REVIEW ARTICLE

Hypofractionation and Stereotactic Body Radiation Therapy in Inoperable Locally Advanced Non-small Cell Lung Cancer

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ABSTRACT

Background and Aim: Radiotherapy (RT) plays a key role in the control of locally advanced non-small cell lung cancer (LA-NSCLC). Throughout the years, different doses and fractionations of RT have been used in an attempt to optimize the results. Recently, special interest has been given to hypofractionation (hypoRT) and stereotactic body radiation therapy (SBRT). HypoRT is a relatively widespread treatment, although the accompanying level of evidence is limited. For its part, SBRT has been used specially to overdose specific areas of the disease as a boost after radiochemotherapy. In both cases, the study of how to integrate these RT tools with chemotherapy and immunotherapy is fundamental. In addition, the 2020 COVID-19 pandemic situation has sparked increased interest in hypofractionated treatments. In this review, we analyze the role of SBRT and hypoRT in the management of LA-NSCLC in accordance with current scientific evidence.
Relevance for Patients: The objective of this article is to introduce professionals to the role that hypoRT and SBRT can play in the treatment of LA-NSCLC to offer the best treatment to their patients.

1. Introduction

The Pacific study showed how the administration of durvalumab after radiotherapy (RT) and chemotherapy (CRT) significantly improved survival in patients with unresectable Stage III non-small cell lung carcinoma (NSCLC). It was an important milestone in the treatment of this disease [1]. Studies have shown that the most common type of recurrence in LA-NSCLC is distant [2,3]. Despite this, locoregional control is still essential to increase survival, so it is of great interest to optimize RT treatments [4]. Over the years, different strategies have been used to improve the results with RT by altering the doses, the fractionations and applying the latest technological advances. In recent times, special emphasis has been placed on the use of hypofractionated treatments. The progressive knowledge and expansion of stereotactic body RT (SBRT) has prompted the study of its application in this disease. In addition, with the impact of the COVID-19 pandemic, different scientific societies gave recommendations aimed at shortening treatment times by paying special attention to hypofractionated treatments. Finally, the emergence of immunotherapy has meant a true paradigm shift in the management of lung cancer. The best way to combine RT with these new treatments remains to be defined. In this context, in this publication, we intend to review the status of hypoRT and SBRT in the changing scenario of locally advanced and unresectable lung cancer.

2. Materials and Methods

We searched the National Comprehensive Cancer Network, the European Society for Medical Oncology (ESMO), European Society for Radiation Oncology (ESTRO), and the

American Society for Radiation Oncology updated guidelines. The following search strategy was performed of the PubMed database on July 2020: (lung AND (non-small cell OR NSCLC) NOT metast * [TI]) AND (stage III OR locally advanced OR locally-advanced) AND (radiation therapy OR radio -therapy) AND (hypofract * OR hyperfract * OR adaptive RT OR SBRT) NOT case reports. Clinical studies, clinical trials, meta-analysis, and reviews were selected. References were also analyzed. We classified in hyperfractionation (hyperRT), hypofractionation (hypoRT), adapted therapy, or SBRT.

3. Results and Discussion

3.1. State of the art: Current management, conventional dose escalation, and hyperfractionation

Treatment of Stage III N0 or N1 NSCLC consists of surgery followed by adjuvant treatment. When there is mediastinal involvement, the role of surgery is controversial. A 2007 Phase III study of the European Organization for Research and Treatment of Cancer (EORTC) randomized CT followed by RT or surgery to N2 patients and showed no differences between both treatments [5]. Regarding neoadjuvant treatment, there is evidence of the benefit of CT as neoadjuvant treatment in Stage III [6]. Considering neoadjuvant CRT, a Phase III intergroup study randomized to CRT followed by surgery versus exclusive CRT. Although no differences in survival were demonstrated between the two groups, an unplanned analysis found that those patients treated with lobectomy had a longer survival when compared to patients treated with CRT [7]. In any case, the role of surgery in N2 patients is still subject to debate in part due to the great diversity of this group of patients. There is evidence to suggest that the prognosis after surgery depends on the burden of mediastinal involvement [8]. In this way, in cases with few affected lymph nodes or in a single station, surgery could be indicated.

In unresectable situations, the evidence favors treatment with RT at doses of 60 Gy–70 Gy in 2 Gy fractions concomitant with CT and followed by durvalumab, based on the results of the Pacific trial [1,9,10]. In this study, patients received concurrent CRT and the administration or not of adjuvant durvalumab was randomized. Latest data reported at ESMO 2020 maintained impressive results with increased follow-up. In the experimental arm with durvalumab, median overall survival (OS) was 47.5 months and 4-year OS was 49.6%, while in the placebo arm, the median survival and 4-year OS were 29.1 months and 36.3%, respectively [10]. Anyway, in Europe, durvalumab is only approved by the European Agency of Medicaments (EMA) for patients with PDL1> 1% [11].

In non-randomized studies, RT dose escalation has shown improvements in survival and local control (LC) both in exclusive RT and administered with CT [12-16]. OS in these studies ranged from 19 to 24 months. In an analysis by Machtay *et al.*, 1356 patients drawn from Radiation Therapy Oncology Group (RTOG) clinical trials were retrospectively analyzed. This study showed that 1% increases in bioequivalent dose (BED) were related with 3% improvement in LC and 4% relative improvement in OS [17].

Based on these encouraging results, the Phase III trial RTOG 0617 trial explored the benefits of increasing the dose of RT by randomizing patients to receive 74 Gy versus 60 Gy. This trial was prematurely closed due to the low survival in the experimental arm. Median OS in the control arm was 28.7 months (the same as in the control arm in the Pacific study) and the 2-year OS was 58%, while in the experimental arm, median OS and 2-year OS were 20.3 months and 45%, respectively. Surprisingly, the LC and locoregional control were also worse in the experimental arm. It was concluded that increasing the dose to 74 Gy provided no benefits [18]. There were several coincidence factors in the experimental arm that may have contributed to these results, such as the increased doses received by the heart, less adherence to RT protocols, worse compliance to the CT schemes, and increased toxicity deaths. Finally, the use of intensity modulated RT (IMRT) and the volume of patients treated by the participating centers may have influenced the results [19-22].

Although the main clinical guidelines propose conventional fractionation RT as the standard of care [9,23,24], the controversy about the benefit of dose escalation remains open. In 2016, Ramroth *et al*. published a meta-analysis examining studies with patients randomized to different RT schemes, including regimes with splits, hypoRT, hyperRT, or dose escalation with conventional fractionation. The results showed that the increased of BED administered without CT improved survival [25].

On the other hand, it is known that the prolongation of the global treatment time has a negative impact on the control of the disease as a consequence of the accelerated repopulation of cells, which could also contribute to the results of the RTOG 0617 trial. For each day that RT treatment is prolonged beyond 6 weeks, the chances of survival are reduced by 1.6% [20,21,26,29]. Based on this, other ways to elevate BED without prolonging the overall treatment time have been explored.

3.2. Hyperfractionation

HyperRT consists in increasing the total number of fractions delivered twice (or more) per day, at a reduced dose per fraction and it has shown uneven results.

Treatment with continuous hyperfractionated accelerated RT (CHART), administering 54 Gy in 12 days, in three 1.5 Gy fractions per day, showed an increase in survival [30]. However, the same scheme without treatments on the weekends (CHARTWEL) showed no benefit over conventional treatment [31]. Similarly, an Australian study on hyperRT and the study RTOG 9410 comparing various treatment schemes including hyperRT did not show benefit through this strategy [32,33]. A meta-analysis analyzed 2000 patients from 10 trials comparing conventional fractionation with hyperRT showed a survival benefit with hyperRT of 3.8% and 2.5% at 3 and 5 years, respectively, but with a significant increase in acute esophagitis (9% vs. 19%) [34].

The diffusion and widespread implementation of hyperRT has been hampered by logistical barriers. Furthermore, it is not well known how these treatments should be supplemented with CT. Finally, hyperRT has been consistently observed to increase

esophageal toxicity. Therefore, although the 2019 National Institute for Health and Care Excellence (NICE) guidelines propose hyperRT as an alternative to conventional fractionation in patients not candidates for CRT treatment, its use is minority [35,36].

3.3. Hypofractionation

Nowadays, there is a greater interest in exploring fractionations aimed at shortening the global treatment time by increasing the doses per fraction and thus increasing the BED. It has been observed that there is a moderate linear relationship between BED and OS when using hypoRT so that for each 1 Gy increase in BED, there would be a benefit of 0.36–0.7% in OS [37]. In most of the published studies, they use moderate hypoRT with doses of 2.5–3 Gy per fraction.

3.3.1. Hypofractionation without concurrent CT

It is important to highlight that patients in the Pacific and RTOG 0617 trials had a performance status (PS) of 0 or 1 and median age of 64 years, what, undoubtedly, has its implications in the results. In routine clinical practice, patients' PS is frequently ≥2, median age at diagnosis is 70 years, and they often have comorbidities that jeopardize treatment strategy. In fact, it is estimated that between 55% and 59% of the patients are not candidates for concurrent CRT [38,39]. Some experiences have shown good results with acceptable toxicity using hypoRT in this group of patients [40]. A retrospective Spanish study analyzed the results treating patients no candidates to CRT with hypoRT (66 Gy in 24 fractions). In Stage III subgroup, 2-year OS was 37.5% and no Grade 3 toxicity was reported [41]. Din *et al*. published a retrospective analysis with 609 patients treated with hypoRT (55 Gy in 20 fractions of 2.75 Gy) without concurrent CT (28% received sequential CT). Median OS and 2-year OS for locally advanced disease were 20 months and 40%, respectively, with no Grade 3 or 4 toxicities [42]. Another retrospective analysis by Amini *et al*., with 300 patients, compared hypoRT (45 Gy in 15 fractions of 3 Gy) with conventional fractionations in patients not candidates for CRT treatments. They concluded that hypoRT was an acceptable treatment option for poor PS patients, with similar results to those achieved with conventional RT [43].

Recently, it has been published an analysis of the National Cancer Database (NCDB) comparing hypoRT versus conventionally fractionated RT in patients treated with RT alone. A total of 6490 patients were evaluated, 5378 with conventional RT (median dose of 66 Gy in 2 Gy) and 1112 with hypoRT (median dose 58.5 Gy in 2.5 Gy fractions). HypoRT was associated with older age, lower BED, academic facility type, higher T-stage, and lower N-stage. After adjusting by these covariates, no difference in OS was observed between both groups [44].

In a review by Kaster *et al*., analyzing the studies with hypoRT without concurrent CT, the reported weighted mean acute esophageal and pulmonary toxicity were 1.9% and 1.2%, respectively. Late esophageal and pulmonary toxicity were 1.4% and 6.9%, respectively. Two-year survival ranged from 18% to 42%. Toxicities were defined as events that could be scored as Grade 3 or more [37].

In a 2019 review, Parisi *et al*. analyzed up to 29 studies published since 2007. In hypoRT treatments without CT, the dose range ranged from 45 to 85.5 Gy. Acute grade ≥3 esophageal toxicity was 0–15% and acute pulmonary toxicity was 0–44%. The late esophageal and pulmonary toxicity found was 0–16% and 0–47%, respectively, with pulmonary toxicity being most commonly ≤Grade 3. Two-year OS ranged from 22 to 68.7% [45].

More aggressive hypoRT schemes have been employed, although, as with SBRT, the central location of the lesions is of particular concern. In a Phase I dose escalation trial, 55 patients with poor PS were treated with doses of 50, 55, or 60 Gy in 15 fractions. It was concluded that precision hypoRT with 60 Gy in 15 fractions is generally well tolerated [46]. The same group developed a Phase III trial in which patients with a PS ≥2, not candidates for concurrent CRT, were randomly assigned to either 60 Gy in 30 fractions or 60 Gy in 15 fractions. In an interim analysis, the median OS was 11.5 months with no intergroup differences. The authors concluded that hypoRT may be an alternative for these groups of patients [47]. A retrospective analysis published in 2020 with 42 patients with KI ≥70% treated with doses of 60 Gy in 15 fractions (and mostly with sequential CT), showed a 2-year survival of 69%, with 14% esophageal toxicity ≥G3 and 14% pulmonary toxicity ≥G3 [48].

With the emergence of immunotherapy in the treatment of LA-NSCLC, the use of hypoRT treatments is controversial. On the one hand, there is a concern of a cumulative risk for severe pneumonitis. On the other hand, the immunomodulatory role of hypoRT could increase the effectiveness of treatments. In this sense, the Phase II TRADE-hypo trial will investigate two radiation regimens combining durvalumab therapy with either conventionally fractionated or hypoRT (55 Gy in 20 fractions), in patients not candidates for CT. Another Phase II study (DUART trial) will explore the role of durvalumab after RT in patients not candidates for CT, also including hypofractionated schemes. Both studies are in recruitment [49,50].

During the COVID-19 pandemic, many recommendations have emerged by different societies with the common message that hypofractionated schedules without concurrent CRT are appropriate [51-53]. In the practical guideline carried out by ESTRO, there is consensus to recommend hypoRT alone or with sequential CT. The most recommended regimens are 60 Gy in 20 fractions, 60–66 Gy in 24–30 fractions, and 55 Gy in 20 fractions [52].

As we can see, there is great heterogeneity in the doses and fractionation schemes published in the literature. In any case, and despite the difficulty in obtaining conclusions about the efficacy of hypoRT in patients not candidates for concurrent CRT, these treatments are increasingly becoming part of routine clinical practice.

3.3.2 Hypofractionation with concurrent CRT

The Phase I trial called Alliance, studied RT dose escalation using advanced RT techniques with weekly carboplatin-based concurrent CT. The daily fractionation was escalated from 2.22 Gy to a maximum of 3 Gy per fraction to a total fixed dose of 60

Gy over four planned cohorts. The MTD was reached and defined as 60 Gy in 24 fractions of 2.5 Gy [45]. In other small Phase I study with 3DRT, 13 patients were treated with 3 Gy per fraction with concurrent CT. The MTD was 69 Gy at 3 Gy per fraction with no treatment related deaths reported [55].

In the systemic review by Kaster *et al.*, in the hypoRT with concurrent CT subgroup, the weighted mean acute esophageal and pulmonary toxicity were 14.9% and 7.9%, respectively. Weighted mean late esophageal and pulmonary toxicity were 16.6% and 12.2%, respectively. The 2-year OS ranged from 24% to 58% [37]. In the previously referenced review by Parisi *et al.*, in the hypoRT treatments with concurrent CT, the acute Grades 2 and 3 esophagitis ranged between 3% and 41.7% and acute pneumonitis ranged from 0 to 23%. Late esophageal and pulmonary toxicity ranged from 0 to 8.3% and from 0 to 47%, respectively. The 2-year survival was 38.6–68.7% [45]. These results reflect, with the limitations inherent in this type of study, an increase in toxicity in combined hypoRT-CT treatments.

In 2014, the SOCCAR trial compared concurrent versus sequential hypoRT (55 Gy in 20 fractions of 2.75 Gy) and CT. Initially, it was planned to be a Phase III study, but due to poor recruitment, it was restructured to a Phase II study. The main objective was to assess the tolerability of the treatment. The results showed low toxicity, with 9.3% and 8.2% Grade 3 esophageal toxicity in the concurrent and sequential arms, respectively. Two-year OS in the concurrent CRT arm was 50% versus 46% in the sequential arm. The median OS for concurrent versus sequential was 24.3 and 18.4 months, respectively.

In 2019, a retrospective analysis was published with 100 patients treated with hypoRT (55 Gy in 20 fractions) with 2 cycles of concurrent CT followed by 2 cycles of adjuvant CT with vinorelbine and cisplatin. The 2-year OS was 58%, higher than in the SOCCAR study, possibly due to the incorporation of advances in disease staging and modern RT techniques [56]. Although this scheme of RT with concurrent CRT has not ever been directly compared with conventional CRT, it has not hindered it from being the most employed RT fractionation in the UK, according to a survey carried out about the most common practices in the treatment of NSCLC [36]. In fact, in the NICE guidelines for NSCLC updated in 2019, this scheme is presented as an alternative for radical treatments [35].

The EORTC 08972-22973 study randomized hypoRT (66 Gy in 24 fractions of 2.75 Gy) with concurrent CT (daily low-dose cisplatin) versus sequential CT (two cycles of cisplatin and gemcitabine). The study was prematurely discontinued due to poor recruitment, and no significant differences were seen between the two arms, maybe because of the poor power of the study. The median OS and 2-year OS for the concurrent arm were 16.5 months and 39%, respectively. Acute G3 esophagitis was higher in concurrent than sequential CRT (14% vs. 5%). Anyway, this 2007 study, employed elective nodal irradiation and old planning techniques [57,58].

This 66 Gy in 24 fractions scheme is still used in common clinical practice in some centers incorporating new planning and delivery techniques and positron emission tomography (PET)-based nodal

treatment. In a Phase II trial, the addition or not of cetuximab was randomized to concurrent CRT (66 Gy in 24 fractions and low-dose cisplatin). The results were excellent independently of the administration of cetuximab, with a median OS of 31.5 months and 2-year OS of 59.4%. On the other hand, it was observed that the dose on the esophagus, the PS, and the comorbidities of the patients influenced the OS [50]. A retrospective analysis with 469 patients was published in 2017 using the same scheme of hypoRT and low-dose CT. The authors found a significant association between heart dose and OS [60]. This shows the importance of selecting cases for hypoRT treatments with concomitant CT, as well as optimizing RT techniques and adjusting CT treatments. The use of 4DCT, IMRT, volumetric modulated arc therapy (VMAT), and advanced image-guided RT (IGRT) techniques such as cone-beam CT (CBCT) may be especially necessary when performing this type of treatment to try to minimize esophageal, cardiac, and pulmonary toxicity.

The ESTRO recommendations for the COVID-19 pandemic argue against the use of hypoRT with concurrent CT [61]. However, the British group proposes the use of hypoRT with concurrent CT as per SOCCAR protocol for selected cases [53]. This divergence reflects the limitations of the current evidence to be able to give firm recommendations in this regard. Going further, a recent systematic review has questioned the benefit of performing concurrent CRT treatments over sequential treatment when the dose is increased through fractionation modifications [62].

3.4. Personalized hypofractionated radiation therapy

Typically, RT treatments use fixed doses of radiation for a particular disease. However, the possibility of individualizing dose escalation based on the tolerance limits of healthy organs has been explored. This has been called isotoxic radiation therapy [63].

Cannon *et al*. published a Phase I dose escalation study using isotoxic hypoRT without concurrent CT. In this study, patients were treated in 25 fractions, escalating the dose from 2.28 Gy to 3.42 Gy individually, according to the risk of developing pneumonitis. The MTD was defined as 63.25 Gy in 25 fractions of 2.53 Gy, similar to other dose escalation studies. Late Grade 4–5 toxicities were attributable to damage to central and perihilar structures and were correlated with dose to the proximal bronchial tree [64]. Once again, we verify the importance of limiting the dose received by the central structures. The importance of employing advanced RT techniques is evident if the dose is to be increased through hypofractionation.

The IDEAL-CRT trial evaluated dose escalation up to 73 Gy in 30 fractions over 6 weeks with dose escalation calculated on an individual patient basis according to either lung or esophageal radiation dose. Median OS was 37.5 months and 2-year OS was 62.9% [65,66].

The ADSCAN Phase II study, currently in recruitment, includes different forms of fractionation for patients treated with CT and sequential RT. It randomizes to five different RT schemes: STANDARD RT: 55 Gy in 20 fractions; CHART-ED: 54 Gy (three fractions of 1.5 Gy/day for 12 days), followed by 10.8 Gy (two fractions of 1.8 Gy/day for 3 days); IDEAL: 30 daily

fractions of isotoxic RT (63–71 Gy); I-START: 20 daily fractions of isotoxic RT (55–65 Gy); and ISOTOXIC-IMRT: bidaily fractions of isotoxic RT over 4 weeks (max dose 79.2 Gy). The aim of this study is to find the most promising way to increase doses to subsequently develop a Phase III trial [67].

Other studies have used PET to adapt the volume of treatment. In a Phase II carried out by Kong *et al*., a PET was performed at 40–50 Gy to redefine the treatment target and a hypoRT boost was administered on the observed residual disease. The threshold dose was defined as the dose over which the risk of Grade 2 pneumonitis was above 17.2% (approximately equivalent to 20 Gy mean lung dose). In this study, the median dose administered over the tumor was 83 Gy in 30 fractions and most patients received CT concurrently. LC at 2 years was 82% and median OS was 25 months [68].

The randomized Phase II PET-boost trial aimed to improve LC by boosting either the whole primary tumor (arm A) or the high FDG uptake region inside the primary tumor (arm B). The boost dose was maximized by normal tissue constraints (isotoxic treatment). The results were presented at ESTRO 2020 congress, showing a median total dose of 78 Gy for the arm A and 84 Gy for the arm B and a LC >90% at 1 year for both arms, respectively, although the trial did not reach predefined sample size and many scans were not evaluable [69].

The RTOG 1106 is a Phase II study with a control arm (60 Gy in 30 fractions) and an experimental arm (21 fractions at 2.2 Gy and 9 fractions applied on the residual disease seen in a PET, at doses between 2.2 and 3.8 Gy without exceeding the mean lung dose of 20 Gy). The experimental arm is a hypofractionated, adaptive, and isotoxic scheme [70]. The first results of this study were presented at World Conference on Lung Cancer 2020. Adaptive RT increased numerically local and local-regional control, but these differences were not statistically significant. There were no differences in Grade 3 or worse toxicity, OS, progression-free survival, and lung cancer-specific survival between treatment arms [71].

Although this type of treatment can make it possible to increase the dose on the disease, there is still no clear evidence about its clinical benefit. In the future, studies exploring this type of fractionation should include immunotherapy and consider customizing the RT dose based on radiosensitivity profiles [72].

3.5. SBRT

Conventionally, wide margins have been used to compensate movement of thoracic lesions during the respiratory cycle, thus limiting the radiation dose that could be delivered. SBRT consists of the administration of high doses of radiation with high precision with a narrow margin and with a strong gradient to protect the surrounding healthy tissue. To be able to carry this out, it is essential to have 4DCT images, use strategies to compensate for the movement during the respiratory cycle (as dampening, gating, active breathing control, or tracking) and to have a good IGRT system during treatment. As IGRT strategy, the use of CBCT and more recently 4D-CBCT are widely disseminated [56,57]. In this way, it has become feasible to administer radiation doses hitherto

unimaginable with limited toxicity [58]. It is of interest to note that some of the strategies used in SBRT to improve precision can be similarly used in hypoRT treatments to reduce possible toxicity, as previously noted.

SBRT achieves LC in more than 90% of patients with Stage I NSCLC and increases survival when compared to conventional RT, becoming the alternative to surgery in inoperable patients [73,74]. From this experience, the SBRT role at LA-NSCLC has become an area of great interest. The objective of SBRT in this context would be to optimize LC of the disease while trying to minimize toxicity. However, to this day, it is still unclear how best to integrate SBRT with established treatments.

There are several publications that have proposed different treatment schemes, paying special attention to its safety. The University of Kentucky group published a tolerability study in which the patients were treated with CRT (60 Gy in 30 fractions) and then SBRT was administered on the residual tumor (<5 cm) observed in PET. The SBRT dose was 20 Gy in two fractions and 19.5 Gy in three fractions for central lesions, always above 100 Gy BED (alpha/beta = 10). Thirty-seven patients were treated with a follow-up of 25.5 months. Median OS was 25.2 months LC was 78%. Grade 3 pneumonitis occurred in 13.5%. Two patients died due to fatal hemorrhage although no dosimetric differences were seen. Anyway, they proposed 175 Gy (BED10) as an estimated MTD for combined CRT and SBRT boost planning for the pulmonary artery for future studies. The authors concluded that it is a safe treatment resulting in good LC with not increased risk for toxicity above that for standard radiation therapy [75,76].

Other groups have developed Phase I dose escalation studies with SBRT toxicity boost following CRT, but with small number of patients and limited follow-up. Hepel *et al*. carried out a Phase I dose escalation study after CRT with 50.4 Gy, exploring four dose levels: 16 Gy in two fractions, 20 Gy in two fractions, 24 Gy in two fractions, and 28 Gy in two fractions. One-year locoregional control was 100% with boost doses ≥24 Gy. One patient died of bronchopulmonary hemorrhage associated to the dose applied to the proximal bronchovascular tree. Based on their results, the authors recommend limiting the doses applied to the bronchovascular tree or increase the number of fractions [77]. In a previous dosimetric pilot study, the authors proposed dose limits for the organs at risk and showed how it is feasible to respect these constraints, but there were no predetermined limits for the bronchovascular tree [78]. Higgins *et al*. analyzed four dose levels (18 Gy in two fractions, 20 Gy in two fractions, 30 Gy in five fractions, and 35 Gy in five fractions) following concurrent CRT at 44 Gy. Two patients developed Grade 5 toxicities (a tracheoesophageal fistula and one case of hemoptysis). The authors concluded that although 30 Gy in five fractions is the maximum tolerated dose calculated, 20 Gy in two fractions may be a reasonable dose as no Grade 5 toxicities were observed with this scheme [79]. In a retrospective study, 16 patients received conventional CRT to a median dose of 50.40 Gy followed by an SBRT boost with an average dose of 25 Gy given over five fractions. One-year LC was 76%, 25% developed Grade 2 acute pneumonitis, and no Grade 5 toxicities were observed [80]. In Table 1, we collect and summarize these studies.

Table 1. Stereotactic body radiotherapy as boost after chemoradiotherapy

Publications	N	RT dose in CRT	SBRT dose	Cumulative BED10	Local control	Survival	Toxicity
Kumar *et al.* [75]	37	60 Gy	10 Gy×2fx 6.5 Gy×3fx for central tumors	110 Gy 102.2 Gy	78%	25.2 m OS	13.5% Grade3 5.4% Grade 5 (fatal hemorrhage)
Hepel *et al.* [77]	12	50.4 Gy	8 Gy×2fx 10 Gy×2fx 12 Gy×2 fx 14 Gy×2fx	88.3 Gy 99.5 Gy 112.3 Gy 126.7 Gy	1 year – LRC: 78% 1 year – LRC<24 Gy: 50%, 1 year – LRC≥24 Gy: 100%	1 year – OS: 67%	8% Grade 3–5 (fatal hemorrhage)
Higgins *et al.* [79]	19	44 Gy	9 Gy×2fx 10 Gy×2fx 6 Gy×5fx 7 Gy×5fx	87 Gy 92.8 Gy 100.8 Gy 112.3 Gy	3 years – LRC: 56%	3 years – OS: 39%	10.5% Grade 5; (tracheoesophageal fistula and fatal hemoptysis) With 10 Gy×2fx: no grade≥3
Karam *et al.* [80]	16	50.4 Gy (45 Gy-60 Gy)	4–6 Gy×5 fx	97 Gy (81 Gy–120 Gy)	1 year – LC: 76%	1 year – OS: 78%	25% Grade 2 acute pneumonitis. No grade≥3

N: Number of patients; RT: Radiotherapy; CRT Chemoradiotherapy; SBRT: Stereotactic body radiotherapy; fx: Fractions; LC: Local control; LRC: Locoregional control; OS: Overall survival; m: Months; n.a.: Not available.

In a study performed by a Korean group in 2018, Kim *et al.* combined CRT for nodal areas and SBRT on the primary lesion, when the targets were distant from each other. With 21 treated patients, 2-year OS was 60.5%, there were no relapses regarding the primary tumor and 14% of the cases developed Grade 3 pneumonitis, all in patients aged over 79 years. The methodological limitations of the study do not allow drawing conclusions, but it opens the door to another possible therapeutic application for SBRT. The use of SBRT has also been examined as part of a multimodal treatment with CRT and surgery in the locally advanced disease. The currently on-going Linnearre I is a Phase I viability study in which SBRT is given as a neoadjuvant treatment in N0-N1 patients [81]. In other prospective study published in 2018 by Singh *et al.*, SBRT was employed as an adjuvant treatment after surgery and before adjuvant CRT. A 10 Gy single fraction was applied on the affected nodal stations or in cases of positive margins with good results in terms of LC [82].

The Phase I hybrid study proposes combining CT with hypoRT on lymph node disease (24 fractions of 2.42 Gy) with SBRT (3 fractions of 18 Gy) on the primary tumor, which must be peripheral and smaller than 5 cm. This way, the aim is to increase the dose on the primary tumor, without increasing the dose at centrally to avoid major toxicity. This study has completed recruitment [83].

Following the publication of the Pacific study, interest has grown about how to combine SBRT with CRT and durvalumab treatment. The immunomodulatory role of SBRT makes it a particularly interesting tool in this context [84].

It is known that RT can induce an immune response that acts against the tumor by increasing immunogenic cell death and stimulating a systemic immunity against the disease. However, this effect seems to be counteracted by the immunosuppressive capacity of the tumor microenvironment itself. The synergistic role that can be established between RT and drugs that reduce the immunosuppressive capacity of the tumor is currently under investigation. The effect that dose and fractionation may have on the immunomodulatory capacity of RT is also being investigated, although there is evidence that the immunogenic response is greater when high doses per fraction are used [85]. For this reason, it is of the utmost interest to try to combine immunotherapy with SBRT, which may contribute to improving LC of the lesion both due to its direct role against the tumor and through its immunoregulatory contribution. In this context, a Phase II study consisting of the administration of CRT followed by durvalumab and a boost of 20 Gy in 2–3 fractions on the primary tumor has started recruitment [86]. This type of schema is a model of how LA-NSCLC might be handled in the future.

4. Conclusions

HypoRT can shorten the treatment time, which may provide clinical benefit by reducing the repopulation of tumor cells during RT. In addition, it allows a more efficient use of services. The efficacy of hypoRT regimens with or without CT should be contrasted in prospective studies designed for it. These studies should introduce technological advances in the field of RT as well as immunotherapy, as they are already part of the LA-NSCLC treatment. For its part, SBRT treatments may increase LC in patients with LA-NSCLC with an acceptable safety profile, although the level of evidence is still poor.

Given the immunomodulatory role of RT and especially of SBRT, it is presumable that, in the coming years, new treatment schemes will be proposed that tend to integrate hypoRT and boost with high doses of RT per fraction together with immunotherapy. Undoubtedly, it is a research area full of possibilities that in the future will bring great changes in the management of the LA-NSCLC.

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Conflicts of Interest

The authors indicate no potential conflicts of interest.

References

[1]   Antonia SJ, Chiappori A, Gray JE, Villegas A, Mekhail T, Daniel D, *et al*. Overall Survival with Durvalumab after

Chemoradiotherapy in Stage III NSCLC. N Engl J Med 2018;379:2342-50.

[2] Zhu X, Hou R, Li X, Jiang C, Xia W, Fu X. Predictive Model of the First Failure Pattern in Patients Receiving Definitive Chemoradiotherapy for Inoperable Locally Advanced Non-small Cell Lung Cancer (LA-NSCLC). Radiat Oncol 2020;15:43.

[3] Grass GD, Naghavi AO, Abuodeh YA, Perez BA, Dilling TJ. Analysis of Relapse Events After Definitive Chemoradiotherapy in Locally Advanced Non-Small-Cell Lung Cancer Patients. Clin Lung Cancer 2019;20:e1-7.

[4] van Diessen JN, Chen C, van den Heuvel MM, Belderbos JS, Sonke JJ. Differential Analysis of Local and Regional Failure in Locally Advanced Non-small Cell Lung Cancer Patients Treated with Concurrent Chemoradiotherapy. Radiother Oncol 2016;118:447-52.

[5] van Meerbeeck JP, Kramer GW, Van Schil PE, Legrand C, Smit EF, Schramel F, *et al*. Randomized Controlled Trial of Resection Versus Radiotherapy after Induction Chemotherapy in Stage IIIA-N2 Non-small-cell Lung Cancer. J Natl Cancer Inst 2007;99:442-50.

[6] Scagliotti GV, Pastorino U, Vansteenkiste JF, Spaggiari L, Facciolo F, Orlowski TM, *et al*. Randomized Phase III Study of Surgery Alone or Surgery Plus Preoperative Cisplatin and Gemcitabine in Stages IB to IIIA Non-small-cell Lung Cancer. J Clin Oncol 2012;30:172-8.

[7] Albain KS, Swann RS, Rusch VW, Turrisi AT, Shepherd FA, Smith C, *et al*. Radiotherapy Plus Chemotherapy with or Without Surgical Resection for Stage III Non-small-cell Lung Cancer: A Phase III Randomised Controlled Trial. Lancet 2009;374:379-86.

[8] Yoo C, Yoon S, Lee DH, Park SI, Kim DK, Kim YH, *et al*. Prognostic Significance of the Number of Metastatic pN2 Lymph Nodes in Stage IIIA-N2 Non-Small-Cell Lung Cancer After Curative Resection. Clin Lung Cancer 2015;16:e203-12.

[9] National Comprehensive Cancer Network. Non-Small Cell Lung Cancer (version 2.2019); 2019. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

[10] Faivre-Finn C, Vicente D, Kurata T, Planchard D, Paz-Ares L, Vansteenkiste JF, *et al*. LBA49 Durvalumab after Chemoradiotherapy in Stage III NSCLC: 4-Year Survival Update from the Phase III PACIFIC Trial. Ann Oncol 2020;31 Suppl 4:S1178-9.

[11] European Medicines Agency. Imfinzi (Durvalumab) An Overview of Imfinzi and why it is Authorised in the EU; 2018. Available from: https://www.ema.europa.eu/en/documents/overview/imfinzi-epar-medicine-overview_en.pdf. [Last accessed on June 2020].

[12] Kong FM, Ten Haken RK, Schipper MJ, Sullivan MA, Chen M, Lopez C, *et al*. High-dose Radiation Improved Local Tumor Control and Overall Survival in Patients with Inoperable/Unresectable Non-small-cell Lung Cancer: Long-term Results of a Radiation Dose Escalation Study. Int J Radiat Oncol Biol Phys 2005;63:324-33.

[13] Rengan R, Rosenzweig KE, Venkatraman E, Koutcher LA, Fox JL, Nayak R, *et al*. Improved Local Control with Higher Doses of Radiation in Large-volume Stage III Non-small-cell Lung Cancer. Int J Radiat Oncol Biol Phys 2004;60:741-7.

[14] Bradley JD, Bae K, Graham MV, Byhardt R, Govindan R, Fowler J, *et al*. Primary Analysis of the Phase II Component of a Phase I/II Dose Intensification Study Using Three-dimensional Conformal Radiation Therapy and Concurrent Chemotherapy for Patients with Inoperable Non-small-cell Lung Cancer: RTOG 0117. J Clin Oncol 2010;28:2475-80.

[15] Salama JK, Stinchcombe TE, Gu L, Wang X, Morano K, Bogart JA, *et al*. Pulmonary Toxicity in Stage III Non-small Cell Lung Cancer Patients Treated with High-dose (74 Gy) 3-Dimensional Conformal Thoracic Radiotherapy and Concurrent Chemotherapy Following Induction Chemotherapy: A Secondary Analysis of Cancer and Leukemia Grou. Int J Radiat Oncol Biol Phys 2011;81:1-6.

[16] Rosenman JG, Halle JS, Socinski MA, Deschesne K, Moore DT, Johnson H, *et al*. High-dose Conformal Radiotherapy for Treatment of Stage IIIA/IIIB Non-small-cell Lung Cancer: Technical Issues and Results of a Phase I/II Trial. Int J Radiat Oncol Biol Phys 2002;54:348-56.

[17] MacHtay M, Bae K, Movsas B, Paulus R, Gore EM, Komaki R, *et al*. Higher Biologically Effective Dose of Radiotherapy is Associated with Improved Outcomes for Locally Advanced Non-small Cell Lung Carcinoma Treated with Chemoradiation: An Analysis of the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 2012;82:425-34.

[18] Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, *et al*. Standard-dose Versus High-dose Conformal Radiotherapy with Concurrent and Consolidation Carboplatin Plus Paclitaxel with or without Cetuximab for Patients with Stage IIIA or IIIB non-small-cell Lung Cancer (RTOG 0617): A Randomised, Two-by-Two Factorial p. Lancet Oncol 2015;16:187-99.

[19] Speirs CK, DeWees TA, Rehman S, Molotievschi A, Velez MA, Mullen D, *et al*. Heart Dose Is an Independent Dosimetric Predictor of Overall Survival in Locally Advanced Non-Small Cell Lung Cancer. J Thorac Oncol 2017;12:293-301.

[20] Eaton BR, Pugh SL, Bradley JD, Masters G, Kavadi VS, Narayan S, *et al*. Institutional Enrollment and Survival among NSCLC Patients Receiving Chemoradiation: NRG Oncology Radiation Therapy Oncology Group (RTOG) 0617. J Natl Cancer Inst 2016;108:1-8.

[21] Chun SG, Hu C, Choy H, Komaki RU, Timmerman RD, Schild SE, *et al*. Impact of Intensity-modulated Radiation Therapy Technique For Locally Advanced Non-small-Cell

Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. J Clin Oncol 2017;35:56-62.

[22] Wang K, Eblan MJ, Deal AM, Lipner M, Zagar TM, Wang Y, *et al*. Cardiac Toxicity after Radiotherapy for Stage III Non-small-cell Lung Cancer: Pooled Analysis of Dose-escalation Trials Delivering 70 to 90 Gy. J Clin Oncol 2017;35:1387-94.

[23] Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, *et al*. Early and Locally Advanced Non-small-Cell Lung Cancer (NSCLC): ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up. Ann Oncol 2017;28 Suppl 4:iv1-21.

[24] Rodrigues G, Choy H, Bradley J, Rosenzweig KE, Bogart J, Curran WJ, *et al*. Adjuvant Radiation Therapy in Locally Advanced Non-small Cell Lung Cancer: Executive Summary of an American Society for Radiation Oncology (ASTRO) Evidence-Based Clinical Practice Guideline. Pract Radiat Oncol 2015;5:149-55.

[25] Ramroth J, Cutter DJ, Darby SC, Higgins GS, Mcgale P, Partridge M, *et al*. Dose and Fractionation in Radiation Therapy of Curative Intent for Non-Small Cell Lung Cancer : Meta-Analysis of Randomized Trials. Radiat Oncol Biol 2016;96:736-47.

[26] Mehta M, Scrimger R, Mackie R, Paliwal B, Chappell R, Fowler J. A New Approach to Dose Escalation in Non-small-Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2001;49:23-33.

[27] Machtay M, Hsu C, Komaki R, Sause WT, Swann RS, Langer CJ, *et al*. Effect of Overall Treatment Time on Outcomes after Concurrent Chemoradiation for Locally Advanced Non-small-Cell Lung Carcinoma: Analysis of the Radiation Therapy Oncology Group (RTOG) experience. Int J Radiat Oncol Biol Phys 2005;63:667-71.

[28] Withers HR, Taylor JM, Maciejewski B. The Hazard of Accelerated Tumor Clonogen Repopulation during Radiotherapy. Acta Oncol (Madr) 1988;27:131-46.

[29] Fowler J. Non-small Cell Lung Tumors Repopulate Rapidly during Radiation Therapy. Int J Radiat Oncol 2000;46:516-7.

[30] Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Parmar M. Continuous, Hyperfractionated, Accelerated Radiotherapy (CHART) Versus Conventional Radiotherapy in Non-small Cell Lung Cancer: Mature Data from the Randomised Multicentre Trial. Radiother Oncol 1999;52:137-48.

[31] Baumann M, Herrmann T, Koch R, Matthiessen W, Appold S, Wahlers B, *et al*. Final Results of the Randomized Phase III CHARTWEL-trial (ARO 97-1) Comparing Hyperfractionated-Accelerated Versus Conventionally Fractionated Radiotherapy in Non-small Cell Lung Cancer (NSCLC). Radiother Oncol 2011;100:76-85.

[32] Curran WJ, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, *et al*. Sequential vs Concurrent Chemoradiation

for Stage III Non-Small Cell Lung Cancer: Randomized Phase III Trial RTOG 9410. J Natl Cancer Inst 2011;103:1452-60.

[33] Ball D, Bishop J, Smith J, O'Brien P, Davis S, Ryan G, *et al*. A Randomised Phase III Study of Accelerated or Standard Fraction Radiotherapy with or without Concurrent Carboplatin in Inoperable Non-small Cell Lung Cancer: Final Report of an Australian Multi-centre Trial. Radiother Oncol 1999;52:129-36.

[34] Mauguen A, Le Péchoux C, Saunders MI, Schild SE, Turrisi AT, Baumann M, *et al*. Hyperfractionated or Accelerated Radiotherapy in Lung Cancer: An Individual Patient data Meta-analysis. J Clin Oncol 2012;30:2788-97.

[35.] National Institute for Health and Care Excellence N. Lung Cancer Diagnosis and Management (NG122). NICE Guidel 2019;2019:1-40.

[36] Prewett SL, Aslam S, Williams M V., Gilligan D. The Management of Lung Cancer: A UK Survey of Oncologists. Clin Oncol 2012;24:402-9.

[37] Kaster TS, Yaremko B, Palma DA, Rodrigues GB. Radical-intent Hypofractionated Radiotherapy for Locally Advanced Non-small-cell Lung Cancer: A Systematic Review of the Literature. Clin Lung Cancer 2015;16:71-9.

[38] De Ruysscher DK, Botterweck A, Dirx M, Pijls-Johannesma M, Wanders R, Hochstenbag M, *et al*. Eligibility for Concurrent Chemotherapy and Radiotherapy of Locally Advanced Lung Cancer Patients: A Prospective, Population-Based Study. Ann Oncol 2009;20:98-102.

[39] Al-Shamsi HO, Al Farsi A, Ellis PM. Stage III Non-small-cell Lung Cancer: Establishing a Benchmark for the Proportion of Patients Suitable for Radical Treatment. Clin Lung Cancer 2014;15:274-80.

[40] Valeriani M, Marinelli L, Nicosia L, Reverberi C, De Sanctis V, Mollo D, *et al*. Locally Advanced Inoperable Primary or Recurrent Non-small Cell Lung Cancer Treated with 4-Week Hypofractionated Radiation Therapy (3 Gy/Fraction). Radiol Med 2019;124:1324-32.

[41] de Dios NR, Sanz X, Foro P, Membrive I, Reig A, Ortiz A, *et al*. Accelerated Hypofractionated Radiation Therapy (AHRT) for Non-small-Cell Lung Cancer: Can we Leave Standard Fractionation? Clin Transl Oncol 2017;19:440-7.

[42] Din OS, Harden SV, Hudson E, Mohammed N, Pemberton LS, Lester JF, *et al*. Accelerated Hypo-fractionated Radiotherapy for Non Small Cell Lung Cancer: Results from 4 UK Centres. Radiother Oncol 2013;109:8-12.

[43] Amini A, Lin SH, Wei C, Allen P, Cox JD, Komaki R. Accelerated Hypofractionated Radiation Therapy Compared to Conventionally Fractionated Radiation Therapy for the Treatment of Inoperable Non-small Cell Lung Cancer. Radiat Oncol 2012;7:33.

[44] Iocolano M, Wild AT, Hannum M, Zhang Z, Simone CB, Gelblum D, *et al*. Hypofractionated vs. Conventional Radiation Therapy for Stage III Non-small Cell Lung

Cancer Treated without Chemotherapy. Acta Oncol (Madr) 2020;59:164-70.

[45] Parisi G, Mazzola R, Ciammella P, Timon G, Fozza A, Franceschini D, *et al*. Hypofractionated Radiation Therapy in the Management of Locally Advanced NSCLC: A Narrative Review of the Literature on Behalf of the Italian Association of Radiation Oncology (AIRO) Lung Working Group. Radiol Med 2019;124:136-44.

[46] Westover KD, Loo BW, Gerber DE, Iyengar P, Choy H, Diehn M, *et al*. Precision Hypofractionated Radiation Therapy in Poor Performing Patients with Non-small Cell Lung Cancer: Phase 1 Dose Escalation Trial. Int J Radiat Oncol Biol Phys 2015;93:72-81.

[47] Choy H, Timmerman RD, Saunders MW, Court LE, Patel MK, Li Y, *et al*. A Phase III Randomized Study of Image Guided Conventional (60 Gy/30 fx) Versus Accelerated, Hypofractionated (60 Gy/15 fx) Radiation for Poor Performance Status Stage II and III NSCLC Patients an Interim Analysis. Int J Radiat Oncol 2016;96:E451.

[48] Kong C, Zhu X, Shi M, Wang L, Chen C, Tao H, *et al*. Survival and Toxicity of Hypofractionated Intensity Modulated Radiation Therapy in 4 Gy Fractions for Unresectable Stage III Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2020;107:710-9.

[49] Bozorgmehr F, Chung I, Christopoulos P, Krisam J, Schneider MA, Brückner L, *et al*. Thoracic Radiotherapy Plus Durvalumab in Elderly and/or Frail NSCLC Stage III Patients Unfit for Chemotherapy employing Optimized (Hypofractionated) Radiotherapy to Foster Durvalumab Efficacy: Study Protocol of the TRADE-hypo Trial. BMC Cancer 2020;20:806.

[50] NCT04249362 C go. I. Study of Durvalumab Following Radiation Therapy in Patients With Stage 3 Unresectable NSCLC Ineligible for Chemotherapy (DUART); 2020.

[51] Kumar S, Chmura S, Robinson C, Lin SH, Gadgeel SM, Donington J, *et al*. Alternative Multidisciplinary Management Options for Locally Advanced NSCLC During the Coronavirus Disease 2019 Global Pandemic. J Thorac Oncol 2020;15:1137-46.

[52] Guckenberger M, Andratschke N, Dieckmann K, Hoogeman MS, Hoyer M, Hurkmans C, *et al*. ESTRO ACROP Consensus Guideline on Implementation and Practice of Stereotactic Body Radiotherapy for Peripherally Located Early Stage Non-small Cell Lung Cancer. Radiother Oncol 2017;124:11-7.

[53] Faivre-finn C, Fenwick JD, Franks KN, Harrow S, Hatton MQ, Hiley C, *et al*. Reduced Fractionation in Lung Cancer Patients Treated with Curativeintent Radiotherapy during the COVID-19 Pandemic. Clin Oncol 2020;32:481-9.

[54] Urbanic JJ, Wang X, Bogart JA, Stinchcombe TE, Hodgson L, Schild SE, *et al*. Phase 1 Study of Accelerated Hypofractionated Radiation Therapy With Concurrent Chemotherapy for Stage III Non-Small Cell Lung Cancer: CALGB 31102 (Alliance). Int J Radiat Oncol 2018;101:177-85.

[55] Lin Q, Liu YE, Ren XC, Wang N, Chen XJ, Wang DY, *et al*. Dose Escalation of Accelerated Hypofractionated Three-dimensional Conformal Radiotherapy (at 3 Gy/Fraction) with Concurrent Vinorelbine and Carboplatin Chemotherapy in Unresectable Stage III Non-small-cell Lung Cancer: A Phase I Trial. Radiat Oncol 2013;8:1.

[56] Iqbal MS, Vashisht G, McMenemin R, Atherton P, McDonald F, Simmons T, *et al*. Hypofractionated Concomitant Chemoradiation in Inoperable Locally Advanced Non-small Cell Lung Cancer: A Report on 100 Patients and a Systematic Review. Clin Oncol 2019;31:e1-10.

[57] Belderbos J, Uitterhoeve L, van Zandwijk N, Belderbos H, Rodrigus P, van de Vaart P, *et al*. Randomised Trial of Sequential Versus Concurrent Chemo-radiotherapy in Patients with Inoperable Non-small Cell Lung Cancer (EORTC 08972-22973). Eur J Cancer 2007;43:114-21.

[58] Uitterhoeve AL, Koolen MG, van Os RM, Koedooder K, van de Kar M, Pieters BR, *et al*. Accelerated high-dose Radiotherapy Alone or Combined with Either Concomitant or Sequential Chemotherapy; Treatments of Choice in Patients with Non-Small Cell Lung Cancer. Radiat Oncol 2007;2:1-10.

[59] Walraven I, Van Den Heuvel M, Van Diessen J, Schaake E, Uyterlinde W, Aerts J, *et al*. Long-term Follow-up of Patients with Locally Advanced Non-small Cell Lung Cancer Receiving Concurrent Hypofractionated Chemoradiotherapy with or without Cetuximab. Radiother Oncol 2016;118:442-6.

[60] Stam B, van der Bijl E, van Diessen J, Rossi MM, Tijhuis A, Belderbos JS, *et al*. Heart Dose Associated with Overall Survival in Locally Advanced NSCLC Patients Treated with Hypofractionated Chemoradiotherapy. Radiother Oncol 2017;125:62-5.

[61] Guckenberger M, Belka C, Bezjak A, Bradley J, Daly ME, Deruysscher D, *et al*. Practice Recommendations for Lung Cancer Radiotherapy during the COVID-19 Pandemic: An ESTRO-ASTRO Consensus Statement; 2020.

[62] Zehentmayr F, Grambozov B, Kaiser J, Fastner G, Sedlmayer F. Radiation Dose Escalation with Modified Fractionation Schedules for Locally Advanced NSCLC: A Systematic Review. Thorac Cancer 2020;11:1375-85.

[63] Van Baardwijk A, Wanders S, Boersma L, Borger J, Öllers M, Dingemans AM, *et al*. Mature Results of an Individualized Radiation Dose Prescription Study Based on Normal Tissue Constraints in Stages I to III Non-small-cell Lung Cancer. J Clin Oncol 2010;28:1380-6.

[64] Cannon DM, Mehta MP, Adkison JB, Khuntia D, Traynor AM, Tomé WA, *et al*. Dose-Limiting Toxicity After Hypofractionated Dose-Escalated Radiotherapy in Non-Small-Cell Lung Cancer. J Clin Oncol 2013;31:4343-8.

[65] Landau DB, Hughes L, Baker A, Bates AT, Bayne MC, Counsell N, *et al*. IDEAL-CRT: A Phase 1/2 Trial

of Isotoxic Dose-Escalated Radiation Therapy and Concurrent Chemotherapy in Patients With Stage II/III Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2016;95:1367-77.

[66] Fenwick JD, Landau DB, Baker AT, Bates AT, Eswar C, Garcia-Alonso A, *et al*. Long-Term Results from the IDEAL-CRT Phase 1/2 Trial of Isotoxically Dose-Escalated Radiation Therapy and Concurrent Chemotherapy for Stage II/III Non-small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2020;106:733-42.

[67] Hatton MQ, Lawless CA, Faivre-Finn C, Landau D, Lester JF, Fenwick J, *et al*. Accelerated, Dose Escalated, Sequential Chemoradiotherapy in Non-small-cell lung Cancer (ADSCaN): A Protocol for a Randomised Phase II Study. BMJ Open 2019;9:e019903.

[68] Kong FM, Ten Haken RK, Schipper M, Frey KA, Hayman J, Gross M, *et al*. Effect of Midtreatment PET/CT-Adapted Radiation Therapy With Concurrent Chemotherapy in Patients With Locally Advanced Non-Small-Cell Lung Cancer: A Phase 2 Clinical Trial. JAMA Oncol 2017;3:1358-65.

[69] Lalezay F. The PET-Boost Trial: Isotoxic Homogeneous or FDG-Directed Dose Escalation in Stage II-III NSCLC. ESTRO Congress; 2020.

[70] Roach MC, Bradley JD, Robinson CG. Optimizing Radiation Dose and Fractionation for the Definitive Treatment of Locally Advanced Non-small Cell Lung Cancer. J Thorac Dis 2018;10:S2465-73.

[71] Kong FM. Randomized Phase Trial (RTOG1106) on Midtreatment PET/CT Guided Adaptive Radiotherapy in Locally Advanced Non-Small Cell Lung Cancer. IASLC 2020 WCLC; 2020.

[72] Scott JG, Sedor G, Scarborough JA, Kattan MW, Peacock J, Grass GD, *et al*. Personalizing Radiotherapy Prescription Dose Using Genomic Markers of Radiosensitivity and Normal Tissue Toxicity in NSCLC. J Thorac Oncol 2021;16:428-38.

[73] Ball D, Mai GT, Vinod S, Babington S, Ruben J, Kron T, *et al*. Stereotactic Ablative Radiotherapy Versus Standard Radiotherapy in Stage 1 Non-small-cell Lung Cancer (TROG 09.02 CHISEL): A Phase 3, Open-Label, Randomised Controlled Trial. Lancet Oncol 2019;20:494-503.

[74] Soldà F, Lodge M, Ashley S, Whitington A, Goldstraw P, Brada M. Stereotactic Radiotherapy (SABR) for the Treatment of Primary Non-Small Cell Lung Cancer; Systematic Review and Comparison with a Surgical Cohort. Radiother Oncol 2013;109:1-7.

[75] Kumar S, Feddock J, Li X, Shearer AJ, Hall L, Shelton BJ, *et al*. Update of a Prospective Study of Stereotactic Body Radiation Therapy for Post-Chemoradiation Residual Disease in Stage II/III Non-Small Cell Lung Cancer. Radiat Oncol Biol 2017;99:652-9.

[76] Feddock J, Arnold SM, Shelton BJ, Sinha P, Conrad G, Chen L, *et al*. Stereotactic Body Radiation Therapy Can Be Used Safely to Boost Residual Disease in Locally Advanced Non-Small Cell Lung Cancer : A Prospective Study. Radiat Oncol Biol 2013;85:1325-31.

[77] Hepel JT, Leonard KL, Safran H, Ng T, Taber A, Khurshid H, *et al*. Stereotactic Body Radiation Therapy Boost After Concurrent Chemoradiation for Locally Advanced Non-Small Cell Lung Cancer: A Phase 1 Dose Escalation Study. Int J Radiat Oncol Biol Phys 2016;12:1687-95.

[78] Hepel JT, Peter J, Hiatt JR, Patel S, Osibanjo O, Safran H, *et al*. Dosimetric Feasibility of Dose Escalation Using SBRT Boost for Stage III Non-Small Cell Lung Cancer. Front Oncol 2012;2:124.

[79] Higgins KA, Pillai RN, Chen Z, Tian S, Zhang C, Patel P, *et al*. Concomitant Chemotherapy and Radiotherapy with SBRT Boost for Unresectable Stage III Non-Small Cell Lung Cancer: A Phase I Study. J Thorac Oncol 2017;12:1687-95.

[80] Karam SD, Horne ZD, Hong RL, McRae D, Duhamel D, Nasr NM. Dose Escalation with Stereotactic Body Radiation Therapy Boost for Locally Advanced Non Small Cell Lung Cancer. Radiat Oncol 2013;8:1-8.

[81] Nguyen NT, Isfahanian N, Pond G, Hanna W, Cutz JC, Wright J, *et al*. A Novel Neoadjuvant Therapy for Operable Locally Invasive Non-Small-Cell Lung Cancer. Phase I Study of Neoadjuvant Stereotactic Body Radiotherapy. LINNEARRE I (NCT02433574). Clin Lung Cancer 2017;18:436-40.e1.

[82] Singh AK, Hennon M, Ma SJ, Demmy TL, Picone A, Dexter EU, *et al*. A Pilot Study of Stereotactic Body Radiation Therapy (SBRT) after Surgery for Stage III Non-small Cell Lung Cancer. BMC Cancer 2018;18:1183.

[83] Peulen H, Franssen G, Belderbos J, van der Bijl E, Tijhuis A, Rossi M, *et al*. SBRT Combined with Concurrent Chemoradiation in Stage III NSCLC: Feasibility Study of the Phase I Hybrid Trial. Radiother Oncol 2020;142:224-9.

[84] Alcibar OL, Candini D, López-Campos F, Antequera MA, Macías VM, Conde AJ, *et al*. Time for Radioimmunotherapy: An Overview to Bring Improvements in Clinical Practice. Clin Transl Oncol 2019;2019:0123456789.

[85] Walshaw RC, Honeychurch J, Illidge TM. Stereotactic Ablative Radiotherapy and Immunotherapy Combinations: Turning the Future into Systemic Therapy? Br J Radiol 2016;89:20160472.

[86] Durvalumab and Consolidation SBRT Following Chemoradiation for Locally Advanced Stage III Non-Small Cell Lung (358). US National Library of Medicine; 2020. Available from: https://www.clinicaltrials.gov/ct2/show/NCT03589547. [Last accessed on June 2020].