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Optimizing lung cancer radiation treatment worldwide in COVID-19 outbreak

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Running title: Lung cancer in COVID-19 outbreak

Highlights

- Lung Cancer patients are at high risk for COVID-19 infection
- All steps should be taken to protect patients and the healthcare workforce
- Shortened RT overall treatment time is an important consideration during the COVID-19 pandemic
- Twelve recommendations in the use of RT are proposed by an international panel
- The proposed recommendations require urgent consideration during this pandemic

Abstract

COVID-19 has spread around the planet, sending billions of people into lockdown as health services struggle to cope. By April 2020, there are over a million two hundred thousand confirmed cases and more than sixty-five thousand deaths worldwide Meanwhile in Asia, where the disease began, the spread continues, in China it seems for now to have passed its peak. Italy, Spain, France, and the US have been the countries more affected in terms of deaths. The coronavirus is more dangerous to the elderly and those with certain pre-existing medical conditions which is precisely the profile of lung cancer patients. Essential cancer services should be delivered but all

steps should be taken to protect patients and the health workforce from infection with COVID-19. This presents a major challenge to radiotherapy (RT) departments worldwide in curbing the spread of COVID-19 while ensuring the continuity of services. In RT, shortening overall treatment time to reduce the number of patients present in the department is an important consideration. An international panel, including the majority of countries most affected by the COVID-19 pandemic, with expertise in the management of cancer in high-volume comprehensive centres from the largest societies of radiation oncology worldwide have come together to share their experience on COVID-19 preparedness in the context of lung cancer RT to deliver optimal care in such exceptional circumstances, based on the latest evidence. A comprehensive systematic review of the literature through a PubMed search was undertaken. Given that lung cancer is one of the most common and severe pathologies in radiation oncology departments, the following recommendations require particularly urgent consideration. The decision-making paths strongly depend on locally available resources, and a tailored approach should be used to attend lung cancer patients during this pandemic.

Keywords: Lung cancer; Radiation therapy; COVID-19; Pandemic; Outbreak

Introduction

COVID-19 has spread around the planet, sending billions of people into lockdown as health services struggle to cope. By April 2020, there are over a million two hundred thousand confirmed cases and more than sixty-five thousand deaths worldwide [1]. Meanwhile in Asia, where the disease began, the spread continues, in China it seems for now to have passed its peak. Italy, Spain, France, and the US have been the

countries more affected in terms of deaths. However, limited testing and challenges in the attribution of the cause of death means that the number of confirmed deaths may not be an accurate count of the true total number of deaths from COVID-19.

We know the coronavirus is more dangerous to the elderly and those with certain pre-existing medical conditions. A prospective cohort study from China suggested that cancer patients have a higher risk of infection and poorer outcomes after COVID-19, compared to patients without cancer [2]. Five of the 18 cancer patients included in this report had lung cancer (28%). A separate retrospective study from China demonstrated that chronic obstructive lung disease, a condition often co-existent in lung cancer patients, is more common in non-surviving COVID-19 patients [3]. Lung cancer patients receiving immunosuppressive anticancer treatments are also likely to be at hightened risk of morbidity and mortality from COVID-19.

Moreover, the data shows that over half of all those hospitalized across Spain are over 70 years old [4]. In China, the case-fatality rate was 8% in 70 to 79 years and was 14.8% in 80 years or older [3]. Although men and women are testing positive to coronavirus in similar numbers, men are more likely to be admitted into hospital and treated in intensive care units. Elderly men with certain pre-existing medical conditions is precisely the profile of lung cancer patients. The main route of viral transmission is respiratory droplets, and rigorous protective measures are essential to limit the extent of transmissibility and guarantee healthcare workers' safety while delivering oncologic treatments.

Essential cancer services should be delivered, but all steps should be taken to protect patients and the health workforce from infection with COVID-19. This presents a major challenge to radiotherapy (RT) departments worldwide in curbing the spread of COVID-19 while ensuring the continuity of services. Individual risk from exposure to COVID-19 varies from person to person, and all risks of COVID-19 infection should be balanced

against the need for tumour control and discussed on a case-by-case basis with the patient and their care givers.

Everyone can still change the course of this pandemic by taking timely and concrete actions. Radiation oncologists are encouraged to follow protective measures as recommended by the World Health Organisation (e.g., frequent hand washing, social distancing) [5]. Additionally, many radiation oncology departments worldwide, especially in China, have implemented temperature screening for all users of the RT centre and request all patients to wear protective masks during their stay in the RT department even if asymptomatic [6]. In addition, keeping social distance to flatten the peak of the epidemic curve is a critical strategy to control the COVID-19. In RT, shortening overall treatment time to reduce the number of patients present in the treatment area at same time is an important consideration. To further reduce the time patients spend in the RT facilities, it is advisable to limit on-treatment visits as well, for instance, on demand of patients while maintaining optimal care conditions.

Methods

An international panel, including the majority of countries more affected for COVID-19 disease, with expertise in the management of cancer at high-volume comprehensive centres from the largest societies of radiation oncology worldwide (European, American, Asian and Chinese: ESTRO, ASTRO, FARO, and CSTRO) have come together to share their experience on COVID-19 preparedness in the context of lung cancer RT to deliver optimal care to their patients in such exceptional circumstances based on the latest evidence. A comprehensive systematic review of the literature through a PubMed search was undertaken. Given that lung cancer is one of the most common and severe pathologies in radiation oncology departments, the following recommendations require particularly urgent consideration. The decision-making paths strongly depend on locally available resources, and a tailored approach is should be

used to attend lung cancer patients during this pandemic. Twelve recommendations in the use of RT considering shorter courses, delays, and omission of RT for lung cancer are proposed by the panel.

Suggested recommendations (Table 1)

Precautions for patients and health care professionals

1. One of the most important lessons learned from RT departments in China is the screening of every single person who is able to get into the treatment room, including patients and staff. The treatment room is a confined space and is not easy to sterilize. Therefore, COVID-19 virus infection evaluation for all lung cancer patients before RT is mandatory. Recent relevant symptoms/contact history should be reported. COVID-19 virus should be tested before RT for patients with suspected infection. If positive, RT should start after the recovery of the infection. If negative but still suspicious, they should be treated in a single treatment machine at the end of the LINAC shift to limit the chances of infection for other patients. RT technologists and other health care personnel at simulation and treatment need to wear appropriate personal protective equipment and disinfection of the scanner/bunker must be performed afterwards. In the case of COVID-19 confirmed infection during treatment, the decision to continue or discontinue treatment should be on a case per case basis, keeping with the previous recommendations for protection of personnel and disinfection. Decision making should include patient prognosis, pre-existing medical conditions and the extent and symptoms of the COVID-19 infection [6]. For those patients with concurrent chemotherapy, it may be continued at full or reduced dose, or suspended, depending on the aforementioned aspects.

Image guided radiation therapy (IGRT)

2. It is well known that COVID-19 pneumonia has computerized tomography (CT) presentations of bilateral lung opacities in 98% of chest CTs in infected patients and lobular and subsegmental areas of consolidation, ground glass consolidation, rounded morphology as the most typical radiographic findings [7, 8]. CT finding was included as a diagnostic criteria for COVID-19 pneumonia. Asymptomatic infected patients pose a potential risk of spreading the virus without being noticed and which is a great challenge in RT clinics. Most recently, there have been case reports from the US and Europe that new ground glass opacities were caught on the images obtained by CT on rail and cone beam CT (CBCT) for IGRT delivery of lung stereotactic ablative radiotherapy (SABR). Those patients were later all tested positive for COVID-19 even though they were totally asymptomatic. Therefore, during the COVID-19 pandemic, we recommend careful review of simulation CT images for new ground glass opacities, consolidations, round morphology, and other suspicious image findings. IGRT imaging (CT on rail, or CBCT) before the first fraction of the treatment, and subsequently, should be compared with the images of the simulation CT for any new image changes suspicious for COVID -19 infection. Patient with suspicious CT images should be sent for COVID-19 testing and be quarantined until the test result is known.

Non-small lung cancer (NSCLC) patients

3. During this pandemic, the availability of operating rooms for surgical treatment may be compromised. SABR can play a critical role to offer curative treatment to these patients. To optimize resources, shorter schedules should be privileged, allowing access to more patients. Centres with experience in SABR treatment may deliver SABR in 1-3 fractions for stage I-II patients requiring thoracic RT with NSCLC. Options include 30-34Gy in one fraction for tumors < 2 cm and ≥ 1 cm from the chest wall [9-11] and 48-54Gy in 3 fractions over 1

week for peripheral lesions [12]. More mild hypofractionation (45 to 60 Gy in 4 to 8 fractions) could be considered for central and ultra-central lesions [13]. Lower quality evidence led to conditional recommendations on use of SABR for tumors >5 cm, patients with prior pneumonectomy, T3 tumors with chest wall invasion, synchronous multiple primary lung cancer, and as a salvage therapy after prior RT [14]. Consider 55-60 Gy in 20 fractions in early-stage patients not suitable for SABR [15].

4. Deliver RT in 20 fractions (55 Gy) for stage II-III patients requiring thoracic RT with NSCLC. In the United Kingdom, 55 Gy in 20 fractions (2.75 Gy daily fractions) is the most commonly used radical NSCLC radiotherapy schedule, particularly for patients treated with sequential chemoradiotherapy. The phase II SOCCAR trial showed that schedule is associated with 50% and 46% 2-year survival and 2.9% and 1.7% treatment-related mortality when combined with concurrent and sequential chemotherapy, respectively therapy [15]. Based on these data, this is an acceptable approach for stage II-III NSCLC patients in the era of COVID-19. However, due to the lack of confirmatory level I trial evidence, caution needs to be exercised when using this schedule concurrent with chemotherapy in patients with bulky mediastinal disease. Accelerated hypofractionated radiation therapy with 45 Gy in 15 fractions appears to be an acceptable treatment option for poor performance status NSCLC patients with stage III inoperable tumours. A retrospective study [16] showed no differences between 45 Gy and standard RT (60 Gy at 2 Gy/fraction) in terms of the patterns of local or distant tumor control or overall survival in this subset of patients.

5. The use of postoperative RT (PORT) for NSCLC patients is controversial. Multiple older studies [17] showed no survival benefit to PORT but recent data

suggest benefit of modern PORT for pN2 patients [18]. PORT in pN2 or incompletely resected stage II and III NSCLC could be reasonably delayed with an imaging re-evaluation before treatment at 2-3 months or treated in 20 fractions (55 Gy) [15, 19].

6. In NSCLC patients with limited metastases, there is a role for more aggressive treatment in all disease sites. There is a benefit to either early or late radiation in the setting of limited metastatic disease [20, 21]. RT could be either delayed while the patient is receiving systemic maintenance therapy or be an alternative to systemic therapy, especially when using SABR. NSCLC patients with a limited number of brain metastasis could be treated with stereotactic radiosurgery (SRS) at 1-3 fractions [22] in order to delay or potentially avoid whole brain radiation (WBI).

Small-cell lung cancer (SCLC) patients

7. Deliver SABR in 3-5 fractions for stage I-II SCLC patients requiring thoracic RT for peripheral lesions. Options include 60 Gy in 3 fractions, 48 Gy in 4 fractions, and 50 Gy in 5 fractions [23, 24]. More mild hypofractionation could be considered in very select patients (i.e. ultra-central lung lesions), akin to treatment approaches in NSCLC [13].

8. Standard of care for limited-stage SCLC patients is early or upfront concurrent chemoradiation with [25] thoracic RT in 15 days (45 Gy in 30 twice daily fractions of 1.5 Gy) [26]. During this pandemic, it may be logistically preferable to avoid twice-daily treatments. Studies show that perhaps doses of 40-42 Gy in 15 daily fractions [27, 28] or 50-55 Gy in 20-25 daily fractions are comparable to the twice daily regimen [29, 30]. If tumor shrinkage might allow for a decrease in

radiation toxicities, starting RT with cycle 3 of chemotherapy may be more optimal for a subset of patients [31].

9. Thoracic RT for extensive-stage SCLC patients could be offered to patients with limited extrathoracic tumour burden after good thoracic and extrathoracic response to systemic treatment [32] at 30 Gy in 10 fractions [33, 34]. Slotman et al. [34] reported 2-year overall survival (OS) of 13% in the thoracic radiotherapy group versus 3% for the control group (p=0.004).

10. Prophylactic cranial irradiation (PCI) has shown an improvement in OS and a reduction in the incidence of brain metastasis in limited-stage SCLC patients [35, 36] delivered at 25 Gy in 10 fractions [37]. PCI could be performed during radio(chemo)therapy [38] in order to avoid more days of treatment or may be delayed since this is a prophylactic treatment. Omission of PCI in patients with p-stage I SCLC may be an option due to the lower incidence of brain metastasis (12% at 5 years) [36, 39]. In addition, a retrospective analysis of the M.D. Anderson Cancer Center [40] reported no benefit of PCI in OS for patients ≥70 years old with tumor size ≥ 5cm (2-year OS: 39% vs 41%). The role of PCI in extensive-stage SCLC after good response to systemic treatment is controversial [41]. In a Japanese trial [41], PCI did not result in longer OS compared with observation when patients received periodic magnetic resonance imaging examination during follow-up, therefore that could be an option. The role of reirradiation after PCI for brain metastasis is also controversial. A retrospective study [42] showed an OS of 58%, 50%, 21%, and 5% after SRS, chemotherapy only , repeat whole brain irradiation (WBI; 20Gy at 2Gy/fraction), and observation, respectively. Therefore, it could be omitted in patients receiving systemic treatment. SRS could be an option for patients with

reduced number of brain metastasis, good performance status, and controlled extracranial disease.

Palliative RT

11. Lung cancer patients with brain metastases unsuitable for resection or SRS could receive dexamethasone and supportive care without WBI. The QUARTZ study [43] showed absence of a difference in survival, quality of life or dexamethasone use between patients with and without WBI. However, for patients with urgent indications (i.e. neurologic symptoms), WBI at 20 Gy in 5 fractions is an option that has shown similar survival compared with longer courses [44]. WBI after surgery or SRS could be omitted since there is a modest benefit in OS in only a very selected group of patients [22, 45, 46].

12. Use of single-fraction RT (8 Gy) could be an option for stage IV lung cancer patients with symptomatic (i.e. pain, hemoptysis, etc.) or medical emergency (non-brain) metastasis (i.e., superior vena cava syndrome or spinal cord compression) [47, 48]. Re-irradiation with the same dose to the same site could be considered after initial palliative RT if there is no response or an additional benefit from repeat treatment is expected (i.e. pain relapse after initial satisfactory response). Among other dose options available, we favor 20 Gy in 5 fractions [49].

Conclusions

These recommendations on optimizing lung cancer radiation treatment worldwide during the COVID-19 outbreak includes the latest evidence and the combined experience of an international panel to help colleagues around the world for adapting reduced RT fractionation schemes and delay or omit RT whenever possible. This approach limits patient visits to protect our patients and health care professionals from

potential exposure to COVID-19. These tips may ease the workflow in radiation oncology departments during this exceptional situation. Finally, whether thoracic low doses and the application of radiation to treat viral pneumonia by the induction of an anti-inflammatory phenotype which may facilitate disease resolution [50] should be explored in a near future as an open window for another treatment approach.

Conflict of interest

All authors declare that they have no any conflict of interest.

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Table 1. Summary of recommendations in the use of radiation therapy during the COVID-19 pandemic.

Context		Recommendations
Patients and health care professionals		• Screening of every single person accessing the treatment room. • COVID-19 symptom assessment for all lung cancer patients before RT. • COVID-19 virus should be tested before RT for those patients with clinical and/or radiological suspected infection: ➢ If positive, RT should start after the recovery of the infection. ➢ If negative but still suspicious, they should be treated in a single treatment machine at the end of the LINAC shift, disinfected afterwards. • RT technologists and other healthcare personnel need to wear personal protective equipment, at least mask and gloves during the procedure. • If COVID-19 confirmed infection during treatment: decide to continue/discontinue treatment depending on patient prognosis, pre-existing medical conditions and the extent and symptoms of the COVID-19 infection. • Not compromising the prognosis of lung cancer patients by departing from guideline-recommended RT practice according ESTRO-ASTRO recommendations.
NSCLC	Early stage	Offer SABR or consider hypofractionation: • SABR in 1-3 fx for stage I-II patients. ➢ Peripheral lesions: – 30-34Gy in one fx for tumors < 2 cm and ≥ 1 cm from the chest wall. – 48-54Gy in 3 fx for tumors ≤5 cm. ➢ Central/ultra-central lesions: 45-60 Gy in 4-8 fractions. • 55-60 Gy in 15-20 fx in patients not suitable for SABR.
	Locally advanced stage	Offer hypofractionation: • 55-60 Gy in 20 fx. • 20-45 Gy in 5-15 fx for poor performance status patients.
	PORT	Delay RT with an imaging re-evaluation before RT at 2-3 m. Consider hypofractionation: • 55-60 Gy in 20 fx.
	Oligometastasis	Local consolidative therapy with RT could be either delayed or even omitted.
SCLC	Limited-disease Early stage	There is no need to modify SABR or use it in lieu of standard RT. When SABR is used, several options are available: • SABR in 3-5 fx for stage I-II patients. ➢ Peripheral lesions: 60 Gy in 3 fx, 48 Gy in 4 fx, 50 Gy in 5 fx. ➢ Central/ultra-central lesions: as in NSCLC.
	Limited-disease Locally advanced stage	It may be logistically preferable to avoid twice-daily RT. Consider hypofractionation: • 40-42 Gy in 15 fx or 50-55 Gy in 20-25 fx.
	Extensive-disease	Consider optional in the context of limited resources. If delivered, offer a short course: • 30 Gy in 10 fx.
	PCI	• Limited-stage: ➢ May be delayed. ➢ 25 Gy in 10 fx during thoracic RT. ➢ May be omitted in patients with p-stage I or ≥70 years

		with tumor size ≥ 5cm. This option implies surveillance with brain MRI every 3-4 months. • Extensive-stage: PCI could be omitted. Follow-up with MRI.
IGRT	• Carefully review the IGRT images for suspicious image findings. • Patient with suspicious CT images should be sent for COVID 19 testing and be quarantined until the test result is known. Asymptomatic infected patients pose a potential risk of spreading the virus without being noticed.	
Palliative RT	Brain metastases	Unsuitable for resection or SRS: dexamethasone and supportive care without RT. • Patients with urgent indications: 20 Gy in 5 fx. • RT after surgery or SRS could be omitted.
	Other sites	Offer single-fraction RT or short regimens: • Single-fraction of 8 Gy. • 20 Gy in 5 fractions.

Abbreviations: RT, radiation therapy; LINAC, linear accelerator; CT, computerized tomography; IGRT, image guided radiation therapy; NSCLC, non-small lung cancer; SCLC, Small lung cancer SABR, stereotactic ablative radiotherapy; PORT, postoperative radiation therapy; Fraction, fx; SRS, stereotactic radiosurgery; PCI, prophylactic cranial irradiation; MRI, magnetic resonance imaging.