The role of modern radiation therapy in treating lung cancer

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Five-year survival rates in the best radiochemotherapy schedules are approximately 15% for locally advanced (LA) non-small cell lung cancer (NSCLC) [1,2] and 20% for limited-disease (LD) small cell lung cancer (SCLC) [3–5]. Modern trials focus mostly on the chemotherapy component and on integrating chemotherapy with radiation while the radiation component is typically left with outdated techniques. The progress in radiation technology that has led to improved outcome for many cancer sites (CNS, head and neck, prostate, rectum, cervix), is only scarcely incorporated in radiochemotherapy for lung cancer.

For LD-SCLC and LA-NSCLC, concurrent dose-intensive upfront radiation and chemotherapy seems to be the paradigm but safe delivery of radiation involves multiple technical improvements including: (1) decrease of the internal margin of the planning target volume (PTV) by breathing control techniques [6]; (2) decrease of the external PTV margin by on-line imaging-correction [7]; (3) dose computation algorithms that accurately model electron non-equilibrium [8]; (4) decreased beam apertures by a rind-boost technique and (5) focused dose escalation using biological imaging. Combinations of improvements allow increasing the dose to the tumour at the same or lower complication probability. In early stage NSCLC, modern radiation technology allowed to apply extreme hypofractionated radiation therapy resulting in local control rates exceeding 70% without threatening toxicity [9]. However, radiation pneumonitis (RP) and pulmonary fibrosis remain the most cumbersome complications [10]. Risk of RP depends on total dose [11], the dose per fraction [12], percent of the lung receiving at least 20 and 30 Gy (V20 Gy and V30 Gy respectively) [13, 14], mean lung dose (MLD) [15,16] and chemotherapy [17, 18]. Patient-related risk factors comprise age, gender, race, smoking, co-morbidity factors such as impaired vascularity, cold or pre-existing fibrotic diseases [19]. It is not surprising that physical indices like V20 Gy and V30 Gy or MLD feature a negative predictive value of only 60–80% (i.e. 60–80% of patients with safe physical indices will develop no symptomatic lung injury) [20]. Physical index-based dose escalation studies of radiochemotherapy are typically halted nearby 20–30% incidence of symptomatic RP, which translates to about 5% of patients exposed to life-threatening toxicity.

The molecular mechanisms underlying radiation injury offer another approach in risk assessment. Studies have demonstrated involvement of pro-inflammatory, pro-fibrotic, pro-angiogenic cytokines in development of radiation induced lung injury [21]: interleukin (IL)-1α, IL-6, intracellular adhesion molecule (ICAM), and transforming growth factor beta 1 (TGF-β1) [22–24]. TGF-β1 mediates tissue response to radiotherapy [25] and is considered as a master switch for initialisation, development and persistence of fibrosis [26]. Inter-individual differences in TGF-β1 production can be a consequence of specific genetic polymorphisms in the regulatory regions of the TGF-β1 gene [27] with increased risk of normal tissue complications after radiotherapy [28]. We hypothesise that a predictor of individual radiosensitivity (like the presence of certain polymorphisms in the regulatory region of TGF-β1) will improve patient-specific toxicity predictions for radiochemotherapy, whereas a reporter of activation of key lung toxicity pathways (like plasma TGF-β1) will be required to avoid life-threatening toxicity in all patients and to prescribe dose escalation in radiochemotherapy-tolerant patients.

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