Editorial

Individualized altered fractionation as a more effective radiotherapy for non-small cell lung cancer

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Submitted May 31, 2014. Accepted for publication Jun 04, 2014.

doi: 10.3978/j.issn.2072-1439.2014.06.39

View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2014.06.39

Treating non-small cell lung cancer (NSCLC), it seems altered fractionations either by hypo- or hyper-fractionated radiotherapy (RT) improves overall survival as compared with conventional schedules (1). With innovative technologies of modern RT, altered fractionation can generally deliver higher biologically effective doses for a better clinical outcome without causing significant side effects. The technologies include imaging studies for tumor delineation, computerization of RT planning, intensity modulation RT, image guidance RT, respiratory motion assessment and stereotactic targeting technology. Today, stereotactic ablative RT (SABR) or stereotactic body RT (SBRT) is considered a standard treatment for patients with T1 or T2 N0 NSCLC when surgery is not an option due to refusal or comorbidities. In addition, since surgical metastectomy has been shown to cure patients with oligometastatic cancer to the lung, it is expected that SABR will play a major role for such patients in the future as well. Compared to surgical metastectomy, patients might favor to undergo SABR because it is non-invasive, out-patient treatment and likely more cost effective. It is however essential to understand that with the complexity and variation inherent in SABR, a potential catastrophic consequence could happen if mistakes in the process of implementation were not identified or corrected. Therefore, issues related to staffing training, simulation and planning technologies, equipment commissioning, and quality assurance must be addressed to ensure treatment efficacy and safety.

This special issue on hypo- and hyper-fractionated RT in NSCLC using cutting-edge technologies has been long awaited. Chang and Ruysscher are to be congratulated for being able to gather and compile nine reviews and one original article on the hottest subject related to hypo- and hyper-fractionated RT in NSCLC using cutting-edge technologies. All the authors are truly experts in the world on each topic. From biological, physical and clinical aspects, the authors discuss utilization of altered fractionated RT for early-stage and locally-advanced NSCLC and oligometastatic cancer to the lung. Followings are brief summaries for each article.

From preclinical laboratory studies to clinical trials, Prasanna *et al.* describe aspects from radiobiology point of view related to hyper- and hypo-fractionated RT for NSCLC. Novel concepts either by hyperfractionated or hypofractionated RT are presented. Other than discussing the classical 4-Rs (repair, re-assortment, re-oxygenation and re-population), unique phenomenon of hyper-radiation sensitivity at lower doses (0.1 to 0.6 Gy) combining with chemotherapy in hyperfractionated setting, and mechanisms underlying the effects of high-dose hypofractionated RT including abscopal/bystander effects, activation of immune system, endothelial cell death and effect of hypoxia with re-oxygenation are described. Molecular events in low dose hyperfractionated RT and impact of SABR are illustrated nicely in their article. In addition, clinical trials combining low doses hyperfractionated RT with chemotherapy in solid tumors are updated in details.

Challenges to treat patients with lung cancer from aspects of radiation physics include tumor motion, accurate dose calculation in low density media, limiting dose to nearby organs at risk, and changing anatomy over the treatment course. Glide-Hurst and Chetty nicely provide an overview of current state-of-the-art technologies regarding target volume definition, dose calculation, 4D dose accumulation, on-line IGRT, tumor tracking, and image-guided adaptive RT.

Accurate delineation and characterization of primary tumors and lymph nodes are prerequisites for successful RT. Van Elmpt *et al.* summarize the latest available imaging

techniques including FDG-PET/CT, hypoxia PET, MRI, dynamic contrast-enhanced CT, and dual energy CT (DECT) for target volume delineation and quantification, and SPECT/CT, CT, PET/CT, MRI, and DECT for normal tissue characterization.

It is believed that locoregional treatment of lung cancer is a critical starting point to cure a patient. For patients with locally advanced lung cancer, to increase RT therapeutic gain for a better locoregional control, hyperfractionated or accelerated RT provides promising ways for dose escalation. Haslett *et al.* provide a detailed overview of the current literature on hyperfractionated and accelerated RT in NSCLC. Novel concepts of "isotoxic" RT using hyperfractionated accelerated regimen and related trials are explained.

As mentioned, there is convincing evidence showing a clear radiation dose effect in NSCLC patients. The review article by Kong *et al.* is one of the highlight of this special issue. From the biological consideration point of view, issues related to radiation dose effect in locally advanced NSCLC are reviewed. As explained by the authors, although the benefit of using conventional dose/fractionation regimens for radiation dose escalation has been challenged by the preliminary results from RTOG0617, there are potential more effective approaches based on the sensitivity of tumor and critical organs of each individual patient. Promising ongoing trials including a European phase II PET-boost trial and RTOG1106 are presented.

Have the theoretical advantages of Bragg peak characteristics of proton particles been exploited on NSCLC for better results? From the point of view of dosimetric analyses and clinical analyses, in a review article of this special issue, Gomez and Chang nicely summarize the use of hypofractionated dose-escalated proton beam therapy for both early-stage and locally advanced NSCLC. Two ongoing trials using stereotactic body proton therapy for NSCLC are illustrated.

With advances in understanding of molecular biology of NSCLC, the treatment of NSCLC has started the era of personalized medicine. In the review article by McDonald and Popat, the concepts of combining targeted agents to isotoxic dose escalated accelerated RT are brought up. In addition, the authors concisely explain the molecular mechanisms of EGFR inhibitors related to treatment of NSCLC. Published studies in various clinical settings, including EGFR inhibitors with conventional fractionation RT alone, EGFR inhibitors with conventional fractionation sequential chemo-RT, EGFR inhibitors with conventional fractionation concomitant chemo-RT, and targeted agents with altered fractionation RT are discussed.

With more effective systemic therapy and advances in local therapy including minimally invasive surgery and SBRT, patients with oligometastatic lung metastases have now been considered as potential candidates for curative treatment and indeed, prolonged tumor local control rate and overall survival have been reported. Singh *et al.* in their original article in this special issue report their 34-case experiences utilizing SBRT in the treatment of oligometastatic cancer to the lung. Cases included patients with 1 to 5 lung metastases, tumor size <5 cm, and with locally controlled primary tumor. The median prescription dose was 50 Gy in 5 fractions. In parallel with experiences using SBRT for primary lung cancer, an excellent local control rate up to 80% in 3 years and no symptomatic pneumonitis were reported. This paper is surely original and important and it is expected to become a highly cited reference in the relevant field.

Radiologic lung changes occur in nearly all patients after SBRT. It is of paramount importance to distinguish between tumor recurrence and lung fibrosis after treatment for early intervention and therefore better results. In addition to summarize the current clinical approach for assessing response by conventional imaging modalities, such as CT or PET, Mattonen *et al.* focus their discussion on the emerging field of quantitative image feature analysis.

Lung cancer comprises of a heterogeneous group of tumor types and each type carries individualized genetic signature in multiple driver gene pathways. In addition to the conventional approach of surgical resection, chemotherapy, and RT, personalized approach to incorporate targeted treatment based on molecular abnormalities of the cancer has become a current trend and promising results have been reported. In the review article by Palmer *et al.*, lung cancer genetic aberrations and mechanisms of associated targeted therapy as well as novel biomarkers related to radiation pneumonitis are nicely elucidated.

Acknowledgements

Disclosure: The author declares no conflict of interest.

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Cite this article as: Chen YJ. Individualized altered fractionation as a more effective radiotherapy for non-small cell lung cancer. J Thorac Dis 2014;6(7):E161-E162. doi: 10.3978/j.issn.2072-1439.2014.06.39