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Original Article

One Public Health Crisis into Many Others: The Impact of COVID-19 on Upstaging of Gastric Cancer

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Abstract

Background: This study aimed to investigate how COVID-19 affects patients with Gastric Cancer (GC) and what should be expected to happen in post-CVOID-19 era.

Methods: A retrospective study of GC patients referring to Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences in two parallel time periods of February 25th to December 25th of 2020 and the same period in 2019 was conducted.

Results: Twenty-six patients during COVID-19 pandemic and 54 patients during pre-COVID-19 time were recruited. Mean age, gender, tumor location and T status distribution did not show statistically significant difference between study groups (all p-values >0.05). Regarding N status, distributions of N0, N1, N2 and N3 in pre-COVID group were as follows: 2(3%), 21(39%), 25(48%) and 6(10%). In COVID-19 period, group N0 was not reported and N1, N2 and N3 were 7(27%), 7(27%) and 13(46%), respectively (p-value <0.05). Among pre-COVID patients, 6(11%) patients had gross metastasis in Staging Laparoscopy (SL) and 10(18.5%) patients had positive malignant cytology. In COVID-19 group positive SL and positive cytology were found in 9(35%) and 11(42%) patients, respectively (all p-values <0.05).

Conclusion: Health care systems should adopt reasonable approaches to cancer management, otherwise we might face the upcoming pandemic of locally advanced and metastatic cancers.

Keywords: COVID-19, Cytology, Delivery of health care, Hospitals, Laparoscopy, Neoplasms

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Introduction

Late months of 2019 was the beginning of a new era, not only in medical history but in the human race existence. This was the time when the World Health Organization (WHO) declared a pandemic of Coronavirus Disease 2019 (COVID-19) (1). Although this disease commonly presents with mild to moderate symptoms, but the extraordinary potential to spread, relatively high rate of asymptomatic carriers and the fact that the disease course is not completely known resulted in the health care systems getting off guard worldwide (2). In this regard, it was necessary to rearrange staff and capacity toward management of COVID-19. Numerous international and local guidelines were published which endorsed deferment of non-emergent medical and surgical cases (3). However, this approach will not be without consequences. One of the most important aspects of upcoming changes in caregiving is cancer management (4-6). Slowdowns in national screening programs, diagnosis, initiation of treatment, postponed surgery, clinical trials, and research will lead to high cancer mortality over the coming decade with the potential to "turn one public health crisis into many others" said Director of the National Cancer Institute, Norman Sharpless (7,8).

On the other hand, it was proposed that cancer patients may have higher susceptibility to be affected by COVID-19 and have elevated mortality rate from COVID-19 compared to patients without cancer due to higher hospital visits, poor nutritional state, systemic underlining disease and immune-suppression (8-10). Thus, in many cases chemotherapy treatments were postponed, elective curative surgeries were delayed or changed into urgent palliative ones, radiotherapy session were abbreviated, and even intravenous therapies changed to oral therapies at home (11-13). Gastric Cancer (GC) is amongst the ten most common malignancies worldwide and it is still one of the leading causes of cancer-related mortality worldwide (14,15). The incidence of GC relies on geographic location, race, and socioeconomic status. Surprisingly, those regions with high incidence of COVID-19 are the same as areas with the highest occurrence of GC (16). The most important prognostic factor determining the survival of patients with GC is early detection of the disease which might be hindered during COVID-19 pandemic (17).

In this study, the management of GC in the biggest cancer center of Iran in the post-COVID-19 time was shared. Also it was shown how COVID-19 affected GC presentation in terms of local invasiveness. To our knowledge this is the first national study specifically dedicated to assess changes occurred in GC presentation and stage.

Materials and Methods

This was a retrospective study designed and conducted under the approval of the ethics committee of Tehran University of Medical Sciences (IR.TUMS.IKHC.REC.1399.414). All patients with GC referred to Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran, during February 25th and December 25th 2020, were enrolled to the study. February 25th was the day Ministry of Health and Medical Education announced COVID-19 as a national disaster and set restrictive rules of social distancing.

The control group consisted of GC patients whom referred to Cancer Institute during

February 25th and December 25th of 2019. Thus, two groups of GC patients; one in the era of COVID-19 pandemic and the other group from previous year when there was no COVID-19 were compared.

Cancer Institute as the pioneer of cancer management in Iran set institutional regulation for hospitalization of cancer patients during COVID-19 pandemic with primary goal of delivering the best available treatment as timely as possible. In order to achieve this, each patient, regardless of cancer type, must proceed these steps before elective admission to hospital and during preoperative, operation and postoperative days:

Prior to hospital admission, patients were referred to infectious disease clinic, where they were visited by attending infectious disease specialists. Every patient monitored for COVID-19 sign and symptoms and those with high susceptibility were examined utilizing Spiral Chest Computed Tomography scan (SCCT) and Polymerase Chain Reaction (PCR) for SARS-CoV-2. If a patient had positive result of either SCCT or PCR, he/she would be managed either in outpatient or inpatient setting for COVID-19 treatment based on national protocol and subsequent cancer management

was postponed. If it was confirmed that patient is eligible for hospitalization and entering operation room, he/she would be admitted to surgical oncology ward.

During pre-operative days, all patients were hospitalized in single or double bed room, family members were not allowed to accompany except for under legal age patients and those who need special attention due to low performance status. All patients were educated about COVID-19 transmission routes and preventive measures. They also were asked to respect social distancing, wear facial mask and wash hands using alcohol-based antiseptic formulas given. Each patient was under daily surveillance for sign and symptoms of COVID-19, heart rate, blood pressure, temperature and oxygen saturation by commercially available pulse oximetry devices. In case of developing signs and symptoms related to COVID-19 or unexplained temperature > 38°*C*, oxygen saturation <93% or >5 unit drop in oxygen saturation from the baseline, infectious disease consultation was ordered. During operation time, the minimum number of personnel needed to activate a safe operation environment whom were fully equipped with personal preventive clothing including surgical cap, gown, facial mask and shield were present at the theater. The operation theater was well ventilated.

During post-operative days, for both Intensive Care Unit (ICU) and ward patients, daily monitoring of signs and symptoms related to COVID-19 along with unexplained temperature >38°*C*, oxygen saturation <93% or >5 unit drop in oxygen saturation from the baseline, C-Reactive Protein Level >40 persistent for 3 days, activated infectious disease consultation.

Patients of both groups were enrolled to the study if they gave written consent of participation, had confirmed GC using esophago-gastro-duodenoscopy and pathologically proven biopsy and spiral thoraco-abdomino-pelvic computed tomography scan prior to surgery. All patients became candidates to undergo Staging Laparoscopy (SL) in order to investigate local and peritoneal invasion of the tumor based on National Comprehensive Cancer Network guideline for GC 2020. Patients with following criteria were excluded from the study: radiological evidence of metastatic disease, current or previous history of chemotherapy.

All patients underwent SL by the same surgical team, using the same technique and the same laparoscopic device. Under general anesthesia and in supine position SL was performed. A 10 *mm* optic laparoscopic port was inserted *via* the midline incision below the umbilicus using Hasson technique. All four quadrants of the abdomen as well as pelvis were inspected during laparoscopy and biopsy was taken from any suspicious lesion through insertion of 5 *mm* port. All specimens underwent cytological evaluation by two independent pathologists. The presence of any malignant cells, regardless of the number, confirmed the positive cytology. In the event of discordant reports between two pathologists, specimens were sent for the third review by a pathologist who was blinded to the previous results. Laparoscopic evaluation was considered positive as if adjacent organ involvement, omental involvement or peritoneal seeding were seen.

Data were collected on the following variables: age, gender, tumor location, gastric lesion pathology and clinical stage based on the 8th edition of the American Joint Committee on Cancer tumor-node metastasis staging system for GC (18).

Categorical variables are shown as number and relative frequency. Also, continuous variables are shown as mean±SD. Collected data for categorical variables were compared using the chi-squared test. Prior to analysis, data were assessed for normal distribution using the Shapiro-Wilk test. An independent student t-test was used to compare means between the two groups. All analyses were performed by the two-sided method using Statistical Package of Social Science software (SPSS version 22; IBM Corp., Armonk, NY, USA), and the p-value of <0.05 was set as statistically significant.

Ethics committee approval code

IR.TUMS.IKHC.REC.1399.414

Results

Data on 26 patients during COVID-19 and 54 patients during pre-COVID-19 were analyzed. Mean age±SD of COVID and pre-COVID-19 groups were 59.7±11.9 (minimum and maximum: 30-76) and 67±1.2 (minimum and maximum: 44-86) years, respectively. In both groups male gender was higher in numbers and

male to female ratio was 18:8 and 36:18 in COVID and pre-COVID-19 group, respectively. The distribution of tumor locations in pre-COVID-19 group were cardia, fundus, body, and antrum in 31(57%), 3(6%), 13(24%), and 7(13%) cases, respectively. In COVID-19 group, the tumors were located in the cardia, fundus, body, and antrum in 9(35%), 5(19%), 10(38%), and 2(8%) cases, respectively. Regarding T status, distribution of T3 and T4 in pre-COVID group was as follows: 32(59%) and 22(41%). T3 and T4 in COVID-19 group were found in 16(61.5%) and 10(38.5%) patients, respectively. Regarding N status, distribution of N0, N1, N2 and N3 in pre-COVID group were as follow: 2(3%), 21(39%), 25(48%) and 6 (10%) cases, respectively. In COVID-19 group N0 was not reported and N1, N2 and N3 were found in 7(27%), 7(27%) and 13(46%) cases, respectively.

Pathology reports of gastric lesions in pre-COVID group were as follow: 8(15%) well-differentiated adenocarcinoma, 20(37%) moderately differentiated adenocarcinoma, 17(31.5%) poorly differentiated adenocarcinoma and 9(16.5%) signet ring cell carcinoma. COVID-19 group had 5(19%) well-differentiated adenocarcinoma, 8(31%) moderately-differentiated adenocarcinoma, 7(27%) poorly-differentiated adenocarcinoma and 6(23%) signet ring cell carcinoma. Among pre-COVID patients 6 (11%) patients had gross metastasis in SL in form of peritoneal seeding or omental involvement and 10(18.5%) patients had positive cytology report of peritoneal lavage specimen. In COVID-19 group positive SL and positive cytology were found in 9(35%) and 11(42%) cases, respectively.

The statistical analysis regarding the difference observed between age, gender, tumor location, T status and gastric lesion pathology failed to show significant difference (all p-values >0.05). However, the difference between pre-COVID-19 and COVID-19 groups in terms of N status, peritoneal involvement by tumor and positive peritoneal lavage for malignancy was statistically significant (all p-values <0.05). After multivariate analysis using logistic regression model, N status, peritoneal involvement by tumor and positive peritoneal lavage for malignancy showed to be independently different between groups (all p-values <0.05). Table 1 demonstrates study variables

Table 1. Study groups characteristics

		COVID-19 group	Pre-COVID-19 group	p-value
Age (yr), mean ± SD		59.7±11.9	67±1.2	0.843
Gender, n (%)	Male	18(69%)	36(66.5%)	0.900
	Female	8(31%)	18(33.5%)	
Tumor location	Cardia	9(35%)	31(57%)	0.081
	Fundus	5(19%)	3(6%)	
	Body	10(38%)	13(24%)	
	Antrum	2(8%)	7(13%)	
T status	T3	16(61.5%)	32(59%)	0.829
	T4	10(38.5%)	22(41%)	
N status	N0	0(0%)	2(3%)	0.004*
	N1	7(27%),	21(39%)	
	N2	7(27%)	25(48%)	
	N3	13(46%)	6(10%)	
Gastric lesion pathology	Well-differentiated adenocarcinoma	5(19%)	8(15%)	0.614
	Moderately-differentiated adenocarcinoma	8(31%)	20(37%)	
	Poorly-differentiated adenocarcinoma	7(27%)	17(31.5%)	
	Signet ring cell carcinoma	6(23%)	9(16.5%)	

Contd. table 1.

Gross peritoneal metastasis	-	9(35%)	6(11%)	0.025 *
Positive peritoneal lavage for malignancy	-	11(42%)	10(18.5%)	0.001 *

* Statistically significant result.

among two groups.

Discussion

In this study, it was shown that although the age, gender and tumor location of GC have not changed during COVID-19 pandemic, but there is a shift toward more locally advanced and peritoneally disseminated tumors; as the numbers of higher N stages (N2 and N3, 73 *vs*. 58%) is increasing and more cases are presented with gross peritoneal metastasis (35 *vs*. 11%) and positive peritoneal lavage (42 *vs*. 18.5%) at the time of SL.

These findings may be due to the interruption in national cancer screening programs, the use of diagnostic modalities, closure of medical facilities related to oncological evaluation because of resource modification, delay in multidisciplinary sessions for treatment planning of the cancer patients, patients' fear to come to hospitals and overcrowded hospitals with COVID-19 patients (19-22).

New York Society for Gastrointestinal Endoscopy (23,24) and the European Society of Gastrointestinal Endoscopy (ESGE) (25). emphasized to minimize endoscopy utilization during the pandemic because its aerosol-generating potential which may cause COVID-19 virus spread. Zhu *et al* (26). adopted these guidelines and demonstrated that there was an expeditious decrease in elective endoscopic procedures compared to pre-COVID-19 time (911 *vs*. 5746). Their study was suggestive of an increase in the detection rate of upper gastrointestinal malignancies during the pandemic (7.2 *vs*. 2.2%) but, it is assumed that this finding is because of reduction in total number of endoscopic procedures performed. This conclusion is supported by the study performed by Huang *et al* (27). Also, Lui *et al* (28). reported that each 20% decrease in upper endoscopy performed, would result in decrease of the average GC diagnosed per week by 54.1% (17). In the present study, a significant decrease in total number of GC diagnosed was not found. Moreover, data from gastro-enterology ward indicates that GC diagnosis rate during upper endoscopy was lower in COVID-19 pandemic, but did not reach statistical significance.

In a cohort study of 1388 GC patients by Kuzuu *et al*, they tried to find an answer to the following question: Is the COVID-19 pandemic associated with the stage at which GI cancer is diagnosed in Japan? They found that significant decrease was observed in the diagnosis of stage I GC (from 21.55 [5.66] cases/month in pre-COVID time to 13.90 [5.99] cases/month during pandemic; $p < 0.001$). Also, significant decreases were also observed in the mean (SD) number of cases at the localized stage (22.92 [5.95] cases/month *vs*. 15.70 [6.45] cases/month, $p=0.002$) and regional stage (3.76 [0.31] cases/month *vs*. 2.40 [1.26] cases/month; $p=0.04$). All these data can be interpreted to the fact that during the COVID-19 pandemic, there have been fewer cases of GC have been detected using upper endoscopy (29).

COVID-19 pandemic subtracted resources away from all other disease; thus, even in developed countries and properly funded facilities there would be short comings in the budget (30-32). This may be a reason to cancel elective surgeries including gastrectomy. Torzilli *et al* (33), reported a vast reduction in surgical beds dedicated to cancer patients, decline in number of oncologic surgeries performed per week and increased interval time between multidisciplinary team decisions for surgery and performing it in Italy after the pandemic. In the preset studied center, the same situation as described above was experienced. Unfortunately, a tragedy happened in te present study operation room. Before the beginning of the

first wave of national lockdown during June 21th and June 28th nearly all the staff of operation room became infected with the COVID-19. As a result, the operation room was shut down for one week. This disaster ringed a bell to reconsider all the protocols of patient admission, personal protective equipment quality and availability and daily number of staff attending to work.

The Society of Surgical Oncology (SSO) (34) and the European Society for Diseases of the Esophagus (ESDE) (35) proposed guidelines for the surgical management of esophageal and GC cases during the pandemic which are quite the same in principle rules and adoption of more conservative approaches toward early stages of cancer and leaving the surgery for hemorrhage or gastric outlet obstruction which are refractory to endoscopic/interventional radiological management.

The other group of GC patients who needed to be operated, were those who had already completed their neoadjuvant chemotherapy and had undergone a post-chemotherapy assessment of resectability and treatment response. A quite remarkable study was done by Fligor *et al* (36), in form of a systematic review aiming to investigate the impact of time to surgery on oncologic outcomes of GC. Although the studies included in this systematic review had heterogeneous populations in terms of GC stage, neoadjuvant chemotherapy, number of participants and time interval to surgery, but finally the authors concluded that the interval to surgery did not impact overall survival or disease-free survival, but the time to surgery over 6 weeks improved pathologic complete response. This statement is in contrast with what was found in Sud *et al* (37), study. They designed a per-day hazard ratios of cancer progression from observational studies and applied these to age-specific, stage-specific cancer survival in England. It was revealed that the greatest rates of deaths were observed following even modest delays to surgery in aggressive cancers, with >30% reduction in survival at 6 months and >17% reduction in survival at 3 months for patients with stage 2 or 3 cancers of the bladder, lung, esophagus, ovary, liver, pancreas and stomach. This finding is shocking that each day delay may have devastating results. Turaga *et al* (38), used the National Cancer Database and developed models to examine the effect of each one week delay in definitive surgery from diagnosis. The earliest interval when the effect estimate was worse than the previous interval, and statistically different from the baseline was defined as the inflection point. Time to inflection point beyond median current wait time was considered the safe postponement period. For patients with GC whom underwent surgery prior to chemotherapy; 6, 12, 12 and 12 weeks can be safely deferred from the time of diagnosis without significant impact on 1-year, 3-year, 5-year mortality rates and possibility of complete tumor resection, respectively. Also, for those patients underwent neoadjuvant chemotherapy 12, 12, 9 and 12 weeks are safe intervals without jeopardizing survival benefits after 1-year, 3-year, 5-year and feasibility to completely resect the tumor, respectively.

Kang *et al* (39), reported that in South Korea, a retrospective study of 101 patients with GC showed that early stage GC requires approximately 34 months to progress from stage I to II. However, from stage III to stage IV, it only needs 1.8 months. The doubling time of GC was 11.8 months at T1 stage and 6.2 months at T4 stage (40). This means that even few months of delay in treatment of patients with advanced GC, which is very common in COVID-19 era, would result in extensive tumor progression.

Based on the current guidelines for management of GC like NCCN 2020 and UpToDate®, SL is needed to accurately investigate the stage of local invasion of the tumor. Nevertheless, the performance of this modality can be challenging as the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and the European Association for Endoscopic Surgeons (EAES) advised to defer elective laparoscopic surgeries. As shown, this delay might result in an increase in N stage of the tumor and change in treatment plan. Furthermore, in patients who received neoadjuvant chemotherapy, presumptive peritoneal seeding might be cleared with treatment but as the time interval between chemotherapy cession and surgery gets longer, the possibility to reach R0 resection gets lower.

The current study suffers from limitations which should be kept in mind while interpreting the results. A retrospective design with limited numbers of patients in each group was used. Also, the diagnostic

evaluations were not completely unified as some patients had their CT scan or upper endoscopy in facilities other than Cancer Institute, Tehran University of Medical Sciences, which might have impact on the reported T and N. Also, patients may have been lost due to travel restrictions and patients' fear of coming to tertiary center which is notorious for hospitalization of COVID patients.

Conclusion

In conclusion the medical world after COVID-19 is not the same as before and it needs justification to meet its old responsibilities. The world after COVID-19 pandemic might face higher numbers of GC patients at their late stages. Thus, today is our chance to get prepared for upcoming cancer waves of tomorrow among those affected by the COVID-19 pandemic and those not.

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The ethics committee of Tehran University of Medical Sciences approved study protocol and it can be validated using this ID (IR.TUMS.IKHC.REC.1399.414).

Conflict of Interest

There was no conflict of interest in this manuscript.

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