Impact of the COVID-19 pandemic on the surgical treatment of a patient with colorectal carcinoma

Pudić, Antonio

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UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Antonio Pudić

IMPACT OF THE COVID-19 PANDEMIC ON THE SURGICAL TREATMENT OF A PATIENT WITH COLORECTAL CARCINOMA

Graduation Thesis

Zagreb, 2023

This graduation paper was made at the Department of Surgery, University Hospital Centre Zagreb, Medical School of the University of Zagreb, mentored by Petar Matošević, MD, PhD, Assist. Prof. and it was submitted for evaluation in the academic year 2022/2023.

Abbreviations

ACS – American Cancer Society
AJCC – American Joint Commission on Cancer
APC – Adenomatous polyposis coli
ASA – American Society of Anesthesiologists
BRAF – V-Raf murine sarcoma viral oncogene homolog B
CIMP – CpG island methylator phenotype
CIN – Chromosomal instability
CME – Complete mesocolic excision
COVID19 – Corona Virus Disease 2019
CRC – Colorectal carcinoma
CT – Computed tomography
CTC – Computed tomographic colonography
DCCG – Danish Colorectal Cancer Group
DNA – Deoxyribonucleic acid
EGFR – Epidermal growth factor receptor
ESMO – European Society for Medical Oncology
FAP – Familiar adenomatous polyposis
FIT – Fecal immunochemical test
FOBT – Fecal occult blood test
HDI – Human development index
HNPCC – Hereditary non-polyposis colorectal cancer
HS-g-FOBT – High sensitivity guaiac fecal occult blood test
ICD – International Classification of Diseases
KRAS – Kirsten rat sarcoma viral oncogene homolog
MRI – Magnetic resonance imaging
MSH-2 – MutS homolog 2
MSI – Microsatellite instability
NCI – National Cancer Institute
nCOV – Novel Corona Virus
NHS – National Health Service (United Kingdom)
NICE – National Institute for Health and Professional Excellence
NSQIP – National Surgical Quality Improvement Program
OS – Overall survival
PET – Positron Emission Tomography
PHEIC – Public health emergency of international concern
PHSM – Public Health and Social Measures
PPV – Positive predictive value
QoL – Quality of life
SARS-CoV-2 – Severe Acute Respiratory Syndrome Corona Virus 2
SEER – Surveillance, Epidemiology and End Results program
TME – Total mesorectal excision
TNM – Tumor-, Node-, Metastasis classification
UICC – Union for International Cancer Control
UK – United Kingdom
US – United States
WHO – World Health Organization

Contents

Summary

IMPACT OF THE COVID-19 PANDEMIC ON THE SURGICAL TREATMENT OF A PATIENT WITH COLORECTAL CARCINOMA

Antonio Pudić

Colorectal carcinoma (CRC), also called large bowel cancer, is a malignant neoplasm of the mucosal lining of the colon, rectum, or both. Colorectal cancer has been investigated for decades and despite of the scientific effort or the fast-developing new medical technologies, this disease, which demonstrates a very complex and multifactorial set of causes in its development, remains an important cause of morbidity and mortality globally. In March 2020 the WHO declared the infection with SARS-Cov-2 and the related COVID-19 a pandemic with exponential increase of infection rates and fast spread throughout the whole world, quickly becoming a global health threat and at the same time impacting health care system on multiple levels. Countries adapted to the high numbers of COVID-19 patients in need of medical care with a shift of resources from other medical specialties towards the management and research of the viral disease. Governments in cooperation with various professional medical societies established public health and social measures (PHSM) in order to mitigate further spread and thereby decrease the pressure of the pandemic on the health care systems. However, medical care for cancer patients in general has been compromised by means of decreasing patients encounters in the primary sector, seizing of cancer screening, delays of diagnostic and therapeutic procedures, decreasing surgery volumes, etc. and by that potentially impacting the outcome, defined as overall survival (OS) and quality of life (QoL), of these patients.

This graduate thesis outlines the current knowledge of colorectal carcinoma and analyzes the impact of the COVID-19 pandemic on the surgical treatment of patients with colorectal carcinoma (CRC) by presenting data from different regions with high prevalence of CRC in order to make a statement on whether and how the pandemic impacted the preoperative characteristics of patients (e.g. ASA-score and stage of cancer at time of treatment) and different parts of the treatment of CRC patients.

KEYWORDS: *Colorectal carcinoma, COVID-19 pandemic, Colorectal surgery, Surgical treatment and management of CRC*

Sažetak

UTJECAJ COVID-19 PANDEMIJE NA KIRURŠKO LIJEČENJE PACIJENATA S KOLOREKTALNIM KARCINOMOM

Antonio Pudić

Kolorektalni karcinom, koji se naziva i rak debelog crijeva, zloćudna je neoplazma sluznice debelog crijeva, rektuma ili oboje. Rak debelog crijeva istražuje se desetljećima i unatoč znanstvenim naporima ili brzom razvoju novih medicinskih tehnologija, ova bolest, koja pokazuje vrlo složen i multifaktorski skup uzroka u svom razvoju, ostaje važan uzrok morbiditeta i mortaliteta na globalnoj razini. U ožujku 2020. godine WHO je infekciju SARS-Cov-2 i povezanim COVID-19 proglasio pandemijom s eksponencijalnim porastom stope zaraze sa brzim širenjem po cijelom svijetu, brzo postajući globalna prijetnja zdravlju i istovremeno utječući na zdravstvenu skrb pacijenata. Zemlje su se prilagodile velikom broju pacijenata s COVID-19 kojima je potrebna medicinska skrb preusmjeravanjem resursa s drugih medicinskih specijalnosti na liječenje i istraživanje virusne bolesti. Vlade su u suradnji s raznim stručnim medicinskim društvima uspostavile javnozdravstvene i socijalne mjere kako bi ublažile daljnje širenje i time smanjile pritisak pandemije na zdravstvene sustave. Međutim, medicinska skrb za oboljele od raka općenito je ugrožena smanjenjem broja pacijenata u primarnom sektoru, obustavom probira raka, kašnjenjem dijagnostičkih i terapijskih postupaka, smanjenjem volumena kirurških zahvata itd., a time potencijalno utječući na ishod, definiran kao ukupno preživljenje i kvaliteta života, ovih pacijenata.

Ovaj diplomski rad ocrtava dosadašnje spoznaje o kolorektalnom karcinomu i analizira utjecaj COVID-19-pandemije na kirurško liječenje bolesnika s kolorektalnim karcinomom reprezentirajući podatke iz različitih regija s visokom prevalencijom kolorektalnog karcinoma kako bi se dala izjava je li i kako pandemija utjecala na predoperativne karakteristike bolesnika (npr. ASA-score i stadij raka u vrijeme liječenja) i različite dijelove liječenja bolesnika s kolorektalnim karcinomom.

KLJUČNE RIJEČI: Kolorektalni karcinom, COVID-19-pandemija, Kolorektalna kirurgija, Kirurško liječenje kolorektalnog karcinoma

1. Introduction

1.1 SARS-CoV-2 and the COVID-19 pandemic

In December 2019 44 new cases of a pneumonia of at that time unknown origin appeared and were reported by the local hospitals in Wuhan city, Hubei province, China. All these cases were clustered around the Huanan Seafood market, which sold a wide variety of animal species. (1,2) Sequencing in early 2020 identified a novel virus (nCoV), phylogenetically related to the SARS-virus causing severe morbidity and mortality in the Asian region in 2002/2003, as cause of the respiratory disease, which manifested in patients mainly with fever and flu-like symptoms but also more severe clinical picture of difficulty in breathing up to respiratory failure and showed invasive infiltrates of both lungs in chest radiographs. (1,3,4) SARS-CoV-2, as named by the WHO from February 2020, spread quickly throughout China and reached other countries around the world by March 2020, leading the World Health Organization to declare a Public Health Emergency of International Concern (PHEIC) on January 30th 2020 and declaring the outbreak of COVID-19 as a pandemic on March 11th 2020. (3) In the period of January 3rd 2020 until May 31st 2023 over 760 million confirmed cases and almost 7 million deaths caused by COVID-19 have been reported to the World Health Organization. Table 1 shows the stratification of 10 countries with the most confirmed cases of SARS-Cov-2 infections globally. (4) With the nature of the virus spreading very quickly causing a dramatic impact on health care system with daily raising numbers of hospitalizations, and therefore calling for measures in order to mitigate the infection and contain the outbreak. Countries had to adapt by reallocation of resources from other medical specialties towards the management of SARS-COV-2 infected patients with severe clinical picture and protection of vulnerable population groups. From that it is obvious that the COVID-19 outbreak and pandemic had profound impact on the detection and medical care of cancer patients, including patients with colorectal malignancies. Numerous multinational studies indicated that the pandemic and the associated measures to contain the outbreak have been implicated in not adequate medical services of cancer patients by means of reduction in diagnostic procedures, deliver of anti-cancer therapy, fear and reluctance of cancer patients. (5–9) Additionally, one study showed increased risk of severe morbidity and mortality in 53.6 % and 28.6 %, respectively, in patients with cancer and suffering from COVID-19. (10) Further, multiple studies demonstrated an increased risk for morbidity and mortality in patients infected with SARS-CoV-2 and suffering from the associated disease and undergoing surgery, even some period after recovery of COVID-19. (11–13)

Now in 2023, after countless multi-national studies around the world were conveyed and numbers of analyzed variables regarding the outcome of cancer care, including colorectal cancer, during the COVID-19 pandemic have been published, it is of utmost importance to review these studies, in order to give an overview of the consequences the pandemic had on the treatment of patients with colorectal cancer, specifically the surgical management of the disease, and thereby make conclusions on the potential difficulties we could face in the near future, as the world finds itself in the post-pandemic period with a set of challenges due to the pandemic.

Country	Cases confirmed	Deaths	Vaccine doses administered
United States of America	103,436,829	1,127,152	668,168,096
China	99,268,660	121,235	3,515,872,818
India	44,990,278	531,867	2,206,710,296
France	39,035,040	163,570	158,014,193
Germany	38,426,308	174,247	193,232,623
Brazil	37,579,028	702,664	509,835,734
Japan	33,803,572	74,694	383,172,235
Republic of Korea	31,646,973	34,754	135,716,807
Italy	25,857,572	190,392	150,311,519
United Kingdom	24,618,436	226,278	151,248,820

Table 1:Overview of the numbers of confirmed COVID-19 cases, deaths and vaccine doses applied, as reported to the World Health Organization in the period from 3rd Jan 2020 to 31st May 2023. Table presents data of ten countries with the highest number of confirmed cases reported to the WHO. Source: WHO Coronavirus (COVID-19) Dashboard, Geneva: World Health Organization. (4)

2. Colorectal carcinoma (CRC)

2.2 Epidemiology

Colorectal cancer belongs among the most common and lethal cancer diseases worldwide. In 2020, for both sexes and among all ages more than 1.9 million new cases and 930,000 deaths have been estimated (see fig. 1). (14) Classified by regions, highest incidence rates were observed in Australia/ New Zealand and Europe, whereas African and Southern Asian countries showed lowest incidence numbers. (14) When comparing the age-standardized incidence rates for both sexes of all ages, globally, one can see, that among the 15 countries with the highest incidence rate of CRC, 13 out of 15 are European countries with Hungary leading in incidence rate (see fig. 2). Mortality rates followed the same trend with the European region leading. Besides, with taking the HDI into account it is estimated that until 2040 the number of new cases and deaths will increase to 3.2 million and 1.6 million, respectively. (14) However, in females it is the second most common cancer after breast cancer, while for males it takes the third place after prostate and lung cancer. As with other cancer types, the risk for developing CRC increases with age for both sexes and therefore the major population affected by colorectal carcinoma is older than 50 years (2012-2016). The median age, at which CRC is diagnosed, is 66 years in men and 69 years in women. Some studies propose, that CRC is increasing in prevalence in the younger population. (15,16)

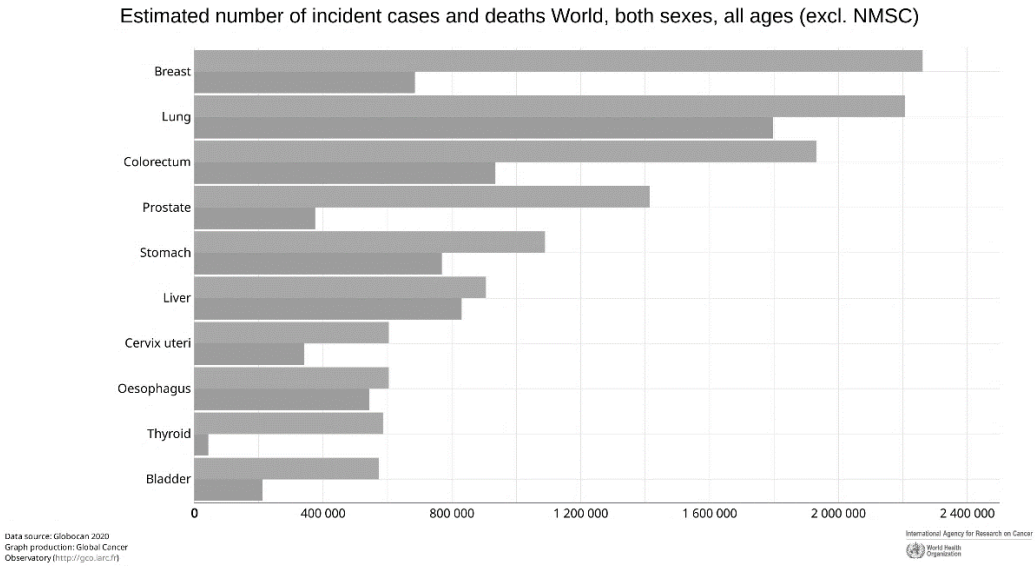

Fig. 1: Estimated number of incidence and deaths for all cancers (non-melanoma skin cancer excluded) in 2020, globally. Source: Global Cancer Observatory/International Agency for Research on Cancer. Adapted from: https://gco.iarc.fr/

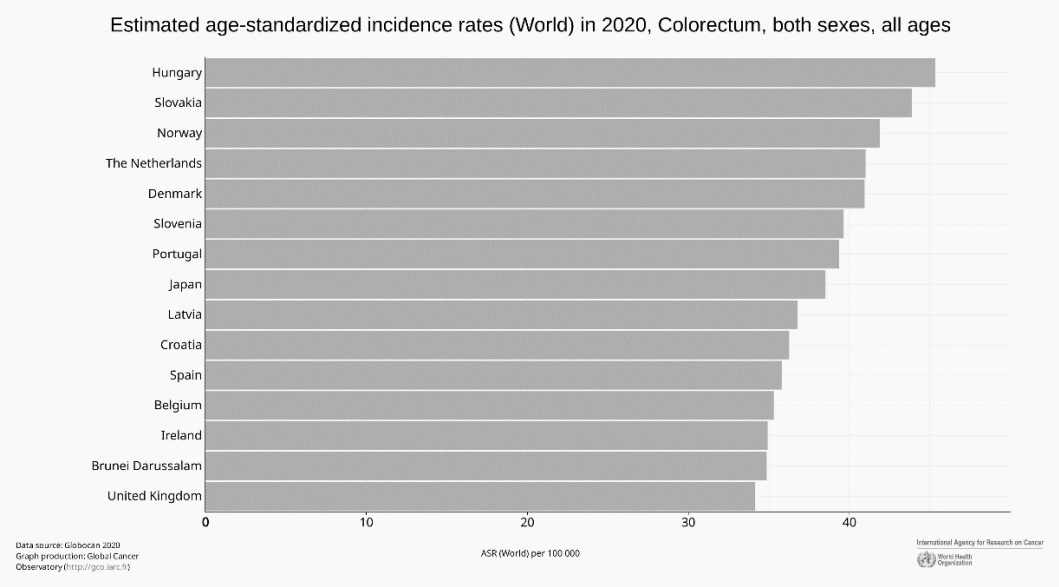

Fig. 2 Estimated age-standardized incidence rates of colorectal cancer for both sexes among all ages in 2020, globally. Source: Global Cancer Observatory/International Agency for Research on Cancer. Adapted from: https://gco.iarc.fr/

2.3 Classification and Carcinogenesis

Carcinogenesis of colorectal cancer begins in the crypts of the intestinal mucosa, where stem cells continuously go through cell divisions and the emerged daughter cells differentiate into functional colonic epithelial cells. This process describes the normal renewal of the epithelium, which balances the continuous loss of epithelial cells. By acquisition of mutations in the genetic code, loss of the DNA-repair mechanism and evasion from apoptosis normal cells become mutated and eventually this leads to the development of adenomas, also called benign polyps, in the normal mucosa. These adenomas are categorized by shape into tubular, serrated or mixed forms, which have tubular and villous characteristics. With additional successive mutations in specific genes over time these benign lesions grow in size and show histologically more and more dysplastic features, which are congruent with the increasing risk of malignant transformation of these lesions. The described development of cancer from a normal cell through benign lesions has been traditionally designated as the adenoma-carcinoma sequence, which was proposed by Fearon and Vogelstein (1990). (17–20) The model, seen in figure 3, shows the acquisition of mutations in specific genes in a normal mucosal cell in the colon and thereby eventually developing over years into colorectal carcinoma. (21)

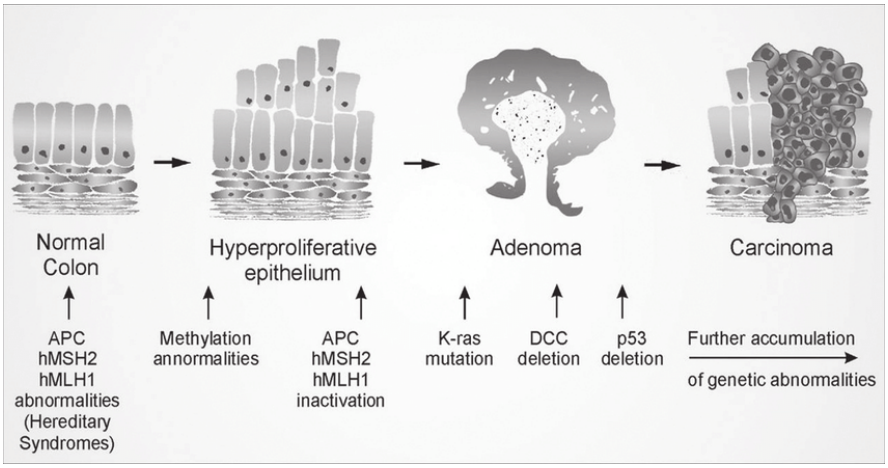

Fig. 3: Model showing the carcinogenesis of colorectal cancer by successive aquisition of mutations causing normal cells to progress to cancer through the stages of hyperproliferative epithelium and adenoma. Adapted from: Brosens et. al. (2008) (21)

In the comprehension of carcinogenesis, research has elaborated three main mechanism by which colorectal cancer can emerge from normal mucosal cells. The pathways that either alone or combined can lead to colorectal carcinoma are chromosomal instability (CIN), CpG island methylator phenotype (CIMP) and Microsatellite Instability. (19) Understanding the genotype and phenotype of the cancer could open new doors in diagnostics, early detection, but also, as already being implemented, new therapy strategies, e.g. the use of immune checkpoint inhibitors in MSI tumors, use of EGFR inhibitors in K-ras-wild type tumors (not mutated). (17)

2.4 Etiology and risk factors

When analyzing causes of colorectal cancer, it can be safely stated, that there is not one specific cause of the disease and therefore the etiology of colorectal cancer remains unknown. As stated already, the disease develops by acquisition of mutations over years and over decades of research some modifiable and non-modifiable factors have been identified rendering the individual being at a higher risk of developing cancer in the colon, rectum or both. Some studies also suggested that there are factors in daily life, which seem to be protective and thereby reduce risk of developing CRC.

Among the risk factors of CRC is a positive personal and/or positive family history. Within the family history studies showed that the closer the person, who suffered from CRC, is related (1st versus 2nd generation) or the younger the person was at time of diagnosis, the higher the risk for other members of family to develop CRC. Further, the more family members within a family suffered from CRC or other malignancies the higher the risk for an individual to develop colorectal cancer. Some genetic diseases render individuals at higher risk. (22) This family clustering seems to be responsible for around 20 % of CRC patients. There are also hereditary

CRC-syndromes following Mendelian inheritance principles, which are responsible for around 5-10 %. Among these diseases the most common is hereditary non-polyposis colorectal cancer (HNPCC), an autosomal dominant inherited disease with mutation of the MSH 2 gene, causing an early development of CRC around the age of 44 with predominant location in the right sided colon and an increased rate of synchronous and metachronous tumors. (23–25) Further, patients with HNPCC are at increased risk of suffering extracolonic cancers, most commonly in the endometrium, ovary, stomach, etc. (23,26) Another autosomal dominant inherited disease, worth mentioning as genetic susceptibility of developing CRC, is familiar adenomatous polyposis (FAP) with somewhat varying degrees of penetrance, causing hundreds of thousands polyps throughout the entire colon and rectum and rendering the patient to an almost 100 % risk of developing colorectal carcinoma by the age of 40. FAP is caused by a mutation in the tumor suppressor gene APC and in addition of causing colorectal cancer, also manifests with extracolonic cancers, e.g. desmoids, gastric/duodenal cancers, hepatoblastomas, cancers of the thyroid gland, etc. (27,28) Most colorectal cancer, however, appear sporadically and multiple modifiable and non-modifiable factors seem to be involved in the process. The age of the individual has been considered the main independent risk factor of developing CRC with increasing risk after the age of 50, reaching the peak at age 70, even though in recent years there is a trend of developing CRC at a younger age. (29) Nevertheless, modifiable life-style factors are associated with colorectal cancer. For example, individuals with high dietary intake of red, processed meat in combination with a low fiber, low vegetable/fruits and low calcium/vitamin D diet seem to be at higher risk of CRC-development. (30) As can be seen in figure 4, other modifiable risk factor for CRC are overweight, obesity, physical inactivity, tobacco use and alcohol consumption. (22)

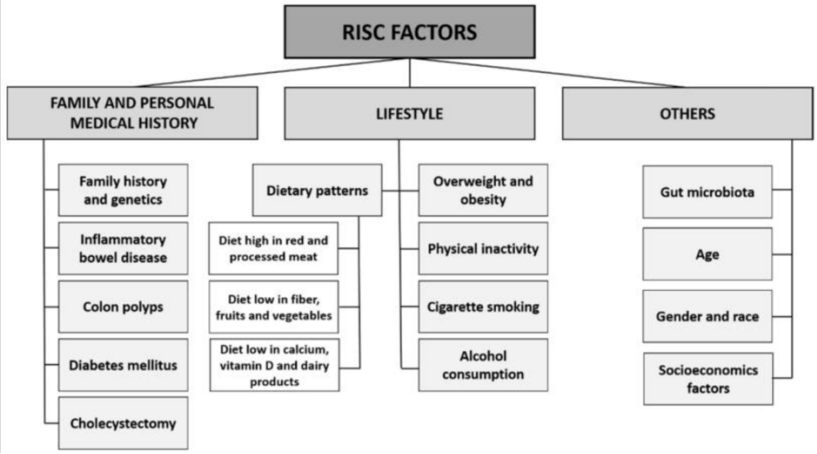

Fig. 4: Risk factors for colorectal cancer categorized by family and personal medical history, lifestyle and others. Adapted from: Sawicki et. al. (2021) (22)

2.5 Clinical presentation

As shown in multiple studies over decades, colorectal carcinoma doesn't follow a set of pathognomonic symptoms and signs. As already stated, CRC usually develops through the adenoma carcinoma pathway by forming benign lesions, which over time transform to malignant tumors. These lesions usually do not produce any specific clinical picture, and people with low stage carcinoma often stay asymptomatic and get diagnosed by means of national screening programs. (31) In case the cancer manifests clinically, the most common symptoms are usually related to the growth of the tumor into the bowel lumen. The most common described signs and symptoms in literature were (32–36):

- Any unexplained and/or persistent bowel habit change, which can present as diarrhea, constipation, change of stool consistency
- Abdominal pain, bloating, distension, cramping
- Discomfort at defecation and feeling of incomplete defecation
- Rectal bleeding, bloody or mucous stools, or melena
- Unexplained and unintended weight loss
- Anemia with or without iron deficiency
- Weakness and fatigue

However, colorectal cancer usually presents with, if any, very unspecific symptoms, which could indicate other diseases in the differential diagnosis. Additionally, patients don't present with symptoms at their first consultation, but may develop symptoms in successive consultations. Beside rectal bleeding, which has a specificity of 99.4 % and a positive predictive value (PPV) of 4.0 % (36), and thereby would approve further investigations in a primary care setting, no other single symptom reaches the 3 % NICE-threshold, rather the combination of symptoms and the overall clinical picture should raise suspicion of colorectal cancer and lead to further investigations. (32,36,37)

2.6 Diagnosis

There are different scenarios in which patients get diagnosed with colorectal cancer. Some of them develop above mentioned symptoms and together with their personal, social, and family history/risk factors suspicion is raised by their general practitioners, who either investigate further by using most commonly fecal occult blood tests or refers these patients to more specialized centers, where procedures like colonoscopies, sigmoidoscopies or CT-scans are

performed and definitive diagnosis can be made. Another way of diagnosis of colorectal cancer in asymptomatic patients is through governmental organized screening programs, where benign or malignant lesions are searched for in the bowel. (22)

2.6.1 Fecal occult blood tests (laboratory tests)

Fecal occult blood tests (FOBTs) are the most commonly used test in the primary care setting. They are based on the fact, that benign or malignant lesion have pronounced vascularization and these often microscopically bleed into the bowel. The blood often cannot be seen by the bare eye in the stool, therefore, FOBTs detect microscopical amounts of human-specific hemoglobin in the fecal sample. Fecal immunochemical test (FIT), one example of a FOBT, detects undigested hemoglobin, which is a protein in the red blood cells, and thereby is sensitive to lower gastrointestinal bleeding, since hemoglobin has not been digested by the gastrointestinal acids and proteinases. FIT uses antibodies, which are specific and bind to human hemoglobin and these antigen-antibody complexes can be detected and quantified in the stool sample. Hereby FIT is preferred over high-sensitivity guaiac fecal occult blood test (HS-g-FOBT) for patients with a low risk of colorectal carcinoma. In addition, NICE-guidelines recommend the use of FIT in primary care practices for patients over 60 years of age with changes of bowel habits, which cannot be explained, with or without iron-deficiency anemia. (22,37) The guaiac smear test uses somewhat similar principles of testing for blood in feces. The test cards are coated with a chemical substance, so called guaiac-acid, which under the effect of pseudo-peroxidation by the heme in the hemoglobin changes the color and by that free and bound heme in feces can be detected. (38)

2.6.2 Endoscopic diagnostic procedures

Endoscopies, including colonoscopies, sigmoidoscopies, are procedures, where flexible tubes with optical devices are used to visualize the lumen of the gastrointestinal tract and inspect the bowel for cancerous or pre-cancerous lesions. During these medical procedures, biopsies from polyps or cancerous lesion can be obtained in order to be histopathologically analyzed and to establish a definitive diagnosis of CRC. Sigmoidoscopies are limited to the visualization of the left colon, while tubes used in colonoscopy are able to visualize the entire colon (ascending, transverse, descending), rectum and terminal part of the ileum and by that it is the procedure with the highest sensitivity and specificity for diagnosis of colorectal cancer. Endoscopic procedures are very effective in cancer screening and detection and up to 95% of tumors are found by these procedures. (22,39,40)

2.6.2 Radiological imaging

Computed tomographic colonography (CTC), is a non-invasive radiological scan, where the bowel is insufflated with contrast agents and images are taken from different axes. CT-colonography is very sensitive for detecting colorectal cancer and comparable to the performance of colonoscopy, but is less effective in detection of polyps smaller than 8 mm when compared to colonoscopy. (22,39) Nevertheless, CTC together with native or contrast CT-scans of the abdomen and thorax for example are very useful in establishing clinical staging of the cancer (cTNM-stage) prior to surgical resection or other treatment modalities. Additionally, magnetic resonance imaging (MRI), positron emission tomography (PET) are all further options in establishing staging of the cancer, searching for metastases or for the primary tumor, but have less significance in screening programs or initial diagnosis of CRC.

2.6.1 Screening of colorectal carcinoma

Screening is a population based, organized testing for cancer and precancerous lesions in asymptomatic people at average risk. Usually these screening programs are based on evidence from studies by multiple professional societies, which balance the benefit, risk, cost-effectiveness of different medical test and thereby qualify these as suitable for screening programs. Therefore, screening programs should be effective in early detection, slowing progression and potentially foster cure of a disease, but at the same time they need to be accessible, affordable and acceptable. (41) Wilson's & Jungner's (1968) "principles and practice on screening for a disease" summarized the cornerstones of requirements of a screening test and they proposed ten principles on the relations between the disease, the public, and the screening test, which are widely accepted. (42) According to the American cancer society (ACS) it is recommended that men and women in the age of 45-75 get regular screened with an fecal occult blood test (High-sensitivity guaiac fecal occult blood test [every 12 months], fecal immunochemical test [every 12 months], or multi-target stool DNA-test [every 36 months]) or any of the visual examination like colonoscopy every 10 years, CT-colonography every 5 years or flexible sigmoidoscopy every 5 years. Additionally, if patients get tested positive for any of the fecal occult blood tests, they should be followed up with one of the visual examinations, with colonoscopy being preferred. Men and women in the age of 76-85 years of age should be evaluated by their physician individually according to personal history, family history, screening history, health condition, associated risk factors, patients' preferences and life expectancy >10 years. For people, male and female, older than 85 years of age screening for colorectal carcinoma is not recommended. (43,44)

2.7 Staging

American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), have established the tumor/node/metastasis (TNM)-classification as the most common system used to classify cancers internationally. This evidence based system divides colorectal carcinoma into groups by their size, tissue and lymph node infiltration and spread to distant tissues or organs (metastasis), and thereby can give information to clinicians about prognosis and individual treatment options, since every patient is staged and treated by a multidisciplinary team consisting of surgeons, oncologists, gastroenterologists, etc. (45)

2.7.1 TMN-Classification in colorectal cancer:

The T-category of TNM describes the size of the tumor and the amount of infiltration to the primary locations or nearby tissue. Whether and how extensively the tumor has spread to regional lymph nodes, which anatomically are found around the bowel's vasculature, is depicted by the N-category. Finally, the M-category describes, whether the primary tumor has metastasized to other organs, most common liver, peritoneum, lungs and less common bones, adrenal gland, ovaries or brain. Table 2 shows the exact tumor infiltration site, spread extent and organ involvement on each TNM-category defined by AJCC. (45)

T	T_{is} (Carcinoma in situ)	Infiltration from mucosa to maximally muscularis mucosae
	T_1	Infiltration of submucosa
	T_2	Infiltration of muscle layer of the bowel (muscularis propria)
	T_3	Infiltration of the serosa and the visceral peritoneum
	T_4	T_{4a}: Tumor infiltrates beyond visceral peritoneum T_{4b}: Tumor infiltrates neighboring organs
N	N_0	No spread to regional lymph nodes
	N_1	N_1: spread to 1-3 regional lymph nodes N_{1a}: 1 lymph node involved N_{1b}: 2 or 3 lymph nodes positive for tumor cells N_{1c}: infiltration of pericolic/perirectal lymph nodes by tumor or satellite cells
	N_2	Involvement of >4 lymph nodes N_{2a}: 4-6 lymph nodes

		N_{2b}: > 7 lymph nodes
M	M_0	No metastasis
	M_1	Metastasis to other organs M_{1a}: one organ involved M_{1b}: 2 or more organs involved M_{1c}: Peritoneal metastasis (Carcinosis peritonei)

Table 2: TNM-classification for colorectal carcinoma according to the AJCC Cancer Staging Manual (8th edition). Source: AJCC Cancer Staging Manual, 8th edition. Springer International Publishing, 2017. (45)

2.7.2 Colorectal cancer staging according to AJCC:

The described TNM classification is further grouped into stages I-IV. Carcinoma in situ, which by definition mustn't break through the lamina propria mucosae is defined as stage 0. Stage I CRC is any tumor, which infiltrates the mucosal, submucosal layer up to the thick muscle layer of the bowel, but do not spread to any lymph nodes. In stage II the lymph nodes must still be negative for cancer cells, but the tumor grows beyond the muscle layer and infiltrates the outer wall of the colon/rectum, pericolic/perirectal fat and or surrounding organs like for example the urinary bladder, prostate gland, uterus, vagina, etc. Further any tumor of any size, which spreads to the regional lymph nodes will be staged into stage III and in addition subclassified into IIIA-C by extent of infiltration and number of lymph nodes it spread to. If the malignant tumor metastasizes to other organs (liver, lung, bones, etc.) or the peritoneum, it is classified as Stage IVA-B or IVC, respectively, depending on the number of involved organs (see table 3).

Stage	**TNM**	
0	T_{is}, N_0, M_0	Carcinoma in situ or mucosal carcinoma (must not infiltrate beyond lamina propria mucosae)
I	T_1, N_0, M_0 T_2, N_0, M_0	Infiltration of mucosa, submucosa and max. up to lamina muscularis propria
IIA	T_3, N_0, M_0	Infiltration of pericolic and perirectal fatty tissue
IIB	T_{4a}, N_0, M_{0C}	
IIC	T_{4b}, N_0, M_0	
IIIA	T_{1-2}, $N_{1/1c}$, M_0 T_1, N_{2a}, M_0	Lymph node spread
IIIB	T_{3-4a}, $N_{1/1c}$, M_0 T_{2-3}, N_{2a}, M_0 T_{1-2}, N_{2b}, M_0	
IIIC	T_{4a}, N_{2a}, M_0 T_{3-4a}, N_{2b}, M_0 T_{4b}, N_{1-2}, M_0	

IVA	Any T, Any N, M_{1a}	Spread to other organs or the peritoneum
IVB	Any T, Any N, M_{1b}	
IVC	Any T, Any N, M_{1c}	

Table 3: Colorectal cancer group staging according to the AJCC Cancer Staging Manual (8th edition). Source: AJCC Cancer Staging Manual, 8th edition. Springer International Publishing, 2017. (45)

Nowadays, pathologists in addition to the mentioned staging denotation also give statements about the invasion of the tumor into lymphatic, vasculature or perineural tissues and others, by using L, V, PN denotation after the TNM classification. By using biomolecular tests, they can further specify whether the primary tumor shows mutations in specific genes like KRAS, BRAF, MSH, etc., which are important to the multi-disciplinary team in the tailoring of the patient's treatment plan (e.g. targeted therapy).

2.8 Therapy strategies in patients with colorectal carcinoma

Treatment of patients with colorectal cancer is complex and it involves multiple medical specialties like abdominal surgery, gastroenterology, oncology and radiology, optimally meeting as a tumor board on a regular base and discussing individual patients, in order to tailor the optimal treatment plan for a patient regarding the surgical modality, neoadjuvant or adjuvant chemotherapy, radiotherapy or a combination of these with taking the pathology, stage and localization of the tumor, the individual's medical status, comorbidities and risk factors into consideration.

2.8.1 General principles of oncologic surgery of colorectal cancer

Oncologic surgery, thus surgical treatment of colorectal cancer, in general has the ultimate aim to remove the malignancy, which means removing optimally all malignant cells from the body, to avoid recurrences and metastatic spread, to treat complications caused by the tumor such as intestinal obstruction or bleeding and thereby improving the patient's outcome or improving survival, while causing as less harm as possible. (46,47) Therefore, radical surgical treatment is still the golden standard in the management of patients with colorectal cancer with curative intent. It follows the principles of surgical oncology, where solid neoplasms are resected en bloc, which means that all structures containing the tumor or invaded by the tumor together with the major supplying blood vessels and the corresponding draining lymphatic vessels and lymph nodes are resected with tumor free resection margins (R0) proven by an intraoperative pathology consultation. (48,49)

2.8.2 Oncologic surgery for colon cancer

Hohenberger et. al. (2009) introduced the complete mesocolic excision (CME) as an analogue to the total mesorectal excision (TME) in rectal cancer. It follows the principle by removing the tumor en bloc with disease free margins (R0), dissecting the lymph nodes and lymphatic tissue up to the primary feeding artery including the apical lymph nodes. According to location that means with tumors in the cecum or ascending colon, a right hemicolectomy with ligation of the ileocolic artery and eventually depending on tumor location the right colic artery. The dissection of the central vessels mandates the extent bowel resection. Tumors in the descending colon or sigmoid colon are managed by a left hemicolectomy with dissection and ligation with the associated vessels (inferior mesenteric artery). Colon carcinoma in the transverse colon require the removal of the whole transverse colon in addition to the right and left colic flexures and their central vessels. Due to overlapping blood supply by the Riolan's arc in that region an extended transverse colectomy is recommended. Special considerations should be made in patients with synchronous tumors or hereditary cancer syndromes, where a total colectomy with ileorectostomy and proctocolectomy with ileoanostomy is recommended. (50–52)

For rectal cancer the same principles are applied and depending on the location of the tumor different methods can be used. Tumors in the upper third of the rectum are managed with anterior rectal resection (acc. to Dixon) with removal of the rectum with an aboral margin of 5 cm, while another 5 cm of disease-free tissue to the dentate line are saved. (50,52,53) Rectal cancers in the middle third are most commonly treated with total mesorectal excision (TME) by removing the whole mesorectal fatty tissue, including the lymph nodes. Here a 2 cm aboral safety margin is sufficient for low coloanal anastomosis (Colon-J-Pouch). (50,52,54) If the tumor involves the low third of the rectum and eventually the sphincter-apparatus an abdominoperineal excision (acc. to Miles) is recommended. (50,52)

An important principle is the resection of the tumor by mobilizing the colon/rectum and its mesentery, ligating the corresponding vessels without touching or cutting into the tumor tissue at any time during the operation (no touch isolation technique). It has been published that no touch isolation technique reduces intraoperative tumor shedding into the portal vein during resection of colon cancer and by that reduces liver metastasis occurrence in patients. (55,56) It seems that surgery is the superior treatment modality for localized tumors and tumors involving regional lymphatics, however, patients with solitary colorectal liver metastasis have better 5-year survival after hepatic resection and in addition resection is superior to radiofrequency ablation when comparing local recurrence rates, recurrence free and overall survival rates. (57)

2.8.2 Open and laparoscopic treatment options

Colorectal cancer can be surgically treated either by open surgery or laparoscopic surgery. When comparing these two approaches in published studies, open surgery doesn't seem to be superior to laparoscopic surgery. The results of laparoscopic approaches are comparable with open surgery techniques when observing the occurrence of incisional hernias, reoperations for incisional hernias or adhesions, recurrence rate at the primary tumor site and general recurrence rate (58–60). Schwenk et. al. reviewed the two methods by analyzing the short-term postoperative period (<3 months after surgery). They found that laparoscopic colorectal resection takes longer, but the patients' blood loss was less intraoperatively than with conventional surgery. Postoperatively, patients have less pain and the duration of postoperative bowel paralysis (ileus) is shorter and thereby the total and surgical morbidity in addition to duration of hospital stay is less in laparoscopically treated patients versus conventionally treated patients. Comparing laparoscopic surgery to open surgery, none is superior when observing overall morbidity and mortality. (58,61)

2.8.3 Colorectal cancer (CRC) treatment and management recommendation in the COVID-19 pandemic

With the impact of the COVID-19 pandemic on the healthcare systems globally, the quick depletion of hospital capacities and a general shift of resources towards the mitigation of the negative effects of the pandemic, new recommendations and guidelines from multiple institutions have been proposed.

The European Society for Medical Oncology (ESMO) designed a guideline for the management of patients with CRC, among other cancers, on base of three levels of priorities, which are high priority, medium priority and low priority. According to ESMO these priority are defined as (62,63):

- **High priority**: The condition is an emergency with being immediately life threatening to the patient and/or the patient being clinically unstable, and/or the intervention increases the overall survival (OS) and/or substantially improves quality of life (QoL), which renders the intervention to one with high priority

- **Medium priority**: Patient's condition cannot be defined as critical. The intervention, however, could benefit the patient in QoL and OS and should be performed within 6 weeks, since longer delays (>6 weeks) could negatively impact the outcome.

- **Low priority**: Patient's situation is stable, and intervention can be delayed for the length of the COVID-19 pandemic and/or the intervention does not change OS/QoL.

Thereby, regarding the surgical management of patients with CRC the ESMO recommends following (62,63):
Radiological-confirmed intestinal occlusion, emergency conditions like bowel perforations, peritonitis, massive GI-bleeding and bone fractures with compression of the spinal cord or post-surgical, post-colonoscopy complications or any other post-intervention complication should be considered as indication for an intervention, which qualifies as high priority.
Indications for intervention with a delay of maximal 6 weeks (medium priority) are clinical stage I, II, III colon cancer and clinical stage I rectal cancer, as well as clinical stage II, III rectal cancer after performed neoadjuvant treatment. Additionally, metastasis in patients with a few metastases (oligometastatic CRC) should be resected with curative intent before or after neoadjuvant therapy with medium priority.
Low priority indications are early stage rectal cancer with a complete response after radiotherapy, where a watch-and-wait strategy is followed. Any prophylactic surgery for familiar CRC or any biopsies, which are done in the frame of molecular analysis for late-line treatments should be considered with low priority and if possible delayed till after the pandemic.
This recommendation does not qualify or disqualify interventions needed in the care of colorectal cancer patients in general. They just help prioritizing interventions and managing conditions in an era, where healthcare resources shifted towards treatment of COVID-19 and resources for the management of cancer patients in general have become scarce. It tries to balance the benefit of an intervention on OS/QoL and the harm of delaying treatment in certain conditions.

2.9 Prognosis

5-year survival in the United States:

According to the SEER program, a surveillance research program of the National Cancer Institute (NCI), the five-year relative survival rate for cancer of the colon and rectum in the United States in 2013-2019 for all stages and both sexes combined was 65.0 %. (64) The SEER program, unlike the AJCC/UICC cancer staging, classifies colorectal cancer into localized, regional and distant stages. A primary malignant tumor, which is confined to the site of origin is staged as localized. If the tumor infiltrates the surrounding tissues and/or involves regional lymph nodes, it is considered in the survival rate of regional cancers. Distant cancers involve other organs or tissues beyond the site of origin by means of for example lymphatic spread. Depending on the SEER-stage at diagnosis of the cancer the survival at 5 years varies widely from 90.9 percent for localized cancers to 73.4 percent for regional cancers and 15.6 percent for cancers, which spread to organs and tissues remote from the primary tumor site (see table 4) (64) Further, cancer of the colon has, even though comparable, somewhat worse prognosis than rectal cancer (64.0 vs. 67.1 percent), except in localized stage, when colon cancer shows somewhat better prognosis. In general, the survival of patient depends highly on the stage at diagnosis. The survival at 5 years decreases drastically with increasing stage from localized tumors (90.9 %) to regional stage (73.4 %) and cancers with distant involvement (15.6%).

	ALL STAGES	LOCALIZED	REGIONAL	DISTANT
COLON & RECTUM	65.0	90.9	73.4	15.6
COLON	64.0	91.4	73.2	14.7
RECTUM	67.1	89.8	73.7	17.8

Table 4: SEER 5-Year Relative Survival Rates in % by cancer site & stage at diagnosis for both sexes, all ages, all races & ethnicities, 2013-2019, US. Data Source: SEER Incidence Data, Nov 2022 Submission (1975-2020), SEER 22 registries (excluding Illinois and Massachusetts). Expected Survival Tables by Socio-Economic Standards. (64)

Overall and stage-specific survival in Europe (65):

Cardoso et. al. (2022) conveyed a population-based study on overall survival and stage-specific survival of colorectal carcinoma in patient groups, in which cancer has been detected by screening, and in patients with non-screen-detected cancer in nine European countries. They

showed that overall 5-year survival for stage I cancer in screen-detected patients was 92.4 %, in non-screen detected patients 86.7%, and in all patients combined 89.1%. In stage II cancer the survival varied from 87.9% in screen-detected to 79.2% in non-screen-detected and 81.2% overall. The same trend could be observed in stage III cancers, where 80.7% of the screen-detected group survived 5-years or more, while the non-screen-detected and group with all patients combined showed a survival of 66.2% and 69.4%, respectively. The 5-year survival after diagnosis of stage IV cancer in screen-detected patients, even though very rare, was 32.3%, in non-screen detected patients 13.9% and in all patients 15.4%. (65) Overall the numbers can be compared to the prognosis of patients with colorectal cancer in the United States, according to the SEER program.

4. Goals of the Review

After publishing the first cases of SARS-CoV-2 infected patients and the it seemed unstoppable fast spread of the virus to other countries, there was a need for emergent reaction of all the parties of the health care sector in order to stop further infection spreading and to establish an adequate therapy strategy for patients suffering of COVID-19 by decreasing seemingly unnecessary medical procedures and by increasing intensive care capacities for seriously ill patients. By drastically shifting resources towards the COVID-19 pandemic (clinical sector and research) other medical sectors, even though unwanted, became neglected to an unknown extent.

Therefore, it is part of the medical profession to review the pre-pandemic and pandemic period to find out the impact of the SARS-CoV-2 and its associated COVID-19 disease not just on the morbidity and mortality of the disease itself, but also on care of patients in other medical specialties. Thus, this thesis reviews scientific papers, which published the statistics on the pre-pandemic surgical treatment plan for patients suffering from colorectal cancer and at the same time compares them to the surgical care of patients with CRC during the pandemic in different countries of Europe, the United States as example of regions, including countries with high incidence of COVID-19. Further, this graduate thesis compared the different results and tried to depict the similar or different impacts of COVID-19 on surgical treatment of patients with colorectal cancer.

5. CRC surgical treatment in countries under the COVID-19 pandemic

5.1 CRC treatment during COVID-19 pandemic in a tertiary institution in Croatia

Matošević et. al. (2021) investigated the impact of the pandemic on the CRC treatment in the University Hospital Centre Zagreb in Croatia by measuring variables, which have prognostic value on the survival of patients with CRC. These variable were "deferral time from diagnosis to commencement of treatment, lapse of time between different phases of the treatment process, time of presentation (elective versus emergent surgery), the physical status of the patient at the time of surgery (ASA classification) and metastatic index (positive lymph node ration)" (66) in 661 patients treated for C18-C20 diagnoses according to the *International Statistical Classification of Diseases and Related Health Problems (ICD-Version 10)* during the pre-pandemic (347 patients) and pandemic period (314 patients) 2019 to 2020, respectively. Further inclusion criteria were primarily curative surgical treatment of patients, which means the surgical approach was an oncologic resection of the tumor with or without anastomosis, no differentiation between patients with or without neoadjuvant chemotherapy and inclusion of all surgeries performed in these patients, elective and emergent. On the other hand, excluded were patients with recurrent, synchronous, metachronous tumors or metastatic, disseminated disease and these patients who were treated with palliative therapy intent or for postoperative complications. Further not taken into the study were histopathological proven colorectal adenomas. After all criteria being applied the study was conveyed on 330 patients with 173 being treated in 2019 versus 157 patients in 2020, which shows a slight decline in the operation volume for the pandemic period. (66)

They also found a significant increase in operations performed in an emergency setting from 15.03 % to 26.11 %, while the elective surgeries decreased by 11.08 % (84.97 % vs. 73.89 %). Additionally, the minimal invasive procedures decreased during the pandemic from 13.87 % to 10.19% and at the same time the open surgeries were performed more frequently (86.13 % vs. 89.81 %). (see figure 5 and 6) (66)

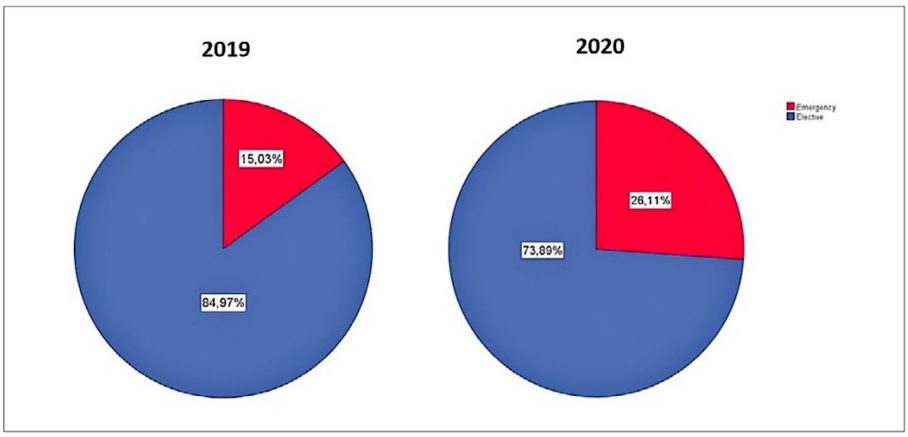

Fig. 5: Proportions of procedures performed in an emergency setting versus elective procedures, comparing 2019 and 2020. Adapted from: Matošević et. al. (2021) (66)

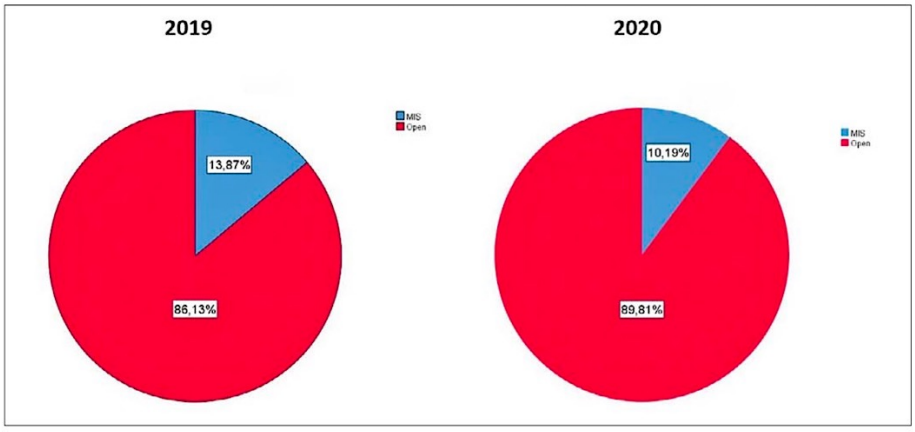

Fig. 6: Percentages of minimal invasive procedures versus open performed surgeries, comparing 2019 and 2020 . Adapted from: Matošević et. al. (2021) (66)

When comparing the patient's health status with the ASA-physical status classification from 2019 to 2020, they found a significant decrease by 11.21% (46.24 % vs. 35.03 %) in patients with ASA II (patients with mild system disease) (67). However, there was no change in stratification of the ASA-subgroups, which means that most common were patients with ASA II and ASA III, while normal healthy patients without comorbidities (ASA I), patients with severe, life-threatening systemic disease (ASA IV) and ASA V subgroup remained very uncommon. (66) Furthermore, as a prognostic factor and late diagnosis parameter, the TNM-staging according to the AJCC/UICC was observed in patients being treated for CRC. In 2019 the most common stage found histopathologically was stage III followed by stage IV (50.3 % and 27.7 %). Stage I CRC was quite uncommon with 6.4 % among treated patients in the pre-pandemic period. Compared to the pandemic period 2020, the ratio of patients with stage I more than doubled (6.4 % vs. 14.0 %) and stage II cancer increased by 11.8 % (15.6 % vs. 27.4 %). On the other hand advanced tumor stages, including stage III and IV, being most common in

2019, decreased in 2020 from 78.0 % to 55.4 %. (66) When they compared, as can be seen in table 5, the referral times from diagnosis to surgery and further to oncologic treatment in the pre-pandemic and pandemic group, they found delay, measured in days, in all the stages of the treatment process. Beside increased deferrals in surgeon referral to surgery (24.32 vs. 32.0 days), surgery to oncologist referral (35.48 vs. 44.63 days) the highest delay with 17.4 days was found in the time between surgery and chemotherapy (59.03 vs. 76.43 days), when comparing 2019 with 2020. (66)

	Year	N	Mean (Days)	Std. Deviation	Sig.
Colonoscopy to Surgery	2019	91	40,4725	36,70160	,115
	2020	65	45,1846	74,70649	
Surgeon referral to Surgery	2019	135	24,3111	32,83574	,005
	2020	96	32,0000	63,16645	
Surgery to Oncologist referral	2019	128	35,4766	20,99567	,004
	2020	122	44,6311	28,43877	
Surgery to Chemotherapy	2019	70	59,0286	26,64200	,005
	2020	81	76,4321	41,78724	

Table 5: Comparison of delays in days in the referral process from time of colonoscopy to surgical and oncological treatment for 2019 and 2020. Adapted from: Matošević et. al. (2021) (66)

Finally, they investigated possible changes in the lymph node number, dissected during tumor resection, the lymph node positivity and the metastatic index, which present the ratio out of the two variables and is connected to overall survival of patients. Comparing 2019 and 2020, the lymph node count was 17.28 and 16.57, respectively. Out of these 1.80 (2019) and 1.36 (2020) were positively tested for containing tumor cells. Thereby, lymph node ratio decreased by 2.33 between 2019 and 2020 (7.97 vs. 10.30), which could be connected and consistent with the falling numbers of patients with advanced tumor stages. (66)

5.2 Impact of COVID-19 on surgical management of patients with CRC in other countries of Europe

Multiple studies were conveyed on the COVID-19 impact on the detection and management of colorectal cancer in numerous countries in Europe.

Studies in England observed significant reductions in referral of patients, in whom colorectal cancer is suspected, in addition to reduced numbers of diagnostic procedures, as colonoscopies, and markedly decrease in surgery volumes. (68–70)

Morris et. al. (2021) investigated in their population-based study the impact of the COVID-19 pandemic on the detection and management of patients with colorectal cancer in the period of Jan 1st, 2019 to Oct 31st, 2020 in England. Thus, they analyzed the timeframe of referral from the general practitioner or primary care to the specialist, the total number of performed colonoscopies as most used diagnostic test, and multiple variable on surgical treatment of CRC patients, e.g. surgical modality and procedure, treatment within target time according to NHS guidelines (31-day standard), open versus laparoscopic surgery, surgeries performed in an emergency setting, etc. (71) The colleagues found that the referrals from primary care physician to specialist for patients with suspected cancer within the 2-week wait (NHS-guideline) were decreased by 23 % (with peak of 63 % in April 2020) compared to the pre-pandemic period. Additionally, less patients with a confirmed diagnosis of colorectal cancer entered the 31-day standard, which means less patients after being diagnosed with CRC received cancer treatment within 31 days according to NHS-guidelines. This decrease was highest in May 2020 (35 %) and overall 19 %, when comparing 2019 with 2020 (see figure 7). Another reduction was observed in the proportion of procedures performed for colorectal, colon and rectal surgery. Here, the overall reduction for the pandemic period compared with the pre-pandemic period was 18 % with a peak reduction of 33 % in May 2020 (see figure 8). The numbers of referrals and surgical volume, however, increased by the end of the year 2020 and met the numbers from 2019. This recovery after the national lockdown in England can be seen in figure 7 and figure 8. (71)

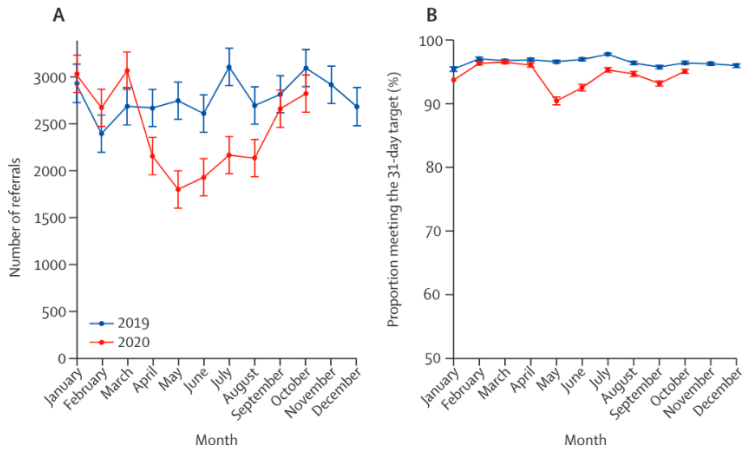

Fig. 7: Numbers of referrals in accordance with the diagnosis to treatment within 31 days guideline (A) and the percentage of these referrals meeting 31 days to treatment pathway (B). (A) and (B) are both measured in the period of January-December 2019 (blue line) and 2020 (red line). Adapted from: Morris et. al. (2021) (71)

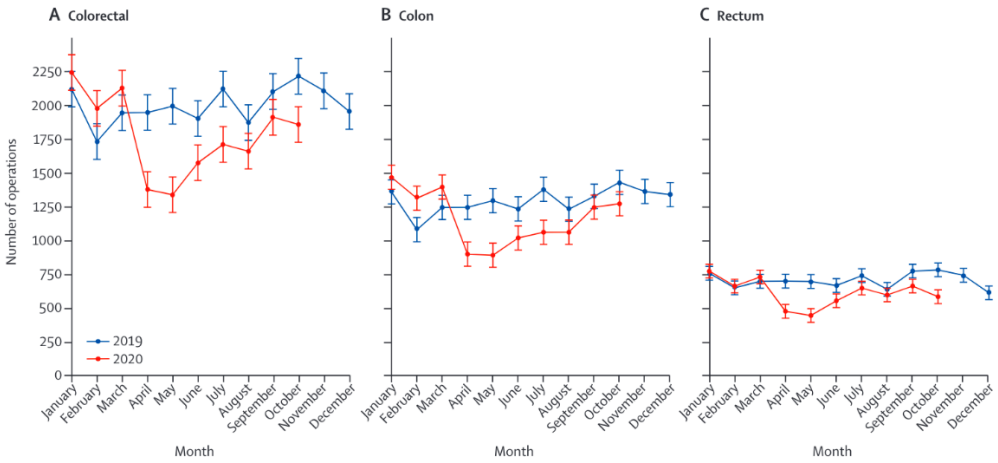

Fig. 8: Development of surgical volume measured by numbers of procedures performed for colorectal cancer (A), colon cancer (B) and rectal cancer (C) in the period of January-December 2019 (blue line) and 2020 (red line). Adapted from: Morris et. al. (2021) (71)

When observing intraoperative variables, Morris et. al. found that there was a decrease of laparoscopically performed procedures (59 % vs. 25 %) and the proportion of procedures with ostomy formation/creation increased (44 % vs. 56 %), more commonly for rectal cancer (80 % vs. 83 %) than for colon cancer (25 % vs. 42 %), comparing 2019 with 2020. It shows significant increase in stoma formations in procedures undertaken in patients with colon cancer. (71)

Lesi et. al. (2022) demonstrated in their retrospective cohort study conveyed during the pandemic in an NHS Foundation Trust hospital in the UK that delays in the treatment of colorectal cancer carry a three times higher likelihood of higher staged cancers at time of treatment. (72) They investigated the treatment delay in patients with histological (colonoscopy, sigmoidoscopy) confirmed cases of colorectal cancer, which was defined as treatment in form of neoadjuvant chemoradiotherapy or surgery being performed more than 62 days after the referral by a general practitioner to a specialist hospital, according to NHS guidelines. (72,73) Additionally, they defined upstaging of a tumor as change of a lower stage to a higher stage tumor using the AJCC/UICC classification of colorectal cancer. (45,72) In 107 patients they observed that 49.5 % of patients had a pre-treatment stage III cancer, while stage I and II were equal in proportion (23.4 %). The proportions of disease location in patient with and without treatment delay combined were 43.9 %, 23.4 %, 30.8 % for right, left colon and rectum, respectively. The mean time until treatment was 72.7 days for both patient groups combined. In the patient group without treatment delay (46.7 %) the mean time patients had to wait until treatment was 46.3 days. The mean days until treatment for the patients, who experienced delays, was 95.8. When comparing disease progression at time of receiving first treatment,

20 % of the patients without deferral and 38 % of patients with delay showed a higher stage of their disease at time of treatment. Finally, they observed that patients with a delay in their treatment had an odds ratio of 3.27 for progression of their disease.

Germany, as ranked 5th among the 10 countries with the highest reported number of COVID-19 cases with over 38 million infected patients and over 170,000 COVID-19 related death (4), was impacted quite similar by the pandemic regarding surgical treatment of colorectal cancer patients. A study conveyed by Brunner et. al. (2020) by using an online questionnaire to ask about the current surgical situation in addition to surgical treatment of oncologic patients during the pandemic in Germany. They invited members of a consortium of German colorectal cancer centers, where 122 surgeon performing colorectal surgery in 101 hospitals in different German states participated in the online survey. Hospitals were chosen on base of surgical volume in the pre-pandemic period and on base of the state, which was just included if the SARS-CoV-2 incidence was more than 150 per 100,000 people. (74) When they analyzed the answers, they observed that 87 % of hospitals had to reduce their general surgical volume, while the majority of the hospitals in that proportion had remaining 20-60 % of the previous case load. More specific 33 % of the surgeons stated, that the number of oncologic surgeries was decreased, while 67 % did not notice any changes and the volume of oncologic procedures remained 100 %. On the question of justification of COVID-19 measures and thereby surgical limitations, 16 % of participants consider measures not justified and 78 % justify the measures just in case oncologic patients are treated within recommended time. 95 % were of the opinion that oncologic surgery for colorectal carcinoma should continue despite the pandemic, if surgery is indicated. (74)

Contrary results have been observed in Sweden and Denmark. Eklöv et**.** al (2022) found neither an increase in postoperative complications within 30 days of treatment nor increased percentages of emergency operations. Further they couldn't observe any delays in the referral process from diagnosis to surgical treatment of colon and rectal cancer. The authors conveyed their observational, population-based cohort study on a total of 1,140 patients, using the Swedish Colorectal Cancer Registry, in the Stockholm-Gotland region, which includes 8 hospitals with 5 of the 8 hospitals functioning as colorectal cancer centers, in the period of March 1st to August 31st 2019 and 2020. During the pandemic one out of the 8 hospitals was declared a COVID-19 free institution and surgeons continued surgical treatment of CRC patients during the pandemic. (75) They observed an upstaging of tumors, when comparing the 2019 with 2020 group. Thus, according to the TNM staging T1-T2 stage cancers and T3 stage

cancers decreased from 27 % to 22 % and 41 % to 33 %, respectively, and at the same the proportion of T4 stage cancers increased by 8 % (22 % vs. 30 %). Inconclusive results have been observed in the comparison of stage N0 cancers, which was lower during the pandemic (46 % vs. 41 %), but that decrease did not correlate with the simultaneous increase in N1-2 stage disease, which remained almost the same (50 % vs 51 %). No difference was observed when analyzing the metastatic stage (M0, M1 stage), the numbers of patients with planned surgery (81 % vs 84 %) or patients being treated with any other kind of surgical intervention (73 % vs. 77 %) for the 2019 and 2020 cohorts. (75) For patients with colon cancer they found no difference in proportion of patients treated with laparoscopic procedures or patients being treated in an emergency setting. The choice of type of resection was comparable between 2019 and 2020, as was the postoperative complication rate, the hospital length of stay, but they found an almost doubled proportion of created stomas (17 % vs 31 %) in 2020. (75) When they compared the pre-pandemic and pandemic patients with rectal cancer, they observed no change in proportion of patients treated with neoadjuvant chemotherapy (18 % vs. 16%) or neoadjuvant radiotherapy (45 % vs. 44 %), as well as no difference in the median time from diagnosis to surgery with neoadjuvant (146 days vs. 137 days) and without neoadjuvant therapy (37 days vs. 35 days). Further, no impact on surgical practice (changes < 5 % for type of resection surgery, stoma formation, laparoscopic surgeries) except a decrease in the 30 days postoperative complications (20 % vs. 13 %) have been reported. (75)

When comparing the impact of COVID-19 on the surgical practice or the postoperative mortality at 30 or 90 days after surgery, no difference could have been observed by Smith et. al. (2021) between the 2019 and 2020 cohorts in a study from Denmark, which has comparable results to the Swedish study. Nevertheless, they reported less total CRC diagnoses and less screening diagnoses in addition to almost 50 % reduction in the number colonic and rectal surgeries during the pandemic, while these did not differ in the Swedish study. (76) In the population based, nationwide cohort study using the Danish Colorectal Cancer Group (DCCG) database with 2,794 patients enrolled the authors compared demographic variables in patients like e.g. age, sex, ASA-score, UICC-stage of the diagnosed cancer, etc. and variables involved in the pre-/intra-/postoperative treatment of patients with CRC in the pre-pandemic and pandemic period (March 1st – August 1st 2019/2020). (76) Smith & colleagues reported a drastic decrease in the number of CRC-diagnoses made (45.4 %), a corresponding reduction in diagnoses made by screening pathways (48.2 %) in addition to a significant decrease in the surgical volume. The number of surgical procedures for colon cancer patients reduced from 187 to 96 operations/month and for rectal cancer patients from 63-32 operations/month (see fig. 9).

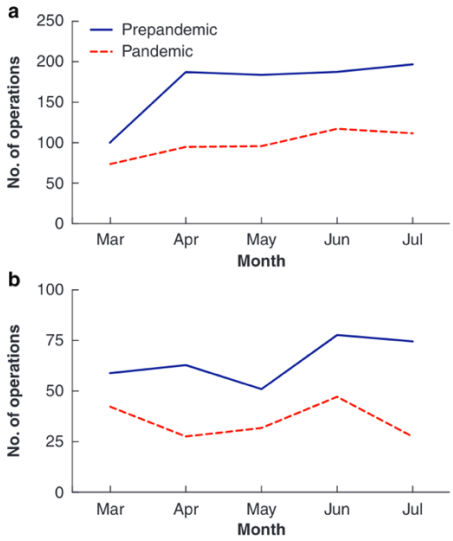

Fig. 9: Number of operations performed for colon cancer (A) and for rectal cancer (B) per month in 2019 (blue line; prepandemic) and in 2020 (red line; pandemic). Adapted from: Smith et. al. (2021) (76)

As reported in the UK study from Lesi. et. al. (2022), the Danish study could not confirm any change in the tumor stage stratification when comparing the two cohorts, and thereby stage I and stage III cancer remained the most common stages. Further, they observed a slight in increase in the proportion of patients with ASA 3 or above, while the proportion of patients with ASA 1 slightly reduced from 17.4 to 13.1 %. When analyzing the reported proportions of the variables involved in the treatment of patients with colon cancer, no difference in time from diagnosis to treatment, acute presentation, operative approach (laparoscopic vs. open), type of anastomosis (hand-sewn vs. stapled), stoma formation or neoadjuvant therapy can be seen. Nevertheless, during the pandemic less patients with colon cancer were referred for adjuvant therapy (35.1 % vs. 29.9 %), while the proportion of patients having received an adjuvant therapy has not changed. On the other hand, more changes have been observed in the treatment of patients with stage I-III rectal cancer. Comparing the pre-pandemic and pandemic cohort, there was an increase in robotic surgical approaches (40.5 % vs. 45.9 %), while the proportions for laparoscopic and open surgeries remained unchanged. Analyzing the procedures performed, one can see a decrease in anterior resections (56.6 % vs. 48.8 %), an increase in abdominoperineal excisions (34.2 % vs. 41.3 %) and similar proportions for Hartmann's procedures and proctocolectomies, comparing 2019 with 2020. Patients, who underwent neoadjuvant treatment, proportionally less patients received chemoradiotherapy (66.2 % vs. 54.0 %) and more patients were treated with neoadjuvant radiotherapy (25.7 % vs. 34.0 %). (76)

5.3 Impact of COVID-19 on the outcome of colorectal surgery and overall care of patients with colorectal carcinoma in the U.S.

Chen et. al. (2023) conveyed a retrospective analysis on the surgical outcomes of colorectal carcinoma in the pre-pandemic and pandemic period (April 2019 to December 2020) by using data from ACS-NSQIP database and its files on colectomies and proctectomies in that time interval. (77) In the study included where all patients older than 18 years of age, who were treated for all stages of colorectal cancer except non-operable, disseminated CRC and other diseases as benign neoplasms, diverticular disease, volvulus, etc. falling under the indication for surgical procedures as partial, total colectomies, total proctocolectomies, abdominoperineal resection, LAR and formation or revision of ostomies. (77) Included were just patients with a known ASA I-IV, who underwent open/laparoscopic and robotic surgical approaches, patients with a known hospital length of stay (LOS) and known destination they have been released to after the hospital stay. (77)

In the total number of 62,393 cases with 34,810 (55.8 %) and 27,583 (44.2) in the pre-pandemic and pandemic period, respectively, they observed beside the overall decrease in surgical volume by 11.6 %, that there was an increase in emergency cases (12.7 % vs. 15.2 %) with the largest increase in the second quarter (12.6 % vs. 17.1 %), when comparing the pre-pandemic with the pandemic period. At the same time the electively performed procedures decreased by 4.5 % (87.4 % pre-pandemic versus 82.9 % pandemic). (77) When they analyzed patients' physical status, they found that patients were somewhat younger during the pandemic (63 vs. 62 years of age) and that these had a higher ASA classification. In the pre-pandemic group 39.3 % of patients presented with ASA I-II, 51.9 % with ASA III and 8.8 % of patients had ASA IV. During the pandemic the percentage of patients with ASA I-II slightly decreased to 37.3 % while the percentage for ASA III and ASA IV increased slightly to 53.3 % and 9.4 %, respectively. Another interesting finding, which was observed among the patients presenting to hospitals from home, even though remaining the largest group, whose number decreased from 32,475 (93.3 %) to 25,564 (84.8 %), while the number of patients, who were referred from outside the hospital or other chronic care facilities remained almost unchanged, when the pre-pandemic group is compared with the pandemic group. (77) Another change was observed in the operative approach with the number of open performed surgeries slightly increasing (30.3 % vs. 32.8 %) and the number of laparoscopic surgeries decreasing (54 % vs. 51.0 %), while the proportion of surgeries performed robotically remained somewhat the same during the pandemic. Additionally, colorectal malignancies remained the most common indication for

colorectal surgeries and remained almost unchanged in both groups (pre-pandemic 41.0 % vs. pandemic 41.2%), while the proportions of other indications for colorectal surgeries (benign neoplasms, diverticular disease, volvulus, etc.) were lower during the COVID-19 pandemic. Further, Chen et. al. couldn't observe any significant differences in proportions of surgical procedures performed in both groups. (77) Finally, when they analyzed postoperative complications within 30 days of surgery in the pre-pandemic and pandemic group, they found increased proportions of bleeding, which required transfusion, (8.6 % vs. 10.2 %), higher rates of patients, who developed shock and sepsis (7.6 % vs. 9.0 %) and all of these contributed to the increase of overall morbidity (24 % vs. 27.0 %), which increased by a two-fold odd in patients with ASA IV , emergency surgeries, and open performed procedures among others. However, a change in the hospital length of stay could not be observed when comparing the pre-pandemic and pandemic group. (77)

In another retrospective analysis, conveyed by Patt et. al. (2020) by means of analyzing the number of cancer-specific procedures for chosen cancers (colon, lung, prostate, breast), which have been billed by various health care providers, and thereby estimating and comparing the change in the amount of these procedures for the months March-July 2019 and 2020. (78)

They found significant decreases in the frequency of billings for screening procedures for all cancers (colon screening 24.96-75.24 %), as well as decreases in performed biopsies with largest drop in April 2020 (colon biopsies 79.41 %). In addition, the frequency of billings for colectomy procedures decreased by 20.95-61.50 % depending on the month with April 2020 being impacted the most when comparing to April 2019. (78)

6. Discussion

Colorectal cancer is a complex disease and with the nature of the disease it is obvious that multiple levels and institutions of medical care involved in the detection, diagnosis, treatment and follow up and ultimate goal of increasing survival are impacted by the COVID-19 pandemic. The impact of COVID-19 on the different variables, including demographic, clinicopathological and variables regarding the treatment of patients with CRC, whether surgical or conservatively, is very difficult to measure and there are significant variations in the choice of study methods, variables and results of these when reviewing numerous studies from different countries in Europe, studies from the United States, and taking other international studies into consideration. (66,71,72,74–78) The different results can be partially explained with the different course regarding the COVID-19 pandemic, including incidence rates,

mortality rates, timing of the disease intervals/waves in the countries. Additionally, even though recommendations for introducing public health and social measures by numerous professional societies arrived quickly, the response and timing of the adaptation varied widely among the countries. Therefore, some countries adapted with initially more strict containment strategies, while others had a more liberal approach. (76) Further, studies, which have been reviewed, chose different variables when measuring changes in the surgical treatment of CRC in the pre-pandemic and pandemic period, which made it very difficult to compare these results with each other. However multiple variables were extracted and are showing similar trends among the countries. Since colorectal patients are not managed solely by surgical therapy, rather managed by a multidisciplinary team consisting of different specialties, and thereby impacting surgical treatment regarding treatment modality, short-term and long-term outcomes. Therefore, if any level of oncologic management is impacted by the pandemic, it could certainly impact the surgical treatment of these patients, which makes statements about the impact of COVID-19 solely on the surgical treatment of a complex disease like colorectal cancer difficult. However, after reviewing, all of the included studies show a decreased number/proportion of referrals of patients with diagnosed CRC from primary care to definitive treatment with more or less changed proportions. (66,71,72,74–78) It is evident that COVID-19 pandemic and its consequences on medical health care caused a reduction in number of diagnoses, diagnostic procedures, especially colonoscopies as the most common chosen procedure for definitive diagnosis and a reduction in screening of colorectal carcinoma and by that delaying medical treatment (66), partially explaining the decreased numbers of surgeries, since less patients were detected and referred to treatment, as shown by multi-national studies. (71,74–76,78–81) This postponement of detection of colorectal cancer through screening programs or routine check-ups, as known will negatively impact the short-and long-term outcome of cancer patients detection of more advanced cancer (79,82). Beside the surgical volume, when analyzing the pandemic impacting surgical treatment by reviewing changes in surgical approach (open vs. laparoscopic), surgical setting (emergencies vs. elective surgeries), surgical technique, surgical quality, it can be concluded, that COVID-19 had just a limited effect on these. Multiple studies observed increases in surgeries performed in an emergency setting, which could be explainable with the decreased referrals rendering these patients to higher stages and thereby developing emergent symptoms, e.g. intestinal obstruction, bleeding, etc. or with the hesitancy of patients seeking health care due to fear of SARS-CoV-2 infection. (77) Further laparoscopic and laparoscopic assisted procedures decreased, while at the same time an increase of open performed surgery was noticed. (66,77) This could be connected to the fear of medical staff

being infected during laparoscopy, since laparoscopy is considered to produce aerosols, which could potentially viral vectors (77,83). Another theory could be that in case of a converted laparoscopic colorectal surgery the post-operative morbidity, e.g. ileus, operating time, thereby time under anesthesia and hospital stay are prolonged (84), which would lead to an additional pressure on the health care, since hospital capacities were scarce due to resource allocations. Never the less some studies showed no significant change in the chosen procedures. (75,76) Additionally, some studies noticed an upstaging of colorectal cancer (higher TNM-stages) and an increase in the ASA-score, which means patients presented in a worse overall condition, or just a decrease in the presentation of patients with a lower ASA-score. (66,72,77). Matosević et. al. showed that the number of dissected lymph nodes did not change significantly during the pandemic, which indicates that surgical quality did not suffer in the operating theatre, since number of dissected lymph nodes correlates with surgical performance quality and is associated with better survival especially in patients with stage I and stage II cancer. (52,66,85). Furthermore, perioperative complications, meaning complications within 30 day of surgery, did not change significantly and were comparable in 2019 and 2020. (75–77) Finally, whether or how much COVID-19 impacted the overall survival and quality of life of patients with colorectal cancer remains unknown, even though some studies suggest upstaging of tumors (72,75), which is one of the main prognostic factors on survival of colorectal cancer patients, the exact impact on long-term survival will be seen at a later point of time. Additionally, there is an unknown number of undetected patients with CRC, which unavoidable will progress to more advanced stages and thereby cause more morbidity and mortality in the near future. One prediction model suggests that with a 24-month recovery there will be over 7,000 excess cases of CRC and almost 7,000 excess deaths associated with CRC during 2020-2040 in the US. (86) Other models predict the same trend of excess cancer-related deaths, decrease of overall survival and years of life lost in the UK. In conclusion, COVID-19 had definitely an significant impact on screening, diagnosis and early detection of disease due to national restrictions, resource allocations and effects on patients behavior, even though surgical treatment, surgical approach, surgical techniques and quality have been impacted limited pre-/intra- and postoperatively, and therefore did not change the surgical treatment of colorectal cancer patients per se.

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10. Biography

Antonio Pudić was born on the 7th of September 1994 in Munich, Germany. After attending four years of elementary school, he went to Heinrich-Heine grammar school where he finished the German Abitur, which is a requirement for attending Universities, with focus on sciences in 2013. Firstly, studying biology at the Technical University of Munich (TUM) during which time he found his interest particularly in cell biology and oncology especially in gastrointestinal cancers. The individual work with patients and the social work in the management and treatment of these diseases, however, was limited. Therefore, in 2017 Antonio decided to follow his long wish and dream of studying medicine at the Medical School of the University of Zagreb, which he finished in 2023, and thereby contribute actively in the management of patients. During various courses of medical studies and the clinical rotations, he was interested in the anatomy, pathology and treatment of patients with gastrointestinal cancers. Additionally, from the beginning of studies he participated in the activities of the Student Surgical Society, where he became familiar with surgical techniques, the surgical management of patients and developed fascination for the surgical specialty. While being part of the managing board of Student Surgical Society and contributing to organization of various workshops as vice-president (2022-2023), he was able to collect first experiences as lecturer on topics e.g. primary wound management and participating in congresses e.g. the 8th Croatian Surgical Congress. All these experiences led to the decision of finishing Medical School with a graduation thesis on the surgical management of patients with the most common gastrointestinal cancer, namely colorectal carcinoma under the mentorship of Petar Matošević, MD., PhD., Assist. Prof., and pursue further education in the field of abdominal surgery as a resident in the future.