Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Guidelines

Reduced Fractionation in Lung Cancer Patients Treated with Curative-intent Radiotherapy during the COVID-19 Pandemic

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Abstract

Patients treated with curative-intent lung radiotherapy are in the group at highest risk of severe complications and death from COVID-19. There is therefore an urgent need to reduce the risks associated with multiple hospital visits and their anti-cancer treatment. One recommendation is to consider alternative dose-fractionation schedules or radiotherapy techniques. This would also increase radiotherapy service capacity for operable patients with stage I-III lung cancer, who might be unable to have surgery during the pandemic.

Here we identify reduced-fractionation for curative-intent radiotherapy regimes in lung cancer, from a literature search carried out between 20/03/2020 and 30/03/2020 as well as published and unpublished audits of hypofractionated regimes from UK centres. Evidence, practical considerations and limitations are discussed for early-stage NSCLC, stage III NSCLC, early-stage and locally advanced SCLC. We recommend discussion of this guidance document with other specialist lung MDT members to disseminate the potential changes to radiotherapy practices that could be made to reduce pressure on other departments such as thoracic surgery. It is also a crucial part of the consent process to ensure that the risks and benefits of undergoing cancer treatment during the COVID-19 pandemic and the uncertainties surrounding toxicity from reduced fractionation have been adequately discussed with patients. Furthermore, centres should

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document all deviations from standard protocols, and we urge all colleagues, where possible, to join national/international data collection initiatives (such as COVID-RT Lung) aimed at recording the impact of the COVID-19 pandemic on lung cancer treatment and outcomes.

Keywords: COVID-19; fractionation; lung cancer; radiotherapy

Introduction

The World Health Organization declared COVID-19, the disease caused by the 2019 novel coronavirus SARS-CoV-2, a pandemic on 11 March 2020. This situation is resulting in unprecedented demands on the National Health Service as a whole, posing a major burden on cancer services in the UK.

About 49 000 new patients are diagnosed with lung cancer each year in the UK and >50% require radiotherapy treatment. The lung cancer population requiring active treatment has been classified as 'extremely vulnerable', with a significant proportion of previously treated lung cancer patients included in this category due to coexisting severe comorbidities [1,2]. There is, therefore, a need to mitigate the risks of their anti-cancer treatments by addressing risks associated with multiple visits to hospital, treatment-induced immune suppression and radiation-associated lung injury. This means adapting our current treatment protocols rapidly to reflect the shifting risk–benefit ratio and diminished resources. Furthermore, the impact of this pandemic will probably last for a significant length of time beyond the resumption of normal services. This is due to the anticipated backlog of patients diagnosed with lung cancer and the increased demands on the radiotherapy departments due to the deferral of radiotherapy for disease sites such as breast and prostate.

General guidance on the delivery of radiotherapy during the COVID-19 pandemic has been provided by the National Institute for Health and Care Excellence [3]. One recommendation is to consider alternative dose-fractionation schedules or radiotherapy techniques.

The objectives of this article are: to identify reduced-fractionation and curative-intent radiotherapy regimens in lung cancer, assess their evidence base and provide organ at risk (OAR) dose constraints. We also discuss limitations and practical considerations associated with the implementation of these reduced-fractionation regimens. The anticipated impact of this work is first, to reduce hospital visits and limit exposure to COVID-19 in patients having curative-intent radiotherapy for lung cancer and, second, to increase radiotherapy service capacity for operable patients with stage I–III lung cancer, who may not be able to have surgery during the pandemic.

Methods

Systematic reviews and relevant papers were identified by a group of UK clinical oncologists through a PubMed search between 20 and 30 March 2020. We also included published and unpublished audits of hypofractionated regimens from UK centres.

Early Stage Non-small Cell Lung Cancer

UK practice is based on the recommendations from the UK stereotactic ablative radiotherapy (SABR) consortium [4]. Here we outline the evidence for a reduction in SABR fraction number and provide OAR dose constraints from existing international protocols. We also outline the evidence for hypofractionation (beyond 55 Gy in 20 fractions) for central/ultra-central early stage non-small cell lung cancer (NSCLC) not suitable for SABR due to OAR constraints being exceeded.

Single-Fraction Stereotactic Ablative Radiotherapy

Advice

- Consider 30–34 Gy in a single fraction in patients with tumours that are ≤2 cm, >1 cm from the chest wall and are outside of the no-fly zone. This is in keeping with the current National Comprehensive Cancer Network (NCCN) guidelines [5].

Evidence

Single-fraction schedules of 30–34 Gy have been compared with multi-fraction SABR in two phase II studies (RTOG 0915, Roswell Park) [6–8]. Local control rate, progression-free survival (PFS) and overall survival, as well as late toxicity and quality of life, were comparable between single-fraction and multi-fraction SABR regimens. Chest wall toxicity did not exceed grade 2 in either arm of both studies. A retrospective study including 146 lesions showed that grade 2–4 chest wall toxicity was 30.6% for lesions abutting the chest wall, 8.2% for tumours ≤1 cm from the chest wall and 3.8% for tumours 1–2 cm from the chest wall [9]. Overall grade ≥3 chest wall toxicity was 1.4%.

Limitations

- A range of SABR dose/fractionation schedules have been described, but no single regimen has been established as the standard of care.
- Evidence is based on phase II data only, where the numbers treated within 2 cm of the chest wall are very small.

Practical considerations

- Only centres with prior experience of delivering lung SABR should offer single-fraction SABR.

- Patients considered for single-fraction SABR are those typically treated with 54 Gy in three fractions, rather than 55 Gy in five fractions.
- It is advised only to consider tumours that move less than 1 cm after appropriate motion management on four-dimensional computed tomography imaging.
- The dose constraints recommended are those set out in the RTOG 0915 study (see supplementary Tables S1 and S2).

Stereotactic Ablative Radiotherapy for Tumours within 2.5 cm of the Chest Wall

Advice

- Consider three-fraction regimens (e.g. 54 Gy/three fractions).
- Where the planning target volume (PTV) abuts or overlaps the chest wall, consider 54 Gy/three fractions or a reduced dose to minimise toxicity (e.g. 48 Gy/three fractions).

Evidence

The rate of grade 3 chest wall toxicity with SABR from a large meta-analysis (combining several different dose and fractionations) is 1.2% [10]. Individual papers have found that the tumour to chest wall distance is a significant factor, as well as the maximum dose (Dmax) and the volume of chest wall receiving 30 Gy (V30) [11–14]. Multi-fraction retrospective data specifically looking at patients with tumours near the chest wall are shown in supplementary Table S3. Where the gross tumour volume is within 2.5 cm of the chest wall, no increased risk is seen with three fractions compared with five fractions (1.6% compared with 3.2%, respectively) [13]. Where the PTV is abutting the chest wall, data from Andolino *et al.* [11] suggest that 48 Gy/three fractions has a lower toxicity than 54 Gy/three fractions.

Limitations

- The effect of fractionation schedules on chest wall toxicity has not been investigated in prospective trials.

Practical considerations

- Suggested chest wall dose constraints for three-fraction schedules are $D0.5cm^3 < 60$ Gy, $D5cm^3 < 40$ Gy and $V30 < 30\ cm^3$ (see supplementary Tables S4.1 and S4.2).

Stereotactic Ablative Radiotherapy for Moderately Central Tumours

Advice

- Consider 50 Gy/five fractions in moderately central tumours.

Evidence

Moderately central early stage NSCLC is defined as a lesion within 2 cm of the bronchial tree, trachea, major vessels, oesophagus, heart, pericardium or brachial plexus, or a PTV abutting mediastinal pleura or pericardium, excluding ultra-central disease. An ultra-central lesion is where the PTV abuts either the main bronchi or trachea.

Two fractionations are commonly used:

- four to five fractions as per American Society for Radiation Oncology (ASTRO) guidelines (based largely on studies using a total dose of 45–50 Gy) [15].
- eight fractions as per the UK SABR consortium (total dose 60 Gy) [4].

Retrospective studies show similar grade 3 or above toxicity rates between 0 and 7.7% and local control rates between 77.6 and 95%. There is a lack of prospective evidence to suggest which regimen is superior. The safest arm in the prospective RTOG 0813 trial was the 50 Gy/five fractions cohort with no $\geq$ grade 3 toxic events. 50 Gy in five fractions has been used in Glasgow based on the RTOG 0813 dose constraints [16]. In a study of 50 patients, there was a 4% grade 3 toxicity rate and a median overall survival of 27 months, which is consistent with other published literature (see supplementary Table S5). 50 Gy in four fractions has also been used in North America but lacks prospective trial data and dose constraints.

Limitations

- There is no evidence to support one dose-fractionation regimen being superior in terms of efficacy or safety.

Practical considerations

- The dose constraints set out in RTOG 0813 are recommended (see supplementary Tables S6–S8).

Stereotactic Ablative Radiotherapy for Tumours >5 cm

Advice

- Tumours >5 cm in diameter can be treated with caution, provided that the OAR constraints for tumours <5 cm can be met.

Evidence

SABR is currently recommended for T1–2 tumours (or T3 tumours by virtue of invading chest wall) with a maximum size of 5 cm [4]. Clinical trials have predominantly excluded lesions larger than 5 cm and, therefore, conventional fractionation schedules have been favoured in this group. Woody *et al.* [17] reported on 40 patients with a median tumour size of 5.6 cm (range 5.1–10 cm) treated with a

median dose of 50 Gy in five fractions. The 18-month local control, overall survival and grade 3 toxicity rates were 91.2, 59.7 and 7.5%, respectively. A Dutch series reported on 63 patients with a median diameter of 5.8 cm (range 5.1–10.1) with a longer median follow-up of 54.7 months [18]. The median overall survival, 2-year local control and out-of-field distant recurrence rates were 28.3 months, 95.8% and 10%, respectively. Thirty per cent developed grade ≥3 toxicity (radiation pneumonitis was the most common toxicity) and 19% of deaths were treatment related.

Limitations

- There are no prospective data to support SABR for tumours >5 cm.

Practical considerations

- Dose constraints to OARs must be met as when treating lesions ≤5 cm.
- Following treatment, patients should be closely followed-up to detect and manage toxicity and expected higher distant relapse rates.

Hypofractionation for Central/Ultra-central Early Stage Tumours Not Suitable for Stereotactic Ablative Radiotherapy

Advice

- Consider 50–60 Gy in 15 fractions in patients with central/ultra-central early stage NSCLC not suitable for SABR based on OAR constraints.

Evidence

A prospective phase I dose-escalation trial for patients of performance status ≥2 with stage ≥ II NSCLC not suitable for surgery, SABR or chemoradiation used increasing doses in 15 fractions (50 Gy, 55 Gy or 60 Gy) to validate OAR constraints for a 15-fraction schedule in the intensity-modulated radiotherapy (IMRT)/image-guided radiotherapy era. They reported acceptable toxicities and no dose-limiting toxicity was documented [19]. The subsequent randomised phase III study comparing 60 Gy in either 15 or 30 fractions in patients with performance status ≥2 stage II–III NSCLC has published interim results in abstract form [20]. Sixty patients had been enrolled (88% stage III). Chemotherapy was given to some patients sequentially (before or after radiotherapy) but not concurrently. Less toxicity was reported in the 15-fraction arm. Cho *et al.* [21] retrospectively reviewed hypofractionated radiotherapy for medically inoperable T1–T3 N0 NSCLC using a risk-adaptive dose schedule (60 Gy in four, 15 or 20 fractions depending on location, size and geometry of the tumour in relation to the oesophagus). In total, 124 patients were included in the study: 72.6% had T1–2 N0 tumours; 65.3% had centrally located disease; 44.1% had performance status 2–3; and 20.2% received 60 Gy/15 fractions. In patients treated with 15 fractions, the rate of grade 3 pneumonitis was 4% with no grade 4–5 pneumonitis and no grade 2–5 oesophagitis reported.

Limitations

- OAR constraints for 15-fraction schedules were mostly derived from studies including patients with performance status ≥2 and stage II–III disease.
- There are no prospective data to support 50–60 Gy in 15 fractions specifically in central or ultra-central early stage NSCLC.

Practical considerations

- Dose constraints to OARs for the 15-fraction schedule must be met with particular attention to the oesophageal constraint (see supplementary Table S9).

Stage III Non-small Cell Lung Cancer

Concurrent Chemoradiotherapy

Advice

- Consider for selected patients (see practical considerations below).
- Consider accelerated fractionation (i.e. 55 Gy/20 fractions).
- Limit chemotherapy dose (see practical considerations below). Consider limiting chemotherapy to two cycles only and starting radiotherapy with cycle one.

Evidence

The randomised phase II SOCCAR trial [22] compared sequential versus concurrent chemotherapy combined with 55 Gy in 20 fractions. The median number of cycles delivered was 2.8 in the concurrent arm. Toxicity was similar across both arms, with a median survival of 24 months (concurrent arm) in a UK population of patients with stage III NSCLC using three-dimensional planning and treatment techniques. Following the study, a number of the participating centres adopted the schedule, fine-tuning chemotherapy regimens and evolving treatment techniques by applying positron emission tomography-computed tomography staging, four-dimensional planning, IMRT and volumetric modulated arc radiotherapy (VMAT). With these adaptions, UK centres are reporting encouraging 58% 2-year survival and acceptable rates of acute toxicity [23], which compares favourably with more recent trials, e.g. PACIFIC [24].

Limitations

The SOCCAR study only included 70 patients in the concurrent arm. It was published before many of the more modern staging and treatment techniques were in routine

use. The evidence base for contemporary concurrent chemoradiotherapy using a hypofractionated accelerated fractionation schedule is therefore limited (particularly concerning acute and late toxicity) and of a retrospective nature [23].

Practical Considerations

- The inclusion criteria for the SOCCAR study can guide patient selection [22]. OAR constraints as per the SOCCAR protocol are detailed in supplementary Table S9.
- Chemotherapy as per the SOCCAR protocol [22] can be adapted during the COVID-19 epidemic. Consideration should be given to omitting the adjuvant cycles and delivering the concurrent chemotherapy cycles only (intravenous cisplatin 60 mg/m^2 or carboplatin AUC5 day 1 and oral vinorelbine 40 mg/m^2 days 1 and 8).

Radical Radiotherapy ± Sequential Chemotherapy

Advice

- Consider for selected patients (see practical considerations below).
- Offer accelerated fractionation (55 Gy/20 fractions).
- Consider further hypofractionation (50–58 Gy in 15 fractions).
- If offered, limit chemotherapy to two cycles and consider delivering it following radiotherapy (see practical considerations below).

Evidence

The hypofractionated regimen of 55 Gy/20 fractions has been widely used in the UK [25], with audit data showing similar outcomes to CHART, 99% of patients completing treatment and a 7% grade ≥3 toxicity rate [26]. Retrospective data on 45 Gy in 15 fractions over 3 weeks (BED_{10} 58.5 Gy) showed comparable outcomes to doses ≥60 Gy given with conventional fractionation [27]. However, radiobiological calculation suggests that this schedule would not be isoeffective in comparison with 55 Gy/20 fractions (BED_{10} 70.1 Gy). A higher dose hypofractionated regimen of 60 Gy/15 fractions (BED_{10} 90 Gy) has been reported by Sunnybrook in patients with stage I–III NSCLC [28]. Forty-seven patients (52.8%) had stage II–III disease and the 2-year survival was 68% for this group. Importantly, the dose constraints derived for this study correspond well to those generated by Fenwick *et al.* [29] using conversion from the I-START 20-fraction schedule (see supplementary Table S9).

Limitations

Fifteen-fraction schedules have generally been used to treat central early stage disease, with the treatment of stage III patients limited to selected patients [28]. It should be noted that the toxicity of this regimen has not been reported specifically for patients with stage II–III.

Practical considerations

- Concerns over hypofractionated dose-escalated radiotherapy in NSCLC are dominated by late radiation toxicity involving central and perihilar structures [30]. The experience of accelerated schedules led to a UK research strategy that tested four separate escalation protocols in phase I/II studies. Two of these protocols used once daily hypofractionated schedules (IDEAL-CRT, I-START) with reassuring toxicity profiles [31,32]. Applying the principles that Fenwick *et al.* [29] used to develop these schedules to a 15-fraction schedule delivered over 19–21 days:
  - using an α/β of 10, 52 Gy/15 fractions is the isoeffective dose for tumour control and using an α/β of 3, 50 Gy/15 fractions is isotoxic to 55 Gy/20 fractions for late complications.
  - 58 Gy/15 fractions would be the equivalent of the highest dose cohorts in these two studies (IDEAL-CRT 73 Gy/30 fractions over 6 weeks, I-START 65 Gy/20 fractions over 4 weeks).
- The use of IMRT/VMAT is strongly recommended. The radiotherapy planning guidelines for current stage III studies [33] are a resource that can help guide patient selection, outlining and planning using the modified dose constraints in supplementary Table S9.
- The addition of chemotherapy in the sequential setting will need careful consideration, balancing a 4% absolute overall survival benefit over radiotherapy alone [34] against the additional infective risk posed by COVID-19. Consideration should be given to radiotherapy first, with deferred chemotherapy given later when the risks related to COVID-19 start decreasing.

Small Cell Lung Cancer

Early Stage Small Cell Lung Cancer

Advice

- Consider SABR (with or without chemotherapy) in T1-2 N0 M0 patients as an alternative to surgery or fractionated radiotherapy. Dose/fractionation and OAR constraints should be the same as those used for early stage NSCLC.

Evidence

SABR is standard of care in medically inoperable early stage NSCLC and is increasingly being delivered for early stage SCLC [35–38]. SABR for early stage SCLC is a treatment

option in the ASTRO 2020 guidelines [39] and in the 2020 NCCN guidelines [40].

The largest series of SABR for limited stage SCLC is a retrospective multicentre study including 74 patients [38], of which only 59% of the patients received chemotherapy, 23% received prophylactic cranial irradiation (PCI) and >30% of patients had an Eastern Cooperative Oncology Group performance status 2–3. Toxicity was mild, with 5.2% grade ≥2 pneumonitis. Local PFS was 96.1% and overall survival was 34% at 3 years.

Limitations

- Evidence base for SABR is limited to the peripheral early stage SCLC setting. The risk of toxicity and development of lymph node metastases for central/ultra-central tumours is higher compared with peripheral tumours [41,42]. As data are lacking in ultra-central early stage SCLC, conventionally fractionated radiotherapy is more appropriate for these patients.
- Given the risk of distant metastases, chemotherapy is generally considered in this setting for those patients who are suitable [35,38].

Practical considerations

- In the context of the COVID-19 pandemic, the risk–benefit ratio of giving chemotherapy should be considered carefully. In patients who are suitable for chemotherapy, it is advisable to give SABR first as the tumour volume may decrease significantly after the first or second cycle of chemotherapy and become difficult to visualise on image guidance.

Radiotherapy Fractionation in Good Performance Status Limited Stage Small Cell Lung Cancer Patients

Advice

- Consider 40 Gy in 15 daily fractions given with the first or second cycle of chemotherapy in patients with good performance status limited stage SCLC.
- Consider 40 Gy in 15 daily fractions after induction chemotherapy in patients who are not suitable for concurrent treatment.
- Limit chemotherapy to a maximum of four cycles.

Evidence

The current standard of care is twice-daily radiotherapy (45 Gy in 30 fractions) delivered concurrently with cycle 1 or 2 chemotherapy [43–45]. However, hypofractionated regimens are also used in UK centres and include: 40 Gy in 15 fractions and 50–55 Gy in 20 fractions. A randomised study by the National Cancer Institute of Canada showed a survival benefit with early concurrent radiotherapy (week 1) versus late (week 15) using 40 Gy in 15 daily fractions [46]. Toxicity in both arms was acceptable. Grade 4 neutropenia was common and pneumonitis was <3%. Grønberg *et al.* [47] reported a randomised phase II trial of 157 patients with limited stage SCLC treated with 42 Gy in 15 fractions once daily or 45 Gy in 30 fractions twice daily. There was no difference in 1-year or median PFS. There were no differences in ≥grade 3 oesophagitis (once daily 31%, twice daily 33%, $P = 0.80$) or pneumonitis (once daily 2%, twice daily 3%, $P = 1.0$) [47]. Videtic *et al.* [48] retrospectively reviewed 122 limited stage SCLC patients who received concurrent chemotherapy with 50 Gy in 25 fractions over 5 weeks (92 patients) or 40 Gy in 15 fractions over 3 weeks. There was no difference in treatment-related toxicity, overall survival and thoracic local control. Xia *et al.* [49] reported results on 59 limited stage SCLC patients treated with 55 Gy in 22 fractions over 30 days and concurrent chemotherapy. Twenty-five per cent of patients developed ≥ grade 3 oesophagitis and 10% of patients developed ≥ grade 3 pneumonitis. 40 Gy in 15 fractions has been used concurrently and sequentially in Leeds for limited stage SCLC for >10 years. Institutional dose constraints are listed in supplementary Table S10 and a recent unpublished audit of 43 limited stage SCLC patients treated with concurrent chemoradiotherapy (40 Gy in 15 fractions) showed a 1-year overall survival of 88% and a median overall survival of 26.9 months (15.6–50.4).

Limitations

- The initial data on 40 Gy in 15 fractions are from 1993 [46] and, therefore, radiotherapy planning and delivery would be considered suboptimal.
- Most data on hypofractionated regimens are from retrospective single-institution studies.
- A variety of different hypofractionated regimens are used in the published literature and in routine UK practice.

Practical considerations

- When treating limited stage SCLC with hypofractionated radiotherapy, intravenous contrast (if not contraindicated) and three-dimensional computed tomography/IMRT planning with an offline image-guided radiotherapy protocol with volumetric imaging are considered the standard of care. Four-dimensional computed tomography planning and daily online cone-beam computed tomography (CBCT) are highly recommended, particularly if OAR doses are close to tolerance.
- Leeds' OAR constraints for the 40 Gy/15 fractions regimen are listed in supplementary Table S10.

Discussion

This guidance document on reduced fractionation for lung cancer being treated with curative intent during the COVID-19 pandemic builds on a long tradition of hypofractionated radiotherapy in the UK. It reflects the current published literature and the combined experience of the

authors and their colleagues in the UK and globally. However, it is acknowledged that for many centres, the fractionation regimens outlined will represent a significant change to current practice and standard of care. The extent of adoption of this guidance may reflect geographical pressures, although it is likely that all radiotherapy departments will need to adapt during this global pandemic.

This guidance document should be discussed with other specialist lung multidisciplinary team members, as access to adequate nodal staging procedures (e.g. endobronchial ultrasound-guided transbronchial needle aspiration [EBUS-TBNA]) and respiratory function testing will probably be compromised during the peak of the virus pandemic. That discussion will disseminate the potential changes to radiotherapy practice that could be made in order to alleviate pressure on other departments, such as thoracic surgery.

Adequate discussion with the patient about the risks and benefits of treatment during the COVID-19 pandemic and uncertainties about toxicity from reduced fractionation where there is limited experience in a department are an essential component of the consent process.

Centres should document deviations from standard pre-treatment work-up as well as deviations from standard of care treatments. We consider prospective and multi-centre documentation of outcome (including toxicity) from these reduced-fractionation regimens as essential. We also urge colleagues to join national/international data collection initiatives on the impact of the COVID-19 pandemic, such as COVID-RT Lung.

Conflicts of interest

C. Faivre-Finn reports grants from AstraZeneca and Elektra during the conduct of the study. F. McDonald reports speaker fees and consulting fees from AstraZeneca, speaker fees from Elektra and consulting fees from Accuray outside the study.

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Appendix A. Supplementary data

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