Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Research

Impact of the COVID-19 pandemic on disease stage and treatment for patients with pancreatic adenocarcinoma: A French comprehensive multicentre ambispective observational cohort study (CAPANCOVID)

Mathias Brugel [a,*,1], Léa Letrillart [a,1], Camille Evrard [b], Aurore Thierry [c], David Tougeron [d], Mehdi El Amrani [e], Guillaume Piessen [f], Stéphanie Truant [e], Anthony Turpin [g], Christelle d'Engremont [h], Gaël Roth [h], Vincent Hautefeuille [i], Jean M. Regimbeau [j], Nicolas Williet [k], Lilian Schwarz [l], Frédéric Di Fiore [m], Christophe Borg [n], Alexandre Doussot [o], Aurélien Lambert [p], Valérie Moulin [q], Hélène Trelohan [q], Marion Bolliet [r], Amalia Topolscki [r], Ahmet Ayav [s], Anthony Lopez [t], Damien Botsen [a,u], Tulio Piardi [v], Claire Carlier [a,u], Olivier Bouché [a]

[a] *University of Reims Champagne-Ardenne (URCA), Digestive Oncology and Hepatogastroenterology Department, CHU Reims, Reims, France*
[b] *Medical Oncology Department, CHU Poitiers, Poitiers, France*
[c] *Department of Research and Public Health, CHU Reims, Reims, France*
[d] *University of Poitiers, Hepatogastroenterology Department, CHU Poitiers, Poitiers, France*
[e] *Digestive Surgery and Liver Transplantation Department, CHRU Lille, CANTHER Laboratory Inserm UMR-S1277, University of Lille, Lille, France*
[f] *Digestive and Oncological Surgery Department, CHRU Lille, CANTHER Laboratory Inserm UMR-S1277, University of Lille, Lille, France*
[g] *Medical Oncology Department, CHRU Lille, CANTHER Laboratory Inserm UMR-S1277, University of Lille, Lille, France*
[h] *Digestive Oncology and Hepatogastroenterology Department, CHU Grenoble-Alpes, Grenoble-Alpes University, Grenoble, France*
[i] *Digestive Oncology and Gastroenterology Department, CHU Amiens-Picardie, Amiens, France*
[j] *Digestive Surgery Department, CHU Amiens-Picardie, SSPC (Simplification of Complex Patient Care) UR UPJV 7518, University of Picardie-Jules Verne, Amiens, France*
[k] *Hepatogastroenterology Department, CHU Saint Etienne, Saint-Priest-en-Jarez, France*
[l] *Digestive Surgery Department, CHU Rouen, UNIROUEN, Inserm 1245, IRON Group, Normandie University, Rouen, France*

* *Corresponding author*: Digestive Oncology and Hepatogastroenterology Department, CHU de Reims, Rue du General Koenig, 51092, Reims CEDEX, France.
E-mail address: mbrugel@chu-reims.fr (M. Brugel).
[1] Equally contributing first authors.

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[m] Hepatogastroenterology Department, CHU Rouen, UNIROUEN, Inserm 1245, IRON Group, Normandie University, Rouen, France
[n] Medical Oncology Department, CHU Besançon, INSERM, EFS BFC, UMR1098, RIGHT, University Bourgogne Franche-Comté, Besançon, France
[o] Digestive Surgical Oncology and Liver Transplantation Department, CHU Besançon, Besançon, France
[p] Medical Oncology Department, Lorraine Cancer Institute, Vandoeuvre-lès-Nancy, France
[q] Oncology Department, GH La Rochelle, La Rochelle, France
[r] Hepatogastroenterology Department, CH Colmar, Colmar, France
[s] Hepatobiliary and Pancreatic Surgery Departement, CHRU Nancy, Lorraine University, Vandoeuvre-lès-Nancy, France
[t] Gastroenterology and Digestive Oncology, CHRU Nancy, Lorraine University, Vandoeuvre-lès-Nancy, France
[u] Department of Medical Oncology, Godinot Cancer Institute, Reims, France
[v] General, Digestive and Endocrine Surgery Department, CHU Reims, Research Unit EA 3797 (VieFra) University of Reims Champagne-Ardenne (URCA), Reims, France

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Care pathway

Abstract ***Background:*** The COVID-19 pandemic caused major oncology care pathway disruption. The CAPANCOVID study aimed to evaluate the impact on pancreatic adenocarcinoma (PA) – from diagnosis to treatment – of the reorganisation of the health care system during the first lockdown.
Methods: This multicentre ambispective observational study included 833 patients diagnosed with PA between September 1, 2019 and October 31, 2020 from 13 French centres. Data were compared over three periods defined as before the outbreak of COVID-19, during the first lockdown (March 1 to May 11, 2020) and after lockdown.
Results: During the lockdown, mean weekly number of new cases decreased compared with that of pre-pandemic levels (13.2 vs. 10.8, −18.2%; $p = 0.63$) without rebound in the post-lockdown period (13.2 vs. 12.9, −1.7%; $p = 0.97$). The number of borderline tumours increased (13.6%–21.7%), whereas the rate of metastatic diseases rate dropped (47.1% –40.3%) ($p = 0.046$). Time-to-diagnosis and -treatment were not different over periods. Waiting neoadjuvant chemotherapy in resectable tumours was significantly favoured (24.7% –32.6%) compared with upfront surgery (13%–7.8%) (p = 0.013). The use of mFOLFIRINOX preoperative chemotherapy regimen decreased (84.9%–69%; $p = 0.044$). After lockdown, the number of borderline tumours decreased (21.7%–9.6%) and advanced diseases increased (59.7%–69.8%) ($p = 0.046$). SARS-CoV-2 infected 39 patients (4.7%) causing 5 deaths (12.8%).
Conclusion: This cohort study suggests the existence of missing diagnoses and of a shift in disease stage at diagnosis from resectable to advanced diseases with related therapeutic modifications whose prognostic consequences will be known after the planned follow-up.
Trial registration: Clinicaltrials.gov NCT04406571.

1. Introduction

Pancreatic adenocarcinoma (PA) is the most lethal gastrointestinal cancer and the fourth cause of cancer-related deaths in Europe with few therapeutic perspective [1,2]. The severity of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome – coronavirus 2 (SARS-CoV2) required most countries to take measures to contain the pandemic in 2020. Health care systems were reorganised to prioritise resources towards the management of critically ill patients. Patients with severe medical conditions and cancer have an increased risk of severe forms of COVID-19 [3–6].

The oncology care pathway was heavily disrupted at this time [7,8]. Screening and diagnosis of many cancers were impacted, delaying time to treatment [9]. New guidelines were published proposing surgery deferral for resectable PA with waiting chemotherapy, palliative chemotherapy adjustments, and telemedicine promotion [10–14]. The consequences of oncological care pathway disruption on PA patient management remain unknown.

The CAPANCOVID study aimed to evaluate the impact of the reorganisation of the health care system

during the COVID-19 pandemic on the number of new cases, disease stages at diagnosis, and treatment of patients newly diagnosed with PA. Secondary objectives were to describe COVID-19 incidence, severity, and consequences on management of PA patients.

2. Patients and methods

2.1. Study design

We performed a comprehensive multicentre ambispective (retro-prospective) observational cohort study in nine French tertiary hospitals, two cancer institutes, and two general hospitals. To simplify the interpretation of the influence of COVID-19 incidence on our data, we assembled them into larger geographical areas: Grand East (Reims, Nancy, Besançon, Colmar); East (Saint Etienne, Grenoble); North (Lille, Amiens), and West (La Rochelle, Poitiers, Rouen). This study followed the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines [15].

2.2. Patients

Adult patients diagnosed with a PA between September 1, 2019, and October 31, 2020, whose files were discussed in a multidisciplinary tumour board meeting (MTBM) were included. As every patient's file had to be discussed in an MTBM, histological proof was not mandatory in order to consider the diagnosis (association of typical radiological findings and increased CA 19-9 levels). Patients under guardianship, with non-malignant tumours, neuroendocrine tumours or who were opposed to the study were not included.

2.3. Data collection

All data were collected online from patients' medical files after being screened using MTBM working lists. All data from patients diagnosed from September 1, 2019 to April 15, 2020 were collected retrospectively. Data from patients included after April 15, 2020 were collected both prospectively and consecutively.

Three periods were defined according to French COVID-19 governmental containment measures. The first period (P0), prior to COVID-19, was defined from before the onset of the epidemic until February 29, 2020. From this date, French government instituted a first lockdown [16]. The second period (P1) was defined as the first epidemic wave and lasted from March 1 to May 11, 2020, when the first lockdown ended. A third period (P2) was defined from May 12, 2020 to the end of the study.

Data collection included patient characteristics such as age, gender, weight, body mass index, ECOG performance status (PS) and distance between home and care centre. We also collected primary tumour location, histological type, date and type of first symptom, disease stage at diagnosis (resectable, borderline, locally advanced or metastatic according NCCN classification), and CA19-9 levels [1,17]. Diagnostic management was described using dates of the first specialist care consultation or admission, imaging technique, biopsy, and MTBM. Times from symptoms onset to first imaging, to diagnosis and to treatment, time from diagnosis to MTBM, and time from first imaging to treatment were calculated according to existing standards [18]. The first therapeutic strategy (upfront surgery, preoperative (neoadjuvant or induction) chemotherapy, palliative chemotherapy or exclusive best supportive care) was defined using date of application, modalities, and justification (COVID-19 guidelines or usual guidelines) [1,12]. All treatment adaptations due to the COVID-19 pandemic were collected. COVID-19 infections, their complications (admission to the medical or intensive care unit, death), and their impact on treatment were also assessed.

2.4. Ethical approval

As this study was non-interventional, approval by an independent ethical committee was not required. The institutional review board at Reims University Hospital approved the study. All analysed patients were informed and did not express their opposition to the study. It was registered on ClinicalTrials.gov (NCT04406571). The database was built in accordance with the MR004 protocol of the *Commission Nationale de l'Informatique et des Libertés* (CNIL).

2.5. Aims and endpoints

The main objective was to assess the impact of the COVID-19 pandemic on the management of PA patients. The primary endpoints were the comparison of the number of newly-diagnosed patients, the disease stage, and the first therapeutic strategy within periods (P0, P1, and P2). Secondary objectives were to describe COVID-19 incidence and severity among PA patients, and their consequences on treatment.

2.6. Statistical analysis

Quantitative data were described using means with standard deviation or median with interquartile range, whereas qualitative data were expressed as percentages. As the number of persons at risk is not known and MTBM data are not as exhaustive as a population-based registry, we described an estimation of new cases. Trends were compared visually using temporal curves.

We compared data per periods (P0, P1, and P2) using Student's tests, Wilcoxon tests, chi2 tests or fisher's exact tests depending on conditions of applications. The P1 mean weekly number of new PA cases was compared with P0 and P2 levels using poisson regression. The significance

level was set at 0.05. All statistical analyses were performed using RStudio (RStudio Team, Boston, USA, 2021) after data collection on CleanWeb (Telemedecine Technologies, Boulogne-Billancourt, France, 2021).

3. Results

3.1. Patients' characteristics

Among the 850 screened patients, a total of 833 eligible patients were included in the analysis (Fig. 1). Main characteristics of patients are presented in Table 1. Two thirds of the patients (66.5%) were diagnosed with an advanced disease (locally advanced (20.2%) or metastatic diseases (46.3%)). Upfront surgery, preoperative chemotherapy, palliative chemotherapy, and exclusive best supportive care were proposed in 13.2%, 23.0%, 54.6%, and 9.1% of patients, respectively.

3.2. Impact of the COVID-19 pandemic on number of weekly PA cases

As shown in Table 1, prior to the pandemic (P0), 369 patients were diagnosed with PA in 181 days yielding a mean number of 13.2 new weekly cases. During the pandemic (P1), this number fell by 18.2% (129 cases in 72 days; 10.8 weekly cases) without statistical significance ($p = 0.63$). After lockdown (P2), this number rose again without a rebound (336 cases in 175 days; 12.9 weekly cases). No difference was shown comparing pre-pandemic (P0) and post-pandemic (P2) mean weekly number of new cases ($p = 0.97$).

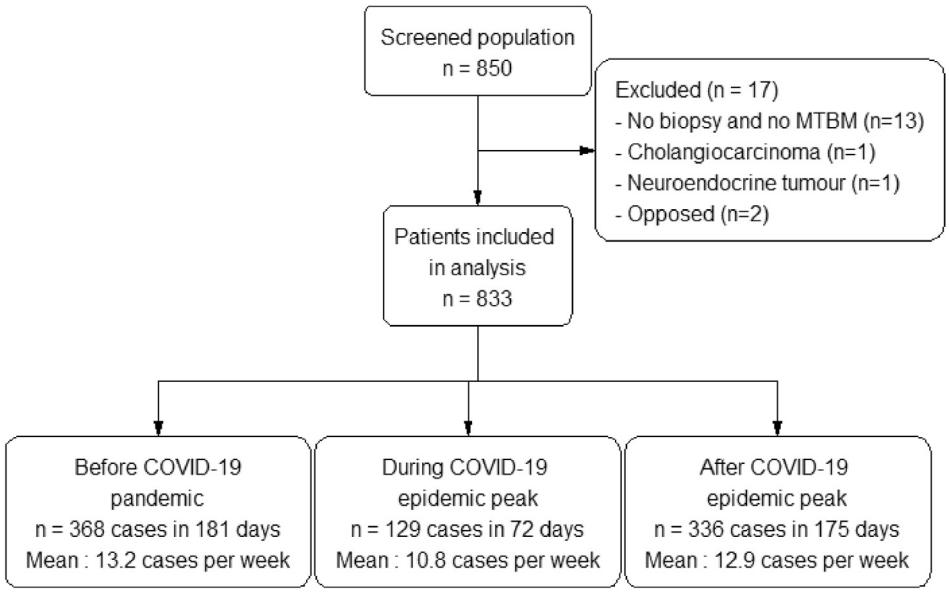
3.3. Impact of the COVID-19 pandemic on disease stages at diagnosis

As shown in Table 1, clinical and tumoural characteristics and times to diagnosis were similar within the three periods of diagnosis. However, disease stage at diagnosis significantly differed between periods ($p = 0.046$). During lockdown, fewer patients had a resectable tumour (from 20.4% in P0 to 18.6% in P1) or a metastatic disease at diagnosis (from 47.1% in P0 to 40.3% in P1), whereas borderline resectable tumour rates increased (from 13.6% in P0 to 21.7% in P1). After lockdown, the number of locally advanced diseases increased (from 19.4% in P0-P1 to 22.2% in P2), while resectable borderline diseases declined (from 21.7% in P1 to 9.6% in P2) and the number of metastatic PA reached their pre-pandemic levels (47.6% in P2). The trends are presented in Fig. 2.

3.4. Impact of the COVID-19 pandemic on treatments

As shown in Table 1 and Fig. 3, first-line strategies differed significantly from one period to another ($p = 0.013$). Times to treatment were similar within the three periods of diagnosis. The inclusions in therapeutic trials were interrupted during lockdown without complete recovery after lockdown.

For resectable tumours, upfront surgery declined during lockdown (62.7% in P0 to 37.5% in P1; $p = 0.037$) and neoadjuvant chemotherapy was favoured (28.0% in P0 to 50.0% in P1) (Table 2A). For borderline tumours, first-line treatment was similar with



n: number of patients; MTBM: multidisciplinary tumour board meeting; COVID-19: Coronavirus Disease 2019.

Fig. 1. Consort diagram.

Table 1
Overall population characteristics and COVID-19 pandemic impact on diagnosis and treatment.

Variables	Levels	Overall (n = 833)	P0 Diagnosis before COVID-19 (n = 368)	P1 Diagnosis during COVID-19 lockdown (n = 129)	P2 Diagnosis after COVID-19 lockdown (n = 336)	P value
Impact of COVID-19 pandemic on clinical and tumoural characteristics						
Gender (%)	Male	385 (46.2)	181 (49.2)	53 (41.1)	151 (44.9)	0.236
Age (y)	Mean (SD)	68.7 (11.0)	68.3 (11.1)	67.9 (11.9)	69.4 (10.6)	0.276
Geographical area (%)	Grand East	339 (40.7)	147 (39.9)	51 (39.5)	141 (42.0)	0.904
	Northern	168 (20.2)	80 (21.7)	22 (17.1)	66 (19.6)	
	Eastern	134 (16.1)	58 (15.8)	24 (18.6)	52 (15.5)	
	Western	192 (23.0)	83 (22.6)	32 (24.8)	77 (22.9)	
Distance between home and care centre (km)	Mean (SD)	46.3 (57.7)	43.6 (42.0)	44.3 (42.5)	50.0 (75.2)	0.315
ECOG performance status (%)	0–1	637 (79.6)	286 (80.8)	103 (83.1)	248 (77.0)	0.280
	2–3–4	163 (20.4)	68 (19.2)	21 (16.9)	74 (23.0)	
BMI (kg/m^2)	Mean (SD)	24.9 (5.1)	25.0 (5.0)	24.9 (5.3)	24.8 (5.1)	0.917
Primary tumour location (%)	Head/Uncinate process	516 (62.5)	217 (59.6)	79 (61.7)	220 (65.9)	0.099
	Body	169 (20.5)	78 (21.4)	21 (16.4)	70 (21.0)	
	Tail	141 (17.1)	69 (19.0)	28 (21.9)	44 (13.2)	
	Missing	6 (0.7)	4 (1.1)	1 (0.8)	1 (0.8)	
Histopathological proof (%)		762 (91.5)	333 (90.5)	122 (94.6)	307 (91.4)	0.473
	ND	3 (0.4)	0 (0.0)	1 (0.8)	2 (0.6)	
	Missing	2 (0.2)	1 (0.3)	0 (0.0)	1 (0.3)	
CA19-9 (IU/mL)	Mean (SD)	12065.0 (53222.4)	10683.6 (50108.3)	13240.4 (66389.7)	13163.8 (50958.6)	0.822
Disease stage at diagnosis (%)	Resectable	168 (20.2)	75 (20.4)	24 (18.6)	69 (20.7)	0.046
	Borderline	110 (13.3)	50 (13.6)	28 (21.7)	32 (9.6)	
	Locally advanced	168 (20.2)	69 (18.8)	25 (19.4)	74 (22.2)	
	Metastatic	384 (46.3)	173 (47.1)	52 (40.3)	159 (47.6)	
First clinical symptoms (%)	Isolated abdominal pain	250 (30.2)	108 (29.4)	40 (31.5)	102 (30.4)	0.188
	Jaundice	229 (27.6)	102 (27.8)	41 (32.3)	86 (25.7)	
	Altered general condition associated with other symptoms	107 (12.9)	44 (12.0)	15 (11.8)	48 (14.3)	
	Isolated altered general condition	71 (8.6)	24 (6.5)	10 (7.9)	37 (11.0)	
	Incidental	70 (8.4)	38 (10.4)	7 (5.5)	25 (7.5)	
	Diabetes	33 (4.0)	17 (4.6)	8 (6.3)	8 (2.4)	
	Pancreatitis	36 (4.3)	15 (4.1)	4 (3.1)	17 (5.1)	
	Others	33 (4.0)	19 (5.2)	2 (1.6)	12 (3.6)	
Number of new weekly PA cases	Mean (SD)	12.3 (1.3)	13.2 (4.3)[a]	10.8 (5.2)[a,b]	12.9 (4.6)[b]	0.625[a] 0.966[b]
Impact of COVID-19 pandemic on treatments						
First therapeutic decision (%)	Upfront surgery	110 (13.2)	48 (13.0)	10 (7.8)	52 (15.5)	0.013
	Preoperative chemotherapy	192 (23.0)	91 (24.7)	42 (32.6)	59 (17.6)	
	Chemotherapy alone	455 (54.6)	198 (53.8)	68 (52.7)	189 (56.2)	
	Exclusive best supportive care	76 (9.1)	31 (8.4)	9 (7.0)	36 (10.7)	
First therapeutic decision justification (%)	Inclusion in clinical trial	71 (8.6)	40 (10.9)	4 (3.1)	27 (8.1)	< 0.001
	Standard French TNCD guidelines	684 (82.5)	292 (79.8)	96 (75.0)	296 (88.4)	
	French COVID-19 guidelines	53 (6.4)	23 (6.3)	26 (20.3)	4 (1.2)	
	Non-standard treatment	21 (2.5)	11 (3.0)	2 (1.6)	8 (2.4)	
Delays to management						
Time from symptoms onset to first imaging (days)[c]	Median (IQR)	14.0 (4.0–41.5)	18.0 (6.0–50.0)	13.5 (1.8–36.2)	13.5 (3.0–35.0)	0.022
Time from symptoms onset to diagnosis (days)[d]	Median (IQR)	29.0 (14.0–65.0)	32.0 (15.8–72.2)	31.0 (11.8–64.0)	26.0 (14.0–59.0)	0.149
Time from symptoms onset to treatment (days)[e]	Median (IQR)	67.0 (45.0–106.0)	72.0 (49.0–106.5)	65.5 (48.0–96.2)	62.0 (38.0–102.0)	0.090
Time from diagnosis to MTBM (days)[f]	Median (IQR)	14.0 (6.0–25.0)	13.0 (6.0–27.0)	14.0 (7.0–24.5)	14.0 (6.0–22.0)	0.637
Time from first imaging to	Median (IQR)	44.0 (27.0–64.0)	46.0	46.0	42.0	0.338

Table 1 (*continued*)

Variables	Levels	Overall (n = 833)	P0 Diagnosis before COVID-19 (n = 368)	P1 Diagnosis during COVID-19 lockdown (n = 129)	P2 Diagnosis after COVID-19 lockdown (n = 336)	P value
treatment (days)[g]			(30.0–66.0)	(32.2–61.0)	(25.0–62.0)	
Impact of COVID-19 pandemic on chemotherapy		72 (8.7)	47 (12.8)	19 (14.7)	6 (1.8)	< 0.001
Waiting chemotherapy before upfront surgery (%)		22 (30.6)	11 (23.4)	11 (57.9)	0 (0.0)	0.005
Number of waiting chemotherapy cycles	Mean (SD)	4.1 (2.2)	3.5 (1.8)	4.7 (2.5)	0 (0.0)	0.186
Patients with cancelled or delayed chemotherapy cycle due to COVID-19 pandemic (%)		28 (38.9)	23 (48.9)	2 (10.5)	3 (50.0)	0.013
Number of cancelled or delayed chemotherapy cycles	Mean (SD)	3.5 (7.4)	2.1 (1.2)	3.0 (2.8)	14.0 (22.5)	0.026
Number of patients undergoing chemotherapy modification due to COVID-19 pandemic		22 (30.6)	15 (31.9)	6 (31.6)	1 (16.7)	0.742
Type of chemotherapy intensity modifications (%)	Triplet to doublet	13 (65.0)	8 (61.5)	4 (66.7)	1 (100.0)	0.786
	Triplet to mono-chemotherapy	5 (25.0)	3 (23.1)	2 (33.3)	0 (0.0)	
	Doublet to mono-chemotherapy	2 (10.0)	2 (15.4)	0 (0.0)	0 (0.0)	
Type of neoadjuvant or induction chemotherapy regimen administered (%)	mFOLFIRINOX	150 (77.7)	79 (84.9)	29 (69.0)	42 (72.4)	0.044
	5-FU-based bi-chemotherapy	18 (9.3)	5 (5.4)	6 (14.3)	7 (12.1)	
	LV5FU2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Gemcitabine	3 (1.6)	0 (0.0)	1 (2.4)	2 (3.4)	
	Others	22 (11.4)	9 (9.7)	6 (14.3)	7 (12.1)	
LV5FU2 to capecitabine due to COVID-19 pandemic (%)		8 (36.4)	6 (40.0)	2 (33.3)	0 (0.0)	0.711
Impact of COVID-19 pandemic on surgery		31 (3.7)	16 (4.3)	9 (7.0)	6 (1.8)	0.018
Surgery delay[h] (days)	Mean (SD)	43.1 (28.6)	47.1 (27.9)	84.0 (NA)	20.0 (7.2)	0.117
Impact of COVID-19 pandemic on chemo-radiotherapy		1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	ND
Impact of COVID-19 pandemic on clinical research						
Unincluded patient due to COVID-19 pandemic (suspended trial) (%)		44 (5.3)	12 (3.3)	23 (17.8)	9 (2.7)	< 0.001
	Missing	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.6)	
Cancelled inclusion due to COVID-19 pandemic (%)		25 (3.0)	13 (3.5)	10 (7.8)	2 (0.6)	0.001
	Missing	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)	

COVID-19: Coronavirus Disease 2019; y: years; SD: standard deviation; km: kilometres; m: metres; kg: kilograms; IU/mL: International Unit per millilitre; TNCD: Thésaurus National de Cancérologie Digestive; MTBM: multidisciplinary tumour board meeting; ND: not determined.

[a] Use of Poisson regression between pre-pandemic (P0) and epidemic (P1) weekly number of PA incidental cases.

[b] Use of Poisson regression between pre-pandemic (P0) and post-epidemic (P2) weekly number of PA incidental cases.

[c] Missing information for 210 patients.

[d] Missing information for 208 patients.

[e] Missing information for 277 patients.

[f] Missing information for 43 patients.

[g] Missing information for 116 patients.

[h] Missing information for one patient.

a consistent use of induction chemotherapy (from 94.0% in P0 to 85.7% in P1 and 81.2% in P2; $p = 0.206$) (Table 2B). Among 190 operated patients, 31 (16.3%) had their surgery postponed by a mean of 43.1 days (SD: 28.6). R0 resection was 77.2% for resectable diseases and 68.0% for borderline diseases, with no period influence. Although tumour (T) and node (N) stages remained steady, metastasis (M) discoveries during surgery were more frequent during lockdown (from 2.2% in P0 to 13.8% in P1; $p = 0.015$). One patient out of 18 with

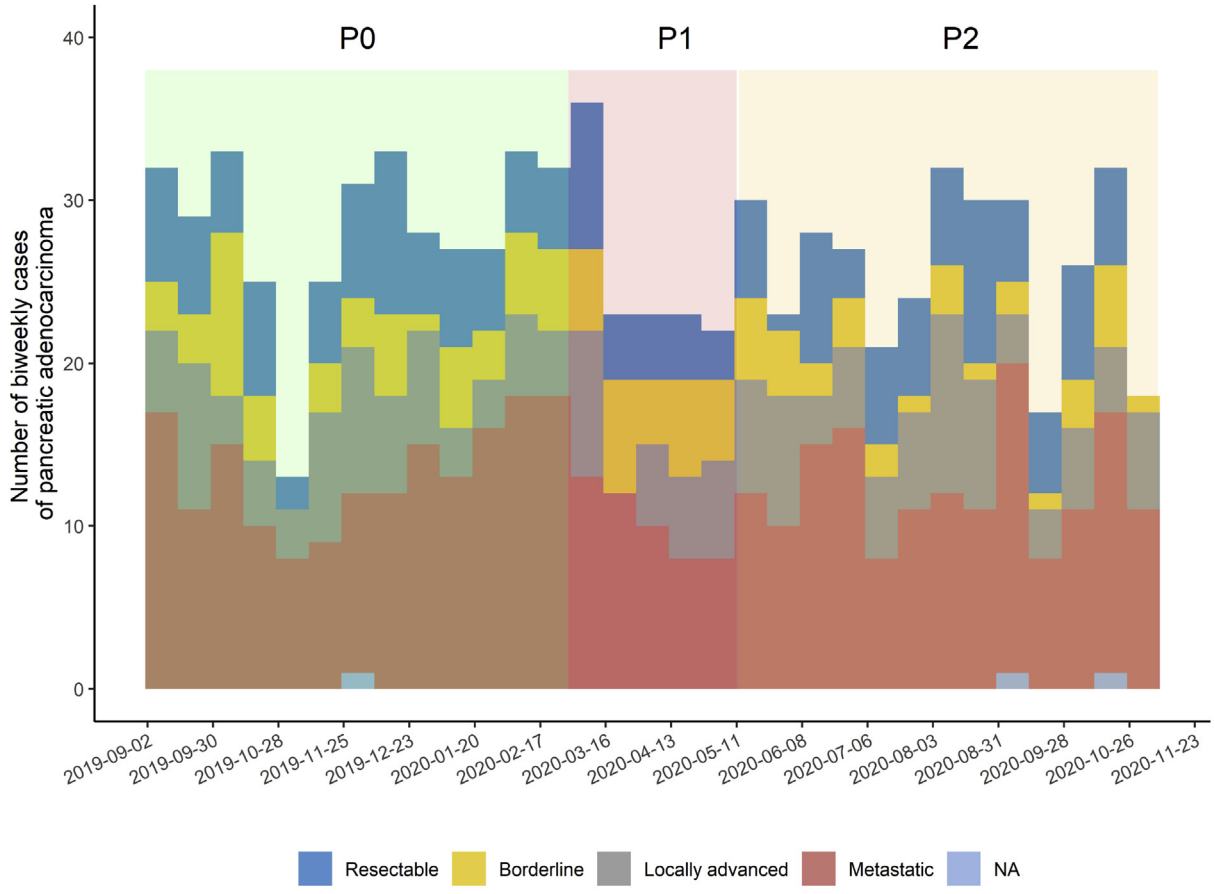


Fig. 2. Number of new biweekly cases of pancreatic adenocarcinoma based on disease stage at diagnosis (comparison per periods (P0, P1, and P2) using Chi2 tests: p = 0.046).

delayed surgery had metastases discovered during the surgical procedure.

The use of mFOLFIRINOX neoadjuvant or induction chemotherapy regimen decreased significantly during P1 (from 84.9% in P0 to 69% in P1; $p = 0.044$) (Table 1). In palliative settings, the use of FOLFIRINOX decreased ($p = 0.262$) during lockdown (from 49.2% in P0 to 39.3% in P1), contrasting with the more frequent use of gemcitabine (from 18.8% in P0 to 26.2% in P1) (Table 3). Among 550 treated patients, 72 (13.1%) had their chemotherapy cycles modified, cancelled, or postponed due to the pandemic.

3.5. Frequency and impact of COVID-19 infections

According to COVID-19 status, no significant differences were observed in terms of patient characteristics or treatment options except for geographical area ($p = 0.011$) (Supplemental Data). A total of 39 patients (4.7%) were suspected or confirmed cases of infection by SARS-CoV2 (Table 4). Three (7.7%) patients were admitted to the intensive care unit and 13 in standard medical units (33.3%). Five patients died from COVID-19 (12.8%). Among infected patients, chemotherapy was cancelled in 22 cases (56.4%) with a mean postponement of 1.6 weeks (SD: 1.1).

4. Discussion

To our knowledge, CAPANCOVID is the first cohort study to evaluate the COVID-19 pandemic's impact on the PA care pathway, from diagnosis to treatment. A decline of the weekly mean number of new PA diagnoses was observed without complete recovery. During the COVID-19 epidemic, significant migration of stage to diagnosis occurred from resectable to borderline tumours, then to locally advanced disease ($p = 0.046$). The first chosen treatment was adapted to the pandemic context: neoadjuvant chemotherapy was favoured compared to upfront surgery ($p = 0.013$) and tri-

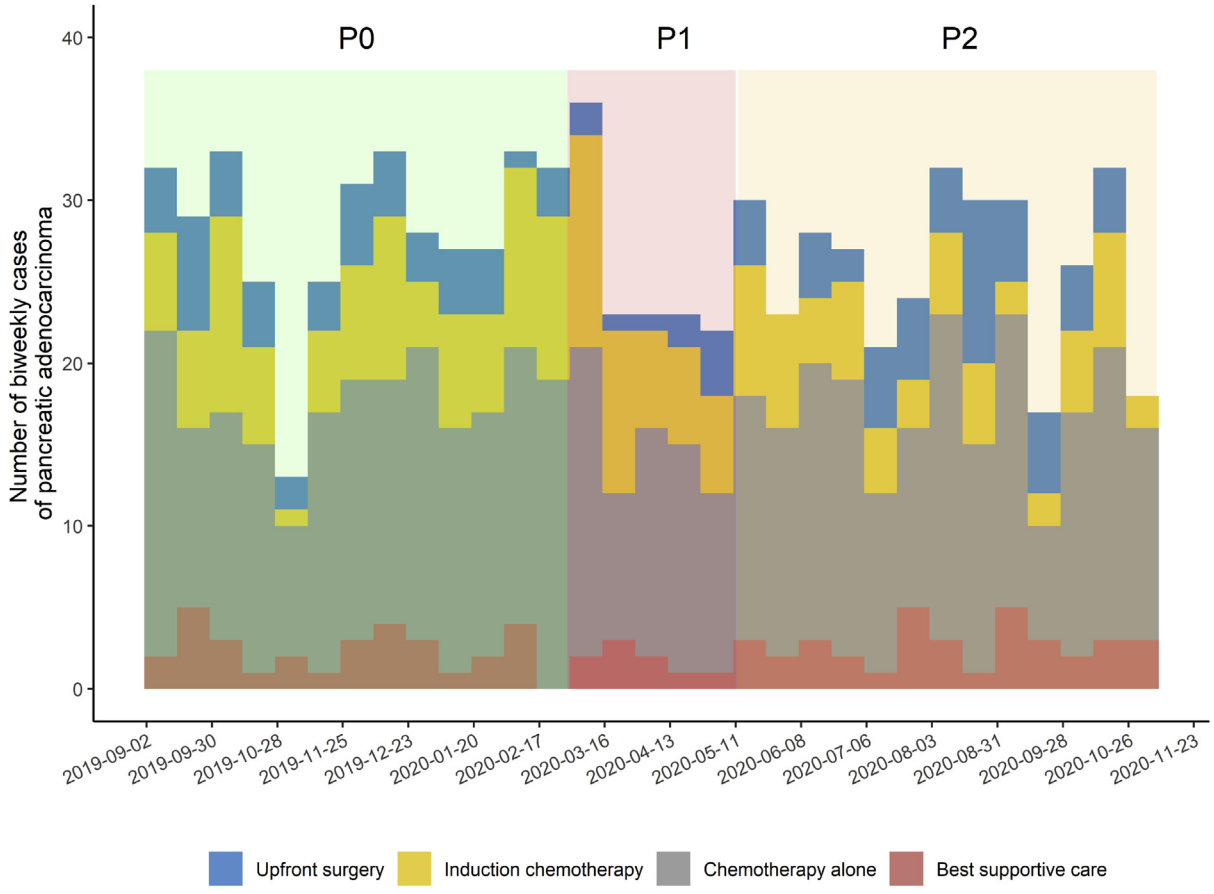


Fig. 3. Number of new biweekly cases of pancreatic adenocarcinoma based on first therapeutic decision (comparison per periods (P0, P1, and P2) using Chi2 tests: p = 0.013).

chemotherapy FOLFIRINOX regimen use declined ($p = 0.044$).

In the present study, the number of new PA diagnoses declined of 18.2% during the COVID-19 lockdown without diagnostic activity rebound in accordance with other studies. A US cross-sectional study showed a significant decline of 21.2% in PA cases, compared with baseline levels [19,20]. Another US multicentre network study observed a similar decrease of pancreatic, gallbladder, and extra-hepatic bile duct healthcare encounters [21]. However, this decline seemed less pronounced for cancers with poorer prognosis or obvious symptoms including PA [9,22–25]. In Belgium, the estimated number of missing PA diagnoses was 85 in 2020 [22]. In France, regarding the previous yearly number of new PA cases, this could represent around 500 missed diagnoses during this period.

Our results suggest a disease stage shift from resectable to advanced disease. Moreover, metastasis discoveries during surgery were more frequent during lockdown. Surprisingly, despite a decline of metastatic stages during the lockdown, no diagnostic activity rebound was observed afterwards. These undiagnosed metastatic patients may have been managed at home with exclusive supportive cares without visiting a care centre once. A previous Japanese study suggested a non-significant increase in the number of later-stage diseases [26]. To finish, evidence of patients with other malignancies diagnosed during lockdown periods showed heavier tumour burden [22,27].

These missing diagnoses and disease stage migrations could illustrate the disrupted health care pathway. From the healthcare delivery perspective, diagnostic procedures for less urgent diagnoses such as abdominal pain, diabetes, weight loss, intraductal papillary mucinous

Table 2
A. Treatment characteristics for resectable disease at diagnosis and COVID-19 pandemic impact on treatment. B. Treatment characteristics for resectable borderline disease at diagnosis and COVID-19 pandemic impact on treatment.

Variables	Levels	Overall (n = 168)	P0 Diagnosis before COVID-19 (n = 75)	P1 Diagnosis during COVID-19 lockdown (n = 24)	P2 Diagnosis after COVID-19 lockdown (n = 69)	P value
First therapeutic decision (%)	Upfront surgery	108 (64.3)	47 (62.7)	9 (37.5)	52 (75.4)	0.037
	Neoadjuvant chemotherapy	43 (25.6)	21 (28.0)	12 (50.0)	10 (14.5)	
	Chemotherapy alone	10 (6.0)	4 (5.3)	2 (8.3)	4 (5.8)	
	Best supportive care alone	7 (4.2)	3 (4.0)	1 (4.2)	3 (4.3)	
Neoadjuvant chemotherapy (%)		43 (25.6)	20 (26.7)	12 (50.0)	11 (15.9)	0.004
Type of chemotherapy regimen (%)	mFOLFIRINOX	31 (72.1)	14 (70.0)	7 (58.3)	10 (90.9)	0.326
	5-FU-based bi-chemotherapy	8 (18.6)	4 (20.0)	3 (25.0)	1 (9.1)	
	LV5FU2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Gemcitabine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Others	4 (9.3)	2 (10.0)	2 (16.7)	0 (0.0)	
Number of chemotherapy cycles	Mean (SD)	5.1 (2.4)	5.4 (2.5)	5.1 (2.9)	4.6 (0.9)	0.646
Chemotherapy in a clinical trial (%)		26 (13.5)	20 (21.5)	0 (0.0)	6 (10.3)	0.002
Surgery (%)		134 (80.2)	61 (81.3)	17 (70.8)	56 (82.4)	0.452
Resection performed (%)		123 (91.8)	55 (90.2)	16 (94.1)	52 (92.9)	0.810
T status (%)	Tis − T0 − T1 − T2	85 (69.1)	40 (72.7)	11 (68.8)	34 (65.4)	0.377
	T3 − T4	35 (28.5)	15 (27.3)	5 (31.3)	15 (28.8)	
	ND	3 (2.4)	0 (0.0)	0 (0.0)	3 (5.8)	
N status (%)	0	46 (37.4)	26 (47.3)	7 (43.8)	13 (25.0)	0.142
	N1−N2	75 (61.0)	29 (52.7)	9 (56.3)	37 (71.2)	
	ND	2 (1.6)	0 (0.0)	0 (0.0)	2 (3.8)	
M status (%)	0	116 (94.3)	54 (98.2)	13 (81.2)	49 (94.2)	0.039
	1	6 (4.9)	1 (1.8)	2 (12.5)	3 (5.8)	
	Missing	1 (0.8)	0 (0.0)	1 (6.2)	0 (0.0)	
R status (%)	0	95 (77.2)	44 (80.0)	13 (81.2)	38 (73.1)	0.746
	1	21 (17.1)	7 (12.7)	3 (18.8)	11 (21.2)	
	2	1 (0.8)	1 (1.8)	0 (0.0)	0 (0.0)	
	ND	6 (4.9)	3 (5.5)	0 (0.0)	3 (5.8)	

Variables	**Levels**	**Overall (n = 110)**	**P0 Diagnosis before COVID-19 (n = 50)**	**P1 Diagnosis during COVID-19 lockdown (n = 28)**	**P2 Diagnosis after COVID-19 lockdown (n = 32)**	***P* value**
First therapeutic decision (%)	Surgery	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.206
	Induction chemotherapy	97 (88.2)	47 (94.0)	24 (85.7)	26 (81.2)	
	Chemotherapy alone	10 (9.1)	3 (6.0)	2 (7.1)	5 (15.6)	
	Exclusive supportive care	3 (2.7)	0 (0.0)	2 (7.1)	1 (3.1)	
Induction chemotherapy (%)		91 (82.7)	44 (88.0)	22 (78.6)	25 (78.1)	0.410
Type of chemotherapy regimen (%)	mFOLFIRINOX	73 (80.2)	40 (90.9)	16 (72.7)	17 (68.0)	0.103
	5-FU-based bi-chemotherapy	9 (9.9)	1 (2.3)	3 (13.6)	5 (20.0)	
	LV5FU2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Gemcitabine	1 (1.1)	0 (0.0)	0 (0.0)	1 (4.0)	
	Others	8 (8.8)	3 (6.8)	3 (13.6)	2 (8.0)	
Number of induction chemotherapy cycles (%)	Mean (SD)	6.2 (2.6)	6.3 (2.6)	6.2 (2.5)	6.1 (2.7)	0.985
Surgery performed (%)		56 (51.4)	28 (56.0)	14 (50.0)	14 (45.2)	0.518
	ND	1 (0.9)	0 (0.0)	0 (0.0)	1 (3.2)	
Resection performed (%)		49 (87.5)	26 (92.9)	11 (78.6)	12 (85.7)	0.267
	Missing	1 (1.8)	1 (3.6)	0 (0.0)	0 (0.0)	

Table 2 (*continued*)

Variables	Levels	Overall (n = 168)	P0 Diagnosis before COVID-19 (n = 75)	P1 Diagnosis during COVID-19 lockdown (n = 24)	P2 Diagnosis after COVID-19 lockdown (n = 69)	P value
	ND	1 (1.8)	1 (3.6)	0 (0.0)	0 (0.0)	
T status (%)	T1 − T2	43 (86.0)	24 (88.9)	9 (81.8)	10 (83.3)	0.836
	T3	6 (12.0)	2 (7.4)	2 (18.2)	2 (16.7)	
	ND	1 (2.0)	1 (3.7)	0 (0.0)	0 (0.0)	
N status (%)	N0	13 (26.0)	7 (25.9)	2 (18.2)	4 (33.3)	0.870
	N1−N2	36 (72.0)	19 (70.4)	9 (81.8)	8 (66.7)	
	ND	1 (2.0)	1 (3.7)	0 (0.0)	0 (0.0)	
M status (%)	0	47 (94.0)	26 (96.3)	9 (81.8)	12 (100.0)	0.141
	1	3 (6.0)	1 (3.7)	2 (18.2)	0 (0.0)	
R status (%)	0	34 (68.0)	21 (77.8)	7 (63.6)	6 (50.0)	0.216
	1	16 (32.0)	6 (22.2)	4 (36.4)	6 (50.0)	

COVID-19. Coronavirus Disease 2019; SD: standard deviation; T: tumour; N: node; M: metastasis; R: resection; ND: not determined.

neoplasm, which may be the initial presentation of PA, were not prioritised at pandemic's peak [24,28,25]. In contrast, patients with jaundice or pancreatitis, considered as emergencies, may have been referred more easily [25]. In a Japanese retrospective study, the number of endoscopic retrograde cholangiopancreatographies was not significantly reduced as a result of urgent procedures for jaundice, but the number of endoscopic ultrasonography cases was significantly reduced [24].

In our study, patients were not significantly affected by the lockdown regarding times to diagnosis and treatment, reflecting the maintenance of the quality of care. However, from the patient's perspective, fear and anxiety about COVID-19 may have resulted in reluctance to have medical contact or to perform imaging exams [25]. Although the influence of time to diagnosis or treatment on PA prognosis remains unclear, a surge in later disease stages at diagnosis and a poorer prognosis than expected could be feared [9,29,30].

The first treatment is determined by disease stage at diagnosis. Resectable tumours should be treated with upfront surgery according to PA management guidelines [1,17]. Every patient but one (n = 20, 95.2%) treated by neoadjuvant chemotherapy for a resectable PA diagnosed before COVID-19 epidemic were included in clinical trials. In our study, we observed a mean 43-days postponement period for scheduled surgeries, with a major switch from upfront surgery to waiting neoadjuvant chemotherapy in patients with resectable disease. The diminished access to operating rooms and postoperative care in intensive care units justified the use of neoadjuvant chemotherapy [31−33]. Neoadjuvant chemotherapy could have improved the prognosis but clinical trial results are still pending. As recommended in

Table 3
Treatment characteristics for locally advanced and metastatic diseases at diagnosis and COVID-19 pandemic impact on treatment.

Variables	Levels	Overall (n = 550)	P0 Diagnosis before COVID-19 (n = 241)	P1 Diagnosis during COVID-19 lockdown (n = 76)	P2 Diagnosis after COVID-19 lockdown (n = 233)	P value
First therapeutic decision (%)	Palliative chemotherapy	434 (78.6)	191 (78.9)	64 (83.1)	179 (76.8)	0.560
	Exclusive best supportive care	64 (11.6)	27 (11.2)	6 (7.8)	31 (13.3)	
	Induction chemotherapy	52 (9.4)	23 (9.5)	6 (7.8)	23 (9.9)	
Palliative chemotherapy		416 (76.2)	192 (80.0)	61 (79.2)	163 (71.2)	0.130
	ND	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)	
Type of chemotherapy regimen administered (%)	FOLFIRINOX	200 (48.7)	94 (49.2)	24 (39.3)	82 (51.6)	0.759
	5-FU-based bi-chemotherapy	45 (11.0)	22 (11.5)	8 (13.1)	15 (9.4)	
	Gemcitabine	81 (19.7)	36 (18.8)	16 (26.2)	29 (18.2)	
	Nab paclitaxel-Gemcitabine	43 (10.5)	21 (11.0)	8 (13.1)	14 (8.8)	
	LV5FU2	2 (0.5)	2 (1.0)	0 (0.0)	0 (0.0)	
	Others	40 (9.7)	16 (8.4)	5 (8.2)	19 (11.9)	
Type of chemotherapy regimen administered (%)	FOLFIRINOX	200 (48.7)	94 (49.2)	24 (39.3)	82 (51.6)	0.262
	Others	211 (51.3)	97 (50.8)	37 (60.7)	77 (48.4)	

COVID-19: Coronavirus Disease 2019; ND: not determined.

Table 4
COVID-19 outcomes and clinical characteristics.

Variables	Levels	Overall (n = 39)	P0 Diagnosis before COVID-19 (n = 12)	P1 Diagnosis during COVID-19 lockdown (n = 10)	P2 Diagnosis after COVID-19 lockdown (n = 17)	P value
COVID-19 infection	Confirmed	34 (4.1)	10 (2.7)	8 (6.2)	16 (4.8)	0.150
	Suspected, unconfirmed	5 (0.6)	2 (0.5)	2 (1.6)	1 (0.3)	
	Not infected	789 (95.3)	352 (96.7)	119 (92.2)	318 (94.9)	
Confirmed via RT-PCR		28 (82.4)	8 (80.0)	6 (75.0)	14 (87.5)	0.289
	ND	3 (8.8)	0 (0.0)	1 (12.5)	2 (12.5)	
Confirmed via thoracic CT-scan		11 (32.4)	3 (30.0)	3 (37.5)	5 (31.2)	0.846
	ND	3 (8.8)	0 (0.0)	1 (12.5)	2 (12.5)	
Confirmed via serology		2 (5.9)	1 (10.0)	1 (12.5)	0 (0.0)	0.246
	ND	4 (11.8)	0 (0.0)	2 (25.0)	2 (12.5)	
Admitted at hospital for COVID-19 infection		17 (43.6)	4 (33.3)	5 (50.0)	8 (47.1)	0.458
	ND	1 (2.6)	0 (0.0)	1 (10.0)	0 (0.0)	
Admitted to conventional medical unit		13[a] (33.3)	4 (100.0)	4 (80.0)	5 (62.5)	0.882
Admitted to intensive care unit		3 (7.7)	0 (0.0)	1 (20.0)	2 (25.0)	0.882
Patients with chemotherapy cycles cancelled due to COVID-19 infection (%)		22 (56.4)	9 (75.0)	7 (70.0)	6 (35.3)	0.078
Delay of reported chemotherapy cycles due to COVID-19 infection (weeks)	Mean (SD)	1.6 (1.1)	1.8 (1.3)	1.3 (0.5)	1.7 (1.2)	0.748
Death due to COVID-19 infection		5 (12.8)	1 (8.3)	1 (10.0)	3 (17.6)	0.844

COVID-19: Coronavirus Disease 2019; ND: no determined; RT-PCR: Reverse Transcription-Polymerase Chain Transcription; CT: Computed Tomography.
[a] Unknown admission status for one infected patient.

the guidelines, oncologists switched from tri-chemotherapy to bi- or mono-chemotherapy during the first lockdown [12]. ESMO recommendations in the COVID-19 era considered newly diagnosed resectable and advanced PA as 'high priority to treat' [11,14]. The COVID-19 pandemic also had a dramatic impact on all aspects of pancreatic cancer research [34]. In France, all clinical research trials were stopped for 3 months. During the second wave, the improved knowledge on COVID-19 management and risk factors allowed new French guidelines to step up research and treatment to their previous levels [35].

Cancer patients are particularly vulnerable to SARS-CoV2 infections with a higher rate of severe forms [3–6]. In our cohort, 4.7% of the patients were contaminated by SARS-CoV2 with a mortality rate of only 12.8%, lower compared to previous declarative studies [3–6]. A recent large cohort study reported a mortality rate of only 7.8% for patients with recent cancer treatment [36]. SARS-CoV-2 PCR tests availability and increasing expertise in the management of COVID-19 severe forms could have made mortality rate estimation evolve all along previous published descriptive studies [6,36,37]. Our ambispective setting allows us to consider these results as non-biased real-life observations in a population with initial good performance status (79.6% of PS 0-1). However, these infections may have disrupted patients' treatment schedules. In our study, these modifications occurred in 56.4% of infected patients, with a mean delay of less than two weeks. In a French monocentric study, COVID-19 management caused a median 20-days delay for 41% of patients [6]. As the first French epidemic wave was concentrated in the Eastern regions, we observed a majority of COVID-19 infections in these Eastern centres (58.8%) but no differences in PA management, contrary to results reported in an Italian survey [38]. In France, a unique health policy was applied to the whole national territory without considering regional epidemic situation.

The CAPANCOVID study has some limitations. Firstly, in this ambispective setting, the first part of the study was retrospective. However, very few data are missing. Secondly, despite a multicentre design, COVID-19 incidence remained very heterogeneous between participating centres, while the Paris area, significantly impacted by the epidemic, was not represented. A study reported a higher decline of PA new cases by 34% in Paris [39]. In an Italian survey, a reduction in the number of PA diagnoses was recorded only in the North and Centre of the country (14.1% and 4.7%, respectively) [38]. Thirdly, this cohort was not a population-based study. Data collection from MTBM could have introduced a selection bias: some patients' files, particularly those receiving exclusive supportive care, might not be addressed. Another limitation is due to the low number of certain subgroups and the inability to perform multivariate analysis in these specific subgroups.

Finally, COVID-19 pandemic's impact on PA prognosis remains unknown. In this study, given the short

follow-up time, no survival data is available to date. The prognostic consequences were solely estimated via model-based analyses [40–42]. The CAPANCOVID study is still in progress, with a longer follow-up and a programmed survival analysis.

In conclusion, this cohort study confirms that the care pathway of PA patients was disrupted during the first COVID-19 epidemic wave. The missing diagnoses, the disease stage shifts and the treatment modifications may have impacted prognosis and this should be investigated in the future.

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Author contributions

Mathias Brugel: Conceptualization, methodology, formal analysis, project administration, validation, visualisation, writing – original draft, writing – review and editing, funding acquisition. **Léa Letrillart:** Investigation, visualisation, writing – original draft. **Aurore Thierry:** Methodology, data curation, formal analysis, software, writing – original draft. **Claire Carlier:** Conceptualization, investigation, validation, visualisation, writing – original draft. **Olivier Bouché:** Conceptualization, investigation, project administration, resources, supervision, visualisation, writing – original draft, writing – review and editing, funding acquisition. **All other authors:** Investigation, resources, writing – original draft.

Conflict of interest statement

D.T. reports personal fees as a speaker and/or in an advisory role from Merck KGaA, Roche, Bayer, Astra-Zeneca, BMS, MSD, Amgen, Sanofi, Servier, Ipsen and Pierre Fabre, outside the submitted work. G.P. reports personal fees as a speaker and/or in an advisory role from BMS, MSD, Stryker and Medtronic, outside the submitted work. A.T. reports personal fees as a speaker and/or in an advisory role from Amgen, Merck KGaA, Servier, Mylan and Pierre Fabre and travel accommodations expenses from Pfizer and Sanofi, outside the submitted work. G.R. reports personal fees as a speaker and/or in an advisory role from Accord Healthcare, Abbvie, Amgen, Ipsen, Sanofi, Servier, and MSD, outside the submitted work. F.D.F. reports personal fees as a speaker and/or in an advisory role from Roche, Amgen, Merck KGaA, Sanofi, Ipsen, Pierre Fabre, Servier, Janssens, Mylan, Sandoz and Bayer, outside the submitted work. C.B. reports personal fees as a speaker and/or in an advisory role from MSD, Sanofi, Bayer and a research grant from Servier, Roche, outside the submitted work. V.M reports personal fees as a speaker and/or in an advisory role from Sanofi, outside the submitted work. A.L. reports personal fees as a speaker and/or in an advisory role from Amgen, Vifor-Pharma, Bayer, Merck KGaA, Sanofi, Ipsen, Servier, Pierre Fabre, a research grant from Roche, and travel accommodation expenses from Abbvie, Amgen, Bayer, MSD, Vifor-Pharma, Mundi Pharma, Ipsen, Novartis outside the submitted work. D.B. reports personal fees as a speaker and/or in an advisory role from Accord Healthcare, Amgen, Sanofi, Servier, and Pierre Fabre, outside the submitted work. C.C. reports personal fees as a speaker from Bristol Myers Squibb, outside the submitted work. O.B. reports personal fees as a speaker and/or in an advisory role from Merck KGaA, Roche, Bayer, Astra-Zeneca, Grunenthal, MSD, Amgen, Sanofi, Servier, and Pierre Fabre, outside the submitted work.

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Appendix A. Supplementary data

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