ESMO Open
Cancer Horizons

How we treat patients with lung cancer during the SARS-CoV-2 pandemic: *primum non nocere*

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To cite: Banna G, Curioni-Fontecedro A, Friedlaender A, *et al*. How we treat patients with lung cancer during the SARS-CoV-2 pandemic: *primum non nocere*. *ESMO Open* 2020;**4**:e000765. doi:10.1136/esmoopen-2020-000765

Received 27 March 2020
Accepted 27 March 2020

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ABSTRACT

New cases of the novel coronavirus, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continue to rise worldwide. A few reports have showed that mortality due to SARS-CoV-2 is higher in elderly patients and other active comorbidities including cancer. To date, no effective treatment has been identified and management for critically ill patients relies on management in intensive care units. Patients with lung cancer are at risk of pulmonary complications from COVID-19. Furthermore, the use of chemotherapy might have a negative impact in patient's outcome. Therefore, the risk/benefit ratio of systemic anticancer treatment (SACT) has to be considered. For each patient, several factors including age and comorbidities, as well as the number of hospital visits for treatment, can influence this risk. Each hospital around the world has issued some internal policy guidelines for oncologists, aiming to limit risks during this difficult time. We hereby propose a tool to support oncologists and physicians in treatment decision for patients with lung cancer. There are several variables to consider, including the extent of the epidemic, the local healthcare structure capacity, the risk of infection to the individual, the status of cancer, patients' comorbidities, age and details of the treatment. Given this heterogeneity, we have based our suggestions bearing in mind some general factors There is not easy, universal solution to oncological care during this crisis and, to complicate matters, the duration of this pandemic is hard to predict. It is important to weigh the impact of each of our decisions in these trying times rather than rely on routine automatisms.

New cases of the novel coronavirus, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continue to rise worldwide. On 11 March 2020, the WHO declared a pandemic, with 118 326 confirmed cases and 4292 deaths reported[1] with a case mortality rate of 3.6%[2] whereas the mortality can reach 62% for critical patients and 81% for those requiring mechanical ventilation.[3] A report from the Italian Superior Institute of Health based on 3200 patients who died of SARS-CoV-2 has related mortality to elderly age and other active comorbidities including cancer.[4] Patients had a median age of 80 (range 38–100 years), a relevant increase in the mortality occurred after 70 years (from 2.7% in patients aged 60–69 years to 9.6% in those 70–79 years and 16.6%–19% in those more than 80 years). 19.4% were patients with cancer; other active comorbidities were: hypertension (76.5%), cardiac ischaemic disease (37.3%), diabetes (37.3%), atrial fibrillation (26.5%) and chronic renal insufficiency (17.5%). The presence of two or three of these comorbidities was associated with 25.7% and 47% of deaths, respectively.[4] To date, no effective treatment has been identified. Management for patients who are critically ill relies on management in intensive care units. Global health organisations are scurrying to implement preventive measures, aiming to limit transmission, through public safety measures and restrictions. In Italy and the UK, as in some other countries, recommendations aimed at limiting access of patients with cancer and their caregivers to the hospital and prioritising curative treatments have been provided by the Italian Association of Medical Oncology and the National Institute for Health and Care Excellence, respectively.[5 6]

Patients with lung cancer are at risk of pulmonary complications from coronavirus disease (COVID-19). Liang *et al* report data on 18 patients with cancer for whom the use of chemotherapy had a negative impact in patient's outcome.[7] Therefore, the risk:benefit ratio of systemic anticancer treatment (SACT) has to be considered. For each patient, several factors including age and comorbidities, as well as the number of hospital visits for treatment, can influence this risk.[8 9] Each hospital around the world has issued some internal policy guidelines for oncologists, aiming to limit risks during this difficult time. We hereby propose a tool to support oncologists and physicians in making treatment decisions for patients with lung cancer.

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.

There are several variables to consider, including the extent of the epidemic, the local healthcare structure capacity, the risk of infection to the individual, the status of cancer, patients' comorbidities, age and details of the treatment.[10] Given this heterogeneity, we have made our suggestions bearing in mind some general factors (see table 1).

All regimens with a survival benefit should be maintained and prioritised whenever possible. Palliative treatments which are less likely to improve overall survival or positively impact on a patient's quality of life would require a specific assessment of the treating physician to be discussed with the patient.

Adjuvant and neoadjuvant treatments require particular attention. For adjuvant treatment, the risk:benefit ratio may favour not giving therapy, following careful discussion with patients in terms of absolute risks, when the survival benefit is modest. Neoadjuvant chemotherapy might become attractive in delaying the need for surgery while these services would be interrupted.

Radiotherapy (RT) concurrent or sequential to chemotherapy with curative intent should be reserved for those patients with adequate respiratory function. Palliative or ablative RT (stereotactic body radiotherapy, SBRT) outside the lung should not be denied, if this does not require multiple visits to the hospital, while treatment to the lung should be limited to cases with compression of airways or bleeding. Fractions of SBRT could be reduced depending on organ at risk constraints (from eight fractions to five or three). Palliative RT as a single fraction

or two (8–10 Gy or 17 Gy, respectively) should be used where possible. MRI surveillance should be preferred to prophylactic cranial irradiation for limited or extensive-stage small cell lung cancer (SCLC) in order to reduce the number of visits; thoracic consolidation RT should be avoided in extensive-stage SCLC.

For stage III non-SCLC, RT should be started on day 1 of chemotherapy, so only two cycles will be needed. Three cycles of chemotherapy will be administered if starting RT with cycle 2, or for sequential treatment.

Patients with family members or caregivers who tested positive for COVID-19 should be tested before or during any cancer treatment, whenever possible. If a patient tests 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.

Furthermore, the following measures could be considered to limit accesses to the hospital, when possible. Regimens with longer interval, including immune checkpoint inhibitors (eg, nivolumab 480 mg every 4 weeks or pembrolizumab 400 mg every 6 weeks), should be preferred. Shorter duration of chemotherapy (eg, four cycles of chemotherapy instead of six) should be discussed with patients and maintenance chemotherapy can be withheld. Oral chemotherapy for Eastern Cooperative Oncology Group Performance Status 2 and elderly patients or instead of the corresponding intravenous drug should be considered. Guidelines to prevent and manage neutropenic sepsis should be enforced and strongly adopted; use of prophylactic granulocyte colony-stimulating factor with SACT should be considered and home delivery of antibiotics should be implemented.

This pandemic is also going to affect recruitment and participation in clinical trials. This requires careful consideration: halting recruitment into cancer trials to divert resources to fight the pandemic may be appropriate and in certain centres is mandatory.

As such, there is no easy, universal solution to oncological care during this crisis and, to complicate matters, the duration of this pandemic is hard to predict. As with all challenges, we need to adapt and evolve rapidly to treat our patients the best we can. It is important to weigh the impact of each of our decisions in these trying times rather than rely on routine automatisms, lest we forget: *primum non nocere*.

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Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

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