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# 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)

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1 Original research article

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

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62

63

64 Abstract (248/250 words)

65 **Background**

66 The COVID-19 pandemic caused major oncology care pathway disruption. The  
67 CAPANCOVID study aimed to evaluate the impact on pancreatic adenocarcinoma  
68 (PA) – from diagnosis to treatment – of the reorganisation of the health care system  
69 during the first lockdown.

70 **Methods**

71 This multicentre ambispective observational study included 833 patients diagnosed  
72 with PA between September 1<sup>st</sup>, 2019 and October 31<sup>st</sup>, 2020 from 13 French  
73 centres. Data were compared over three periods defined as before the outbreak of  
74 COVID-19, during the first lockdown (March 1<sup>st</sup> to May 11<sup>th</sup>, 2020) and after  
75 lockdown.

76 **Results**

77 During the lockdown, mean weekly number of new cases decreased compared with  
78 that of pre-pandemic levels (13.2 vs. 10.8, -18.2%;  $p=0.63$ ) without rebound in the  
79 post-lockdown period (13.2 vs. 12.9, -1.7%;  $p=0.97$ ). The number of borderline  
80 tumours increased (13.6% to 21.7%) whereas the rate of metastatic diseases rate  
81 dropped (47.1% to 40.3%) ( $p=0.046$ ). Time-to-diagnosis and -treatment were not  
82 different over periods. Waiting neoadjuvant chemotherapy in resectable tumours was  
83 significantly favoured (24.7% to 32.6%) compared with upfront surgery (13% to 7.8%)  
84 ( $p=0.013$ ). The use of mFOLFIRINOX preoperative chemotherapy regimen  
85 decreased (84.9% to 69%;  $p=0.044$ ). After lockdown, the number of borderline  
86 tumours decreased (21.7% to 9.6%) and advanced diseases increased (59.7% to  
87 69.8%) ( $p=0.046$ ). SARS-CoV-2 infected 39 patients (4.7%) causing 5 deaths  
88 (12.8%).

89 **Conclusion**

90 This cohort study suggests the existence of missing diagnoses and of a shift in  
91 disease stage at diagnosis from resectable to advanced diseases with related  
92 therapeutic modifications whose prognostic consequences will be known after the  
93 planned follow-up.

94 **Trial registration**

95 Clinicaltrials.gov NCT04406571.

96

97 **Keywords**

98 COVID-19; SARS-CoV-2; pandemic; cancer; pancreatic neoplasms; care pathway

99 2591/2500 words

## 100 Introduction

101 Pancreatic adenocarcinoma (PA) is the most lethal gastrointestinal cancer and the  
102 fourth cause of cancer-related deaths in Europe with few therapeutic perspective<sup>1, 2</sup>.  
103 The severity of Coronavirus disease 2019 (COVID-19) caused by Severe Acute  
104 Respiratory Syndrome – Coronavirus 2 (SARS-CoV2) required most countries to take  
105 measures to contain the pandemic in 2020. Health care systems were reorganised to  
106 prioritise resources towards the management of critically ill patients. Patients with  
107 severe medical conditions and cancer have an increased risk of severe forms of  
108 COVID-19<sup>3-6</sup>.

109 The oncology care pathway was heavily disrupted at this time<sup>7, 8</sup>. Screening and  
110 diagnosis of many cancers were impacted, delaying time to treatment<sup>9</sup>. New  
111 guidelines were published proposing surgery deferral for resectable PA with waiting  
112 chemotherapy, palliative chemotherapy adjustments and telemedicine promotion<sup>10-14</sup>.  
113 The consequences of oncological care pathway disruption on PA patient  
114 management remain unknown.

115 The CAPANCOVID study aimed to evaluate the impact of the reorganisation of the  
116 health care system during the COVID-19 pandemic on the number of new cases,  
117 disease stages at diagnosis and treatment of patients newly diagnosed with PA.  
118 Secondary objectives were to describe COVID-19 incidence, severity and  
119 consequences on management of PA patients.

120

## 121 Patients and methods

### 122 Study design

123 We performed a comprehensive multicentre ambispective (retro-prospective)  
124 observational cohort study in nine French tertiary hospitals, two cancer institutes and  
125 two general hospitals. To simplify the interpretation of the influence of COVID-19  
126 incidence on our data, we assembled them into larger geographical areas: Grand  
127 East (Reims, Nancy, Besançon, Colmar); East (Saint Etienne, Grenoble); North (Lille,  
128 Amiens) and West (La Rochelle, Poitiers, Rouen). This study followed the  
129 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)  
130 guidelines<sup>15</sup>.

### 131 Patients

132 Adult patients diagnosed with a PA between September 1<sup>st</sup>, 2019, and October 31<sup>st</sup>,  
133 2020, whose files were discussed in a multidisciplinary tumour board meeting  
134 (MTBM) were included. As every patient's file had to be discussed in an MTBM,  
135 histological proof was not mandatory in order to consider the diagnosis (association  
136 of typical radiological findings and increased CA 19-9 levels). Patients under  
137 guardianship, with non-malignant tumours, neuroendocrine tumours or who were  
138 opposed to the study were not included.

### 139 Data collection

140 All data were collected online from patients' medical files after being screened using  
141 MTBM working lists. All data from patients diagnosed from September 1<sup>st</sup>, 2019 to  
142 April 15<sup>th</sup>, 2020 were collected retrospectively. Data from patients included after April  
143 15<sup>th</sup>, 2020 were collected both prospectively and consecutively.

144 Three periods were defined according to French COVID-19 governmental  
145 containment measures. The first period (P0), prior to COVID-19, was defined from  
146 before the onset of the epidemic until February 29<sup>th</sup>, 2020. From this date, French  
147 government instituted a first lockdown<sup>16</sup>. The second period (P1) was defined as the



148 first epidemic wave and lasted from March 1<sup>st</sup> to May 11<sup>th</sup>, 2020, when the first  
149 lockdown ended. A third period (P2) was defined from May 12<sup>th</sup>, 2020 to the end of  
150 the study.

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

## 166 Ethical approval

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

## 173 Aims and endpoints

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

## 180 Statistical analysis

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

186 We compared data per periods (P0, P1 and P2) using Student's tests, Wilcoxon  
187 tests, Chi2 tests or Fisher's exact tests depending on conditions of applications. The  
188 P1 mean weekly number of new PA cases was compared with P0 and P2 levels  
189 using Poisson regression. The significance level was set at 0.05. All statistical  
190 analyses were performed using RStudio (RStudio Team, Boston, USA, 2021) after  
191 data collection on CleanWeb (Telemedecine Technologies, Boulogne-Billancourt,  
192 France, 2021).

193

## 194 Results

### 195 Patients' characteristics

196 Among the 850 screened patients, a total of 833 eligible patients were included in the  
197 analysis (**Fig. 1**). Main characteristics of patients are presented in **Table 1**. Two

198 thirds of the patients (66.5%) were diagnosed with an advanced disease (locally  
199 advanced (20.2%) or metastatic diseases (46.3%)). Upfront surgery, preoperative  
200 chemotherapy, palliative chemotherapy and exclusive best supportive care were  
201 proposed in 13.2%, 23.0%, 54.6% and 9.1% of patients, respectively.

## 202 Impact of the COVID-19 pandemic on number of weekly PA cases

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

## 210 Impact of the COVID-19 pandemic on disease stages at diagnosis

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

## 221 Impact of the COVID-19 pandemic on treatments

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

226 For resectable tumours, upfront surgery declined during lockdown (62.7% in P0 to  
227 37.5% in P1;  $p=0.037$ ) and neoadjuvant chemotherapy was favoured (28.0% in P0 to  
228 50.0% in P1) (**Table 2A**). For borderline tumours, first-line treatment was similar with  
229 a consistent use of induction chemotherapy (from 94.0% in P0 to 85.7% in P1 and  
230 81.2% in P2;  $p=0.206$ ) (**Table 2B**). Among 190 operated patients, 31 (16.3%) had  
231 their surgery postponed by a mean of 43.1 days (SD: 28.6). R0 resection was 77.2%  
232 for resectable diseases and 68.0% for borderline diseases, with no period influence.  
233 Although tumour (T) and node (N) stages remained steady, metastasis (M)  
234 discoveries during surgery were more frequent during lockdown (from 2.2% in P0 to  
235 13.8% in P1;  $p=0.015$ ). One patient out of 18 with delayed surgery had metastases  
236 discovered during the surgical procedure.

237 The use of mFOLFIRINOX neoadjuvant or induction chemotherapy regimen  
238 decreased significantly during P1 (from 84.9% in P0 to 69% in P1;  $p=0.044$ ) (**Table**  
239 **1**). In palliative settings, the use of FOLFIRINOX decreased ( $p=0.262$ ) during  
240 lockdown (from 49.2% in P0 to 39.3% in P1), contrasting with the more frequent use  
241 of gemcitabine (from 18.8% in P0 to 26.2% in P1) (**Table 3**). Among 550 treated  
242 patients, 72 (13.1%) had their chemotherapy cycles modified, cancelled or postponed  
243 due to the pandemic.

#### 244 Frequency and impact of COVID-19 infections

245 According to COVID-19 status, no significant differences were observed in terms of  
246 patient characteristics or treatment options except for geographical area ( $p = 0.011$ )

247 **(Supplemental Data)**. A total of 39 patients (4.7%) were suspected or confirmed  
248 cases of infection by SARS-CoV2 (**Table 4**). Three (7.7%) patients were admitted to  
249 the intensive care unit and 13 in standard medical units (33.3%). Five patients died  
250 from COVID-19 (12.8%). Among infected patients, chemotherapy was cancelled in  
251 22 cases (56.4%) with a mean postponement of 1.6 weeks (SD: 1.1).

252

## 253 Discussion

254 To our knowledge, CAPANCOVID is the first cohort study to evaluate the COVID-19  
255 pandemic's impact on the PA care pathway, from diagnosis to treatment. A decline of  
256 the weekly mean number of new PA diagnoses was observed without complete  
257 recovery. During the COVID-19 epidemic, significant migration of stage to diagnosis  
258 occurred from resectable to borderline tumours, then to locally advanced disease  
259 ( $p=0.046$ ). The first chosen treatment was adapted to the pandemic context:  
260 neoadjuvant chemotherapy was favoured compared to upfront surgery ( $p = 0.013$ )  
261 and tri-chemotherapy FOLFIRINOX regimen use declined ( $p=0.044$ ).

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

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

281 These missing diagnoses and disease stage migrations could illustrate the disrupted  
282 health care pathway. From the healthcare delivery perspective, diagnostic  
283 procedures for less urgent diagnoses such as abdominal pain, diabetes, weight loss,  
284 intraductal papillary mucinous neoplasm which may be the initial presentation of PA,  
285 were not prioritised at pandemic's peak<sup>24, 28, 25</sup>. In contrast, patients with jaundice or  
286 pancreatitis, considered as emergencies, may have been referred more easily<sup>25</sup>. In a  
287 Japanese retrospective study, the number of endoscopic retrograde  
288 cholangiopancreatographies was not significantly reduced as a result of urgent  
289 procedures for jaundice, but the number of endoscopic ultrasonography cases was  
290 significantly reduced<sup>24</sup>.

291 In our study, patients were not significantly affected by the lockdown regarding times  
292 to diagnosis and treatment, reflecting the maintenance of the quality of care.  
293 However, from the patient's perspective, fear and anxiety about COVID-19 may have  
294 resulted in reluctance to have medical contact or to perform imaging exams<sup>25</sup>.  
295 Although the influence of time to diagnosis or treatment on PA prognosis remains

296 unclear, a surge in later disease stages at diagnosis and a poorer prognosis than  
297 expected could be feared<sup>9, 29, 30</sup>.

298 The first treatment is determined by disease stage at diagnosis. Resectable tumours  
299 should be treated with upfront surgery according to PA management guidelines<sup>1, 17</sup>.

300 Every patient but one (n = 20, 95.2%) treated by neoadjuvant chemotherapy for a  
301 resectable PA diagnosed before COVID-19 epidemic were included in clinical trials.

302 In our study, we observed a mean 43-days postponement period for scheduled  
303 surgeries, with a major switch from upfront surgery to waiting neoadjuvant

304 chemotherapy in patients with resectable disease. The diminished access to  
305 operating rooms and postoperative care in intensive care units justified the use of

306 neoadjuvant chemotherapy<sup>31-33</sup>. Neoadjuvant chemotherapy could have improved

307 the prognosis but clinical trial results are still pending. As recommended in the  
308 guidelines, oncologists switched from tri-chemotherapy to bi- or mono-chemotherapy

309 during the first lockdown<sup>12</sup>. ESMO recommendations in the COVID-19 era considered

310 newly diagnosed resectable and advanced PA as “high priority to treat”<sup>11, 14</sup>. The

311 COVID-19 pandemic also had a dramatic impact on all aspects of pancreatic cancer  
312 research<sup>34</sup>. In France, all clinical research trials were stopped for 3 months. During

313 the second wave, the improved knowledge on COVID-19 management and risk  
314 factors allowed new French guidelines to step up research and treatment to their

315 previous levels<sup>35</sup>.

316 Cancer patients are particularly vulnerable to SARS-CoV2 infections with a higher  
317 rate of severe forms<sup>3-6</sup>. In our cohort, 4.7% of the patients were contaminated by

318 SARS-CoV2 with a mortality rate of only 12.8%, lower compared to previous  
319 declarative studies<sup>3-6</sup>. A recent large cohort study reported a mortality rate of only

320 7.8% for patients with recent cancer treatment<sup>36</sup>. SARS-CoV-2 PCR tests availability

321 and increasing expertise in the management of COVID-19 severe forms could have  
322 made mortality rate estimation evolve all along previous published descriptive  
323 studies<sup>6, 36, 37</sup>. Our ambispective setting allows us to consider these results as non-  
324 biased real-life observations in a population with initial good performance status  
325 (79.6% of PS 0-1). However, these infections may have disrupted patients' treatment  
326 schedules. In our study, these modifications occurred in 56.4% of infected patients,  
327 with a mean delay of less than two weeks. In a French monocentric study, COVID-19  
328 management caused a median 20-days delay for 41% of patients<sup>6</sup>. As the first  
329 French epidemic wave was concentrated in the Eastern regions, we observed a  
330 majority of COVID-19 infections in these Eastern centres (58.8%) but no differences  
331 in PA management, contrary to results reported in an Italian survey<sup>38</sup>. In France, a  
332 unique health policy was applied to the whole national territory without considering  
333 regional epidemic situation.

334 The CAPANCOVID study has some limitations. Firstly, in this ambispective setting,  
335 the first part of the study was retrospective. However, very few data are missing.  
336 Secondly, despite a multicentre design, COVID-19 incidence remained very  
337 heterogeneous between participating centres while the Paris area, significantly  
338 impacted by the epidemic, was not represented. A study reported a higher decline of  
339 PA new cases by 34% in Paris<sup>39</sup>. In an Italian survey, a reduction in the number of PA  
340 diagnoses was recorded only in the North and Centre of the country (14.1% and  
341 4.7% respectively)<sup>38</sup>. Thirdly, this cohort was not a population-based study. Data  
342 collection from MTBM could have introduced a selection bias: some patients' files,  
343 particularly those receiving exclusive supportive care, might not be addressed.  
344 Another limitation is due to the low number of certain subgroups and the inability to  
345 perform multivariate analysis in these specific subgroups.



346 Finally, COVID-19 pandemic's impact on PA prognosis remains unknown. In this  
347 study, given the short follow-up time, no survival data is available to date. The  
348 prognostic consequences were solely estimated via model-based analyses<sup>40-42</sup>. The  
349 CAPANCOVID study is still in progress, with a longer follow-up and a programmed  
350 survival analysis.

351  
352 In conclusion, this cohort study confirms that the care pathway of PA patients was  
353 disrupted during the first COVID-19 epidemic wave. The missing diagnoses, the  
354 disease stage shifts and the treatment modifications may have impacted prognosis  
355 and this should be investigated in the future.

356

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## 366 Author Contributions

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368 administration, Validation, Visualization, Writing - original draft, Writing- review &  
369 editing, Funding acquisition. **Léa Letrillart:** Investigation, Visualization, Writing -

370 original draft. **Aurore Thierry:** Methodology, Data curation, Formal analysis,  
371 Software, Writing – original draft. **Claire Carlier:** Conceptualization, Investigation,  
372 Validation, Visualization, Writing - original draft. **Olivier Bouché:** Conceptualization,  
373 Investigation, Project administration, Resources, Supervision, Visualization, Writing -  
374 original draft, Writing- review & editing, Funding acquisition. **All other authors:**  
375 Investigation, Resources, Writing- original draft.

376

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508 **Tables:**

509 Table 1. Overall population characteristics and COVID-19 pandemic impact on  
510 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
<b>Impact of COVID-19 pandemic on clinical and tumoral characteristics</b>						
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 <sup>2</sup> )	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

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
	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)*	10.8 (5.2)*†	12.9 (4.6)†	0.625* 0.966†
<b>Impact of COVID-19 pandemic on treatments</b>						
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)	
<b>Delays to management</b>						
Time from symptoms onset to first imaging (days)**	Median (IQR)	14.0 (4.0 to 41.5)	18.0 (6.0 to 50.0)	13.5 (1.8 to 36.2)	13.5 (3.0 to 35.0)	0.022
Time from symptoms onset to diagnosis (days) <sup>††</sup>	Median (IQR)	29.0 (14.0 to 65.0)	32.0 (15.8 to 72.2)	31.0 (11.8 to 64.0)	26.0 (14.0 to 59.0)	0.149
Time from symptoms onset to treatment (days) <sup>Ω</sup>	Median (IQR)	67.0 (45.0 to 106.0)	72.0 (49.0 to 106.5)	65.5 (48.0 to 96.2)	62.0 (38.0 to 102.0)	0.090

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
Time from diagnosis to MTBM (days) <sup>€</sup>	Median (IQR)	14.0 (6.0 to 25.0)	13.0 (6.0 to 27.0)	14.0 (7.0 to 24.5)	14.0 (6.0 to 22.0)	0.637
Time from first imaging to treatment (days) <sup>£</sup>	Median (IQR)	44.0 (27.0 to 64.0)	46.0 (30.0 to 66.0)	46.0 (32.2 to 61.0)	42.0 (25.0 to 62.0)	0.338
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		8 (36.4)	6 (40.0)	2 (33.3)	0 (0.0)	0.711



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
pandemic (%)						
Impact of COVID-19 pandemic on surgery		31 (3.7)	16 (4.3)	9 (7.0)	6 (1.8)	0.018
Surgery delay <sup>β</sup> (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)	

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512 COVID-19: Coronavirus Disease 2019; y: years; SD: standard deviation; km:

513 kilometres; m: metres; kg: kilograms; IU/mL: International Unit per millilitre; TNCD:

514 Thésaurus National de Cancérologie Digestive; MTBM: multidisciplinary tumour

515 board meeting; ND: not determined.

516 \* use of Poisson regression between pre-pandemic (P0) and epidemic (P1) weekly

517 number of PA incidental cases; † use of Poisson regression between pre-pandemic

518 (P0) and post-epidemic (P2) weekly number of PA incidental cases, \*\* missing

519 information for 210 patients; †† missing information for 208 patients; ††† missing

520 information for 277 patients; †††† missing information for 43 patients; ††††† missing

521 information for 116 patients; †††††† missing information for one patient.

522 Table 2. A. Treatment characteristics for resectable disease at diagnosis and COVID-  
523 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

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
	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)	

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525 B. Treatment characteristics for resectable borderline disease at diagnosis and

526 COVID-19 pandemic impact on treatment.

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)	

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
	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)	

527

528 COVID-19. Coronavirus Disease 2019; SD: standard deviation; T: tumour; N: node;

529 M: metastasis; R: resection; ND: not determined

530 Table 3. Treatment characteristics for locally advanced and metastatic diseases at  
 531 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)	

532

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

534 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 <sup>‡</sup> (33.3)	4 (100.0)	4 (80.0)	5 (62.5)	0.882
Admitted to intensive care unit		3 <sup>‡</sup> (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

535

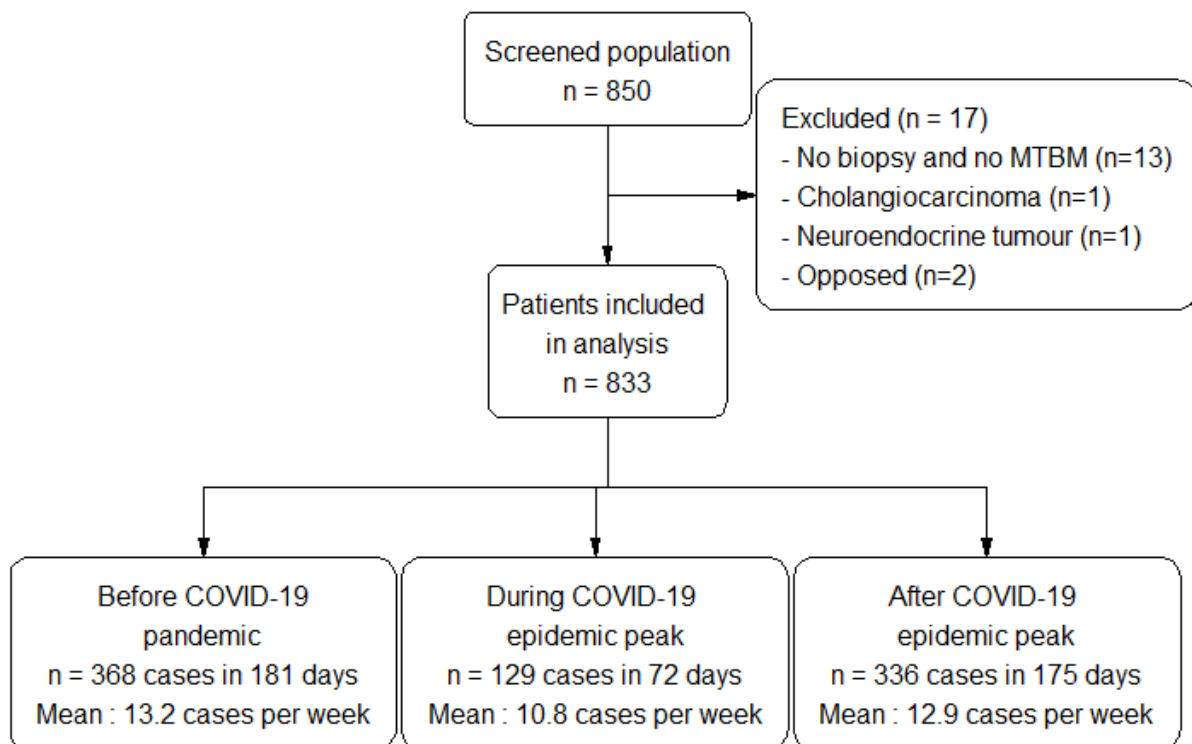
536 COVID-19: Coronavirus Disease 2019; ND: no determined; RT-PCR: Reverse

537 Transcription-Polymerase Chain Transcription; CT: Computed Tomography.

538 <sup>‡</sup> Unknown admission status for one infected patient

539 **Figures:**

540 Figure 1. Consort diagram.

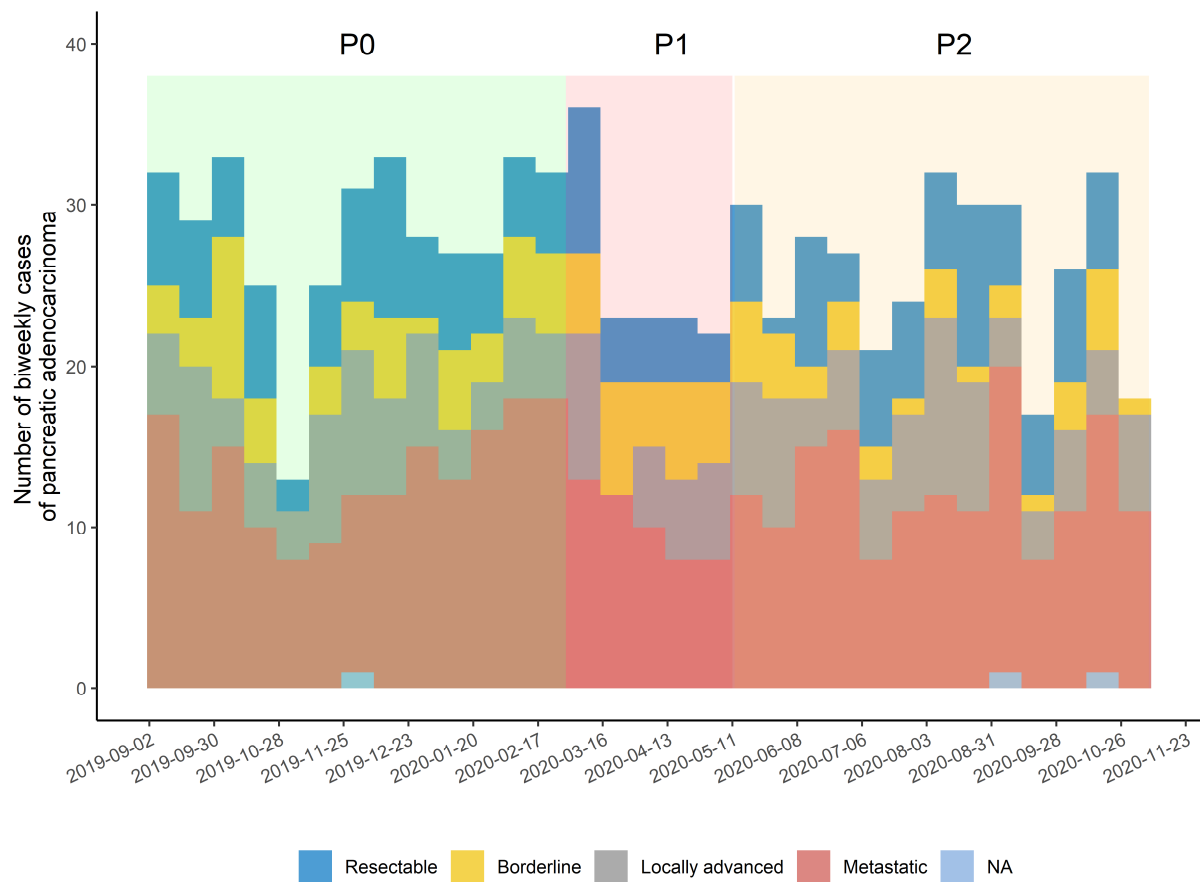


541

542 n: number of patients; MTBM: multidisciplinary tumour board meeting; COVID-19:

543 Coronavirus Disease 2019.

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



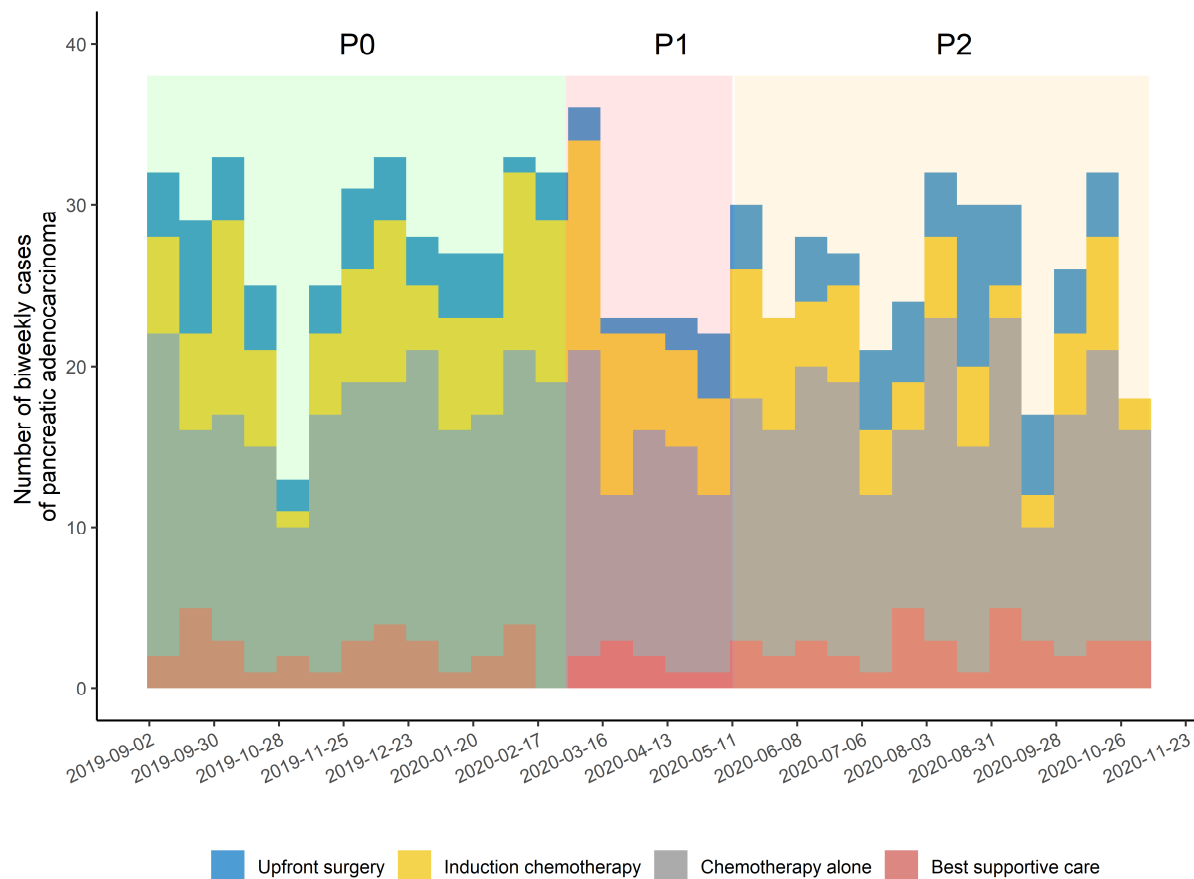
547

548 P0: from September 1<sup>st</sup>, 2019 to February 29<sup>th</sup>, 2020; P1: March 1<sup>st</sup> to May 11<sup>th</sup>,

549 2020; P2: May 12<sup>th</sup> to October 31<sup>st</sup>, 2020; NA: not available.



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



553  
 554 P0: from September 1<sup>st</sup>, 2019 to February 29<sup>th</sup>, 2020; P1: March 1<sup>st</sup> to May 11<sup>th</sup>,  
 555 2020; P2: May 12<sup>th</sup> to October 31<sup>st</sup>, 2020