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AIM: *The aim of this study is to point out the changes and possible delay in diagnosis or treatment of malignancies and an added risk of COVID-19 exposure emerging from these interventions, as well as to underline the increase of surgical demand once the pandemic measures are eased.*
METHODS: *This study is a retrospective review of the patients operated between 11.03.2020 and 31.05.2020 in a center with a high incidence of COVID-19 infection during the pandemic. The numbers of emergency, elective and oncological surgeries as well as the increasing or decreasing trends of these interventions between March 11 and May 31 of previous years were compared with the corresponding period of 2020 or in other words the pandemic period.*
RESULTS: *From March 11 to May 31, 2020 there was a progressive reduction in surgical activity, with only 195 operations: 61(31,28%) on a scheduled basis for tumor pathology, 59(30,25%) for benign pathology and 75(38,46%) for emergency indications. When the surgical trends of previous years are considered, all types of oncological surgeries decreased significantly in pandemic period March 11 to May 31, 2020.*
CONCLUSION: *One of the most striking changes in medical care settings during the COVID-19 pandemic was observed in surgical management strategies. The most significant among these were the limitation of elective surgical procedures and the prioritization of emergency or non-delayed oncological operations. One may speculate that the standstill of elective surgeries including the oncological surgeries might have long term impacts on the clinical outcomes of patients as well as the healthcare workers and organizations.*

KEY WORDS: COVID-19, Emergency, Oncology, Pathology, SARS-CoV-2, Surgery

Introduction

SARS-CoV-2 was first identified in Wuhan, China in December 2019 and spread rapidly to almost all over the world and infected millions of people [1]. The disease caused by SARS-CoV-2 was named as COVID-19 by World Health Organization (WHO). The virus is a novel agent potentially affecting the lower respiratory tract and causing pneumonia. A world-wide alarm situation was declared by WHO on March 11, 2020 [2]. Turkey reported the first COVID-19 case on March, 10, 2020 and by 1 April, it was confirmed that the virus had spread all over the country. On 14 April 2020, the spread of the virus in Turkey has reached the peak value by the fourth week and started to decrease [3]. At that time, a total number of 65111 confirmed cases, 1403 deaths and 4799 recovered cases were reported in Turkey [4].

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The SARS-CoV-2 is a RNA virus with a size ranging between 0.06 and 0.14 microns. The virus has been traced throughout the entire gastrointestinal tract from the mouth to the rectum, and in the nasopharynx, the upper respiratory tract and lower respiratory tract, feces and peritoneal fluid. On the other hand, it has not been observed in urine and CSF [5].

The COVID-19 pandemic caused an overwhelming stress to almost all countries particularly and imposed a burden to national health-care systems. Despite being debatable, most experts agree that the COVID-19 is not just an issue of today but will have further impacts in future. Patients who require oncological treatment are at high risk of COVID-19 associated disease. The common sense behind the measures of hospital settings and to postpone the elective surgeries is to minimize the possible exposure to virus for the risk groups. On the other hand, there are different approaches regarding the elective surgical interventions for malignancies. Individually evaluation of cancer patients based on their current clinical status and additional comorbidities is considered as a rational approach.

During the COVID-19 pandemic, triage was needed particularly in oncological surgery for various reasons, such as minimizing the contact of patients to hospital environment, potential shortage of personal protective equipments (PPEs), potential insufficiency of health care professionals and limited availability of hospital beds, intensive care unit (ICU) beds and ventilators for COVID-19 patients. According to the triage criteria reported by American College of Surgeons (ACS) there are three acute pandemic phases. In phase 1, the number of COVID-19 patients in hospitals is low, resources such as hospital and ICU beds, ventilators and healthcare professionals to manage services are sufficient, and elective surgeries are restricted to patients in need of an operation as soon as possible. In phase 2, the number of COVID-19 patients is higher and the hospitals have limited resources. In phase 3, hospitals are full of COVID-19 patients and the medical resources are insufficient. During the phase 2 and 3, only the emergency operations can be performed [6].

More than 100 clinical trials worldwide are being conducted in order to contribute to our knowledge about the novel coronavirus. Previous experiences with viral disorders, particularly the Spanish flu pandemic in 1918 showed that the multiple waves are to be expected and unfortunately the highest mortality was reported in the second wave in Spanish flu pandemic [7]. Experts speculate that a second wave of COVID-19 pandemic is to be foreseen in fall 2020. On the other hand, even the most optimistic projections do not promise an accessible vaccine until early 2021. Therefore it is very important to get ready for a possible flare in order to adjust the health care facilities in case of a medical emergency condition as a whole.

Methods

The data regarding the patients operated between the declaration of the National State of Alarm in March 11 and May 31 in a third-degree university hospital in Istanbul, Turkey was retrospectively analyzed. Between March 11 and March 31, there were only a few COVID-19 patients and hospital resources were sufficient. The institution still had enough ventilator capacity in ICUs and the spread of COVID-19 was not rapidly escalating.

By the declaration of the National State of Alarm on March 31 the elective surgeries were almost completely suspended until further notice. On 1st April 2020 the Turkish Ministry of Health declared that the COVID-19 has spread to the whole country. The maximum number of COVID-19 cases was reached on 14th April 2020 and the spread decelerated in following days. Between 1st and 20th April there were many proven COVID-19 cases hospitalized in our center, ICU and ventilator capacities were overwhelmed, the operating room (OR) supplies were limited and the number of COVID-19 cases possessed an increasing trend. The peak number of COVID-19 cases was passed in our center by 20th April and fewer cases were diagnosed in following days.

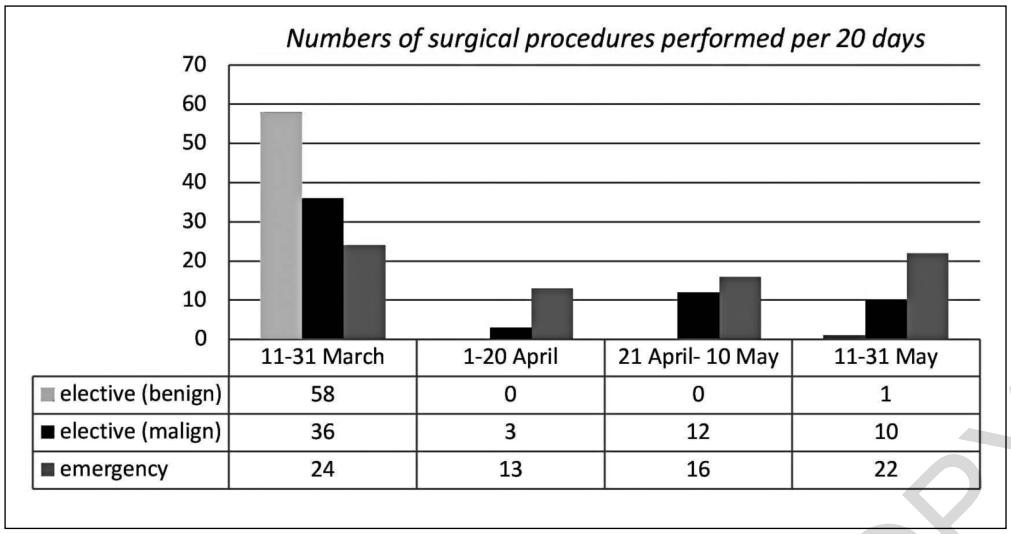
The medical resources namely the hospital as well as the ICU beds, ventilators, blood products, healthy medical professionals, PPEs, and critical testing were back to sufficient and elective levels. The number and the decreasing or increasing trends of emergency, elective as well as the oncological surgeries performed between March 1st and May 31st were compared to that performed between the corresponding dates of 2017 and 2019 in order to point out the change in surgical operations in pandemic conditions.

Results

On 1st April 2020 the Turkish Ministry of Health announced that the coronavirus has the whole country. During this alarm period, elective surgeries were still being performed in our center between 11th and 31st March. By 31st March, it was decided to perform only emergency and oncological operations which cannot be further postponed in accordance with an individual evaluation of each case.

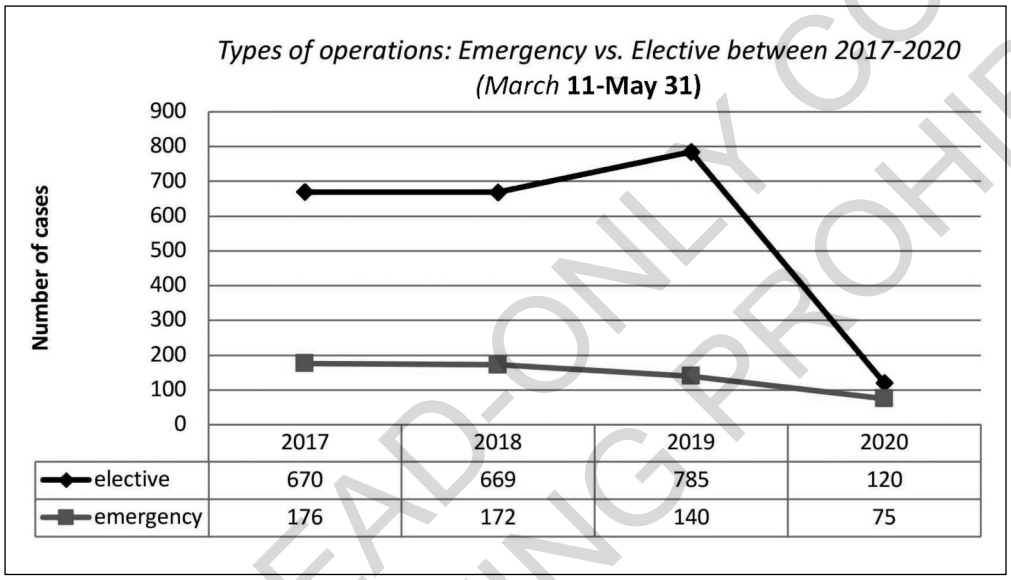
Between 11th March and 31st May 2020, a total of 195 patients were operated: 61 (31,28%) on a scheduled basis for tumor pathology, 59 (30,25%) on a scheduled basis for benign pathology and 75 (38,46%) with an emergency indication. Until 31st March 2020, the usual healthcare activity was maintained, which then decreased subsequently initially at the expense of scheduled procedures for benign pathology. By 20th April almost all surgical interventions were suspended. By this date the patients with an oncological pathology have been select-

Table I



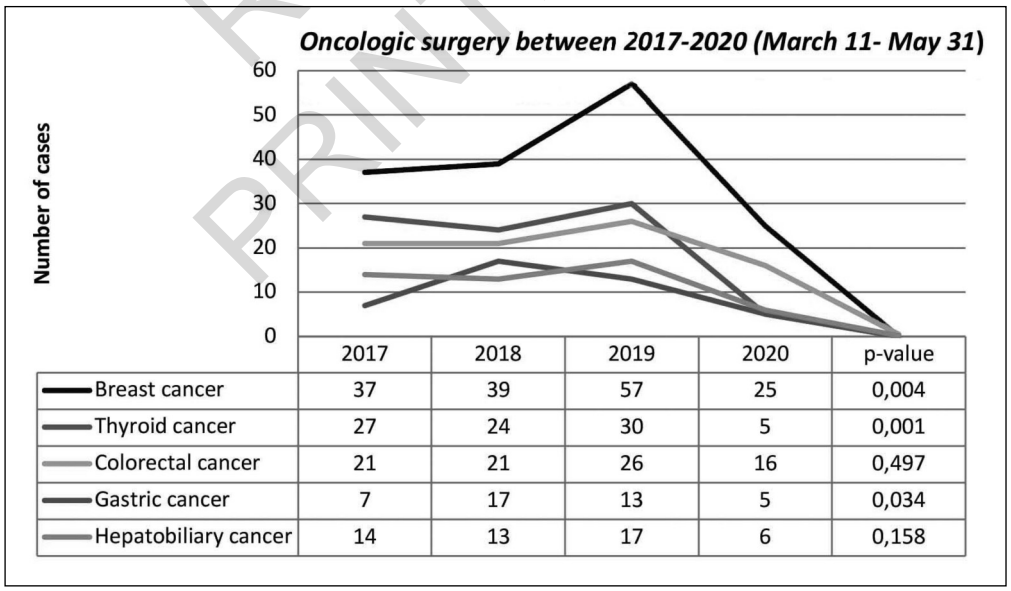
	11-31 March	1-20 April	21 April- 10 May	11-31 May
elective (benign)	58	0	0	1
elective (malign)	36	3	12	10
emergency	24	13	16	22

Table II



	2017	2018	2019	2020
elective	670	669	785	120
emergency	176	172	140	75

Table III



	2017	2018	2019	2020	p-value
Breast cancer	37	39	57	25	0,004
Thyroid cancer	27	24	30	5	0,001
Colorectal cancer	21	21	26	16	0,497
Gastric cancer	7	17	13	5	0,034
Hepatobiliary cancer	14	13	17	6	0,158

ed, giving a priority to those with a high risk of imminent complications. Table I demonstrates the activity level of the service per 20 days between 11th March and 31st May. None of the patients operated in our center had a postoperative COVID-19 infection.

Among 120 elective cases, 94 were operated between 11th March and 31st March, and the remaining 26 were operated in April and May due to the potential hazard to the patient in case of delay as a result of pandemic settings. The elective surgical procedures performed for these 26 cases were as follows: low anterior resections (for rectum adenocarcinoma) (n=6), liver metastasectomy (hepatic metastases from adenocarcinoma of rectum) (n=1), total gastrectomies (for gastric adenocarcinoma) (n=3), Hartmann operation (for rectum tumor) (n=1), right hemicolectomy (for obstructive right colon tumor) (n=1), 1 left hepatectomy (for klatzkin tumor), hepaticojejunostomy (for gallbladder cancer) (n=1), whipple procedure (for periampullary tumour) (n=1), loop colostomy (for unresectable and obstructive sigmoid colon cancer) (n=1), breast conserving surgery (n=2) and mastectomy (for breast cancer) (n=5), parathyroidectomy (for primary hyperparathyroidism with life-threatening hypercalcemia that cannot be controlled medically) (n=1), stamm gastrostomies (for nutritional palliation of upper esophageal cancer) (n=2).

The number and the decreasing or increasing trends of emergency, elective as well as the oncological surgeries performed between March 1st and May 31st were compared to that performed between the corresponding dates of 2017 and 2019. During the period of pandemic, despite the modest decrease in emergency surgeries than that in elective surgeries, emergency surgeries actually decreased due to the conservative measures (Table II). The average number of daily emergency surgeries in March decreased from 1.14 to 0.66 in April. By the end of April, we past the peak number of COVID-19 cases and emergency surgical interventions increased to 1.0 in May. Similarly, the average number of daily elective surgical interventions was 4.47 in March and to 0.3 in April and increased to 0.54 in May. Breast cancer incidence increased remarkably from 2017 to 2019. The trends of thyroid cancer, colorectal cancer, hepatobiliary cancer were stable between 2017 and 2019; a slight increase was evident for each. Despite the increase in gastric cancer surgery in 2018, the rate was decreased in 2019 and was significantly decreased in pandemic period as in other types of oncological surgeries such as breast and thyroid cancer ($p < 0.05$, chi square test) (Table III).

Discussion

The COVID-19 pandemic has a drastic impact on healthcare systems and it has altered the way surgical management worldwide. Emergency surgery is still considered as a priority for admission and selected patients should be consulted reasonably and thoroughly. Tumor doubling time varies between malignancies. Therefore, postponing the surgery and follow-up, if possible, should be decided according to the type of malignancy in pandemic settings. Laparoscopic surgeries must follow strict rules through the concerns regarding the safety of medical professionals during these procedures. Since there is a risk of viral spread through carbon dioxide aerosolization, laparoscopic surgery should be avoided as much as possible [8].

In case of cancer-related intestinal perforation, complete intestinal obstruction and acute hemorrhage, patients are urgently operated in all phases. For pre-cancerous lesions invading submucosa and muscularis propria (T1-T2, N0), it is advised to postpone surgery according to level of the epidemic. Neoadjuvant chemotherapy is recommended for locally advanced (T3-T4) resectable colon cancers. In pandemic settings, 5 fraction short-term radiotherapy should be considered instead of 28 fraction radiotherapy. Recent data suggest that the operation may be delayed for at least 4-8 weeks as tumor stage regression develops with short-term radiotherapy. In case of regression of the tumor grade, surgery can be delayed up to 12-16 weeks with neoadjuvant therapy. Additional systemic chemotherapy regimens should be considered in case of a longer delay [9,10]. All these situations must be evaluated individually according to the overall oncological risk, the risk of occlusion and the risks of immunosuppression. All rectum tumor cases operated during the pandemic period in our center have completed neoadjuvant therapies and have been operated at the time when the hospital resources were adequate.

Percutaneous endoscopic gastrostomy (PEG) tube placement is the mainstay approach for a durable enteral access, replacing the more interventional surgical gastrostomy. Unfortunately the endoscopic PEG insertions were also suspended during the pandemic period [11]. During this period two surgical gastrostomies were performed in our center. One of the cases had a massive lesion infiltrating the esophagus at the apical segment in the upper lobe of the right lung. Endoscopic passage at the 30th cm from the teeth in the esophagus was not evident. The other patient had a malignant lesion which invaded trachea at the anterior part, filling the lumen prominently at the level of the pharyngoesophageal junction, and there was a tumoral formation which invaded 80% of the lumen starting from the pharyngeal entrance up to the middle part of the esophagus.

Endoscopic passage was blocked due to tumor bleeding. Surgical gastrostomy procedures were performed for these two cases while the PEG tube placement was already impossible.

Three gastric cancer surgeries were performed in our center during the pandemic period. One of these cases had an ulcerovegetant tumoral mass with a diagnosis of adenocarcinoma which presented with a hemorrhagic gas-

tric tumour requiring intermittent transfusion and gastric outlet obstruction. One of the cases were being treated based on an intention-to-treat approach and had completed his neoadjuvant chemotherapy and post-chemotherapy assessment for resectability, was suitable for surgical resection. Total gastrectomy and Whipple procedure were performed for the other case with the indication of gastric carcinoma irresponsive to neoadjuvant chemotherapy and was penetrating the pancreas and causing gastric outlet obstruction.

Those with fast-growing breast cancers (triple negative and HER2 positive) receive the exact same standard of care with preoperative chemotherapy. On the other hand, those who have slower progressing breast cancer such as ER positive and HER2 negative types are preferably treated with an endocrine (anti-hormone) approach first instead of surgical management strategies [12]. Among 7 breast cancer cases operated in our center, 5 had completed neoadjuvant chemotherapy and the 2 were newly diagnosed breast cancer. Primary surgery could not be delayed in 2 newly diagnosed breast cancer cases since the benefit of chemotherapy or endocrine therapy was predicted to be low. The other 5 breast cancer cases have completed neoadjuvant chemotherapy treatment and the surgical priority has been given to these cases when hospital resources were back to normal.

In the case of primary hyperparathyroidism due to a parathyroid adenoma, hypercalcemia, a potentially life-threatening condition irresponsive to medical treatment may emerge. Hypercalcemia irresponsive to medical management must be scheduled as an urgent surgical condition also in the case of an epidemic [13]. A potential exposure to COVID-19 might be more hazardous to a dialysis patient, therefore a surgical approach is not recommended for secondary hyperparathyroidism during the pandemic [14]. Preoperative and postoperative laryngoscopic vocal cord examinations were avoided as much as possible. Since the prognosis of the differentiated thyroid malignancies are favorable and the management of anaplastic, poorly differentiated thyroid cancers and lymphoma are primarily medical or oncological; benign or malign thyroid disorders were not surgically managed in our center during the pandemic and the elective surgeries were postponed [15].

Urgent surgery should be performed for obstructive or nearly-obstructing colorectal cancer (CRC), acute transfusion-dependent tumors, cancers with a suspected local perforation and sepsis and post-operational complications. A case of obstructive right colon tumor and a sigmoid colon tumor were operated in our center during the pandemic period.

In one of the cases with a periampullary tumor which caused jaundice, biliary colic emerged as a result of early biliary obstruction. During the Endoscopic Retrograde Cholangiopancreatography (ERCP) procedure, a hemorrhagic and ulcerated lesion at the second part of the duodenum invading the 70% of the papillae and the surrounding lumen was visualized. Resection of the periampullary malignancies have been reported to be promising in terms of long-term survival rates and the non-operative management strategies are generally inefficacious. Pancreaticoduodenectomy with (Whipple operation) pylorus preservation was performed for our case following an intensive preparation. A case with Klatzkin tumor of cholangiocarcinoma type which emerges at the hilum was managed with left hepatectomy. An elective definitive surgery including Roux-en-Y hepaticojejunostomy was performed for the patient with gallbladder cancer. Right hepatectomy was performed on metastasis in the 6th and 7th segments for the case with who had a surgical history of rectum tumor. Each patient with an aggressive hepatobiliary malignancy should be operated as indicated. However if they respond to and tolerate the neoadjuvant chemotherapy the non-surgical approaches should be maintained and surgical management can be delayed [16].

The readily accessible COVID-19 tests performed in our center are nasopharyngeal swab or bronchoalveolar lavage polymerase chain reaction rapid testing for the genetic material of COVID-19. Preoperative testing is was mandatory for all cases. For semi-urgent cases, COVID-19 was tested 48 hours before the scheduled procedure if possible [17]. None of our patients who were operated in during the pandemic was tested positive for COVID-19 in the postoperative period.

The majority of the population shows only mild –if any- symptoms even if they are infected with COVID-19. However serious manifestations have been noted particularly in patients with a pre-existing medical condition or in elderly population. Cancer patients are generally considered as high-risk population for infectious diseases and COVID-19 does not seem to be an exception. Cancer itself not only deteriorates the immune functions but the oncological and surgical management weaken the immune system. Liang et al. was first to evaluate the patients with cancer in COVID-19 settings and reported a higher-than-normal risk of morbidity and mortality in a small population of cancer patients in comparison with the healthy patients. However the sample is small and heterogeneous with different types of cancer and additional comorbidities [18].

According to our preliminary experience, we state that the cancer patients might safely be operated during the pandemic. The numbers of hospital visits during a standard chemotherapy or radiotherapy are generally a lot higher and the immunosuppressive effects of these management strategies make these patients even more susceptible for infectious diseases. If the medical resources are not scarce, we believe that operating these cases once all the necessary precautions are taken is relatively safe during a pandemic and the potential hazard of a delayed surgery can be avoided.

The incidence of thyroid cancer surgery decreased more than other cancer types in COVID-19 period in com-

parison with that in previous years since the diagnostic procedures such as ultrasound and fine needle aspiration biopsy were performed only to a limited population during this period and the patients with indeterminate nodules (Bethesda III and IV categories) were preferred to be followed up. The risk of malignancy that the nodules of Bethesda categories III and IV possess range between 5% and 15%. Intrathyroidal Papillary Microcarcinoma (PTMC) was also preferred to be actively followed up [19].

Gastric and esophageal cancers are both aggressive and difficult to diagnose in early stages. It is to speculate that during this period, self-medication and empirical treatment of dyspepsia with antacids and H2-receptor antagonists increased, since the patients avoid going to outpatient clinics [20]. Unfortunately, we expect high-risk patients to appear in the advanced stages in the following months due to a possible delay in endoscopic procedures and diagnosis.

Delayed diagnosis of breast cancer leads to progression of the disease, the need of aggressive treatments, risk of complications and sequelae and an overall poor prognosis [21]. Although breast cancer has a good prognostic outcome when compared with many other malignancies, over the last 5 years survival rates reported from high-income countries range between 84 and 89% survival rate which is attributable to a the advanced stages at presentation [22]. Delayed diagnosis of breast cancer in women presenting symptoms for 3 months or more is associated with poor prognosis and survival rates [23]. The change in behavior during the pandemic, in other words a delayed administration of the patient to a medical facility since the first symptoms is the patient factor, but there is also a systematic factor which means the delay in concrete diagnosis and management since the first consultation.

A routine screening of CRC traces most of the cases and the CRC cases are only rarely diagnosed since they present with symptoms [24]. The screening programs were not properly functioning during the pandemic period and the number of diagnosed of CRC cases decreased significantly. Patients with locally advanced rectum tumors who had completed neoadjuvant therapies were operated once the resources were sufficient. Therefore, CRC surgery did not decrease significantly in this period compared to other oncological surgeries. When asymptomatic pancreatic neuroendocrine tumors (NETs), duodenal and ampullary adenomas, gastrointestinal stromal tumors (GISTs) or high-risk intraductal papillary mucinous neoplasms were evident, surgeries were postponed if the delay was not hazardous to the patient. In case of a liver tumor, chemotherapy and other alternative procedures such as ablation were recommended if possible [25]. If possible, all other aggressive hepatobiliary malignancies were operated during this period.

Recent regulations of the hospitals required designated COVID-19 zones in almost each medical facility. In case of a concomitant wave, there might be centers assigned to treat COVID-19 cases and centers that are 'non-COVID-19' or so-called 'uncontaminated'. With the help of these measures and our cumulative experience with COVID-19, the resources of medical care facilities might be used more reasonably and the 'non-COVID-19' hospitals might have somewhat more opportunity to fight with other diseases particularly with oncological and surgical conditions in order to avoid systematic delay in diagnosis and treatment. Where there are no designated hospitals for COVID-19 cases but the given medical facility is not completely overwhelmed by COVID-19 and the medical resources are not scarce, it might be reasonable to maintain elective procedures. Not only the treatment but also the diagnostic procedures, such as endoscopy, biopsy or other imaging modalities were delayed and limited until the medical resources improved. Delayed diagnosis in malignancies, particularly in some certain types might increase the number of patients with a worse prognosis, requiring aggressive treatments and might also decrease the survival rates [26].

Conclusion

The impacts of COVID-19 pandemic in clinical outcomes are especially significant in cancer patients. Rapid changes in diagnostic modalities and treatment protocols, social distancing measures, the behavioral changes of patients seeking for medical care and the economic impact of the pandemic as well as the deaths secondary to COVID-19 infection are some leading factors that deteriorate the overall output of heath care systems. 'Returning to normal' should be gradually concerned especially in medical facilities once the COVID-19 burden is lifted, since there will be an increasing demand in medical care for non-COVID-19 indications due to delay in optimal management and the limitations in outpatient clinical settings during the pandemic.

Riassunto

Lo scopo di questo studio è di evidenziare i cambiamenti e il possibile ritardo nella diagnosi o nel trattamento di tumori maligni e un ulteriore rischio di esposizione a COVID-19 che emerge da questi interventi, nonché di sottolineare l'aumento della domanda chirurgica una volta che le misure pandemiche saranno alleviate.

Questo studio è una revisione retrospettiva dei pazienti operati tra l'11.03.2020 e il 31.05.2020 in un centro con un'alta incidenza di infezione da COVID-19 durante la pandemia. Il numero di interventi chirurgici di emergenza, elettivi e oncologici, nonché le tendenze crescenti o decrescenti di questi interventi tra l'11 marzo e il 31 maggio degli anni precedenti sono stati confrontati con il corrispondente periodo del 2020 cioè con il periodo di pandemia.

Risultati: dall'11 marzo al 31 maggio 2020 si è verificata una progressiva riduzione dell'attività chirurgica, con solo 195 interventi: 61 (31,28%) su base programmata per patologia tumorale, 59 (30,25%) per patologia benigna e 75 (38,46%) per indicazioni di emergenza. Quando si considerano le tendenze chirurgiche degli anni precedenti, tutti i tipi di interventi chirurgici oncologici sono diminuiti significativamente nel periodo di pandemia dall'11 marzo al 31 maggio 2020.
Conclusione: uno dei cambiamenti più sorprendenti nelle impostazioni di assistenza medica durante la pandemia di COVID-19 è stato osservato nelle strategie di gestione chirurgica. I più significativi tra questi sono stati la limitazione delle procedure chirurgiche elettive e la definizione delle priorità delle operazioni oncologiche di emergenza o non ritardate. Si potrebbe ipotizzare che l'arresto di interventi chirurgici opzionali, inclusi quelli oncologici, potrebbe avere impatti a lungo termine sugli esiti clinici dei pazienti, nonché degli operatori sanitari e delle organizzazioni.

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