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Implications of COVID-19 pandemic on lung cancer management: A multidisciplinary perspective

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ABSTRACT

Treatment of patients with lung cancer during the current COVID-19 pandemic is challenging. Lung cancer is a heterogenous disease with a wide variety of therapeutic options. Oncologists have to determine the risks and benefits of modifying the treatment plans of patients especially in situation where the disease biology and treatment are complex. Health care visits carry a risk of transmission of SARS-CoV-2 and the similarities of COVID-19 symptoms and lung cancer manifestations represent a dominant problem. Efforts to modify treatment of lung cancer during the current pandemic have been adapted by many healthcare institutes to reduce exposure of lung cancer patients to SARS-CoV-2. We summarized the implications of COVID-19 pandemic on the management of lung cancer from the perspective of different specialties of thoracic oncology multidisciplinary team.

1. Background

The COVID-19 pandemic has a catastrophic impact on healthcare system worldwide due to the overwhelming infection rate with significant morbidity and mortality. Cancer patients have a high risk of serious complications and death if they acquired the infection in addition to their risk of treatment delay or interruption which can be detrimental to their outcome, and patients with lung cancer are no exception to the rule (Guan et al., 2020). Actually, the impact of COVID-19 on patients with lung cancer is multi-faceted and physicians managing this disease should pay attention to issues that may impact patient outcome negatively.

In ASCO 2020 meeting, the TERAVOLT study was presented as multinational consortium studying COVID-19 infection in thoracic malignancies. Among the 400 reported patients, 78 % required admission with 141 death (35.5 %). Age >65 years, performance status of 1, receiving steroid or chemotherapy was associated with higher risk of death (Garassino et al., 2020).

In this manuscript, we are presenting the implications of COVID-19 pandemic on lung cancer management from the perspective of various specialties of multidisciplinary team managing lung cancer.

1.1. Overview of COVID-19

In 2003 the severe acute respiratory syndrome (SARS) resulted from SARS-CoV, a coronavirus in south east Asia, caused an international epidemic. In 2012 another corona virus caused the Middle East respiratory syndrome MERS-CoV, mainly in the Arabian Peninsula with contained outbreaks outside. SARS-CoV and MERS-CoV share about 80 % and 50 % of their genome respectively with SARS-CoV-2, now better known as COVID-19 which started in China and caused the recent pandemic late in 2019 and continues to spread worldwide (Raoult et al., 2020). Sudden outbreaks of large numbers of critically ill patients have overwhelmed many communities with limited resources increasing the

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fatalities from this pandemic.

SARS-CoV-2 virus gain entry via ACE2 receptors present in the nose, mouth, throat and enriched in epithelial type II cells in lungs. Infection is associated with a broad range of clinical respiratory syndromes, ranging from mild upper airway symptoms to progressive life-threatening viral pneumonia. Most of the infections are mild (80 %) with a usual recovery period of 2 weeks. COVID-19 commonly affects males in the middle age and elderly age group, with highest case fatality (8–15 %) among those aged >80 years (Chen et al., 2020). According to the largest current report from Wuhan China among 72,314 cases, 81 % of cases were classified as mild, 14 % severe and 5 % were having critical illness requiring intensive care treatment and prolonged mechanical ventilation for most (Liang et al., 2020). Initial symptoms are fever, cough, fatigue, anorexia, anosmia, myalgias, sore throat and headache. Unlike SARS and MERS gastrointestinal symptoms such as nausea and vomiting and diarrhea are relatively uncommon (Chen et al., 2020). Progression to severe illness, when it happens, usually begins around a week from onset of symptoms (Richardson et al., 2020). Dyspnea and hypoxemia are the main presentation of severe disease with tachypnea, severe hypoxemia, lymphopenia, and acute onset of bilateral infiltrates more to peripheral lung zones that can progress to respiratory failure and ARDS. The pathogenesis of lung damage was described extensively by other authors highlighting different mechanisms such as inducing excessive and aberrant non-effective host immune responses or cytokine release syndrome from uncontrolled severe acute inflammation. The release of proinflammatory cytokines including interleukin (IL)-6, IL-1 and tumor necrosis factor-α may lead to immune-related pneumonitis (Addeo et al., 2020; Addeo and Friedlaender, 2020). This can progress to sepsis and septic shock, acute kidney injury (AKI) (Mao et al., 2020). Acute cardiac injury (arrhythmias, heart failure, MI), coagulopathy, rhabdomyolysis and acidosis can also happen. Complications are more in severe disease vs. non-severe disease.

Patients with severe COVID-19, defined as dyspnea, a respiratory rate of 30 or more, O2 saturation of 93 % or less, or infiltrates in 50 % of the lung fields should be hospitalized under strict infection-control procedures (Guan et al., 2020). Patients should be monitored by direct observation and pulse oximetry with supplemental oxygen to keep the saturation 90–96 %. Deciding when a patient with severe COVID-19 should receive endotracheal intubation is an essential component of care. After intubation, patients should receive lung-protective ventilation with plateau pressure less than or equal to 30 cm of water and with tidal volumes based on the patient's height. Prone positioning is a potential treatment strategy for refractory hypoxemia. Thromboembolic events are also more common (Wichmann et al., 2020). Increased doses of VTE prophylaxis critically ill patients with confirmed or highly suspected COVID-19 have been suggested (Barnes et al., 2020).

Severe disease is followed in some patients by multiorgan failure with acute cardiac, kidney, and liver injury, arrhythmias, rhabdomyolysis, coagulopathy, and shock (Addeo et al., 2020; Addeo and Friedlaender, 2020; Mao et al., 2020). These may be associated with a cytokine release syndrome hyper-inflammation characterized by high fevers, thrombocytopenia, hyperferritinemia, and increased inflammatory markers (Mehta et al., 2020), with development hemophagocytic lymphohistiocytosis picture. Reports on use of corticosteroid at the onset of dyspnea, may attenuate progression to the hyper-inflammation phase (Clinical Infectious Diseases, 2020). Anti-IL6 receptor antibody, immunoglobulins and other immune modulators are also undergoing trials for use for this syndrome but no definitive evidence is available so far for any of these treatments (Michot et al., 2020). Progressive respiratory failure is usually the primary cause of death in the COVID-19 pandemic. Patients especially when intubated and mechanically ventilated should receive empiric broad spectrum antibacterial coverage. Remdesivir, an inhibitor of the viral RNA-dependent, RNA polymerase with inhibitory activity against SARS-CoV and MERS-CoV, was studied in COVID-19 patients who required supplemental oxygen. It shortened the time to recovery in adults with evidence of lower respiratory tract infection but had no effect on mortality (Grein et al., 2020).

The diagnosis of COVID-19 is usually made based on suggestive clinical history and presence of SARS-CoV-2 RNA in respiratory secretions by PCR testing usually by nasopharyngeal specimen. Chest Imaging is usually done in patients with moderate-to-severe clinical features or if worsening respiratory symptoms in mild cases. Of these individuals, 75 % will have evidence of bilateral consolidations or ground-glass opacities (Rubin et al., 2020). Since there are no clear guidelines about testing asymptomatic patients with lung cancer for SARS-CoV-2, practitioners should follow the local and institutional guidelines. Although testing symptomatic patients is justified, the challenge remains how to sort out symptoms related to progressing lung cancer versus COVID-19 infection (Passaro et al., 2020a).

2. Implication of COVID-19 on pulmonary medicine

2.1. Diagnosis and management of the disease

Pulmonary physicians are one of the front-line specialists in diagnosis and managing both diseases lung cancer and COVID-19 which has a predilection to the lungs. Since many of the COVID-19 respiratory symptoms overlap with lung cancer symptoms, it is very critical to take careful in delineating the differential diagnosis between the two entities.

The decision is usually based on the change in the clinical pictures such as worsening of baseline symptoms, worsening the imaging studies including having new patchy infiltrate that are distinct from the pattern of lung cancer progression and finally the positive PCR tests for the virus.

2.2. Diagnostic procedures and invasive procedures

It is very critical to make careful decision about diagnostic procedures especially interventional and invasive ones. Non- invasive tests should be utilized to confirm the diagnosis such as clinical picture and laboratory tests. However, when an invasive procedure is needed risk and benefits should be weighed and elective procedures should be postponed till the infection is cleared by PCR negative tests and resolutions of symptoms. If a procedure is needed urgently, all precautionary measures should be taken to protect staff form contagion.

2.3. The use of critical care resources

The pandemic overwhelmed the healthcare systems in many countries and especially critical care resources such as ventilators and intensive care unit beds.

Prioritizations of dispensing these resources to individual basis including age and comorbidities. Pulmonary physicians and other team members have to make these decisions on individual lung cancer patients taking into account the specific prognosis of the patient disease, overall treatment plans and options, where is the patient in his disease trajectory and available resources. Having in advance clear guidelines on how to utilize these resources and make these decisions would be helpful (Rubin et al., 2020).

2.4. Implication of COVID-19 on lung cancer prevention and screening

The predilection of the COVID-19 virus to the lung and the negative impact of patients with chronic disease especially among smokers should be a motivating factor for health care promotion activists, experts and regulators to energize the anti-tobacco campaigns to control tobacco use in all its forms due to the public awareness of the virus damaging effect on the lung and the risk of morbidity and mortality from COVID-19 infection (Garassino et al., 2020). All initiatives to screen for lung cancer should be delayed till the pandemic peak passes and the risk of exposure becomes minimal. There are multiple reasons for halting lung cancer screening activities including increasing the exposure of

patients to unnecessary risk of COVID-19 infection; incidental lung findings in asymptomatic patients who get infection with the COVID-19 may increase the false positive rate and expose patients to unnecessary procedures. Finally, halting the screening temporarily will save resources to manage the patients with life threatening infection including physicians and staff time, imaging machines, hospital beds and others.

3. Implication of COVID-19 on radiology

Different radiology modalities chest x-ray, CT scan, and PET scan are the cornerstone for diagnosis, management and follow up for acute and chronic lung diseases such as COVID-19 pneumonia, lobar pneumonia, lung cancer, lung metastases, radiation pneumonitis, radiation fibrosis and pulmonary arterial thromboembolism, etc. In the era of COVID-19 pandemic usage of different radiological modalities for suspected or confirmed cases of COVID-19 differs globally due to local facilities, different published guidelines and sociocultural approaches to imaging. However, CT scan or Chest x-ray has limited sensitivity for the diagnosis of COVID-19 pneumonia as in the initial course of the disease up to 18 % CT scan or Chest x-ray appears normal while in severe disease this reduces to 3 % only (Rodrigues et al., 2020). Moreover, the CT scan is of great help in the diagnosis of COVID-19 infection in asymptomatic patients with negative PCR test (Lin et al., 2020). Typical CT chest features attributed with COVID-19 infections are multifocal posterior peripheral/subpleural rounded ground-glass opacities with lower lobes zonal predilection bilaterally, air space consolidations, vascular dilatation, atoll sign described as focus of ground-glass opacity (GGO) surrounded by at least 2 mm thick crescentic shaped consolidation, crazy paving pattern, peribronchovascular thickening in the consolidations, architectural distortion and traction bronchiectasis (Scott Simpson DO and Kay, 2019). The radiologists play essential roles in the diagnosis and monitoring of both disease lung cancer and COVID-19. Radiologists need to be aware of imaging findings of COVID-19 and keep that while reading imaging studies for lung cancer patients. Radiologists should be careful not to upstage the disease or reporting disease progression if the findings may result from COVID-19 infection. It is also critical for radiologists to have alert system to notify managing physicians of the initial finding of suspected infection in order to implement precautionary measure in their clinical care settings. Finally, radiologist can provide consultation to managing clinical team on best imaging modalities to address various clinical questions encountered.

4. Implication of COVID-19 on pathology

Lung cancer patients may undergo pathological evaluation of newly arising lung infiltrates through imaging by tissue sampling or cytopathology. In most patients who deteriorate rapidly, the most common histopathologic correlate of acute respiratory distress syndrome (ARDS) is diffuse alveolar damage (DAD). DAD is microscopically characterized by different stages: in the acute stage hyaline membranes form in the alveoli, and in the organizing stage there is interstitial widening by fibroblastic proliferation and edema, and a fibrotic end-stage with fibrosis and chronic inflammation (Hasleton and Flieder, 2013). The other findings reported in other organs such as liver and heart are likely secondary findings or related to underlying pathology (Tian et al., 2020). These changes such as pneumocyte II hyperplasia and organizing features can result in nuclear and cytological atypia which can overlap with features of cancer, which pathologists can resolve by careful microscopic examination, correlation with radiological findings, and utilization of ancillary techniques when needed.

The role of digital pathology is rapidly evolving and the contribution of pathologists to the multidisciplinary care through virtual tumor board meetings (e-Tumor Board) which are utilized through electronic platforms is reshaping our model of care. Albeit, the times of SARS−COV-2 present us with numerous challenges related to how we humans communicate and interact, many opportunities will emerge and develop that may lead to improvements and might further remodel the role of laboratories in the personalized medicine paradigm of care (Williams et al., 2020). Avoiding repeating invasive procedure should be pursued, if possible, like doing a liquid biopsy for molecular studies.

In summary, pathologists should be aware of the COVID-19 findings and take this into account when generating reports, discuss with managing clinicians the interpretation of the findings, and alert them as early as possible of alarming findings. As risk of laboratory staff is high due to handling biological specimens from affected patients, precautionary measures can-not be overemphasized.

5. Implication of COVID-19 on surgery

Surgical interventions in lung cancer consist of three category, diagnostic, therapeutic and palliative. Although interventional radiology managed to handle majority of diagnostic cases, surgical intervention is occasionally needed.

During the era of COVID-19, routine and elective surgical procedures should not be given a priority to avoid spread of the virus and for the safety of both patients and healthcare workers. All patients should have screening or testing to COVID-19 prior to any surgical intervention at least 3 days and be assessed for any symptoms on admission and reviewed if a second screening test is needed. That should also be part of the procedure consent signed by the patient. The later should also include the possible risk of hospital cross infection and the policy of care that will be provided. Consultation should be documented if patient elected to refuse the surgical intervention indicating the risk of any delay.

Patient with lung cancer and positive for COVID-19 should be discussed in tumor boards to handle the best management plan and the associated risks. This should be dependent on symptomatic versus asymptomatic patients and the stage of the lung cancer.

Symptomatic patients should be treated according to the hospital protocol and should be delayed 28 days from the disease, and 14 days from the cure of symptoms and negative testing. Precautions for handling COVID-19 positive patients should be applied whenever surgical intervention is due. Asymptomatic patients can be delayed 14 days from the last negative test made and it will be safe to subject them to surgical intervention. Minimally invasive procedures may be recommended although no evidence of its superiority than open procedures in reducing the infection risk (American College of Surgeons, 2020). Tumor board may elect alternative less invasive procedures for patients with higher risk or prolonged positive results or if the patient elected not to proceed with surgical intervention and that may include outpatient chemotherapy or Radiotherapy (Cafarotti and Patella, 2020).

All procedures should be explained to the patient with its potential outcome and documented.

6. Implication of COVID-19 on radiotherapy

Radiotherapy plays a major role in lung cancer management (Baker et al., 2016). This role ranges from curative intent as component of concurrent chemo-radiotherapy for stage III disease and stereotactic ablative body (SABR) radiotherapy for early stage NSCLC to palliative intent for advanced stage for pain and hemoptysis (Maher et al., 1993). Delay in radiotherapy more than 24 days associated with a risk up to 30 % of disease progression for NSCLC patients mainly stage III disease (Everitt et al., 2010). As a protective measure during COVID-19 pandemic hypofractionation regimens is generally recommended to reduce exposure and minimize risk of infection.

For early stage I disease, the decision of delaying radiotherapy for 3–4 weeks can be considered if patient had worked up with PET-CT scan within a window of 2 months, otherwise postponement of radiotherapy is not encouraged (Guckenberger et al., 2020). During the COVID-19 pandemic, SABR is encouraged to be considered for early stage I disease as an alternative to surgery or as a primary treatment for selected

cases (Chang et al., 2015). SABR can delivered using the standard four to five fractionations to a total dose of 48–50 Gray (Guckenberger et al., 2020). Considering current COVID-19 pandemic aiming to reduce patients visit to the minimum, using the regimen of one fraction to a total dose of 30 Gy is an attractive option (Singh et al., 2019). Based on best available evidence, change of standard fractionations for stage III NSCLC patients is not recommended (Baker et al., 2016).

According to available evidence hypofractionation regimens for small cell lung cancer (SCLC) is comparable to standard fractionation therefore, it is encouraged during COVID-19 pandemic (Socha et al., 2014). Timing of thoracic radiotherapy is crucial in those patients for which it recommended to be delivered no longer than three weeks (Murray et al., 1993). Prophylactic cranial irradiation can be postponed within a window of 4–6 weeks using fewer fractionations (Baker et al., 2016). For palliative thoracic radiotherapy using fewer fractionation using a single or two weekly fractions is highly encouraged (Rodrigues et al., 2011).

Testing for COVID-19 prior to thoracic radiotherapy is advisable. Clinical picture of radiation pneumonitis which mainly present with fever and cough might be obscured with COVID-19 therefore testing prior to thoracic radiotherapy is of clinical value. Table 1.

7. Implication of COVID-19 on interventional radiology

Interventional radiology (IR) plays a key role in the multidisciplinary management of lung cancer at all stages at all stages of lung cancer management (Duka et al., 2017) (Table 2). However, IR service is facing challenges from many aspects during the current Corona pandemic COVID-19 affecting the healthcare systems. As with any interventional procedure, the potential benefits of any procedure must outweigh the risks; and in each case the technique should be considered likely to affect patient management. Under such extraordinary circumstances of resources scarcity or reallocation in addition to the exposure risk of to COVID-19 infection, the management of patients with lung cancer should be balance the risk of delay diagnosis or potentially curative or palliative treatment against the obvious risk of infection. As for image-guided procedures in the management of lung cancer patients, they have been categorized as emergent or with high priority (De Gregorio et al., 2020).

Interventional radiology service must comply with the advice and directives given by the institutional infection prevention and control for different clinical settings to ensure operator's safety. Ultrasound should be used whenever possible and appropriate for guiding procedures as such procedures can be performed at the patient's bedside giving the advantages of minimizing the movement of patients outside the designated ward and the associated risk of nosocomial transmission of infection. Dedicated portable ultrasound equipment should be marked and sequestered for contaminated use and decontamination cycles including the wheels.

Percutaneous transthoracic biopsy of a lung nodule or a mass should not be delayed as they are needed for definite diagnosis that will decide the curative treatment or for follow-up current treatment that showed no proportional response (Yoon et al., 2012). The baseline chest CT images should be carefully reviewed to plan the procedure based on the size and location of the lesion and other abnormal findings especially that associated with COVID-19 infection (Morris et al., 2020), availability of imaging systems, and local expertise. The procedure is usually performed under local anesthesia with relatively higher complication rates compared to other percutaneous solid organs biopsies. The most common complications include pneumothorax and hemorrhage which occur during or immediately after the procedure (Yeow et al., 2004). Pneumothorax after CT-guided percutaneous lung biopsy has been reported to occur in up to 54 %, as CT imaging can detect even very small pneumothorax. However, the rate for pneumothoraces requiring treatment with chest tube varies from 5 to 18 %.

Percutaneous thermal ablation has been effectively used in the treatment of early-stage primary lung carcinoma especially in the medically inoperable population, oligometastatic and oligorecurrent disease (Tafti et al., 2019).

The choice of ablative modality should be selected based on the tumor location, operator experience and patient factors and device availability. RFA is the most extensively utilized and studied technique for ablation of primary lung tumors (Palussière et al., 2018). RFA requires general anesthesia and it can be sued at the time of biopsy in high risk patients to avoid additional pleural puncture. With technological advancements in microwave ablation and cryoablation, large tumor could be ablated. Both MWA and cryoablation appear safer than RFA as they induce less pneumothorax and they can be used in patient with implanted cardiac pacemaker (Aufranc et al., 2019). Given the advantages of cryoablation and the limitations of RFA with the scarcity of anesthesia during the COVID-19 pandemic, it seems that cryoablation, if available, should be selected over other ablation techniques (Table 3).

8. Implication of COVID-19 on systemic therapy

Patients on anticancer treatments have frequent visits to health care facilities to receive therapy or to seek care related to complications, like febrile neutropenia, dehydration or drug-related adverse events. Health care visits carries the risk of acquiring SARS-CoV-2 via human-human droplet transmission (Yu et al., 2020), that can be from asymptomatic individuals, or by indirect transmission when touching infected surfaces (Ong et al., 2020). General precautionary measures to reduce infection in the outpatients sitting, clinics and chemotherapy infusion units, incorporate utilizing screening algorithm designed by the local healthcare facility for early detection of symptomatic and possible infectious patients (Shi et al., 2020). Emphasis on physical distancing at checking

Table 1
Precautionary measures for radiotherapy.

Measures	Indication (examples)
Implement social distancing and infection control measures	• All patients, all the times including COVID-19 negative patients
Screen and testing patients before treatment	• All patients if possible (preferred).
Postpone initiation of treatment by 4 weeks.	• Post-Operative Radiotherapy (PORT) NSCLC. • Prophylactic Cranial Irradiation (PCI) SCLC.
Offer alternatives for non-clinically Justified RT treatment.	• Whole Brain Radiotherapy (WBRT) for poor performance status (PS3–4) NSCLC.
Use less treatment sessions	• Use of Stereotactic Ablative Body Radiotherapy (SABR) as possible. • Evidence based hypo-fractionated RT regimens. • Single or tow weekly fractions for palliative thoracic radiotherapy.
Reduce departmental patient's crowdedness.	• Minimize intradepartmental waiting time prior to RT treatment.
Reduce patient's crossover.	• Establish an accurate RT treatment scheduling.
Sustain Personal Protective Equipment (PPE).	• Vigilant disinfection of SABR immobilization devices. e.g. bodyfix, Body Pro-Lok System.

Table 2
Common image-guided procedures performed in lung cancer patients.

Indication	Examples of procedures
Diagnosis	• Percutaneous image-guided transthoracic biopsy
Treatment	• Pulmonary nodule localization: Fiducial markers placement for surgical resection or radiotherapy • Lung tumor thermal ablation (Radiofrequency, Microwave, Cryotherapy) • Lung tumor transarterial embolization
Palliation	• Transarterial embolization for hemoptysis • Drainage of malignant pleural effusions • Stenting for superior vena cava syndrome

Table 3
Common aerosol generating procedures commonly performed by interventional radiology team on lung cancer patients*.

Any procedure involving a patient who:	Any procedure that may induce coughing:
• Requires intubation/extubation • Requires active airway suctioning (i.e. tracheostomy patient) • Is receiving a form of ventilator support associated with the risk of mechanical dispersal of aerosols • Undergoing sedation may require airway rescue, which would require utilization of aerosol precautions.	• Lung biopsy • Lung ablation • Thoracentesis • Pleural drains • Chest tube for pneumothorax • Bronchial artery embolization • Bronchial stenting

* Adapted from the Society of Interventional Radiology (SIR) website (Rodrigues et al., 2011).

and waiting areas, universal masking, hand hygiene and avoidance of touching face with possible contaminated hands and using disposable tissues to cover mouth and nose when sneezing or coughing. Advise using mask for patients with respiratory and cough symptoms, if it will not compromise their care (GOV.UK, 2020). The most important factor in the management of lung cancer in the current pandemic is whether the patients are required to visit the hospital for treatment or can have modifications in the treatment plans that will not jeopardize their outcomes. Systemic therapy for cancer can render the patient vulnerable to infection with SARS-CoV-2.In patients with lung cancer, aggregated risk of COVID-19 complications is associated with factors like age, smoking history and cardiovascular comorbidities (de Marinis et al., 2020). Telemedicine can be utilized for follow up of patients, and response evaluation for asymptomatic patients can be delayed. Oral anticancer therapy and supportive medications can be delivered to patients via courier services or drive-through drug stores to minimize number of patients waiting at pharmacy department (de Marinis et al., 2020).

8.1. *Managing patients with different scenarios*

The choice of chemotherapy, immunotherapy, targeted therapy or best supportive care must be tailored to the patients' tumor characteristics, biomarkers and comorbidities, with consideration of decreased risk of side effects and COVID-19 infection. Prioritizing which treatment to continue on schedule and which to delay is dependent on the surge of COVID-19 cases in the local areas with the strain on health care facility. Many hospitals are overcrowded with COVID-19 cases and operating rooms are turned into intensive care units. Some hospitals have reduction in the number of staff working as they are in quarantine or infected with SARS-CoV-2. The overarching theme and most important guiding principles in treating lung cancer and other cancers is to provide timely appropriate care without unjustified delays of treatment (Passaro et al., 2020b; Banna et al., 2020).

Targeted therapy with TKIs is offered to patient with oncogenic-addicted NSCLC found through biomarker testing. It results in improved survival and response rate with well tolerability and less side effects (Yuan et al., 2019). Patients who have minimal progression and are asymptomatic can be monitored every 4–8 weeks. Radiation therapy may be offered for Local disease progression. Symptomatic progression or TKI-induced pneumonitis must be differentiated from COVID-19. If a patient is diagnosed with COVID-19 while on TKI, treat COVID-19 and continue TKI. For TKI-induced pneumonitis, health care providers must weigh benefit-risk of steroid use (Russell et al., 2020).

If rebiopsy is needed to look for emerging mutations, liquid biopsy is preferred, as rebiopsy is a complex procedure with multiple departments involved. (Fig. 1)

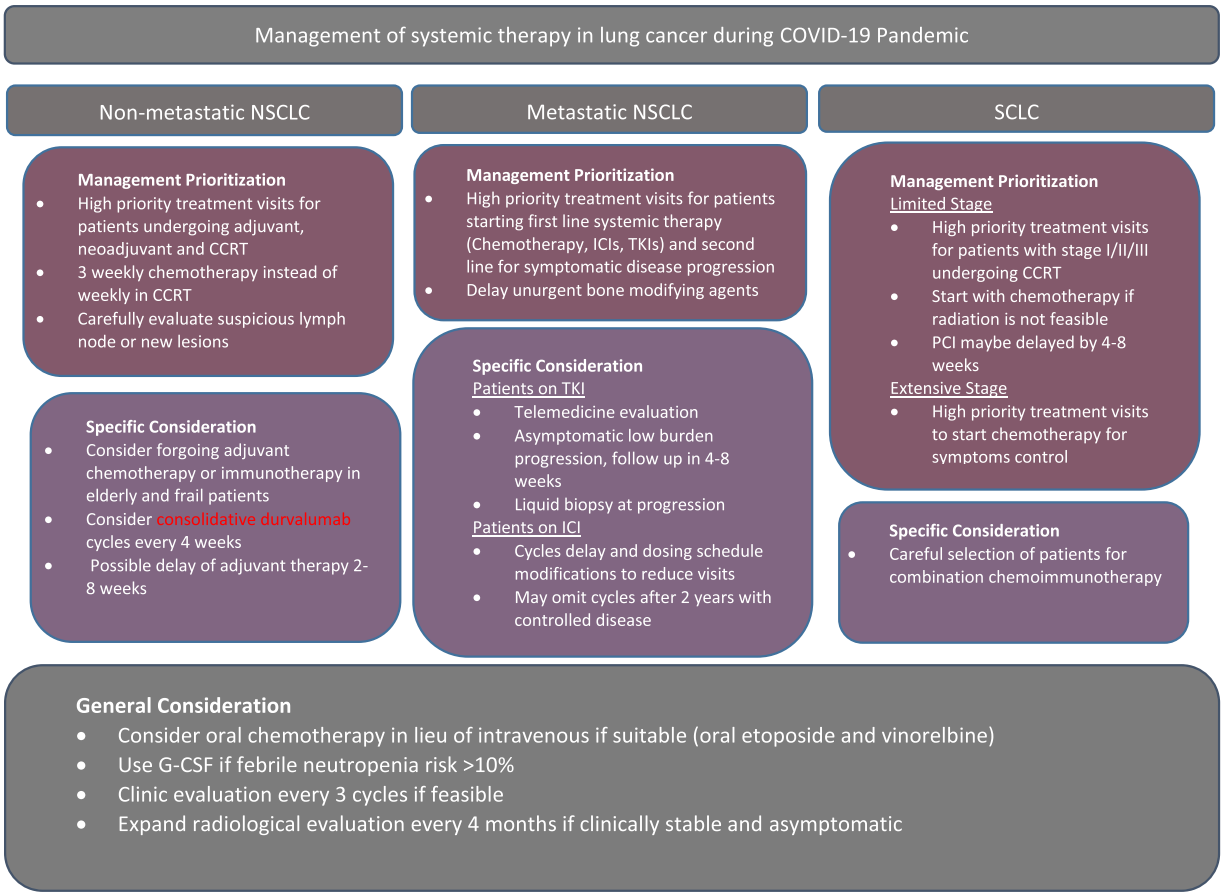

Fig. 1. Flowchart for the evaluation of patients with lung cancer undergoing systemic therapy.

Over the past few years, immune checkpoint inhibitors (ICIs) have been incorporated in the care of lung cancer, either solely or in combination with chemotherapy, in stage III and IV NSCLC with no oncogenic driver (Friedlaender et al., 2020). Many questions are raised about the effect of ICIs and COVID-19, and whether immunotherapy has a protective effect with enhanced T cell function and protection against SARS-CoV-2,or causes exacerbated COVID-19 with cytokines storm that results in higher mortality with COVID-19 (Coperchini et al., 2020). Up to now there is no clear answer to these questions. Recent evidence for TERAVOLT study did not reveal any detrimental impact of receiving ICI on patients with lung cancer (Garassino et al., 2020). However, if there are concerns about hospital visits to minimize exposure to the virus, then accurate patients' selection with modifications of cycles such as using longer interval of treatment cycles (Nivolumab every 4 weeks or permbrolizumab every 6 weeks) is an option. Furthermore, discontinuing therapy in patients with no evidence of relapse after 2 years while on therapy may be considered.

Chemotherapy represents the standard of care for patients undergoing concurrent chemoradiation (CCRT), preoperative sitting, and as systemic palliative therapy in patients with low or no expression of PD-L1 and no oncogenic driver mutation. As such, patients on chemotherapy must be assessed carefully to avoid treatment interruption with consideration of immunosuppression risk and hospitalization in frail patients as there are other factors may impact the outcome of cancer patients with COVID-19 infection which may not be necessarily related to chemotherapy (Lee et al., 2020). Adjuvant and neoadjuvant chemotherapy (NACT) should be considered in a case-by-case basis. For instance, adjuvant chemotherapy in locally advanced disease at a younger age, and NACT that will enable delaying surgery for 3 months in centers with limited operative capacity during the pandemic (Burki, 2020).

For patients who have had long treatment disease control, delaying or forgoing maintenance therapy can be discussed with the patients (Hanna et al., 2020). To minimize the risk for infection, all patients should be carefully screened before any visit to the facility including physician visit, laboratory or imaging testing or procedure. In certain setting doing COVID-19 testing maybe required routinely such as undergoing major surgery as patient may harbor infection without symptoms.

8.2. Implication of COVID-19 on patient follow-up

Intervals between clinic visits can be extended or even avoided by obtaining CT Scan/imaging surveillance and follow up with phone call, and if patient is asymptomatic, there is no need for clinic visit up to a year. The interval of CT scan can be expanded based on the clinical scenario. Reducing patients visits can be done by multiple approaches including: Scheduling as many patients possible in a virtual or telephone clinic, delaying regular clinic visits and the chemotherapy as safe as possible, using oral therapy especially TKI or oral chemotherapies agents (e.g. Etoposide) as much as possible, switching to a longer interval of approved dosing schedule, and increasing the interval of imaging to a safe period; such as every 3 cycles rather than 2 cycles in stable patients. Doing laboratory tests at point of care or near patient home, if possible, will reduce patients travel and exposure. It is important to make a decision based on where the patients are in their treatment journey. Newly diagnosed patients may require more visits and early initiation of treatment. Reducing immune suppression can be done by selecting medication with less bone marrow suppression effect, using hematopoietic growth factors, giving chemotherapy holidays (for patients on maintenance therapy).

9. Implications for all providers

The COVID-19 pandemic presented many significant challenges to healthcare providers that require attention from both leaders and the individual providers. The healthcare providers are at increased risk of acquiring the infection, experiencing exhaustion, burnout, and mental and emotional disorders. Protecting staff form infection should be assured by implementing general infection control precautions such as social distancing between staff and between staff and patients, universal masking, and others. Implementing measures for prevention, early recognition and providing timely help for emotional and well being support is essential to mitigate any negative impact of the pandemic (Rahman Jazieh, 2020; Brooks et al., 2020).

10. Conclusion

COVID-19 pandemic has caused a significant health care crisis worldwide. Modifications of treatment plans for patients with lung cancer have been adapted by many oncologists to ensure safe delivery of care within the accepted standards and new guidelines. As stated in recent ESMO recommendation: "In this environment, cancer practitioners have great responsibilities: provide timely, appropriate, compassionate, and justified cancer care, while protecting themselves and their patients from being infected with COVID-19. In case of shortages, resources must be distributed fairly."(Passaro et al., 2020b)

Finally, although not discussed in the manuscript, managing healthcare staff providing oncology care to protect from various harms including infection, exhaustion and emotional disturbance is essential for them and the patients they serve. (Rahman Jazieh, 2020).

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Declaration of Competing Interest

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