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REVIEW ARTICLE

Impact of the COVID-19 Outbreak on the Management of Patients with Cancer

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Abstract

The coronavirus SARS-CoV-2 (COVID-19) outbreak is having a profound impact on the management of patients with cancer. In this review, we comprehensively investigate the various aspects of cancer care during the pandemic, taking advantage of data generated in Asia and Europe at the frontline of the COVID-19 pandemic spread. Cancer wards have been subjected to several modifications to protect patients and healthcare professionals from COVID-19 infection, while attempting to maintain cancer diagnosis, therapy, and research. In this setting, the management of COVID-19 infected patients with cancer is particularly challenging. We also discuss the direct and potential remote impacts of the global pandemic on the mortality of patients with cancer. As such, the indirect impact of the pandemic on the global economy and the potential consequences in terms of cancer mortality are discussed. As the infection is spreading worldwide, we are obtaining more knowledge on the COVID-19 pandemic consequences that are currently impacting and may continue to further challenge cancer care in several countries.

Key Points

The coronavirus SARS-CoV-2 (COVID-19) outbreak is impacting several aspects of the management of patients with cancer.

Protection of patients with cancer and health caregivers remains a high priority.

An impact on the overall mortality of patients with cancer may result from acute COVID-19 infection as well as from remote effects related to the breakdown of healthcare and the economic crisis.

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1 Introduction

Globally, cancer, including solid tumors and hematological malignancies, still ranks as the second leading cause of death, being responsible for an estimated 9.6 million annual deaths in 2018. With more than 18.0 million new cases every year globally, about 50,000 new patients are diagnosed and require treatment every day [1]. Progress has been substantial over the last 40 years and the decline in mortality has been linked to prevention, early diagnosis, and the quality of treatment [2].

The unprecedented worldwide occurrence of the coronavirus SARS-CoV-2 (COVID-19) pandemic [3] is not like any other seasonal infection and is having a profound effect on the entire oncology community [4] by impacting patients with cancer and reducing healthcare activities for a duration that cannot yet be accurately estimated [5]. Moreover, the high contagiousness of the virus appears to be associated with a risk of contamination of caregivers, which may seriously limit healthcare capacities [6]. Although the management of patients with serious infections (viral, bacterial, and fungal) is well known to oncologists and hematologists and has always been part of cancer management, occurrence of COVID-19 in patients with cancer has been reported to be associated with an increased mortality [7]. Furthermore, available data on patients with cancer are currently primarily

derived from limited experience in China, with very limited information in Western populations [8]. As the COVID-19 pandemic is spreading across the world, several initiatives for data collection, recommendations, and guidance have been made available to help physicians and patients with cancer to protect themselves from the COVID-19 infection (Table 1).

While one may wonder if it is wise to look at cancer consequences during the peak incidence of COVID-19 infection, it should be emphasized that mid-term consequences on cancer shall remain a priority to avoid excesses morbidity and mortality during and after the end of the pandemic. In this paper, we aimed to look at various aspects and consequences of the COVID-19 infection for cancer caregivers and patients from a global standpoint, taking advantage of information generated in Asia.

2 Diagnosis of COVID-19 Infection in Patients with Cancer

The COVID-19 crisis started in China in December 2019 with a cluster of pneumonia cases from an unknown pathogen identified first in Wuhan [9]. There are no specific clinical features that can yet reliably distinguish COVID-19 from other viral respiratory infections. Thus far, there is no specific symptom of COVID-19 infection in patients with cancer. The most prevalent clinical signs of infection [9] are fever (99%), fatigue (70%), dry cough (59%), anorexia (40%), myalgias (35%), dyspnea (31%), and sputum production (27%), with anosmia and ageusia also being reported in many patients [10]. Laboratory features are leukopenia, leukocytosis, lymphopenia, elevated liver enzymes, elevated lactate dehydrogenase, elevated inflammatory markers such as C-reactive protein and ferritin, elevated D-dimer, elevated creatine phosphokinase, and elevated creatinine levels [5, 7]. Consistent with viral pneumonia, chest CT scan in patients with COVID-19 most commonly demonstrates bilateral ground-glass opacifications preferentially distributed in the periphery of lower lobes [11].

Importantly, those signs are also routinely reported in patients with cancer due to the cancer, cancer therapy, or common cancer infections, generating some confusion in ascertaining the diagnosis of COVID-19 infection in patients with cancer. However, particular attention is given to the occurrence of any of those signs during the period of the pandemic to minimize the risk of underdiagnosing COVID-19 infection in patients with cancer during the entire duration of the outbreak. This is particularly important (but not restricted to) in patients with lung cancer, who also frequently present with tobacco exposure and chronic underlying pulmonary disorders that are additional factors of vulnerability. From Chinese data, patients who underwent both reverse-transcription polymerase chain reaction (PCR) testing and chest CT scan for evaluation of COVID-19, a "positive" chest CT for COVID-19 (as determined by a consensus of two radiologists) had a sensitivity of 97%, using the PCR tests as a reference; however, specificity was only 25%. In cases where there is suspicion of COVID-19 infection in patients with cancer, PCR testing and chest CT scan evaluation are highly recommended to consolidate the diagnosis [12].

3 Lessons Learned from Cancer Data Generated in Asia

Particular attention was immediately given to patients with cancer in the Chinese nationwide cohort, recognizing that patients with cancer, representing about 1% of the COVID-19-infected population, were particularly vulnerable, with a case fatality rate of 5.6% compared to 2.3% in the general population. More recently, the retrospective experience from Wuhan hospitals identified a total of 28 PCR-confirmed patients with cancer who were admitted for in-patient care [13]. The population of patients with cancer comprised 60.7% males with a medium age of 65 years, with lung cancer being the most frequent tumor type (25%). Anticancer therapies provided within 14 days prior to admission were chemotherapy (10.7%), targeted therapy (7.1%), radiotherapy (3.6%), and immunotherapy (3.6%). Patients with cancer in this cohort also have concomitant morbidities associated with a higher risk of COVID-19 morbidity such as diabetes (14.3%), chronic cardiovascular and cerebrovascular diseases (14.3%), chronic liver diseases (7.1%), and pulmonary diseases (3.6%). Contamination of patients with cancer was suspected to have occurred during hospitalization in 28.6% of patients. COVID-19-related symptoms were similar in patients with cancer to those reported in the overall population, including ground-glass opacity on CT scan. Oxygen therapy was required in 78.6% of this cancer population and 7.1% of patients required intubation and mechanical ventilation. Patients with lung cancer and worse baseline lung function or endurance were more likely to develop severe hypoxia. Severe events occurred more frequently in stage 4 patients (70%) compared to other stages (44.4%) and in patients exposed to anticancer therapies within 14 days prior to COVID-19 infection (83%). Severe secondary complications occurring during COVID-19 infections were acute respiratory distress syndrome (28.6%), septic shock (3.6%), myocardial infarction (3.6%), and pulmonary embolism (7.1%). Importantly, deaths occurred in eight (28.6%) patients, with a median time from admission to death of 16 days. Although statistical analyses remain limited by the number of patients, multivariate-adjusted Cox proportional analysis adjusted by age and gender showed that antitumor

Table 1 Selected worldwide initiatives and recommendations for patients with cancer during the COVID-19 pandemic

World areas	Weblinks/references
Global	
WHO	https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen
America	
Canadian Cancer Society	https://www.cancer.ca/en/support-and-services/support-services/cancer-and-covid19/?region=on
CDC	https://www.cdc.gov/coronavirus/2019-ncov/index.html
FDA	https://www.fda.gov/about-fda/oncology-center-excellence/message-patients-cancer-and-health-care-providers-about-covid-19
ASCO	https://www.asco.org/asco-coronavirus-information
ASH	https://www.hematology.org/covid-19
ASTRO	https://www.astro.org/Daily-Practice/COVID-19-Recommendations-and-Information
SIOP	https://global.stjude.org/en-us/global-covid-19-observatory-and-resource-center-for-childhood-cancer.html
Fox Chase Cancer Center	https://annals.org/aim/fullarticle/2764022/war-two-fronts-cancer-care-time-covid-19
Mount Sinaï	https://www.esmo.org/oncology-news/first-report-on-the-prognosis-of-covid-19-patients-with-cancer-in-the-us https://www.annalsofoncology.org/article/S0923-7534(20)39303-0/fulltext
Crowdsourcing in USA	https://www.nature.com/articles/s43018-020-0065-z
Cancer Support Community	https://www.cancersupportcommunity.org/blog/2020/04/what-cancer-patients-survivors-and-caregivers-need
Asia	
Australian government	https://canceraustralia.gov.au/about-us/news/information-people-cancer-about-covid-19
Global Asian initiatives	https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30161-2/fulltext
Korea	https://www.nejm.org/doi/full/10.1056/NEJMc2001801
China	https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
Australia	https://www.cancer.org.au/cancer-and-covid-19/
Europe	
European commission	https://ec.europa.eu/info/live-work-travel-eu/health/coronavirus-response_en
EMA	https://www.ema.europa.eu/en/news-events/therapeutic-areas-latest-updates/cancer
ESMO	https://www.esmo.org/oncology-news/first-results-from-the-teravolt-registry-mortality-among-thoracic-cancer-patients-with-covid-19-is-unexpectedly-high
ECCO	https://www.ecco-org.eu/Global/News/COVID-19/Resources
UICC	https://www.uicc.org/news/cancer-and-coronavirus-coping-double-challenge
Cancer center initiatives	https://www.nature.com/articles/s41591-020-0874-8
Cancer Research UK	https://www.cancerresearchuk.org/about-cancer/cancer-in-general/coronavirus-and-cancer
Blood Cancer UK	https://bloodcancer.org.uk/support-for-you/coronavirus-covid-19/coronavirus-blood-cancer/
UK	https://www.annalsofoncology.org/article/S0923-7534(20)36373-0/fulltext
France	https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(20)30087-6/fulltext
Belgium (BSMO)	https://www.bsmo.be/covid-19-and-cancer/
Spain	https://cancerletter.com/articles/20200409_1/
Switzerland	https://www.admin.ch/opc/en/classified-compilation/20200744/index.html
Germany	https://www.ejcancer.com/article/S0959-8049(20)30192-1/fulltext
Italian experience	https://theoncologist.onlinelibrary.wiley.com/doi/full/10.1634/theoncologist.2020-0267

WHO World Health Organization, *CDC* Centre for Disease Control, *FDA* Food and Drug Administration, *ASCO* American Society for Clinical Oncology, *ASH* American School of Hematology, *ASTRO* American Society for Radiation Oncology, *SIOP* St. Jude Global and the International Society of Pediatric Oncology, *EMA* European Medical Agency, *ESMO* European School of Medical Oncology, *ECCO* European Cancer Organization, *UICC* Union for International Cancer Control, *UK* United Kingdom, *BSMO* Belgium Society of Medical Oncology

treatment and patchy consolidation on CT scan at admission were associated with a higher risk of severe events.

Although retrospective and based on a relatively small number of patients, Chinese data are important in starting to set out appropriate measures for prevention of COVID-19 infection during hospitalization (substantial cause of contamination) and the treatment of COVID-19 infection in patients with cancer. However, it seems difficult to draw definitive conclusions related to data generated from the Chinese nationwide cohort where the majority of patients identified with COVID-19 infection were survivors who had no prior cancer therapy within a month prior to COVID-19

infection. Multivariate assessment of the impact of cancer staging and cancer-associated co-morbidities such as diabetes and cardiovascular and pulmonary diseases were not found to be significantly associated with the severity of COVID-19 infection but may have been underestimated because of the limited number of patients. Moreover, the cohort is restricted to PCR-confirmed COVID-19 patients, which considering the false-negative rate of this testing may underestimate the overall COVID-19 diagnosis in patients with cancer, such as when patients are only diagnosed as being COVID-positive based on specific CT-scan images. Finally, this report appears to be restricted to the worst cases, requiring in-hospital admission, and providing no evidence of COVID-19 incidence, morbidity, and mortality in patients with cancer who had recommendations to stay at home and were not referred to a hospital. Nevertheless, this publication highlights the specific vulnerability of patients with cancer to COVID-19 infection and identifies recent prior therapy and patchy consolidation on CT scan at admission as major factors predicting the severity of infection.

4 Protection of COVID-Negative Individuals in Cancer Wards During the Pandemic

Protecting both patients and caregivers in cancer wards is a high priority, needing to be reinforced by all possible means, and is essential for the continuity of cancer care [14]. Most hospitals are avoiding moving patients into the hospital when it is not strictly necessary, developing teleconsultations and shortening stays in outpatient clinics [15]. Several recommendations have been provided to prevent droplet and hand contamination, requiring patients and healthcare professionals to wear protective masks, use hydroalcoholic solutions, and/or wash hands before and after patient-to-professional contacts, reinforce disinfection of surfaces, avoid waiting rooms, and maintain at least a 1-m distance when circulating in the oncology ward [16]. Avoiding mixing COVID-19-positive or -suspected patients with COVID-19-free patients has become a mandatory requirement in oncology and hematology to keep oncology wards COVID-19 free [17]. Conversely, patients suspected of or confirmed as having COVID infection must be hospitalized in specifically separated COVID-19 units. This has encouraged cancer and hematology departments to consider systematically testing patients with a new cancer diagnosis or in need of cancer treatment for COVID-19 contamination, even in asymptomatic patients [18]. This is particularly applicable for patients with acute leukemia, aggressive lymphoma, or myelodysplasia, where the clinical presentation and/or treatment with high-dose therapy with or without stem cell transplantation is associated with neutropenia, leading to an increased risk of febrile complications, due in most cases to bacterial or fungal infections. In this context, viral infection may be complicated with more frequent bacterial and fungal co-infections, with an increased likelihood of fatal outcome. Furthermore, surgery may be considered as an additional risk factor, especially in patients with co-morbidities requiring post-surgery intensive care resuscitation and long-term hospitalization. In many cases such as with breast cancer, the delays have been associated with higher breast cancer-specific mortality. As a result, tumor resection for early operable stages is recommended, but whenever possible diagnostic or staging surgery should be replaced by radiologic diagnostics. Adapting surgical techniques to reduce the risks of exposure of caregivers in the surgical theater is recommended. For instance, with open surgery, surgeons should attempt to avoid exposure to aerosolized viral particles and reduce operative times.

Avoiding COVID-19 infection in cancer survivors is wise considering the risk of a detrimental outcome in cases of COVID-19 infection [19]. Home containment must be strictly maintained in cancer survivors, avoiding unnecessary in-hospital visits, imaging, and consultations. Remote follow-up using teleconsultations for cancer survivors are to be preferred for maintaining regular contacts with patients, postponing non-essential follow-up imaging whenever possible. Advantage should be taken of call or videoconference contacts with patients to reinforce information on protective measures against COVID-19 infection and to provide psychological support.

In most cases, scheduled and ongoing cancer therapy should be maintained or adapted according to recommendations provided by the scientific society or governmental health offices to ensure the quality of care.

5 Testing Patients with Cancer for COVID-19 Infection

Diagnosis of COVID-19 infection in patients with cancer remains challenging. Currently used PCR methods for COVID-19 infection, albeit not widely available in all states and countries, allow detection of infected patients with high specificity when positive but are also acknowledged to have a relatively high level of false negatives [12]. Many patients with cancer may harbor negative viral PCR expression but may still be infected and contagious. Conversely, clinical signs of COVID-19 infection are non-specific, especially in patients with cancer where occurrence of infection is highly prevalent. Testing patients before surgical procedures may have been adopted by many centers but remains a matter of controversy in many others as the sensitivity of PCR testing (as well as most rapid immunological testing) is associated with a high number of false-negative results. Some centers are also doing

a second round of PCR testing to improve sensitivity. However, until more accurate diagnostic tests are available, negative PCR testing results do not fully guaranty the absence of occult infection and may still lead to surgical procedures be carried out in infected patients.

As a result, clinical symptoms, radiological CT-scan images, and any other signs suggesting COVID-19 infection may be regarded as non-specific but sufficient to take preventive actions and initiate specific follow-up for patients with cancer. In many units the development of daily teleconsultations is allowing the establishment of a COVID-19-supected patient with cancer registry, quantifying the prevalence of COVID-19 infection in survivors and outpatient clinics [20].

From our own experience, several patients followed daily by phone or through teleconsultations have been identified with clinical signs of COVID-19 infection (pulmonary infection with no other COVID-19 etiology, specific CT-scan, and/or PCR positivity) that has been fully reversible, suggesting that the prevalence of non-severe infection may be higher than that expected from retrospective registries developed in hospitals from patients admitted for severe infection. Careful follow-up of COVID-19-suspected patients with cancer is also providing advantages in cases of worsening of clinical signs to facilitate admissions in emergency and intensive care units. Finally, one advantage of developing a specific registry and broad testing of patients with cancer is to obtain information on the prevalence of the disease in the patient population and facilitate inclusion of patients in COVID-19-specific clinical trials.

6 Challenges for COVID-19-Positive Patients with Cancer

At present, there are few data, but these suggest that only 1% of patients with cancer have been hospitalized (Chinese data), provided that all patients have been identified in the databases [5]. Infection with COVID-19 was associated with an increased risk of seriousness, possibly linked to cancer and the other co-morbidities frequently associated with cancer (pre-existing pulmonary pathology, tobacco use, cardiovascular pathology, obesity, immunosuppression, etc.) [21].

When cancer is cured or in remission (long-term survivors), cancer may appear as just one severity factor among others, and management will not differ from that of other patients in the management of COVID-19 infection. Concomitant-to-cancer co-morbidities are often but not always associated with the diagnosis of cancer. From currently available data, lung cancer and other tobacco-related lung and cardiovascular diseases have been frequently observed as detrimental factors associated with severe complications of COVID-19 infection. Conversely, no data are available suggesting that patients with few or no co-morbidities such as patients with breast and colon cancer may share a similarly poor outcome when infected with COVID-19. More data are therefore required to define conditions leading to severe complications of COVID-19 infection in cancer patient subpopulations.

In COVID-19-infected patients with cancer scheduled for surgery or treated with radiotherapy and/or medical oncology therapy, including high-dose therapy with autologous stem cell transplantation, allograft, or CAR T-cell infusion, common sense would strongly suggest postponing therapy until the complete disappearance of any clinical and radiological signs and negativity of COVID-19 PCR. In the event of needing intensive care resuscitation and mechanical ventilation, oncologists should quickly liaise with the resuscitators to discuss which prognostic factors of cancer (and other co-morbidities) may affect the decision to intubate. Interdisciplinary boards, including palliative-care teams and ethics committees, have been incorporated in several anticancer centers, and it is recommended to pre-emptively discuss with them the most acute severe cases requiring intensive care.

Following recovery from COVID-19 infection, therapeutic management of cancer should resume as soon as possible to limit the risk of cancer-related death. Not all medical oncology therapies—including chemotherapy, immunotherapy, and targeted therapy—are associated with immunosuppression. Different anticancer therapies may not lead to the same risk and more data are needed to identify which anticancer therapies are more frequently associated with risk for cancer patients. However, so far there are no data suggesting that therapy with minimal immunosuppression may be associated with better outcome, and therefore it may be wise to carefully consider all medical oncology therapy as providing an equally detrimental risk in case of COVID-19 infection. Most COVID-19 infections seem to be controlled within 2 weeks, although some patients may remain PCR positive for 4 weeks, suggesting that postponing anticancer therapy for at least 2–4 weeks may be required.

7 Antiviral Therapies in Patients with Cancer

Several antiviral therapies against COVID-19 infection have been used compassionately (retrospectively analyzed) or as part of prospective uncontrolled and controlled clinical trials (most trials are ongoing). In the emergency of the healthcare crisis, first uncontrolled data generated expectations but were also subjected to a high degree of controversy. In data published thus far, there are no subgroup analyses for patients with cancer. However, publications of upcoming

clinical trials should be scrutinized for subgroup analyses of patients with cancer. Moreover, several clinical trials specifically designed for patients with cancer are ongoing, which may help in our understanding of how patients with cancer should be treated for COVID-19 infection. The use of antiviral therapy outside clinical trials in COVID-19-infected patients remains controversial. Thus far, limited data are available in patients with cancer. In the report from the Wuhan cohort of patients during the Chinese COVID-19 outbreak [13], antiviral agents were used empirically in 20 (71.4%) patients, including arborol in 14 (50%) patients, lopinavir/ritonavir in ten (35.7%) patients, ganciclovir in nine (32.1%) patients, and ribavirin in one (3.6%) patient; nine (32.1%) patients received combinations of several antiviral agents. Systemic corticosteroids were given to 15 (53.6%) patients, mainly in severe cases (12 patients). Moreover, intravenous immunoglobin was prescribed to 12 (35.7%) patients. These data did not report benefits in outcome or conversion from mild to severe cases in this patient population. No safety concerns were reported. However, this patient population remains limited. Including patients with cancer in antiviral treatment registries and clinical trials investigating COVID-19 antiviral therapies is highly advisable. Although very limited information is available, the use of anticancer agents concomitantly with antiviral therapy outside clinical trials is not recommended to avoid unpredicted pharmacokinetic interactions and toxicity, as previously described with antiviral agents for hepatitis B [22].

8 Organization of Cancer Care During the Outbreak (Fig. 1)

Contradictory injunctions frequently occur when trying to maintain continuity and quality of care to limit cancer mortality, while contingencies in healthcare capacity are restricting non-COVID-19 activities in most hospitals and cancer wards [23]. For many cancers, earlier stages of cancer and lack of delay in diagnosis and therapy are associated with significant benefits in terms of morbidity and mortality. Postponed diagnoses and treatment delays are usually regarded as detrimental factors for patients with cancer [24]. However, it is becoming more difficult to convince of the importance of maintaining functional cancer wards in healthcare institutions currently focused in short-term emergency care following nationwide mobilizations in response to COVID-19 infection. In many places, difficulties are currently observed in mobilizing diagnosis, surgery, radiation oncology, medical oncology, hematology units, and their professionals, some of whom are off duty due to caregiver infections. Oncology societies have rapidly provided specific recommendations for various tumor types in trying to maintain essential actions for cancer care according to staging and prognosis, suggesting postponing non-essential imaging in cancer survivors, and attempting to limit the frequency of medical therapy in currently treated patients to avoid contamination during in-hospital visits. For instance, it has been proposed that some cancer surgeries are delayed

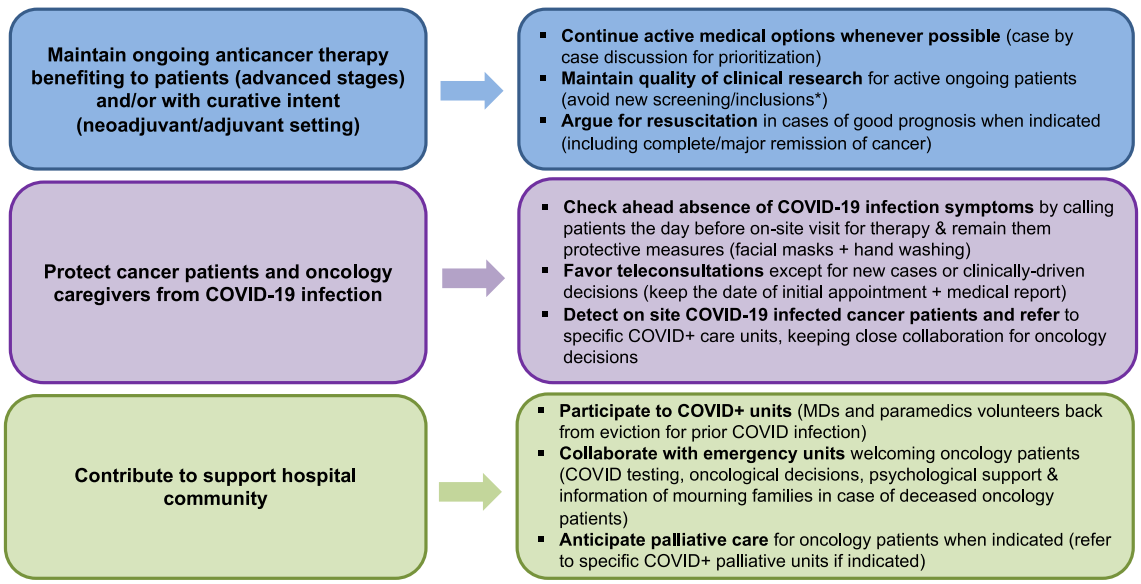

Fig. 1 Practical objectives in cancer units during the COVID-19 outbreak. Asterisk indicates many sponsors (either institutional or industrial sponsors) decided to stop accrual to avoid the risk of covid-19 toxicity during trials and/or because monitoring and assurance quality for safety could not be continued due to limited human resources including Clinical Research Associates

or postponed using neoadjuvant therapies. Carrying out radiotherapy may become complex [25].

More specifically, COVID-19 protection during transportation of patients for daily treatment, protection of professional (manipulators, physicists, radiotherapists, etc.), and disinfection of radiotherapy equipment during therapies have been regarded as potential factors limiting treatment availability in several centers [26]. Moreover, difficulty in carrying out chemotherapy and other medical treatments for cancer (availability and protection of teams, risks of aplasia, estimation of risk benefit, etc.) is making it difficult to maintain quality of care in medical oncology. Although medical society recommendations may be relatively easy to implement in comprehensive cancer centers, they may be more difficult to implement in university and community hospitals and clinics. Furthermore, low evidence-based medicine specifically developed during COVID-19 outbreak may be subject to individual legal actions from patients and families if it can be demonstrated that casualty was related to a lack of optimal patient care at the completion of the COVID-19 outbreak.

While most cancer hospital administrations are convinced that cancer wards will be preserved and remain functional during the COVID-19 outbreak, it remains important to emphasize for others the importance of patient protection from COVID-19 infection, keeping cancer wards COVID-19 free (taking care of COVID-19-diagnosed patients outside the cancer wards) and allocating sufficient resources to maintain the quality of care for patients with cancer during the outbreak.

9 Protection of Professionals

One of the specific features of COVID-19 infection is its contagiousness, which can directly impact professionals who are in contact with patients [27]. Despite no clinical symptoms and a negative COVID-19 PCR, patients may carry on viral replication and may transmit infection to professionals. Education and preventive barriers (facial masks, hydroalcoholic hand wash solutions, disposable overalls, etc.) are mandatory for all professionals who are in contact with patients with cancer. There has been no obvious specificity related to patients with cancer as compared to others, but considering the high degree of specialization required from professionals for cancer care, it is highly advisable to take protective measures to ensure the safety of caregivers and to maintain an efficient staff. The anxiety induced by the risk of personal contamination is often an added stress factor associated with the care of patients suffering from cancer and exposed to cancer treatment-related side effects. Particular attention to the psychological tension associated with cancer care during the COVID-19 outbreak is recommended for professionals dealing with cancer treatment [28].

10 Impact on Vulnerable Populations

The COVID-19 outbreak has exposed weaknesses in healthcare systems [23]. Many countries are facing the consequences of shortages of personal protective equipment, tests, ventilators, and professionals regardless of the type of healthcare systems. Public health officials are bracing for surges in the number of patients, urging people with symptoms to stay home and call their doctor before seeking in-person medical care. Unfortunately, for many low-income individuals, poorly educated populations, jailed prisoners, and undocumented immigrants, access to primary medical care remains challenging [29]. Social distancing aiming at mitigating the spread of severe cases among the entire population that was hailed as a solution to reducing casualty, is or will be associated with reduced incomes and losses of employment. It is likely that social consequences may facilitate the maintenance of COVID-19 infection and contamination. As those individuals are also recognized as highly vulnerable populations for cancer-related mortality, COVID-19 may be regarded as an additional detrimental factor for highly vulnerable patients with cancer.

11 Direct Impact on Cancer Mortality

Cancer is still the second leading cause of death globally, and it may be further impacted by the COVID-19 outbreak, with a worldwide mortality rate that may be ranging up to 5.6% in China and up to 15.2% outside China for newly diagnosed people [30]. Indeed, mortality seems to vary from one country to another. However, COVID-19 infection is likely to increase cancer-related mortality, as case fatality rates are much higher for vulnerable populations, such as the elderly (over 80 years of age, > 14%) and those with co-existing conditions (10% for those with cardiovascular disease, 7% for those with diabetes, and around 6% for those with chronic respiratory diseases, high blood pressure, and cancer) [5]. Although data remain sparse and derive essentially from China, patients with cancer, who also often present with several of the aforementioned co-morbidities, appear therefore as being highly vulnerable, and potential subjects for high mortality rates.

Indirect impact may also be anticipated. As healthcare providers are reorganized to provide high priority to the COVID-19 pandemic, shortages of hospital beds and availability of the healthcare workforces are being observed, asking professionals in charge of chronic diseases including cancer to postpone diagnosis and

treatment. As a result, the COVID-19 outbreak is currently having a profound impact on cancer care. Most actions aiming at prevention, screening, and early diagnosis of cancer are currently on hold or are severely restricted. In most cancer wards, initiatives have been immediately placed to protect patients with active or a prior history of cancer. However, in routine practice, restricting in-hospital visits aiming at avoiding contagious contacts for patients with cancer often results in postponing primary diagnosis and delaying complex high-tech therapies such as surgery, radiotherapy, and chemotherapy/immunotherapy [31]. How much normalization of cancer diagnostics and therapy will be possible after the COVID-19 outbreak remains unknown, but will be highly dependent on the ability of healthcare systems to resume standard activities without being flooded with delayed cancer care. Moreover, the duration of the outbreak (which is still unknown) is likely to last for at least 3 months, a duration that may be associated with cancer progression that could impact the prognosis of several patients. Furthermore, medical societies have also implemented low-evidence-based but convenient recommendations during COVID-19 outbreak to balance standard-of-care requirements and healthcare accessibility. As early diagnosis and quality of evidence-based cancer therapy have been the driving forces behind reducing cancer mortality for the last 50 years, the current COVID-19 outbreak is likely to have an indirect mid-term impact on cancer-related mortality. We believe that awareness of oncologists and their sustained involvement within multidisciplinary teams could help to limit the impact of COVID-19 outbreak on cancer mortality.

12 Remote Consequences of the COVID-19 Crisis on Cancer Diagnosis and Mortality

As a consequence of the COVID-19 outbreak, most countries have decided to take aggressive measures of prevention that are currently strongly impacting the global economy. Economists are foreseeing a global post-COVID-19 outbreak economic downturn and recession [32]. The modeling of a year-long lockdown shows that the economy would shrink by approximately 22% at a cost of $4.2 trillion. Without containment measures, the economy would be contracted by about 7% within a year but as many as 500,000 additional lives would be lost; this would translate into a loss of about $6.1 trillion [33]. While it is currently difficult to anticipate the medical consequences of the post-COVID-19 economic crisis, data deriving from the subprime mortgage crisis may help in identifying factors with an impact on diagnosis and mid-term cancer mortality. For instance, data from the California Cancer Registry data showed that the cancer incidence rate declined yearly by 3.3% in males and 1.4% in females during the USA recession/recovery period [34]. This decrease in cancer incidence affected particularly male patients with prostate, lung, and colorectal cancers and female patients with breast cancer, melanoma, and ovarian cancer. The decreased incidence was associated with unemployment and may have occurred as a result of decreased engagement in prevention and early diagnosis, particularly for malignancies that may have been considered clinically less urgent cancers. On a global perspective, data from the World Bank and WHO generated from more than 2 billion people from 1990 to 2010 showed that rises in unemployment were significantly associated with an increase in all-cancer mortality and all specific cancers except lung cancer in women [35]. These data have highlighted that the 2008–2010 economic crisis was associated with about 260,000 excess cancer-related deaths in the Organization for Economic Co-operation and Development (OECD). Universal health coverage and public-sector expenditure on healthcare were shown to protect against this excess in cancer mortality rate.

Altogether, an increased mortality rate is expected in patients with cancer as a direct consequence of the COVID-19 infection and a remote aftermath effect on the outbreak on the global economy. High-performing health systems are expected to be sufficiently resilient to the consequences of the COVID-19 epidemic and may hopefully be more able to counteract the remote impact on cancer mortality.

13 Psychological Support for Patients with Cancer and Their Relatives

The COVID-19 outbreak is generating important traumatic psychological consequences in the general population due to the constant exposure to stressful headline news, unemployment, home restriction, and social distancing [36]. Patients with cancer and healthcare providers are exposed to similar stresses, with the addition of facing the diagnosis and treatment of a dreadful disease. Relatives who usually accompany patients for diagnosis, treatment, and palliative care are discouraged from visiting patients in hospitals. As a result, frontline healthcare workers have become the main people to provide psychological interventions to patients in hospitals. Professionals who are devoted to their patients are facing the risk of contamination at work for themselves and their relatives. In oncology wards, reinforcement should be made in terms of identifying professional teams that comprise mental health personnel as a basic tenet in dealing with emotional distress for patients with cancer and healthcare providers. Furthermore, careful follow-up of lonely patients with cancer confined at home can be proposed, using telephone or video consultation, taking advantage of the availability of many home-confined mental health professionals [37].

14 Cancer Research During and After the COVID-19 Outbreak

The mobilization of teams for internal reorganization to continue oncology care and/or participate in COVID-19 activities, along with transient eviction of COVID-19-positive caregivers, may result in an effective shortage of human resources to screen or include new patients in clinical trials exploring anticancer agents during the COVID outbreak [38]. Consistently, the majority of pharmaceutical or academic sponsors have provided official guidance to investigative sites to hold whenever possible new screenings and inclusions until the resolution of the COVID-19 outbreak, with the exception of urgent cases (such as particular life-threatening situations in hematology). Instead, hematology and oncology research teams have to focus on maintaining the safety of patients already included in ongoing trials via reinforced monitoring and optimized communication with the sponsor. Detecting and scrutinizing the onset of COVID-19 infection symptoms in patients treated with innovative anticancer therapeutics is mandatory for optimal reporting to the sponsor and for early management of research patients. Remote instead of on-site monitoring may be proposed to maintain real-time close collaboration between investigators and sponsor representatives. This can ensure the quality and contemporaneous assessment of data, and partially limit the accumulation of monitoring duties during the post-COVID-19 aftermath period.

On the other hand, patients with cancer treated outside prospective oncology trials and developing COVID-19 infection may participate in clinical research projects under development against COVID-19 infection if they comply with inclusion criteria, their history of cancer being one among other possible concomitant morbidities, and given the fact that anticancer therapy is likely to be halted until they recover from COVID-19 infection.

Finally, given the limited data from the epidemic in China, a COVID-19 cancer registry seems essential to adapt our practices based on wider evidence of data, especially in Western populations. The French hematology and oncology community among others are launching a descriptive analysis of patients with cancer hospitalized for COVID-19 infection to characterize prospectively their outcome and identify prognosis factors [39].

15 Post-Outbreak Normalization of Cancer-Related Activities

Data from China and Korea [40] as well as modeling data from the UK [41] strongly suggest that home containment aimed to mitigate the impact of COVID-19 outbreak on intensive care requirements and casualties may prolong the duration of the epidemic. Infestations from non-symptomatic reservoirs occurring after the initial epidemic peak may result in the maintenance of COVID-19 infection with remnant waves of COVID-19 cases occurring as a result of transient releases of home containment. Altogether, it is likely that protection of patients and healthcare providers may be required for several weeks or months until at least 80% of the population develop post-infection immunity or (still non-available) vaccination (Fig. 2). Whenever available, serological COVID-19 diagnosis may facilitate the identification of immune patients and healthcare workers who are no longer at risk for COVID-19 infection. Until this time, all protection procedures, including COVID-19-free oncology wards, will have to be maintained.

Most of the healthcare systems will have to promptly reorganize themselves to prioritize the rescheduling of patients who have been postponed for diagnosis and treatments during the wave of COVID-19 infection. Patients underdiagnosed during the COVID-19 home containment may also appear with urgent needs for diagnosis and care at the end of the wave of infection. Further, many patients and primary-care physicians distracted by the COVID-19 infection for whom guidelines were to avoid contact with hospital facilities during the COVID-19 outbreak, may be reluctant and afraid to resume usual contacts with hospital

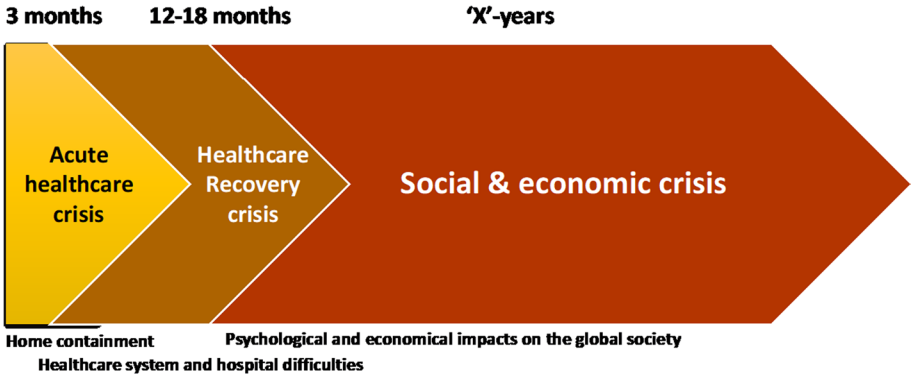

Fig. 2 The COVID-19 outbreak multistep crisis. Each country (one after another) foresees multiple-step crises. New COVID-19 infections may occur during all stages

wards. Moreover, fatigue as well as the impact of income from the economic recession for healthcare providers is a parameter that is yet difficult to estimate, but may be a limiting factor to containing the anticipated increased post-COVID-19 activity.

As the COVID-19 infection may remain prevalent for several weeks with strong psychological and economic impact on the entire society, resuming normal cancer care activities will be challenging. In particular, access to high technical-care facilities such as imaging, surgery facilities, and radiotherapy, which are frequently close to optimal availability in normal conditions, may be flooded with COVID-19-delayed appointments in many hospitals and clinics.

At this stage, no global recommendations can be made, but awareness by oncologists could help to limit the impact of COVID-19 post-outbreak crisis.

16 Conclusions

The COVID-19 outbreak is yielding unprecedented consequences on cancer care that may have direct and remote consequences on patients and caregivers. Listing ongoing issues may allow the oncology community to identify solutions to minimize the impact of the pandemic on current and future management of patients with cancer.

Compliance with Ethical Standards

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin. 2018;68:394–424.
2. Ward EM, Sherman RL, Henley SJ, Jemal A, Siegel DA, Feuer EJ, et al. Annual report to the nation on the status of cancer, featuring cancer in men and women Age 20–49 years. J Nat Cancer Instit. 2019;111:1279–97.
3. Johnson HC, Gossner CM, Colzani E, Kinsman J, Alexakis L, Beauté J, et al. Potential scenarios for the progression of a COVID-19 epidemic in the European Union and the European Economic Area. Euro Surveill. 2020;25(9):2000202.
4. Bulki TK. Cancer Guidelines During the COVID-19 Pandemic. Lancet Oncol. 2020;21(5):629–30.
5. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet. 2020;21:335–6.
6. Fauci AS, Lane C, Redfield RR. Covid-19 navigating the uncharted. N Engl J Med. 2020;382(13):1268–9.
7. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20.
8. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet. 2020;395(10231):1225–8.
9. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.
10. Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and ageusia: common findings in COVID-19 patients. Laryngoscope. 2020. https://doi.org/10.1002/lary.28692 **(Epub ahead of print)**.
11. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020;20(4):425–34.
12. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of Chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology. 2020;26:200642. https://doi.org/10.1148/radiol.2020200642 **(Epub ahead of print)**.
13. Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan. China. Ann Oncol. 2020. https://doi.org/10.1016/j.annonc.2020.03.296.
14. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. JAMA Oncol. 2020. https://doi.org/10.1001/jamaoncol.2020.0980 **(Epub ahead of print)**.
15. Ngoi N, Lim J, Ow S, Ying Jen W, Lee M, Teo W, et al. A segregated-team model to maintain cancer care during the COVID-19 outbreak at anacademic center in Singapore. Ann Oncol. 2020;S0923–7534(20):36410–3.
16. Hellewell J, Abbott S, Gimma A, Bosse NI, Jarvis CI, Russell TW, et al. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. Lancet Glob Health. 2020;8(4):e488–e496496.
17. Shankar A, Saini D, Roy S, Jarrahi AM, Chakraborty A, Bharati SJ, et al. Cancer care delivery challenges amidst coronavirus disease-19 (COVID-19) outbreak: Specific precautions for cancer patients and cancer care providers to prevent spread. Asian Pac J Cancer Prev. 2020;21(3):569–73.
18. Lambertini M, Toss A, Passaro A, Criscitiello C, Cremolini C, Cardone C, et al. Cancer care during the spread of coronavirus

disease 2019 (COVID-19) in Italy: young oncologists' perspective. ESMO Open BMJ. 2020;5:e000759.
19. Wang Z, Wang J, He J. Active and effective measures for the care of patients with cancer during the COVID-19 spread in China. JAMA Oncol. 2020;6(5):631–2.
20. Porzio G, Cortellini A, Bruera E, Verna L, Ravoni G, Peris F, et al. Home care for cancer patients during COVID-19 pandemic: the "double triage" protocol. J Pain Symptom Manag. 2020. https://doi.org/10.1016/j.jpainsymman.2020.03.021 **(in press)**
21. William KOh. COVID-19 infection in cancer patients: early observations and unanswered questions. Ann Oncol. 2020;S0923–7534(20):36384–5.
22. Talavera Pons S, Boyer A, Lamblin G, Chennell P, Châtenet FT, Nicolas C, et al. Managing drug-drug interactions with new direct-acting antiviral agents in chronic hepatitis C. Br J Clin Pharmacol. 2017;83(2):269–93.
23. Emanuel EJ, Persad G, Upshur R, Thome B, Parker M, Glickman AC, et al. Fair allocation of scarce medical resources in the time of Covid-19. N Engl J Med. 2020. https://doi.org/10.1056/NEJMsb2005114 **(Epub ahead of print)**.
24. Hansen RP, Vedsted P, Sokolowski I, Søndergaard J, Olesen F. Time intervals from first symptom to treatment of cancer: a cohort study of 2,212 newly diagnosed cancer patients. BMC Health Serv Res. 2011;25(11):284.
25. Ueda M, Martins R, Hendrie PC, McDonnell T, Crews JR, Wong TL, et al. Managing cancer care during the COVID-19 pandemic: agility and collaboration toward a common goal. J Natl Compr Canc Netw. 2020;20:1–4.
26. Filippi AR, Russi E, Magrini SM, Corvò R. Covid-19 outbreak in northern Italy: first practical indications for radiotherapy departments. Int J Rad Oncol. 2020;S0360–3016(20):30930–5.
27. Lancet T. COVID-19: protecting health-care workers. Lancet. 2020;395(10228):922.
28. Schwartz J, King CC, Yen MY. Protecting health care workers during the COVID-19 coronavirus outbreak—lessons from Taiwan's SARS response. Clin Infect Dis. 2020;12:255.
29. Page KR, Venkataramani M, Beyrer C, Polk S. Undocumented US immigrants and Covid-19. N Engl J Med. 2020. https://doi.org/10.1056/NEJMp2005953 **(Epub ahead of print)**.
30. Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. Lancet Infect Dis. 2020. https://doi.org/10.1016/S1473-3099(20)30195-X **(Epub ahead of print)**.
31. Hanna TP, Evans GA, Booth CM. Cancer, COVID-19 and the precautionary principle: prioritizing treatment during a global pandemic. Nat Rev Clin Oncol. 2020;17:268–70.
32. Craven M, Mysore M, Singhal S, Smit S, Wilson M. COVID-19: briefing note, March 30, 2020. Report from the McKinsey & Company.
33. Cornwall W. Can you put a price on COVID-19 options? Experts weigh lives versus economics. Science. 2020. https://doi.org/10.1126/science.abb9969.
34. Gomez SL, Canchola AJ, Nelson DO, Keegan TH, Clarke CA, Cheng I, et al. Recent declines in cancer incidence: related to the Great Recession? Cancer Causes Control. 2017;28(2):145–54.
35. Maruthappu M, Watkins J, Noor AM, Williams C, Ali R, Sullivan R, et al. Economic downturns, universal health coverage, and cancer mortality in high-income and middle-income countries, 1990–2010: a longitudinal analysis. Lancet. 2016;388(10045):684–95.
36. Duan L, Zhu G. Psychological interventions for people affected by the COVID-19 epidemic. Lancet Psychiatry. 2020;4:300–2.
37. Qiu J, Shen B, Zhao M, Wang Z, Xie B, Xu Y. A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: implications and policy recommendations. Gen Psychiatr. 2020;33(2):e100213.
38. Shuman AG, Pentz RD. Cancer research ethics and COVID-19. Oncologist. 2020. https://doi.org/10.1634/theoncologist.2020-0221 **(Epub ahead of print)**.
39. Wang CJ, Ng CY, Brook RH. Response to COVID-19 in Taiwan: big data analytics, new technology, and proactive testing. JAMA. 2020;323(14):1341–2.
40. https://www.worldometers.info/coronavirus/
41. Enserink M, Kupferschmidt K. With COVID-19, modeling takes on life and death importance. Science. 2020;367(6485):1414–5.