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AIM: *The aim of the study was to analyze whether COVID-19 cause a delay in the diagnosis of gastric cancer patients particularly in the TNM staging of the tumor, or not.*
MATERIAL AND METHODS: *This retrospective single-center study included the patients diagnosed with gastric cancer from March, 2019 to December 2020. The patients were divided into two groups: baseline and the pandemic groups. The following parameters were compared between the groups; demographic data, numbers of newly diagnosed patients, type of the surgery, location of the tumor, frequency of neoadjuvant treatment, ASA score, length of hospital stay, clinical staging and pathologic TNM staging.*
RESULTS: *The mean monthly number of newly diagnosed gastric cancer patients showed a significant decline from 7.5 to 5.6 ($p< .001$). There were no statistically significant differences between the groups with regard to the demographic factors, except CA 19-9 levels. Patients in the pandemic group had higher both clinical and pathological T-stages ($p<0.05$).*
CONCLUSIONS: *Our study showed a decline in the number of the newly diagnosed patients with gastric cancer during the pandemic and also more patients presented with advanced stage during the pandemic period. This study showed that the pandemic causes a potential delay in the diagnosis of gastric cancer patients.*

KEY WORDS: Cancer surgery, COVID-19, Gastric cancer, Gastric surgery SARS-COV-2, Pandemic

Introduction

On 11 March 2020, the World Health Organization declared a global Coronavirus Disease 2019 (COVID-19) pandemic [1]. Since then, the Turkish government has taken many strict control measures, including travel restrictions and a curfew. Also, the ministry of health has closely monitored the COVID-19 infection and mortality rates. Elective operations other than emergency surgeries were postponed during periods of increased patient burden. Outpatient clinic admissions were also restricted to reduce both social interaction and healthcare staff's workload. In addition, COVID-19 pandemic has caused changes in both individual behaviors and also health system priorities.

While the entire healthcare system has struggled with pandemic under heavy patient burden and stress, it may have had a negative effect on patients with chronic diseases and oncological patients. The delay in the screening programs during the pandemic period has already been reported in the literature [2-4]. During the pandemic, issues such as which type of cancer is more urgent than another, and how long the treatment of which can be delayed have become to be discussed [5-8]. Gastric adenocarcinomas are usually insidious pathologies. In the current literature, data regarding the effect of the pandemic particularly on the clinical and pathological stages of the gastric tumor is very limited.

Our hospital is a tertiary reference center and has a high volume of patients with gastrointestinal system cancers. In this study, we aimed to analyze whether COVID-19 cause a delay in the diagnosis of the gastric cancer

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patients particularly in the TNM staging of the tumor, or not and to compare the number of the newly diagnosed patients with gastric cancer before and during the COVID-19 pandemic periods.

Materials and Methods

This retrospective cross-sectional study was approved by the Ethics Committee of the Adana City Training and Research Hospital (date: 13.01.2021, decision number: 74/1248). This study was conducted in accordance with the 1983 Helsinki Declaration.

The study included the patients diagnosed with gastric cancer during the period between March 1, 2020 and December 31, 2020 in the pandemic group at the Adana City Training and Research Hospital, Department of General Surgery, Divisions of Gastroenterological Surgery and Surgical Oncology. For the baseline group, patients diagnosed with gastric cancer between January 1, 2019 and December 31, 2019 was included at the same department. At our hospital, the patients were evaluated in a multidisciplinary council attended by oncologists and surgeons. All patients that completing neoadjuvant treatment were evaluated in the multidisciplinary council. Thus, our study included those patients. The flow diagram summarizes the patient selection protocol.

Clinical and pathological data of the patients were retrospectively collected from the hospital medical records. The following parameters were compared between the pandemic and baseline periods; age and gender distributions, mean monthly numbers of newly diagnosed patients, CEA and CA 19-9 levels, the type of the surgery, the location of the tumor, the frequency of the patients receiving neoadjuvant treatment, American Society of Anesthesiologists (ASA) score, length of the hospital stay, clinical staging and pathologic TNM staging.

Clinical staging was determined based on the results of a physical exam, biopsy, and imaging tests including computed tomography (CT), PET CT, endoscopy and the endoscopic ultrasound. Surgical stage refers to the pathologic stage of the surgical specimen determined based on the American Joint Committee on Cancer (AJCC) TNM system. The resectability criteria were as follows: not having metastatic or T4b tumor according to the TNM stage, not having any evidence of peritoneal implant, or invasion of major vascular structures. Our data included the patients operated for curative surgery. Palliative surgery patients were not included in the study.

Statistical analysis was performed using the statistical package SPSS software (version 25.0,_Armonk, NY: IBM Corp,USA). If continuous variables were normal, they were described as mean ± standard deviation, and if they were not normal, they were described as the median. Comparisons between groups were applied using the Student t test or Pearson Chi-square test. Values of $p<0.05$ were considered statistically significant.

Results

One hundred and forty six newly diagnosed gastric cancer patients were assessed as eligible for the study. Ninety of these patients were in the baseline group and fifty-six of the patients were in the pandemic group. The mean monthly number of newly diagnosed gastric cancer patients showed a significant decline from 7.5 to 5.6 ($p< .001$). At the time of the diagnosis 24.4 % of the patients in the baseline group and approximately 28.6% of the patients in the pandemic group had distant metastases; however the difference was not statistically significant ($p\geq 0.05$). The flow diagram of the patients was summarized in Fig. 1. As a result, a total of 106 patients were included in the analyses and among all patients, 34.9 % (n=37) were female, and 65.1% (n=69) were male. The demographical characteristics of the patients in both groups were listed in Table I.

The study included 40 patients with a mean age of 60.23±12.9 years from the pandemic period and 66 patients with a mean age of 60.85±12.8 years from the baseline period.

There were no statistically significant differences between the groups with regard to the demographic factors including age, gender and CEA levels (p values were as follows respectively; p=0.81, p=0.20, p=0.47). CA 19-9 level was higher at the pandemic group when compared with the baseline group (p=0.019).

When we compared the tumor locations, there was not a statistically significant difference among the groups (p=0.58). We also had no statistically significant differences between the groups regarding the surgical types (total gastrectomy vs subtotal gastrectomy/ wedge resection) (p=0.20), ASA scores (p=0.16), the frequency of the patients receiving neoadjuvant chemotherapy (p=0.89), the length of the hospital stay (p=0.42).

Table II shows clinical and pathological features of the study population.

The patients in the pandemic group had higher clinical T-stages (p=0.03). The frequency of the clinical T-stages of the patients in the baseline group was as follows; clinical T1 or T2 tumor: 48.5% (n=32); clinical T3 or T4 tumor: 51.5% (n=34) whereas that were 22.5% (n=9) and 77.5% (n=31) respectively in the pandemic group. The frequency of the clinical N1 tumors was higher in the pandemic group when compared with the baseline group (p=0.014). The frequency of the clinical N-stages of the patients in the baseline group was as follows; N0: 62.1% (n=41), N1: 37.9% (n=25) and in the pandemic group that were N0: 37.5% (n=15), N1: 62.5% (n=25).

Clinical M-stages did not show a significance between the groups (p=0.71)

Table I - *Demographic characteristics of the study population*

Characteristics	Baseline Group (n= 66)	Pandemic Group (n= 40)	P
Age (year) (mean ± SD)	60.8±12.8	60.2±13.9	0.81
Gender (male/female) (n)	46/20	23/17	0.20
CEA levels (mean ± SD)	4.2±7.8	3.4±6.3	0.47
CA 19-9 levels (mean ± SD)	37.4±104.5	89.2±239.5	0.01
The frequency of the tumor location (n)			0.58
Cardia	15	9	
Corpus	24	11	
Antrum	27	20	
Surgical type			0.20
Total gastrectomy	50	25	
Subtotal gastrectomy	15	15	
Wedge resection	1	0	
Neoadjuvant chemotherapy			0.89
Received	44	20	
Not received	22	20	
Length of hospital stay (day) (mean ± SD)	10.4±6.8	10.9±6.9	0.42
ASA scores (n)			0.16
1	0	1	
2	34	13	
3	27	23	
4	5	3	

SD, Standard deviation; p values <0.05 were considered statistically significant.

The patients in the pandemic group had higher pathological T-stages (p=0.02). The frequency of the pathological T-stages of the patients in the baseline group was as follows; T0/T1: 25.8 % (n=17), T2/3/4: 74.2% (n=49) whereas that were 7.5% (n=3) and 92.5% (n=37) respectively in the pandemic group.

Pathological N and M stages of the patients among the groups did not show any significance (p values were p=0.47 and p=0.11 respectively). In each group, one patient had metastatic deposits on the liver surface and two patients in the pandemic group had peritoneal implants that could only be detected during surgical exploration.

Also, the mean number of the retrieved lymph nodes did not differ between the groups (p=0.55). The number of the metastatic lymph nodes at the pathology specimen was higher in the baseline group when compared with the pandemic group (p=0.03). But, when we compared the patients having no metastatic lymph nodes with having at least one positive lymph node, there was not a statistically significant difference among the groups (p=0,61)

The stage of the disease was more advanced stage at the pandemic group when compared with the baseline group (p=0.01)

Table II - *Clinical and Pathological Features of the Study Population*

Characteristics	Baseline Group (n= 66)	Pandemic Group (n= 40)	p value
Clinical T stage			0.03
T1	6	0	
T2	26	9	
T3	30	27	
T4	4	4	
Clinical N stage			0.01
N0	41	15	
N1	25	25	
Clinical M stage			0.71
M0	65	39	
M1	1	1	
Pathological T stage			0.02
T0	6	2	
T1	11	1	
T2	8	11	
T3	24	18	
T4	17	8	
Pathological N stage			0.47
N0	28	15	
N1	10	11	
N2	12	8	
N3	16	6	
Pathological M stage			0.11
M0	65	37	
M1	1	3	

SD, Standard deviation; p values <0.05 were considered statistically significant

Discussion

There are limited data in the literature evaluating the effect of COVID-19 pandemic on the stage of gastric

cancer at diagnosis. Additionally, we analyzed both clinical and pathological stages in details. We believe that the results of our study will be helpful in in deciding on treatment management and the diagnostic procedures during the pandemic period.

Our study showed a decrease in the number of the newly diagnosed gastric cancer patients during the pandemic period. We saw less cancer patients at our department because the endoscopy units were closed during the first three months of the pandemic period. Thus, endoscopic biopsy could not be done. Similar to our results, a decrease in newly diagnosed cancer patients was reported in the literature previously [2,9]. A recent retrospective cohort study from Japan showed that the mean monthly number of patients diagnosed with gastric cancer decreased significantly during the COVID-19 pandemic [10]. Several reasons can be identified for the falling rates of gastric cancer diagnosis in our study population. First the patients with symptoms may hesitate to admit a hospital during the pandemic with a fear of being infected. The insidious course of the disease and absence of obvious symptoms may also delay hospital admissions. Restrictions in hospital appointments and transportation system during the pandemic may prevent patient from admitting the hospitals. Also, during the first period of the pandemic, the elective surgeries were restricted by the ministry of health. However, at our department, we did not cancel the potentially curative cancer surgery operations. The number of the newly diagnosed gastrointestinal system cancer patients is closely related to diagnostic procedures such as endoscopy. Particularly, reduced diagnostic procedures including endoscopy, is one of the main factors in this decline on March and April 2020, at our study. According to a current study, the volume of endoscopy was reduced by more than 50% in Hong Kong, the number of patients diagnosed with gastric and colorectal cancer dropped by 49.1% and 38.1%, respectively [11]. During the pandemic period especially when the patient burden decreased, endoscopic procedures has restarted in a controlled manner and the number of the newly diagnosed patients has become increasing.

Our study also showed that the patients were presented at more advanced clinical and pathological T stage during the pandemic period. However pathological N stage was not differing between the groups. This may be due

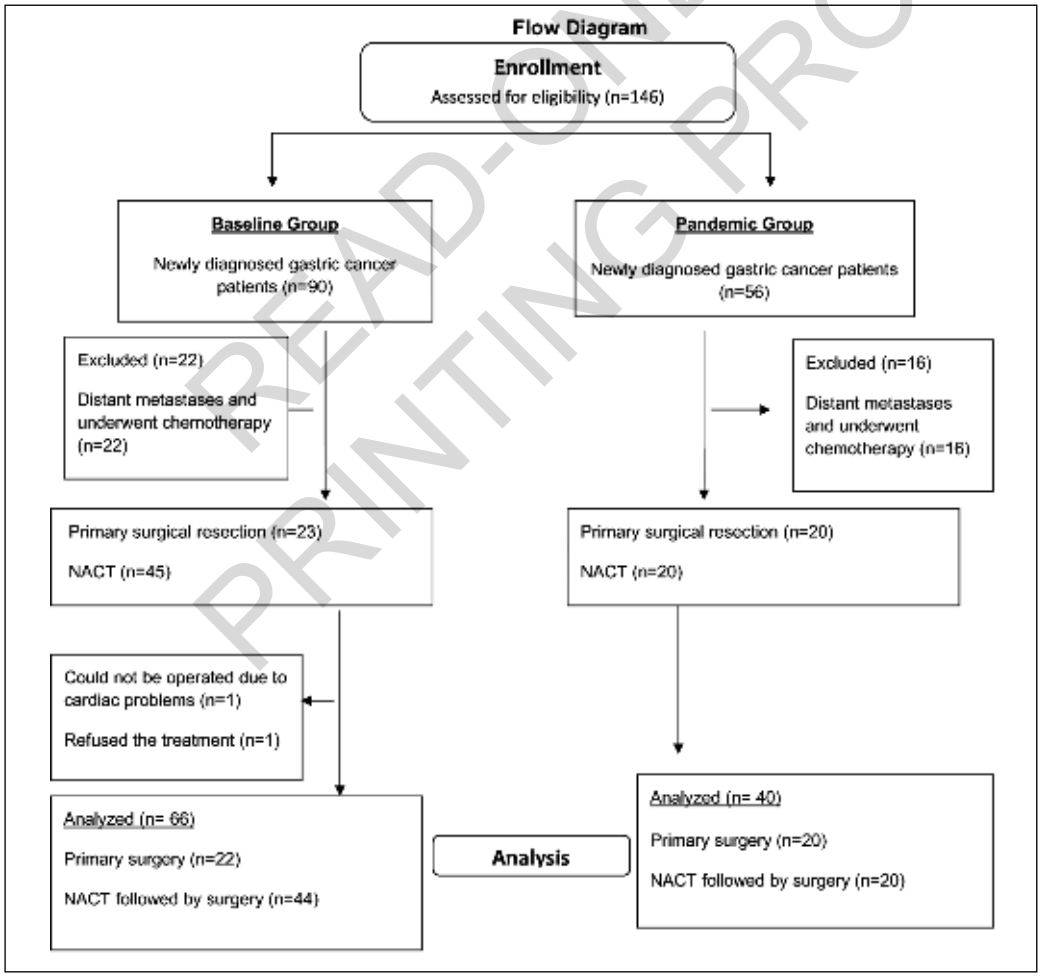

Fig.1 Flow Diagram of enrollment. NACT: Neoadjuvant chemotherapy

to the different response rates to the neoadjuvant chemotherapy, although the frequency of the patients receiving neoadjuvant chemotherapy did not differ among the groups. If the pandemic period gets longer, we might see more advanced N stage patients in the long term. A recent study analyzed the impact of SARS-COV-2 Pandemic on Colorectal Cancer Screening Delay and searched its effects on stage and mortality by a procedural model. Based on the results of the study the author proposed screening delays beyond 4-6 months would significantly increase advanced colorectal cancer cases, and also mortality if lasting beyond 12 months [12]. Another study based on the ARIMA prediction and Markov model, estimated that 4.6% and 6.4% of gastric and colorectal patients would have cancer stage upshifting at 6 months [11]. A recent retrospective cohort study showed a significant decrease in the mean number of cases of stage I gastric cancer and an increase in the number of stage IV gastric cancer cases [10]. Another recent study from Chile analyzing a microsimulation model of five cancers including gastric cancer showed a sharp decrease in the number of diagnosed cancer cases during the COVID-19 pandemic, with a large projected short-term increase in future diagnosed cases. They estimated thousands of extra cases. They showed a worse stage distribution for detected cancers in 2020–2022 as a result of delayed diagnosis [13].

The length of the hospital stay did not differ between the groups. We routinely test the patients for COVID-19 with real-time polymerase chain reaction assay by nasal and pharyngeal swabbing and thorax computed tomography before surgery. Also, patients were hospitalized in single-bed rooms. All patients were strongly cautioned to reduce social interaction during the pandemic period. As we previously reported, gastrointestinal system cancer surgery can be safely performed even within a pandemic hospital if proper isolation measures can be achieved for both patients and health workers [14].

There are some limitations of the study. The retrospective design of the study was one of the limitations. Second, the patients undergoing non-operative treatment could not be included in the analyses. Additionally our study reflects the results of a single center study. The strength of this study is that it included pathology data when compared to other articles in the literature.

Our study showed higher CA 19-9 levels and higher pathological T-stages in the pandemic group when compared with the baseline group. Our findings support following studies in the literature showing the relationship between levels and the stage of the disease. Previously, Dirican et al. reported that CA 19-9 levels showed a significant relationship with tumor stage [15]. In addition to this Jaypaul et al. showed that CA 19-9 and CA72.4 levels were higher in advanced stage cancers [16]. Also, Kodera et al. stated that CA 19-9 positivity is associated with lymph node metastasis, invasion depth and tumor size [17].

Conclusions

Our study showed a decline in the number of the newly diagnosed patients with gastric cancer during the pandemic and also more patients presented with advanced stage (particularly T stage of the tumor) during the pandemic period. This study shows that the pandemic causes a delay in the diagnosis of gastric cancer. This delay may have a catastrophic effect on oncologic outcomes. Therefore, gastric cancer patients should not be overlooked while dealing with the pandemic. Our study included the data until the end of 2020, thus longer observation period might show an accurate results of pandemic on tumor stage and diagnosis.

Riassunto

Lo scopo Di questo è quello di analizzare se il COVID-19 abbia provocato o meno un ritardo nella diagnosi dei pazienti con cancro gastrico, in particolare nella stadiazione TNM del tumore.

Si tratta di uno studio retrospettivo monocentrico comprendente pazienti con diagnosi di cancro gastrico da marzo 2019 a dicembre 2020. I pazienti sono stati divisi in due gruppi: gruppo di base e gruppo riferito al periodo pandemico. I seguenti parametri sono stati confrontati tra i gruppi; dati demografici, numero di pazienti di nuova diagnosi, tipo di intervento chirurgico, localizzazione del tumore, frequenza del trattamento neoadiuvante, punteggio ASA, durata della degenza, stadiazione clinica e stadiazione patologica TNM.

Risultati: Il numero medio mensile di pazienti con nuova diagnosi di cancro gastrico ha mostrato un calo significativo da 7,5 a 5,6 ($p<.001$). Non ci sono state differenze statisticamente significative tra i gruppi per quanto riguarda i fattori demografici, ad eccezione dei livelli di CA-19,9. I pazienti nel gruppo pandemico avevano stadi T sia clinici che patologici più elevati ($p<0,05$).

Conclusione: Il nostro studio ha mostrato un calo del numero dei pazienti di nuova diagnosi con cancro gastrico durante la pandemia e anche più pazienti che presentavano uno stadio avanzato durante il periodo della pandemia. Questo studio ha dimostrato che una pandemia provoca un potenziale ritardo nella diagnosi dei pazienti con cancro gastrico.

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