



Quantitative assessment of the impact of COVID-19 pandemic on pancreatic surgery: an Italian multicenter analysis of 1423 cases from 10 tertiary referral centers

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Received: 9 April 2021 / Accepted: 16 September 2021
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Abstract

Few evidences are present on the consequences of coronavirus disease 2019 (COVID-19) pandemic on pancreatic surgery. Aim of this study is to evaluate how COVID-19 influenced the diagnostic and therapeutic pathways of surgical pancreatic diseases. A comparative analysis of surgical volumes and clinical, surgical and perioperative outcomes in ten Italian referral centers was conducted between the first semester 2020 and 2019. One thousand four hundred and twenty-three consecutive patients were included in the analysis: 638 from 2020 and 785 from 2019. Surgical volume in 2020 decreased by 18.7% ($p < 0.0001$). Benign/precursors diseases ($-43.4%$; $p < 0.0001$) and neuroendocrine tumors ($-33.6%$; $p = 0.008$) were the less treated diseases. No difference was reported in terms of discussed cases at the multidisciplinary tumor board ($p = 0.43$), mean time between diagnosis and neoadjuvant treatment ($p = 0.91$), indication to surgery and surgical resection ($p = 0.35$). Laparoscopic and robot-assisted procedures dropped by 45.4% and 61.9%, respectively, during the lockdown weeks of 2020. No difference was documented for post-operative intensive care unit accesses ($p = 0.23$) and post-operative mortality ($p = 0.06$). The surgical volume decrease in 2020 will potentially lead, in the near future, to the diagnosis of a higher rate of advanced stage diseases. However, the reassessment of the Italian Health Service kept guarantying an adequate level of care in tertiary referral centers. Clinicaltrials.gov ID: NCT04380766.

Keywords COVID · Pancreatic surgery · Pancreatic disease · Pandemic

Introduction

After the first cases of pneumonia of unknown origin were reported in Wuhan, Severe Acute Respiratory Syndrome Coronavirus-Type 2 (SARS-CoV-2) was identified as the virus causing the Coronavirus Disease 2019 (COVID-19) [1]. On March 11, 2020, as a consequence of its rapid worldwide spread, the World Health Organization (WHO) declared COVID-19 a global pandemic [2–4].

Italy (especially the northern part of the peninsula) was one of the most affected countries, especially at the beginning of the first wave of virus spread in Europe, with both social and economic implications. According to the national data (Istituto Superiore di Sanità), Italy reported 257,065 confirmed cases and 35,427 deaths on August 21st, 2020. Such an impressive COVID-19 outbreak led to the hospitalization of 20% of patients, 15% of whom needed intensive care unit (ICU) assistance [5].

As a consequence, a massive effort by the National Healthcare Service was necessary to properly allocate most of the hospitals resources (i.e., ICU beds, healthcare staff and entire units) to fulfill COVID-19 patients' medical assistance request, with subsequent suspension or significant reduction of other important services.

Inevitably, this massive reassessment also caused relevant consequences on the daily surgical activities. The creation

Ugo Boggi, Alessandro Zerbi, Roberto Salvia, Massimo Falconi and Sergio Alfieri constituted the scientific Committee of this study and contributed equally to this work.

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of prioritization criteria and the reduction of healthcare staff availability led to postponing elective operations and/or repurposing operative rooms [6]. In this unexpected scenario, cancer patients became a major concern, since delays in surgical treatment could have led to disease progression and potentially poor long-term prognosis [7]. Pancreatic surgery for cancer represents an adequate prototype, as pancreatic cancer is widely recognized as one of the deadliest gastrointestinal tumors [8], and surgical resection remains the mainstay of treatment for localized disease [9]. The current pancreatic diseases management is based on a multidisciplinary approach in few high-volume centers [10–12], needing not only multiple and coordinate healthcare providers (surgeons, gastroenterologists, endoscopists, oncologists, radiation oncologist), but also a complex and integrated environment composed of operative rooms, ICU, endoscopy rooms, oncology and radiation therapy units. Thus, it appears clear that COVID-19 pandemic represents an unprecedented challenge for the current approach to pancreatic diseases.

To date, while literature concerning the clinical course of COVID-19 continues to grow [13–15], only a limited number of studies analyzed the effect of this pandemic on pancreatic surgical practice [16]. On these premises, the aim of this study is to present a real-time picture of the impact of COVID-19 pandemic on pancreatic surgery in the major Italian referral centers. To accomplish this purpose, data relating to the first semester of 2020 were compared with the ones relating to the first semester of 2019 (before COVID-19 pandemic breakout) with focus on the consequences of the infection spread on the clinical care pathways for pancreatic diseases treatment and in particular on surgical practice.

Methods

This is a multicenter comparative study, involving ten Italian tertiary referral centers for the treatment of pancreatic diseases. The research was preregistered on <http://clinicaltrials.gov> (clinicaltrials.gov ID: NCT04380766) and adheres to the disclosure requirements of the institutional registry. The choice of focusing the analysis only on Italian centers was justified by the recognition of Italy as the first European and one of the most affected countries in the world by COVID-19 pandemic (that required a lockdown period [17]) and by the need to avoid potential biases due to different healthcare system organizations.

All the centers involved in the study are classified as high volume [18] and, thus, equipped with dedicated diagnostic and therapeutic pathways for the surgical treatment of pancreatic diseases. More specifically, all centers had to meet the following criteria to be included in the study:

- At least 20 pancreaticoduodenectomies per year;

- The presence of a multidisciplinary tumor board (MDTB) attended by surgeons, radiologists, oncologists and radiation oncologists, pathologists, gastroenterologists, endoscopists and diabetologists;
- Hospitals equipped with multislice CT scan, magnetic resonance imaging (MRI), ICUs, Endoscopy and Interventional Radiology Units available 24/24 h and 365/365 days;
- Hospitals equipped with Pathology Units with proven experience in pancreatic diseases evaluation (pathological diagnosis and staging, frozen section analysis and immunochemistry evaluations).

According to the above-mentioned criteria, further confirmed by the Italian Health Ministry volume classification (<https://pne.agenas.it/>), 14 centers were firstly involved in the study. Four of them were excluded, since no data for analysis were received at the end of the recruitment period. Thus, the included centers were: AOUI di Verona Borgo Roma (Verona); IRCCS S. Raffaele (Milano); Ospedale Pederzoli (Peschiera del Garda); Azienda Ospedaliera-Universitaria Pisana (Pisa); Istituto Clinico Humanitas (Rozzano); Fondazione Policlinico Universitario IRCCS, A. Gemelli (Roma); Azienda Ospedaliera-Universitaria di Bologna (Bologna); Ospedale Ca' Granda-Niguarda (Milano); Azienda Ospedaliera-Universitaria Careggi (Firenze); Fondazione IRCCS “Istituto nazionale dei tumori” (Milano) (Fig. 1).

Data were retrospectively collected from prospectively maintained databases at each center for the first semester of 2019 (1st January–30th June) and from 1st January to 14th April, 2020, while data from the 15th April, 2020 onwards were prospectively collected by means of a unique database.

After the approval of the Ethical Committee of each center, the study was registered on clinicaltrials.gov (ID: NCT04380766).

Study outcomes

The first aim of the study was to evaluate the effects of the COVID-19 pandemic on pancreatic surgery. To accomplish this purpose, a comparison between the first 6 months of 2020 (January–June 2020) and the first 6 months of 2019 (January–June 2019) was performed.

The 2020 semester was additionally subdivided into four phases on the base of the Italian Prime Minister's decrees on the measures to be adopted to contain the spread of COVID-19:

- Phase 0 (from the 1st of January to the 8th of March 2020): pre-lockdown period;
- Phase 1 (from the 9th of March to the 3rd of May 2020): lockdown period;

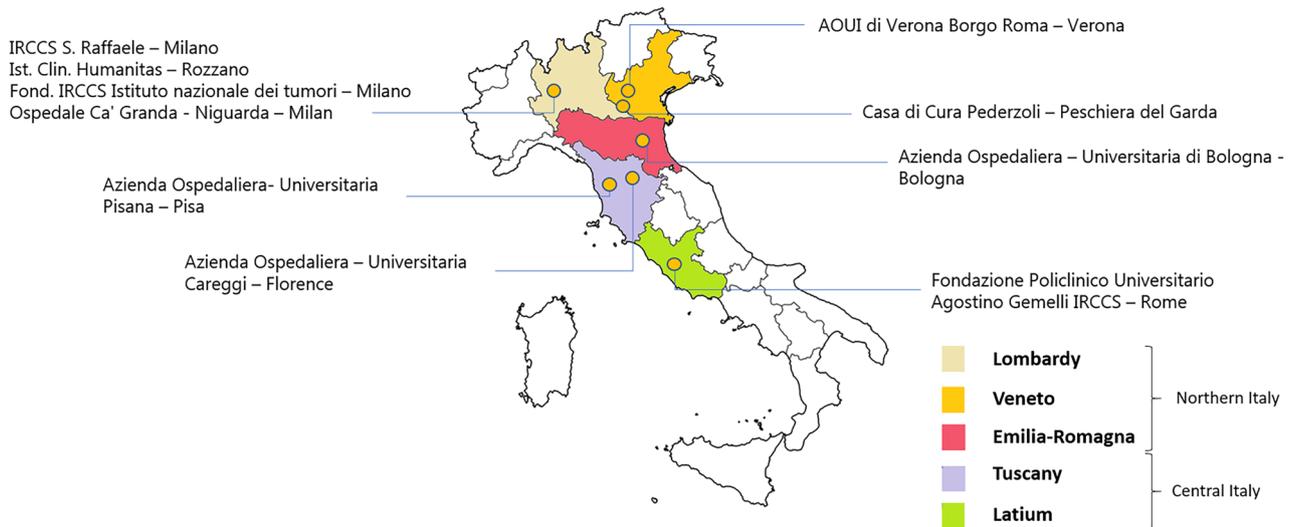


Fig. 1 Tertiary referral centers involved in the study

- Phase 2 (from the 4th of May to the 14th of June 2020): partial easing of restrictions;
- Phase 3 (from the 15th of June to the 30th of June 2020): additional easing of restrictions.

A comparative analysis between these phases and the corresponding weeks of 2019 was additionally conducted.

To evaluate the effects of COVID-19 pandemic on pancreatic surgery, data on clinical, surgical and perioperative outcomes were analyzed and compared between the two semesters of study and phase-by-phase (details of outcomes analyzed are reported as Online Resource 1).

Post-operative complications were classified according to Clavien–Dindo grades [19].

The oncological diseases treated and included in the analysis were classified according to the World Health

Organization (WHO) classification 2019 for digestive system tumors [20].

A schematic flowchart diagram of the study design is reported in Fig. 2.

Statistical analysis

Means and standard deviations (SDs) were used for all continuous data as appropriate, while numbers and percentages were calculated for all categorical data. Univariate analysis included Student’s *t* tests, Mann–Whitney *U* test, χ^2 test, and Fisher exact tests. All tests were two-tailed and a *p* value ≤ 0.05 was considered statistically significant for all analyses. All data were analyzed using SPSS for Windows, version 25 (SPSS Inc., Chicago, IL, United States).

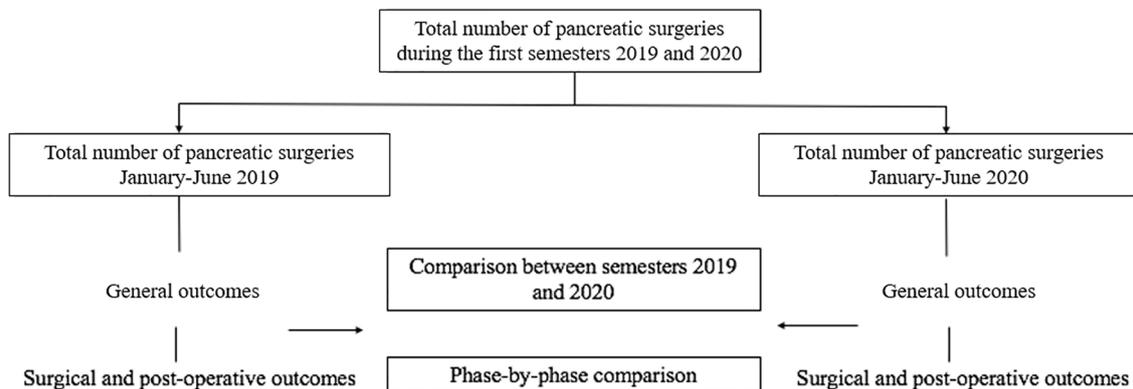


Fig. 2 Flowchart diagram of the study design

Results

General outcomes and pancreatic diseases management

During the first semesters of 2019 and 2020, 1423 patients underwent pancreatic surgery in the selected ten tertiary referral centers in Italy and, thus, included in the study. Overall, a reduction of the surgical activity took place in the first semester of 2020 (638 surgical procedures) compared to 2019 (785), with an 18.7% decrease of surgeries ($p < 0.0001$). The most significant volume reduction was registered in phase 1 (-33.9% ; $p < 0.0001$) and 2 (-23.9% ; $p = 0.01$) of 2020 as compared to the same weeks of 2019 (Table 1; Fig. 3).

In the first semester of 2020, a total of 240,578 SARS-CoV-2 positive patients were detected in Italy. The highest

percentage of infections was recorded in Lombardy (93,901 positive cases), while a milder spread was documented in Emilia-Romagna (28,492 cases), Veneto (19,286 cases), Tuscany (10,250 cases) and Latium (8110 cases) [21]. The number of COVID-19 positive cases, the related mortality and the number of pancreatic surgical procedures per region in 2020 are reported as Online Resource 2.

There was an inversely proportional relationship between the number of positive cases per region and the number of surgeries performed, with the most relevant reduction of surgical procedures in Lombardy (-25.5% ; $p = 0.001$) and Veneto (-22.5% ; $p = 0.003$). A substantial stability of surgical volumes emerged from the analysis of the remaining regions, with the exception of Latium, where a 14.6% increase was registered (Table 1; Fig. 4). This significant reduction in Lombardy and Veneto was related to a relevant decrease of patients coming from out-of-region (-29.3%

Table 1 Clinical and demographic characteristics of patients undergoing surgery during the two study periods

	1st January–30th June 2019	1st January–30th June 2020	<i>p</i>
Number of patients, (%)	785 (55.2)	638 (44.8)	< 0.0001
Phase 0	307 (39.1)	279 (43.7)	0.24
Phase 1	224 (28.5)	148 (23.2)	< 0.0001
Phase 2	201 (25.6)	153 (24)	0.01
Phase 3	53 (6.8)	58 (9.1)	0.63
Sex, <i>n</i> (%)			
Male	408 (52)	328 (51.4)	0.87
Female	377 (48)	310 (48.6)	
Age, mean (\pm SD)	63.9 (\pm 11.3)	64.1 (\pm 12.4)	0.19
ASA score, <i>n</i> (%)			
1	46 (5.8)	35 (5.5)	0.93
2	506 (64.5)	400 (62.7)	
3	222 (28.3)	193 (30.2)	
4	11 (1.4)	10 (1.6)	
Type of disease, <i>n</i> (%)			
Malignant epithelial tumors	530 (67.5)	468 (73.3)	0.05
Benign epithelial tumors and precursors	122 (15.5)	69 (10.8)	< 0.0001
Neuroendocrine neoplasms	104 (13.2)	69 (10.8)	0.008
GIST	5 (0.6)	4 (0.6)	0.73
Inflammatory diseases	8 (1)	15 (2.3)	0.14
Other malignant lesions	16 (2)	13 (2)	0.57
Surgical procedures per region ^a , <i>n</i> (%)			
Veneto	315 (40.1)	244 (38.2)	0.003
Lombardy	306 (39)	228 (35.7)	0.001
Tuscany	84 (10.7)	79 (12.4)	0.66
Latium	48 (6.1)	55 (8.6)	0.73
Emilia-Romagna	32 (4.1)	32 (5.1)	1

ASA American Society of Anesthesiologists

^aThe total number of cases does not represent the whole region but only the cases of the centers involved in the study

Bold signifies statistically significant value of *p*

Fig. 3 Volume variation of pancreatic surgeries per phase during 2020 as compared to 2019

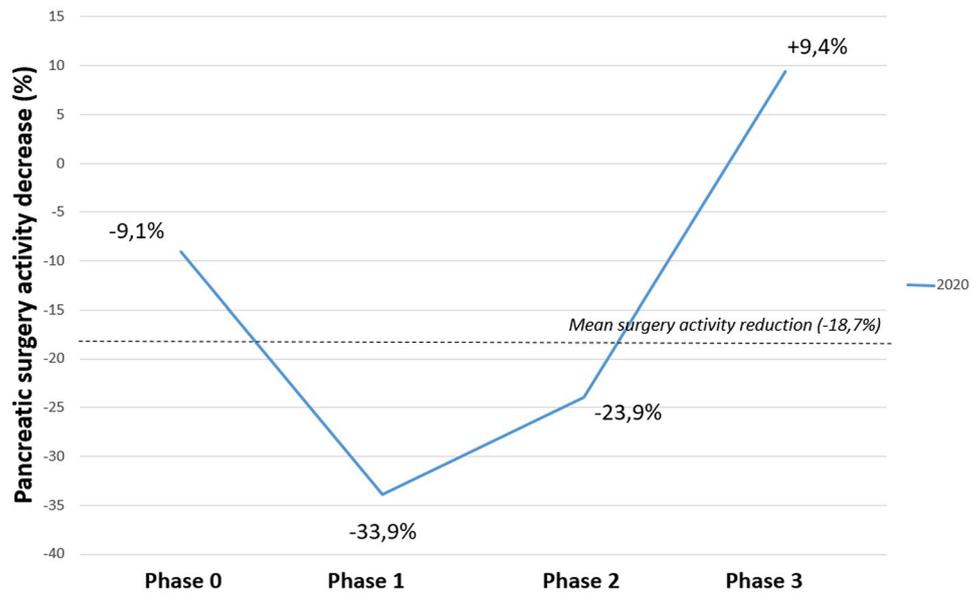
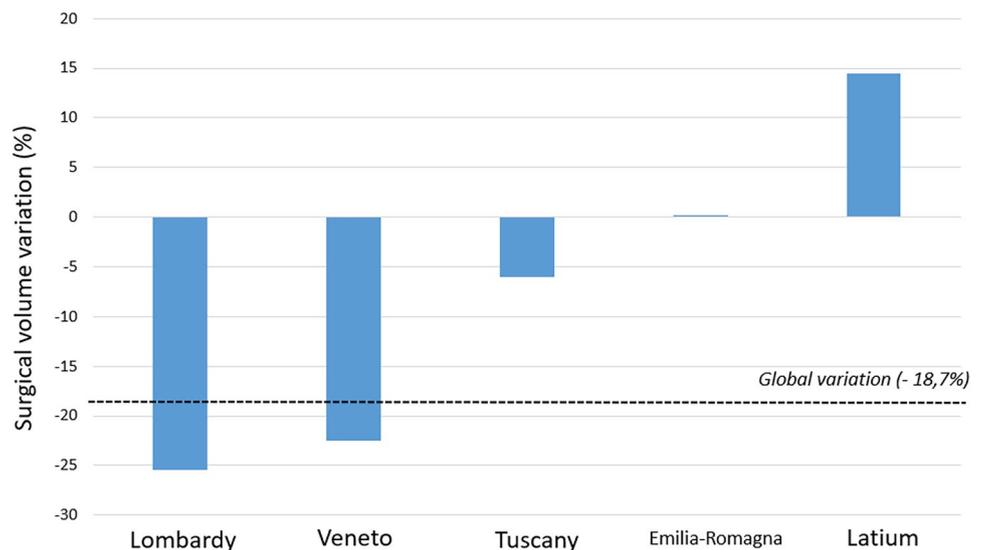


Fig. 4 Volume variation of pancreatic surgeries per region during 2020 as compared to 2019



and -44.4% for Veneto and Lombardy, respectively). As counterpart, a significant increase of patients who underwent surgery in the same region of origin was evidenced in Latium (85.7%; $p=0.005$), with the highest rate reached in 2020 phase 0 (22.2%; $p=0.02$) and 1 (275%; $p=0.03$) (Online Resource 3).

By stratifying the surgical procedures by disease type, the 2020 semester was characterized by a significant treatment reduction of benign/precursors diseases (-43.4%; $p<0.0001$) and neuroendocrine tumors (-33.6%; $p=0.008$), while a milder decrease was evidenced for malignancies (-11.7%; $p=0.05$) (Table 1; Online Resource 4).

Overall, 691 out of 1423 (48.5%) cases were discussed at a multidisciplinary tumor board (MDTB), with similar

rates between the first 6 months of 2019 ($n=373$, 47.5%) and 2020 ($n=318$, 49.8%) ($p=0.43$), and also among the different phases. No interruptions of the MDTB were documented during the semester 2020. However, all cases during phases 1, 2 and 3 of 2020 were discussed via a dedicated web platform rather than by face-to-face meetings.

Patients in 2020 underwent neoadjuvant treatment more frequently (2.7%; $p=0.009$), with the highest increase registered for patients who underwent surgery during phase 2 (9.8%; $p=0.02$) and 3 (92.3%; $p=0.04$), as compared to the same weeks of 2019.

Notably, no significant prolongation of waiting time between diagnosis and neoadjuvant treatment was documented in 2020 with 75.1 (± 110.9) days vs 60.6 (± 81.6)

days in 2019 ($p=0.91$). Comparable values were also documented when the different phases were compared. Similarly, neither the length of the neoadjuvant treatment

($p=0.84$) nor the waiting time between the end of neoadjuvant therapy and surgery ($p=0.37$) were influenced by COVID-19 pandemic (Table 2).

Table 2 Impact of COVID-19 pandemic on the diagnostic-therapeutic pathway of pancreatic cancer

	1st January– 30th June 2019	1st January– 30th June 2020	<i>p</i>
Number of patients, (%)	785 (55.2)	638 (44.8)	< 0.0001
MDTB, <i>n</i> (%)	373 (47.5)	318 (49.8)	0.43
Phase 0	150 (40.2)	135 (42.5)	0.91
Phase 1	99 (26.9)	72 (22.6)	0.42
Phase 2	97 (26)	82 (25.8)	0.36
Phase 3	27 (7.2)	29 (9.1)	0.84
Neoadjuvant treatment, <i>n</i> (%)	186 (23.7)	191 (29.9)	0.009
Phase 0	67 (36)	73 (38.2)	0.21
Phase 1	55 (29.6)	37 (19.4)	0.86
Phase 2	51 (27.4)	56 (29.3)	0.02
Phase 3	13 (7)	25 (13.1)	0.04
Neoadjuvant chemotherapy, <i>n</i> (%)	148 (79.6)	153 (80.1)	0.81
Phase 0	54 (36.5)	53 (34.6)	0.92
Phase 1	42 (28.4)	33 (21.6)	0.25
Phase 2	42 (28.4)	48 (31.4)	0.52
Phase 3	10 (6.7)	19 (12.4)	0.09
Neoadjuvant radio-chemotherapy, <i>n</i> (%)	36 (19.4)	37 (19.4)	0.9
Phase 0	13 (36.1)	20 (54.1)	0.22
Phase 1	11 (30.6)	4 (10.8)	0.07
Phase 2	9 (25)	7 (18.9)	0.61
Phase 3	3 (8.3)	6 (16.2)	0.31
Neoadjuvant radiotherapy, <i>n</i> (%)	2 (1)	1 (0.5)	0.56
Phase 0	0	0	–
Phase 1	2	0	–
Phase 2	0	1	–
Phase 3	0	0	–
Mean time diagnosis-neoadjuvant treatment, days (\pm SD)	60.6 (\pm 81.6)	75.1 (\pm 110.9)	0.91
Phase 0	66.9 (\pm 96.7)	76.8 (\pm 117.4)	0.25
Phase 1	64.5 (\pm 87.9)	70 (\pm 102.5)	0.57
Phase 2	54.2 (\pm 59.2)	67.3 (\pm 86.7)	0.71
Phase 3	39.7 (\pm 38.8)	94.1 (\pm 149.3)	0.33
Length of neoadjuvant treatment, days (\pm SD)	144.3 (\pm 83.3)	163.6 (\pm 90.7)	0.84
Phase 0	143.7 (\pm 65.1)	164.7 (\pm 95.8)	0.73
Phase 1	134.9 (\pm 107)	143.9 (\pm 80.1)	0.58
Phase 2	158.8 (\pm 89.6)	168.7 (\pm 95.3)	0.54
Phase 3	100.2 (\pm 39.3)	180.5 (\pm 79.9)	0.21
Mean time end of neoadjuvant treatment-surgery, days (\pm SD)	54.4 (\pm 37.2)	58.7 (\pm 38.6)	0.37
Phase 0	51.9 (\pm 29.4)	57 (\pm 33.6)	0.24
Phase 1	55.3 (\pm 49)	67.7 (\pm 50.8)	0.32
Phase 2	52.9 (\pm 23.1)	56.3 (\pm 36)	0.63
Phase 3	49 (\pm 22.1)	36.5 (\pm 2.1)	0.23

Phase 0: from the 9th of March to the 3rd of May; Phase 1: from the 1st of January to the 8th of March; Phase 2: from the 4th of May to the 14th of June; Phase 3: from the 15th of June to the 30th of June

MDTB multidisciplinary tumor board

Bold signifes statistically significant value of *p*

Table 3 Comparison of surgical outcomes by semester and phase-by-phase

	1st January–30th June 2019	1st January–30th June 2020	<i>p</i>
Number of patients, (%)	785 (55.2)	638 (44.8)	< 0.0001
Biliary stenting positioning, <i>n</i> (%)	245 (31.2)	195 (30.6)	0.54
Plastic	96 (12.2)	67 (10.5)	
Metallic	149 (19)	128 (20.1)	
Mean time MDTB-surgery, days, mean (± SD)	29.8 (± 43)	34.4 (± 58)	0.55
Phase 0	30.9 (± 47)	37 (± 68.5)	0.06
Phase 1	35.9 (± 50.9)	34.9 (± 60)	0.11
Phase 2	24.7 (± 29.9)	26.7 (± 34.4)	0.66
Phase 3	22.6 (± 28.9)	37.7 (± 42.7)	0.21
Tumor resectability,			
Resectable, <i>n</i> (%)	661 (84.2)	485 (76)	< 0.0001
Phase 0	263 (39.8)	224 (46.2)	0.07
Phase 1	193 (29.2)	117 (24.1)	< 0.0001
Phase 2	165 (25)	103 (21.2)	< 0.0001
Phase 3	40 (6)	41 (8.5)	0.91
Borderline, <i>n</i> (%)	86 (11)	114 (17.9)	0.06
Phase 0	31 (36.1)	42 (36.8)	0.19
Phase 1	22 (25.6)	22 (19.3)	0.88
Phase 2	23 (26.7)	36 (31.6)	0.09
Phase 3	10 (11.6)	14 (12.3)	0.41
Non-resectable, <i>n</i> (%)	38 (4.8)	39 (6.1)	0.9
Phase 0	13 (34.2)	13 (33.3)	1
Phase 1	9 (23.7)	9 (23.1)	1
Phase 2	13 (34.2)	14 (35.9)	0.84
Phase 3	3 (7.9)	3 (7.7)	1
Vascular resections, <i>n</i> (%)	89 (11.3)	92 (14.4)	0.1
Phase 0	32 (36)	36 (39.1)	0.35
Phase 1	22 (24.7)	18 (19.6)	0.57
Phase 2	29 (32.6)	23 (25)	0.88
Phase 3	6 (6.7)	15 (16.3)	0.05
ICU admission, <i>n</i> (%)	272 (34.6)	205 (32)	0.23
Phase 0	104 (38.2)	75 (36.6)	0.07
Phase 1	74 (27.2)	54 (26.3)	0.67
Phase 2	77 (28.3)	55 (26.8)	0.58
Phase 3	17 (6.3)	21 (10.3)	0.64
Number of retrieved lymph nodes ^a , mean (± SD)	33.1 (± 16.7)	31.5 (± 14.4)	0.21
Post-operative complications, <i>n</i> (%)			
Clavien–Dindo grade I	101 (12.9)	90 (14.1)	0.17
Clavien–Dindo grade II	246 (31.3)	164 (25.7)	
Clavien–Dindo grade III	113 (14.4)	92 (14.4)	
Clavien–Dindo grade IV	19 (2.4)	20 (3.1)	
30-day mortality, <i>n</i> (%)	16 (2)	24 (3.8)	0.06
LOS, days, mean (± SD)	18.6 (± 28.9)	16.6 (± 17)	0.97
Phase 0	21.6 (± 37.7)	17.1 (± 21.9)	0.07
Phase 1	16.2 (± 13.6)	17.8 (± 12.7)	0.01
Phase 2	17.7 (± 28.9)	15.1 (± 10.3)	0.97
Phase 3	14.1 (± 10.7)	14.2 (± 11.4)	0.99
Adjuvant treatment, <i>n</i> (%)	196 (25)	142 (22.3)	0.2
Phase 0	75 (38.3)	61 (42.9)	0.47
Phase 1	55 (28)	48 (33.8)	0.08

Table 3 (continued)

	1st January–30th June 2019	1st January–30th June 2020	<i>p</i>
Phase 2	48 (24.5)	24 (16.9)	0.03
Phase 3	18 (9.2)	9 (6.3)	0.02
Mean time surgery-adjuvant treatment, days (\pm SD)	85.1 (\pm 72.3)	59.5 (\pm 30.7)	<0.0001
Phase 0	84.6 (\pm 83.7)	61.3 (\pm 33.4)	0.05
Phase 1	78.4 (\pm 45.6)	50.7 (\pm 20.9)	<0.0001
Phase 2	75.1 (\pm 50.7)	73.3 (\pm 38)	0.88
Phase 3	98.1 (\pm 73.2)	59.3 (\pm 3.2)	0.21

Phase 0: from the 9th of March to the 3rd of May; Phase 1: from the 1st of January to the 8th of March; Phase 2: from the 4th of May to the 14th of June; Phase 3: from the 15th of June to the 30th of June

MDTB multidisciplinary tumor board, ICU intensive care unit, LOS length of hospital stay

^aOnly periampullary adenocarcinomas were included for the analysis

Bold signifies statistically significant value of *p*

Surgical and postoperative outcomes

Table 3 shows surgical outcomes in the two time periods. The preoperative rate of biliary stent positioning was similar between 2019 ($n=245$, 31.2%) and 2020 ($n=195$, 30.6%) ($p=0.54$), with comparable use of either plastic or metallic stents. No difference was also noted in terms of mean value

of total bilirubin as indication to biliary stent positioning [12 (\pm 9.6) mg/dl in 2019 vs 9.4 (\pm 5.8) in 2020; $p=0.2$].

The mean waiting time between MDTB decision and surgery was similar between 2019 and 2020 [29.8 (\pm 43) and 34.4 (\pm 58) days, respectively; $p=0.55$]. Furthermore, no difference was documented when the phases were compared.

Regarding tumor resectability, a significant reduction of resectable pancreatic tumors was noted in the 2020 semester

Table 4 Comparison of the surgical approach by semester and phase-by-phase

	1st January–30th June 2019	1st January–30th June 2020	<i>p</i>
Open, <i>n</i> (%)	632 (80.5)	510 (79.9)	0.78
Laparoscopic, <i>n</i> (%)	87 (11.1)	77 (12.1)	
Robotic, <i>n</i> (%)	66 (8.4)	51 (8)	
	Phase 0 2019	Phase 0 2020	<i>p</i>
Open, <i>n</i> (%)	257 (83.7)	213 (76.3)	0.06
Laparoscopic, <i>n</i> (%)	27 (8.8)	41 (14.7)	
Robotic, <i>n</i> (%)	23 (7.5)	25 (9)	
	Phase 1 2019	Phase 1 2020	<i>p</i>
Open, <i>n</i> (%)	181 (80.8)	128 (86.5)	0.24
Laparoscopic, <i>n</i> (%)	22 (9.8)	12 (8.1)	
Robotic, <i>n</i> (%)	21 (9.4)	8 (5.4)	
	Phase 2 2019	Phase 2 2020	<i>p</i>
Open, <i>n</i> (%)	156 (77.6)	120 (78.4)	0.84
Laparoscopic, <i>n</i> (%)	30 (14.9)	20 (13.1)	
Robotic, <i>n</i> (%)	15 (7.5)	13 (8.5)	
	Phase 3 2019	Phase 3 2020	<i>p</i>
Open, <i>n</i> (%)	38 (71.7)	49 (84.5)	0.24
Laparoscopic, <i>n</i> (%)	8 (15.1)	4 (6.9)	
Robotic, <i>n</i> (%)	7 (13.2)	5 (8.6)	

Phase 0: from the 9th of March to the 3rd of May; Phase 1: from the 1st of January to the 8th of March; Phase 2: from the 4th of May to the 14th of June; Phase 3: from the 15th of June to the 30th of June

[485 out of 638 (76%)] as compared to 2019 [661 (84.2%)] ($p < 0.0001$), with the most significant decrease evidenced during the phases 1 ($-39.3%$; $p < 0.0001$) and 2 ($-37.5%$; $p < 0.0001$). Conversely, no significant variation was noted for borderline and non-resectable tumors.

Table 4 reports the type of surgical approach used during the two semesters, with similar rates of open, laparoscopic and robot-assisted procedures ($p = 0.78$). Although only approaching the significance ($p = 0.06$), phase 0 of 2020 was characterized by an increase of laparoscopic (51.8%) and robot-assisted procedures (8.7%) as compared to the same weeks of 2019. These values subsequently dropped in the remaining phases, with the most relevant decrease reached during the phase 1 of 2020 ($-45.4%$ of laparoscopic and $-61.9%$ of robot-assisted procedures).

Of note, no variation in vascular resection rates was registered between the two semesters, although a higher rate was noted in the 2020 phase 3 (15–16.3%) as compared to the same time period of 2019 (6–6.7%) ($p = 0.05$). As regard the immediate post-operative care, patients were similarly admitted to the ICU between the two semesters [272 (34.6%) in 2019 and 205 (32%) in 2020; $p = 0.23$], with no difference when phases were compared (Table 3).

Length of hospital stay did not differ between the two study periods [18.6 (± 28.9) and 16.6 (± 17) days in 2019 and 2020, respectively; $p = 0.97$]. However, hospitalization was 1.6 days longer in the phase 1 of 2020 compared to the same weeks of 2019 ($p = 0.01$) (Table 3).

Two (0.3%) patients of the 2020 semester developed a COVID-19 syndrome during hospitalization. Both patients were asymptomatic and transferred to dedicated wards until discharge. None of them needed ICU assistance.

Although no difference was noted in terms of adjuvant treatments between the semesters ($p = 0.2$), a 50% decrease was documented in the phases 2 ($p = 0.03$) and 3 ($p = 0.02$) of 2020. A substantial difference was noted in terms of waiting time between surgery and adjuvant treatment, with a shorter time-elapse in 2020 [59.5 (± 30.7) days] than in 2019 [85.1 (± 72.3) days] ($p < 0.0001$). This discrepancy was related to a significant reduction in the waiting time during 2020 phase 1 [50.7 (± 20.9) days] in comparison to the same weeks of 2019 [78.4 (± 45.6) days] ($p < 0.0001$).

Discussion

The rapid worldwide spread of COVID-19 pandemic has required an urgent reassessment of the healthcare systems, with re-allocation of medical resources and the creation of prioritization criteria of treatment [22, 23]. The main objective of this priority setting remained protecting patients' safety, maximizing, at the same time, the health benefits. In this context, cancer patients represented the major concern,

due to a higher risk of severe complications in case of potential COVID-19 infection during hospitalization and, on the other hand, to the even more relevant risk of cancer progression if not promptly treated [7]. The current literature on the impact of COVID-19 in the oncological field is still limited. In addition, only few evidences, mainly based on surveys studies, are present on the consequences of COVID-19 on pancreatic surgery [16].

To the best of our knowledge, the current multicenter study is the first that quantitatively assessed this impact, giving a real-time snapshot of one of the most affected countries in the world by COVID-19 pandemic, as Italy was.

Overlooking the data, two main aspects should be underlined: the negative impact of the COVID-19 outbreak on the daily surgical activity, with particular consequences in the regions of northern Italy, and the impressive rearrangement of the health system that permitted to maintain a high level of assistance for patients undergoing pancreatic surgery.

From the comparative analysis we conducted, the number of pancreatic surgeries in the first semester of 2020 decreased by 18.7% compared to the same period of 2019, with the lowest value ($-33.9%$) reached during the lockdown weeks. This significant reduction was particularly related to a relevant drop of pancreatic procedures in the most affected regions of Italy, such as Lombardy ($-25.5%$) and Veneto ($-22.5%$), while a moderate negative variation (Tuscany), stable numbers (Emilia-Romagna) or even an increased volume of procedures (Lazio) characterized the remaining regions. In the Italian National Health Service, patients are allowed to be cured free of charge in a different region from the one of residence; because of this, there is a significant phenomenon of cross-border mobility towards regions with high volume centers for higher complexity procedures. During the pandemic, inter-regional mobility appeared limited, also reflecting the reluctance of patients of receiving treatment in "red zones", as demonstrated by the significant decrease of out-of-region patients in the referral centers of Lombardy ($-44.4%$) and Veneto ($-29.3%$).

Of note, the global reduction of surgical procedures significantly affected the routine treatment of benign tumors/precursors and neuroendocrine tumors, with a 43.4% and 33.6% decrease, respectively, as compared to the semester 2019. On the counterpart, despite a reduction in the absolute number of treated cases, there was a proportionate increase in the number of malignant pathologies treated in 2020 (73.3% vs 67.5% in 2019). These data derive from the application of the current guidelines and related prioritization criteria for the treatment of pancreatic diseases during the pandemic [16, 22, 24], according to which it is strongly recommended deferring surgery for frankly non-malignant pathologies, while ensuring a high standard and appropriate treatment for pancreatic malignancies.

In line with this need, the MDTBs (recognized as a key component of the best practice of neoplastic diseases [25, 26]), were maintained during all the semester 2020, despite being performed in a different way. The remote discussion was by far the preferred one, given the need to minimize the risk of contagion even among medical personnel. The data are totally in line with the wide use and greater legitimacy of telemedicine all over the world, considered indispensable in medical practice during the pandemic and at the same time effective not only for patients, but also for the whole health systems [27].

The maintenance of a high standard of treatment was also highlighted by the similarity between semesters and phases in terms of time interval between the diagnosis and the beginning of neoadjuvant therapy, as well as in the evaluation of the mean time between the end of neoadjuvant therapy, the indication to surgery and surgery.

As further confirmation, there was no variation in the overall numbers and indications to endoscopic biliary drainage. Indeed, the procedure was performed in the same way and in equal measure between the two semesters of study (245 (31.2%) and 195 (30.6%) in 2019 and 2020, respectively; $p=0.54$), starting from comparable bilirubin levels and without any difference in the type of stent.

Regarding the type of surgical approach, we noted an interesting, although not significant, trend inversion for minimally invasive surgeries throughout the semester 2020. More specifically, the increase of minimally invasive procedures in the pre-lockdown weeks was followed by a dramatic reduction in the following phases, with the lowest values registered during the lockdown period (-45.4% and -61.9% for the laparoscopic and robot-assisted approaches). This could be related to the need of performing surgeries with the shortest duration possible, to reduce the occupancy time of the operating rooms, and the deployment of medical and nursing staff. In addition, the current concerns on the potential role of COVID-19 diffusion through gases during the pneumoperitoneum desufflation [25, 28] might have played an additional role in reducing the rates of laparoscopic and robotic-assisted procedures. Furthermore, the reduction of surgical treatments of benign/precursor diseases (more frequent indication to the minimally invasive approach) might be an additional justification for the reduced rate of minimally invasive procedures in 2020.

Despite the unexpected COVID-19 outbreak brought to an increasing need of ICU assistance [29, 30], implying a potential reduction of ICU beds availability for post-operative patients, we did not find any difference in terms of ICU occupation rate, neither by comparing the two semesters nor by analyzing the individual phases separately. This evidence could be attributable to the lower number of patients who underwent surgery in 2020, and also to the preparation of

special units for intensive support, specifically dedicated to COVID-19 patients. Indeed, some Italian regions, such as Latium, and more specifically the Gemelli Hospital, quickly organized COVID-19 hubs, to preserve, as much as possible, the treatment and post-operative care of oncological patients in referral institutions.

The lack of variation in the post-operative management of PC patients led also to a similar length of hospitalization when the two semesters were compared. However, from the phase-by-phase analysis, patients who underwent surgery in 2020 phase 1 had a longer hospitalization (1.6 days; $p=0.01$) as compared to the same weeks of 2019. We can speculate that the introduction of several new anti-contagion safety measures for the execution of the usual diagnostic and therapeutic services could have played a key role in such a variation, especially during the major reassessment that took place in the lockdown weeks.

Our study presents multiple strengths. First, the large number of patients involved, the multicenter nature of the study, and the inclusion of centers with an already demonstrated wide experience in pancreatic surgery, that inevitably give a substantial support to the reliability of our data.

However, if the involvement of tertiary referral centers represents a point of strength, on the other hand, the exclusion of non-referral institutions gave a limited picture of the COVID-19 impact on pancreatic surgery in a nationwide perspective.

Conclusions

In conclusion, it is evident how COVID-19 pandemic significantly affected the surgical treatment of pancreatic diseases, causing an 18.7% reduction of surgical procedures. The overwhelming COVID-19 outbreak particularly affected the northern regions of the country, where the most relevant surgical activity reduction was registered. Despite these data, it is undeniable that the Italian Health Care Service gave proof of great efficiency in keeping guarantying a high-standard level of care for patients affected by pancreatic diseases, as demonstrated by the maintenance of a multidisciplinary approach and an appropriate therapeutic pathway. On the other hand, the significant reduction of the number of treated patients may lead, in the near future, to the presentation of PC at more advanced stages, with potential consequences in terms of long-term prognosis.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s13304-021-01171-8>.

Acknowledgements The authors thank the Associazione Italiana per lo Studio del Pancreas (AISP) for the conceptualization and support to this work.

Author contributions Conceptualization: SA, GQ, CF, MF. Methodology: NP, SP, MCP, FR, GC, VL, EK. Formal analysis and investigation: GQ, SN, GB, GF, AC. Writing—original draft preparation: GQ, CF, NC, VL. Writing—review and editing: GQ, CF, NC, VL. Funding acquisition: not applicable. Resources: not applicable. Supervision: RC, VM, GB, AZ, RS, MF, SA.

Funding The authors did not receive support from any organization for the submitted work.

Data availability Data and material are available at claudio.fiorillo@policlinicogemelli.it.

Code availability Not applicable.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval Ethic approval was obtained at each center.

Informed consent Not applicable.

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