Editorial

Breaking the dose ceiling: proton therapy for locally advanced non-small cell lung cancer

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Chang *et al.* recently reported on the final outcomes of a phase II trial evaluating the use of concurrent chemotherapy and passively scattered proton therapy (PSPT) in patients with unresectable stage III non-small cell lung cancer (NSCLC) (1). Of note, the dose of proton radiotherapy used in this trial, 74 Gy relative biological effectiveness (RBE), is one of the highest proton radiation doses delivered with concurrent chemotherapy that has been prospectively evaluated in this group of patients to date.

This trial included 64 patients with pathologically proven, inoperable stage III NSCLC who had a Karnofsky Performance Status score of 70 or higher and no more than 10% weight loss in the 6 months preceding diagnosis. Treatment involved conventionally fractionated PSPT to 74 Gy RBE delivered concurrently with carboplatin and paclitaxel chemotherapy, with or without induction and adjuvant chemotherapy. At final analysis, the median overall survival was 26.5 months, with just 16% of patients experiencing local recurrence at 5 years. These outcomes are superior to those seen in landmark trials establishing concurrent chemotherapy with photon radiotherapy as the optimum approach for locally advanced NSCLC (LA-NSCLC), in which the median overall survival was in the range of 16–17 months and in-field failure occurred in over 25% of patients (2,3).

Several factors could account for these clinical outcome differences. More ubiquitous incorporation of advanced imaging such as PET/CT in the modern day treatment planning process has resulted in more accurate staging and target delineation (4). Improvements in intrafraction tumor tracking, respiratory gating, and motion management have allowed for increased accuracy in treatment delivery. Elective inclusion of pathologically or radiographically uninvolved regional lymph nodes in older trials may have impacted the ability to deliver plans with optimal dose coverage due to larger target volumes and higher doses to adjacent organs at risk, while disparities in the degree of conformality that can be achieved with older 2D and 3D treatment planning and proton therapy may have also affected the rates and severities of treatment toxicities (5).

Likely the most significant difference of this study is the higher prescription dose of 74 Gy RBE used, in contrast to doses ranging from 56 to 63 Gy commonly used in prior landmark cooperative group studies. The improvements in outcomes reported with stereotactic body radiation therapy (SBRT) for early stage disease have demonstrated the profound impact that adequate dose has in the definitive treatment of NSCLC. With delivery of a dose equivalent BED10 of 100 Gy or greater, local tumor control in excess of 95% can be achieved (6-8). The importance of

optimizing BED has also been demonstrated outside of the SBRT setting. A prospective trial in which 35 medically inoperable patients with early stage NSCLC were treated with proton radiotherapy to a dose of 87.5 Gy in 2.5 Gy per fraction demonstrated a 5-year local recurrence free survival rate of 85%, with limited toxicities reported (grade 3 dermatitis in 2.9%, pneumonitis in 2.9%) (9). This regimen delivered a dose equivalent BED10 of 109.4 Gy, illustrating that excellent long-term local control with limited toxicity can also be achieved with mild hypofractionation.

While early stage tumors requiring smaller treatment volumes generally can be safely and effectively treated with dose-escalated photon or proton radiotherapy, the same benefit of dose escalation has not been realized in LA-NSCLC that typically requires larger radiotherapy treatment fields. Furthermore, due to the often close proximity of primary and nodal disease to sensitive thoracic structures such as the esophagus, heart, normal lungs, trachea and bronchi, and spinal cord, radiation dose for LA-NSCLC has historically been limited by normal tissue tolerances and expected toxicities and not by optimizing the chance for locoregional tumor control.

Advances in photon radiotherapy techniques, such as intensity-modulated radiation therapy (IMRT), image-guided radiotherapy (IGRT), respiratory motion management, and adaptive planning, have improved radiation treatment for LA-NSCLC by allowing for more conformal dose delivery, superior avoidance of normal tissues, and more accurate and reproducible dose delivery to tumor. However, even with these technologies, the ability to deliver the higher, tumoricidal doses needed for definitive treatment of LA-NSCLC is still lacking due to quality of life (QoL)-limiting and life-threatening normal tissue toxicities to adjacent thoracic structures. This was demonstrated most notably in the reporting of RTOG 0617 by Bradley *et al.* (10). In that phase III trial, patients with locally advanced, stage III NSCLC were randomized in a two-by-two fashion to concurrent and consolidation carboplatin and paclitaxel chemotherapy with or without cetuximab, and with photon radiotherapy (3D-CRT or IMRT) to a dose of 60 or 74 Gy. On analysis of the effect of radiation dose, the investigators found that for patients who received 74 Gy, the median survival was worse when compared with those who received 60 Gy (20.3 *vs.* 28.7 months, P=0.004), results that were unexpected given the superior clinical outcomes seen with increasing doses in the SBRT experience.

Several hypotheses have been developed in an attempt to understand these outcomes. An excess of treatment-related deaths was seen in the high dose arm (8 in the 74 Gy arm *vs.* 3 in the 60 Gy arm), prompting an analysis of dosimetric parameters. Mean lung dose, lung V20, and doses received by the esophagus and heart were found to be higher in the 74 Gy arm, and on multivariate analysis, increasing heart doses, larger planning target volume, and maximum esophagitis grade were shown to be negative predictors of survival. The overall rate of grade 3 or worse toxicity in this trial was quite high, ranging from 76% to 79%. These findings show that radiation dose and toxicity to normal thoracic structures is critical, and that dose escalation with photon therapy at its current state can lead to unacceptable levels of toxicities and a survival decrement.

In the study by Chang *et al.* (1), acute and late toxicities were evaluated using the common terminology criteria for adverse events, version 3 (CTCAE v3), with acute events defined as those occurring within 90 days of treatment completion. Acute grade 2 esophagitis and pneumonitis occurred in 28% and 2% of patients, respectively. Additionally, 8% of patients developed grade 3 acute esophagitis, and no grade 3 acute radiation pneumonitis was reported. Late grade 3 pneumonitis occurred in 12% of patients and esophagitis in 2%. Two patients experienced late grade 4 events in the form of esophageal toxicity and bronchial fistula. Grade 2 or 3 cardiac toxicities occurred in 9% of patients. No patient experienced a grade 5 toxicity. These rates of toxicity are considerably lower than those seen in RTOG 0617, despite the use of the same dose used in the dose escalation arm of that study, supporting the profound potential of proton therapy to provide superior sparing of key thoracic organs and reduce clinically meaningful toxicities (8-10).

Radiation dose to the esophagus can significantly impact a patient's QoL early in the treatment course given the sensitivity of the mucosal lining to the damaging effects of radiotherapy. In LA-NSCLC treatment, the incidence of esophagitis is substantially increased with the concurrent administration of chemotherapy, as well as by dose escalation (2,10-14). The normal tissue impact of dose escalation was clearly demonstrated in RTOG 0617, in which the rate of grade 3 or greater esophagitis tripled from 7% to 21% with the use of the higher prescription dose (P<0.001). On multivariate analysis, increasing severity of esophagitis was found to be a negative predictor of survival. These findings highlight the need to define more stringent esophageal dose constraints in the treatment NSCLC when delivering concurrent chemoradiation.

In addition, the use of radiation modalities that can provide superior sparing of the esophagus to meet these constraints, such as with proton therapy, may be beneficial. In an analysis by Sejpal *et al.*, the incidence of toxicities in patients treated with chemotherapy and proton therapy to a median dose of 74 Gy RBE was compared with case-matched controls treated with chemotherapy and 3D-CRT or IMRT photon radiotherapy to a median dose of 63 Gy. The authors found that the rate of grade 3 or greater esophagitis was markedly increased for patients receiving non-proton radiotherapy despite the lower prescription doses (5% proton, 18% 3D-CRT, 44% IMRT; P<0.001) (15). These results, in combination with the low rates of esophageal toxicity observed in the study by Chang *et al.* (1), suggest that the use of proton therapy may be an optimal strategy by which to decrease esophageal toxicity, even in the setting of dose escalation.

In recent years, cardiac dose has emerged as a more significant dosimetric parameter than previously recognized. The potential for late cardiac events after radiation therapy has long been understood among patients treated for lymphoma and breast cancer (16-18). Despite this, a clear understanding of the relationship between dose of radiation, volume of heart irradiated, and subsequent risk of cardiac morbidity has been lacking. This is in part due to the use of older 2D and 3D radiation techniques and non-CT-based planning in older trials, which precluded robust attempts to spare heart or perform precise dosimetric analyses, limitations that have resulted in a limited ability to establish cardiac dose constraints relevant to modern radiotherapy.

Several recent studies have helped to shed some light on this issue. In a population-based case-control study evaluating the incidence of major coronary events in 2,168 women with breast cancer who received radiation therapy, Darby *et al.* found that the rate of major coronary events increased linearly with mean heart dose with no apparent threshold. The increase in cardiac events was found to begin within the first 5 years after radiotherapy, which is much earlier than previously thought (19). In addition, this difference was noted regardless of the presence of pre-treatment cardiac risk factors. A retrospective analysis by Wang *et al.* of 127 patients with stage III NSCLC treated on six prospective dose escalation studies demonstrated that the rate of cardiac events increased precipitously with increasing cardiac doses. That analysis found that approximately half of the cardiac events occurred early, within the first 2 years following treatment (20,21). These findings dispel previously-held beliefs that cardiac toxicities become a significant concern only after many years following radiotherapy or are of concern primarily in patients with predisposing comorbid conditions. As such, it is now clear that heart dose deserves more careful attention than has historically been given.

On primary and secondary analyses of RTOG 0617, several cardiac dose parameters including increasing heart V5, V30 and V40, emerged as negative predictors of survival, demonstrating the need to give more consideration to cardiac dose-volume parameters (10,22). In their secondary analysis of the impact of radiation delivery with 3D-CRT versus IMRT, Chun *et al.* also found that the use of IMRT resulted in substantially less cardiac dose (P<0.05) (22). This is likely attributed to the improved conformality achieved by IMRT and suggests that a modality such as proton therapy that can further reduce cardiac dose compared even with IMRT may in turn positively impact survival (5). This is demonstrated in the study by Chang *et al.*, as cardiac adverse events were limited, with 3% of patients experiencing cardiac arrhythmia and ischemia, 6% of patients developing grade 2 cardiac arrhythmias, and 3% of patients developing grades 2 and 3 pericardial effusions, even in the setting of dose-escalated radiation therapy (1). Proton radiotherapy, therefore, could enable more safe dose escalation by more readily meeting heart constraints and decreasing cardiac toxicities.

Delivery of radiotherapy in the setting of LA-NSCLC is challenging in part due to the large volume of surrounding normal lung included in the radiation field and the difficulty adhering to normal tissue constraints while still delivering adequate dose to the tumor volume. In contrast to cardiac dose constraints, dose-volume constraints for the lung are relatively well-defined due to early recognition of radiation pneumonitis as a potentially lethal side effect of radiotherapy with limited treatment options (13,23).

Due to uniformly strict adherence to these dose constraints, rates of radiation pneumonitis seen in clinical trials are relatively low. In the landmark trial by Curran *et al.* establishing concurrent chemoradiotherapy as the standard treatment of choice for patients with LA-NSCLC, patients developed grade 3 or greater acute pulmonary toxicities at a rate ranging from 2% to 9% (2). This is comparable to the 4–7% incidence of clinically significant grade 3 or greater radiation pneumonitis found in RTOG 0617. The incidence of pulmonary toxicity was not different between those patients who received 60 *vs.* 74 Gy, although there was a significantly lower incidence of grade 3 pneumonitis with the use of IMRT versus 3D-CRT. In addition, lung V20 was

associated with increased grade 3 or greater pneumonitis risk on multivariate analysis.

In the report by Chang *et al.*, acute radiation pneumonitis was a rare event, with only 2% of patients developing grade 2 toxicity and none experiencing grade 3 or higher events (1). However, the rates of late grade 2 and grade 3 radiation pneumonitis were 16% and 12%, respectively. This may be a reflection of the small sample size and, therefore, limited statistical power of this study, but could also be in part be a consequence of the limitations in the ability of PSPT to provide a degree of conformality significantly superior to that seen with modern photon radiotherapy due to factors such as tissue heterogeneity, proximal dose spread, and range uncertainty corrections (24,25). Intensity-modulated proton therapy (IMPT) offers further reductions in normal tissue doses compared with PSPT and can further improve upon current strategies to minimize lung irradiation doses and pulmonary toxicities (26).

Proton therapy may be the answer to safe dose escalation required for better disease control outcomes in the treatment of LA-NSCLC. As in the case of SBRT, delivery of higher BED radiation may improve local tumor control, which can in turn translate to a benefit in survival for NSCLC. Efforts to date to raise the standard dose of photon radiation for LA-NSCLC have been thwarted by unacceptably high rates of toxicities to the surrounding thoracic structures. Recent data have emerged demonstrating with increasing clarity that the irradiation doses to these structures have a profound impact not only on QoL, but also clinical outcomes, potentially negating or even outweighing any positive effect provided by higher doses. The findings of the study by Chang *et al.* (1) show promise in the use of proton therapy to provide a safe and effective solution to these barriers to dose escalation in LA-NSCLC. Due to the improved conformality and more precise targeting allowed by the physical properties of proton therapy, the amount of dose delivered and the volume of tissues receiving clinically relevant doses of irradiation can be minimized, thereby providing allowing for a less toxic treatment strategy.

While this important study lays the groundwork for the use of dose-escalated proton therapy in the definitive management of LA-NSCLC, there is work left to be done to confirm these findings. The role of proton therapy in the treatment of NSCLC is being actively defined and continues to evolve, with new data and technology constantly emerging. While both PSPT and the newer generation of proton therapy with pencil beam scanning technology and IMPT are effective methods of proton delivery, each has unique considerations that should be accounted for and optimized during treatment planning to address variables such as range uncertainties and tissue heterogeneity corrections (24). In addition, continued improvements in motion management and adaptive planning algorithms may not only provide opportunities for improved targeting and treatment with proton therapy, but they may also positively impact the ability of photon therapy to deliver higher radiation doses without the high rates of treatment toxicities that have been seen to date (10,25). Additional studies incorporating the use of newer proton technologies are needed, as are multicenter, randomized phase III trials that can provide additional data on the safety and efficacy of dose-escalated proton therapy with concurrent chemotherapy for LA-NSCLC. Only then can we continue to push the envelope and in the future consider even further dose escalation, establish a new standard radiation dose, and ultimately improve outcomes for patients with LA-NSCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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