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CASE SERIES

THE CLINICAL CONSEQUENCES OF SARS-CoV-2 INFECTION IN PATIENTS WITH PANCREATICODUODENECTOMY FOR MALIGNANT DISEASE

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Abstract

Introduction. The coronavirus disease 2019 (COVID-19) pandemic has constrained healthcare units to reorganize hospital departments, substantially reducing their capacity to perform oncology-related surgeries. Despite the efforts to reduce the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during hospitalization, COVID-19 has complicated the recovery of many surgical patients. Our objective was to assess the impact of SARS-CoV-2 infection on the postoperative evolution of patients with pancreatic surgery.

Cases presentation. We present four patients with pancreaticoduodenectomy for malignant disease, operated in our hepato-biliary-pancreatic surgery department, who presented COVID-19 in the postoperative period, despite initial negative screening. 10% of

Résumé

Les conséquences cliniques de l'infection par le SARS-CoV-2 chez les patients ayant subi une pancréato-duodénectomie pour une maladie maligne

Introduction. La pandémie de la maladie à coronavirus 2019 (COVID-19) a contraint les unités de soins de santé à réorganiser les services hospitaliers, réduisant considérablement la capacité d'effectuer des chirurgies liées à l'oncologie. Malgré les efforts déployés pour réduire le risque de syndrome respiratoire aigu sévère coronavirus 2 (SRAS-CoV-2) pendant l'hospitalisation, le COVID-19 a compliqué le rétablissement de nombreux patients chirurgicaux. Notre objectif était d'évaluer l'impact de l'infection par le SRAS-CoV-2 sur l'évolution postopératoire des patients avec des interventions pancréatiques.

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patients who had pancreaticoduodenectomies were subsequently detected with minimal, moderate to severe forms of COVID-19 in the postoperative period, which led to an extension of the hospitalization period, in some cases, by up to five weeks.

Conclusions. The side effects of COVID-19 pandemic are yet to have reached their limits. Pancreaticoduodenectomy is a complex surgery with high morbidity rates, but during the COVID-19 pandemics it has become more challenging.

Keywords: SARS-CoV-2, pancreaticoduodenectomy, pancreatic cancer.

List of abbreviations:

COVID-19 – coronavirus disease 2019
SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2
RT-PCR – real time polymerase chain reaction
CT scan – computed tomography
GEMOX – gemcitabine plus oxaliplatin
FOLFIRINOX – folinic acid, 5-fluorouracil, irinotecan, oxaliplatin

Présentation des cas. Nous présentons quatre patients avec pancréato-duodénectomie pour pathologie maligne, opérés dans notre service de chirurgie hépato-bilio-pancréatique, qui ont présenté le COVID-19 en période postopératoire, malgré un dépistage initial négatif. 10% des patients ayant subi une duodénectomie pancréatique ont ensuite été dépistés avec des formes minimes, modérées à sévères de COVID-19 dans la période postopératoire, ce qui a entraîné une prolongation de la période d'hospitalisation, dans certains cas, jusqu'à cinq semaines.

Conclusions. Les effets secondaires de la pandémie de COVID-19 n'ont pas encore atteint leurs limites. La pancréato-duodénectomie est une chirurgie complexe avec des taux de morbidité élevés, mais pendant les pandémies de COVID-19, elle est devenue plus difficile.

Mots-clés: SARS-CoV-2, pancréato-duodénectomie, cancer du pancréas

Introduction

The current pandemic context has had a major impact on the healthcare systems. Many hospitals were forced to completely reorganize for treating patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. At the same time, many hospitals had to offer healthcare services for patients without infection with the new coronavirus and simultaneously treat patients with coronavirus disease 2019 (COVID-19). This had a major impact on the inflow of patients with chronic diseases and determined a marked reduction on the hospital volume because of creation of circuits and new COVID-19 areas. Many surgical interventions were delayed, to not overburdening the intensive care units.

Delaying surgery after neoadjuvant chemotherapy or delaying adjuvant chemotherapy after surgery represent a threat for both patient's survival and the healthcare system, particularly in the case of pancreatic cancer[1].

We present the evolution of four patients who underwent pancreaticoduodenectomy for malignant disease in the 2nd Department of Surgery, "Sfanta Maria" Clinical Hospital, Bucharest, Romania, and were infected with the SARS-CoV-2 in the postoperative period. Informed consent was obtained from all the patients included in the study.

All our patients with pancreatic surgery are introduced in a prospectively maintained database in our department and are reported to the National Pancreatic Registry[2]. Our experience in pancreatic surgery was published by Stroescu et al in 2021[3]. From the 1st of March 2020 to the 1st of March 2021, there were 40 patients with pancreaticoduodenectomy in our department. Four patients were diagnosed postoperatively with SARS-CoV-2 infection by real-time polymerase chain reaction (RT-PCR).

In our institution, all patients without a negative RT-PCR test for COVID-19, performed within 48 hours, are admitted and RT-PCR tested in a buffer zone designed for preoperative screening. If the test is negative, they are transferred to the non-COVID-19 surgical department. The COVID-19 intensive care unit is completely separated from the postoperative and non-COVID-19 intensive care unit. All patients diagnosed with symptomatic COVID-19 who do not require intensive care are transferred and treated by a multidisciplinary team (infectious diseases specialist, pneumologist and other specialties) in the hospital's "red zone". In any patient with suspicion of infection, both rapid antigen test and RT-PCR are performed.

From March 2020 to October 2020, all the patients with a positive RT-PCR test for SARS-CoV-2 infection during hospitalization had to be transferred in designated COVID-19 hospitals, decision dictated by national laws. From October 2020, all SARS-CoV-2 positive patients were managed in our hospital by thorough reorganization of all departments, including

new COVID-19 intensive care unit, to provide maximal patient care and staff safety.

All patients admitted to our surgical unit were informed regarding the additional risk of SARS-CoV-2 infection during hospitalization.

Cases presentation

In the period mentioned above, four patients with pancreaticoduodenectomy were diagnosed postoperatively with SARS-CoV-2 infection by RT-PCR test. The data of the four patients are summarized in Table 1.

Patient #1

Patient #1 is a 66-year-old male admitted to AM in our department in August 2020, initially with a negative preoperative RT-PCR test for SARS-CoV-2 infection. His medical history included a Pean-Billroth type I gastric resection for ulcer disease. The patient was investigated for upper digestive stenosis symptoms and diagnosed with an adenocarcinoma at the level of the anastomosis with pancreatic head and left liver lobe invasion on computed tomography (CT) scan. A pancreaticoduodenectomy in-*block* with total gastrectomy and partial liver left lobe resection were performed, with eso-jejunostomy and a Roux-en-Y limb for pancreato-jejunostomy and hepatic-jejunostomy.

The postoperative evolution was marked by the appearance of a biliary fistula from the liver cut surface, with a bilioma which was drained percutaneously by ultrasonographic guidance. The patient was reoperated on the 12th postoperative day for hemoperitoneum, from a ruptured left hepatic artery pseudoaneurysm secondary to local septic complications. Multiple biliary fistulas were identified on the liver cut surface and sutured. An anterior wall dehiscence of the hepatic-jejunostomy was identified and sutured over a T-tube.

In the 19th postoperative day, the patient suddenly desaturated, and he was admitted to the intensive care unit with suspicion of pulmonary thromboembolism. He was intubated and therapy with unfractioned heparin was initiated, with a good response, being re-transferred to the surgical unit in the 24th postoperative day.

In the 27th day, a RT-PCR test was performed, because the patient developed fever and no abdominal

Table 1. Data of patients with pancreatoduodenectomy and SARS-CoV-2 infection postoperatively.

Patient	*Comorbidities*	*Neoadjuvant therapy*	*Type of surgery*	*Postoperative complications*	*SARS-CoV- 2 infection*	*ICU stay (days)*	*ETI-MV*	*Time before adjuvant therapy*
Male, 66-year-old	none	No	pancreatoduodenectomy en bloc with total gastrectomy and partial liver left lobe resection	-biliary fistula and bilioma -hemoperitoneum (ruptured left hepatic artery pseudoaneurysm secondary to local septic complications) -pulmonary embolism	POD 27	20	No	0
Female, 67-year-old	-grade I obesity –grade III hypertension, -hypertensive cardiomyopathy -sleep apnea syndrome -angina	No	pancreatoduodenectomy with pancreato-gastroanastomsis	-grade A delayed gastric emptying with conservative treatment	POD 10	0	No	8 weeks
Female, 39-year-old	none	no	pancreatoduodenectomy with pancreato-gastroanastomosis	-grade B post-pancreatectomy hemorrhage from the pancreatic stump controlled by endoscopic hemostasis.	POD 7	0	No	12 weeks
Male, 69-year-old	none	FOLFIRINOX 6 cycles	pancreatoduodenectomy with segmental resection of the superior mesenteric vein with primary end-to-end anastomosis with pancreato-gastroanastomosis.	-POD 14 upper digestive hemorrhage - urgent relaparotomy -splenic pseudoaneurysm rupture was found and sutured Grade B pancreatic fistula with drain removal after 20 days	POD 4	41	Yes	16 weeks

Note: ETI-MV = oral endotracheal intubation and mechanical ventilation, POD = postoperative day, ICU = intensive care unit, FOLFIRINOX = Leucovorin Calcium (FOL), Fluorouracil (F), Irinotecan Hydrochloride (IRIN), Oxaliplatin (OX).

collections or other causes were identified. The result of the test was positive, and the patient was transferred to a COVID-19 designated hospital. He received conservative treatment for three weeks and was discharged home with a good clinical status.

The final histopathological examination revealed a diffuse gastric carcinoma with pancreatic head and liver invasion, pT4bpN3b with positive margin at the esophagus level. He did not receive postoperative chemotherapy. The T-tube drainage was removed two months after surgery.

The patient was admitted to our unit after three months and diagnosed with stenosis secondary to recurrent carcinoma at the level of the eso-jejunostomy. A tumoral stent was placed endoscopically and the patient was discharged, with exitus within a month.

Patient #2

Patient #2 is a 67-year-old female admitted to our unit in November 2020, with a negative RT-PCR test for SARS-CoV-2. Her medical history included grade I obesity, grade III arterial hypertension, hypertensive cardiomyopathy, sleep apnea syndrome and angina. She was diagnosed with a pancreatic head tumour with duodenum invasion. A pancreaticoduodenectomy was performed with pancreato-gastro-anastomosis. Postoperatively, she developed a grade I delayed gastric syndrome, with good response on conservative treatment. During admission in the postoperative intensive care unit, the patient was retested during routine screening, with a positive result at the RT-PCR test for SARS-CoV-2. She had minimal respiratory symptoms, with good response on oxygen therapy, and was transferred to the surgical "red zone" department, being discharged two weeks thereafter, with a good clinical status.

The final histopathological examination revealed an anaplastic undifferentiated pancreatic ductal adenocarcinoma pT3pN2 R0, with giant multinucleate cells. After discharge, the patient performed respiratory physiotherapy in a specialized centre and started gemcitabine plus oxaliplatin (GEMOX) chemotherapy two months after surgery.

Patient #3

Patients #3 is a 39-year-old-female with irrelevant medical history admitted in our department in November 2020, with a negative RT-PCR test for SARS-CoV-2. She was investigated for jaundice and diagnosed at CT scan with a pancreatic head tumour. A pancreaticoduodenectomy was performed, together with a pancreato-gastro-anastomosis. During the postoperative period, she developed a grade B post-pancreatectomy hemorrhage from the pancreatic stump, which was controlled by endoscopic hemostasis. Also, she developed mild respiratory symptoms, with minimal changes on the chest X-ray, with good response on oxygen therapy. The RT-PCR test was positive. She was discharged after 13 days.

The final histopathological examination revealed a G1 pancreatic ductal adenocarcinoma pT-3pN2 R0. The patient started chemotherapy three months after surgery.

Patient #4

Patient #4 is a 69-year-old patient diagnosed in January 2020 with a locally advanced pancreatic ductal adenocarcinoma, with superior mesenteric vein invasion and less than 180 degrees contact with the superior mesenteric artery. He underwent six courses of neoadjuvant chemotherapy with folinic acid, 5-fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX), with good response. The patient was admitted to our department in November 2020, with a negative RT-PCR test for SARS-CoV-2. A pancreaticoduodenectomy was performed, with segmental resection of the superior mesenteric vein, and primary end-to-end anastomosis with pancreato-gastro-anastomosis.

In the 4th postoperative day, the patient developed respiratory symptoms with no apparent changes on the chest X-ray. A rapid antigen test for SARS-CoV-2 was performed, with negative result, but the RT-PCR test was positive. The patient was transferred from the COVID-19 intensive care unit to the surgical "red zone" in a good clinical condition and respiratory function with supplemented oxygen. The abdominal drains were removed, due to no amylase content.

In the 14th postoperative day, the patient became tachycardic, with hypotension. A nasogastric tube was placed and confirmed an upper digestive hemorrhage. The patient was immediately transferred to the operating room and an urgent relaparotomy was performed. Intraoperatively, a ruptured splenic pseudoaneurysm was found and sutured. After surgery, the patient was extubated and transferred to the COVID-19 intensive care unit. From the surgical point of view, he developed a grade B pancreatic fistula with drain removal after 20 days. He developed severe COVID-19 symptoms and necessitated endotracheal intubation with mechanical ventilation. Lung infiltrates were confirmed on the CT scan. The COVID-19 treatment consisted in general measures, such as respiratory nursing, oxygen therapy, anticoagulant, antibiotics, anti-inflammatory (corticosteroid and non-corticosteroid) drugs, and vitamins.

After 41 days of maximal treatment in the intensive care unit, the patient was finally transferred to the surgical department and discharged five days later. He was discharged with a positive RT-PCR test, but with no clinical symptoms of respiratory illness.

The final histopathological examination revealed a poorly differentiated pancreatic ductal adenocarcinoma ypT3ypN1 with confirmed microscopic invasion in the superior mesenteric vein, no tumour infiltration at the superior mesenteric artery margin. The patient started adjuvant chemotherapy with FOLFIRINOX in February 2021.

Discussion

Cancer patients infected with SARS-Co-V2 are a vulnerable population, with a high mortality rate compared to the general healthy population[1]. Their immunocompromised state because of malignancy, anti-cancer treatment (surgery, chemotherapy, radiotherapy, immunotherapy) and nutritional deficiencies is making them more susceptible to infections and complications[2]. Advanced age and other comorbidities are associated with an even higher risk of poor prognosis[1]. For oncologists, it is a difficult choice whether to treat these patients, already at high-risk, with cytotoxic drugs or hold treatment, with the risk of aggressive malignant disease progression[3]. The rapid spread of the virus, its aggressive behaviour and limited data make this decision even more difficult.

A Chinese study that included 1572 COVID-19 patients examined 18 patients with a history of cancer and concluded that cancer patients have a higher risk of severe respiratory complications that necessitate admission to intensive care units and invasive ventilation or death compared with non-cancer patients (7 patients (39%) of 18 patients *vs* 124 (8%) of 1572 patients)[4]. The same study showed a more rapid deterioration time than in those without cancer (median time to severe events 13 days [IQR 6–15] *vs* 43 days)[4]. In another study in Wuhan, China, that included 138 patients with COVID-19 pneumonia, 10 (7.2%) had cancer[5]. The results of the descriptive analysis of all infections with coronavirus in China, as of February 2020, indicated that the mortality rate among people with cancer is superior to that of the general population (5.6% vs 2.3%)[6]. It is well known that the SARS-CoV-2 infection causes lymphopenia, which could increase the mortality rate in patients with pancreatic cancer and neutropenic chemotherapy[1]. The combination chemotherapy regimen in pancreatic cancer (FOLFIRINOX) is associated with an increased survival, but also with an increased toxicity regarding febrile neutropenia compared to gemcitabine (grade 3 or 4 neutropenia in 45.7% patients vs 21%)[7].

For the management of cancer patients during pandemic, efforts have been made to give them access to medical care, according to specific statements published by National Comprehensive Cancer Network and European Society of Medical Oncology[2]. The healthcare systems were diverted to the treatment of the SARS-Co-V2 infection in a manner that substantially reduced the capacity of treating cancer. At least two surveys showed a significant increase in the number of cancelled surgical interventions in oncologic patients during COVID-19 pandemic, globally[8]. A global study estimated a revocation of approximately 38% of all cancer surgery during the 12 weeks of COVID-19 peak disruption[9].

The European-African Hepato-Pancreato-Biliary Association and The United European Gastroenterology-affiliated society European Digestive Surgery surveys reported a mean reduction for cancer surgery of 29.3%, the hepato-biliary-pancreatectomies being the most affected (31.6%-33.8%)[10] because of the complexity, high risk of complications and high mortality rates in patients developing COVID-19 during the postoperative period[11]. Pancreatic adenocarcinoma is a highly aggressive disease, for which the only curative treatment is surgical resection. Chemotherapy can result in immunosuppression, predisposition to SARS-Co-V2 infection and sometimes disease progression and death[8]. The Society of Surgical Oncology is clearly assigning a priority to surgery of hepato-biliary-pancreatic malignancies[12].

The need for surgery is the most critical factor that can influence the perioperative care of cancer patients[13]. Pancreatic cancer surgery has a high complexity, with need for hospitalization in intensive care unit. During the pandemic situation, surgery for pancreatic cancer was postponed because of the infectious burden, the lack of intensive care beds, quarantined staff, absence of appropriate protective equipment and patients' anxiety to get infected with SARS-Co-V2 during the postoperative period[14].

A systematic review of 22 papers conducted in Italy concluded that all resectable pancreatic cancers, including cystic lesions with high grade dysplasia, should undergo surgery and surgery will be postponed in special situations like pandemic escalation; in this scenario, only life-threatening complications should be treated[15]. The UK consensus position regarding the treatment of pancreatic cancer during pandemics supports surgery for resectable lesions, while maximizing the general measures of prevention, antibiotic prophylaxis and other medication to improve the immunity of these patients[16]. Neoadjuvant chemotherapy is indicated in borderline resectable and locally advanced pancreatic adenocarcinoma[16].

In contrast, the guidelines of the MD Anderson Cancer Centre Departments of Surgical Oncology and Breast Surgical Oncology in Houston, Texas, regarding the surgery decision in patients with pancreatic cancer during pandemics suggest a more conservative management and recommend neoadjuvant

chemotherapy for curable lesions and chemoradiation for borderline resectable or locally advanced tumours, because of the high mortality and complications' rate after surgery, that will delay the initiation of adjuvant chemotherapy[15]. A French group released a strategy for oncological patients and recommended deferral surgery in favour of neoadjuvant chemotherapy for cephalic pancreatic cancer and surgery for low-risk procedures requiring splenopancreatectomy[17].

Our patients presented above were screened for SARS-CoV-2 infection at admission. Most probably, they got infected from the health-care workers. All efforts had been made to minimize the risk, but because of personnel shortage, who worked in shifts both in the COVID-19 area and non-COVID-19 area, it was impossible to avoid the risk. An important key factor is the prevention of hospital-acquired infections in these patients[18].

Adjuvant chemotherapy after pancreatic cancer resection is mandatory, although the optimal time initiation is not well-known. The ESPAC-3 study revealed no difference in outcome if chemotherapy is initiated up to 12 weeks after surgery[19]. There is no data regarding the benefits of chemotherapy initiation beyond this time, supposing that patients are not recovered after surgery[20].

In fact, in contrast to the patients with colon cancer, in whom delaying the chemotherapy with every four weeks is associated with a poor overall and disease-free survival, initiation of adjuvant therapy in pancreatic cancer, when the patient is not fully recovered after surgery, may result in unfavorable evolution and complications[20]. Moreover, the completion of all cycles of planned chemotherapy is far more important than early initiation, in term of overall survival[20,21]. For patients who haven't completed the chemotherapy cycles, it seems that late initiation was a considerable survival factor[22,23].

It is essential to provide the maximum of care, manage all complications in a multidisciplinary team and have unlimited access to treatment, according to the local epidemic situation[24,25]. This vulnerable group of patients can be very difficult to manage during the pandemic situation; the risk of complex surgery should be balanced in favor of an aggressive tumour progression, with a poor outcome even with treatment.

In our case series, COVID-19 complicated the postoperative evolution of the patients. Only one patient needed prolonged intensive care unit stay, with mechanical ventilation, because of the severe form of disease. The early identification of SARS-Co-V2 infection is essential, to not have a delay in the treatment of specific complications of pancreaticoduodenectomy.

Conclusions

The side effects of COVID-19 pandemic are yet to have reached their limits. With a thorough organization and good management, we can limit the negative consequences in patients in need for oncological treatment.

Author Contributions:

Conceptualization, M.A.; methodology, T.D and M.A.; Visualization S.A., R.C., P.L. C.D.; formal analysis, N.F.A and B.A.; investigation, P.R., D.R. and G.R.R.; data curation, T.D.; writing–original draft preparation, M.A and T.D.; writing–review and editing, M.A, S.C.; supervision, S.C.; project administration S.C.; All authors have read and agreed to the published version of the manuscript.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

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