the mortality and the necessity of erythrocyte concentrate administration was reported ($p<0.05$) as well as between the mortality and the stage of the disease ($p=0.013$). During all the periods of the study, the 90 day postoperative mortality was associated with the value of Charlson index.

6. The Covid-19 pandemic influence on 90 days postoperative mortality in patients who underwent emergency surgery for treatment of colon cancer

The Covid-19 generated pandemic generated multiple consequences on the clinical and therapeutic management of the patients with colon cancer.

Early, at the beginning of the pandemic period, elective surgeries have been postponed, with a decrease in the number of surgeries performed worldwide. The patients presented at the emergency room with more severe symptoms, with a more advanced disease stage, influencing their outcome.

Results

From the total of elective surgeries performed in the First Surgery Clinic throughout the 3 periods of time, 24.57% took place during the pandemic, in 2018-2019 there were 41.52% and in the first period of the study 33.89%.

The 90 days postoperative mortality rate decreased from 22.5% (2016-2017) to 18.4% in 2018-2019 and rose again during the pandemic to 34.5%. From the total patients that died in the first 90 days after the surgery 60% were male.

Regarding the patients who presented 90 day postoperative mortality, 76.92% were presenting severe symptoms at their admission (during the pre-pandemic the rate was 55%, respectively 66.6%), and 75% had a stage III or IV disease.

After an extensive statistical analysis, during the pandemic, multiple relations were detected between the variables of the study. The presence of 90 days postoperative mortality was associated with the presence of severe symptoms ($p=0.039$). Moreover an association between the mortality and the necessity of erythrocyte concentrate administration was reported ($p<0.05$) as well as between the mortality and the stage of the disease ($p=0.013$). During all the periods of the study, the 90 day postoperative mortality was associated with the value of Charlson index.

7. Conclusions

There was a significant decrease in the number of elective and emergency surgeries performed for patients with colon cancer during the pandemic. Patients presented at the hospital with more severe symptoms, and a more advanced stage of disease.

The average length of the surgical act increased during the pandemic.

Protective stoma has been realized in a higher proportion during the pandemic.

The number of patients who spent at least one day in intensive care units was significantly higher during the pandemic. The total length of hospital stay decreased during the pandemic period.

There was a negative correlation between the age of the patients and the duration of surgery during the pandemic in patients undergoing emergency surgery.

There was a reorganization of clinic's room and the number of admitted patients and a decrease in the number of surgeries performed in order to treat the colon cancer patients and reduce the risk of Covid-19 infection. With a rate of 1.26% regarding the infected patients after more than 7 days from admission, we can say

that as long as the created protocols are pursued, the patients can undergo surgery for colon cancer safely even in critical situations such as this pandemic.

The parameter with the higher impact was represented by the 90 day postoperative mortality rate. This rate increased during the pandemic from 4.41% to 13.79% in patients that underwent elective surgeries and from 20% to 34.5% in patients who underwent emergency surgery.

Worldwide it is estimated that 2.3 million patients have postponed their surgical treatment for colon cancer. These patients will come to the hospitals, and the surgeons number is limited, this emphasizes the need of an efficient strategy in order to cope with the next period.