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Consequences of the COVID-19 pandemic on the diagnosis and treatment of gastric cancer in referral centers in Italy

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Abstract

Background: The coronavirus pandemic had a major impact in Italy. The Italian health system's re-organization to face the emergency may have led to significant consequences especially in the diagnosis and treatment of malignancies. This study aimed to assess the impact of the pandemic in the diagnosis and treatment of gastric cancer in nine Gruppo Italiano RIcerca Cancro Gastrico (GIRCG) centers.

Methods: All patients assessed for gastric adenocarcinoma at nine GIRCG centers between January 2019 and November 2020 were included. Patients were grouped according to the date of "patient 1's" diagnosis in Italy: preCOVID versus COVID. Clinico-pathological and outcome differences between the two groups were analyzed.

Results: A total of 632 patients were included in the analysis (205 in the COVID group). The cT4 weighted ratios were higher in 2020 from April to September, with the greatest differences in May, August and September. The cM+ weighted ratio was significantly higher in July 2020. The mean number of gastrectomies had the greatest reduction in March and May 2020 compared with 2019. The median times from diagnosis to chemotherapy, to complete diagnostic work-up or to operation were longer in 2019. The median time from the end of chemotherapy to surgery was 17 days longer in the preCOVID group.

Conclusions: A greater number of advanced or metastatic cases were diagnosed after the spread of SARS-CoV-2 infection, especially after the "full lockdown" periods. During the pandemic, once gastric cancer patients were referred to one of the centers, a shorter time to complete the diagnostic work-up or to address them to the best treatment option was required.

Keywords

Advanced gastric cancer, Coronavirus, Gastrectomy, Gastric cancer, Pandemic, Surgery

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Introduction

Italy was the first Western country to be severely hit by the COVID-19 pandemic. This identified our country as a pioneer in the reorganization of the health system to face the coronavirus pandemic. The dramatic impact that the spreading infection had had between March and May 2020 led to major changes, which influenced the prevention, diagnosis and treatment of all diseases. As such, screening programs were suspended in most of the regions between March and June 2020, preventing the detection of early diagnoses during this period. It has been estimated that approximately 10,000 patients may have had a missed diagnosis during the "Lockdown of Breast Cancer Screening" for COVID-19[1]. In addition, access to standard endoscopy services was discontinued during the full lockdown and was significantly limited during the following waves. A recent British study found an 88% reduction in endoscopic procedures during the first six weeks of the COVID-19 crisis, resulting in 66% fewer cancer diagnoses[2]. A 2021 survey among gastroenterology services in Italy found that in 2020 gastric cancer diagnoses decreased by 15.9%[3].

Similarly, all surgical disciplines were affected by the pandemic, eventually leading to the suspension of elective surgeries for an indefinite period. Torzilli et al[4] reported data from a survey analyzing the impact of the COVID-19 emergency on elective oncological surgical activity in Italy. The authors found that the number of surgical procedures significantly decreased during the pandemic, with a doubling of the time required between multidisciplinary discussion and surgery[4].

To date, little is known about the impact of the COVID-19 pandemic on gastric cancer surgery.

This study aimed to present the data on gastric cancer diagnosis and treatment in nine centers belonging to Gruppo Italiano Ricerca Cancro Gastrico (GIRCG) in order to understand the epidemiological, clinical and surgical changes that occurred during the pandemic.

Material and Methods

This study was performed according to the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) guidelines[5].

Study design and patients

In this retrospective cohort study, all consecutive patients who were assessed for gastric adenocarcinoma at nine GIRCG centers between 1 January 2019 and 30 November 2020 were screened for inclusion. Siewert type I or II tumors were excluded from the analysis. Patients were grouped according to date of diagnosis by taking into consideration the cutoff date of 15 February 2020, which corresponded to the diagnosis of SARS-CoV-2 infection in the so-called "Patient 1" in Italy. Thus, the cohort was divided into two groups: preCOVID versus COVID.

This study was approved by the Institutional Review Board (approved 20/04/2021, pr. nr. 2980).

Variables and definitions

Patient diagnosis, preoperative work-up, operative oncologic principles, postoperative care and follow-up schedules were carried out as recommended by current GIRCG Guidelines[6] in both periods.

Variables collected included sex, age, body mass index (BMI, kg/m^2, American Society of Anesthesiologists (ASA) score, Charlson Comorbidity Index[7], administration of neoadjuvant chemotherapy, tumor location, procedure type (open, minimally invasive), conversion, additional organ resection, lymph node harvest, clinical staging (cTNM status), complications, length of hospital stay (days), readmission, and in-hospital mortality. In addition, the time (days) from diagnosis to complete diagnostic workup or to starting of the therapeutic pathway (that is, chemotherapy administration for those patients who needed to receive chemotherapy before surgery, or operation in cases referred for upfront surgery) was calculated. Moreover, in cases treated with preoperative chemotherapy, the time from the end of chemotherapy to operation was evaluated; the time from operation to the start of adjuvant/postoperative treatments was computed. The date of diagnosis was defined as the date of esophagogastroduodenoscopy proving the presence of gastric adenocarcinoma cells at biopsies. The diagnostic work-up was considered complete when the last imaging/procedure to confirm the indication for the treatment path was performed.

The primary outcome variable was the rate of advanced tumors (cT4) per period. The 8th edition of the AJCC Cancer Staging Manual was used to stage the disease[8].

Statistical analysis

The median and interquartile ranges (IQR) were used to present continuous variables, while frequencies and percentages were used for categorical variables. The Mann-Whitney U test was used to compare continuous variables, while the chi-square or Fisher exact test was used for categorical variables. The rates of cT4 or cM1 tumors were also reported as pooled rates with 95% confidence intervals (95% CI) weighted per number of procedures performed in the given institution per month exploiting the Freeman–Tukey transformation[9]. The same analysis was used to provide the pooled weighted resected/diagnosed ratio. Graphs were constructed using GraphPad *Prism* version 8.0, while statistical analyses were performed using MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015).

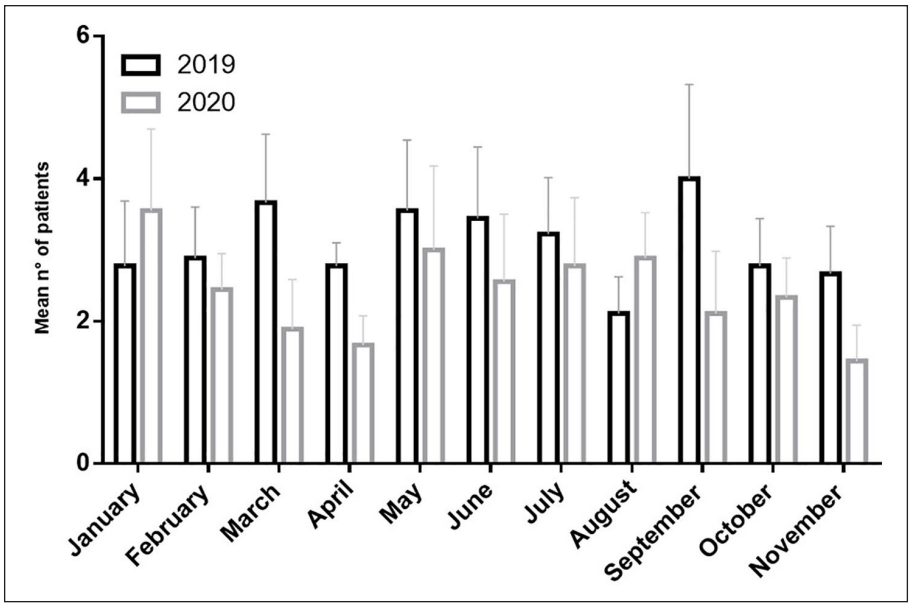

Figure 1. Mean number of patients evaluated per participating center per month.

Results

A total of 632 patients were included in the analysis, and 205 were included in the COVID group. One center that had the highest number of COVID-19 cases was not able to accept gastric cancer cases during the COVID period. The mean number of patients evaluated per participating center was lower during the pandemic (Figure 1). There were no differences with regard to demographic characteristics between the preCOVID and COVID groups (Table 1). At diagnosis, hemoglobin levels were lower in the COVID group (11.2, 9.6-12.7 versus 12, 10.5-26.7; $p = 0.002$). Overall, cTNM status were similar. There was a trend toward significance in the difference between the rate of cT1 in the preCOVID (n=35, 8.1%) versus COVID groups (n=8, 3.9%) (0.061). The cT4 weighted ratios divided per month were higher in 2020 from April to September, with the greatest differences in May, August and September (Figure 2). The cM+ weighted ratio per month is shown in Figure 3. The mean number of procedures had the greatest reduction in March and May 2020 compared with those in 2019 (Figure 4). The resection/diagnosis weighted ratio was lower in 2020 (Figure 5). The number of patients who could not undergo surgery in the preCOVID group was 48 (12.7%) (28 peritoneal carcinomatosis, 5 liver metastases, 3 distant nodes, 2 bones, 4 multiple sites metastases, 4 cT4 and 2 patients unfit for surgery) versus 54 (35.8%) (25 peritoneal carcinomatosis, 6 liver metastases, 9 multiple site metastases, 10 cT4 and 4 patients unfit for surgery) ($p<0.0001$).

A higher rate of conversion to open surgery was found in the COVID group ($p = 0.038$). The median times from diagnosis to complete diagnostic work-up/to chemotherapy/to operation were longer in 2019. The median time from the end of chemotherapy to surgery was 17 days longer in the preCOVID group.

Discussion

The COVID-19 pandemic influenced all aspects of gastric cancer care.

The patients evaluated for gastric cancer in the participating centers had more advanced disease. This was evident only in the comparison month by month, as highlighted in Figure 2, in which a persistently higher cT4 weighted ratio was seen from May to September 2020 compared to the same period of the preCOVID era. Similarly, the cM+ weighted ratio was higher in 2020, with the most significant difference in July. These data likely reflect the consequences of the very first impact of COVID-19 on the diagnosis of gastric cancer. In particular, we hypothesize that what we observed from May to September 2020 was a direct consequence of the suspension of endoscopy services during the first lockdown, which was undoubtedly associated with the fear of being infected during an in-hospital procedure that kept patients with mild symptoms away from being diagnosed with gastric cancer.

A recent study by Turkington et al[10] described the findings on the pathologic diagnosis of esophagogastric cancer within population-based databases in Northern Ireland during the COVID-19 pandemic: the authors found that cancer diagnosis declined by 26.6% from March to September 2020 compared to the equivalent time frame in 2017 to 2019[10]. In our data, a reduction of 13.5% of the patients evaluated in the participating center was found in 2020 compared to 2019. The lower diagnosis reduction

Table 1. Patients' characteristics, operative and postoperative variables.

Variables		Pre-COVID (n=427)	COVID (n=205)	P
Age, years (IQR)		71 (62-79)	71 (64-80)	0.486
Sex (%)				0.862
Female		173 (40.5)	81 (39.5)	
Male		254 (59.5)	124 (60.5)	
BMI (IQR)		23.9 (21.5-26.7)	24.0 (22.1-26.6)	0.626
Charlson Comorbidity Index >5 (%)	Yes	191 (44.7)	76 (31.1)	0.071
	No	236 (55.3)	129 (62.9)	
ASA>2 (%)	Yes	222 (52.0)	124 (60.5)	0.060
	No	202 (47.3)	81 (39.5)	
Hb -g/dl- (IQR)		12 (10.5-13.2)	11.2 (9.6-12.7)	0.002
Tumor size, cm (IQR)		4 (2.5-6)	4.1 (2.8-6)	0.220
cT status (%)				0.189
cT1		35 (8.1)	8 (3.9)	
cT2		53 (12.4)	23 (11.2)	
cT3		139 (32.5)	66 (32.2)	
cT4		184 (43.1)	99 (48.3)	
cN status (%)				0.284
cN+		284 (66.5)	131 (63.9)	
cN-		131 (30.7)	48 (23.4)	
cM status (%)				0.922
cM+		109 (25.5)	`51 (24.9)	
cM-		318 (74.5)	154 (75.1)	
Staging laparoscopy (%)	Yes	209 (48.9)	98 (47.8)	0.799
	No	218 (51.1)	107 (52.2)	
Neoadjuvant/Palliative chemotherapy (%)	Yes	180 (42.1)	73 (35.6)	0.118
	No	243 (56.9)	131 (63.9)	
Resected (%)	Yes	379 (88.7)	151 (64.2)	<0.001
	No	48 (12.7)	54 (35.8)	
Total gastrectomy (%)	Yes	167 (39.1)	65 (31.7)	0.924
	No	212 (49.6)	86 (41.9)	
Minimally invasive surgery (%)	Yes	75 (19.8)	38 (25.5)	0.294
	No	304 (71.1)	113 (55.1)	
Conversion to open surgery (%)	Yes	6 (8.0)	9 (23.7)	0.038
	No	69 (92.0)	29 (76.3)	
Additional resection (%)	Yes	63 (14.7)	19 (9.3)	0.149
	No	316 (74.0)	132 (64.4)	
HIPEC (%)	Yes	25 (5.8)	9 (4.4)	0.702
	No	354 (82.9)	142 (69.3)	
Time from diagnosis to chemotherapy, days (IQR)		35 (24-47)	28 (14-45)	0.007
Time from diagnosis to complete diagnostic workup, days (IQR)		18 (10-30)	13 (8-24)	0.001
Time from diagnosis to operation, days (IQR)		81 (32-146)	46 (25-104)	0.001
No neoadjuvant chemotherapy		36 (19-60)	31 (14-48)	0.031
Neoadjuvant chemotherapy		147 (117-207)	116 (90-146)	<0.001
Time from end of chemotherapy to operation, days (IQR)		39 (28-50)	22 (17-42)	0.003
Time from operation to adjuvant treatment, days (IQR)		45 (32-53)	44 (7-51)	0.335
Lymph node harvested, n (IQR)		36 (26-51)	33 (22-50)	0.203
Postoperative complications (%)	Yes	111 (29.3)	59 (39.1)	0.060
	No	268 (70.7)	92 (60.9)	
Clavien Dindo >2 (%)	Yes	53 (14.0)	36 (23.8)	0.109
	No	58 (86.0)	23 (76.2)	
Mortality (%)	Yes	10 (2.6)	9 (5.9)	0.211
	No	369 (97.4)	142 (4.9)	
Length of Hospital stay, days (IQR)		10 (8-14)	10 (7-15)	0.707

IQR: interquartile range; BMI: body mass index; ASA: American Society of Anesthesiologists; Hb: Hemoglobin; HIPEC: Hyperthermic intraperitoneal chemotherapy.

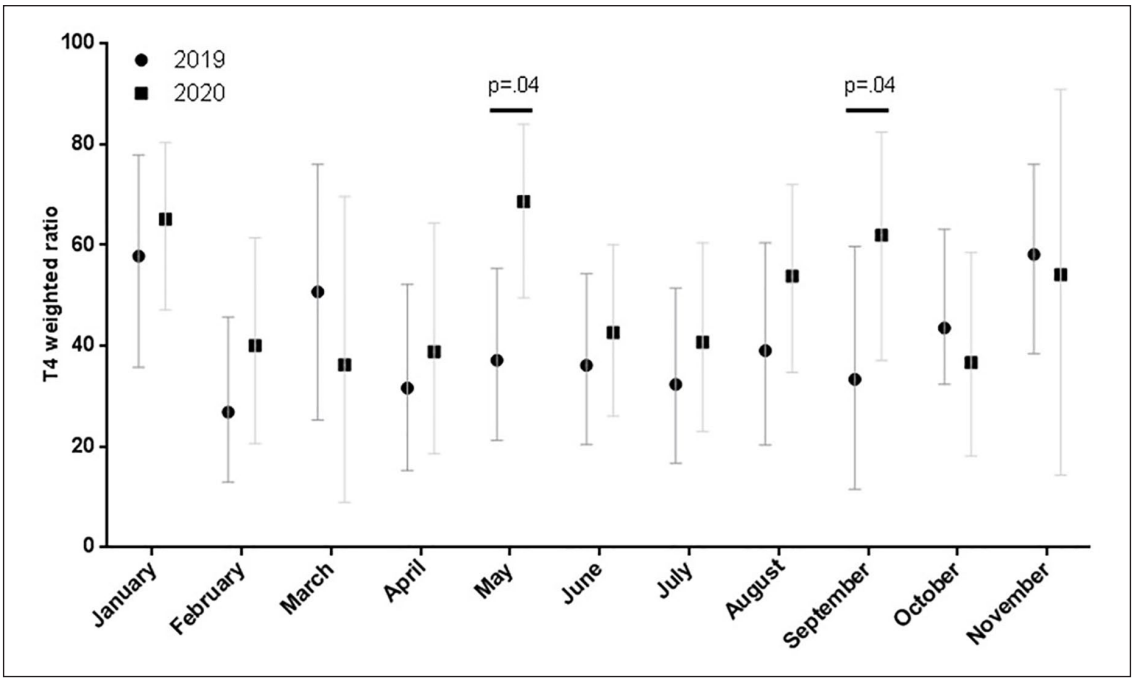

Figure 2. The cT4 weighted ratios per month.

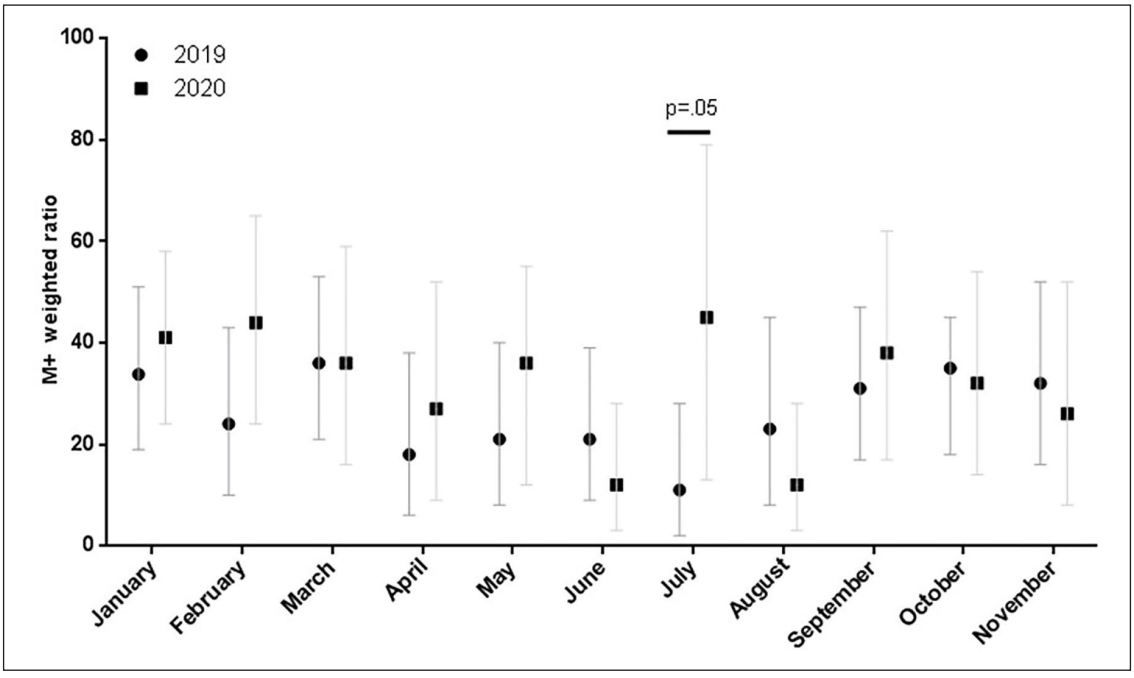

Figure 3. The cM+ weighted ratios per month.

rate observed in our study compared to the Irish experience may be due to differing populations: indeed, Turkington et al analyzed a national cancer registry, while in the present study, only patients evaluated within surgical units were included.

The number of resections was significantly lower during the pandemic. Our results showed a reduction in both the absolute number of resections and the weighted diagnosis/resection ratio in 2020. This may be due to the fact that the pressure on the included centers had been extremely high since the end of February 2020, and, in most cases, there was a major reduction in the number of operating rooms available for elective surgery[11]. To face this emergency, the Italian Society of Surgical Oncology

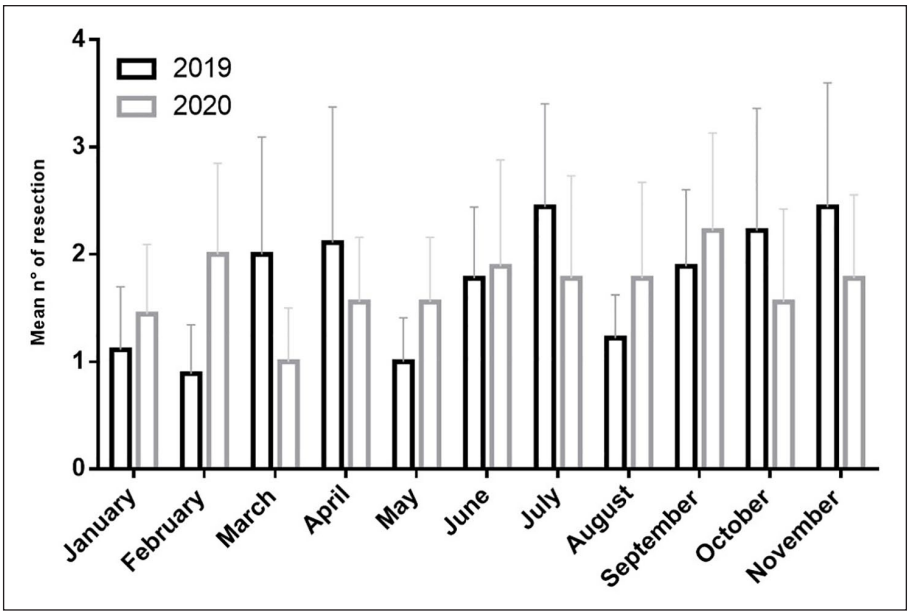

Figure 4. Mean number of procedures per participating center per month.

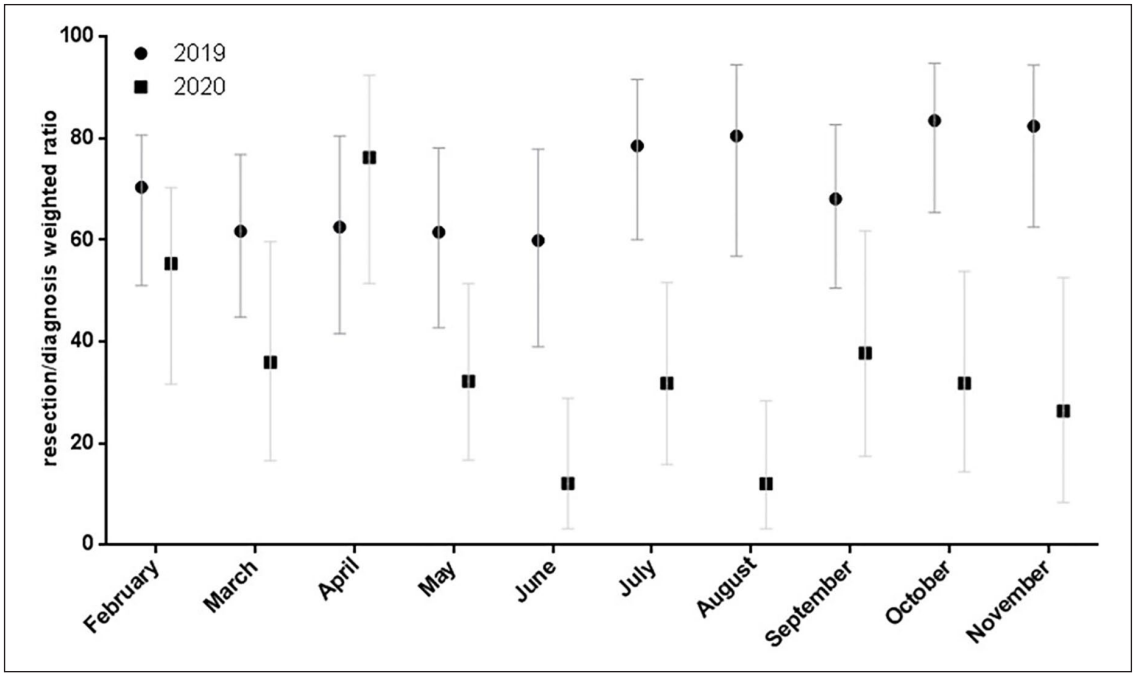

Figure 5. The resection/diagnosis weighted ratios per month.

recommended neoadjuvant chemotherapy for all gastric cancer patients with cT2N0 tumors and to continue medical treatment for those who responded and could tolerate further cycles[12]. This, along with the suspension of endoscopy services, led to a significant reduction in the number of gastrectomies performed.

As expected, the rates of minimally invasive resections, which have been trending upwards over the last 5 years, were similar between the groups. At the beginning of the pandemic, some concerns were present with regard to the use of minimally invasive surgery and the risk of infection with SARS-CoV-2 with exposure to gases during laparoscopy[11,12]. This might have had an impact on the number of minimally invasive procedures. To date, the safety of minimally invasive esophagogastric surgery in patients and healthcare workers in the COVID-19 era has been confirmed by a recent multicenter study[13].

The long-term results of the randomized clinical trials confirming the non-inferiority of the minimally invasive approaches for advanced gastric cancer were published from late 2019 to 2021[14-16]. The encouraging results of these studies may have induced surgeons to approach more cases of advanced disease with the minimally invasive approach. This might partially explain the higher rate of conversion and, thus, the trends towards significance of overall complication rates in the COVID group.

A few Western authors have highlighted a delay in the treatment of patients with cancer[4,11,17]. However, this was not found in the results reported in the present study. Instead, we found during the pandemic there was a significant reduction in the time required to complete the diagnostic work-up and to refer for the various treatments. We hypothesize that one of the main causes of the shorter diagnosis-to-treatment time during the COVID period is the greater number of non-resectable cases. Indeed, a lower number of cases to be managed surgically surely had an impact in terms of shorter time from diagnosis to gastrectomy. However, a higher rate of non-resectable patients, that in some cases could be managed only with the best supportive care (included in the present series), could have also caused a reduction in time from diagnosis to chemotherapy for those patients addressed to palliative chemotherapy.

This study has a few limitations. First, it reports a surgical perspective from nine Italian referral centers; therefore, the real impact on the rate of advanced tumors may be partly underestimated, as the most advanced cases may not have been referred for surgical evaluation. Moreover, the present study involved only surgical referral centers, as such the reported findings may not fully reflect the real situation of surgical management of patients with gastric cancer throughout Italy during the pandemic. Nevertheless, our results suggest that, during the pandemic, the hub and spoke model should be applied to cancer care: centralizing patients would reduce the impact of healthcare's state of emergency on neoplastic patients.

Another limitation is that the study period included only the first ten months of the COVID-19 emergency, and some of its consequences may require more time reveal themselves. However, we believe that the data reported in the present study are of fundamental importance in planning health policies to prevent negative effects on cancer patients in the event of future pandemics.

In conclusion, gastric cancer patients experienced diagnostic but not therapeutic delays during the COVID pandemic. A greater number of advanced or metastatic cases were diagnosed after the spread of SARS-CoV-2 infection, especially after the "full lockdown" periods, and the number of resections was significantly lower in the COVID group. Health systems should be reorganized focusing on ensuring safe access to outpatient screening and diagnostic paths even in extraordinary situations.

Declaration of Conflicting Interests

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References

1. Vanni G, Pellicciaro M, Materazzo M, et al. Lockdown of breast cancer screening for COVID-19: Possible scenario. *In Vivo*. 2020;345:3047-3053.
2. Longcroft-Wheaton G, Tolfree N, Gangi A, et al. Data from a large Western centre exploring the impact of COVID-19 pandemic on endoscopy services and cancer diagnosis. *Frontline Gastroenterol*. 2021;12(3):193-199.
3. Buscarini E, Benedetti A, Monica F, et al. Changes in digestive cancer diagnosis during the SARS-CoV-2 pandemic in Italy: A nationwide survey. *Dig Liver Dis*. 2021;53(6):682-688.
4. Torzilli G, Viganò L, Galvanin J, et al. A snapshot of elective oncological surgery in Italy during COVID-19 emergency: Pearls, pitfalls, and perspectives. *Ann Surg*. 2020;272(2):e112-e7.
5. Agha RA, Borrelli MR, Vella-Baldacchino M, et al. The STROCSS statement: Strengthening the reporting of cohort studies in surgery. *Int J Surg*. 2017;46:198-202.
6. De Manzoni G, Marrelli D, Baiocchi GL, et al. The Italian Research Group for Gastric Cancer (GIRCG) guidelines for gastric cancer staging and treatment: 2015. *Gastric Cancer*. 2017;20(1):20-30.
7. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
8. Brierley JD and Gospodarowicz MKWC. TNM classification of malignant tumours, 8th edn.: Wiley-Blackwell, Oxford, 2017.
9. Freeman MF and Tukey JW. Transformations related to the angular and the square root. *Ann Math Statist*. 1950;21(4):607-611.
10. Turkington RC, Lavery A, Donnelly D, et al. The impact of the COVID-19 pandemic on Barrett's esophagus and esophagogastric cancer. *Gastroenterology*. 2021;160(6):2169-2171.e1.
11. Rosa F and Alfieri S. Possible impact of COVID-19 on gastric cancer surgery in Italy. *Minerva Chir*. 2020;75(5):380-381.
12. Cavaliere D, Parini D, Marano L, et al. Surgical management of oncologic patient during and after the COVID-19

outbreak: practical recommendations from the Italian society of Surgical Oncology. *Updates Surg*. 2021;73(1):321-329.
13. Alasmar M, Kausar A, Borgstein AB, et al. Is re-introducing major open and minimally invasive surgery during COVID-19 safe for patients and healthcare workers? An international, multi-centre cohort study in the field of oesophago-gastric surgery. *Ann Surg Oncol*. 2021; 28(9):4816-4826.
14. Hyung WJ, Yang HK, Park YK, et al. Long-term outcomes of laparoscopic distal gastrectomy for locally advanced gastric cancer: The KLASS-02-RCT randomized clinical trial. *J Clin Oncol*. 2020;38(28):3304-3313.
15. van der Wielen N, Straatman J, Daams F, et al. Open versus minimally invasive total gastrectomy after neoadjuvant chemotherapy: results of a European randomized trial. *Gastric Cancer*. 2021;24:258-271.
16. Yu J, Huang C, Sun Y, et al. Effect of laparoscopic vs open distal gastrectomy on 3-year disease-free survival in patients with locally advanced gastric cancer: The CLASS-01 randomized clinical trial. *JAMA*. 2019;321(20):1983-1992.
17. De Rosa M, Pasculli A, Rondelli F, et al. Could diagnostic and therapeutic delay affect the prognosis of gastrointestinal primary malignancies in the COVID-19 pandemic era? *Minerva Surg*. 2021;76:467-476.