



HAL
open science

Delayed care for patients with newly diagnosed cancer due to COVID-19 and estimated impact on cancer mortality in France

J.Y. Blay, S. Boucher, B. Le Vu, C. Cropet, S. Chabaud, D. Perol, E. Barranger, M. Campone, T. Conroy, C. Coutant, et al.

► To cite this version:

J.Y. Blay, S. Boucher, B. Le Vu, C. Cropet, S. Chabaud, et al.. Delayed care for patients with newly diagnosed cancer due to COVID-19 and estimated impact on cancer mortality in France. *ESMO Open*, 2021, 6 (3), pp.100134. 10.1016/j.esmoop.2021.100134 . hal-03249504

HAL Id: hal-03249504

<https://hal.science/hal-03249504>

Submitted on 24 May 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Delayed care for patients with newly diagnosed cancer due to COVID-19 and estimated impact on cancer mortality in France

Blay JY¹, Boucher S², Le Vu B², Cropet C¹, Chabaud S¹, Perol D¹, Barranger E³, Campone M⁴, Conroy T⁵, Coutant C⁶, De Crevoisier R⁷, Debreuve-Theresette A⁹, Delord JP⁹, Fumoleau P¹⁰, Gentil J⁶, Gomez F¹, Guerin O⁴, Jaffré A¹¹, Lartigau E¹², Lemoine C¹³, Mahe MA¹⁴, Mahon FX¹¹, Mathieu-Daude H¹⁵, Merrouche Y⁸, Penault-Llorca F¹⁶, Pivot X¹⁷, Soria JC¹⁸, Thomas G¹⁴, Vera P¹⁹, Vermeulin T¹⁹, Viens P¹³, Ychou M¹⁴, Beaupere S²

Correspondence to Prof J.-Y Blay, Department of Medical Oncology, Centre Léon Bérard, 28 rue Laënnec, 69373 Lyon Cedex 08, & Université Claude Bernard Lyon I France. Tel: +33 (0)4 78 78 51 26, jean-yves.blay@lyon.unicancer.fr

Affiliations:

1. Centre Leon Berard, Lyon , France
2. Unicancer, 101, rue de Tolbiac, 75013 Paris
3. Centre Antoine Lacassagne, Nice, France
4. Institut de Cancerologie de l'Ouest, Nantes et Angers, France
5. Institut de Cancerologie de Lorraine, Nancy, France
6. Centre George Françoise Leclerc, Dijon, France
7. Centre Eugene Marquis, Rennes , France
8. Institut Jean Godinot, Reims, France
9. Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France.
10. Institut Curie, Paris , France
11. Institut Bergonié, Bordeaux, France
12. Centre Oscar Lambret, Lille, France
13. Institut Paoli-Calmettes, Marseille, France
14. Centre François Baclesse, Caen , France
15. Institut de Cancerologie de Montpellier, France
16. Centre Jean Perrin, Clermont Ferrand, France
17. Centre Paul Strauss/ICANS, Strasbourg France
18. Gustave Roussy, Villejuif, France
19. Centre Henri Becquerel, Rouen, France

Summary

Rationale

The impact of the first COVID-19 wave on cancer patient management was measured within the nationwide network of the Unicancer comprehensive cancer centers in France.

Patients, Material and Methods

The number of patients diagnosed and treated within 17 of the 18 Unicancer centers was collected in 2020 and compared to that during the same periods 2016 to 2019. Unicancer centers treat close to 20% of cancer patients in France yearly. The reduction in the number of patients attending the Unicancer centers was analyzed per regions and cancer types. The impact of delayed care on cancer-related deaths was calculated based on different hypotheses.

Results

A 6.8% decrease in patients managed within Unicancer in the first 7 months of 2020 vs 2019 was observed. This reduction reached 21% during April and May, and was not compensated in June and July, nor later until November 2020. This reduction was observed only for newly diagnosed patients, while the clinical activity for previously diagnosed patients increased by 4% similarly to previous years. The reduction was more pronounced in women, in breast and prostate cancers and for patients without metastasis. Using an estimated hazard ratio of 1.06 per month of delay in diagnosis and treatment of new patients, we calculated that the delays observed in the 5-month period from March to July 2020 may result in an excess mortality due to cancer of 1,000 to 6,000 patients in coming years.

Conclusions

In this study, the delays in cancer patient management were observed only for newly diagnosed patients, more frequently in women, for breast and prostate cancer, and in non-metastatic cancers. These delays may result in an excess risk of cancer-related deaths in the coming years.

Keywords: COVID-19, cancer, delay, diagnosis, outbreak, treatment, SARS-COV-2, patient pathway

Highlights:

- A reduction of the number of cancer patients attending cancer centers was observed in France from Jan to July 2020
- This reduction was observed only for newly diagnosed patients
- The reduction of new diagnosis was more pronounced for women, breast cancer, and prostate cancer , and non metastatic cancer
- No compensation observed for the last months of 2020. The magnitude of delays may be larger in centers in the same countries
- An estimation of the excess cancer death resulting from these delays is presented

Introduction

The recent COVID-19 epidemic has resulted in a massive mobilization of health care systems for the management of patients requiring active treatment and intensive care. Resulting delays in the management of other diseases, in particular cancers, have been reported and identified as a potential risk factor for an increased rate of mortality of cancer patients with curable disease in the coming years (1-6). The magnitude of this increased mortality is not well known.

An extensive number of articles have reported that delays in the diagnosis and management of patients with cancer is associated with an increased risk of death at an advanced stage, an increased risk of relapse, and death in the localized phase (7,8). Reducing the delays in early management is a general strategy proposed to improve patient outcome in low- and middle-income countries (9), as illustrated for breast cancer (10). Public health strategy of nationwide screening for breast, colorectal, cervix and lung carcinoma are based on the reduction of the risk of cancer-related deaths with earlier diagnosis (11-14).

While delayed diagnosis and cancer treatment increases the risk of death due to cancer, with few exceptions such as indolent lymphomas or low risk prostate cancers (15-18) the magnitude of the impact of 1 to 6 months delay in the initial management of curable cancer patients on relapse and death due to cancer is less clear, and varies considerably across studies for almost all cancer types (19-22). Newly diagnosed cancer patients are particularly at risk of a negative impact of delayed diagnosis and treatment (19-22). In addition, cancer patients are a population at risk of major complications and death due to COVID-19, in all countries, including France (23-25).

France has a national security system based on free health service including national screening programs. Unicancer is the French Federation of comprehensive cancer centers with an exclusive public activity gathering 18 centers treating approximately 23% of all cancer patients in this country (unicancer.fr).

We investigated the impact of the COVID-19 pandemic and the first national lockdown in France on the number of patients consulting within Unicancer centers for a new diagnosis of cancer, according to the cancer type.

Patient and methods

Unicancer : new patients per center in 2019 and 2020

Unicancer is the French Federation of Comprehensive Cancer centers. Unicancer includes 18 different hospitals in all regions (<http://www.unicancer.fr/en/unicancer-group/key-figures>). Each Unicancer center was interrogated for the number of total and newly diagnosed patients consulting from January 1st to July 31st of 2019 and 2020, as well as those recorded from 2016 to 2018. Seventeen of the 18 centers were able to contribute to the study, the 18th center did not contribute because engaged in a merger precluding a relevant comparison of 2019 and 2020. The total number of cancers treated as well as that of breast, digestive, thoracic, gynecological, head and neck, urological and hematological malignancies and general characteristics were collected.

Incidence of cancers in France

We collected information on the overall incidence of cancers in France the French National Cancer Institute (INCA) website. In 2018, there were 382,000 new diagnoses of solid tumor cancers in France, and 157,400 cancer-related deaths (41%) (<https://en.e-cancer.fr/>). Raw nationwide data from the publicly available health care system were also used as of

November 24th 2020 (26) to extrapolate the reduction in new cases attending Unicancer centers at the national level.

Analysis of the literature

We analyzed the published literature on Pubmed describing the correlation between cancer treatment (surgery, radiotherapy and chemotherapy) delay and survival. The keywords used for the enquiry on Pubmed were « delay » « cancer » « diagnostic » « time to treatment » « survival ». This research was conducted in Nov 2020 identified 3840 articles. These articles were further selected with manual screening focusing on delays for treatment initiation in localized phase. Meta-analysis, retrospective reviews, trials were selected for all cancer types: breast, colorectal, lung, prostate, head and neck, ovarian, uterine, renal cell carcinoma, bladder, lymphoma, and leukemia; a selection is presented on Supplementary Table 1 (27-56). The level of increase the risk of cancer death associated with 1 week to 6 months of delay (depending on the studies) was investigated. With the exception of studies in indolent lymphomas, and low risk prostate cancer (15-18), the majority of other studies reported an increased risk of death ranging from 0.5% per week of delay to 169% per 12 weeks of delay depending on cancer types and across studies (27-56) (Suppl. Table 1).

Statistics

Comparison of the different proportions and numbers were conducted using the Chi-squared test or the non-parametric Mann-Whitney U test. In general, the Chi-squared test was used to compare the number of patients with different characteristics (e.g. gender) in 2020 vs 2019 (for the total first seven months of these 2 years, or for an individual month). To calculate the potential impact of delays on the risk of cancer-specific deaths, we conducted 3 different analyses.

- 1) As a conservative estimate, we selected a hazard ratio of 1.06 for the increased risk of death related to a one-month delay in therapeutic intervention as indicated within the recent analysis by Hanna et al for frequent cancer types (20). This hazard ratio was applied to all cancer types for simplicity. The studies on other types reported a hazard ratio generally superior to this estimate (Suppl. Table 1). The increased risk of death was compared to general death rates in the French population reported in 2018 (157,400 deaths due to cancer and 382,000 new diagnoses of cancer, i.e. 41% death rate) (e-cancer.fr). The increased risk of death related to one month or multiple months was calculated as follows:

If the rate of death due to delay is "RD_{del}"; if the rate of death without delay is "RD"; HR corresponds to the Hazard ratio of death related to a 1-month delay, while the Hazard Ratio related to a n-months delay is HRⁿ. The risk of death due to delay RD_{del} can be calculated as follows: $RD_{del} = 1 - \exp [\ln(1-RD) * HR^n]$. If N is the difference between the number of newly diagnosed patients seen in 2019 minus the number of newly diagnosed patients seen in 2020 per month, the estimated excess number of deaths related to a delay of 1 month (ND_{exc}) is therefore $ND_{exc} = N (RD_{del} - RD)$ for each individual month of the study.

- 2) Secondly, we applied the same calculation with two extreme hazard ratios (HR=1.02 and HR=1.1) with a similar standard death rate of 41% in order to describe different hypotheses.
- 3) Thirdly, we then applied the same calculation described above in (1) with a) specific mortality rates for 5 individual tumor types (colorectal, head and neck carcinoma,

bladder carcinoma, breast carcinoma, a lung carcinoma (as published in the meta-analysis (15), and b) with specific mortality rates of these 5 individual tumors reported in this country in 2018 (e-cancer.fr).

The statistical analyses were conducted with SPSS 23.0 package (IBM, Paris France).

Results

Patients treated and new patient diagnosed in 2019 vs 2020 in Unicancer (Figure 1).

For the years 2019 and 2020, the total number of cancer patients treated from January to July in Unicancer centers were 90,432 and 89,161, respectively (-1.4%), while this number had continuously increased by 2.7%, 3.1%, and 4.6% between 2016 (N=81,666), 2017 (N=83,877), and 2018 (N=86,493) in this network.

The decrease in the number of patients was observed only for patients with a new (2020) diagnosis of cancer (43,947 vs 47,159, -6.8% for 2020 and 2019, respectively), whereas the number of previously (i.e. before 2020) diagnosed patients attending the hospital increased compared to previous years (46,802 vs 44,938, +4.5%, for 2020 and 2019, respectively) (Chi-squared $p < 0.0001$). An initial increase in the number of newly diagnosed patients of +4.3% was observed for January 2020 (vs 2019) and +5.3% for February 2020 (vs Feb 2019), though this was followed by a reduction of -1.4%, -20.6%, -21.8%, -1.8% and -11.3% from March to July 2020, compared to the same period in 2019 and years 2016 to 2018 (Figure 1). Over those 5 months, the cumulated decrease reached -11.5% (29,844 vs 33,706) in 2020 compared to 2019 (Table 1).

The median reduction from January to July was 9% (ranging from 13% to 5%) vs 6% reduction (ranging from 13% to 3%) in the 5 centers in high vs lower COVID-19 incidence zone (U test, $p = 0.203$).

Reduced incidence according to stage, gender and cancer types

The reduction of new cancers in women was greater as compared to men, both for patients with and without metastasis (Figure 2A). It was significant from January to July 2020 vs 2019, and specifically in April (Chi2 test, $p = 0.03$), May ($p < 0.0001$), June ($p < 0.0001$), July ($p = 0.007$) (Figure 2A). This difference was exclusively observed between 2020 and 2019, in men as well as in women (Figure 2B).

We then analyzed the impact on individual cancer types over this 5-month period from March to July 2020. The level of reduction was the highest for breast cancer (8,428 vs 10,525, -20.0%), digestive tract cancer (3,736 vs 4,153, -10.1%), urological cancers (2,247 vs 2,498, -11.0%), in gynecological (2,673 vs 2,949, -9.4%), in genitourinary malignancies (-10.1%) and head and neck cancers (1,889 vs 2,038, -7.4%). The impact was lower for lung cancers (2,800 vs 2,999, -6.7%), and not detectable for hematological malignancies (2,133 vs 2,058, +3.4%, though -12.2% in April), with a reduction of -8.3% (5,714 vs 6,227) in the number of new diagnoses for all other cancer types (Figure 3A). Figure 3B shows the number of new cases of the most common cancer types from January 2019 to July 2020 (see also Suppl. Figure 1). The relative reduction of the most frequent urological, gynecological, digestive tract and skin cancers are presented in Figure 3C and 3D.

The proportion of reduction was greater for breast cancer vs other gynecological cancers (uterine or ovarian carcinoma) in Jan to Jul 2020 vs 2019 ($p < 0.001$). Similarly, it was larger for prostate cancers vs than other urological malignancies in the same period ($p < 0.001$).

We then assessed the disease stage (metastatic vs non-metastatic) at diagnosis of newly diagnosed cancer patients from March to July 2020 vs 2019. The relative proportion of metastatic patients was higher in 2020 vs 2019 (24.3% vs 22.2%, $p < 0.0001$)

Within the Unicancer network, this decrease in new diagnoses for the first months of 2020 corresponds to 3,862 patients with delayed diagnosis. The extrapolation at the national level (N=31833 newly diagnosed cancer patients (e-cancer.fr) per months) represents a total of 18,304 cancers with delayed diagnosis in the same period. For breast cancer, the number of undiagnosed patients is N=2,097 in this network, and N=6,722 if extrapolated at the national level.

Estimation of the impact of delayed diagnosis on long-term patient survival

We then estimated the impact of delayed diagnosis and treatment occurring in this period on cancer-specific survival. The impact of the time to initiation of treatment on survival varies across studies (see Supplemental Table 1).

We first used the HR of 1.06 to estimate the impact of these delays on patient survival in the Unicancer network based on recent meta-analysis (20). This estimation included the reduced number of new patients from March to July 2020 vs 2019, per month, as well as the absence of compensation in the months following the first lockdown, and using a cumulative rate of increased risk of death for patients not consulting for several consecutive months. If we consider a -1.4%, -20.6%, -21.8%, -1.8%, and -11.3% decrease from March to July (Figure 1), respectively, the estimated additional number of deaths per month was N=9, N=83, N=64, N=4, and N=14 from March to July, with a total of N=174 additional cancer-related deaths within Unicancer centers. Nationwide, extrapolation of these estimates for the months of March to July lead to additional deaths per month of N=42, N=502, N=393, N=20, and N=67, i.e. an estimated total number of deaths due to delayed diagnosis from March to July 2020 of N=1,024 (Table 2A, highlighted in yellow). These tables also include different hypotheses for the additional percentage of patients with delays (on the horizontal bars), and the number of additional months of delays (in the vertical axis, with one additional month of delay representing for instance all patients diagnosed and treated in September).

These estimates are dependent on three different parameters: 1) the actual percentage of patients with delayed treatment, 2) the number of months of delay, and 3) the hazard ratio for a 1-month delay.

In a second step, we evaluated the impact of varying this hazard ratio. Table 2 shows estimates obtained using a HR of 1.06 (Table 2A), a lower HR=1.02 (Table 2B), or a higher HR=1.1 (Table 2C).

On the national social security website (26), a reduction of newly diagnosed cancers of 23.3% for the first seven months of 2020 was described as compared to 2019 (available on the national website November 24th) (26). This represents a further decrease of 15% in the number of cases diagnosed compared to that measured in the Unicancer centers. Based on this national figure and Unicancer estimates, we then extrapolated nationwide excess mortality due to cancer (Table 2A to 2C) from 1872 to 9756 excess cancer deaths with the different hazard ratio.

Next, we calculated the number of cancer-specific deaths due to observed delays in Unicancer centers using the specific mortality rate (e-cancer.fr) and the hazard ratio of 1.06 per months of delays (20) for colorectal adenocarcinoma, head and neck carcinoma, bladder carcinoma, and lung carcinoma, and HR of 1.08 for breast carcinoma). The calculated number of excess cancer-related deaths due to delays in the Unicancer network obtained with the “tumor-specific” method and the “one-size-fits-all” approach were very close

(N=120 vs N=132, Table 2D). Of note these 5 tumors accounted for a large proportion of the calculated excess cancer-related deaths mentioned above (132 of the 174).

It is important to note that these two estimates are based on the assumptions that from August 2020, all patients with delayed diagnosis would have been managed without further delay. Currently (28 Feb 2021) the reported number of new patients seen in the UNICANCER network in 2020 was 28,900 vs 28,955 from August to November in 2019 (the 2020 figures being 99.8% of that of 2019). No further reduction in new diagnoses was thus observed in this period, but no increased activity was measured that would have compensated the reduced activity during the lockdown.

Discussion

In the present work, we 1) present a description of the reduction of the number of new cases of cancers observed during the first lockdown in France, with an analysis on the type of tumors, gender and stage, and 2) propose an estimation of the potential impact on long-term cancer-free survival of patients impacted by these delays.

We describe first the observed reduction in the number of cancer patients seen in the first seven months, including the first lockdown, of the first COVID-19 outbreak in France, from March to July 2020. This was done within 17 of the 18 comprehensive cancer centers in France, Unicancer treating close to one fourth of the cancers in France.

The total number of previously diagnosed cancer patients treated in the Unicancer centers increased in 2020 similarly to levels observed in the previous year. Conversely from January to July 2020, there was a reduction of 6.8% of newly diagnosed cancers in this network, vs a +4.5% between 2019 and 2018. The reduction was detectable as early as March 2020, while an increase in the first two months of 2020 was recorded in agreement with the trends of the past years. This decrease reached >20% in the 2 months (April and May) of the first lockdown and was observed in July 2020 (-11%). It was not significantly different in centers located in regions with a COVID-19 high incidence during this period.

The observed reduction was more pronounced in women, both for patients with and without metastases at diagnosis. It was also higher in breast cancers, prostate cancers, and skin cancers. The number of new patients presenting metastases decreased less than those with localized diseases.

These results show that only patients not previously diagnosed of a cancer were those who postponed their consultation to medical services during the first lockdown and in the following months. This was observed for tumors with national screening plans (breast, colorectal, cervix cancers), which were interrupted during lockdown, but also for other tumors, indicating that this is not only related to delayed access to screening. The reduced breast cancer screening during this period is likely to have contributed to the level of reduction in new breast cancer diagnosis. The fear of contracting COVID-19 as well as difficulties to access primary care centers or general practitioners are mentioned as possible causes (1-6).

The impact of delayed access to diagnosis and treatment for newly diagnosed patients with cancer on the risk of cancer-related death was the second question explored in this work.

A large number of studies have estimated the increased risk of death due to delays in diagnosis and for the initiation of treatment (27-56). This literature is heterogenous in its methodology, and reports a variable magnitude of impact across cancer types, depending on the timing of the delay, and the nature of the treatment. A selection, by no means exhaustive, of studies are presented in the reference section and in the Supplemental Table 1. Delays, ranging from 7 days to over 6 months, for surgery, delays to the administration of chemotherapy or radiotherapy (28-50), were all reported as associated with a reduced cure rate and survival in both localized and advanced and localized phases of a magnitude ranging from 0.5% per weeks of delay up to +169% with 12 weeks of delays in similar cancers.

Recently reported meta-analysis conducted for breast colorectal, lung, bladder, and head and neck cancer (20), showing that a 1-month delay in surgery is associated with a hazard ratio of 1.06 to 1.08 for the risk of cancer-specific death, 1.09 for delay in radiotherapy in head and neck cancer and variable for adjuvant chemotherapy. In other cancer types, 1-

month delays in surgery or neoadjuvant chemotherapy are associated with variable hazard ratio often superior in magnitude summarized in Suppl. Table 1.

Herein, we first selected hazard ratio of 1.06 as a reasonable estimate matching the analysis reported, with the knowledge that lower and higher HR are reported in various tumor types. The mortality rate for cancer of 41% reported in the national population in France was used for these calculation (e-cancer.fr).

With this uniform HR of 1.06, the number of excess cancer deaths calculated for the first months of 2020 was 1024. This number supposes that no further delays were observed after August 2020, and that the percentage of patients with delays was similar across France. These two hypotheses are however unlikely in view of the larger 23.3% reduction of number of new cases observed at the national level on the same period (26). For these reasons, a more realistic number of excess cancer death of 5791 is calculated for the first seven months of 2020. This estimates again supposes that all treatments were initiated shortly after July 2020 which is not known yet. The number of new patients observed between August and November 2020 was stable vs 2019 in Unicancer centers, but no compensation for the backlog of the first seven months of the year was observed.

Differences in the percentages of patients with delayed diagnosis and treatment, as well as the number of months of delay, and the hazard ratio associated with delay all strongly influence the impact of COVID-19 on cancer-specific survival. A hazard ratio of 1.02 for a 1-month delay is below that generally reported for most cancer types, while a 1-month delay associated with an $HR > 1.1$, is reported in several tumor types (27-56 and suppl. Table1). Excess cancer deaths calculated with these HR were intended to provide only a possible estimates of the level of the impact of cancer-related deaths, not an accurate description.

Finally, these estimates do not take in account the yearly increase in new cancer diagnoses, which was + 0.9% from 2018 to 2019 on the nationwide social security platform.

The number observed in Unicancer centers thus represents an “optimistic” evaluation of the percentage of patients with delayed diagnosis and treatments which may be greater in non-specialized centers nationwide.

One of the limitations of this work, is to have selected a unique HR for all cancer types. Ideally, a specific hazard ratio should be provided for each cancer type and for different stages, histotypes and ages. The impact of delay per stage and cancer types was reported recently at the national level in the USA (19), showing variable hazard ratio across different cancer types and stages. In this study, increased time to treatment initiation was associated with poorer survival for stages I and II breast, lung, renal, pancreas and colorectal cancers, with hazard ratios ranging from 1.005 to 1.030 per week of increased time to treatment initiation (19).

It is important to note that stage, age and histotypes are by definition not documented in patients who did not attend to the hospital for diagnosis, and therefore stage-adapted calculations are not possible in the present work. The recently reported online tool (OncCovid) calculates the risk of death due to cancer depending on stage, age, tumor type, and duration of delay to treatment (57). While accurate for a single patient, this tool may not be applied to the present work for the same reasons, and also because the delays for patient attending the Unicancer centers were outside of our scope. Importantly, the COVID-19-specific cause of death (23-25) is not calculated in the present work which focuses on cancer-specific deaths.

However, we tested cancer specific hazard ratio for 5 different cancers. Interestingly, the excess mortality calculated with these five tumor-specific parameters was very similar,

inferior only by less than 10% (N=120 vs N=132) to those obtained with the unique mortality rate of 41% and hazard ratio of 1.06, as shown in Table 2D. Because these 5 tumors were shown to contribute to 132 of the 174 deaths in excess due to delays, this observation supported the rough estimate of the excess cancer deaths calculated in this work.

Altogether, these results indicate that cancer patients attended with delay cancer centers for delayed diagnosis and treatment even in comprehensive cancer centers. This was observed for the majority of cancer types, more frequently in women, in breast cancers and for prostate cancer in particular. It was more frequently observed for non-metastatic patients. It will result in a significant increase of the number of cancer death the future for which an estimation is provided in this study. Maintaining access to rapid diagnostic and treatment procedures is an important medical priority in the months to come before the normalization of the health care system expected following the implementation of vaccination.

Conflict of interest statement:

J-YB : research support and honoraria from Troche, BMS, MSD, Pharmamar, Bayer, Deciphera, GSK, Novartis, AstraZeneca.

J-PD : Institutional fees for advisory or speaker roles for Genentech, Roche, BMS, MSD, Novartis, and Institutional grants for research project with Genentech, Roche, BMS, MSD, DebioPharm and Astra Zeneca

J-CS : Shares : AstraZeneca, Daiichi Sankyo, Gritstone, full time employee of AZ from Sept 2017 to Dec 2019

All remaining authors declared no conflict of interest

Research support :

This work was supported by

Funding :

This work was supported by

JYB : LYRICAN (INCA-DGOS-INSERM-12563), the French National Research Agency [LabEx DEvweCAN (ANR-10-LABX0061)], RHU4-DEPGYN (ANR-18-RHUS-0009), INCA&DGOS (NetSARC, RREPS, RESOS), INCA (InterSARC), European commission (EURACAN-EC739521), Fondation ARC, PIA Institut Convergence François Rabelais PLAsCAN (17-CONV-0002), La Ligue contre le Cancer, La Ligue de L'Ain contre le Cancer.

The funding sources had no role in the making of the manuscript

Contributions to the manuscript:

JYB conceived the study, drafted the first version

SaB, BLV : produced the data

CC, SC, and DP ; performed and reviewed the statistical analysis

All authors contributed to the production of the data, reviewed and approved the final version of this article

Legends of the Figures and tables

Figure 1: Number of newly diagnosed patients per month from 2016 to 2020

Figure 2: Relative number of newly diagnosed patients in 2020 vs 2019 in men and women

A: Relative proportion of cases per month in men and women

Total numbers (blue and orange curves for men and women, respectively) and with metastases (grey and yellow curves for men and women, respectively). The p-values correspond to the comparison of the total new cases in men and women per month in 2019 vs 2020. Significant differences were observed for the months of March to July for the total population. The same trend is observed for metastatic patients at diagnosis, but no significant difference was observed.

B: Relative number of newly diagnosed patients in men

Relative numbers for each month in 2017 vs 2016 (blue), 2018 vs 2017 (orange), 2019 vs 2018 (grey), and 2020 vs 2019 (yellow).

C: Relative number of newly diagnosed patients in women

Relative numbers for each month in 2017 vs 2016 (blue), 2018 vs 2017 (orange), 2019 vs 2018 (grey), and 2020 vs 2019 (yellow).

Figure 3: Relative and absolute numbers of newly diagnosed cancers 2020 vs 2019

Figure 3A: Relative number of newly diagnosed patients with cancers of different organs and sites:

X axis: months of 2020, **Y axis:** Relative proportion of newly diagnosed patients per month in 2020 vs 2019. Highlighted in blue: lockdown 1 period. Highlighted in yellow: higher number of newly diagnosed in patients in 2020 vs 2019.

Figure 3B: Absolute number of newly diagnosed patients with cancers of different organs and sites:

X axis: months of 2020, **Y axis:** Total number of newly diagnosed patients per months in 2020 vs 2019, for the different cancer types. Orange curve represent the total. Green curve breast cancers.

Figure 3C: Relative number of newly diagnosed cancers 2020 vs 2019: Genitourinary and gynecological cancers

X axis: months of 2020, **Y axis:** Relative proportion of newly diagnosed patients per month in 2020 vs 2019. Highlighted in blue: lockdown 1 period. Highlighted in yellow: higher number of new diagnosed in patients in 2020 vs 2019.

Figure 3D: Relative number of newly diagnosed cancers 2020 vs 2019: Gastro-intestinal and skin cancers

X axis: months of 2020, **Y axis:** Relative proportion of newly diagnosed patients per month in 2020 vs 2019. Highlighted in blue: lockdown 1 period. Highlighted in yellow: higher number of new diagnosed in patients in 2020 vs 2019.

Table 1: Newly diagnosed patients per month per center in high and low COVID-19 incidence zones.

Centers were ranked according to the percentage of reduction in new cases in 2020 vs 2019, starting with the greatest reduction. In orange, centers in high COVID-19 incidence zones. In white, cancer centers in other zones. Centers in high incidence zones did not display a significantly superior reduction in the number of new patients (Mann-Whitney U test, $p=0.2$).

Table 2: Estimated excess risk of cancer deaths due to delays in diagnosis and treatment in view of the UNICANCER observations of March-July 2020

Table 2A: Calculated number of additional cancer deaths nationwide with a hazard ratio of 1.06 for risk of death per month of delay (15) for the period from March 2020 to July 2020.

Table 2B: Calculated number of excess cancer deaths with a hazard ratio of 1.02 for risk of death per month of delay for the period from March 2020 to July 2020.

Table 2C: Calculated number of additional cancer deaths nationwide with a hazard ratio of 1.1 for risk of death per month of delay for the period from March 2020 to July 2020.

Table 2D: Compared number of additional cancer deaths nationwide with a specific hazard ratio and a mortality rate of five tumor types vs the one-size-fits-all approach from March 2020 to July 2020.

The number in the left columns of tables 2A to 2C indicate the number of additional months of delay in treatment beyond August 2020 in addition to those observed in the Unicancer network: 0: no additional month (i.e. all patients finally treated in August 2020); 1: 1 additional month of delay (i.e. all patients finally treated in September), 2: 2 additional months of delay (i.e. all patients finally treated in October), and so on.

The percentage in the first line represents the additional percentage of patients “missing” in 2020 vs 2019 (i.e. the number of patients observed in 2020 divided by the number of patients diagnosed in 2019) at the nationwide level: 0: similar percentage as for the Unicancer series (i.e. a reduction observed similar to that of the Unicancer series in the same month, nationwide) ; -5%: -5% percentage as compared to the Unicancer series (i.e. -6.4% in March, -25,6% in April) and so on.

In each box of Table 2A, 2B and 2C, the calculated number of additional cancer-specific deaths due to delays with the different assumptions for the hazard ratio. In yellow, the number calculated with the reduced number of patients observed in the Unicancer series, with the hypothesis that all delayed diagnosis and treatment was completed in August 2020. In orange, similar estimation taking in account the observed reduced number of patients with newly diagnosed cancer nationwide in 2020 vs 2019 according to the access on November 24th, 2020 (-23,3%).

References:

1. Banerjee A, Pasea L, Harris S, et al. Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study. *Lancet*. 2020; 395:1715-1725.
2. Maringe C, Spicer J, Morris M, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. *Lancet Oncol*. 2020; 21:1023-1034.
3. Lai AG, Pasea L, Banerjee A, et al. Estimated impact of the COVID-19 pandemic on cancer services and excess 1-year mortality in people with cancer and multimorbidity: near real-time data on cancer care, cancer deaths and a population-based cohort study. *BMJ Open*. 2020; 10(11):e043828.
4. Sud A, Torr B, Jones ME, et al. Effect of delays in the 2-week-wait cancer referral pathway during the COVID-19 pandemic on cancer survival in the UK: a modelling study. *Lancet Oncol*. 2020; 21:1035-1044.
5. Sud A, Jones ME, Broggio J, et al. Collateral damage: the impact on outcomes from cancer surgery of the COVID-19 pandemic. *Ann Oncol*. 2020; 31:1065-1074.
6. Hanna TP, Evans GA, Booth CM. Cancer, COVID-19 and the precautionary principle: prioritizing treatment during a global pandemic. *Nat Rev Clin Oncol*. 2020; 17:268-270
7. World Health Organization. Guide to Cancer Early Diagnosis. Geneva, Switzerland: World Health Organization, 2017. https://www.who.int/cancer/publications/cancer_early_diagnosis/en/ (date of access, 22 Nov 2020)
8. http://www.iacr.com.fr/index.php?option=com_content&view=article&id=101&Itemid=578 (date of access, 22 Nov 2020)
9. Qu LG, Brand NR, Chao A, Ilbawi AM. Interventions Addressing Barriers to Delayed Cancer Diagnosis in Low- and Middle-Income Countries: A Systematic Review. *Oncologist*. 2020;25:e1382–95. doi: 10.1634/theoncologist.2019-0804.
10. Shulman LN, Willett W, Sievers A, Knaul FM. Breast cancer in developing countries: opportunities for improved survival. *J Oncol*. 2010; 2010:595167. doi: 10.1155/2010/595167.
11. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet*. 2012;380:1778-86
12. Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. *Lancet*. 2019; 393:169-182.
13. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. *Lancet*. 2019 ;394:1467-1480.
14. Oudkerk M, Liu S, Heuvelmans MA, Walter JE, Field JK. Lung cancer LDCT screening and mortality reduction - evidence, pitfalls and future perspectives. *Nat Rev Clin Oncol*. 2020 Oct 12. doi: 10.1038/s41571-020-00432-6.
15. Ardeshtna KM, Qian W, Smith P, Braganca N, Lowry L, Patrick P et al. Rituximab versus a watch-and-wait approach in patients with advanced stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. *Lancet Oncol* 2014; 15: 424–35.
16. Brice P, Bastion Y, Lepage E, Brousse N, Haioun C, Moreau P et al. Comparison in low-tumor-burden follicular lymphomas between an initial notreatment policy, prednimustine,

or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. *J Clin Oncol* 1997; 15: 1110–17.

17. Kunath F, Jensen K, Pinart M, Kahlmeyer A, Schmidt S, Price CL, Lieb V, Dahm P. Early versus deferred standard androgen suppression therapy for advanced hormone-sensitive prostate cancer. *Cochrane Database Syst Rev.* 2019 ; 6:CD003506.

18. van den Bergh RC, Albertsen PC, Bangma CH, Freedland SJ, Graefen M, Vickers A, van der Poel HG. Timing of curative treatment for prostate cancer: a systematic review. *Eur Urol.* 2013; 64: 204-15.

19. Khorana AA, Tullio K, Elson P, et al. Time to initial cancer treatment in the United States and association with survival over time: An observational study. *PLoS One.* 2019; 14:e0213209. doi: 10.1371/journal.pone.0213209.

20. Hanna TP, King W., Thibodeau S. et al. Mortality due to cancer treatment delay: systematic review and meta-analysis *BMJ* 2020;371:m4087 <http://dx.doi.org/10.1136/bmj.m4087>

21. Alexander M, Blum R, Burbury K, et al. Timely initiation of chemotherapy: a systematic literature review of six priority cancers - results and recommendations for clinical practice. *Intern Med J.* 2017;47:16-34.

22. Neal RD, Tharmanathan P, France B et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. *Br J Cancer* 2015;112 (suppl 1):S92–S107.

23. Assaad S, Avrillon V, Fournier ML et al . High mortality rate in cancer patients with symptoms of COVID-19 with or without detectable SARS-COV-2 on RT-PCR. *Eur J Cancer.* 2020;135:251-259.

24. Albiges L., Foulon S., Bayle, A. et al. Determinants of the outcomes of patients with cancer infected with SARS-CoV-2: results from the Gustave Roussy cohort. *Nat Cancer* 1, 965–975 (2020). <https://doi.org/10.1038/s43018-020-00120-5>.

25. Lièvre A, Turpin A, Ray-Coquard I, et al; Risk factors for Coronavirus Disease 2019 (COVID-19) severity and mortality among solid cancer patients and impact of the disease on anticancer treatment: A French nationwide cohort study (GCO-002 CACOVID-19). *Eur J Cancer.* 2020; 141:62-81.

26. <https://acces-securise.atih.sante.fr/vpn/index.html>

27. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. *Lancet.* 1999;353:1119-26.

28. Do V, GebSKI V, Barton MB. The effect of waiting for radiotherapy for grade III/IV gliomas. *Radiother Oncol.* 2000;57:131-6.

29. Ang KK, Trotti A, Brown BW, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2001; 51:571-8.

30. Sánchez-Ortiz RF, Huang WC, Mick R, Van Arsdalen KN, Wein AJ, Malkowicz SB. An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. *J Urol.* 2003; 169:110-5.

31. Ardeshtna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. *Lancet*. 2003; 362:516-22.
32. Wright JD, Herzog TJ, Neugut AI, et al. Effect of radical cytoreductive surgery on omission and delay of chemotherapy for advanced-stage ovarian cancer. *Obstet Gynecol*. 2012;120:871-81.
33. Shin DW, Cho J, Kim SY, et al. Delay to curative surgery greater than 12 weeks is associated with increased mortality in patients with colorectal and breast cancer but not lung or thyroid cancer. *Ann Surg Oncol*. 2013;20:2468-76.
34. Elit LM, O'Leary EM, Pond GR, Seow HY. Impact of wait times on survival for women with uterine cancer. *J Clin Oncol*. 2014; 32:27-33.
35. Perri T, Issakov G, Ben-Baruch G, et al. Effect of treatment delay on survival in patients with cervical cancer: a historical cohort study. *Int J Gynecol Cancer*. 2014;24:1326-32.
36. Nikonova A, Guirguis HR, Buckstein R, Cheung MC. Predictors of delay in diagnosis and treatment in diffuse large B-cell lymphoma and impact on survival. *Br J Haematol*. 2015;168:492-500.
37. van Harten MC, Hoebbers FJ, Kross KW, van Werkhoven ED, van den Brekel MW, van Dijk BA. Determinants of treatment waiting times for head and neck cancer in the Netherlands and their relation to survival. *Oral Oncol*. 2015; 51:272-8.
38. Samson P, Patel A, Garrett T, et al. Effects of Delayed Surgical Resection on Short-Term and Long-Term Outcomes in Clinical Stage I Non-Small Cell Lung Cancer. *Ann Thorac Surg*. 2015; 99:1906-12;
39. Gomez DR, Liao KP, Swisher SG, et al. Time to treatment as a quality metric in lung cancer: Staging studies, time to treatment, and patient survival. *Radiother Oncol*. 2015; 115:257-63.
40. Brooks EG, Connors JM, Sehn LH, et al. Impact of time from diagnosis to initiation of curative-intent chemotherapy on clinical outcomes in patients with classical Hodgkin lymphoma. *Leuk Lymphoma*. 2016;57:872-9.
41. Sanjeevi S, Ivanics T, Lundell L, et al. Impact of delay between imaging and treatment in patients with potentially curable pancreatic cancer. *Br J Surg*. 2016; 103:267-75.
42. Murphy CT, Galloway TJ, Handorf EA, et al. Survival Impact of Increasing Time to Treatment Initiation for Patients With Head and Neck Cancer in the United States. *J Clin Oncol*. 2016; 34:169-78.
43. Franko J, Voynov G, Goldman CD. Esophagectomy Timing After Neoadjuvant Therapy for Distal Esophageal Adenocarcinoma. *Ann Thorac Surg*. 2016;101:1123-30.
44. Bleicher RJ, Ruth K, Sigurdson ER, et al. Time to Surgery and Breast Cancer Survival in the United States. *JAMA Oncol*. 2016; 2:330-9.
45. Mano R, Vertosick EA, Hakimi AA, et al. The effect of delaying nephrectomy on oncologic outcomes in patients with renal tumors greater than 4cm. *Urol Oncol*. 2016 ; 34:239.e1-8.
46. Alexander M, Blum R, Burbury K, et al. Timely initiation of chemotherapy: a systematic literature review of six priority cancers - results and recommendations for clinical practice. *Intern Med J*. 2017; 47:16-34.

47. Cheraghlou S, Kuo P, Judson BL. Treatment delay and facility case volume are associated with survival in early-stage glottic cancer. *Laryngoscope*. 2017; 127: 616-622.
48. Visser E, van Rossum PS, Leeftink AG, Siesling S, van Hillegersberg R, Ruurda JP. Impact of diagnosis-to-treatment waiting time on survival in esophageal cancer patients - A population-based study in The Netherlands. *Eur J Surg Oncol*. 2017; 43:461-470.
49. Tsai WC, Kung PT, Wang YH, Huang KH, Liu SA. Influence of time interval from diagnosis to treatment on survival for oral cavity cancer: A nationwide cohort study. *PLoS One*. 2017; 12:e0175148.
50. Tsai WC, Kung PT, Wang YH, Kuo WY, Li YH. Influence of the time interval from diagnosis to treatment on survival for early-stage liver cancer. *PLoS One*. 2018; 13: e0199532.
51. Ramey SJ, Rich BJ, Kwon D, et al. Demographic disparities in delay of definitive chemoradiation for anal squamous cell carcinoma: a nationwide analysis. *J Gastrointest Oncol*. 2018; 9:1109-1126.
52. Lee YH, Kung PT, Wang YH, Kuo WY, Kao SL, Tsai WC. Effect of length of time from diagnosis to treatment on colorectal cancer survival: A population-based study. *PLoS One*. 2019; 14:e0210465.
53. Chu AT, Holt SK, Wright JL, Ramos JD, Grivas P, Yu EY, Gore JL. Delays in radical cystectomy for muscle-invasive bladder cancer. *Cancer*. 2019; 125: 2011-2017.
54. Iacovelli R, Galli L, De Giorgi U, et al. The effect of a treatment delay on outcome in metastatic renal cell carcinoma. *Urol Oncol*. 2019; 37: 529.e1-529.e7.
55. AlHilli MM, Elson P, Rybicki L, Khorana AA, Rose PG. Time to surgery and its impact on survival in patients with endometrial cancer: A National cancer database study. *Gynecol Oncol*. 2019; 153: 511-516.
56. Russell B, Liedberg F, Khan MS, et al. A Systematic Review and Meta-analysis of Delay in Radical Cystectomy and the Effect on Survival in Bladder Cancer Patients. *Eur Urol Oncol*. 2020; 3:239-249.
57. Hartman HE, Sun Y, Devasia TP, et al. Integrated Survival Estimates for Cancer Treatment Delay Among Adults With Cancer During the COVID-19 Pandemic. *JAMA Oncol*. 2020; 6: 1881-1889.

Figure 1 : Number of newly diagnosed patients from 2016 to 2020

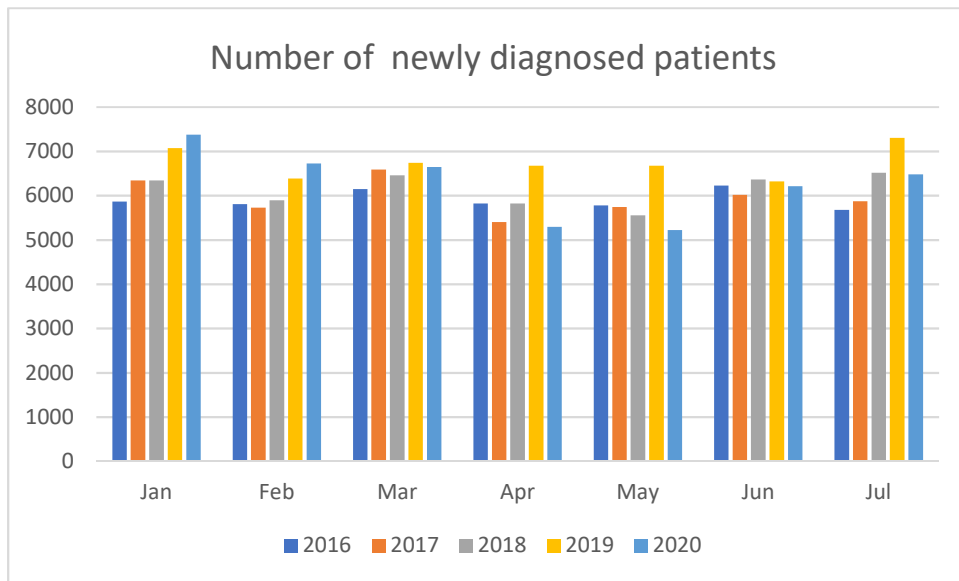
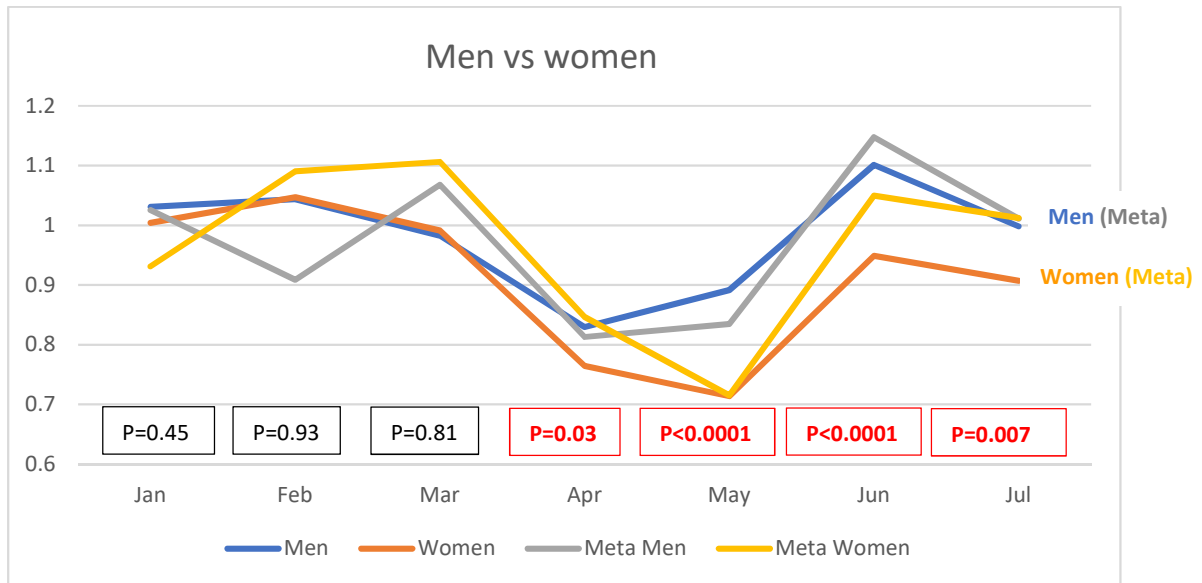


Figure 2: Relative number of newly diagnosed patients in 2020 vs 2019 in men and women

A: 2020 vs 2019



B: Evolution of the relative number of new cases year/year-1 2016-2020

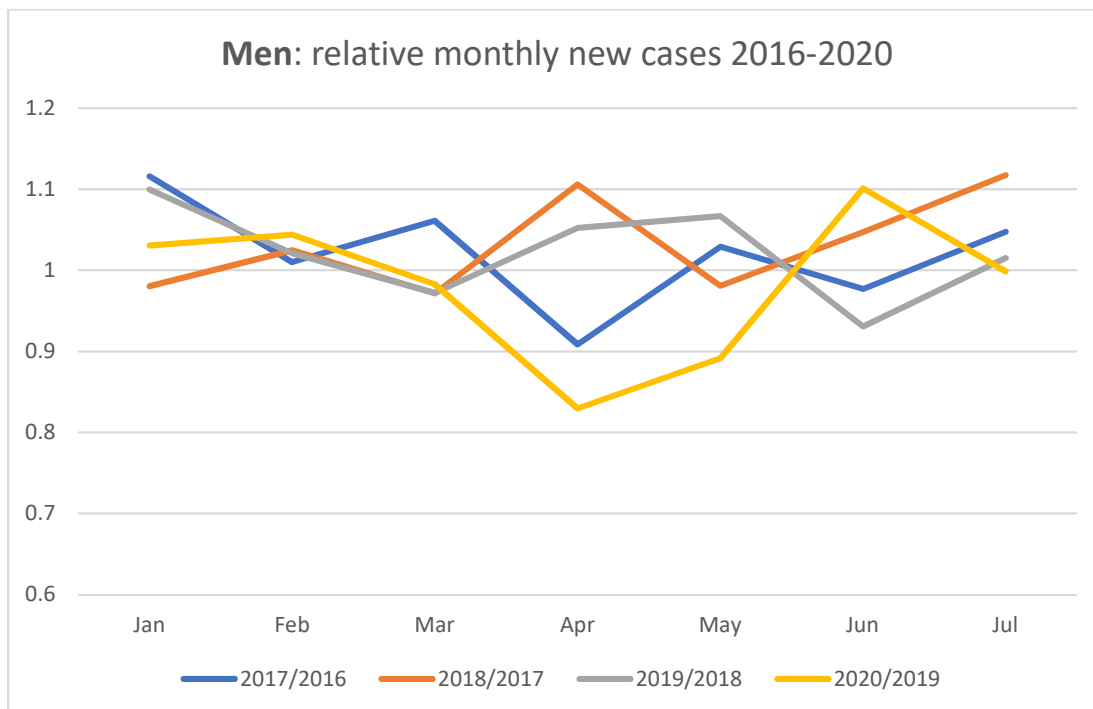
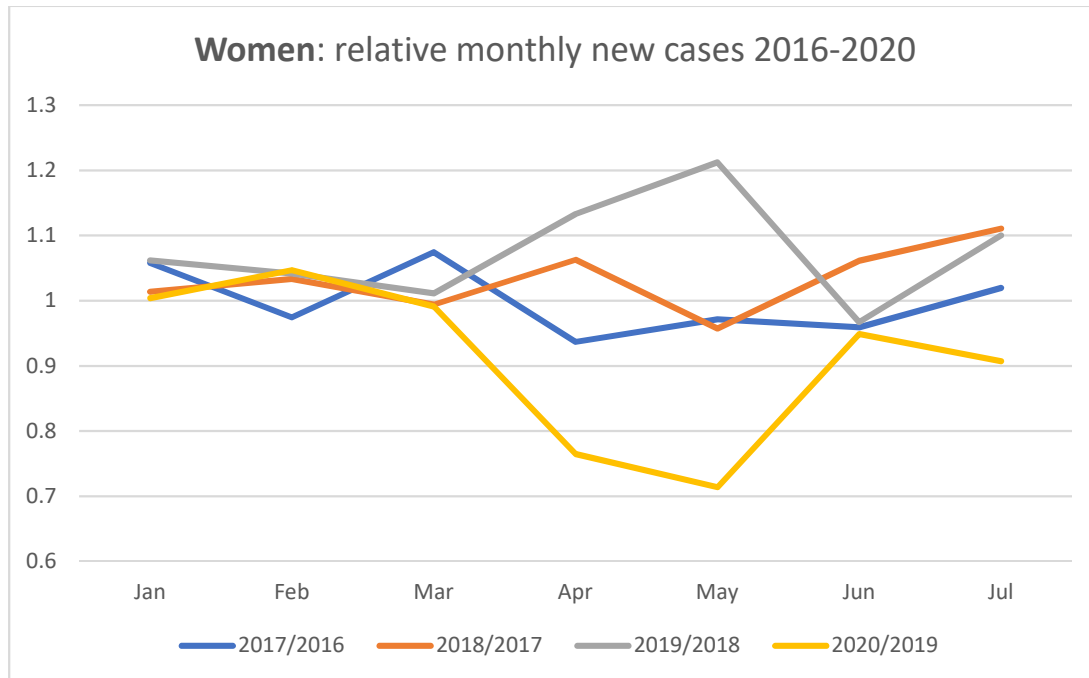
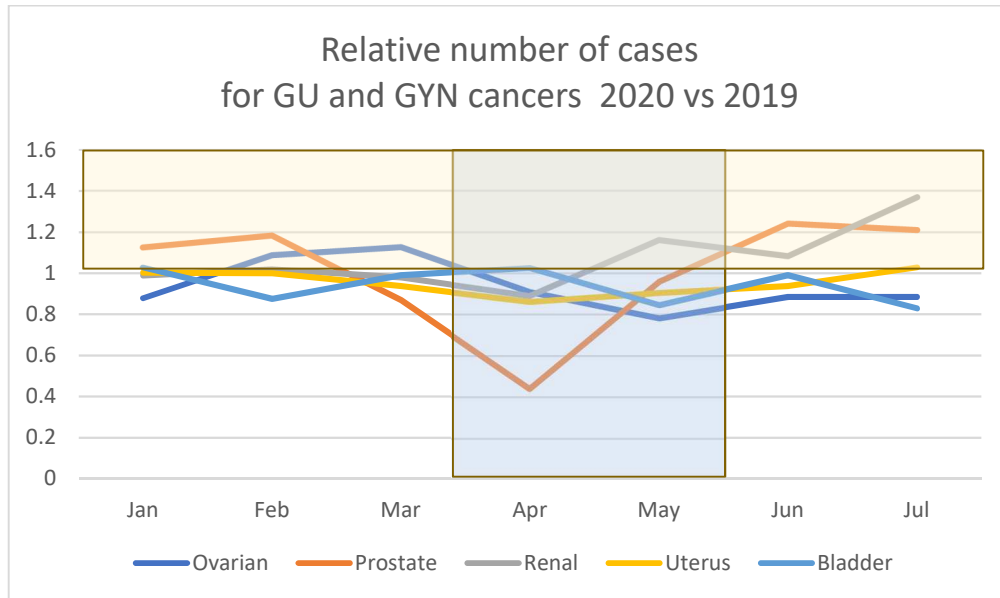


Figure 2B (continued)

C: Relative number of newly diagnosed patients in women



C: Relative number of newly diagnosed cancers 2020 vs 2019 in Genito-urinary & Gynaecological cancers



D: Relative number of newly diagnosed cancers 2020 vs 2019 in Gastro-intestinal and skin cancers

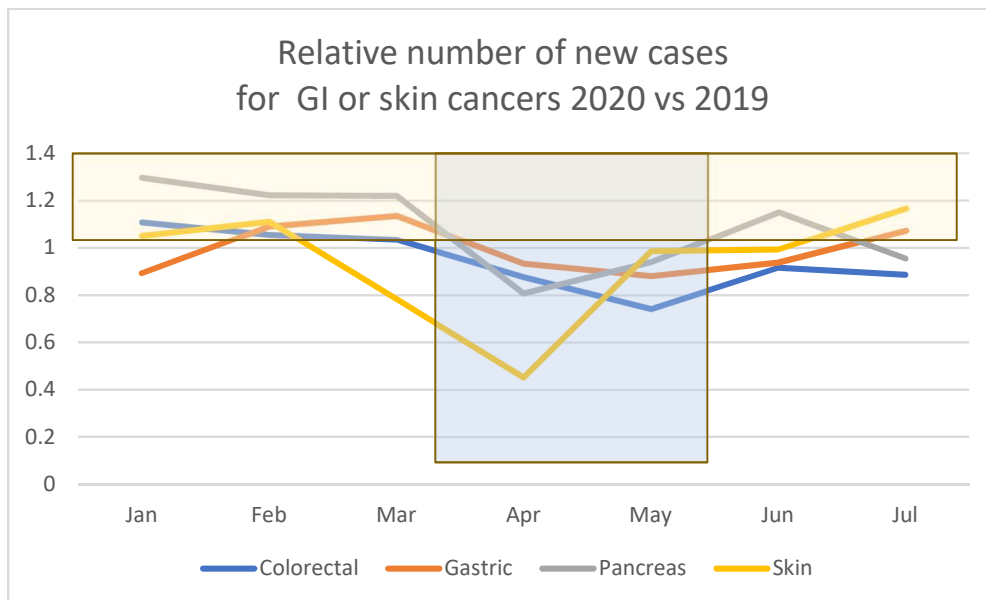


Table 1: New diagnosed patients per months per center : high and low incidence zones of COVID-19

Centre	2019 01	2019 02	2019 03	2019 04	2019 05	2019 06	2019 07	2020 01	2020 02	2020 03	2020 04	2020 05	2020 06	2020 07	Total 2019	Total 2020	Ratio 2020/2019
9	676	564	589	581	598	555	622	587	600	625	395	438	455	490	4 185	3 590	0.86
11	766	750	702	708	764	682	752	785	695	664	520	461	595	686	5 124	4 406	0.86
13	424	362	329	330	307	321	380	389	312	250	241	255	337	353	2 453	2 137	0.87
1	316	257	302	314	291	281	310	300	274	278	201	211	265	287	2 071	1 816	0.88
17	496	435	475	492	488	466	506	500	488	462	335	367	413	440	3 358	3 005	0.89
5	284	240	279	309	253	241	326	307	256	266	210	218	238	250	1 932	1 745	0.90
7	513	471	549	534	493	436	574	509	525	482	389	365	494	502	3 570	3 266	0.91
10	345	321	328	314	334	298	350	344	339	285	279	244	324	346	2 290	2 161	0.94
12	298	245	283	267	269	304	284	328	274	242	228	259	238	288	1 950	1 857	0.95
15	438	380	365	382	381	354	415	399	366	415	339	308	392	371	2 715	2 590	0.95
8	415	356	350	359	352	337	394	399	379	401	298	287	359	345	2 563	2 468	0.96
3	379	326	392	338	408	340	395	391	368	378	299	320	357	334	2 578	2 447	0.95
4	224	228	234	247	209	208	243	281	255	246	194	208	208	134	1 593	1 526	0.96
2	234	253	297	255	260	277	297	310	244	304	179	223	253	280	1 873	1 793	0.96
16	181	176	198	183	180	176	198	196	194	191	123	127	208	214	1 292	1 253	0.97
14	613	538	583	583	586	556	642	606	572	609	563	490	551	600	4 101	3 991	0.97
6	274	281	286	258	285	281	336	294	304	287	291	238	265	278	2 001	1 957	0.98
Total	7 069	6 384	6 736	6 673	6 672	6 319	7 306	7 378	6 725	6 645	5 296	5 218	6 208	6 477	47 159	43 947	0.93

Table 2: Estimated excess risk of cancer deaths due to delays in diagnosis and treatment in view of the UNICANCER observations of March-July 2020

A : Calculated number of additional cancer deaths nationwide with an hazard ratio of 1.06 for risk of death per month of delay (ref 15) for the period from March 2020 to July 2020.

Additional % of patients with delays	0%	-5%	-10%	-15%	-20%	-25%
Additional months of delay						
0	1024	1478	1932	2387	2841	3295
1	1381	1992	2604	3215	3827	4438
2	1746	2517	3289	4060	4832	5603
3	2116	3051	3985	4919	5824	6788
4	2492	3592	4692	5791	6891	7990

B : Calculated number of excess cancer deaths with an hazard ratio of 1.02 for risk of death per month of delay for the period from March 2020 to July 2020.

Additional % of patients with delays	0%	-5%	-10%	-15%	-20%	-25%
Additional months of delay						
0	338	488	638	788	938	1088
1	454	654	855	1056	1256	1457
2	570	822	1074	1325	1577	1829
3	688	991	1294	1597	1901	2204
4	806	1161	1516	1872	2227	2582

C: Calculated number of additional cancer deaths nationwide with an hazard ratio of 1.1 for risk of death per month of delay for the period from March 2020 to July 2020.

Additional % of patients with delays	0%	-5%	-10%	-15%	-20%	-25%
Additional months of delay						
0	1715	2476	3237	3998	4759	5520
1	2322	3349	4376	5404	6431	7458
2	2941	4241	5540	6839	8138	9437
3	3570	5145	6719	8294	9868	11443
4	4202	6053	7905	9756	11608	13459

D: Compared number of additional cancer deaths nationwide with an hazard ratio and a mortality rate of five tumor type vs the one size-fits-all approach from March 2020 to July 2020.

Parameters	Colorectal	Head & neck	Bladder	Breast	Lung	Total
N per year in France (2018)	20120	4298	2448	58547	15132	
N of deaths in FR (2018)	7908	1055	1223	12146	10356	
Mortality (Death/New cases) in 2018	0.39	0.25	0.5	0.21	0.68	
New patients Unicancer in 2020 (Mar-Jul)	1439	1826	514	8194	2590	
New patients Unicancer in 2019 (Mar-Jul)	1626	1977	553	10115	2701	
"Missing" patients in 2020	176	111	36	1921	51	
Hazard ratio per months of delay	1.06	1.06	1.06	1.08	1.06	
Estimated excess deaths with uniform death rate (41%) and uniform HR 1.06 per month	9	6	2	108	7	132
Estimated excess deaths with tumor specific death rate and adapted HR per tumor	9	6	3	88	14	120