PREFACE

Individualized hypo/hyperfractionated radiotherapy for non-small cell lung cancer

Radical radiotherapy has a crucial role in the management of non-small cell lung cancer (NSCLC). Stereotactic ablative radiotherapy [SABR, also known as stereotactic body radiotherapy (SBRT)], which involves the administration of biologically effective doses (BEDs) in excess of 100 Gy in a few large radiation doses in a short overall treatment time, for stage I NSCLC has produced local control rates in excess of 90% and survival comparable to that after lobectomy. Indeed, SABR has become standard treatment for medically inoperable stage I NSCLC. For locally advanced inoperable NSCLC, the standard treatment in the Unites States and Europe is concurrent chemoradiotherapy, with the radiation delivered in 2-Gy fractions. However, the optimal radiation dose and fractionation remain controversial. Retrospective and phase II clinical studies have shown that radiation doses with higher BEDs are associated with improved local control and potentially with better survival. Unfortunately, a recent phase III randomized study [Radiation Therapy Oncology Group (RTOG) 0617] indicated that a high radiation dose (74 Gy, BED 88.8 Gy) given with concurrent carboplatin-paclitaxel chemotherapy was associated with poorer local control and survival than the conventional 60-Gy dose (BED 72 Gy) in that study. Underreported severe toxicity of high radiation doses, especially given concurrently with carboplatin-paclitaxel chemotherapy, could be the main reason for the poor survival, as well as the prolonged treatment time (37 fractions) and the lack of adequate image-guided radiotherapy and quality assurance in this study could explain the poor local control. On the other side, the nearly 29 months of overall survival in the 60 Gy arm is the best ever achieved in a multi-centre phase III trial and should be regarded as a benchmark result.

Advances in radiotherapy technologies allow the radiation dose to be precisely focused to the target while minimizing the inadvertent dose to nearby organs at risk, which may translate into improved local control and reduced toxicity. Thus, although 60 Gy with concurrent chemotherapy remains the "standard of care" for inoperable stage III NSCLC at this time, issues of dose escalation and acceleration should continue to be explored as new techniques and technologies emerge. In addition, not all cases of NSCLC will need radiation dose escalation. Moreover, some patients may not be able to tolerate dose escalation or acceleration. Individualized radiotherapy dose escalation, acceleration, or both that is based on the biological and physical features of tumors and normal tissues should be considered in future studies.

Altered radiotherapy fractionation schedules including hyperfractionated or hypofractionated accelerated radiotherapy regimens have been used for NSCLC in Europe and have shown promising clinical outcomes. In addition to potential reductions in cost (from shortening the treatment period), altered fractionation and image-guided hyper/hypofractionated radiotherapy can be used to safely increase the BED and thereby potentially improve local control and survival for selected patients. However, the greater risk of late toxic effects when higher BEDs are delivered to critical structures remains a concern. Also unknown is how these regimens are best combined with chemotherapy or molecular targeted therapy.

In this special issue of the *Journal of Thoracic Disease*, experts from around the world discuss the potential role of, and associated challenges with, the use of hyper/hypofrationated accelerated radiotherapy for the treatment of lung cancer. This special issue addresses the unique biological, physical, and clinical aspects of altered radiotherapy fractionation regimens for early-stage disease, locally advanced disease, and metastatic NSCLC. The biological rationale underlying the use of altered fractionation and molecular marker-based personalized targeted therapy is discussed as well. Cutting-edge technologies to improve local control while reducing normal-tissue toxicity through the use of 4D CT-based motion management and radiotherapy planning, and image-guided radiotherapy delivery with intensity-modulated radiotherapy, stereotactic ablative radiotherapy, and proton therapy are presented. The novel concept of using radical radiotherapy as a component of systemic treatment, particularly for tumors that are resistant to chemotherapy or targeted therapies, and the potential of synergizing immunotherapy and radiotherapy are also explored.

The challenges of financial constraints and upcoming "bundled" reimbursements for oncologic care, both in the United States, Europe and elsewhere, underscore the urgency of the need to evaluate, verify, and consider adopting these strategies for treating some patients with lung cancer, if hyper/hypofrationated radiotherapy can be shown to improve or at least maintain the efficacy of conventional radiotherapy while minimizing toxic effects to normal tissues.

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