PHILIPPINE SOCIETY OF MEDICAL ONCOLOGY (PSMO)
CONSENSUS RECOMMENDATIONS IN THE MANAGEMENT OF LUNG CANCER DURING COVID-19 PANDEMIC IN THE CORONAVIRUS DISEASE 2019 (COVID-19) ERA

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BACKGROUND

Coronavirus disease – 2019 (COVID-19) has had a devastating impact across the world. With high rates of transmission and no curative therapies or vaccine yet available, the current cornerstone of management focuses on prevention by social distancing. This includes decreased healthcare contact for patients. Patients with lung cancer are a particularly vulnerable population, where the risk of mortality from cancer must now be balanced by the potential risk of a life-threatening infection. In these unprecedented times, a collaborative and multidisciplinary approach is required to streamline, but not compromise care.

The major goal of lung cancer management during the COVID-19 pandemic is to minimize the risk of exposing the patient and staff to infection, while managing all life-threatening aspects of their disease.

Clinical Questions:

Should asymptomatic Lung cancer patients be screened for Covid -19 through RT-PCR?

While all types of malignancies seem to be associated with high COVID-19 prevalence, morbidity and mortality, lung cancer represents a specific scenario of cumulative risk factors for COVID-19 complications, including older age, significant cardiovascular and respiratory co-morbidities, smoking-related lung damage, as well as the unavoidable addition of treatment-related immune impairment or suppression.

Despite the current lack of robust data, it is essential to establish an international consensus on testing for SARS- CoV-2 in lung cancer patients, where the early identification of SARS-CoV-2 may result in tailored management. In this scenario, baseline SARS-CoV-2 testing for all patients affected by lung cancer maybe recommended. In addition, for those patients with a negative swab test and new ground-glass opacities detected on CT scan, with or without new respiratory symptoms, bronchoscopy should be considered to increase testing sensitivity.

(Passaro A, Peters S, Mok TSK, Attili I, Mitsudomi T, de Marinis F, Testing for COVID-19 in lung cancer patients, Annals of Oncology (2020), doi: https://doi.org/10.1016/ j.annonc.2020.04.002.)

Early Stage

1. Should we delay adjuvant chemotherapy in stage T1A-T2bN0 with negative prognostic features? Or adjuvant chemotherapy for patients with significant comorbidities, or elderly patients (more than 70 yrs old)?

- The ESMO-MCBS classified this group of patients as LOW PRIORITY. Discuss risk and benefit to the patient prior to starting the treatment. Adjuvant chemotherapy for patients with significant comorbidities, or elderly patients >70y, should be discussed and possibility omitted. If the patient is stable enough then

the treatment **can be delayed for the duration of the COVID-19 pandemic.** (ESMO 2020)

- Adjuvant therapy is not recommended for stage I NSCLC patients. In cases where local conditions render systemic chemotherapy hazardous resulting in the inability to start adjuvant cytotoxic chemotherapy, adjuvant EGFR tyrosine kinase inhibitor therapy could be considered for resected EGFR mutation-positive NSCLC (59, 60).If patients are clinically stable post adjuvant therapy, follow-up imaging can be delayed for 3-4 months.

  (Dingemans A-MC, Soo RA, Jazieh AR, Rice SJ, Kim YT, Teo LL, Warren GW, Xiao S-Y, Smit EF, Aerts JG, Yoon SH, Veronesi G, De Cobelli F, Ramalingam SS, Garassino MC, Wynes MW, Behera M, Haanen J, Lu S, Peters S, Ahn M-J, Scagliotti GV, Adjei AA, Belani CP, Treatment guidance for lung cancer patients during the COVID-19 pandemic, Journal of Thoracic Oncology (2020), doi: https://doi.org/10.1016/j.jtho.2020.05.001.)

2. When should we start adjuvant chemotherapy in T3/4 or N2 disease for young and medically fit patients?

   - The ESMO-MCBS classified this group of patients as MEDIUM PRIORITY. Treatment must be discussed with the patient considering the clinical and prognosis. If treatment is to be given, it should be given **within 6 weeks** so as not to impact the clinical outcome significantly. (ESMO 2020)
   - In patients with resectable locally advanced disease with a single positive mediastinal station (resectable non bulky IIIA) or T3N1 tumors for which surgical treatment is scheduled after induction therapy (56), the timing of surgery could be planned such that adjuvant chemotherapy starts at a later date. This approach is based on two main reasons; 1) to avoid exposing the patient to the risk of infection during the frequent trips to and from the hospital for chemotherapy cycles at the apex of the COVID-19 emergency period; 2) to reduce chemotherapy induced immunosuppression which can expose the patient to an increased risk of COVID -19 and, in case of infection, to serious pulmonary complications with a delay of potential curative surgical resection.

     (Dingemans A-MC, Soo RA, Jazieh AR, Rice SJ, Kim YT, Teo LL, Warren GW, Xiao S-Y, Smit EF, Aerts JG, Yoon SH, Veronesi G, De Cobelli F, Ramalingam SS, Garassino MC, Wynes MW, Behera M, Haanen J, Lu S, Peters S, Ahn M-J, Scagliotti GV, Adjei AA, Belani CP, Treatment guidance for lung cancer patients during the COVID-19 pandemic, Journal of Thoracic Oncology (2020), doi: https://doi.org/10.1016/j.jtho.2020.05.001.)

3. When is the optimal time to initiate concomitant chemoradiotherapy for SCLC limited disease stage I/II?

    - The ESMO-MCBS classified this group of patients as MEDIUM PRIORITY. Treatment must be discussed with the patient considering the clinical and prognosis. If treatment is to be given, it should be given **within 6 weeks** so as not to impact the clinical outcome significantly.(ESMO 2020)
    - SCLC is a highly aggressive disease and is characterized by a rapid response to chemotherapy. Postponing first line treatment will therefore rarely be possible. For patients with limited disease SCLC the standard treatment is concurrent chemoradiotherapy where radiotherapy is given twice daily for three weeks or once daily for 6 weeks with comparable disease control and toxicity outcomes.

      (Dingemans A-MC, Soo RA, Jazieh AR, Rice SJ, Kim YT, Teo LL, Warren GW, Xiao S-Y, Smit EF, Aerts JG, Yoon SH, Veronesi G, De Cobelli F, Ramalingam SS, Garassino MC, Wynes MW, Behera M, Haanen J, Lu S, Peters S, Ahn M-J, Scagliotti GV, Adjei AA, Belani CP, Treatment guidance for lung cancer patients during the COVID-19 pandemic, Journal of Thoracic Oncology (2020), doi: https://doi.org/10.1016/j.jtho.2020.05.001.)

<u>Locally Advanced</u>

1. When should we start concomitant or sequential chemoradiotherapy for inoperable NSCLC Stage III?

    - Starting treatment for stage III non-small cell lung cancer is categorized as high priority (ESMO guidelines 2020).
    - The standard of care in 2020 pre-pandemic for good performance status unresected Stage III Non Small Cell Cancer patients is concurrent platin-based doublet with 6 weeks of radiotherapy followed by adjuvant Durvalumab (Pacific trial) (International Association for the Study of Lung Cancer (April 2020).
    - Estro-Astro Guidance on stage III patients receiving Chemo-RT or RT (RTO 4/20)
        1. The Delay of Chemo-RT by 4-6 weeks is not recommended by 96% of panelists
        2. Hypofractionated RT is recommended by 46% of the panelists
            - During RT only course: yes 97%
            - During chemo then RT: yes 97%
            - During concurrent chemo-RT: no 73%
    - Estro-Astro Lung Cancer Radiation Oncology Covid-19 Practice Guidelines 2020 (Guckenberger, et al. April 2020)
        - The Postponement or Interruption of care (RT) recommended for covid-19 positive patients
            - Stage III NSCLC: 100% of the panelists agree (strong consensus)

    - In pandemic environment with constraint resources, triage defined for each stage and patient scenario
    - Stage III Non-small Cell Lung Cancer considered as very high priority for RT resources
- Curative intent systemic therapy should continue uninterrupted as local resources permit (Short-term recommendations for non-small cell lung cancer management during the Covid-19 pandemic (NCCN) (4/29/2020)
- For unresectable stage III patients treated with concurrent definitive chemo/RT, consider delaying consolidation immunotherapy with durvalumab for up to 6 weeks following completion of chemoradiation (Short-term recommendations for non-small cell lung cancer management during the Covid-19 pandemic (NCCN) (4/29/2020)

2. When is the optimal time to initiate concomitant chemoradiotherapy for SCLC limited disease stage III?

- Starting treatment for small cell lung cancer limited disease is categorized as high priority (ESMO Guidelines 2020).
- Estro & Astro Covid-19 Practice Recommendation
    - Postponing initiation of treatment by 4-6 weeks is not recommended by 89% of the panelists
    - Hypofractioned RT beyond usual fractionation is not recommended by 67% of the panelists
    - Limited stage Small Cell Lung Cancer considered as very high priority for RT resources
    - The Postponement or Interruption of care (RT) recommended for covid-19 positive patients
        - Stage III NSCLC: 89% of the panelists agree (strong consensus)

Metastatic Lung Cancer

1. Could we postpone bone modifying agent (zoledronic acid, denosumab) that is not needed urgently?

- No data regarding postponement
- Patients receiving denosumab or low-molecular-weight heparin should be taught to self-administer. (British Thoracic Society. Lung cancer and mesothelioma service guidance during the COVID-19 pandemic. www.brit-thoracic.org.uk/about-us/covid-19-information-for-the-respiratory-community).
- Patients receiving denosumab should not routinely consult a dentist before starting.

2. Could we discontinue immunotherapy after 2 years of treatment?

    - For patients who have been on immunotherapy for greater than 2 years, further therapy should be stopped in line with currently available data (Gandhi L, Garassino MC: Pembrolizumab plus Chemotherapy in Lung Cancer. N Engl J Med 379:e18, 2018)

3. Should we continue 1st line treatment (chemotherapy, chemotherapy plus immunotherapy, immunotherapy alone or TKIs) in the metastatic setting?

    - Evaluate the indication for palliative chemotherapy, immunotherapy or both with extra care in elderly patients or patients with significant comorbidity, decreased performance (PS ≥2), social isolation, decubitus, urinary catheters, … especially in second or further lines (British Thoracic Society. Lung cancer and mesothelioma service guidance during the COVID-19 pandemic. www.brit-thoracic.org.uk/about-us/covid-19-information-for-the-respiratory-community)
    - Consider delaying chemotherapy or immunotherapy in patients who are asymptomatic and have indolent disease. (British Thoracic Society. Lung cancer and mesothelioma service guidance during the COVID-19 pandemic. www.brit-thoracic.org.uk/about-us/covid-19-information-for-the-respiratory-community)
    - Usual recommendations for chemotherapy, immunotherapy and targeted therapy apply.
    - Triweekly chemotherapy is preferred over weekly regimens (e.g. docetaxel) to limit time-in-hospital (Haut Conseil de la Santé publique. COVID-19 et Cancers Solides: Recommandations. www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=776)
    - Consider limiting palliative chemotherapy to 4 cycles and omitting pemetrexed maintenance therapy (British Thoracic Society. Lung cancer and mesothelioma service guidance during the COVID-19 pandemic. www.brit-thoracic.org.uk/about-us/covid-19-information-for-the-respiratory-community

4. Should we initiate 2nd-line chemotherapy or immunotherapy in symptomatic and progressive disease patients?

    - During this unprecedented crisis, it is important to emphasize that management of metastatic non-small cell lung cancer (mNSCLC) should still follow the principles of providing the best possible care and palliative management of our patients with an effort to improve overall survival and maintain quality of life. Especially for patients with mNSCLC, there is a fine line between providing incremental benefit in overall survival versus exposing patients to risks of infection and worse outcomes if they were to become infected with SARS-CoV-2. (Singh, A., Berman, A., Marmarelis, M., et al.: Management of Lung Cancer during the COVID-19 Pandemic DOI: 10.1200/OP.20.00286 JCO Oncology Practice)

- The use of molecular targeted therapy, immunotherapy and chemo–immunotherapy in advanced NSCLC has resulted in long term survival in a proportion of patients. Thus, the decision to initiate or interrupt treatment poses a challenge for both the patient and their physicians. (Dingemans A-MC, Soo RA, Jazieh AR, Rice SJ, Kim YT, Teo LL, Warren GW, Xiao S-Y, Smit EF, Aerts JG, Yoon SH, Veronesi G, De Cobelli F, Ramalingam SS, Garassino MC, Wynes MW, Behera M, Haanen J, Lu S, Peters S, Ahn M-J, Scagliotti GV, Adjei AA, Belani CP, Treatment guidance for lung cancer patients during the COVID-19 pandemic, Journal of Thoracic Oncology (2020), doi: https://doi.org/10.1016/j.jtho.2020.05.001.)

5. Could we start 2nd-line TKI in progressive disease patients?

- The use of oral tyrosine kinase inhibitors (TKIs) as the preferred agents managing mNSCLC bearing oncogenic driver mutations should continue, as the risks of adverse events due to these drugs in the setting of the COVID19 pandemic are either yet unknown or minimal. (Singh, A., Berman, A., Marmarelis, M., et al.: Management of Lung Cancer during the COVID-19 Pandemic DOI: 10.1200/OP.20.00286 JCO Oncology Practice)

- If there is disease progression while on targeted therapy, physicians may opt to do the following:

  A. EGFR

  - Gradual progression, continue TKI and see doctor 1-2 months later

  - Local progression, continue TKI + SRS

  - Rapidly progression: differentiate from COVID-19 infection, perform liquid biopsy for T790M after 1st or 2nd generation TKI, prescribe Osimertinib if T790M positive, if T790M negative, switch to oral chemotherapy or multiple TKIs such as anlotinib

  B. ALK

  - Switch to 2nd generation or 3rd generation ALK TKI

  (IASLC Recorded Webinar: Systemic Therapy for Advanced Stage Lung Cancer During the COVID-19 Pandemic Participants: Dr. Suresh S. Ramalingam (Moderator), Dr. Federico Cappuzzo and Dr. Caicun Zhou April 29, 2020, 9PM)

6. Can we modify or delay schedule of giving immunotherapy to reduce clinic/hospital visits?

    - For patients on single agent immunotherapy, a number of approaches have been proposed to minimize the risk of infection. One recommendation is to continue treatment for patients in the early induction phase or short-term maintenance phase of therapy. In these patients, every attempt should be made to limit the number of visits, such as lengthening the duration of cycles. The pharmacology of most of the immune checkpoint inhibitors utilized in lung cancer lends itself to much less frequent dosing than currently utilized. The plasma half-lives of atezolizumab, nivolumab, pembrolizumab, and durvalumab are 27, 26.7, 26 and 12 days respectively. Currently, nivolumab can de dosed at 480mg every 4 weeks. Atezolizumab can be dosed at a 1680 mg flat dose, and durvalumab can be dosed at 1500 mg every 4 weeks as maintenance for SCLC. These regimens can be adopted for NSCLC. Pembrolizumab at doses of 400 mg every 6 weeks for all approved indications just received regulatory approval by the US FDA and should be the schedule of choice in the current COVID-19 pandemic.

      (Dingemans A-MC, Soo RA, Jazieh AR, Rice SJ, Kim YT, Teo LL, Warren GW, Xiao S-Y, Smit EF, Aerts JG, Yoon SH, Veronesi G, De Cobelli F, Ramalingam SS, Garassino MC, Wynes MW, Behera M, Haanen J, Lu S, Peters S, Ahn M-J, Scagliotti GV, Adjei AA, Belani CP, Treatment guidance for lung cancer patients during the COVID-19 pandemic, Journal of Thoracic Oncology (2020), doi: https://doi.org/10.1016/j.jtho.2020.05.001)

Practical suggestions to treat patients with lung cancer during the SARS-COV-2 Pandemic

Table 1 Practical suggestions to treat patients with lung cancer during the SARS-CoV-2 pandemic

	Non-small cell lung cancer	Small cell lung cancer
1. *Should be started* when possible*†	► NACHT for locally advanced resectable disease‡ ► Sequential/concurrent CHT/RT§¶ for stage III disease ► First-line treatment for metastatic disease ► Palliative or ablative radiotherapy (SBRT) outside the lung**	► First-line treatment for extensive-stage disease ► Concurrent CHT/RT§ for limited-stage disease ► Palliative or ablative radiotherapy (SBRT) outside the lung**
2. *Should not be stopped* without justification	► NACHT for locally advanced resectable disease‡ ► Sequential/concurrent CHT/RT§¶ for stage III disease ► First-line treatment for metastatic disease ► Maintenance ICI*	► Concurrent CHT/RT§ for limited-stage disease ► First-line treatment for metastatic disease
3. *Can be given preferentially*	► CT/RT for stage III disease ► Oral chemotherapy for ECOG PS 2 and elderly patients (instead of intravenous)	► Oral rather than intravenous chemotherapy
4. *Can be withheld or delayed* after careful consideration††	► Withhold ACHT in patients at significant COVID-19-related risk‡‡ ► Delay ICI (within 42 days) for stage III disease after CHT/RT ► Withhold maintenance pemetrexed ► Prolong intervals of ICI*	► Prolong intervals of ICI*
5. *Should not be started* without justification	► Third and beyond lines of chemotherapy in patients at significant COVID-19-related risk‡‡	► PCI (favouring MRI surveillance) ► Thoracic consolidation radiotherapy extensive stage ► Third and beyond lines of chemotherapy in patients at significant COVID-19-related risk‡‡

*Regimens with longer interval (including ICI; ie, nivolumab 480 mg every 4 weeks or pembrolizumab 400 mg every 6 weeks) should be preferred.
†Shorter duration of chemotherapy (ie, four cycles of chemotherapy instead of six) should be discussed with patients and use of prophylactic G-CSF should be considered.
‡NACHT could be helpful to bridge time to surgery in case where surgery is not possible.
§In patients with adequate respiratory function.
¶Try to start RT on day 1 of chemotherapy, only two cycles will be needed, three cycles if starting RT with cycle 2, or sequential.
**Exception: indicated if compression of airways or bleeding. Fractions of SBRT could be reduced if organ at risk constraints (from eight fractions to five or three) and palliative RT single or in two fractions (8–10 Gy or 17 Gy, respectively) should be used where possible.
††Patients with family members or caregivers who tested positive for COVID-19 should be tested before or during any cancer treatment, whenever. If a patient results positive and is asymptomatic 28 days of delay should be considered before (re)starting the treatment. In the case of SARS-CoV-2, two negative tests at 1-week interval should be performed before (re)starting the treatment.
‡‡Patients at significant COVID-19-related risk: aged ≥70, with ischaemic cardiac disease, atrial fibrillation, uncontrolled hypertension or diabetes, chronic kidney disease.
ACHT, adjuvant chemotherapy; CHT, chemotherapy; COVID-19, coronavirus disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status; G-CSF, granulocyte colony-stimulating factor; ICI, immune checkpoint inhibitor; NACHT, neoadjuvant chemotherapy; PCI, prophylactic cranial irradiation; RT, radiotherapy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SBRT, stereotactic body radiotherapy.

Banna et al, ESMO open, April 2020.