Dealing with lung cancer in the COVID-19 scenario (A review)

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Abstract. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has caused the coronavirus disease 2019 (COVID-19), first appeared in December 2019 in Wuhan (China) and quickly spread worldwide and has since been assigned a pandemic status. This affected the worlds' social interactions, including within medical practices, thus interfering with routine treatments for a variety of diseases including cancer. Different studies have addressed the fact that patients with cancer are often immunocompromised, making them more susceptible to infections. Since COVID-19 frequently causes respiratory distress, patients with lung cancer are considered to be a high-risk group. Genes that have been indicated to mediate viral entry into host cells such as angiotensin-converting enzyme 2 and transmembrane protease serine 2 are expressed in the lung tissue, a fact that could partially explain COVID-19 pathogenesis and lung involvement. Therefore, the current study offers a disease overview including molecular aspects behind the infection and provide a perspective on already published Chinese data plus recommendations for the management of lung cancer patients according to the two main lung cancer types and stages: non-small cell lung cancer and small cell lung cancer. This review aimed to add to the collective effort of selecting the most appropriate guidelines to follow for the treatment of these patients.

Contents

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus strain responsible for coronavirus disease 2019 (COVID-19) which started in December 2019 in Wuhan (China). The disease became a pandemic in a brief period and the number of infected cases still keep growing worldwide. Up to the 25th of June, the WHO (World Health Organization) released a report counting 9,296,202 cases total confirmed cases globally and 1,145,906 cases in Brazil (1).

COVID-19 is caused by a virus belonging to the coronaviruses family of single-stranded RNA which can infect both humans and some animals (2,3). Upon infection, patients' symptoms are variable. Huang and colleagues published the clinical features of 41 infected patients and observed that the most common clinical symptoms were fever, dry cough, dyspnoea, and bilateral ground-glass opacities on chest computed tomography (CT) scans (4). Patients also had pneumonia and other complications including acute respiratory distress syndrome followed by RNAaemia, acute cardiac injury and secondary infection (4). The level of disease severity could be attributed to different factors such as age, presence of comorbid health conditions and also the viral load of SARS-CoV-2, which was indicated as a potential marker for assessing disease severity and prognosis (5). The higher the viral load, the severe were the clinical outcomes in patients, which also presented a long virus-shedding period (5). The time of symptom's onset varies, however most patients will develop symptoms within 11.5 days with a median incubation period of approximately 5.1 days (6). Most patients who recovered from SARS-CoV-2 infection showed the greatest severity of lung disease on CT-scans at around 10 days after the initial onset of symptoms and the chest CT image improvements appeared at approximately 14 days (7). Current diagnostic tests involve reverse transcription-polymerase chain reaction (RT-PCR) using nasal swab (8), tracheal aspirate or bronchoalveolar lavage samples

which detect active infections (9) and serological testing that can detect an active and also past infection (10). A Cochrane database systematic review recently addressed the diagnostic accuracy of different SARS-CoV-2 antibody tests (11). This study collected, and analysed, results from different reports for IgG, IgM, IgA, total antibodies and IgG/IgM and overall they presented low sensitivity during the first week since onset of symptoms (all less than 30.1%) and the sensitivity increased in the second week, presenting higher values in the third week. Besides, they mentioned that there were not enough studies to evaluate sensitivity of tests beyond 35 days post-symptom onset (11).

Fig. 1 summarises the main symptoms, diagnostic methods and CT-scan findings upon SARS-CoV-2 infection.

2. Cancer and COVID-19

The routine diagnoses and treatments for different diseases including cancer were largely affected by the pandemic outbreak. It is well known that cancer patients are often immunocompromised, which make them more vulnerable than others to infections. For example, when the impact of other infections on cancer patients were analysed, such as the retrospective study analysing influenza A (H1N1), these patients were shown to be more prone to suffer severe symptoms and worse outcomes than the general population (12). Very few studies to date have addressed this issue concerning COVID-19. A recent article published by The Lancet Oncology stated that patients with cancer had a higher risk of severe symptoms and poor outcomes upon COVID-19 infection than patients without cancer (13). Another Chinese study reported that in 1,524 cancer patients, a 2-fold increased risk of COVID-19 infection was observed when compared with the general population (14). Besides, the China Centres for Disease Control and Prevention, after analysing 44,672 laboratory-confirmed cases nationwide, found 2.3% case fatality rate of COVID-19 in the overall population, whereas for cancer patients alone the rate was higher, 5.6% (15). Consequently, the WHO and CDC websites recommend that confirmed COVID-19 patients should be assessed for holding their cancer treatment regimens until they are clear of the infection (16,17).

The mechanism of viral entry into cells and the molecular machinery involved in this process could also explain the disease severity and pathophysiological response of the human host. In the following section, we will discuss briefly one of the mechanisms described for this viral-host interaction.

3. SARS-CoV-2 entry into host cells

There are currently seven different coronaviruses known to infect humans: MERS-CoV, SARS-CoV, SARS-CoV-2, NL63, HKU1, OC43 and 229E. The first three are known to be more severe than the last four (18). They are a large family of single-stranded enveloped RNA viruses which have an envelope-anchored spike protein (the transmembrane spike glycoprotein or S-protein) responsible to mediate its entry into host cells via membrane fusion (19). SARS-CoV-2 genome shows variability in the region called the receptor-binding domain (RBD) in the spike protein and this variability can influence the host range of the SARS-CoV viruses (20,21). The RBD domain of SARS-CoV-2 S-protein has an affinity and recognizes angiotensin-converting enzyme 2 (ACE2) receptors from humans and other species (22). Interestingly, experiments showed that ACE2 knockout diminishes viral infection and replication in mice infected with another type of coronavirus, the SARS-CoV (23) that has a S-protein 80% homologous with the one from SARS-CoV-2 (24). These infected mice were shown to present acute respiratory failure and lung parenchymal injury (23). Regarding structural analysis, the crystal structure of the C-terminal domain of SARS-CoV-2 S-protein in complex with human ACE2 revealed an ACE2-binding mode similar to that observed for SARS-CoV (25). This information could shed a light in the pursuit of effective treatments.

Coronaviruses entry into host cells involve several pathways, including endosomal and non-endosomal, in the presence of different proteases (26-29). In addition to ACE2 receptor, the viral entry was also shown to rely on transmembrane protease serine 2 (TMPRSS2) protease activity which is involved in the priming step of the S-protein (30). In addition, the SARS-CoV-2 cell entrance was shown to be blocked by a TMPRSS2 inhibitor (30). Fig. 2A shows a simplified illustration of SARS-CoV-2 coming closer to the host membrane where ACE2 and TMPRSS2 are membrane-bound. Also, Fig. 2B shows a summary of how ACE2 and TMPRSS2 expression varies in different tissues according to different published data. For example, both genes are expressed in the lung, specially at the alveolar epithelial type II cells. Furthermore, ACE2 is also expressed in other organs such as colon, kidney, blood vessels, nasal epithelium, the mucosa of oral cavity and cornea, which are considered a high risk of infection route (26,31-33). Interestingly, a recent report identified a higher expression of ACE2 in samples of severe COVID-19 patients with comorbidities than those of control individuals (34). Noteworthy, scientists have suggested analysing circulating blood levels of ACE2 as a prognostic indicator for monitoring COVID-infection (35).

Both SARS-CoV and SARS-CoV-2 use ACE2 as a cell surface receptor and TMPRSS2 as the most important protease that facilitates their entry into the host cell (30,24). However, SARS-CoV-2, but not SARS-CoV, also contains a FURIN cleavage site in its S- protein, potentially increasing its priming upon ACE2 receptor binding (36). Therefore, the S- protein cleavage at the FURIN protease site could be responsible for the increased binding affinity of SARS-CoV-2 to the ACE2 receptor. Interestingly, FURIN was also shown to be highly expressed in the lung tissue, being also found co-expressed with ACE2 and TMPRSS2 (37). The involvement of these genes in the viral infection process and their confirmed expression in the lungs might contribute to the severe pulmonary injury observed in some SARS-CoV-2 infected patients. Possibly, alterations in their expression patterns, or even mutations, could be one of the causes for the variability seen in terms of disease severity among patients. Hence, these same genes could be considered as potential therapeutic candidates for the disease treatment. In addition, structural biology experiments on the SARS-CoV-2 S-Proteins binding to ACE-2 and TMPRSS2, could allow the development of targeted therapies aimed to block these interactions (38).

The immune system also plays a vital role in SARS-CoV-2 infection and disease response. The haemophagocytic

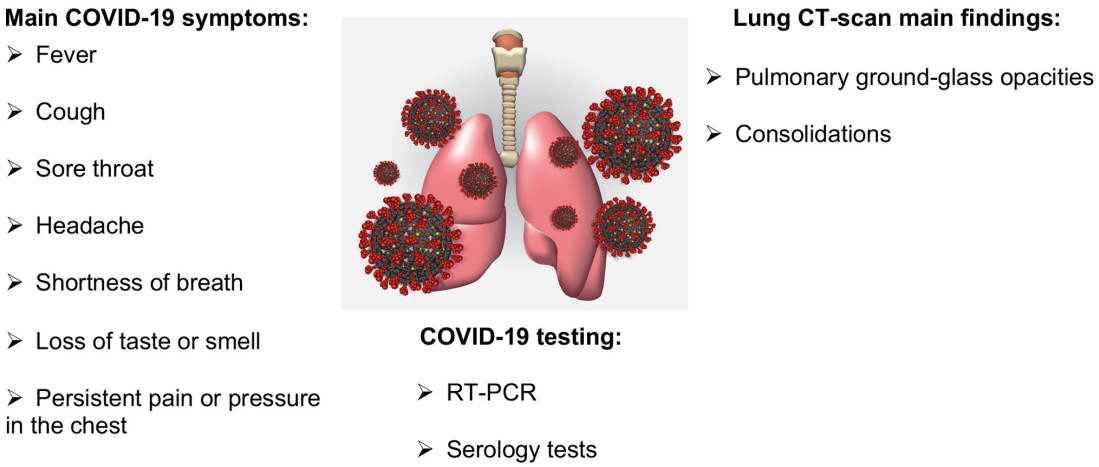


Figure 1. Summary of the main symptoms, diagnostic testing, and CT-scan findings upon SARS-CoV-2 infection. The lung with coronavirus image presented in this figure was created by pongpongching, and was downloaded from the website: www.freepik.com (attribution: Medical vector created by pongpongching - www.freepik.com). COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription-polymerase chain reaction; CT, computed tomography.

lymphohistiocytosis (sHLH) is an inflammatory syndrome known to cause rapid and fatal hypercytokinaemia with multiorgan failure, and this syndrome can be prompted by viral infections (4). Interestingly, COVID19 patients show a similar cytokine profile with elevated interleukins (IL-2 and IL-7), granulocyte- colony stimulating factor (G-CSF), interferon-γ inducible protein 10kD (IP-10), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1-α (MIP-1α), and tumour necrosis factor-α (TNF-α) (39). Patients will respond differently to treatment depending also on their immunosuppression status, with therapeutic options including steroids, intravenous immunoglobulin, selective cytokine blockade (e.g., anakinra or tocilizumab) and JAK inhibition (39). Therefore, a proper investigation on the patients' immune status is important, especially for cancer patients.

4. COVID-19 and Lung Cancer

Lung cancer is one of the deadliest cancers and data from the Brazilian National Cancer Institute (INCA) indicates it as the third most frequent cancer type in men and the fourth in women, whereas in the world it occupies the first position among men and third among women (40). Tobacco smoking is one of the greatest lung cancer risk factors (41). This cancer is divided into two major cell types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), comprising 15 and 85% of all lung cancer, respectively (42). In addition, NSCLC is further separated into the three subtypes: Adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The histology and genetic profile of lung cancer are important factors for treatment choices and preventive strategies. Current treatment options involve surgery, adjuvant and neoadjuvant therapies, chemotherapy, radiotherapy, targeted therapy and immunotherapy.

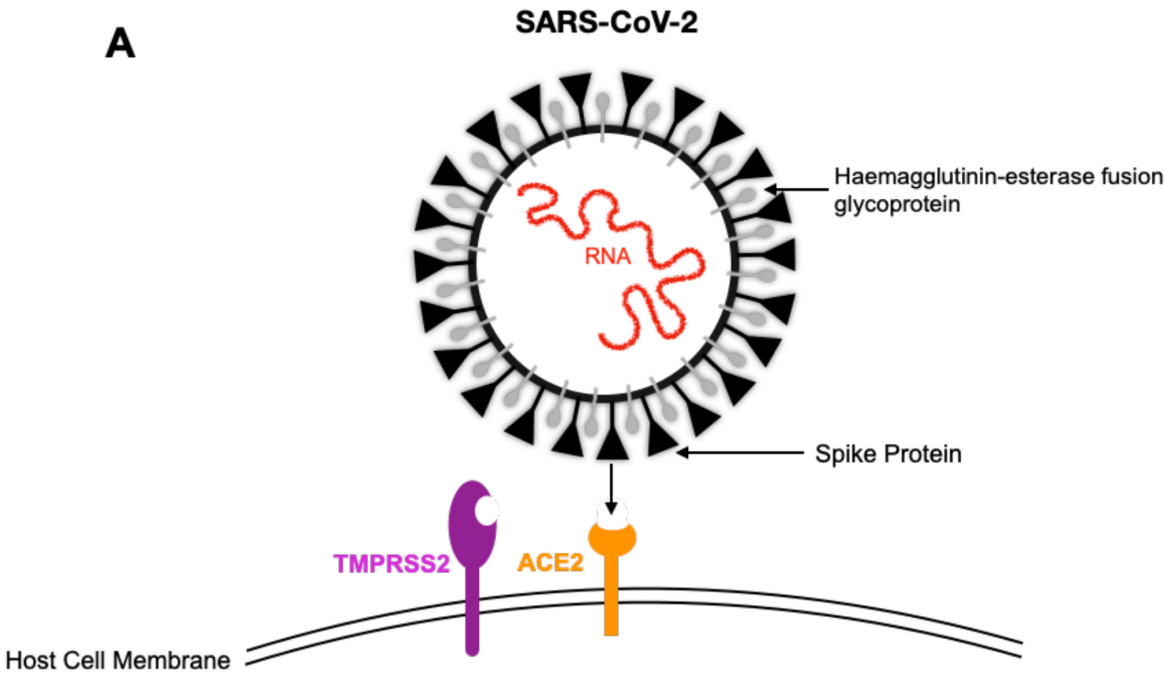
COVID-19 frequently causes respiratory distress that may result in progressive respiratory failure, rendering the lung a key player in the disease process. Hence, the presence of lung tumours could decrease the patient's capacity to recover as faster as other patients with healthy lungs. Interestingly, lung cancer was shown to be the most frequent cancer type in SARS-CoV-2 infected patients when 2,007 cases from 575 Chinese hospitals were investigated (13). Furthermore, a retrospective case study including cancer patients from three different Chinese hospitals, with laboratory confirmation of COVID-19, also identified lung cancer as the most frequent cancer type (43).

The frequent pneumonia observed in COVID-19 patients could be a consequence of the expression of ACE2 by epithelial cells of the lung as aforementioned. Regarding the molecular aspects of lung cancer in relation to COVID-19, the ACE2 and TMPRSS2 gene expression levels were investigated and correlated to prognosis in lung adenocarcinoma and lung squamous cell carcinoma, and surprisingly, TMPRSS2 was downregulated in lung adenocarcinoma compared to normal tissues (44). ACE2 gene expression was shown to be higher in lung adenocarcinoma than in normal lung tissues, whereas for lung squamous cell carcinoma they were similar (44).

Inflammatory pathways in cancer patients could be associated with decreased immune surveillance (45). Hence, SARS-CoV-2 infection could lead to an inflammation scenario that may even help tumour growth, a process called pro-tumour inflammation (PTI) (45). PTI could lead to worse outcomes among patients with NSCLC suggesting the stratification of lung cancer patients according to their immunosuppression profile. This results in a more personalized treatment to fight both inflammation and tumour growth in order to improve mortality rates.

In the face of that, it has become increasingly important to suggest clinical recommendations for lung cancer management during the pandemic. Some Chinese doctors have addressed this issue and indicated that for patients with lung occupying lesions, the whole process of diagnosis and treatment should not be carried out as usual (46). They also proposed that the timing of surgical intervention should be very carefully analysed (46). The European Institute of Oncology, IRCCS from Milan (Italy) proposed to take in consideration the following factors: lung cancer stage, histology, treatment type,

A



B

Genes	Levels of expression in Tissues		
	Low	Medium	High
ACE2	blood, spleen, bone marrow, brain, blood vessels, and muscle.	lungs, colon, liver, bladder, and adrenal gland.	small intestine, male tissues, kidneys, heart, thyroid, and adipose tissue.
TMPRSS2	blood, spleen , brain, blood vessels, adipose tissue and muscle.	bone marrow, Liver and gallbladder.	small intestine, stomach, Lungs, salivary gland, pancreas and prostate.

Figure 2. Important genes involved in the interaction between SARS-CoV-2 and the host membranes. (A) A simplified illustration of SARS-CoV-2 approaching the host-cell membrane. The host cell viral entry depends on the interaction with the receptor ACE2 and the serine protease TMPRSS2 that is used by SARS-CoV-2 for S-protein priming (30). (B) The ACE2 and TMPRSS2 variable expression in human tissues based on data available from *genecards* (https://www.genecards.org) and also based on recent publications (37,54). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin-converting enzyme 2; TMPRSS2, transmembrane protease serine 2.

presence of comorbidities, performance status (PS) and recent pneumonitis (47).

Not such a report has been published in South America, therefore we aim to draw attention to the hard task that oncologists and cancer translational teams are facing to properly advice their patients in a critical situation as this, since infections put the already vulnerable cancer patients at further risks.

5. Recommendations to manage lung cancer patients from a Brazilian perspective

In a large and developing country such as Brazil, it is highly important to critically implement effective primary preventive measures to avoid unwanted exposure of cancer patients to infections such as SARS-CoV-2 and to deal with cancer patients routine during pandemic times. Accordingly, three questions stand out: Are the patients currently receiving immune-suppressive treatments at higher risk of bad outcomes or this also depends on their clinicopathologic characteristics? Do patients receiving anti-programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) immunotherapy face additional risks? Should postponing surgery and neoadjuvant chemotherapy be considered in certain cases? Patients undergoing different treatments such as radiation, surgery or chemotherapy are probably more immunosuppressed and need to be extra careful to avoid unwanted infections, therefore visits to hospitals and surgical procedures could be reduced as much as possible by limiting them to the most urgent cases. This was also mentioned by a recent study from Kumar *et al*, which suggested a reduction in the number of visits to a health care facility in order to reduce chances of contracting the

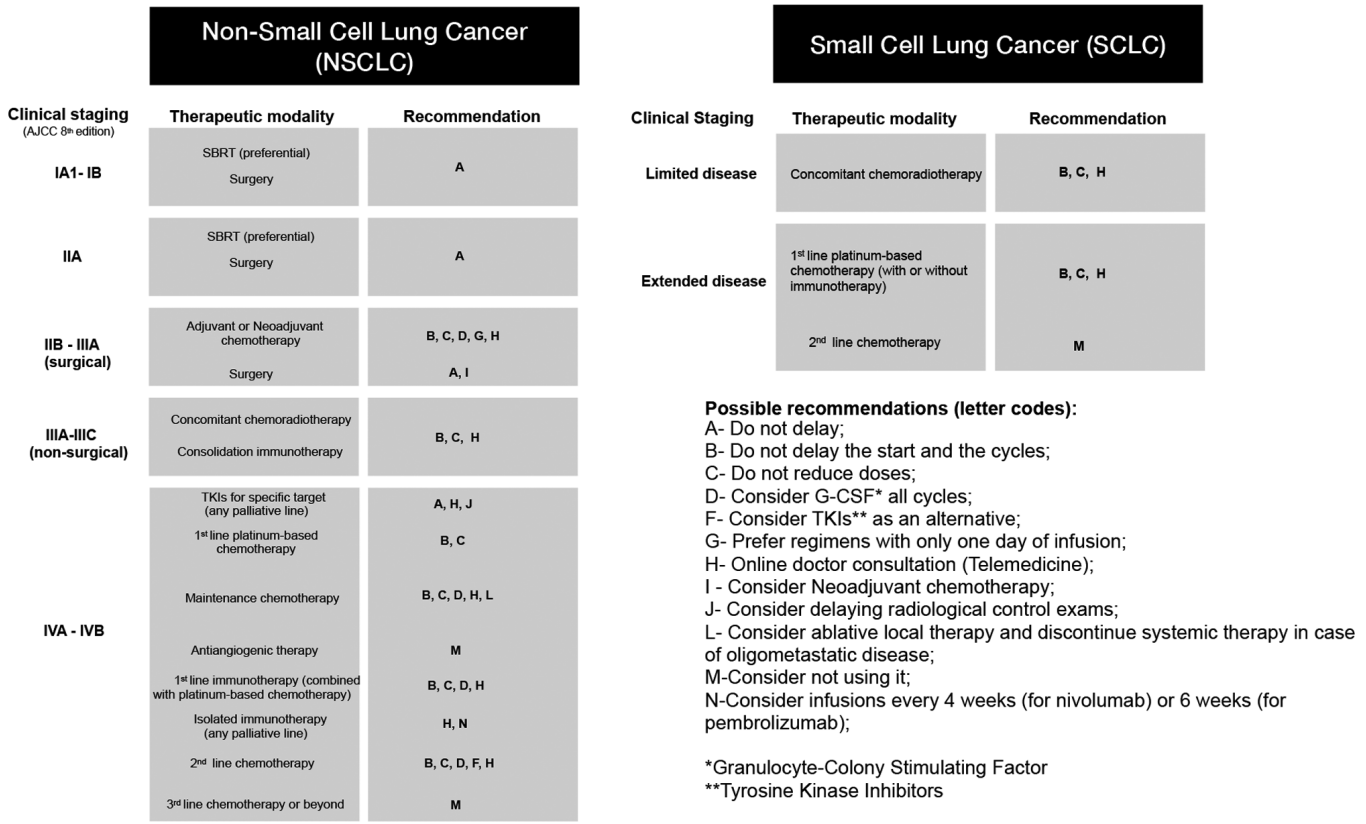


Figure 3. Summary of clinical recommendations for NSCLC and SCLC patients during coronavirus outbreak. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; AJCC, American Joint Committee on Cancer; SBRT, Sociedade Brasileira de Radioterapia; G-CSF, granulocyte colony-stimulating factor; TKI, tyrosine kinase inhibitor.

virus while keep providing effective oncologic therapy (48). For patients with concerning symptoms, the ideal would be testing for COVID-19 at a drive-through facility or at home (lab home-service). Whereas, in the case of severe symptoms the test should be performed upon arrival at the hospital emergency area. Doctors should also pay attention to their patients and consider which drug therapies should be applied, limited or decreased to lower levels in the case of positive SARS-CoV-2 infection.

At INCA, patients are being evaluated following the Brazilian Ministry of health advice. For patients with tumours requiring resection, the idea is to keep the schedule unless the patients, with symptoms, test positive for COVID-19. Since some patients are asymptomatic, having them tested before surgery would be recommendable. For the infected patients, the recommendation would be to wait the necessary time until the patients are free from the virus. In the case of suspicion of infection, and no immediate molecular test available, pneumologists recommend that the CT-scan should be the preferred exam since the X-ray might not give all the resolution needed do distinguish infected from non-infected cases before molecular testing. Although there is not enough evidence of strict association between CT-scan results and COVID-19 infection, it was shown that the CT-scans from COVID-19 patients exhibit different patterns when compared to CT-scans from bacterial pneumonia, the first showing multiple ground-glass opacities with consolidations (4,49). If the images exhibit a total lung involvement greater than 50% plus abnormal O_2 saturation, the patient should be considered as high risk when compared to total lung involvement below 50% with normal O_2 saturation. Regarding pulmonary sequelae after coronavirus pneumonia, we still need more time to evaluate this issue, although there are some discussions concerning the possibility that certain cases may evolve early to pulmonary fibrosis.

After covering information available from the Chinese and local experts, we summarise in Fig. 3 what could be a feasible recommendation during the coronavirus pandemic, for the management of both, NSCLC and SCLC patients. It is important to note that all recommendations are based on expert opinions and are primarily based on seeking therapeutic alternatives that aim to reduce the time of these patients within hospitals and clinics during the pandemic period. These alternatives, however, are strategies already used in clinical practice and all proposals aim to ensure that proven effective treatments are offered. While the presentation of COVID-19 in a more severe way is a possibility for these patients, lung cancer and its aggressiveness are a certainty. Thus, for patients with early stage disease, we suggest a preference for stereotactic body radiotherapy (SBRT) over surgery. For those patients who need surgery and complementary systemic treatment, we suggest performing neoadjuvant chemotherapy with the intention of extending the surgery to a second moment, possibly post pandemic. Regarding platinum-based chemotherapy, we recommend a reduction in the threshold for G-CSF prophylactic use, that no random dose reductions or infusion delays are performed and that the combination with antiangiogenics

should be discouraged, considering a borderline benefit and increased toxicity. For oligometastatic disease, the use of local ablative therapy for all lesions seems to be a better alternative than the continuation of maintenance chemotherapy. Infusions of immunotherapies every 4 (nivolumab) or 6 (pembrolizumab) weeks are desirable instead of every 2 or 3 weeks. When available, oral drugs are preferable and online consultations should be encouraged.

Although more variables could be considered such as age and other comorbidities, there is no universal solution and each case should still be analysed in a personalized manner by the oncologists in charge. Thereby, we based our recommendations mainly on the lung cancer type and stage. Whenever possible, the treatments with a survival benefit should be carried on and the overall risk/benefit ratio should be taken in consideration. In addition, proper information guidance should be undertaken to instruct patients, along with their family members, to increase awareness concerning personal protective measures such as social distancing, constant hand hygiene, the use of masks, and close surveillance by their doctors via telemedicine, for example. In fact, an increasing number of studies are being published pointing out the importance of telemedicine in COVID-19 patient screening and follow-up (47,50,51). These organised and efficient COVID-19 related measures were shown to significantly benefit patients by identifying in advance the ones with suspected symptoms, limiting the need of face-to-face contact at cancer centres (47). It is also important to point out that it is hard to predict how long this pandemic will last, a fact that could interfere with current clinical recommendations. Hopefully, our point of view will be helpful for the local and international community which are fighting non-stop to beat COVID-19.

6. Current Brazilian experience: What have we learned so far?

While the pandemic was spreading across the country, there was an expected increase in the fear of cancer patients, including those with lung cancer. The main concern was to leave home for medical appointments, diagnostic tests or therapeutic procedures. Nevertheless, even at the beginning of the pandemic, two important measures were taken to potentially relieve the negative impacts of the pandemic on the patients' treatment: The first was a very early position by the Brazilian Society of Clinical Oncology (SBOC) (52) emphasizing not only the importance of continuing oncological treatment, but also the discussion with the attending oncologist regarding possible adjustments in therapeutic planning, measures of social distance, the use of masks, and hand hygiene (52); The second was the approval of a governmental bill authorizing telemedicine in the country (53), which was regulated by the Federal Council of Medicine (CFM). These initiatives guaranteed lung cancer patients a safer access to their oncologist, generating greater confidence regarding the continuity of their disease monitoring.

It is important to point out that although the pandemic initially generated great concerns related to treatment losses, reductions and delays in diagnosis in the lung cancer patient population, after few months what many Brazilian oncologists have noticed is quite the opposite. This occurred probably due to a lower threshold for indicating chest CT scans in the country's emergency services resulting in different consequences such as some patients obtaining early COVID-19 diagnosis, while others were incidentally diagnosed with other lung diseases such as lung cancer in the early stages. Therefore, it will be interesting to compare, in the near future, lung cancer data in the year 2020 with historical data.

7. Concluding remarks and future perspectives

Management of patients with cancer, and specially lung cancer, is not an easy task in the everyday medical routine, thus it is reasonable to imagine the tremendous amount of effort the multidisciplinary oncology teams have to cope with during the troubled times such as the one we are facing with the COVID-19 pandemic. The challenge of not having a vaccine or effective therapy yet, only makes things more complicated. Therefore, the implementation of organised and structured interventions in healthcare practice is crucial to enhance effectiveness and improve patient care. Planning and building strategies such as recommendation guidelines for the particularly vulnerable can optimise time and lives in pandemic emergencies. Under stressful and unprecedented times, cancer patients are facing an extra burden which can be softened by personalising their treatment and maintaining them in close surveillance.

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VA conceived the idea for the review and contributed with the molecular and translational aspects discussed, whereas PDM, MZ and CGF contributed with their vast clinical expertise. VA, PDM, MZ and CGF wrote the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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