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COMMENTARY

Standard of care in high-dose radiotherapy for localized non-small cell lung cancer

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Introduction

Radiotherapy (RT) plays a major role in the loco-regional treatment of lung cancer. An accurate definition of the target volumes and use of optimal dose and fractionation schedule are essential to maximize the effectiveness of ionizing radiation. This has become a complex matter as the increasing use of different multimodal treatment strategies, the availability of highly conformal dose delivery systems and the increasing insight into the biology of the disease allow us to vary these variables endlessly. While this flexibility enables us to tailor treatment more specific to the individual tumor and patient, it also continuously challenges our ability to critically interpret the available data when we need to transfer them from bench to clinic.

In this manuscript, we will highlight the available clinical data on dose, fractionation and treated volume for both early and loco-regionally advanced stage non-small cell lung cancer (NSCLC). Palliative RT as well as of the treatment of metastases will not be covered.

Radiotherapy for early stage NSCLC

Stereotactic body radiotherapy (SBRT) has revolutionized radical RT for early stage NSCLC. Through the use of highly conformal RT techniques typically 3–8 high-dose fractions are given over a short overall treatment time to a relatively small volume. Literature consistently reports local control rates about 90% with less than 5% of the patients experiencing important side effects [1–3]. Furthermore, also in patients with impaired lung function, SBRT was shown not to impact on neither the forced expiratory volume at 1 second (FeV1), nor the diffusion lung capacity for carbon monoxide (DLCO) [4,5]. This high efficacy has led to broadening of the indications for radical irradiation to virtually all patients with early stage NSCLC, even the old and frail [6].

In most retrospective series, a higher biological dose to the tumor was associated with higher local control rates [7]. Biological equivalent doses (BED), using an α/β value of 10 Gy (BED_{10}), around and above 100 Gy have been proposed as the dose needed to achieve these excellent local control results [7,8]. However, due to the heterogeneity in the techniques and the retrospective nature of many of the studies there have been considerable doubts whether or not this dose–volume effect is real for small tumors [9]. The recently published randomized phase II SPACE trial randomized patients with stage I medically inoperable NSCLC to receive SBRT to 66 Gy in three fractions or 70 Gy in 35 daily fractions [10]. They did not observe a significant difference in progression-free survival (PFS) between SBRT and conventional 3D conformal RT, however, toxicity was higher in the conventionally fractionated RT arm with significant differences in esophagitis, dyspnea, chest pain and cough. The phase II design, the imbalance in patients characteristics between both arms and the use of different target delineation guidelines in both groups, however, warrants us to be careful not to over-interpret these data but its prospective nature, will undoubtedly provide us with more data on the dose–effect relationship in early stage tumors.

In short, SBRT is well established for medically inoperable peripheral lung tumors less than 5 cm. The optimal dose-fractionation schedule is currently unknown however as previously stated the high rate of local control seems to be related to a BED_{10}>100 Gy. To increase insight and reproducibility and facilitate a more straightforward comparison of different data, it is important to set-up prospective data collection with meticulous registration of outcome and toxicity and adhere to specific dose reporting recommendations such as these proposed by International Commission on Radiation Units and Measurements (ICRU) 83 [11].

While SBRT for peripheral lesions is well established, controversy exists about the safety of SBRT when the planning target volume (PTV) overlaps organs at risk (OAR). In this respect, the literature identified central and ultra-central tumors based on their proximity to OAR. Central tumors are generally defined as lesions located within 2 cm of the bronchial tree (as defined by the Radiation Therapy Oncology Group (RTOG)) while the term 'ultra-central' is reserved in case the tumor directly abuts the central airway structures [12,13]. Whether or not other OAR should be included into

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this definition remains a matter of debate. As a result, different definition of these entities can be found throughout the literature, rendering head to head comparison of different trials difficult. There is however a clear consensus that the use of extreme hypofractionation in these locations can result in serious toxicity. In a seminal article by Timmerman et al., they noted that central location was a significant predictor of treatment-related grade 3–5 toxicity in patients treated with SBRT up to a treatment dose of 60–66 Gy in three fractions [14]. Two recent retrospective series also provide data on the side effects of patients with 'central' tumors or with 'ultra-central tumors' treated with SBRT [15,16].

In the case of 'central' tumors, a dose of 60 Gy delivered in eight fractions was associated with 12% of grade 5 (lethal) toxicities of which half of them were attributed by the authors as being caused by RT [15]. In ultra-central tumors, lethal bleeding exceeded 25% with a dose of 60 Gy in 12 fractions [16]. The safety of severe hypo-fractionation for these (ultra-)central tumors is therefore not established. Several prospective studies, such as the RTOG0813 and the EORTC-22113 are investigating this issue, however, at the time of writing they were not published yet. These trials will provide us with more insight in the tolerance of the 'central' structures.

Aside from the centrally located structures, the dose to the brachial plexus is crucial when treating early stage lung cancer of the apical lung. Retrospective series suggest that the dose to the brachial plexus may not exceed 26 Gy in 3–4 fractions [17,18]. Equally chest wall toxicity should be heeded. Most rib fractures that occur after SBRT are asymptomatic, with less than 5% risk when doses ($\alpha/\beta = 3$ Gy) do not exceed 225 Gy [19]. Chest wall pain is getting more frequent when the D70cc is more than 16 Gy in four fractions or the D2cc over 43 Gy in four fractions [20].

Radiotherapy for stage III NSCLC

The current standard of care in stage III NSCLC is the combination of concurrent chemotherapy and RT. A meta-analysis showed an improved 5-year overall survival (OS) rate compared to the sequential administration of the same chemotherapy and RT [21]. On the whole patient population, the gain in OS was about 4% at 5 years. Most patients were treated with a dose of 60–66 Gy in 2 Gy once-daily fractions. Within this meta-analysis, the gain in OS appeared to be the consequence of the improvement in loco-regional control rather than a reduction in distant metastasis. Considering the steep dose–response curve of NSCLC, the technological revolution in dose delivery escalating the dose on the tumor is the next logical step.

In a randomized phase III trial (RTOG 0617), RTOG randomized patients between 60 Gy and 74 Gy in 2 Gy fractions and concurrent and consolidation carboplatin and paclitaxel with or without cetuximab [22]. Contrary to all expectations, the OS was worse in the 74 Gy arm and cetuximab had no effect on the OS. Furthermore, loco-regional control appeared to be worse in the 74 Gy arm, which might be explained by the reduced protocol adherence in the higher dose arm. The reasons for these observations until now remain largely unclear, but the study made it clear that the dose in the heart, which was highly neglected thus far, had an effect on the OS. The heart has therefore become an important organ at risk in lung cancer irradiation, but the exact constraints remain uncertain as are the susceptibility of the anatomical and functional regions within the heart [23]. While escalating the dose to the entire PTV appears to be of little benefit to the patient, more innovative escalation strategies could provide us with some benefit. With the widespread implementation of functional imaging techniques and highly conformal delivery techniques, we have both the rationale and the tools to selectively escalate the dose within the tumor, while maintaining the dose to the surrounding tumor or the reverse strategy, selectively sparing functional areas within an organ [24–26]. These so-called dose painting strategies have sparked considerable interest in the lung cancer community, and several PET tracers have been advocated and investigated, including FDG, however to date these strategies have failed to produce meaningful clinical results.

Until the 1990s, radical RT for stage III NSCLC consisted of a dose of around 60 Gy in 2 Gy fractions. Increasing insight in the radiobiology of lung cancer sparked the interest in altered fractionation schedules. The results of a large phase III trial from the UK, called CHART (Continuous Hyperfractionated Accelerated RadioTherapy) demonstrated that the OS was better in patients having received 54 Gy in 12 days (3×1.5 Gy/day without discontinuation during the weekend) versus 60 Gy in 6 weeks in once-daily 2 Gy fractions [27]. A meta-analysis based on updated individual patient data of all randomized studies confirmed that acceleration of RT improved the survival at 5 years by 3.5% or a Hazard Ratio (HR) of 0.88 [28]. This provides level I evidence to deliver RT alone with an accelerated schedule. However, the predominant histology was squamous cell cancer, whereas nowadays adenocarcinoma is more prevalent. Both radio-sensitivity and the tumor kinetics might differ between both histologies [29].

These accelerated treatment schedules were also investigated in the setting of concurrent chemotherapy [30]. Although a face-to-face comparison with standard fractionated RT has not been performed, prospective data suggests neither a positive, nor a detrimental effect of accelerated RT in concurrent chemo-radiotherapy in stage III NSCLC.

The question remains why dose-escalation or identification of RT when delivered with concurrent chemotherapy has not lead to improved survival and where research should move to?

First, it is conceivable that similar to head and neck cancer, accelerated RT is for most patients not beneficial when given during chemotherapy because accelerated repopulation of tumor clonogens may already be diminished. Second, radiation dose escalation to the tumor should lead to better local control rates, but as most patients with stage III disease develop distant metastases, many competing events occur. Moreover, dose escalation may cause damage to the normal tissues to an extent that was not expected. The only recently recognized influence of the dose to the heart as well as a

high mean lung dose are correlated with OS is indicative for this [22,31].

Whereas elective mediastinal fields were used until the beginning of the 2000s, prospective trials have shown the safety of selective nodal irradiation based on FDG-PET-CT scans and more recently also including endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS) information [32,33]. Obviously, this drastic reduction of the irradiated volume has a beneficial effect on the radiation dose on the OAR.

Concurrent chemotherapy and RT therefore remain the treatment of choice in most stage III NSCLC patients, delivered at a dose of 60–66 Gy in 2 Gy once-daily fractions without elective nodal irradiation.

Disclosure statement

Dirk De Ruysscher is in the advisory board of Bristol-Myers-Squibb, Merck/Pfizer and Roche/Genentech. The other authors have no conflict of interest to declare.

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