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Recommendations for detection, prioritization, and treatment of thoracic oncology patients during the COVID-19 pandemic: the THOCOoP cooperative group

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ABSTRACT

The world currently faces a pandemic due to SARS-CoV-2. Relevant information has emerged regarding the higher risk of poor outcomes in lung cancer patients. As such, lung cancer patients must be prioritized in terms of prevention, detection and treatment. On May 7th, 45 experts in thoracic cancers from 11 different countries were invited to participate. A core panel of experts regarding thoracic oncology care amidst the pandemic gathered virtually, and a total of 60 initial recommendations were drafted based on available evidence, 2 questions were deleted due to conflicting evidence. By May 16th, 44 experts had agreed to participate, and voted on each of the 58 recommendation using a Delphi panel on a live voting event. Consensus was reached regarding the recommendations (> 66 % strongly agree/agree) for 56 questions. Strong consensus (> 80 % strongly agree/agree) was reached for 44 questions. Patients with lung cancer represent a particularly vulnerable population during this time. Special care must be taken to maintain treatment while avoiding exposure.

1. Introduction

1.1. The COVID-19 pandemic

At the end of 2019, an outbreak of cases of atypical pneumonia was documented in China. The etiological agent was identified as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), and the disease was later known as COVID-19. From that initial site, COVID-19 has been transmitted in an accelerated manner, until it was declared a pandemic by World Health Organization (WHO) on March 11th, 2020, when over 118,000 cases in 114 countries and 4291 deaths had been reported (Shi et al., 2020). In Latin America, the first confirmed case of COVID-19 was documented on February 25, 2020, in a patient from Brazil who came from Milan, Italy (Rodriguez-Morales et al., 2020). Up to May 19th there were 4,979,480 reported cases worldwide, with more than 1,500,000 arising in America.

The lethality of this virus has been variable according to the geographical situation, age, and comorbidities. The WHO estimated a global mortality rate of 3.4 %, ranging from 0.4 % in some small communities from China to more than 7.0 % in countries like Italy.

The clinical manifestations and case fatality rates are greater for the elderly population, smokers, and those with cardiovascular disease (Onder et al., 2020). This is also true for patients who have any type of cancer, especially those with lung cancer, as many of the patients are previous or current smokers and have other comorbidities like chronic obstructive pulmonary disease (COPD), and an impaired immunity due to cancer treatment.

There are some reports related with outcomes in patients infected with COVID-19 and cancer, the first data came from China by Zhang et al., in which patients with SARS-CoV-2 infection and cancer had a rapidly fatal evolution and a more severe disease compared with patients without cancer (13 vs. 43 days) The number of patients that progressed to severe disease is approximately 5 times larger in cancer patients compared with the general population (39 % vs. 8%, $p = 0.0003$). In this analysis, 5 of those patients (28 %) had lung cancer (Zhang et al., 2020).

In another study of 105 cancer patients infected with COVID-19, reported in the 2020 AACR (Dai) the authors documented that lung cancer (22 cases corresponding to 21 %) was the most common type of cancer in these series, followed by gastrointestinal, breast cancer, thyroid and hematological malignancies. Compared with a control group without malignancies of 536 patients with COVID-19, cancer patients had a higher risk of death, (OR = 2.34 $P = 0.03$), admission to the ICU (OR = 2.84, $p = < 0.01$), development of serious symptoms (OR = 2.79, $P = < 0.1$) and a higher probability of requiring mechanical ventilation (Dai et al., 2020). Patients with lung cancer ($n = 22$) included in this analysis represented the group with the second highest risk of complications, preceded only by hematological tumors, 4 died (18.8 %), 6 (27.7 %) were admitted to the ICU, 11 (50 %) developed serious symptoms and 4 (18.8 %) required mechanical ventilation. (Dai et al., 2020)

developed serious symptoms and 4 (18.8 %) required mechanical ventilation. (Dai et al., 2020)

Likewise, during the AACR congress, Garassino et al. reported the preliminary results of the global registry TERA-VOLT, a collaboration of 21 countries aimed to evaluate the impact of COVID-19 infection on patients with thoracic malignancies. This initial report included 200 patients in 8 countries, the median age was 68 years, and 29.5 % of patients were women. The most common histology was non-small cell lung cancer (NSCLC), in 75.5 %, and small cell lung cancer (SCLC), in 14.5 %. 73.5 % of the included patients had clinical stage IV-disease. Among these patients, 152 (76 %) were hospitalized and 66 (33.3 %) died, most of them without undergoing admission to intensive therapy units, suggesting an unexpectedly high mortality among this patient population, Univariate analysis showed that the presence of COPD was associated with the risk of hospitalization and more than one comorbidity with the risk of hospitalization and death.

It has become seemingly clear that the COVID-19 pandemic is a global health problem, with increasing trends in most world regions, including America. As such, public policies have been implemented to counteract the effect on health systems. Given the exponential increase in cases, hospitals have undergone considerable adaptations to offer care for patients with COVID-19, many of which require intensive care management. However, this refocusing has affected the care of patients with other serious diseases, including cancer care. In this regard, the urgent need for an adequate allocation and rational use of health systems is evident. The WHO states that “governments and health systems have an obligation to ensure, to the best of their ability, adequate provision of health care for all”. When this guarantee is flailing due to the current pandemic, the prioritization and rational use of resources should, to the best of our ability, be based upon evidence-based recommendations, particularly in time-sensitive conditions. Delivery of standard-of-care for every patient at any moment should be the goal of all health providers. In the extreme case where saturated or collapsed health care systems challenge the *status quo*, a guideline of evidence-based recommendations which can be implemented provisionally without impacting long-term outcomes can aid decision making in the clinical setting.

The current challenges faced by cancer patients include, among others, the need for traveling, rescheduling previous appointments, and cancellations in clinical visits, as well as delaying of dates of diagnostic and extension studies. Furthermore, the access to potentially curative oncological surgeries has been reduced significantly. In Italy during the year of 2019, 371,000 cancer cases were diagnosed of which 80 % were surgical candidates, and due to the COVID-19 pandemic, the number of surgeries has decreased in the last 30 days (Restivo et al., 2020).

This change and prioritization of health systems in the care of patients with COVID-19 has led professionals in the field of oncology to make decisions about which patients should receive oncological treatment. There are already some guidelines and consensus, for the

Table 1
Results for each question as voted by the consensus of experts.

QUESTION/RECOMMENDATION	CATEGORY 1	CATEGORY 2	CATEGORY 3	CONSENSUS
General recommendations				
Do patients with thoracic malignancies need to be treated preferably through virtual resources when possible reducing hospital visits? Patients with thoracic neoplasms must be followed and whenever possible treated through virtual resources thus avoiding hospital visits	89 %	11 %	0	YES (STRONG)
Do you recommend patients use personal protection equipment (PPE) for special occasions (visits, imaging studies, treatment) when it is strictly necessary to go out of their homes? All patients with thoracic malignancies must be reinforced to use PPE every time they need to go out of their homes.	91 %	9%	0	YES (STRONG)
Detection of SARS-CoV-2				
Does every patient with a thoracic neoplasm need a baseline CT-scan as a first screening test? It is recommended to perform a CT-scan, where available and accessible to patients, as the first detection test, intentionally searching for radiographic findings of COVID-19, especially before initiating treatment in cancer patients	77	10	13	YES (STRONG)
Does every patient with a thoracic neoplasm need a SARS-CoV-2 PCR test to rule out active disease? Ideally every cancer patient will need a SARS CoV-2 PCR test to rule out active COVID-19, especially if there is a suspicious CT-scan.	60	14	26	YES
Could blood cell count-based tests have a role in the screening of cancer patients with suspicious COVID-19 clinical features? Blood cell count and SARS CoV2 RT-PCR is recommended in patients with a suspicious CT- scan.	29	40	31	YES
Diagnosis and staging				
Do you recommend that all cases continue to be evaluated by a multidisciplinary team, ideally in using virtual resources (i.e. virtual tumor boards)? A multidisciplinary team that works collaboratively optimizing available resources and ensuring quality care should evaluate case by case through virtual platform meetings.	100			YES (STRONG)
Do you recommend avoiding the delay in diagnostic approaches for thoracic malignancies? Every patient with a thoracic malignancy must undergo appropriate initial diagnosis, considering available resources, avoiding impacting on their prognosis.	86	6	8	YES (STRONG)
In patients in need of pleural fluid drainage at diagnosis, would you prefer indwelling pleural catheter (IPC) insertion over pleurodesis? Procedures with ambulatory/short hospital stay must be preferred over procedures that require longer inpatient stay	51	23	26	YES
Suspected or confirmed diagnosis of COVID-19				
Should medical treatment for thoracic malignancies (chemotherapy, immunotherapy, or targeted therapy) be suspended in patients with a suspected or confirmed diagnosis of COVID-19? Patients should stop active treatment if a suspected or confirmed diagnosis of COVID-19 is present	77	9	14	YES (STRONG)
Post-COVID-19 status				
Would you consider it safe to restart cancer treatment in patients who have resolved all symptoms from SARS-CoV-2? Patients could restart cancer treatment if symptoms have resolved. Consider the following parameters, individualizing case by case.	63	29	8	YES (STRONG)
General treatment recommendations				
Should all patients with a risk of developing neutropenia (> 10–15%), receive G-CSF? All patients with a neutropenia risk > 10–15 % should receive G-CSF, considering potential complications due to immunosuppressing effects.	56	30	14	YES (STRONG)
Early stage				
In the case of surgery for early-stage disease, could this be delayed for more than 3 months? Surgery should not be postponed. Delayed surgery can have long-term deleterious effects by increasing deaths attributed to cancer.	56	30	14	YES (STRONG)
Would you consider SBRT for T1 surgical patients considering potential delays and shortage in resources for surgery? SBRT could be an acceptable alternative option to treat tumors < 2.0 cm.	83	11	6	YES (STRONG)
Should patients with stage II-III NSCLC continue receiving adjuvant treatment? Adjuvant treatment should be offered, due to the clear benefit in OS.	56	30	14	YES (STRONG)
Would you prefer lower toxicity regimens such as Carboplatin/ Pemetrexed for adjuvant treatment? Carboplatin/ Pemetrexed could be the preferable option because of the toxicity profile.	56	31	13	YES (STRONG)
Would you consider adjuvant RT in patients with pathological N2 or R1 after surgery? RT could be offered as an adjuvant treatment but can be postponed after chemotherapy or 3 months after surgery.	45	33	22	YES
Would you consider an adjuvant hypofractionated approach? Hypofractionated radiotherapy is not recommended in this clinical scenario.	50	23	27	YES
Locally advanced disease				
Should every patient with locally advanced disease be treated with chemoradiation? Every patient should be considered for chemoradiation	71	21	8	YES (STRONG)
Would you prefer concurrent chemoradiation over a sequential approach? A concurrent approach is preferred, although sequential treatment can be kept in mind for specific cases in which toxicity is considerable.	73	25	2	YES (STRONG)
Should durvalumab be administered in a higher dose (1500 mg 4 w) to diminish the number of visits? Yes. The dose of 1500 mg Durvalumab is a safe regimen, though efficacy has not yet been conclusively stated.	46	38	16	YES (STRONG)
Would you prefer 3-weekly regimen concurrently with RT to reduce the hospital visits?	53	29	18	YES (STRONG)
No, the extra treatment duration and number of chemotherapy cycles can prolong immunosuppression unnecessarily.				
Is G-CSF use recommended for routine use? G-CSF should not be routinely used, only if neutropenia develops and represents an issue.	65	27	8	YES (STRONG)
Would you choose a hypofractionated schedule for sequential chemoradiation? Hypofractionated schedules in this clinical setting are not currently fully supported by available evidence. Nonetheless, the approach could be an option for treatment in some patients that have access to the technology.	65	27	8	YES
Advanced disease				
Do you consider a high priority to start systemic treatment in asymptomatic and symptomatic treatment naïve patients? Independently of symptoms and molecular tumor biology all patients with metastatic lung cancer in the first-line setting should be prioritized for treatment initiation.	85	0	15	YES

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Table 1 (continued)

QUESTION/RECOMMENDATION	CATEGORY 1	CATEGORY 2	CATEGORY 3	CONSENSUS
Can patients with oligometastatic disease start with systemic therapy alone, differing or postponing locally-aggressive strategies to metastatic sites? Patients with oligometastatic disease could start systemic treatment only while postponing radiotherapy or surgery for metastatic sites for safer scenarios.	67	30	3	YES (STRONG)
Would you consider postponing second-line treatment in asymptomatic patients (who do not show signs or suspicions of having COVID-19 infection) with contraindications for immunotherapy, or after a first-line treatment with a checkpoint inhibitor-based regimen? Considering risks and potential benefits, patients in second-line treatment suitable for chemotherapy in monotherapy may be delayed or postponed until progression (clinical or radiological).	30	54	16	YES (STRONG)
Would you consider postponing second-line treatment in asymptomatic patients (who do not show signs or suspicions of having COVID-19 infection) with oncogene driver mutations? Patients with oncogene driver mutations after progression to a first line TKI are high priority and ideally treatment should not be delayed	81	11	8	YES (STRONG)
Would you consider postponing second-line treatment in asymptomatic patients who are suitable for immunotherapy? Patients suitable for immunotherapy must be treated, ideally without delays.	73	22	5	YES (STRONG)
When carcinoembryonic antigen (CAE) is elevated in baseline, can we use this biomarker to monitor NSCLC response to treatment and avoid imaging studies? Serum carcinoembryonic antigen (CEA) could be considered in the monitoring of NSCLC patients to obtain prognostic and predictive information during the pandemic.	13	57	30	YES (STRONG)
Immunotherapy				
Considering the risk of pneumonitis and immunological effects, could immunotherapy be considered a safe treatment during the pandemic? Immunotherapy should be administered to all candidate patients. Until now, no evidence of an increased mortality has been documented, and a recent study shows PD-1 blockade in lung cancer is not associated with increased severity of COVID-19.	84	14	2	YES (STRONG)
Should you recommend using immunotherapy alone rather than combination treatments with immunotherapy and chemotherapy in patients with TPS $\geq 1-49\%$? Patients with a TPS $\geq 1-49\%$ and an increased risk of neutropenia or considerable toxicity should consider pembrolizumab monotherapy as an option in this current scenario.	45	29	26	YES
Should you recommend alternative regimens with longer intervals between treatment applications?	85	13	2	YES (STRONG)
Alternative regimens, like 4-weekly or 6-weekly regimens could be used safely during the pandemic to diminish visits to hospital.				
Tyrosine Kinase Inhibitors (TKIs)				
Do you consider TKIs treatment safe during pandemic? Patients on TKIs should be monitored for pulmonary symptoms in every visit or telephone call, but patients suitable to receive TKIs must do so.	82	10	8	YES (STRONG)
Do you recommend maintaining TKIs treatment 2 months beyond progression in asymptomatic patients with a systemic slow growing progression and low disease volume in non-critical sites? TKI treatment could be maintained beyond progression, if asymptomatic and slow growing-disease is present, especially for patients without resistant mutations who are not candidates for targeted therapy.	73	21	6	YES (STRONG)
Would you consider delaying CNS-MRI at diagnosis in asymptomatic patients with oncogene driver mutations? Patients without access to an MRI at diagnosis, could be delayed if no related symptoms are reported, considering availability of active treatments with blood barrier penetration.	60	32	8	YES (STRONG)
Chemotherapy				
Would you consider postponing starting chemotherapy for asymptomatic patients with a functional status of 2 (PS2) or elderly patients? Initiating treatment in PS2 and elderly population may have a higher risk compared with the benefits during pandemic, consider postponing systemic treatment.	37	50	13	YES (STRONG)
Would you consider adjusting IV regimens to oral vinorelbine in asymptomatic elderly patients? Initiating oral vinorelbine schemes could be an acceptable alternative in regions where approved, for asymptomatic patients to avoid hospital visits.	37	50	13	YES
Outpatient follow-up				
Do you recommend telemedicine monitoring for asymptomatic patients and those with a good tolerance of treatment (in patients with > 6 months), as an intermediate assessment between cycles (immunotherapy or TKI)? Selected asymptomatic patients with more than 6 months of treatment, and good tolerance may be monitored by telemedicine resources.	89	8	3	YES (STRONG)
Do you recommend 8-week outpatient follow-up for patients on TKIs treatment? Patients on TKIs treatment may be followed with 8-weekly outpatient visits.	76	24	0	YES (STRONG)
Do you consider that patients on chemotherapy or combination regimens with immunotherapy treatment could be followed with 4-weekly outpatient visits rather than 3-weekly? Patients on chemotherapy or combination treatments with immunotherapy could be monitored with 4-weekly outpatient visits.	71	21	8	YES (STRONG)
Would you consider prolonging the evaluation of response to active treatment to every 4 months in asymptomatic patients (≥ 6 months from starting treatment)? Response evaluation could be delayed until 4 months in asymptomatic patients and ≥ 6 months of treatment, ideally with a PET-CT, if this is not available a contrasted CT-scan could be performed.	60	35	5	YES (STRONG)
Small cell lung cancer Limited Disease				
Should every patient with SCLC have a workup with brain MRI before starting treatment? Patients may start treatment without a brain MRI, since delaying systemic treatment may affect outcomes	84	14	2	YES (STRONG)
Can Surgery be omitted in early stages of small cell lung cancer? If surgery times are prolonged, chemotherapy or SBRT can be used instead.	63	29	8	YES (STRONG)
Can chemotherapy treatment be delayed by 4-6 weeks in limited disease? The omission/delay of chemotherapy treatment is not recommended due to the high rate of growth.	84	14	2	YES (STRONG)
Can radiation therapy be delayed in patients with limited disease? Delaying the starting time of RT treatment is not recommended due to the high rate of growth; moreover, early initiation has a benefit in survival.	74	24	2	YES (STRONG)
Could you omit prophylactic cranial irradiation (PCI) in SCLC patients with limited disease? Considering the current situation, the best option is to delay the administration of radiotherapy until 6 months after the start of the adjuvant treatment without having a significant impact on oncological outcomes.	18	39	43	NO
Would you prefer cisplatin over carboplatin for upfront treatment? Due to lower probability of developing hematological toxicity, cisplatin should be considered.	61	23	16	YES (STRONG)
Small cell lung cancer extensive disease				
Do you consider that first-line chemotherapy alone or in combination with immunotherapy must be delayed in extensive disease? In patients with extensive disease the omission of chemotherapy treatment is not recommended.	87	3	10	YES (STRONG)

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Table 1 (continued)

QUESTION/RECOMMENDATION	CATEGORY 1	CATEGORY 2	CATEGORY 3	CONSENSUS
Would you give consolidative RT to the primary tumor in extensive disease? Due to the controversial benefit in terms of OS, though there is a clear benefit in PFS and local recurrence, consolidative RT could be omitted.	26	31	43	NO
Can prophylactic radiotherapy to the brain be suspended in extensive disease? PCI can be omitted because of the controversial benefit in survival.	53	31	16	YES (STRONG)
Should we administer second or further lines of therapy to SCLC patients during the pandemic? Considering prognosis and treatment effectiveness, delaying or omitting second line treatment could be considered.	24	44	32	YES
Mesothelioma- Local and locally advanced disease				
Do you consider it the preferred option to perform a tru-cut biopsy for the diagnosis of mesothelioma?	66	21	13	YES (STRONG)
Patients with suspicious of malignant pleural mesothelioma preferably may undergo a CT-guided biopsy for diagnosis, avoiding more invasive procedures like thoracoscopy or VATS.				
If a patient starts neoadjuvant chemotherapy, do you recommend surgery to complete treatment in localized (I-IIIA) mesothelioma? Patients with localized disease must be discussed in a multidisciplinary session aimed for curative intent, considering neoadjuvant chemotherapy followed by surgery (preferably total pleurectomy/decortication).	71	24	5	YES (STRONG)
Do you have any consideration for trimodal (cHT, surgery & RT) treatment? We currently do recommend trimodal treatment, including radiotherapy. This is a fast-progressing tumor which is radiosensitive and therefore OS benefit could be achieved with trimodal therapy.	50	42	8	YES (STRONG)
Mesothelioma metastatic disease				
Would you consider deferring systemic treatment 4–6 weeks or until progression (clinical or radiological) in asymptomatic patients? Patients could be considered for deferring cytotoxic therapy if they are asymptomatic and have a low burden of disease.	29	40	31	YES
Do you recommend starting systemic treatment in symptomatic patients with advanced disease and recent diagnosis of mesothelioma? Consider starting first-line treatment in every symptomatic patient preferably with a carboplatin-based regimen in combination with pemetrexed.	84	16	0	YES (STRONG)
Do you consider maintenance therapy has a role?	37	37	26	YES
Due to the lack of efficacy in the available data, pemetrexed maintenance therapy is not recommended. Regarding bevacizumab, we do not consider the benefit could outweigh the risks of COVID-19 infection.				
Do you recommend starting second-line treatment in asymptomatic patients? Second-line treatment in asymptomatic patients could be delayed until clinical or radiological progression, considering risks during the pandemic.	61	32	7	YES (STRONG)

attention of patients with cancer in multiple neoplasia. These guidelines attempt to stratify patients according to risk categories to determine which patients may benefit the most from immediate therapy, and identify those whose clinical scenario will not change because of delayed treatment (Burki, 2020).

This consensus is an effort by a multidisciplinary team of key opinion leaders who are currently faced with the challenge of providing standard-of-care for thoracic malignancies patients in the setting of overwhelmed or collapsed health systems. These recommendations seek to propose management algorithms applicable to a population of patients with thoracic malignancies who might face delays or shortages due to the pandemic. In this way we seek to improve risk stratification, prioritize treatments and reduce complications in the current scenario. It is of utmost important to stress that these should only be considered when the scenario merits it, and not as routine choices. Furthermore, some of these treatment recommendations might be influenced by differences in socio-economic conditions and regulatory approvals of cancer drugs between countries as well as specific government restrictions during the COVID19 outbreak. Additionally, it is imperative that each clinical decision be made considering the baseline characteristics of the patient, including age and comorbidities.

2. Methods

On May 7th, 45 experts (medical oncology, surgeons, pulmonologists and radiotherapists) in thoracic cancers from 11 different countries were invited to participate in this project. By May 16th, 44 had agreed to participate, with a total of 44 experts for the final consensus.

2.1. Questions and recommendations

A core of 6 experts gathered on May 9th in order to compose a set of clinically relevant questions in the COVID-19 pandemic setting. Each question was voted on in terms of relevance, application, frequency and available evidence. In the end, a total of 60 questions were considered for inclusion in the voting panel. All questions were thoroughly reviewed in the literature in order to compose an evidence-based recommendation for each. Questions in which evidence is scarce or controversial were only considered if they were highly clinically meaningful or frequent scenarios in the current setting. Two questions were deleted post-voting due to controversial evidence pertaining to the recommendation, leaving a total of 58 questions and recommendations.

2.2. Voting platform

A modified Delphi process was used to establish consensus about whether and how to adapt clinical care during this pandemic for patients with thoracic malignancies. On May 16th at 10 a.m., all invited experts who agreed to participate logged on to a live voting platform. During this meeting, participants had access to a voting tool in which they would state whether they agreed or disagreed with each recommendation. The Delphi scale for each recommendation included the following options “Totally disagree; strongly disagree; slightly disagree; neither agree nor disagree; slightly agree; agree; strongly agree; totally agree”. During this session, a moderator read each question and displayed in a screen the recommendation, once this was done, panelists had 6 min to vote on an 8-question section, once the voting was completed the moderator moved to the next section until all recommendations had been voted on.

Questions for the Delphi process were stratified according to 16 main categories which are all clinical scenarios frequently assessed in a thoracic oncology unit, or by any practice which routinely treats patients with thoracic cancers, all questions are summarized in Table 1.

Once the voting was complete, all answers were categorized into three main categories for each recommendation, and the percentages of each are presented in Table 1. For this purpose, “Totally agree” and

“strongly agree” were categorized into category 1, “agree” and “slightly agree” into category 2, and “Totally disagree; strongly disagree; slightly disagree; neither agree nor disagree” into category 3.

A threshold of 66 % for agreement (categories 1 and 2) or disagreement (category 3) was required for each question to reach consensus and a threshold of 80 % for strong consensus.

3. Results

Questions and proposed recommendations

4. General recommendations

Do patients with thoracic malignancies need to be treated preferably through virtual resources when possible reducing hospital visits?

Recommendation: Patients with thoracic neoplasms must be followed and whenever possible treated through virtual resources thus avoiding hospital visits.

This recommendation is aimed at reducing the risk of SARS-CoV-2 exposure through lowering the number of visits to healthcare facilities, mitigating the immunocompromising effect in lung cancer patients, while still providing effective oncologic therapy. In a retrospective study from China 138 patients were analyzed with the diagnosis of COVID-19 pneumonia. Hospital associated transmission was suspected as the presumed mechanism of infection in 41.3 % of patients, 29 % in health professionals, and 12.3 % in hospitalized patients (Wang et al., 2020). Thus, suggesting the hospitals are a main source of Infection.

Do you recommend patients use personal protection equipment (PPE) for special occasions (visits, imaging studies, treatment) when it is strictly necessary to go out of their homes?

Recommendation: All patients with thoracic malignancies must be reinforced to use PPE every time they need to go out of their homes

The rational use of face masks and other PPE has been a subject of debate since the earlier days of the pandemic. Up to this date, there is no conclusive evidence to encourage the use of face masks for the general public, however it is important to state, as recently stated by Lancet Respiratory Medicine that “absence of evidence does not mean evidence of absence”. As such, it is important to note that there is also no current evidence of potential harms to subjects who wear PPE. In the particular case of cancer patients, it appears rational to encourage the use of PPE when going out of their homes, in order to prevent potential transmission from asymptomatic patients. In these cases, of vulnerable populations, face masks should be worn if available (Feng et al., 2020).

5. Detection of SARS Cov2 infection in patients with thoracic malignancies

Does every patient with a thoracic neoplasm need a baseline CT-scan as a first COVID-19 detection test?

Recommendation: It is recommended to perform a CT-scan, where available and accessible to patients, as the first detection test, intentionally searching for radiographic findings of COVID-19, especially before initiating treatment in cancer patients

CT-scans in the early phase of COVID-19 infection are normal or characterized by multifocal bilateral and peripheral ground-glass opacities, extensive small nodules or thickening alveolar walls. These findings are described in up to 97 % of COVID-19 patients, with a sensitivity even higher compared with RT-PCR in upper airway exudates (sensitivity of 98 vs. 71% $p = 0.001$) (Ai et al., 2020). Additionally, compatible findings of SARS-CoV-2 infection have been reported during follow-up imaging of cancer patients without necessarily being related. Special attention should be put towards differentiating

pulmonary findings due to COVID-19 and disease progression [10, (Pan et al., 2020; Bernheim et al., 2020).

Does every patient with a thoracic neoplasm need a SARS-CoV-2 PCR test to rule out active disease?

Recommendation: Ideally every cancer patient will need a SARS CoV-2 PCR test to rule out active COVID-19, especially if there is a suspicious CT-scan.

Consider the following cases as mandatory to perform a test:

- Patients with new onset cough, fever, or diarrhea. Patients with other symptoms including anosmia and dysgeusia.
- Patients with preexistence symptoms (cough) that increased in the last 14 days.
- Patients with a contact history with a suspected or confirmed case.
- Patients who require hospitalization, especially if an invasive procedure is planned or any oncological treatment.

Patients with lung cancer may mask evidence of COVID-19 and delay detection and treatment. Cough, fatigue, and sputum production are some of the most frequent clinical manifestations in COVID-19 disease (Zhou et al., 2020), symptoms frequently seen in the lung cancer population. Close monitoring should be maintained to avoid delaying the diagnosis and avoiding exposure to hospital personnel and other patients (Banna et al., 2020)

Could blood cell count-based tests have a role in the detection of cancer patients with suspicious COVID-19 clinical features?

Recommendation: Blood cell count and SARS CoV2 RT-PCR is recommended in patients with a suspicious CT- scan.

Other relevant findings in the clinical approach of patients with suspicion of SARS Cov2 infection is lymphopenia (< 1500 cells / mm³), present in 83.2 % of patients at diagnosis. We recommend screening for COVID-19 among patients who have suspicious findings in symptoms, laboratory tests and imaging studies (Zhu et al., 2020). Nonetheless, an important proportion of lung cancer patients might have lymphopenia, particularly those with advanced disease, which should be considered (Menetrier-Caux et al., 2019; Turcott et al., 2020)

6. Diagnostics and staging

Do you recommend that all cases continue to be evaluated by a multidisciplinary team, ideally in using virtual resources (i.e. Virtual tumor boards)?

Recommendation: A multidisciplinary team that works collaboratively optimizing available resources and ensuring quality care should evaluate case by case through virtual platform meetings.

Do you recommend avoiding the delay in diagnostic approaches for thoracic malignancies?

Recommendation: Every patient with a thoracic malignancy must undergo appropriate initial diagnosis, considering available resources, avoiding impacting on their prognosis.

A multidisciplinary treatment plan is based upon the assessment of the extent of disease, the patient's overall condition including cardiopulmonary function and other comorbidities, and their desire for aggressive treatment. This should include timely access to tomography and / or thoracoscopy-guided pleural biopsy.

In patients in need of pleural fluid drainage at diagnosis, would you prefer indwelling pleural catheter (IPC) insertion over pleurodesis?

Recommendation: Procedures with ambulatory/short hospital stay must be preferred over procedures that require longer inpatient stay (Zarrintan, 2020)

7. Recommendation in patients with a suspected or confirmed diagnosis of COVID-19

Should medical treatment for thoracic malignancies (chemotherapy, immunotherapy, or targeted therapy) be suspended in patients with a suspected or confirmed diagnosis of COVID-19?

Recommendation: Patients should stop active treatment if a suspected or confirmed diagnosis of COVID-19 is present.

In cancer patients, the risk of adverse events was greater for those who had received chemotherapy or surgery in the 14 days prior to the onset of symptoms (odds ratio [OR] 5.34, 95 % CI 1.80–16.18; $p = 0.0026$) (Liang et al., 2020).

8. Post COVID-19

Would you consider it safe to restart cancer treatment in patients who have resolved all symptoms from SARS CoV-2 infection?

Recommendation: Patients could restart cancer treatment if symptoms have resolved. Consider the following parameters, individualizing case by case.

- Oxygen saturation > 90 % at room air or return to baseline supplementary oxygen concentration
- Absence of fever of at least 1-week duration.
- Significant resolution of imaging findings evaluated with a simple chest CT-scan.
- 2 negative COVID-19 RT PCR tests with an interval of at least 1 week between them.

The criteria mentioned above are recommended for hospital discharge and termination of contact isolation after COVID-19 infection (Fang et al., 2020). However, positive SARS Cov 2 RT-PCR results were reported even 13 days after clinical symptoms mentioned resolved (Lan et al., 2020). This may be related to the immune status of each patient, use of glucocorticoids, and time of virus clearance (Kil et al., 2011). ESMO recommends re-starting treatment after 2 negative RT-PCR tests with a one week interval following clinical (Banna et al., 2020).

9. Recommendations for treatment in non-small cell lung Cancer nscLc

General treatment recommendations

Should all patients with a risk of developing neutropenia (> 10–15 %), receive G-CSF?

Recommendation: All patients with a neutropenia risk > 10–15 % should receive G-CSF, considering potential complications due to immunosuppressing effects.

The most common severe adverse events for chemotherapy regimens for adjuvant treatment are hematological, in the ANITA trial, for example, the grade 3 or 4 neutropenia was documented in 70–80% of the patients (Douillard et al., 2006).

10. Early stage disease

In the case of surgery for early-stage disease, could this be delayed for more than 3 months?

Recommendation: Surgery should not be postponed. Delayed surgery can have long-term deleterious effects by increasing deaths attributed to cancer. The surgeries in patients who can progress without treatment should be considered as a high priority according to the institution's resources (for example, tumors > 2 cm).

Would you consider SBRT for T1 surgical patients considering potential delays and shortage in resources for surgery?

Recommendation: SBRT could be an acceptable alternative option to treat tumors < 2.0 cm.

Non-candidate T1 surgical patients can be considered for SBRT (Nicastrì et al., 2008). The oncological outcomes are similar compared with open resection, including a study with 416 patients, in which 5 year survival was non-statistically different between VATS and thoracotomy approaches (Lee et al., 2013). Also, there is information from non-randomized phase I and II studies comparing SBRT with surgery, a conjunct analysis of these trials showed a better OS at 3 years in patients treated with SBRT (Lee et al., 2013). So, SBRT could be considered an option in these patients (Videtic et al., 2019). If a decision is made for SBRT, a single fraction SBRT of 30–34 Gy is recommended (Videtic et al., 2014).

Should patients with stage II-III NSCLC continue receiving adjuvant treatment ?

Recommendation: Adjuvant treatment should be offered, due to the clear benefit in OS.

There is a clear benefit in patients with Stage II and III according to the LACE metanalysis (Pignon et al., 2008), so these patients should have the highest priority when selecting candidates for adjuvant treatment, but when considering a deferment of treatment there is some evidence about the delay without affecting outcomes, as a large retrospective study of the National Cancer Database showed that patients with slow recovery could still get a benefit for chemotherapy starting 4 months after surgery without an increase in mortality (Salazar et al., 2017).

Would you prefer lower toxicity regimens such as Carboplatin/ Pemetrexed for adjuvant treatment?

Recommendation: Carboplatin/ Pemetrexed could be the preferable option because of the toxicity profile.

Would you consider adjuvant RT in patients with pathological N2 or R1 after surgery?

Recommendation: RT could be offered as an adjuvant treatment but can be postponed after chemotherapy or 3 months after surgery.

If the patient is also candidate of adjuvant RT (R1 or pathological N2), the treatment could be administered after the completion of chemotherapy, or delayed till 3 months after surgery. In a review evaluation of 3500 of the National Cancer Database, the patients that received sequential chemoradiation had a better survival compared with the group of concomitant chemoradiation (Videtic et al., 2014; Pignon et al., 2008; Salazar et al., 2017).

Would you consider an adjuvant hypofractionated approach?

Recommendation: Hypofractionated radiotherapy is not recommended in this clinical scenario.

Although hypofractionation is gaining acceptance, high technology is necessary in order to implement this modality. The dose should be 50–60 Gy in 25–30 fractions (Guckenberger et al., 2020; Kumar et al., 2020).

11. Locally advanced disease (clinical stage III)

Should every patient with locally advanced disease be treated with chemoradiation?

Recommendation: Every patient should be considered for chemoradiation

The standard treatment is chemoradiation followed by durvalumab in patients who did not progress during the next 42 days. The two-year survival of stage III NSCLC patients ranges from 24 to 55% (Goldstraw et al., 2016), but increases to 66 % with concomitant chemoradiation followed by durvalumab (Antonia, 2019). Hypofractionation is not recommended concurrently with chemotherapy.

Would you prefer concurrent chemoradiation over a sequential approach?

Recommendation: A concurrent approach is preferred, although sequential treatment can be kept in mind for specific cases in which toxicity is considerable.

Concurrent chemoradiation over sequential treatment is superior in terms of OS, but the benefit is modest and the toxicities could be higher, so the risk for immunosuppression in the pandemic could be less for the sequential therapy (Curran et al., 2011; Aupérin et al., 2010). The choice of treatment should be made based on clinical features like patients' symptoms, rate of disease progression, disease burden, (i.e. patients with hilar tumors or vascular compression) could be treated with RT (Higginson et al., 2012). No hypofractionation or only mild hypofractionation (i.e. 50 Gy in 20Fx) is recommended.

Should Durvalumab be administered in a higher dose (1500 mg 4 w) to diminish the number of visits?

Recommendation: Yes. The dose of 1500 mg Durvalumab is a safe regimen, though efficacy has not yet been conclusively stated.

Evidence from the CASPIAN trial using durvalumab at a dose 1500 mg 4-weekly regimen in extensive SCLC has shown an adequate safety profile; this schedule could diminish the number of visits to receive treatment without compromising efficacy. Also, durvalumab can be administered up to 42 days after the completion of chemoradiation (Paz-Ares et al., 2019).

Would you prefer 3-weekly regimen concurrently with RT to reduce the hospital visits?

Recommendation: No, the extra treatment duration and number of chemotherapy cycles can prolong immunosuppression unnecessarily.

A systematic review shows that patients with preoperative/ induction chemotherapy may have a 13 % reduction in risk of death, so it can be considered as an option to delay treatment with RT or surgery (NSCLC Collaboration Group). In the PACIFIC trial (Antonia, 2019) 25.3 % of patients received induction chemotherapy before chemoradiation therapy. Results from randomized trials have shown similar survival rates (Belani et al., 2005; Vokes et al., 2007). While this modality could prolong the treatment duration it can delay the time to chemoradiation with the expected immunosuppressive effects and daily visits.

Is G-CSF use recommended for routine use?

Recommendation: G-CSF should not be routinely used, only if neutropenia develops and represents an issue.

In this scenario the use of G-CSF is associated with a higher probability of toxicity when administered during chemoradiation, however, a review readdressed this question for the safety of this combination (Benna et al., 2020).

Would you choose a hypofractionated schedule for sequential chemoradiation?

Recommendation: Hypofractionated schedules in this clinical setting are not currently fully supported by available evidence. Nonetheless, the approach could be an option for treatment in some patients that have access to the technology.

Shorter courses of RT are associated with less immunosuppression in other cancers, though currently evidence for lung cancer in this clinical setting is scarce and therefore, an evidence-based recommendation cannot be made (Benna et al., 2020). This approach could, however, diminish the risk of infection by minimizing the number of visits to the hospital to receive treatment (Belani et al., 2005; Vokes et al., 2007). Nonetheless, hypofractionated schedules increase risk of radiation pneumonitis and should be decided in case by case scenario (Torre-Bouscoulet et al., 2018).

12. Advanced non-small cell lung cancer

Do you consider a high priority to start systemic treatment in asymptomatic and symptomatic treatment naïve patients?

Recommendation: Independently of symptoms and molecular tumor biology all patients with metastatic lung cancer in the first-line setting should be prioritized for treatment initiation.

In many retrospective cohorts, delays on treatment have an impact on prognosis, especially in earlier stages (Anggondowati et al., 2016). Similarly, in advanced disease, shorter delays were correlated with poorer outcomes. The association reflects the biology of the disease, as symptomatic patients often receive expedited treatment to control symptoms (Diaconescu et al., 2011; Myrdal et al., 2004). Considering the highly effective therapies available in the first-line setting with a clear impact in OS, PFS, and ORR its necessary to make a counterbalance considering risk and benefits (Planchard et al., 2018).

Can patients with oligometastatic disease start with systemic therapy alone, differing or postponing locally-aggressive strategies to metastatic sites?

Recommendations: Patients with oligometastatic disease could start systemic treatment only while postponing radiotherapy or surgery for metastatic sites for safer scenarios. If patients present symptomatic metastases (pain, obstruction or bleeding) palliative short course hypofractionated radiotherapy (ie 8 Gy/10 Gy or SBRT [when feasible]) is recommended.

Patients that have oligometastatic disease with low disease burden may be suitable for an aggressive approach (surgery or radiotherapy, ablative techniques) to all metastatic lesions looking for a curative intention strategy (Muller et al., 2019).

Would you consider postponing second-line treatment in asymptomatic patients (who do not show signs or suspicious of having COVID-19 infection) with contraindications for immunotherapy, or after a first-line treatment with a checkpoint inhibitor-based regimen?

Recommendations: Considering risks and potential benefits, patients in second-line treatment suitable for chemotherapy in monotherapy may be delayed or postponed until progression (clinical or radiological).

Docetaxel has a modest ORR benefit compared with best supportive care (less than 10 %) and a median PFS of 2–3 months. Meanwhile, pemetrexed has demonstrated similar efficacy but a more favorable

toxicity profile (Planchard et al., 2018). Considering risks of infection and modest benefits, postponing treatment until clinical or radiological progression should be considered.

Would you consider postponing second-line treatment in asymptomatic patients (who do not show signs or suspicious of having COVID-19 infection) with oncogene driver mutations?

Recommendation: Patients with oncogene driver mutations after progression to a first line TKI are high priority and ideally treatment should not be delayed.

TKIs in second line treatment have demonstrated superior outcomes compared with chemotherapy in multiple scenarios in *EGFR*, *ALK*, *ROS1* and *BRAF* mutated population with a considerable impact in ORR and PFS (Planchard et al., 2018). Additionally, a different toxicity profile predominating symptoms like rash, diarrhea and fatigue predominate in targeted therapy compared with more hematologic toxicity in chemotherapy (Planchard et al., 2018).

Would you consider postponing second-line treatment in asymptomatic patients who are suitable for immunotherapy?

Recommendation: Patients suitable for immunotherapy must be treated, ideally without delays.

Evidence has been consistent as to the OS benefit of immunotherapy vs. chemotherapy in second-line (Planchard et al., 2018).

When carcinoembryonic antigen (CEA) is elevated in baseline, can we use this biomarker to monitor NSCLC response to treatment and avoid imaging studies?

Recommendation: Serum carcinoembryonic antigen (CEA) could be considered in the monitoring of NSCLC patients to obtain prognostic and predictive information during the pandemic.

Though this has not been evaluated in this particular scenario, many studies have shown evidence regarding the use of the serum level of CEA as a prognostic and predictive factor for recurrence and death (Arrieta et al., 2009; Arrieta et al., 2013; Holdenrieder et al., 2017). Guidelines do not recommend determination of serum CEA, however, considering potential delays in response evaluation during this pandemic, it could provide valid information (Holdenrieder et al., 2017).

13. Non oncogene-driver mutations and suitable for immunotherapy

Considering the risk of pneumonitis and immunological effects, could immunotherapy be considered a safe treatment during the pandemic?

Recommendation: Immunotherapy should be administered to all candidate patients. Until now, no evidence of an increased mortality has been documented, and a recent study shows PD-1 blockade in lung cancer is not associated with increased severity of COVID-19.

Theoretically patients under immunotherapy could be more immunocompetent than non-users, thus potentially a greater inflammatory response could be established. Cytokine release syndrome (CRS) is a rare complication seen with car-T cells therapy or PD-1 inhibitors characterized by an increased level of IL-6 and IFN γ (Dimitriou et al., 2019). The acute respiratory distress syndrome (ARDS) is one of the most lethal complications in almost one third of patients in this pandemic, due to a secondary cytokine storm that produce a hyperactivation of T-cells that contribute to the severe immune injury. This proinflammatory state in the COVID-19 patients could progress to an acute inflammatory distress syndrome ARDS or even to multiorgan failure (Chen et al., 2020; Rotz et al., 2017). Nonetheless, current evidence suggests that PD-1 blockade does not impact the severity of COVID-19 in patients with lung cancer (Luo et al., 2020).

Should you recommend using immunotherapy alone rather than combination treatments with immunotherapy and chemotherapy in patients with TPS \geq 1–49%?

Recommendation: Patients with a TPS \geq 1–49% and an increased risk of neutropenia or considerable toxicity should consider pembrolizumab monotherapy as an option in this current scenario.

First-line pembrolizumab monotherapy improves OS and PFS in patients with untreated metastatic NSCLC with a TPS of 50 % or greater and this could be the most reasonable treatment during pandemic in this population. However, the KEYNOTE 042 trial tested the benefit of pembrolizumab alone compared with chemotherapy in patients with a TPS greater than 1%. The median OS in patients varied according to TPS [with TPS > 50 % (20 months; HR 0.69), TPS > 20 % (17.7 months; HR 0.77), TPS > 1% (16.7 months; HR 0.81)], and was statistically significant in the pembrolizumab arm in the three groups compared with chemotherapy. Despite this, a subanalysis showed that the benefit was driven by the TPS > 50 %. Similarly, a subanalysis in the % subgrouped showed no benefit over chemotherapy and inferior results when indirectly compared to chemo-IO. (Holdenrieder et al., 2017).

Should you recommend alternative regimens with longer intervals between treatment applications?

Recommendations: Alternative regimens, like 4-weekly or 6-weekly regimens could be used safely during the pandemic to diminish visits to hospital.

Recently in a model-based approach pembrolizumab 400 mg 6-weekly 6 W was compared with 3-weekly 3 W approved regimens in terms of pharmacokinetic and security. The 6 W regimen had similar predicted exposure, likewise, fewer than 1% of patients had transiently lower concentrations compared to 3 W regimens, non-peak concentrations over the security dose of 10 mg/kg (Lala et al., 2020). Nivolumab 480 mg 4 W regimen is recommended too based in a success pharmacokinetic (PK) analyses comparing with 3 mg/kg and flat dose of 240 mg 2 W (Long et al., 2018). In addition, durvalumab 1500 mg 4-weekly regimen has been explored in the CASPIAN trial in extensive SCLC (Paz-Ares et al., 2019) and it is being tested in the ongoing PACIFIC (2,4,5 and 6) trials (Bradley et al., 2019) with an acceptable safety. Additionally, atezolizumab can be administered 1680 q4 w, a dosing regimen that has been shown to be interchangeable with 1200 q3w, but offers patients longer visit intervals (Morrissey et al., 2019). All the regimens are FDA approved.

14. Oncogene driver mutation carriers (EGFR, ALK, ROS1 and BRAF)

Do you consider TKIs treatment safe during pandemic?

Recommendation: Patients on TKIs should be monitored for pulmonary symptoms in every visit or telephone call, but patients suitable to receive TKIs must do so.

One concern is the increased risk of pneumonitis in patients with NSCLC during TKIs treatment. Based on a recent metaanalysis the overall incidence of EGFR-TKI pneumonitis was 1.12 % in patients without prior exposure to EGFR-TKI, and 1.13 % in EGFR-TKI retreatment group. Grade \geq 3 pneumonitis was presented in 0.81 % of patients in the total cohort (Suh et al., 2018). Likewise, all grade and grade \geq 3 pneumonitis were reported in 2.14 % and 1.55 % respectively, of patients with an ALK inhibitors (Suh et al., 2019). Further, data from the ALK in Lung Cancer Trial of Brigatinib in 1 st Line (ALTA-1 L) showed patients treated with brigatinib and crizotinib presented with G3/4 interstitial lung disease or pneumonitis in 3% and 0.7 % of cases, respectively (Camidge et al., 2018).

Do you recommend maintaining TKIs treatment 2 months beyond progression in asymptomatic patients with a systemic slow growing progression and low disease volume in non-critical sites?

Recommendation: TKI treatment could be maintained beyond progression, if asymptomatic and slow growing-disease is present, especially for patients without resistant mutations who are not candidates for targeted therapy.

Most patients will progress to targeted agents, however long-term durable responses and subsequent rebound tumor flare observed on stopping EGFR-TKI therapy support the rationale of maintaining the molecular inhibition which may continue controlling sensitive clones, even beyond progression. Retrospective and prospective data support this strategy, particularly in EGFR-mutated population and is considered safe (Park et al., 2016; Nishie et al., 2012; Asami et al., 2013).

Would you consider delaying CNS-MRI at diagnosis in asymptomatic patients with oncogene driver mutations?

Recommendation: Patients without access to an MRI at diagnosis, could be delayed if no related symptoms are reported, considering availability of active treatments with blood barrier penetration.

There are many trials that have elucidated the activity of third-generation EGFR-TKI inhibitors (osimertinib) and second (alectinib, brigatinib) and third generation ALK inhibitors (lorlatinib) in preventing or delaying the onset of CNS disease, and in leading to intracranial response for patients with preexisting brain metastases. At the end delaying the use of WBRT as longer as possible would be the main purpose (Bulbul et al., 2018)

15. Contraindications for immunotherapy and non-driver mutations

Would you consider postponing starting chemotherapy for asymptomatic patients with a functional status of 2 (PS2) or elderly patients?

Recommendation: Initiating treatment in PS2 and elderly population may have a higher risk compared with the benefits during pandemic, consider postponing systemic treatment.

Chemotherapy has shown to prolong OS in patients with PS2. Also, a metanalysis confirmed the benefit of platinum-based regimens compared with monotherapy in this population, at the cost of an increase in hematologic toxicity, more grade 3–4 anemia and neutropenia (Bronte et al., 2015; Gridelli et al., 2004). Regarding platinum therapy, superiority of carboplatin-based combination over monotherapy has been reported in two large phase III trials with an acceptable toxicity profile (Quoix et al., 2011; Zukin et al., 2013). Therefore, platinum- preferably carboplatin doublets could be considered in eligible PS 2 patients, but during this pandemic the risk of contracting the infection should be considered.

16. Outpatients follow-up and monitorization

Do you recommend telemedicine monitoring for asymptomatic patients and those with a good tolerance of treatment (in patients with > 6 months), as an intermediate assessment between cycles (immunotherapy or TKI)?

Recommendation: Selected asymptomatic patients with more than 6 months of treatment, and good tolerance may be monitored by telemedicine resources.

Health systems that have already invested in telemedicine are well positioned to help ensure that cancer patients could receive appropriate attention. In this instance, it may be a virtual solution to monitor closely our patients that are currently displaying clinical benefit and adequate tolerance to systemic therapy (Elkaddoum et al., 2020).

Do you recommend 8-week outpatient follow-up for patients on TKIs treatment?

Recommendation: Patients on TKIs treatment may be followed with 8-weekly outpatient visits.

TKIs demonstrated in many phases 3 trials a more favorable toxicity profile compared with chemotherapy. Additionally, they help achieve longer responses. On the other hand, treatment beyond progression in slow progressive disease could be employed as a valid strategy. Considering risks during pandemic, longer monitorization of these patients could be considered an option, preferable with intermediate evaluation with telemedicine or phone calls as back-up resources.

Do you consider that patients on chemotherapy or combination regimens with immunotherapy treatment could be followed with 4-weekly outpatient visits rather than 3-weekly?

Recommendations: Patients on chemotherapy or combination treatments with immunotherapy could be monitored with 4-weekly outpatient visits.

Considering the overwhelmed health care systems and potential risk of infection, delaying one-week IV chemotherapy treatment could be considered an option. Prognostic implications are not yet evidenced, but this strategy could avoid SARS-CoV-2 infection.

Would you consider prolonging the evaluation of response to active treatment to every 4 months in asymptomatic patients (≥ 6 months from starting treatment)?

Recommendation: Response evaluation could be delayed until 4 months in asymptomatic patients and ≥ 6 months of treatment, ideally with a PET-CT, if this is not available a contrasted CT-scan could be performed.

Considering hyperprogressive disease (HPD), patterns of response and toxicity profile in the first 6 months of treatment, closer monitorization and imaging is crucial. HPD occurs in around 13 % of patients with advanced NSCLC, conferring an ominous prognosis for those who progress during the first 6 weeks of treatment (Ferrara et al., 2018). Moreover, most responses to therapy based on many phases 3 trials occurred within the first 3 months of treatment, identifying relatively soon the patients who will benefit of treatment. Additionally, most of the severe adverse events and irAEs occurred during the first 6 months after starting treatment, and rarely after 1 year (Remon et al., 2018).

17. Small cell lung cancer

SCLC limited disease

Should patients with SCLC have a workup with brain MRI before starting treatment?

Recommendation: Patients may start treatment without a brain MRI, since delaying systemic treatment may affect outcomes.

Because Limited stage SCLC (LS-SCLC) is a curable disease, the most important issue standing is to determine whether there are any distant metastases, therefore it is not recommended to delay the studies in these patients. However, once a patient has been diagnosed to have extensive stage disease, further standing is not required, except for brain imaging (Cuffe et al., 2011).

Can surgery be omitted in early stages of small cell lung cancer?

Recommendation: If surgery times are prolonged, chemotherapy or SBRT can be used instead.

Only 5% of patients present in early stages are candidates for surgical treatment, and the decision to carry out surgery should be

discussed by a multidisciplinary team, since a complete evaluation of the mediastinum is required, this in addition to post-surgical care of the patient could increase the risks for the patients. Since there are currently no studies comparing surgery against concomitant chemoradiotherapy, one option would be to start treatment with chemotherapy and SBRT if available. The Lung Cancer Study Group conducted the only prospective randomized trial evaluating the role of surgery; however, induction chemotherapy was used followed by surgery plus radiotherapy or only radiotherapy, the results did not show a benefit for surgery. A multicenter study of 74 patients with limited disease suggested that the addition of chemotherapy typically after SBRT improves survival, with a median OS of 31.4 months vs. 14.3 months ($P = .02$) (Jett et al., 2013; Pignon et al., 1992).

Can chemotherapy treatment be delayed by 4–6 weeks in limited disease?

Recommendation: The omission/delay of chemotherapy treatment is not recommended due to the high rate of growth.

Due to the high rate of tumor growth that occurs in the SCLC and that it is considered a systemic disease from the start, the omission/delay of standard chemotherapy treatment is not recommended in these patients (Fried et al., 2004).

Can radiation therapy be delayed in patients with limited disease?

Recommendation: Delaying the starting time of RT treatment is not recommended due to the high rate of growth; moreover, early initiation has a benefit in survival.

The use of concurrent chemotherapy with radiotherapy is the standard of treatment for patients with limited disease due to the impact on survival. In patients with limited disease, the use of etoposide and cisplatin with radiotherapy has response rates of 70%–90% with a 5-year survival of 25%–30%. Use of concurrent vs. sequential therapy has been questioned (Pignon et al., 1992), but several studies, including a Cochrane study, have shown benefit for the early start of RT (De Ruysscher et al., 2006). Therefore, if possible, early radiation initiation is recommended, but if toxicity is an important issue a sequential approach could be an option.

Could you omit prophylactic cranial irradiation (PCI) in SCLC patients with limited disease?

Recommendation: Considering the current situation, the best option is to delay the administration of radiotherapy until 6 months after the start of the adjuvant treatment without having a significant impact on oncological outcomes.

SCLC patients are a high-risk population for developing brain metastases, which are associated with poor survival. As such, it is not recommended to suspend the administration of PCI in these patients. One could, however, consider delaying the administration of the therapy until 6 months after the start of the adjuvant without significantly impacting on the outcomes.

PCI has been shown to be effective in a meta-analysis of seven randomized studies that included 978 patients. It showed a reduction in the incidence of metastases (relative risk [RR] 0.46; 95 % CI 0.38–0.57) and a decrease in mortality (RR 0.84; 95 % CI 0.73–0.97).

In the same study, a subgroup analysis showed there was no difference in mortality when starting radiotherapy less than 6 or more than 6 months after starting chemotherapy treatment, there was only a higher risk of developing brain metastases in patients that started PCI later than 6 months (Aupérin et al., 1999). Regular contrast-enhanced cranial MRI follow up should be available if PCI is not performed.

Would you prefer cisplatin over carboplatin for upfront treatment?

Recommendation: Due to lower probability of developing

hematological toxicity, cisplatin should be considered.

The substitution of cisplatin for carboplatin could be considered due to its different toxicity profile, however taking into account that the neutropenia rate is increased, and that the current evidence shows that the use of granulocyte colony stimulating factor in conjunction with chemotherapy and radiotherapy increases the toxicity. In a meta-analysis of 4 randomized studies, it was shown that the substitution of carboplatin for cisplatin did not result in a difference in response rate (67 % vs. 66 %) and overall survival (9.6 vs. 9.4 months), only in the toxicity profile, with higher rates of neutropenia with carboplatin and more nausea, neuropathy, and nephropathy with cisplatin (Rossi et al., 2012).

18. Extensive disease

Do you consider that first-line chemotherapy alone or in combination with immunotherapy must be delayed in extensive disease?

Recommendation: In patients with extensive disease the omission of chemotherapy treatment is not recommended.

SCLC is an extremely aggressive tumor, and important clinical benefit is obtained with systemic treatment. A delay of no more than two weeks between diagnosis and the onset of treatment is preferred. Based platinum combinations with immunotherapy is the standard of treatment, due to response rates and toxicity profile. Atezolizumab in combination with chemotherapy showed an improvement in the median OS of 12.5 months versus 10.3 months in the chemotherapy arm (Horn et al., 2018), likewise a durvalumab combination regimen showed a similar improvement (Paz-Ares et al., 2019).

Would you give consolidative RT to the primary tumor in extensive disease?

Recommendation: Due to the controversial benefit in terms of OS, though there is a clear benefit in PFS and local recurrence, consolidative RT could be omitted.

For SCLC extensive disease with response to initial treatment, consolidative thoracic RT improves PFS. But the benefit in the median OS is unclear. For patients who are candidates to this treatment a dose of 45 Gy in 15fx or 30 Gy in 10Fx is preferred (Rathod et al., 2019; Slotman et al., 2015).

Can prophylactic radiotherapy to the brain be suspended in extensive disease?

Recommendation: PCI can be omitted because of the controversial benefit in survival.

In extensive disease the benefit of prophylactic radiotherapy to the brain is controversial due to discordant results. In addition to the current systemic treatment, the recommendation is that it could be omitted to decrease the risks of the patients by offering follow-up only.

In the phase III study conducted by the European Organization for Research and Treatment of Cancer (EORTC), the results demonstrated a reduction in the incidence of symptomatic brain metastases with the use of prophylactic radiation therapy (15 % versus 40 %, HR 0.27, 95 % CI 0.16–0.44), with a median overall survival of 6.7 months versus 5.4 months in favor of those receiving prophylactic radiotherapy, however, it should be noted that in this study brain imaging was not routinely performed to confirm the presence of metastases prior to initiation of radiation therapy (Slotman et al., 2007). In a second study conducted in Japan with 224 patients who had previously undergone MRI to rule out occult metastatic disease in the brain, no improvement in overall survival was found in patients undergoing prophylactic radiation therapy (median 11.6 months versus 13.7 months, HR 1.27, 95 % CI 0.96–1.68), it only demonstrated a decreased incidence of brain metastases (33 versus at one year) (Takahashi et al., 2017). Regular contrast-enhanced cranial MRI follow up should be available if PCI is not performed.

Should we administer second or further lines of therapy to SCLC patients during the pandemic?

Recommendation: Considering prognosis and treatment effectiveness, delaying, or omitting second line treatment could be considered.

Even though SCLC responds well to the first line of treatment, most patients relapse with resistant disease. Patients with rapid progressions within less than 3 months have a low probability of response, and in these patients clearly could consider for BSC. Other populations are represented by those patients who progress after 3 months, in this group of patients, prognosis could be less ominous. Remarkably, SCLC in second line therapy have a median OS of 4–5 months, and a poorer prognosis in platinum refractory patients with ORR < 10 %. Even in platinum-sensitive patients ORR does not exceed 25 % (Owonikoko et al., 2012).

19. Malignant pleural mesothelioma

Malignant Pleural Mesothelioma (MPM) is a relatively low-frequency tumor, nonetheless worldwide incidence has been rising during the last decade, and it is likely that this trend will continue. The exposure to asbestos is accountable for approximately 80 % of MPM cases (Baas et al., 2015). Following this pattern, several large-scale epidemiological analyses predicts that incidence in Europe and Latin America will reach its highest historic level in 2020 (Roe and Stella, 2015). Screening for mesothelioma in high risk population has been studied and is not recommended based on the absence of benefit in mortality.

20. Diagnosis

Do you consider it the preferred option to perform a tru-cut biopsy for the diagnosis of mesothelioma?

Recommendation: Patients with suspicious of malignant pleural mesothelioma preferably may undergo a CT-guided biopsy for diagnosis, avoiding more invasive procedures like thoracoscopy or VATS.

Thoracoscopic biopsy is the preferred approach in mesothelioma, however, noninvasive procedures should be preferred during the pandemic. All procedures in symptomatic patients should be guided and scheduled according to local resource availability. Avoiding a delay in diagnosis, especially in symptomatic patients. Cytologic assessment could guide diagnosis and minimize invasive inpatient procedures, nonetheless, significant sampling errors can occur and often are reported as negative or inconclusive (Kindler et al., 2018).

21. Treatment

If a patient starts neoadjuvant chemotherapy, do you recommend surgery to complete treatment in localized (I-IIIa) mesothelioma?

Recommendation: Patients with localized disease must be discussed in a multidisciplinary session aimed for curative intent, considering neoadjuvant chemotherapy followed by surgery (preferably total pleurectomy/decortication).

Patients with mesothelioma often present with high symptoms burden that require attention promptly, even in early stages. Considering the limited access to surgery and hospitalization risks, neoadjuvant treatment could be preferred over adjuvant approaches during the pandemic. Extrapleural pneumonectomy is associated with increased mortality and morbidity, despite this, it is a valid procedure considering pandemic situation, total pleurectomy is considered safer (Cao et al., 2014; Treasure et al., 2011).

Do you have any consideration for trimodality (chT, surgery & RT) treatment?

Recommendation: We currently do recommend trimodal treatment, including radiotherapy. This is a fast-progressing tumor which is radiosensitive and therefore OS benefit could be achieved with trimodal therapy.

The efficacy of trimodal treatment using chemotherapy surgery and hemithoracic radiotherapy has been explored in some retrospective analyses and phase 2 trials with positive results. An increase in the median overall survival up to 20–29 months in patients who complete the treatment has been reported (Krug et al., 2009; Kapeles et al., 2018; Thieke et al., 2015; de Perrot et al., 2009; Santoro et al., 2008). However, an important increased risk of developing pneumonitis up to 30 % has to be assumed (Rimner et al., 2016).

Would you consider deferring systemic treatment 4–6 weeks or until progression (clinical or radiological) in asymptomatic patients?

Recommendation: Patients could be considered for deferring cytotoxic therapy if they are asymptomatic and have a low burden of disease.

Some guidelines recommend deferring treatment in asymptomatic patients with good functional status with unresectable disease, considering starting treatment after clinical or radiographical progression. This could be a good option for selected patients that could be tracked to identify symptoms of progression during pandemic (Kindler et al., 2018).

Do you recommend starting systemic treatment in symptomatic patients with advanced disease and recent diagnosis of mesothelioma?

Recommendation: Consider starting first-line treatment in every symptomatic patient preferably with a carboplatin-based regimen in combination with pemetrexed.

Comparison data has emerged between cisplatin versus carboplatin regimens combined with pemetrexed in medically inoperable population. Oncological outcomes in a cohort of more than 1,700 patients were similar (Santoro et al., 2008). Guidelines recommend carboplatin-based regimen even in patients with good functional status PS 0–1. Options for patients who are not candidates for platinum could be monotherapy regimens with pemetrexed or vinorelbine with poorer outcomes (Muers et al., 2008; Scagliotti et al., 2003).

Do you consider maintenance therapy has a role?

Recommendation: Due to the lack of efficacy in the available data, pemetrexed maintenance therapy is not recommended. Regarding bevacizumab, we do not consider the benefit could outweigh the risks of COVID-19 infection.

Two trials, and one phase 3 trial have demonstrated an OS benefit with bevacizumab both during the induction phase and as maintenance. Remarkably, the median OS benefit does not exceed the 3 months, at the cost of increased grade 3–4 adverse events (Zalcman et al., 2016). Additionally, considering the extra visits, omitting maintenance during the pandemic is advised (Ceresoli et al., 2013). The efficacy of pemetrexed maintenance therapy is not well established and should not be recommended as well.

Do you recommend starting second-line treatment in asymptomatic patients?

Recommendation: Second-line treatment in asymptomatic patients could be delayed until clinical or radiological progression, considering risks during the pandemic.

Limited data are available to guide second-line treatment and beyond. Prognosis in patients who progress is ominous, and a standard of

care is not available. Limited evidence from phase II trials have identified subgroups of patients who will benefit from receiving subsequent therapy. In the other hand checkpoint inhibitors therapy is emerging in this scenario and could be used for symptomatic patients, independently of PDL1- expression. A monotherapy strategy with pembrolizumab (Alley et al., 2017a; Alley et al., 2017b; Metaxas et al., 2018) or nivolumab (Quispel-Janssen et al., 2018) could represent safer options when compared with the combined treatment with nivolumab and ipilimumab (Scherpereel et al., 2019; Disselhorst et al., 2019).

22. Discussion

In the midst of the COVID-19 pandemic, oncologists will need to weigh the risks of death and morbidity from COVID-19 against the magnitude of benefit of intended cancer therapies. Early estimates from China suggest an overall case fatality rate of 2%, increasing to 8% for 70–79 year-olds, and 15 % for those ≥ 80 years of age (Wu and McGoogan, 2020). Case fatality rates (CFR) are also markedly higher among patients with comorbidities, 11 % for cardiovascular disease, 7% for diabetes and 6% for chronic respiratory disease. Patients with cancer are among those most vulnerable to severe illness from respiratory viral infections (Hijano et al., 2018). The pooled prevalence of cancer in patients with COVID-19 was 2.0 % (95 % CI 2–3%). There are clear differences in the frequency of COVID-19 in cancer patients depending on the geographical location, being 5% in Italy, 6% in France, 4% in Korea and 2% in China. Overall, cancer was associated with a 2.84-fold significantly increased risk of severe illness (OR = 2.84, 95 % CI 1.75–4.62, $P < 0.001$) and a 2.60-fold increased risk of death (OR 2.60, 95 % CI 1.28–5.26, $P = 0.008$) in patients with COVID-19 (Gao et al., 2020). Memorial Sloan Kettering Cancer Center experience with COVID-19 demonstrated severe disease in 20 % of cancer patients, with an overall CFR of 9%. Similar to other studies in the general population, they found that age, non-white race, cardiac disease, hypertension, and chronic kidney disease correlated with severe outcomes (Robilotti et al., 2020; Garg et al., 2020).

Some multidisciplinary and expert workgroups have established recommendations regarding the treatment of lung cancer during the COVID-19 pandemic. The main purpose until now was to create guidance for the oncologist, focused on general recommendations; considering patient priorities, and available resources for diagnosis and treatment. This pandemic is a new phenomenon worldwide and, in the course, all health-care workers around the world are learning to face the disease by itself and the collateral damage created by an overwhelmed health-care system.

Recently a publication established interesting recommendations about patients with a lung cancer diagnosis during COVID-19 pandemic with the shared purpose to avoid contagious situations for patients and health professionals (Dingemans et al., 2020). Available information was analyzed deeply and extrapolated to general recommendations about lung cancer care. Nevertheless, mesothelioma was not considered for this purpose and the recommendations about small cell lung cancer were limited. Additionally, considering the lack of information and the low evidence of the available publications, we consider a consensus of experts through a Delphi process an option to reinforce and support clinical approaches, giving more certainty about management in this population throughout COVID-19 pandemic.

In the present consensus, recommendations about common clinical scenarios in the thoracic attention units were presented, regarding diagnosis, attention, and treatment of thoracic malignancies. Those recommendations were formulated based on shared information by academic societies, experts' opinions, and available publications (retrospective data mainly) related to the pandemic; adapted to the standard of care treatment in thoracic malignancies. The formulated recommendations were created to represent options which should only be considered in the face of overwhelmed health systems, such as those currently found in many countries worldwide. Recommendations were

presented in 16 modules and shared with an expert panel. Each panelist was able to make suggestions or changes to the recommendations before and after voting.

All recommendations were voted in a virtual session, one round by each module, to create a consensus. Extra time after consensus was provided to experts to give additional commentaries or suggestions. To the best of our knowledge, this is the first interactive consensus of experts considering the main thoracic neoplasms and specific aspects of medical management. Moreover, the added value given by a consensus of experts in the field is unprecedented in terms of recommendations for thoracic malignancies during the COVID-19 pandemic. This will lead the readers to know the proportion of agreement and disagreement and therefore weight each recommendation according to their specific health care situation.

For example, in clinical Stage I and II, our results regarding voting in these scenarios confirm the results of the previously mentioned publication (Dingemans et al., 2020) about the possible deleterious effects in outcomes by delaying surgery. Furthermore, we provide insights regarding adjuvant treatment and preferable regimens considering toxicity. In the same manner, our consensus gives some interesting consideration about different schedules in terms of radiotherapy (like hypofractionation) and other alternative options of treatment.

In the locally advanced disease scenario, most of the experts agree about the priority of initiating treatment without delays. Our consensus additionally adds discussion related with some acceptable options (like shorter courses of radiotherapy) of treatment that have been described without affecting oncological outcomes and can be considered to provide less toxicity (immunosuppression), and the possible benefit of reducing the number of visits to the hospital or clinics.

In the case of advanced disease setting, a considerable agreement with the previously established recommendations in other publications emerged. For example, some practices related to the administration of TKIs and monitoring of adverse events via phone calls or virtual resources. Considerations about the safety of starting immunotherapy treatment and preference for longer intervals of dosing, looking for the best sake of the patients are also discussed. This reported agreement shows that these alternative practices are safe and before we have more strong evidence, these could represent valid options.

In summary, our work could complement the work recently presented by Dingmans et al., approaching clinical scenarios which are not considered in their publication, reinforcing most of their recommendations with a consensus of experts and considering other neoplasms like mesothelioma that were excluded in their publication.

23. Conclusions

Patients with thoracic malignancies are a vulnerable population during the COVID-19 pandemic. Measures to avoid the collapse of health systems around the world are necessary to guarantee attention to this population. Thoracic cancer patients should be offered treatment according to the accepted standard of care until a shortage of services requires a progressive reduction in medical procedures. At some point during the pandemic, an important deficiency of human, economical, and health resources is expected. The pandemic is an emerging, rapidly evolving situation, and contingency plans are necessary in case the standard of care approaches cannot be implemented. Moreover, alternative recommendations intended not to adversely impact the patients' prognosis must be in the mind of the oncologists to face the pandemic. Most of the surgeries, radiotherapy plans, and systemic therapies can take a long time to deliver and potentially expose patients to multiple visits to healthcare facilities. Medical attention must be prioritized, identifying the most critical situations that require immediate attention and postponing treatment for patients with less severe conditions.

In this consensus, experts in thoracic malignancies from Latin America and Europe give important recommendations regarding

detection of COVID-19, diagnosis, treatment (chemotherapy, radiotherapy, and surgery) and follow-up of these patients. To the best of our knowledge, few recommendations related with thoracic malignancies and active COVID-19 disease are available and this expert panel addressed valuable information to guide medical attention.

The alternative strategies stated in this consensus are focused on risk reduction and should be considered for each patient while the pandemic persists. The multidisciplinary consensus, to individualize patient medical attention, must be maintained as possible. It is reasonable that each multidisciplinary team take specific measures depending on the local severity of the pandemic. Some surgical, radiation, and medical oncology practices may be currently operating in places that have not yet been strongly affected by this pandemic.

There is scarce information about the potential consequences of modifications to the standard of care. Additionally, until now, the impact, timeline, and duration of pandemic remain unknown; consequently, the uncertainty for cancer patients regarding their treatment will last longer. However, with this pandemic having reached all areas across the globe, there is an increasing need for guidance for all oncologists to optimize resources, until this current crisis is over. With some luck, in the short future, we will recover the certainty and security to treat cancer patients using the established standard of care.

Declaration of Competing Interest

Dr. Christian Cagleovic: Honoraria: Andes Biotechnologies. Speaker: MSD, BMS, Lilly. Principal Investigator: MSD, GSK, Bayer, Boehringer Ingelheim, Astellas, Roche, Astra Zeneca, BMS, Novartis. Advisory and Consulting: MSD, BMS, Roche, Boehringer Ingelheim. Sponsored Educational Program (including travel, accommodations and expenses): BMS, MSD, Roche.

Dr. Suraj Samtani: Speaker: MSD. Advisory and Consulting: MSD, Roche. Sponsored Educational Program (including travel, accommodations and expenses) MSD, Roche, AstraZeneca

Mauricio Burotto: Speaker: MSD, Roche, Astra Zeneca, BMS, Novartis. Advisory and Consulting: MSD, BMS, Roche

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Dr. Marisol Arroyo-Hernández: Reports personal fees from AstraZeneca.

Dr. Ludwig Bacon: Speaker: AstraZeneca/ Boehringer Ingelheim/ Roche/ Asopharma /

Advisor Board: Astra Zeneca / Bayer / Novartis/

Dr. Vladmir Cordeiro de Lima, MD, PhD: Speaker: MSD, BMS, Boehringer-Ingelheim, Roche, Astra-Zeneca. Principal Investigator: BMS, Astra-Zeneca, Janssen, Roche, Millennium, Celgene, MSD. Advisory and Consulting: MSD, BMS, Roche, Boehringer Ingelheim, Astra-Zeneca. Sponsored Educational Program (including travel, accommodations and expenses): BMS, MSD, Astra-Zeneca.

Dr. Lucia Viola: Consulting or Advisory Role, Company: AstraZeneca; Travel, Accommodations, Expenses Company: Mundipharma, Boehringer Ingelheim, Astra Zeneca

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