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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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**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)

Likewise, during the AACR congress, Garassino et al. reported the preliminary results of the global registry TERAVOLT, 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...
| QUESTION/RECOMMENDATION | CATEGORY 1 | CATEGORY 2 | CATEGORY 3 | CONSENSUS |
|-------------------------|------------|------------|------------|-----------|
| Do patients with thoracic malignancies need to be treated preferably through virtual resources when possible reducing hospital visits? | 89% 11% | 9% 91% | YES (STRONG) |
| Patients with thoracic neoplasms must be followed and whenever possible treated through virtual resources thus avoiding hospital visits. | 100% | | |
| Detection of SARS-CoV-2 | 77 9 14 | YES | 60 | YES (STRONG) |
| Does every patient with a thoracic neoplasm need a baseline CT-scan as a first screening test? | 77% 10% 13% | YES (STRONG) |
| It is recommended to perform a CT-scan, where available and accessible to patients, with a focused imaging approach for lung nodules. | 86% | 8% 9% | YES | |
| Does every patient with a thoracic neoplasm need a SARS-CoV-2 PCR test to rule out active disease? | 60% 14% 26% | YES |
| 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. | 29% 40% 31% | YES | |
| Diagnosis and staging of all cancer must be performed with a multidisciplinary team, ideally in a virtual environment. | 90% | 10% 90% | YES | |
| Should every patient with a suspicious CT-scan undergo a SARS CoV-2 PCR test to rule out COVID-19? | 90% 10% 90% | YES | |
| Detection of SARS-CoV-2 | 50% 23% 27% | YES | |
| Would you consider SBRT for T1 surgical patients considering potential delays and shortage in resources for surgery? | 83% 11% 6% | YES | |
| SBRT could be an acceptable alternative option to treat patients with a suspicious or confirmed diagnosis of COVID-19. | 56% 30% 14% | YES (STRONG) |
| Should every patient with a stage II-III NSCLC continue receiving adjuvant treatment? | 56% 30% 14% | YES (STRONG) |
| Carboplatin/Pemetrexed could be the preferable option because of the lower toxicity. | 56% 30% 14% | YES (STRONG) |
| Would you prefer lower toxicity regimens such as Carboplatin/Pemetrexed for adjuvant treatment? | 56% 30% 14% | YES (STRONG) |
| RT could be offered as an adjuvant treatment but can be postponed after chemotherapy or 3 months after surgery. | 45% 33% 22% | YES | |
| Is G-CSF use recommended for routine use? | 56% 30% 14% | YES (STRONG) |
| G-CSF should not be routinely used, only if neutropenia develops and represents an issue. | 56% 30% 14% | YES (STRONG) |
| 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. | | | |
| Would you choose a hypofractionated schedule for sequential chemoradiation? | 30% | 33% 45% | YES | |
| Hypofractionated radiotherapy is not recommended in this clinical scenario. | 50% 23% 27% | YES | |
| Advanced disease | 50% 23% 27% | YES | |
| Would you consider an adjuvant hypofractionated approach? | 30% | 33% 45% | YES | |
| Hypofractionated radiotherapy is not recommended in this clinical scenario. | 50% 23% 27% | YES | |
| Would you consider systemic therapy after a negative PET scan? | 50% 23% 27% | YES | |
| Would you prefer to give adjuvant chemotherapy in a sequential approach? | 50% 23% 27% | YES | |
| Would you prefer a sequential approach? | 50% 23% 27% | YES | |
| Would you consider adjuvant chemotherapy over a sequential approach? | 30% | 33% 45% | YES | |
| Would you prefer to give adjuvant chemotherapy in a sequential approach? | 50% 23% 27% | YES | |
| Advanced disease | 50% 23% 27% | YES | |
| Would you consider systemic therapy after a negative PET scan? | 50% 23% 27% | YES | |
| Would you prefer to give adjuvant chemotherapy in a sequential approach? | 50% 23% 27% | YES | |
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| Would you consider adjuvant chemotherapy over a sequential approach? | 30% | 33% 45% | YES | |
| Would you prefer to give adjuvant chemotherapy in a sequential approach? | 50% 23% 27% | YES | |
| Advanced disease | 50% 23% 27% | YES | |
| QUESTION/RECOMMENDATION CATEGORY | 1 | 2 | 3 | CONSENSUS |
|----------------------------------|---|---|---|-----------|
| 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 in monotherapy or after a first-line treatment with a checkpoint inhibitor-based regimen? | 67 | 30 | 3 | YES (STRONG) |
| 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). | 81 | 11 | 8 | YES (STRONG) |
| Would you consider postponing second-line treatment in asymptomatic patients who are suitable for immunotherapy? | 73 | 22 | 5 | YES (STRONG) |
| Ideally without delays. | | | | |
| Tyrosine Kinase Inhibitors (TKIs) | | | | |
| Do you consider TKIs treatment safe during pandemic? | 82 | 10 | 8 | YES (STRONG) |
| Patients on TKIs should be monitored for pulmonary symptoms in every visit or telephone call, but patients suitable to receive TKIs must do so. | 85 | 8 | 0 | YES (STRONG) |
| Do you recommend maintaining TKI treatment 2 months beyond progression in asymptomatic patients with a systemic slow growing-disease in non-critical sites? | 73 | 21 | 6 | YES (STRONG) |
| TKI treatment could be maintained beyond progression, if asymptomatic and slow growing-disease is present, especially for patients without resistant mutations. | 82 | 10 | 8 | YES (STRONG) |
| Patients without access to an MRI at diagnosis, could be delayed if provided by telemedicine. | 60 | 32 | 8 | 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? | 13 | 57 | 30 | YES (STRONG) |
| Carcinoembryonic antigen (CEA) could be considered in the monitoring of NSCLC patients to obtain prognostic and predictive information during the pandemic. | 84 | 14 | 2 | YES (STRONG) |
| Should you recommend using immunotherapy alone rather than combination treatments with immunotherapy and chemotherapy in patients with TPS≥1−49%? | 71 | 21 | 0 | YES (STRONG) |
| Patients with a TPS≥1−49% and an increased risk of neutropenia or considerable toxicity should consider pembrolizumab monotherapy as an option in this current scenario. | 37 | 50 | 13 | 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? | 71 | 21 | 8 | YES (STRONG) |
| Patients on chemotherapy or combination treatments with immunotherapy could be monitored with 4-weekly outpatient visits. | 60 | 35 | 5 | 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 should be considered. | 84 | 14 | 2 | YES (STRONG) |
| Can Surgery be omitted in early stages of small cell lung cancer? | 63 | 29 | 8 | YES (STRONG) |
| Can chemotherapy treatment be delayed by 4−6 weeks in limited disease? | 84 | 14 | 2 | YES (STRONG) |
| Can radiation therapy be delayed in patients with limited disease? | 63 | 29 | 8 | YES (STRONG) |
| Would you prefer cisplatin over carboplatin for upfront treatment? | 61 | 23 | 16 | YES (STRONG) |
| Small cell lung cancer irreversible disease | 68 | 22 | 0 | YES (STRONG) |
| Would you prefer cisplatin over carboplatin for upfront treatment? | 61 | 23 | 0 | YES (STRONG) |
| Do you consider first-line chemotherapy alone or in combination with immunotherapy treatment is not recommended. | | | | |
| Could you consider using alternative regimens with longer intervals between treatment applications? | 85 | 13 | 0 | YES (STRONG) |
| Alternative regimens, like 4-weekly or 6-weekly regimens could be used safely during the pandemic to diminish visits to hospital. | 76 | 24 | 0 | YES (STRONG) |
| Small cell lung cancer limited disease | 85 | 13 | 0 | YES (STRONG) |
| Would you consider using neoadjuvant chemotherapy or TKI? | 89 | 8 | 3 | YES (STRONG) |
| Selected asymptomatic patients with more than 6 months of treatment, and good tolerance may be monitored by telemedicine resources. | 90 | 7 | 2 | YES (STRONG) |
| 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? | 89 | 8 | 3 | YES (STRONG) |
| Patients may start treatment without a brain MRI, since delaying systemic treatment may not be recommended. | 84 | 14 | 2 | YES (STRONG) |
| Can Radiotherapy be delayed in patients with limited disease? | 84 | 14 | 2 | YES (STRONG) |
| Would you recommend maintaining TKI treatment 2 months beyond progression in asymptomatic patients with a systemic slow growing-disease in non-critical sites? | 73 | 21 | 6 | YES (STRONG) |
| Would you prefer cisplatin over carboplatin for upfront treatment? | 61 | 23 | 16 | YES (STRONG) |
| 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. | 24 53 | 44 66 | 32 21 | YES (STRONG) |
| Can prophylactic radiotherapy to the brain be suspended in extensive disease? PCI can be omitted because of the controversial benefit in survival. | 29 71 | 40 24 | 31 5 | YES (STRONG) |
| Do you consider it the preferred option to perform a tru-cut biopsy for the diagnosis of mesothelioma? | 66 6 | 21 71 | 13 8 | YES (STRONG) |
| 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 setting. | 71 16 | 24 84 | 5 0 | YES (STRONG) |
| Would you consider deferring systemic treatment 4−6 weeks or until progression (clinical or radiological) in asymptomatic patients? | 29 29 | 40 37 | 31 37 | YES (STRONG) |
| 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 29 | 32 37 | 61 29 | YES (STRONG) |
| Would you give coronary angiography to this patient? Consideration of factors to determine the benefit and risk should be made. | 16 53 | 8 44 | 5 32 | YES (STRONG) |
| Do you consider maintenance therapy has a role? 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. | 0 0 | 0 0 | 0 0 | YES (STRONG) |
| 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 29 | 32 37 | 61 29 | YES (STRONG) |

Table 1 (continued)

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.
“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 (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 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 (Nicastri 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 hypofractioning 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; Auperin 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 (Higgins 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 readressed 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 naive 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 mono-therapy 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 IFNγ (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 hyper-activation of T-cells that contribute to the severe immune injury. This proinflammatoty 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 ≥ 1-49%?**

**Recommendation:** Patients with a TPS ≥ 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; HR0.69), 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 (Morrissy 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 ≥ 3 pneumonitis was presented in 0.81 % of patients in the total cohort (Suh et al., 2018). Likewise, all grade and grade ≥ 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 metaanalysis 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 monitoring

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 monitoring 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 monitoring 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
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 Ruyscher 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).
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).

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 PD-L1 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 Dingemans 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 Caglevic: 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.

Dr. Santiago Viteri: Dr. Viteri reports personal fees and non-financial support from Roche, personal fees from BMS, non-financial support from OSEPharma, personal fees from MSD, non-financial support from Merck Serono outside the submitted work.

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

Dr. Ludwlng Bacon: Speaker: AstraZeneca/ Boehringer Ingelheim/ Roche/ Asopharma /
Advisor Board: Astra Zeneca / Bayer / Novartis/

Dr. Vladimir 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

Dr. Luis Mas: speaker Roche, MSD, BMS.

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