Is Hypofractionation a Good Idea in Radiotherapy for Locally Advanced NSCLC?

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Conventional or standard radiotherapy (2 Gy/d, 5 d/wk, up to 60 Gy) as used in locally advanced NSCLC (LA-NSCLC) relies on differential cell kill and regeneration between normal tissues and tumors, which has been firmly established across tumor sites. In LA-NSCLC, the Radiation Therapy Oncology Group 06/17 trial confirmed that 60 Gy standard fractionation remains the standard of care in concurrent chemoradiotherapy.1

Hypofractionated radiotherapy (less fractions with a higher dose per fraction) is of interest as it has the potential to save resources (machine time), save costs, and reduce the patient’s logistical burden. In other scenarios, such as breast and prostate cancers, hypofractioned radiotherapy was found to be equally effective to the longer “standard” counterparts2,3 and has become a standard of care. In concurrent radiochemotherapy for LA-NSCLC, hypofractionated and hyperfractionated (more fractions per day) schedules have also been investigated.4 On the basis of an individual patient-based meta-analysis of randomized studies, acceleration was found to be associated with improved long-term survival, especially in nonconcurrent schedules.5 Furthermore, based on this and European Organization for Research and Treatment of Cancer trials, the European Society for Medical Oncology guidelines mention hypofractionation (66 Gy per 24 fractions) as an option for patients receiving sequential chemotherapy and radiotherapy or radiotherapy alone.6

The work by Brada et al.7 in this issue deals with current practice in the United Kingdom and the outcomes for hypofractionated versus standard radiotherapy in LA-NSCLC. The hypofractionated regimen often used in the United Kingdom and investigated by Brada et al.7 was 55 Gy in 20 fractions in 4 weeks (2.75 Gy once-daily). This is in accordance with the current guidelines of the National Institute for Health and Care Excellence, in which no preference between 60 and 66 Gy in 2 Gy or 55 Gy in 2.75 Gy is stated and both are considered “normal National Health Service clinical practice.”8 Although both regimes would be expected to be similar based on traditional radiobiological modeling, high-level clinical evidence to support this recommendation is lacking. The results suggest inferior outcomes with hypofractionated treatments (overall survival of 25 versus 28–29 mo). The number of patients treated with continuous, hyperfractionated, accelerated radiotherapy, a typical hyperfractionated schedule giving three fractions per day in a very short overall treatment time, was too low to draw any relevant conclusions.7

As with any database analysis, the results preclude firm conclusions, which is acknowledged by the authors; even when we accept inferior outcomes, hypofractionated radiotherapy may still be a valid choice in selected settings, especially when the burden of daily visits is high enough to justify a shorter course of treatments or when the risk of daily visits is considered too high, as might be the case during a pandemic. A recent phase 3 trial investigating hypofractionated radiotherapy with 60 Gy in 15 fractions (4 Gy daily) failed to reveal a survival benefit in an interim analysis and the trial was prematurely closed. Nonetheless, the study revealed similar survival and toxicity, positioning hypofractionated radiotherapy as an option in the nonconcurrent chemotherapy setting, especially for patients with comorbidities and a reduced performance status.9

Another lesson from the current report is that radiotherapy details are not only relevant to radiotherapy questions but also to a multidisciplinary approach in the management of lung cancer. Indeed, the...
Current database was limited with details on chemotherapy. The use of standard fractionation was associated with a higher rate of chemotherapy use (sequential or concurrent) than the hypofractionated arm. In isolation, this does not explain the differences in survival, but it may point to overlapping prognostic factors that are related to the use of hypofractionated radiotherapy, the omission of chemotherapy, and survival. Databases should therefore include broadly known and putative prognostic parameters, to enable us to move away from simple correlations and ultimately come as close as possible to causality. There are clearly practical benefits of hypofractionation in LA-NSCLC, but in the future, it will be even more interesting to explore its use in conjunction with immunotherapy. Hypofractionation will lead to reduced lymphopenia\(^\text{10}\) and possibly less suppression of the immune system, which could be of interest when combining radiotherapy with immunotherapy. New technologies such as magnetic resonance linear accelerator and proton therapy are potentially suitable to further reduce the number of fractions while maintaining antitumor efficacy and even reduced toxicity.

For the time being, we seem to be stuck with standard fractionation, where for now, the term "standard" still applies.

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**References**