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 COVID-19 on healthcare organisation and cancer outcomes

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Abstract ***Background:*** Changes in the management of patients with cancer and delays in treatment delivery during the COVID-19 pandemic may impact the use of hospital resources and cancer mortality.
Patients and methods: Patient flows, patient pathways and use of hospital resources during the pandemic were simulated using a discrete event simulation model and patient-level data from a

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large French comprehensive cancer centre's discharge database, considering two scenarios of delays: massive return of patients from November 2020 (early-return) or March 2021 (late-return). Expected additional cancer deaths at 5 years and mortality rate were estimated using individual hazard ratios based on literature.

Results: The number of patients requiring hospital care during the simulation period was 13,000. In both scenarios, 6–8% of patients were estimated to present a delay of >2 months. The overall additional cancer deaths at 5 years were estimated at 88 in early-return and 145 in late-return scenario, with increased additional deaths estimated for sarcomas, gynaecological, liver, head and neck, breast cancer and acute leukaemia. This represents a relative additional cancer mortality rate at 5 years of 4.4 and 6.8% for patients expected in year 2020, 0.5 and 1.3% in 2021 and 0.5 and 0.5% in 2022 for each scenario, respectively.

Conclusions: Pandemic-related diagnostic and treatment delays in patients with cancer are expected to impact patient survival. In the perspective of recurrent pandemics or alternative events requiring an intensive use of limited hospital resources, patients should be informed not to postpone care, and medical resources for patients with cancer should be sanctuarised.

1. Introduction

The COVID-19 pandemic led to a rapid influx of a large number of patients requiring intensive care. The impact of SARS-coV2 infection specifically in patients with cancer has been previously reported [1–3]. The pandemic has also impacted the management of patients with cancer, including delays in treatment delivery and modifications of standards of care [4,5].

In France, the government implemented a first national lockdown that lasted from 17th March to 10th May 2020, and health authorities enjoined all hospitals, including dedicated cancer centres, to open and extend their intensive care beds to patients with COVID-19 during the peak phase of the epidemic. Non-urgent surgeries and most of those requiring intensive care unit beds in the postoperative period had to be postponed. Several treatment plans deviating from standard practice were considered to minimise the number of hospital visits and hospitalisations as well as to prevent anticancer treatment–induced complications of COVID-19 [6–9]. From the patients' side, a significant portion of those expected for diagnosis, treatment or follow-up during lockdown postponed their visits [10–13]. Moreover, reduction in diagnostic examinations in primary care and cancer screening during lockdown led to a drop in patient referrals to hospitals. In October 2020, previously expected and new patients may have postponed their hospital visits during the second epidemic wave and lockdown. All these changes both in healthcare providers and patients may impact survival of patients with cancer.

Delays in cancer diagnosis and treatment can change the patient's prognosis (14–31, Supplementary Table A). Recent projections in the United Kingdom (UK) and the United States of America reported excess mortality in cancer patients induced by pandemic-related changes in cancer care [32–35]. In a UK study, increase in the number of deaths due to cancer up to 5 years after diagnosis was estimated at 5% for lung, 6% for oesophageal, 8–10% for breast and 15–17% for colorectal cancer [33]. However, little is known about how the pandemic will impact the patient's return to the hospital and hospital resources in the coming months and years.

In this study, our objectives were to assess the impact of delays and changes in cancer care on the use of hospital resources and cancer mortality, using data from the largest comprehensive cancer centre in France.

2. Patients and methods

2.1. Study design and data sources

We used a discrete event simulation (DES) model [36] to analyse patient pathways as per different return scenarios (Fig. 1). DES models the hospital care pathway as a series of events that occur over time. We used patient-level data from the Gustave Roussy (GR) Cancer Center (Villejuif, France) hospital discharge database (PMSI [programme de médicalisation des systèmes d'information]) from January 2018 to the end of October 2020. We excluded patients in paediatric oncology, neuro-oncology, oncogenetics and early drug development, representing about 11% of patients, as they did not share the same hospital resources with the other specialities. We considered unique patients defined as all patients attending the hospital during this time period for a new episode of care (initial treatment or treatment of recurrences involving surgery, radiotherapy, medical therapies or haematopoietic stem cell transplant), with a 3-month wash-off period. Patients coming for screening or surveillance with no subsequent treatment were not taken into account.

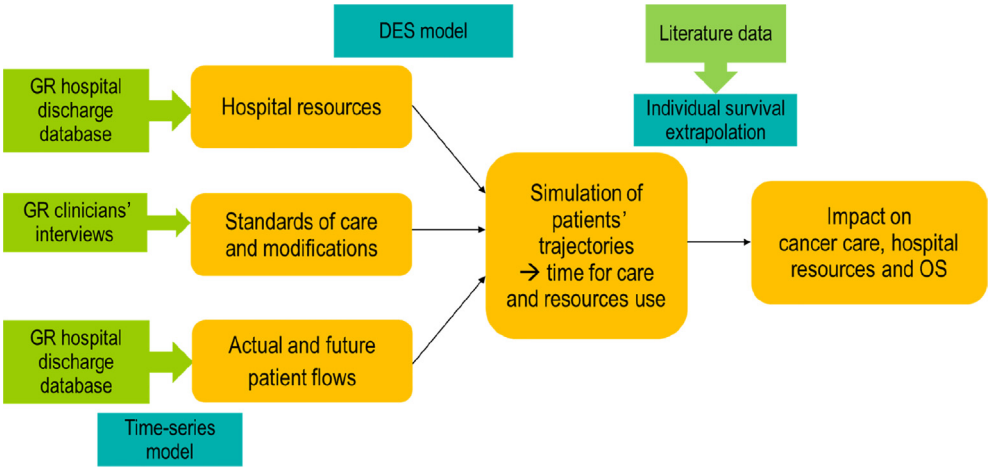

Fig. 1. Study flow chart. Notes: GR: Gustave Roussy; DES: discrete event simulation; OS: overall survival.

2.2. Model development

A DES model was developed to mimic the patient flow and organisation of hospital care, with time-dependent hospital resources corresponding to effective resources available at each time period. The overall study simulation period extended from January 2018 to December 2023. We used patient flows, pathways, treatment changes and hospital resources to populate the model.

Patient flows were modelled using time-series methods fitted with patient-level data from the GR hospital discharge database (Fig. 2, see details in Supplementary methods B). At any time point, the number of observed patients is the sum of patients who came to the scheduled appointment (on-time patients) and those who came later than expected (delayed patients), with each component estimated based on different hypotheses (see Simulation scenarios).

Patients' pathways were defined based on the cancer site, stage or histologic type or treatment line, following interviews with expert clinicians based on a standardised questionnaire. Overall, 75 cancer pathways were considered, with each pathway associated with use of specific hospital resources (Supplementary Table C). The distribution of patients in different pathways in 2019 was applied to the simulated patient on-time flow to split patients into the 75 pathways (Table 1—for ease of presentation, pathways were grouped into 21 broader categories as per cancer site). Using the DES model, care and hospital resource use were simulated at the patient level, as well as the individual time needed to receive care, which combined patient-induced delay (delay occurring before the patient's hospital visit) and healthcare-induced delay (delay while waiting for hospital care).

Available hospital resources (number of surgery blocks, beds in the postsurgery unit, chemotherapy sessions, radiotherapy sessions, beds for haematopoietic stem cell transplant) per week between March and October 2020 were defined based on the GR hospital discharge database. The term 'chemotherapy' refers to medical cancer treatments and includes chemotherapy, targeted treatments, immunotherapies, monoclonal antibodies, etc. Activity in 2019 was considered as maximum capacity (Supplementary Table D).

2.3. Simulation scenarios

We considered two contrasting scenarios. In the earlier return of patients scenario (early-return), usual patient flow was recovered by November 2020. We considered the on-time patient flow from the end of lockdown (week 21, mid-May 2020) to be constant and equal to that of the last lockdown week, until the last observed data date (LODD, week 44, end of October 2020). After the lockdown was lifted, the return of delayed patients was simulated following a first in/first out method: whenever there was a spot available (difference between expected usual patient flow and simulated on-time patient flow), it was given to the patient who had been waiting for the longest time. After the LODD, delayed patients who had not yet returned were added to the expected flow up to the hospital's maximum capacity, until total absorption of delayed patients. In this scenario, we hypothesised that all patients would return after the LODD and that existing delays would only be healthcare-induced delays (the hospital's maximum capacity reached) and not patient-induced delays.

In the later return of patients scenario (late-return), the usual patient flow was recovered by March 2021, taking into account the expected vaccination of people at risk (age, comorbidities) on priority. After the same patient flows as in the first scenario until the LODD, we considered the flow of on-time patients to follow a linear extrapolation from the LODD to reach the level of expected patient flow in the end of March 2021 (week 12).

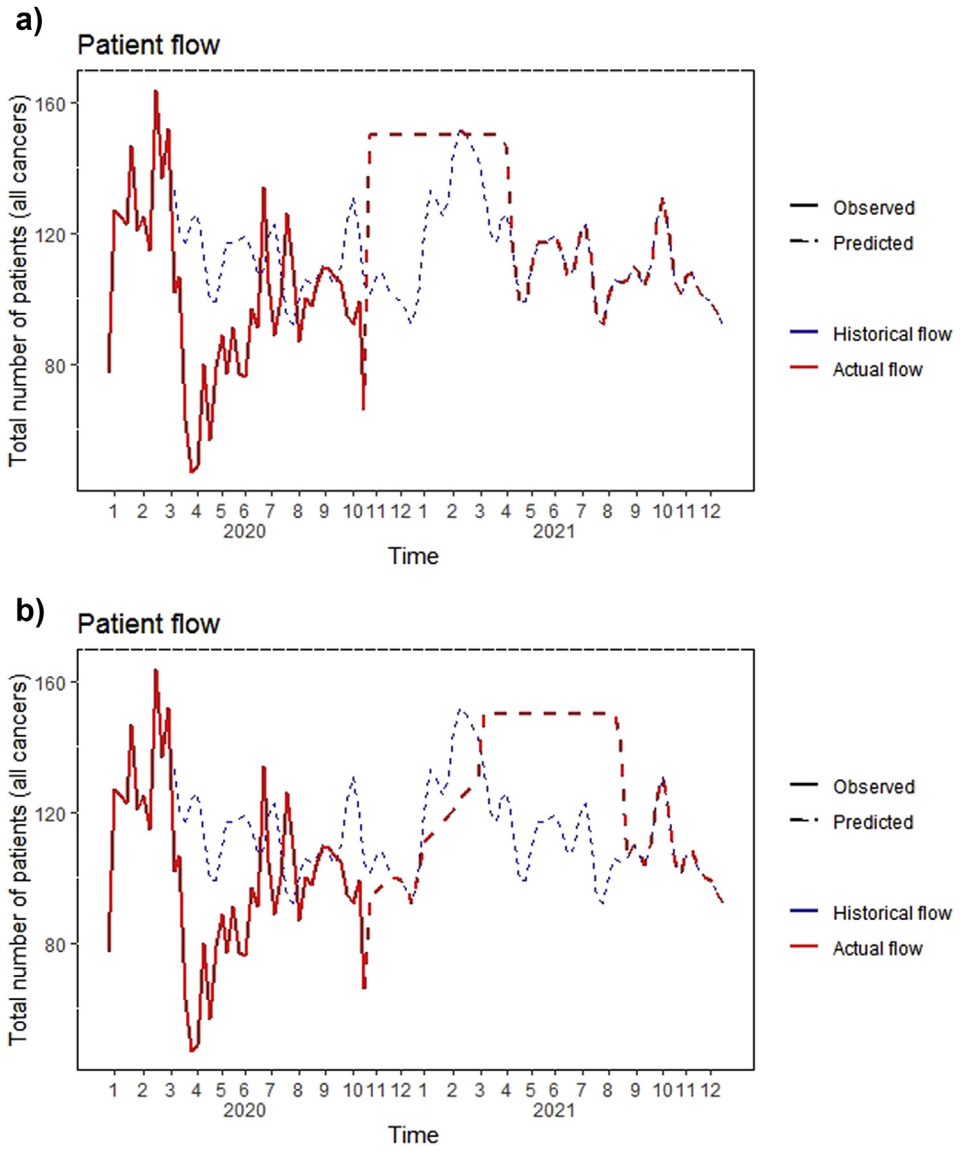

Fig. 2. Observed and predicted patient flows for the simulation period (2019–2022). a) Early-return scenario. b) Late-return scenario. Note: Patients' return is smoothed at 95% of maximum capacity of the centre for ease of visualisation.

We considered the proportion of on-time patients relative to the observed patients to be constant from the LODD to March 2021. We hypothesised that all delayed patients would return after this date. To assess the robustness of results and give additional insights on alternative scenarios, two main sensitivity analyses on the availability of hospital resources were implemented (Supplementary Methods E).

2.4. Statistical analysis

For cancer mortality, an individual hazard ratio for additional cancer death was derived based on literature data [14–30], in accordance with simulated care and time needed for provision of care (Supplementary Table A). This additional risk was applied to the 5-year net mortality rate for patients with cancer [37], and the additional number of cancer-specific deaths at 5 years after treatment for different types of cancer was calculated based on the assumption that net mortality approximates cancer mortality [38] for patients treated during the simulation period. The percentage of additional cancer deaths was calculated with respect to the usual number of cancer deaths at 5 years, for patients expected to receive care in a calendar year, to provide information on time trends of effects.

The model was programmed in open source R v.4.0.2 software using the Simmer and tsModel packages [39,40].

Table 1
Patient characteristics from the Gustave Roussy hospital discharge database for the year 2019.

Cancer type	All patients[a] (%)	New patients by cancer type (%[b])	Metastatic patients by cancer type (%[b])
Acute leukaemia	118 (2.0)	23 (19.5)	NA
Bladder	64 (1.1)	5 (7.8)	36 (56.3)
Breast	1906 (32.0)	817 (42.9)	190 (10.0)
Cervix	256 (4.3)	24 (9.4)	22 (8.6)
Colon	185 (3.1)	43 (23.2)	91 (49.2)
Gastroesophageal	58 (1.0)	16 (27.6)	27 (46.6)
Germinal seminoma	61 (1.0)	2 (3.3)	33 (54.1)
Head and neck	452 (7.6)	183 (40.5)	44 (9.7)
Kidney	46 (0.8)	8 (17.4)	46 (100)
Liver	30 (0.5)	8 (26.7)	10 (33.3)
Lung	426 (7.2)	122 (28.6)	227 (53.3)
Lymphoma	189 (3.2)	46 (24.3)	NA
Myeloma	87 (1.5)	38 (43.7)	NA
Neuroendocrine tumours	46 (0.8)	19 (41.3)	NA
Ovary	143 (2.4)	52 (36.4)	87 (60.8)
Pancreas	41 (0.7)	9 (22.0)	20 (48.8)
Prostate	390 (6.5)	63 (16.2)	85 (21.8)
Sarcomas	268 (4.5)	74 (27.6)	62 (23.1)
Melanoma	585 (9.8)	146 (25.0)	102 (17.4)
Thyroid	376 (6.3)	158 (42.0)	77 (20.5)
Endometrium	237 (4.0)	33 (13.9)	45 (19.0)
ALL	**5964 (100.0)**	**1889 (31.7)**	**1204 (20.2)**

NA: not applicable.
[a] In this table, only patients under active treatment using hospital resources (surgery blocks, beds in the postsurgery unit, chemotherapy sessions, radiotherapy sessions, beds for haematopoietic stem cell transplant) considered in the study are taken into account. Percentages are calculated with respect to the total number of patients.
[b] Percentages are calculated with respect to all patients within each cancer type.

3. Results

3.1. Patient flows, treatment delays and treatment modifications

Patients undergoing treatment at GR were 5964 in 2019, with 32% of them having breast cancer, 10% melanoma and 8% head and neck cancers (Table 1). Proportions of new patients and metastatic patients/patients with advanced cancer were 31.7% and 20.2%, respectively, both with wide variations across cancer types. Return to usual flows (no more delayed patients) and time for care (no more healthcare-induced delays) is expected to be in mid-May 2022 for the early-return scenario and in the beginning of June 2022 for the late-return scenario (Fig. 2). The number of patients requiring hospital care during the simulation period (from the beginning of lockdown in mid-March 2020 until absorption of all delays) was 13,015 patients for the early-return scenario and 13,328 patients for the late-return scenario. The mean delays were 12 days (standard deviation [SD] = 34, range 0–208) for the early-return scenario and 20 days (SD = 56, range 0–322) for the late-return scenario. In the early-return scenario, 18% of patients had a delay of >1 week, 8% > 1 month and 6% >2 months. In the late-return scenario, 25% of patients had a delay of >1 week, 10% >1 month and 8% >2 months.

Treatment modifications were implemented during the first lockdown only (March–May 2020). Among the 4514 patients expected to receive care in 2020 (from March to December, in the early-return scenario), 360 (8.0%) received modified care adapted to the COVID pandemic context, mainly in breast cancer (n = 208).

3.2. Hospital resources

The last resource creating healthcare-induced delay is estimated to be chemotherapy in both scenarios, with delays existing until 2022. Surgery is expected to present overload during about 60 days over the study period, for chemotherapy sessions, 200 days and for radiotherapy, between 3 and 10 days, as per simulation scenarios (Fig. 3).

3.3. Cancer outcomes

Impact on cancer mortality as per cancer type for each scenario is shown in Table 2. In the early-return scenario, the expected number of cancer deaths at 5 years under standard conditions is 4639 for the 13,015 patients in the simulation period. The overall additional cancer deaths at 5 years due to treatment delays were estimated at 88. This excess risk is mainly present for patients who should have received care in 2020, with a cancer mortality increase of 4.4%, whereas it represents 0.5% in both 2021 and 2022. For the late-return scenario, the expected number of cancer deaths at 5 years under standard conditions is 4769 for 13,328 patients, and additional deaths were estimated at 145, which represents a 6.8% increase for patients who should have received care in 2020, 1.3% in 2021 and 0.5% in 2022. The strongest increase in cancer deaths for patients to be treated in 2020, considering the proportion of additional mortality, was found for the following cancer types for the two scenarios: sarcomas (21 and 29%), cervix (16 and 21%), liver (9 and 8%), endometrium (8 and 12%), acute leukaemia (8 and 13%), head and neck (8 and 15%) and breast (7 and 11%). Sensitivity analyses supported findings from the main scenarios (Supplementary Data F).

4. Discussion

This study assessed the impact of COVID-19 disease on patients with cancer and without COVID in France. France has dedicated centres for patients with cancer (Centres de Lutte Contre le Cancer), which represent a protected resource. Although not all patients with cancer are cared for using this pathway, we believe this

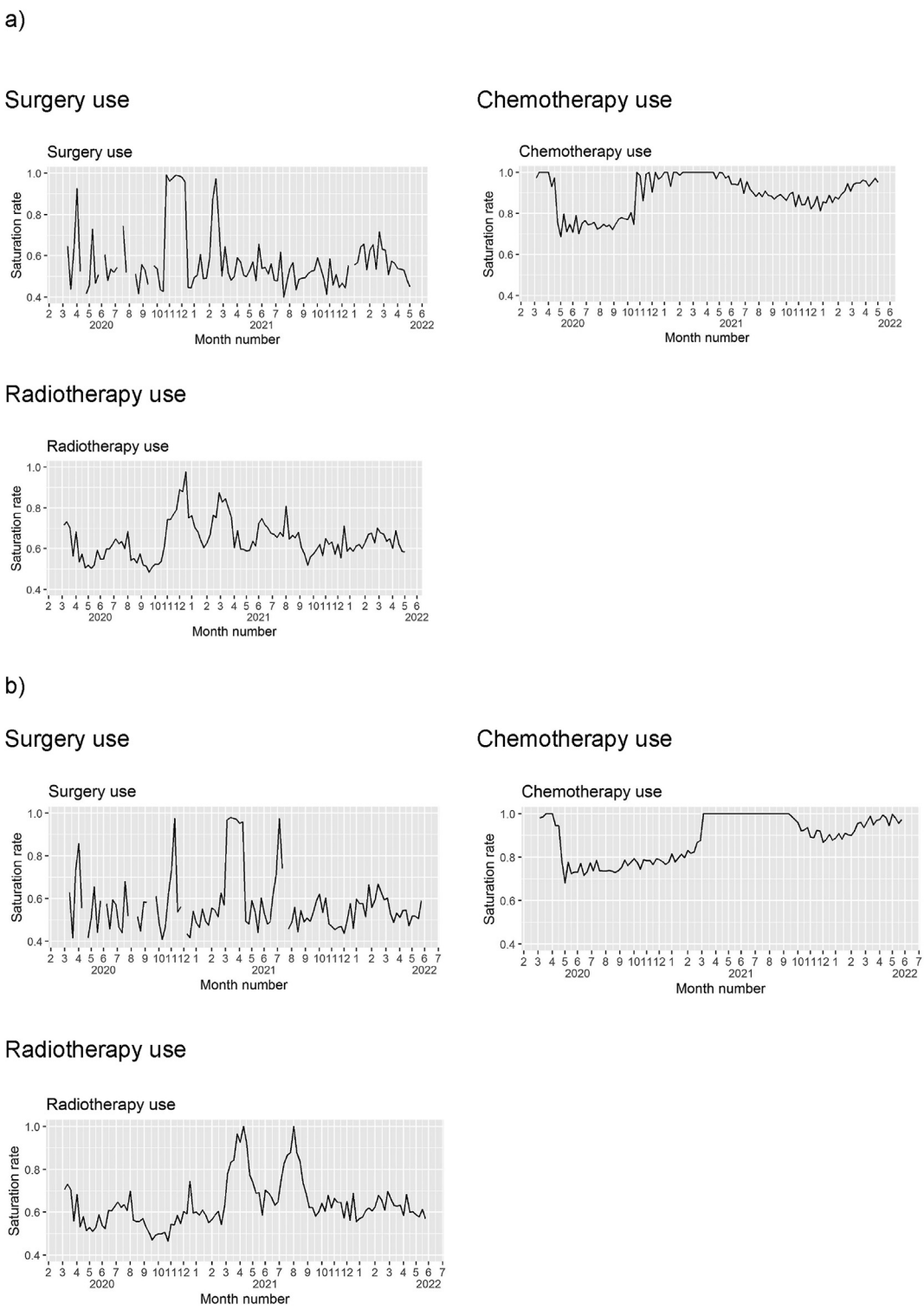

Fig. 3. Hospital resources. a) Early-return scenario. b) Late-return scenario. Notes: Overload is defined by saturation rate equals to 1. Mean weekly saturation rates are represented.

study to be informative for other hospital settings and countries with similar organisations.

The impact we found on sarcomas, gynaecological, liver, head and neck, breast cancer and acute leukaemia can be due to the existence of risk associated with diagnosis and treatment delay, overload in hospital resources needed for patients and/or volume of patients in these cancer types. Absorption of all delays could only be expected in May or June 2022 in the two scenarios, with delays existing until 2022 for chemotherapy. Sensitivity analyses show the sensible impact of punctual disruptions in the care pathways. These results advocate

Table 2
Additional number of deaths at 5 years as per cancer type.

a) Early-return scenario

Cancer type	Patients during the simulation period[a]	Metastatic patients (%)	Expected number of cancer-specific deaths at 5 years	Additional number of cancer-specific deaths at 5 years	Additional cancer mortality rate in year 2020[b] (%)	Additional cancer mortality rate in year 2021[b] (%)	Additional cancer mortality rate in year 2022[b] (%)
Sarcomas	536	138	235	19	20.8	1.4	1.3
Cervix	584	50	177	11	15.5	1.3	1.5
Liver	76	24	63	3	8.7	2.2	1.9
Endometrium	558	107	135	4	8.1	0.3	0.3
Acute leukaemia	355	NA	171	5	7.9	0.2	0.2
Head and neck	960	98	371	12	7.8	0.8	0.8
Breast	3922	401	728	21	6.7	0.9	0.8
Bladder	140	71	80	1	3.2	0.1	0.1
Colon	476	245	249	7	2.6	2.7	2.7
Lung	915	479	749	4	1.5	0.1	0.1
Melanoma	1188	195	643	1	0.5	0	0
Germinal seminoma	147	79	7	0	0	0	0
Lymphoma	419	NA	127	0	0	0	0
Myeloma	207	NA	130	0	0	0	0
Neuroendocrine tumours	128	NA	31	0	0	0	0
Gastroesophageal	168	80	126	0	0	0	0
Ovary	342	214	176	0	0	0	0
Pancreas	96	60	88	0	0	0	0
Prostate	893	197	143	0	0	0	0
Thyroid	760	126	133	0	0	0	0
Kidney	95	95	77	0	0	0	0
All	**13,015**	**2659**	**4639**	**88**	**4.4**	**0.5**	**0.5**

b) Late-return scenario

Cancer type	Patients during the simulation period[a]	Metastatic patients (%)	Expected number of cancer-specific deaths at 5 years	Additional number of cancer-specific deaths at 5 years	Additional cancer mortality rate in year 2020[b] (%)	Additional cancer mortality rate in year 2021[b] (%)	Additional cancer mortality rate in year 2022[b] (%)
Sarcomas	609	152	248	30	29.1	4.7	1.5
Cervix	620	62	194	15	20.7	2.0	1.3
Head and neck	970	94	375	23	14.8	2.0	0.8
Acute leukaemia	365	NA	176	9	13.4	0.8	0.2
Endometrium	573	111	140	6	12.2	1.0	0.2
Breast	4021	404	740	40	10.9	3.3	0.8
Liver	81	26	67	4	8.0	5.4	2.2
Bladder	150	79	87	2	5.7	0.8	0.1
Colon	485	246	251	7	2.6	2.8	2.6
Lung	931	503	766	7	2.1	0.3	0.1
Melanoma	1214	204	656	2	0.8	0.1	0
Germinal seminoma	141	80	7	0	0	0	0
Lymphoma	430	0	130	0	0	0	0
Myeloma	209	0	131	0	0	0	0
Neuroendocrine tumours	122	0	29	0	0	0	0
Gastroesophageal	176	81	132	0	0	0	0
Ovary	342	219	179	0	0	0	0
Pancreas	108	64	98	0	0	0	0
Prostate	901	199	144	0	0	0	0
Thyroid	780	130	138	0	0	0	0
Kidney	100	100	81	0	0	0	0
All	**13,328**	**2754**	**4769**	**145**	**6.8**	**1.3**	**0.5**

Categories are listed by decreasing order of additional cancer mortality rate in year 2020.

[a] Simulation period = from March 2020 until return to normal (mid-May 2022 and June 2022 in Early-Return and Late-Return scenarios respectively).

[b] The mortality rate was calculated considering the number of additional deaths occurring in patients who should have received care in the respective year over the theoretical number of deaths in the same population.

for a refined programming of activity in the coming months, to ensure appropriate allocation and protection of resources, including healthcare professionals.

The strengths of our simulation study should be underlined. First, we used robust individual data from the GR hospital discharge database. The DES model allowed us to make precise predictions on patient delays, rather than relying on strong and impacting hypotheses of generalised delays, and to take into account and adapt to multiple environments. In addition, we used published literature for hazard ratios on mortality. The information relying on best evidence has been used, even if heterogeneity of some cancers (e.g. sarcomas) can limit the validity of data. Two contrasting scenarios based on different dynamics for patients' return were considered, with supportive sensitivity analyses. The use of this additional risk for cancer mortality associated with treatment delay allowed us to implicitly take into account disease progression. Finally, the observation period was long, from March to the end of October 2020, including periods of lockdown, curfew and other restrictive measures.

Several limitations must be acknowledged. First, this study was based on patient flows of a single hospital, and even though it is one of the largest comprehensive cancer centres in Europe (6000 patients treated for cancer every year), the impact on cancer mortality may not be representative of all French patients with cancer. A substantial and heterogeneous decrease in national cancer care activity has been reported, affecting mostly general hospitals [9]. The hospital casemix is not fully representative of the general cancer population, GR being a reference centre for some cancer types (e.g. sarcomas) and a notable proportion of patients being included in clinical trials. However, the model is applicable to other settings, and external data could be integrated in future studies. Second, we had to simplify some of the model inputs. Patients' individual risk factors were not considered, and delays were applied homogeneously to all patients, whatever the cancer type. Patients with no subsequent treatment for cancer were not taken into account because of their low use of limited medical resources, which could lead to an underestimation of delays for care. We assumed that no prioritisation was made between patients, whereas it was actually implemented within each tumour group. However, haematopoietic stem cell transplant beds were considered as not limiting to take into account potential faster return and care for haematological patients. Patient-induced delays can in fact reflect a variety of delays, which may not be due to the patient's choice to postpone. Delays can present differences between patients included or not in clinical trials. Furthermore, additional number of deaths is not as exhaustive as the number of life years lost. Finally, although we chose two contrasting scenarios to address the impact on cancer mortality, the impact of the pandemic appears to be long-lasting, and our scenarios are likely optimistic and the impact on cancer mortality underestimated. Estimates will be updated as more recent discharge data become available.

This work has shown the existence of long-term impacts of COVID-19 pandemic, regarding patients' demand for care, provision of care and cancer outcomes. Further investigations will be implemented from the present work, including patient perspectives and behaviours. It seems important that cancer care providers fully maintain their activities even during lockdown periods and that patients are informed not to postpone their diagnosis and treatment.

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Conflict of interest statement

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Appendix A. Supplementary data

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