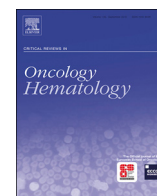




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## Cancer patients and research during COVID-19 pandemic: A systematic review of current evidence



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### ABSTRACT

The novel coronavirus, also known as SARS-Cov-2 or COVID-19 has become a worldwide threat and the major healthcare concern of the year 2020. Cancer research was directly affected by the emerging of this disease. According to some Chinese studies, cancer patients are more vulnerable to COVID-19 complications. This observation led many oncologists to change their daily practice in cancer care, without solid evidence and recommendations. Moreover, the COVID-19 manifestations as well as its diagnosis are particular in this special population. In this review paper we expose the challenges of cancer management in the era of SARS-CoV-2, the epidemiological, clinical, pathological and radiological characteristics of the disease in cancer patients and its outcomes on this population. Finally, we focus on strategies that are followed in cancer management with review of national and international guidelines.

### 1. Introduction

The novel coronavirus, also known as SARS-Cov-2 or COVID-19 has become a worldwide threat and healthcare concern. Human to human transmission of the virus occurs through respiratory droplets (by coughing or sneezing) and through direct contact with an infected patient or indirect contact with fomites in his environment (Li et al., 2020a; Ong et al., 2020). Since its outbreak in China at the end of 2019 and until the 5th of April 2020, the pandemic has affected more than a million of people and caused 62,773 deaths globally (20200405-sitrep-76-covid-19.pdf, 2020). It is thought that patients with comorbid conditions are more susceptible to manifest complications of the viral infection (Guan et al., 2020a). According to a recently published Chinese cohort, patients with cancer had a higher risk of developing severe events (intensive care unit admission, invasive ventilation, or death) compared with patients without cancer (39 % vs 8%,  $p = 0.0003$ ) (Liang et al., 2020). Moreover, public health measures that are implemented in order to control the disease spread aim to decrease preventable hospital admissions and elective procedures (Cao et al., 2020). However, cancer patients need continuous care, and undergoing diagnostic tests or therapeutic interventions is not a luxury, whereas their potential COVID-19 exposure could be very risky, or even fatal. Remarkable efforts are made to understand the particularity of cancer patients who contract the novel coronavirus, to overcome the diagnostic and therapeutic challenges and to implement recommendations

to protect this vulnerable population from the virus exposure as well as from the disease progression resulting from testing and treatment delays. In this article, epidemiological, radiological and clinical features of adult cancer patients with COVID-19 will be reviewed based on an extensive review of the literature, as well as diagnostic and therapeutic strategies suggested by healthcare providers and institutions in endemic areas, particularly China and Italy.

### 2. Materials and methods

In order to review the particularities of COVID-19 in adult patients with cancer, an extensive electronic search of the literature was conducted in the PubMed database until the 5th of April 2020. The following keywords with Boolean operators were used 'covid-19', 'novel coronavirus' and 'SARS-CoV-2' in combination with 'cancer', 'neoplasm', 'oncology' and 'malignancy'. A total of 223 articles were extracted. We included articles in English as well as articles in French because we are familiar with this language. Abstracts in English of articles in Chinese language were also included. Duplicated articles and articles that were published before the era of SARS-Cov-2 (*i.e.*, before December 2019) were excluded. Titles and abstracts of retrieved articles were screened for eligibility, and then entire texts were analyzed and 88 papers that respond to our objectives were included in this review. Our work is summarized in the PRISMA diagram below (Fig. 1).

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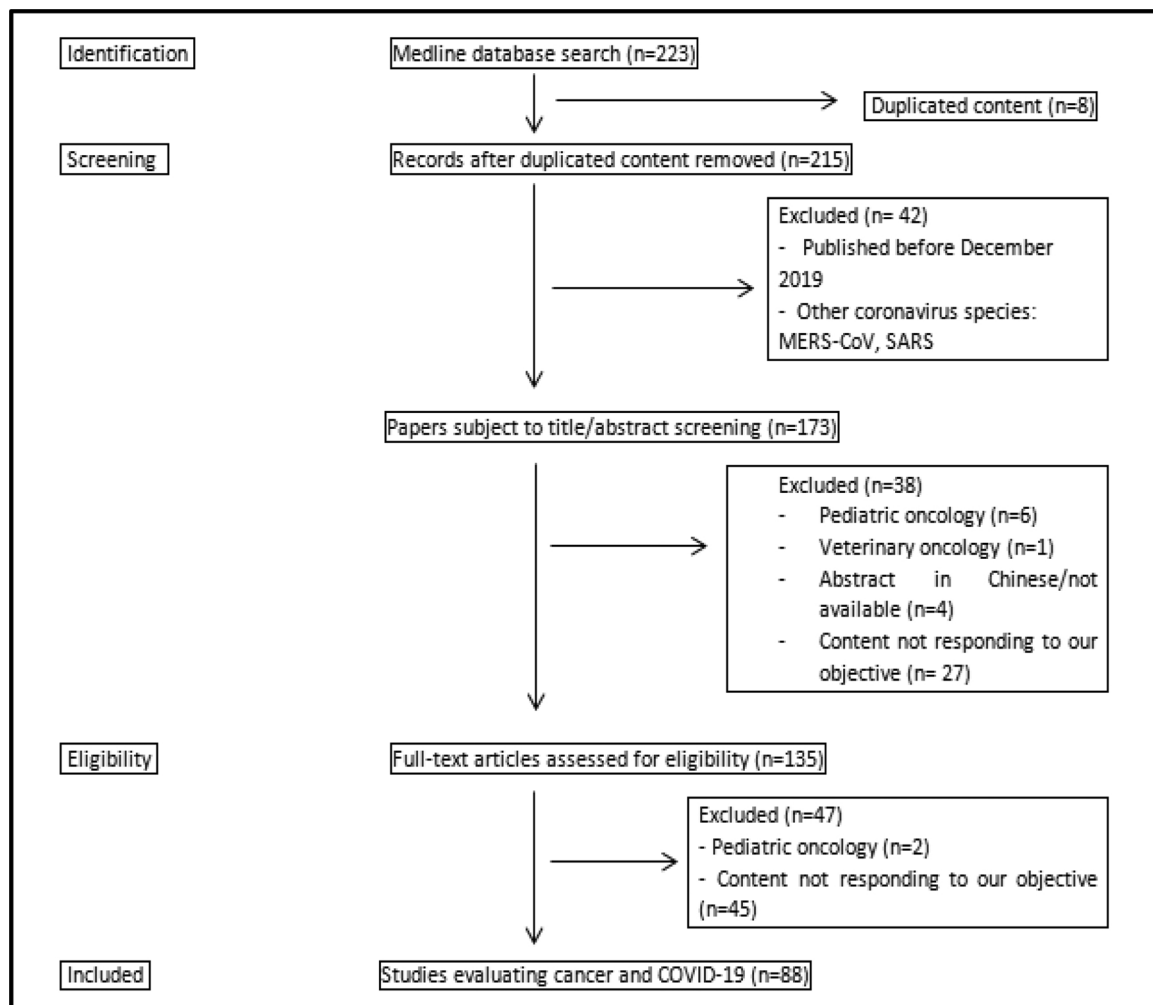


Fig. 1. PRISMA flow chart of article selection process.

### 3. Results

Out of 88 articles, six were in French language and 19 were in Chinese language with English abstracts. Most of the papers consisted of short editorials, letters, correspondence or comments. Ten Cohort studies were identified (retrospective, prospective or cross-sectional analysis) as well as 9 case reports and one case series. Only four of the cohort studies exclusively included cancer patients. Of note, all cohort studies were conducted in China. Most of the reported cases originated from China and Italy.

59 % of the published papers originated from China and Italy (52 of 88). Seven works were multinational and the majority of them were multicontinental, issued in collaboration between researchers from Asia, Europe and the Americas. We identified one article originating from each of the following countries: Canada, India, Singapore, Spain and Saudi Arabia. The pie chart below (Fig. 2) shows the distribution of the articles included in our review according to the country of origin.

Researchers in oncology are preoccupied by more than one aspect of the COVID-19. Subjects of interest in the papers that were included in this review could be divided in four categories:

- Cancer research in the era of COVID-19, and the effect of cancer therapy on COVID-19 patients (6 articles).
- Epidemiological, clinical, pathological and radiographic features of cancer patients with COVID-19 (14 articles).
- Outcomes of cancer patients with a SARS-CoV-2 infection (11 articles).

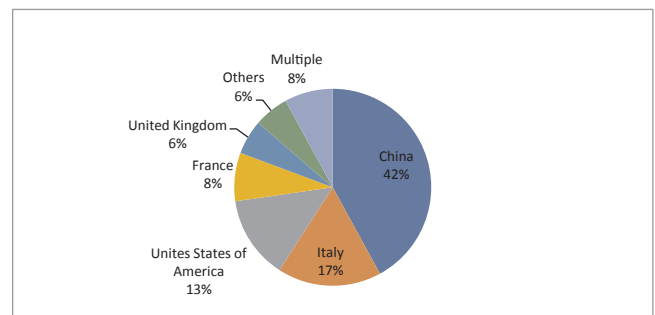


Fig. 2. The percentage of contribution of different countries in the published articles on COVID-19 and cancer.

- Strategies for risk reduction and management of cancer patients during COVID-19 outbreaks (57 articles).

Many expert recommendations on the diagnosis and treatment of cancer patients during the novel coronavirus outbreak were formulated so far. Designs and strategies that focused on gastrointestinal and lung tumors were the most prevalent, followed by urogenital neoplasms and breast and other gynecological malignancies. The management of hematological cancers was also discussed in three papers. Until the end of March, no universal guidelines were adopted. However, the first week of April was marked by the emergence of consensus guidelines and propositions from multiple national and international groups.

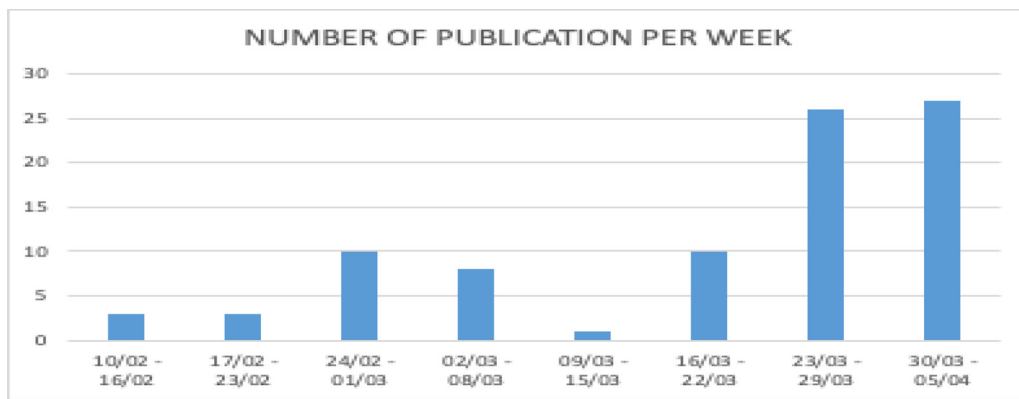


Fig. 3. Number of publications on cancer and COVID-19 per week between the 10th of February and the 4th of April 2020.

Fig. 3 shows the number of published articles per week that are interested in cancer and COVID-19 between the 10th of February and the 4th of April 2020.

This article will discuss the various aspects of COVID-19 in cancer patients assessed in the literature.

### 3.1. Cancer research in the era of COVID-19

With the declaration of COVID-19 pandemic, strict public health measures were recommended by authorities to limit the virus spread. Those measures also apply to cancer research centers that found their activity declining due to quarantining measure, working in shifts and lacking supplies. Thus, researchers faced the necessity to make decisions on continuing or interrupting trials (COVID-19 Challenges Basic Researchers, 2020). While experimental researches are crucial for providing the best care for cancer patients, many centers are trying to make changes to their programs and adapt to the new situation without interrupting their activity. Moreover, high authorities such as the FDA issued guidelines that recommend being more flexible about protocols. Some measure were taken from remotizing communication with patients for follow up, making changes and exceptions to trials protocols to reducing multiple hospital visits and routine follow up, postponing new clinical trials, etc. (Clinical Research Slows as COVID-19 Surges, 2020).

On the other hand, some cancer research laboratories opted for pivoting their experiments in anti-neoplastic agents towards exploring therapeutic options for COVID-19 infection. For instance, Chinese trials are assessing the role of the anti-VEGF bevacizumab, the myeloma drug thalidomide, the PD-1 inhibitor camrelizumab and other anti-cancer agents in the treatment of SARS-CoV-2 infections. The potential benefit of other targeted therapies such as afatinib, carfilzomib and ixazomib was highlighted in the literature (Cancer Labs Pivot to Battle COVID-19, 2020).

Many other cancer drugs are being investigated in this field. For example, a theoretical role of kinase inhibitors in the reduction of infectivity of well-known viruses such as Ebola and Hepatitis C is described, suggesting that drugs like sunitinib and erlotinib would potentially be effective against SARS-CoV-2 (Stebbing et al., 2020).

Moreover, a group of researchers used network proximity analyses of drug targets and virus–host interactions in the human interactome to identify repurposable drugs and potential drug combinations for the treatment of SARS-CoV-2. Three combinations were deemed effective: sirolimus plus dactinomycin, mercaptopurine plus melatonin, and tor-emifene plus emodin, all of which consisting of at least one anti-cancer agent (an immunosuppressant, an antineoplastic agent and a selective estrogen receptor modulator respectively) (Zhou et al., 2020).

Amidst this rapid evolution of the COVID-19 should be kept in mind the need to respect some clinical research ethics. In fact, the medical ethics editorial team of The Oncologist focused on three crucial considerations in cancer research. First one is non-abandonment of a

patient whose prognosis and wellbeing is dependent on an investigational treatment and a protocol to which he is adhering. Second one is making an effort to flatten the curve of COVID-19 infection by minimizing any unnecessary exposure to a suspicious environment. Finally they emphasize on psychosocial support of the patient and of the research team in the middle of the outbreak (Shuman and Pentz, 2020).

### 3.2. Epidemiological, clinical, pathological and radiographic features of cancer patients with COVID-19

At the beginning of the epidemic in China, multiple epidemiological studies were conducted to evaluate characteristics of patients with COVID-19. Some of these studies included a subgroup of cancer patients. For instance, Wei-Gie Guan et al. analyzed data of 1099 patients with laboratory-confirmed COVID-19 through January 29, 2020. They identified in their cohort 261 patients (23.7 %) with comorbidity. Only 10 of these patients had a history of cancer (0.9 % of all patients). 3 of these 10 patients had a severe presentation on admission while the others had mild symptoms (Guan et al., 2020b). Another Chinese retrospective cohort studied 69 cases of COVID-19 in Wuhan. Disease severity at presentation was assessed by the SpO<sub>2</sub> as the sole criteria, with a cutoff of 90 %. Among these 69 patients, four had a history of malignancy of whom only one patient presented with an SpO<sub>2</sub> < 90 % (Wang et al., 2020a).

In both cohorts previously cited the number of patients who had a severe presentation was higher than that of less severe cases, but this observation did not apply to the sub-group of patients with malignancy. However, these data are not enough to conclude that cancer patients tend to present with milder symptoms than the rest of the population.

Liang et al. were the first to publish data regarding cancer patients who are diagnosed with COVID-19. Their Chinese cohort was the largest and the only prospective cohort to date interested in oncology patients. It included 1590 COVID-19 cases of whom 18 (1 %; 95 % CI 0.61–1.65) had a history of cancer. This was higher than the incidence of cancer in the overall Chinese population (0.29 %). The most frequent primary tumor was lung cancer. Four of 16 patients had received chemotherapy or surgery within the prior month, and twelve were in remission at the time of the infection. The mean age was 63.1 years in cancer patients vs 48.7 years in non-cancer patients. There was no difference in gender between the two groups. Clinical presentation was marked by more polypnea in the cancer group (47 % vs 23 %), and imaging findings by more severe CT scan at baseline (94 % vs 71 %), without significant difference in severity on chest X-ray (Liang et al., 2020).

These data were helpful in clarifying epidemiologic and clinical features of cancer patients during the COVID-19 pandemic, but were criticized by Wang et al: the higher incidence of cancer in this cohort compared to that of cancer in the general Chinese population was interpreted as an increased risk for cancer patients to be infected with the

COVID-19. However, only four of the 18 patients had a disease that is actively treated while twelve were in complete remission and two had an unknown treatment status. Therefore their infection might be related to another etiology than their cancer (Wang and Zhang, 2020).

After Liang et al., two other cohorts (one cross-sectional and one retrospective) were conducted during the same time frame in China. Jing et al. (Yu et al., 2020a) published a cross-sectional analysis of 1524 patients with cancer in a tertiary hospital in the city of Wuhan. 12 of these patients (0.79 %) were diagnosed with COVID-19 pneumonia. They concluded that the infection rate of COVID-19 in cancer patients was higher than the cumulative incidence reported over the same period in Wuhan (0.79 % vs 0.37 %, OR 2.31 [95 % CI, 1.89–3.02]). Zhang et al. retrospectively analyzed 28 COVID-19-infected cancer patients (Zhang et al., 2020a). Of note, the median age of infected patients was similar in both studies (66 and 65 years respectively), and lung cancer was also the most predominant type with more than half of the patients (seven of 12 patients) in the first cohort and 25 % (7 of 28) in the second one. These conclusions were compatible with those of the prospective cohort of Liang et al. Moreover, both studies implied that hospital admission was an independent risk factor to acquire a SARS-CoV-2 infection, because most of cancer patients in the first study were receiving active in-hospital treatments (chemotherapy with or without immunotherapy, radiotherapy or surgery), and 8 of 28 patients (28.6 %) in the second study were suspected to have a hospital-associated transmission.

Not only clinical presentation of COVID-19 in patients with cancer is particular, but also diagnosing this disease is challenging due to multiple factors:

- Cancer patients might have atypical radiographic features. Qu et al. reported the case of one patient with lung adenocarcinoma who had a laboratory confirmed COVID-19 infection with diffuse, irregular, small ground-glass opacities with partial consolidation on day 10 of infection on chest CT-scan. This is not compatible with the typical peripheral subpleural ground-glass infiltrates (Qu et al., 2020).
- Cancer patients might have radiographic findings similar to those of a SAR-CoV-2 infection and can be misleading. A Chinese article reported the cases of five of 139 cancer patients who had ground-glass opacities on baseline chest CT-scans. Three of these patients underwent RT-PCR, had a negative test and were considered negative for COVID-19. The most retained diagnosis in these patients was another viral infection (Zhu et al., 2020). Nevertheless, many sources now admit that radiographic findings are more sensitive than RT-PCR in detecting COVID-19 (Fang et al., 2020) and the previously reported cases could have a COVID-19 infection that was missed because of a false negative PCR test.
- Due to the high frequency of routine chest imaging in the follow up of cancer patients, incidental findings suggestive of COVID-19 may not be infrequent. These findings are a source of frustration for the patient and the physician, as they may suggest either another differential diagnosis or a COVID-19 infection at an early asymptomatic stage especially in regions of high disease prevalence as was the case of an Italian patient who was referred for an FDG-PET/CT (Polverari et al., 2020). This was then highlighted by an Italian analysis performed in a nuclear medicine center where incidental findings were recorded in 7 of 65 asymptomatic patients who underwent imaging studies, of whom 5 had a laboratory confirmed infection (Albano et al., 2020).
- Due to similarity in symptoms between the infection and the underlying disease, especially in lung cancer patients and patients with pulmonary metastasis, the diagnosis of COVID-19 may be delayed. In two patients who were programmed for elective lobectomy for early stage lung cancer in China, a retrospective diagnosis of SARS-CoV-2 was made after patients worsened their symptoms post-operatively. The examination of pulmonary pathology showed that inflammatory changes consistent with interstitial disease were

present at the time of surgery (Tian et al., 2020).

- Some clinical and biological features can mask a COVID-19 presentation in cancer patients. This is the case of hematologic malignancies where laboratory results can be misleading. For instance, a Chinese patient with a history of non-Hodgkin lymphoma and CLL treated with chlorambucil presented with signs of disease progression as well as respiratory symptoms. She initially denied any exposure to a confirmed case, and the diagnosis of COVID-19 was delayed because of the high white blood counts count ( $91.85 \times 10^9$  cells/L) and the focus on the treatment of his underlying malignancy (Jin et al., 2020).

### 3.3. Outcomes of cancer patients with a SARS-CoV-2 infection

Few studies that analyze the impact of a SARS-CoV-2 infection on patients with malignancy were found in our literature review. However, we can make some conclusions from cohort studies that included cancer patients.

A study performed on 24 critically ill patients in Seattle found that most of these patients had comorbid conditions, however a history of cancer was not found in any of these patients (Bhatraju et al., 2020). We know that this is a very small sample, but we still can tell that patients who have other underlying chronic conditions such as asthma or diabetes might be more concerned about becoming critically ill if infected with the SARS-CoV-2 than cancer patients.

An analysis of the first 1975 COVID-19 patients in China was performed, and the first 17 deaths were reviewed. Most of the cases who died were elderly patients (median age 75; range 48-89 years) and had comorbidities or a history of recent surgery. Of the 17 deaths, only one patient had a history of cancer. He was an 86-year-old man with a history of colon cancer and underwent a colon cancer surgery (Wang et al., 2020b). Of course, this small sample prevents us from extrapolating these data; however, this patient had other comorbid conditions (hypertension and diabetes mellitus) that, along with his age and male gender make him more vulnerable to a SARS-CoV-2 infection. In fact, a nationwide analysis of 1590 COVID-19 hospitalized patients in 575 Chinese hospitals between December 11th, 2019 and January 31 st, 2020 showed that the most prevalent comorbidities were hypertension (16.9 %) and diabetes (8.2 %). Only 18 patients (1.1 %) had a history on malignancy. However, severe cases in this analysis were more likely to have a malignancy (50.0 % versus 15.6 %) compared with non-severe cases. The composite endpoints consisting of admission to intensive care unit, or invasive ventilation, or death were also analyzed, and after adjustment for age and smoking status a history of malignancy was the fourth most common risk factor of reaching the composite endpoints with a HR of 3.50 (95 %CI 1.60–7.64) (Guan et al., 2020a). On the other hand, in the 1099 patients cohort of Wei-Gie Guan et al. previously mentioned, out of 10 patients who had cancer only one patient experienced an adverse event (ICU admission, ventilation or death) (Guan et al., 2020b). This may suggest that adverse outcomes in malignancy are not as frequent as we think. Moreover, an analysis of 85 fatal cases of COVID-19 in China showed that 58 had comorbidities, of whom 7% had a cancer history while 60 % had hypertension or diabetes mellitus (Du et al., 2020).

We believe that these results should be interpreted with caution in the absence of adjustment to the prevalence of the different comorbidities in the Chinese population.

The nationwide cohort of Liang et al. previously described, specifically targeting cancer patients, concluded that this population was predisposed to higher risk of severe events (ICU admission, mechanical ventilation or death) compared to non-cancer patients (39 vs 8%;  $p = 0.0003$ ), and that among cancer patients, those with a recent history of chemotherapy or surgery had a higher risk of severe events than those who did not receive treatment (Liang et al., 2020). These data should also be carefully interpreted, not only because of the small sample, but also because cancer patients in this cohort had a significantly older

median age than their control (63.1 vs 48.7 years) as well as a more significant history of smoking, suggesting that these two factors might be more associated with worse COVID-19 outcomes than the cancer history itself (Wang and Zhang, 2020).

Conversely, in the Jing et al. cohort, outcome of cancer patients was a secondary endpoint, but authors could conclude that three of 12 patients (25.0 %) developed SARS; 1 patient required an ICU admission and 3 deaths (25.0 %) were recorded (Yu et al., 2020a). Zhang et al. reported a higher rate of adverse events (53.6 %) and mortality (28.6 %) in their 28 cancer patients cohort, with a higher risk of severe events in patients who had their last anti-tumor treatment within 14 days of the infection (HR = 4.079, 95 %CI 1.086–15.322, P = 0.037) (Zhang et al., 2020a).

The three above studies (Liang et al., 2020; Yu et al., 2020a; Zhang et al., 2020a) encouraged physicians to withhold or postpone cancer treatment during the epidemic, and this need was mainly urged by Liang et al. based on an increased risk of adverse events in patients that received chemotherapy or underwent recent surgery prior to the infection, predisposing them to hematological toxicity and to an immunocompromised state.

Regarding patients treated with immunotherapy, no clear data are yet available. A case report appeared on the 27th of March discussing the history of an Italian patient with metastatic lung cancer who has been treated with nivolumab in the second line for 7 years with an excellent response, but died of a COVID-19 infection after a rapid clinical deterioration (Bonomi et al., 2020). Nevertheless, according to an Italian researcher, the conclusions of Liang et al. should be carefully extrapolated to patients receiving immunotherapy, especially in the adjuvant setting or for a curative intent, although the similarity in the mechanism of action of immune-checkpoint inhibitors and the COVID-19 infection in terms of cytokine release, and the common radiological finding of immunotherapy-induced pneumonitis and COVID-19 infection make this issue more challenging (Bersanelli, 2020).

Moreover, no patients in the prospective Chinese cohort were treated with targeted therapy, and only one patient was on osimertinib in the cohort of Jing et al. In the absence of data, the safety of targeted therapy is still unknown, but according to a case reported in China, one patient with EGFR positive lung adenocarcinoma treated with osimertinib was diagnosed with COVID-19 and successfully treated with the antiretroviral lopinavir/ritonavir, without withholding treatment with osimertinib. No adverse outcomes were recorded (Zhang et al., 2020b).

This said, some authors suggest that because no solid evidence exists yet, treatment modification or interruption should not be a standard and should be individualized and discussed with every patient (Shankar et al., 2020).

### 3.4. Strategies for risk reduction and management of cancer patients during COVID-19 outbreaks

While every cancer patient and his healthcare provider are concerned about the risk of transmission of COVID-19 in hospital settings, the risk of disease progression with treatment delay started to become more serious with the pandemic persisting (Burki, 2020a; Extance, 2020; Kutikov et al., 2020; The Lancet Oncology null, 2020), and the healthcare system distraction towards COVID-19 might have harmful consequences on cancer patients (Cortiula et al., 2020). The urgent need for guidelines implementation to protect cancer patients from acquiring a COVID-19 without harming them is discussed by many authors in the literature. In the absence of universal guidelines, most of the strategies adopted involve prioritizing urgent situations such as acute leukemia, curative treatments for aggressive diseases, and adjuvant and neoadjuvant therapies while withholding or postponing palliative therapies for poor prognosis patients (Hanna et al., 2020). Telemedicine is also encouraged (Connor et al., 2020). Measures to protect medical staff are proposed because this indirectly impacts

patients' safety. These measures consist of prioritizing laparoscopic procedures in cancer surgery to minimize the exposure to aerosolized specimen (Kimmig et al., 2020) and limiting endoscopic diagnostic procedures to the necessary with application of strict protective measures particularly in bronchoscopy (Ost, 2020). Some medical and imaging oncology wards were completely re-organized to safely accommodate cancer patients (Ngoi et al., 2020; Jazieh et al., 2020; Czernin et al., 2020).

#### 3.4.1. The Chinese experience

Since the outbreak of SARS-CoV-2 in China, the whole healthcare system was shifted towards the management of SARS-CoV-2 patients. Chinese oncologist faced difficulties in providing the best care for their patients. We add to this that integrative cancer therapy that involves close contact of the care provider with patients is widely available in China and constitutes a great risk during the pandemic (Yang et al., 2020a). As of the 1st of February, almost a month following the declaration of the epidemic, more than a dozen of articles that propose management strategies for oncology patients were published. Most of these articles have their bodies in Chinese. Abstracts of these articles were reviewed to form a picture of the oncology practice in China during the COVID-19 pandemic. Common to all works was the encouragement of a multidisciplinary approach and the delay of every elective procedure. However, the definition of elective procedures is not universal (Wang et al., 2020c).

Most of the Chinese literature emphasized on gastrointestinal tumors, especially the surgical management (Yu et al., 2020b; Ma et al., 2020; Li et al., 2020b; Hu et al., 2020a). A COVID-19 positive patient with early stage colon cancer was successfully treated with colectomy without complications after receiving anti-viral therapy and negating his RT-PCR on two occasions (Ye et al., 2020). Since fecal-oral transmission cannot be excluded to date, experts encourage laparoscopic techniques (Yu et al., 2020b), prioritizing non-surgical and interventional management such as stent placement for gastro-intestinal obstruction, avoiding endoscopic procedures (Chen and Peng, 2020; Hu et al., 2020b; Luo and Zhong, 2020), providing isolation areas for invasive interventions for suspected or confirmed cases (Chen and Peng, 2020; Luo and Zhong, 2020). As for the medical management, a group of experts suggested maintaining chemotherapy for metastatic patients, providing necessary treatment for patients who have a progressive disease and decreasing intensity and frequency of adjuvant chemotherapy (Li et al., 2020). Chinese physicians adopted modifications not only in the therapeutic strategies but also in the diagnostic procedures of cancer patients (Wu et al., 2020; Zhang and Xu, 2020). Delaying gastro-intestinal diagnostic procedures for patients with a stable disease was recommended by a group of practitioners (Luo and Zhong, 2020).

As for lung cancer, keeping a high index of suspicion for a COVID-19 infection and protecting vulnerable patients are priorities (Li et al., 2020c; Xu et al., 2020; Yang et al., 2020b), as three Chinese cohorts demonstrated that lung cancer is the most type of cancer susceptible to COVID-19 infection. Guidelines are directed toward maximizing outpatient follow-up and treatment, delaying possible therapies and procedures, screening patients for COVID-19 infection even with a low index of suspicion due to similarities of symptoms with those of the underlying cancer of the treatment's adverse events (Zhao et al., 2020; Lung Cancer Study Group et al., 2020).

Furthermore, outpatient care for breast cancer patients was also highlighted in one article (Liu et al., 2020). Another small Chinese study identified the lack of strict guides for the management of gynecological cancer in an endemic region (Zhang et al., 2020c).

This said, China obviously witness a change in practice in the management of oncology patients during the COVID-19 pandemic.

#### 3.4.2. The Italian experience

After China, Italy was one of the first countries that experienced a

tragic increase in the incidence and mortality rate of COVID-19 cases, with more than 100,000 cases and up to 11,600 deaths by the end of March 2020 (20200331-sitrep-71-covid-19.pdf, 2020). Italy rapidly complained of a shortage of resources and some oncologists were called to help in the fight of COVID-19, some hospitals were transformed to admit COVID-19 patients only. An Italian young oncologists group suggested some measures to adapt to the situation based on their current practice. Those measures consisted mainly of delaying some anticancer treatment on case-by-case evaluation of the risk/benefit ratio especially for second line treatments and beyond for incurable metastatic disease, maintaining adjuvant and neoadjuvant as well as first line metastatic treatment, delaying imaging assessment for clinically stable patients, encouraging remote follow-up except for patients with clinical complaints suggestive of disease progression or for those who insist to get a physical exam, limiting caregivers company and respecting personal protection and distancing measures (Lambertini et al., 2020).

Similarly, remote monitoring and home care were encouraged (Mussetti et al., 2020). A group of practitioners in Tuscany, Italy, adopted and validated a home care protocol that consisted of a double triage to protect patients with cancer. The first triage aims to screen patients and their cohabiters for any sign or symptom of a COVID-19 infection via a telephone interview, while a second telephone interview aims to schedule home access with variable frequency of visits based on symptoms burden and patient's prognosis (Porzio et al., 2020).

One article in the Italian literature highlighted the lack of recommendations that guide the diagnosis, follow-up and treatment of patients with head and neck cancer in the era of SARS-CoV-2 (De Felice et al., 2020). As for lung cancer, practical suggestions appeared on the 27th of March in the ESMO Open to guide physicians in making decisions on which treatment and procedure to prioritize (Banna et al., 2020).

Most of the other Italian published works targeted urological and gastrointestinal tumors, also with more focus on the surgical aspect than the medical one. In urology practice, one hospital proposed an algorithm to classify procedures for oncological diseases into non-deferrable (such as muscle invasive bladder cancer, high risk locally advanced prostate cancer); deferrable (such as partial nephrectomy for cT1a renal cell carcinoma), semi-non-deferrable (elective procedures in a low disease burden hospital) and replaceable by other treatments, while taking into consideration patients comorbidity profiles and hospital resources (Ficarra et al., 2020). Telephone screening of patients for any suspicious symptom before admission for elective procedures is also recommended by a group of practitioners, with a low threshold for undergoing nasopharyngeal swabs before surgery (Simonato et al., 2020). In gastroenterology, a change in practice was also witnessed (Pellino and Spinelli, 2020). For instance, in colorectal surgery, most elective procedures were limited in many centers over the country, but colorectal cancer surgeries were not part of this strategy and were maintained along with emergent procedures (Lisi et al., 2020; Di Saverio et al., 2020). Some practitioners in rectal cancer opted, in the absence of recommendations to substitute oral capecitabine for 5-FU whenever possible, and to adopt short course radiotherapy in the neoadjuvant setting with delaying surgical interventions (De Felice and Petruccianni, 2020).

An algorithm was also proposed by a northern Italian group of radiation oncology that insisted on continuing to deliver treatment for cancer patients with adoption of hypo fractionated protocols whenever possible, while withholding radiotherapy for benign disease or postponing it if possible, in the adjuvant setting, and withholding treatment only for confirmed or highly suspicious cases of COVID-19 (Filippi et al., 2020).

After reviewing the above resources, we conclude that efforts are gathered to establish management strategies in Italy, but no tool is available to date to test the efficacy and safety of these propositions. We encourage creating tools to validate these protocols in the future.

### 3.4.3. The French experience

Practice of oncology in France was not different than that in China and Italy, but some French societies have recently issued formal guidelines for the management of specific types of malignancy. All these propositions meet the recommendations published on the 14th of March by a group of French experts solicited by the president of Public Health Council on SARS-CoV-2 infection and solid cancers (You et al., 2020; Grellety et al., 2020).

We here summarize some of these guidelines:

- In breast cancer, the Collège Nationale des Gynécologues et Obstétriciens Français (CNGOF), the Société d'Imagerie de la FEMme (SIFEM), the Société Française de Chirurgie Oncologique (SFCO), the Société Française de Sénologie et Pathologie Mammaire (SFSPM) and the French Breast Cancer Intergroup-UNICANCER (UCBG) recommend to withhold screening programs during the pandemic, investigate only BIRADS IV and above lesions, perform ambulatory surgeries and avoid complicated reconstruction surgeries, avoid surgery in COVID-19 positive patients who have low grade tumors, delay adjuvant radiotherapy and privilege hypo fractionated protocols, maintain palliative radiotherapy for metastatic disease in patients with good performance status, maintain neoadjuvant and adjuvant chemotherapy but opt for the shortest possible protocols and prioritize oral chemotherapy in the metastatic setting (Gligorov et al., 2020).
- In gynecological cancer, the FRANCOGYN group for the CNGOF propose recommendations that do not differ much from the standard of care, except that they emphasize on radio-chemotherapy in the first line setting for cervical cancer instead of surgical treatment, and on the neoadjuvant chemotherapy for advanced ovarian cancer even for tumors that are judged to be resectable in order to reduce high risk surgeries and long ICU stays (Akladios et al., 2020). Note that similar suggestions were proposed by a multinational group of practitioners (Ramirez et al., 2020).
- In urological practice, a scheme of therapeutic options was proposed by a group of experts (Fizazi and pour les membres du bureau du Groupe d'étude des tumeurs uro-génitales, 2020) that meet the proposed guidelines of the CCAFU (Comité de Cancérologie de l'Association Française d'Urologie (Mejean et al., 2020): maintain treatment of every curable disease with possible delay of surgery for very small stable renal tumors, encourage active surveillance for low risk prostate cancer, privilege neoadjuvant hormone therapy with differed radiotherapy for intermediate or high risk localized prostate cancer over surgery, discuss neoadjuvant chemotherapy for operable bladder cancer and choose less toxic chemotherapy with use of G-CSF to avoid neutropenia. As for advanced disease, those recommendations agree on minimizing the risk of immunosuppression by avoiding corticosteroids for prostate cancer, substituting highly myelotoxic protocols with fewer toxic ones (gemzar-cisplatin instead of MVAC) with G-CSF use. However, the safety of immunotherapy for renal and urothelial carcinomas remains controversial and should be discussed on a case-by-case basis.
- In sarcoma, The French Sarcoma group issued recommendations that encourage maintaining neoadjuvant and adjuvant chemotherapy and radiotherapy for all patients who are not suspected to have a SARS-CoV-2 infection, and advise to ensure post-operative resuscitation capacities for high risk surgeries (Penel et al., 2020).

### 3.4.4. International guidelines and recommendations

Recently, a huge effort was made by various oncology societies and national authorities to implement recommendations that help practitioners in decision making on cancer care during the SARS-CoV-2 pandemic. An international collaborative group reviewed the challenges encountered in cancer care and proposed some practical measures for the management of cancer patients based on the available data on the 26th of March (Al-Shamsi et al., 2020). International guidelines

were issued with common general principles, and few particularities that emerge from every society's experience (Burki, 2020b).

- In hematology, researchers are most interested in hematopoietic stem cell transplantation, first because of a higher risk of infection in neutropenic patients, and second because of the risk carried by stem cells donation, transportation and preservation as well as the difficulty to find donors with travel bans (Szer et al., 2020; Dholaria and Savani, 2020). A reported case of a Chinese patient who was treated with Cyclosporine A seven months following a bone marrow transplantation for AML and who died after acquiring a COVID-19 infection despite getting adequate care suggests that physicians should rethink the transplantation practice during the pandemic. The European Society of Blood and Marrow Transplantation EBMT issued recommendations to protect patients during the COVID-19 outbreak. They consist of differing transplantation for confirmed cases at least 3 months for low risk disease or until recovery for high risk disease. Symptomatic patients should be screened with multiplex PCR (with or without COVID-19 RT-PCR) and the intervention should be deferred if possible. Deferral also applies for patients who have close contact with a positive case (and is strongly recommended for low risk patients) and COVID-19 PCR should be drawn in this case. Patients traveling from an endemic region should be isolated and have their intervention deferred for 14–21 days especially in low risk disease. As for donors, those who have a confirmed infection with COVID-19 must be excluded from donation. Those who were close contacts with a positive patient or who are travelling from an endemic zone have to be excluded for 21–28 days and isolated with close monitoring of symptoms (EBMT, 2020).
- In breast cancer, guidelines on radiation therapy were issued by an international group of practitioners (Coles et al., 2020) and insisted on the following:
  - o Avoiding radiotherapy for patients 65 years or older with invasive breast cancer without adverse features who are planned for hormone therapy.
  - o Delivering only 5 fractions for patients with node negative tumors that do not require a boost.
  - o Considering omitting nodal radiotherapy in post-menopausal women who require whole breast radiotherapy following sentinel lymph node biopsy and primary surgery without adverse pathological features.
  - o Privileging moderate hypofractionation for all breast/chest wall and nodal radiotherapy.
- Finally, Masumi Ueda et al published their recommendations in the Journal of National Comprehensive Care Network (JNCCN) on cancer care during the COVID-19 crisis based on their experience in three institutions at the epicenter of the disease in the United States. They focused on the following (Ueda et al., 2020):
  - o Reinforcing the environmental control for an effective triage of patients by forming a multidisciplinary “incident command structure” in cancer centers.
  - o Expanding telemedicine for outpatient care.
  - o Maintaining adjuvant therapy with curative intent for solid tumors.
  - o Considering maintaining therapy for metastatic disease to minimize hospital admission for symptom palliation.
  - o Prioritizing surgical interventions for cancer patients based on the rapidity of disease evolution.
  - o Limiting enrollment in clinical trials to patients who are most likely to benefit from it.
  - o Discussing palliative care and end-of-life for COVID-19 positive patients with advanced cancer to limit unnecessary ICU admissions and mechanical ventilation.
  - o Providing emotional and physical support for healthcare workers, as well as protective measures for those of them who have chronic conditions that predispose them to the complications of the

COVID-19 infection.

#### 4. Conclusion

In spite of all the efforts that are made, finding the ideal approach for cancer patients in the middle of the threat of the COVID-19 is not evident. As we are writing this paper the number of cancer patients tested positive is increasing, the capacity of some cancer centers is overwhelmed, and new guidelines are being issued by local and national authorities. The approach of cancer patients must be dynamic and tailored to every patient's condition, every hospital's resources and every physician's experience. Oncologists must keep in mind that beyond any scientific speculations, if the COVID-19 outbreak extends, the risk of unavailability of high-level care in oncology would be greater than that of a SARS-CoV-2 infection in a cancer patient.

#### Declaration of Competing Interest

The authors confirm that they do not have any conflict of interest.

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