AAPM annual meeting 2013 handout

Impact of optimized intensity-modulated proton therapy in non-small cell lung cancer

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The radiation dose does matter for local-regional control, toxicity, and survival in non-small cell lung cancer (NSCLC). Historically, the "standard dose" of 60 Gy was associated with local-regional failure rates of 40%-50% and median survival of 16-17 months in stage III NSCLC (1). Not all cancers are created equal, and dose escalation/acceleration is certainly needed for some patients. However, radiation is a double-edged sword in terms of balancing antitumor efficacy with toxicity. A recent phase III randomized study (Radiation Therapy Oncology Group [RTOG] 0617) indicated that a higher radiation dose (74 Gy) using photon treatment given with concurrent chemotherapy caused higher treatment related mortality, worse local-regional failure (44% vs. 35.5%) and poorer median survival (19.5 months vs. 28.7 months) as compared with the conventional 60 Gy (2). While the reason of poorer local control with higher dose is being analyzed, possibly rooted in tighter PTV margin due to concern of toxicity, 60 Gy remains the "standard" dose for stage III NSCLC. In stage I NSCLC, however, biological effective dose (BED) > 100 Gy has been shown to achieve 98% local control and improve survival using image-guided stereotactic ablative radiotherapy (SABR) (3). However, for centrally located lesions, SABR remains challenging due to potential higher dose exposure to nearby critical structures such as bronchial tree, major vessels and brachial plexus (4, 5).

Using 4-D CT based planning and image-guided radiotherapy with adaptive re-planning, a phase II study showed that passive scattering proton therapy (PSPT) with 74 Gy and concurrent chemotherapy, a similar setting as RTOG 0617, achieved about 20% local-regional failure and 29.4 months median survival with tolerable toxicity and no treatment related mortality (6, 7). Neither radiation nor radiation delivery techniques are created equal. Questions remain as to who needs radiation escalation/acceleration, and where and how boost doses should be given while minimizing severe side effects. Knowledge-guided radiotherapy dose escalation/acceleration using individualized optimized cutting-edge technologies such as 4-D CT based intensity modulated proton therapy (IMPT) may likely lead to improved clinical outcomes, but further studies are needed (8).

Proton therapy may have a greater potential to spare the critical structures as compared with photon therapy in lung cancer (9). However, with the development of IMRT/VMAT optimization and auto-plan, conformality of IMRT/VMAT has

been significantly improved over the past few years (10). With the matured optimization of IMRT/VMAT, passive scatter proton therapy still significantly improves sparing of heart, spinal cord, contra lateral lung and lung lower dose exposure. However, the improvement of lung V20 and/or total mean lung dose and/or esophagus may not be evident when anatomy is complicated, such as tumors located in the contralateral hilum, mediastinum, supraclavicular lymph nodes or tumors curving around critical structure, because PSPT relies on limited 3-D planning with a significant uncertainty margin (11). In such cases, compromised dose coverage has to be considered to avoid damaging critical normal tissue structures.

IMPT using scanning beam therapy can simultaneously optimize the intensities and the energies of all pencil beams using an objective function that takes into account targets as well as normal tissue constraints. We conducted a virtual clinical study to compare dose volume histograms of IMPT with those of IMRT and PSPT for the treatment of stage IIIB non-small-cell lung cancer (NSCLC) and to explore the possibility of individualized radical radiotherapy (12). Compared with IMRT which only can deliver 63 Gy in these clinically challenging cases due to normal tissue constraints, PSPT spared more lung, heart, spinal cord, and esophagus, even with dose escalation from 63 Gy to 83.5 Gy, with a mean MTD of 74 Gy using current dose volume constraints. Compared with PSPT, however, IMPT allowed further dose escalation from 74 Gy to a mean MTD of 84.4 Gy (range, 79.4-88.4 Gy) while all parameters of normal tissue sparing were kept at lower or similar levels. In addition, IMPT prevented lower-dose target coverage in patients with complicated tumor anatomies. For centrally located stage I NSCLC, proton therapy, particularly IMPT, resulted in less dose exposure to nearby critical structures (13).

IMPT reduces the dose to normal tissue and allows individualized radical radiotherapy for extensive stage IIIB NSCLC and better sparing of nearby critical structures in SABR. However, motion uncertainty, treatment planning/optimization and quality assurance of IMPT are much more challenging and complex (14-18). Not all clinical cases can benefit from IMPT using current available planning and delivery techniques.

Supported by NIH program grant, MD Anderson Cancer Center and MGH are studying the optimization of proton therapy with the appropriate management of uncertainties including IMPT. A phase II randomized study to compare IMRT with PSPT using 74 Gy with concurrent chemotherapy in stage III NSCLC radiotherapy is ongoing. Although this study potentially will provide level 1 evidence about the potential benefit of proton therapy in stage III NSCLC, it will not address the issues about individualized clinical case selection for appropriate proton therapy candidates and optimized proton therapy, particularly IMPT. There is a potential risk of comparing matured IMRT with still maturing proton techniques. As we learned from our experiences, not all lung cancers are good candidates for proton

therapy, and not all proton therapy or proton plans are created equal. We believe that appropriate case selection with optimized plan and quality assurance are crucial to achieve the best clinical outcome. Proton therapy, as emerging novel treatment techniques in lung cancer, is still maturing and we are still learning. Phase I/II clinical studies to explore the role of stereotactic ablative proton therapy in clinical challenging stage I, hypofractionated proton therapy (60 Gy in 15 fractions), simultaneous integrated boost to GTV to higher dose while keeping PTV dose at 60 Gy in 30 fractions in stage III NSCLC are ongoing (19).

IMPT in lung cancer using 4-D CT guided adaptive re-planning has been implemented clinically in MD Anderson Cancer Center. We are trying to establish guidelines and strategies to address the critical issues related to IMPT in moving target. We reported here our initial experience of clinical implantation of intensity-modulated proton therapy in lung cancer and seek to address clinical indications, motion analysis/management, plan optimization/robustness and quality assurance.

References:

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