Editorial Commentary

Dose escalation in the era of ablative lung irradiation: is more dose better when it comes to delivery of lung stereotactic body radiation therapy?

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Dose escalation has been an enduring and elusive target when it comes to improving clinical outcomes for both early stage and locally advanced non-small cell lung cancer (NSCLC). In locally advanced disease a dose threshold of 60 Gy delivered in conventional fractionation together with chemotherapy has been solidified after roughly 50 years of prospective investigation namely due to limitations on normal tissues when treating large thoracic volumes (1). In high risk surgical and medically inoperable stage I NSCLC, the application of four-dimensional image guided planning and delivery of highly conformal stereotactic radiation to small volume parenchymal lung tumors with sharp dose gradients has allowed for safe dose escalation above biologically effective dose (BED) of 100 Gy or achievement of "ablative" radiobiological tumor effects (2). The seminal 2004 publication of a large multi-institutional analysis of Japanese patients treated with various stereotactic body radiation therapy (SBRT) dose fractionation schedules showed that, when applying the Linear Quadratic formulation to correct for BED with an alpha/beta ratio of 10, delivering a high BED_{10} ≥100 Gy significantly improved overall survival (3-year overall survival 88% *vs.* 69%) (3). Experience delivering doses in this range has translated to high rates of local control (98% at 2 years) and improved overall survival when compared to conventionally fractionated radiotherapy (4,5). Clinical practice patterns and most institutions have embraced the clear cut-point of BED_{10} of 100 Gy to define SBRT lung delivery, but the optimal dose fractionation beyond this point remains unclear and currently employed prescriptions are heterogenous ranging between 100–180 Gy BED_{10}.

Moreno *et al.* investigated whether dose escalation beyond BED_{10} of 100 Gy imparts improved survival outcomes in patients treated for Stage I NSCLC (6). By retrospectively analyzing the large population based National Cancer Data Base (NCDB), the investigators matched over 20,000 patients treated for Stage I (cT1-T2aN0M0) NSCLC between 2004-2014 and stratified between Low BED_{10} delivery defined as 100–129 Gy and High BED_{10} delivery defined as ≥130 Gy. The authors were able to demonstrate a modest but statistically significant improvement in overall survival in the patients treated with High BED at both 3-year (64% *vs.* 60%) and 5-year (34% *vs.* 26%) (P=0.039). On propensity score matched multivariate analysis adjusting for tumor as well as clinical patient characteristics that importantly includes age and comorbidity burden, the improvements in survival remained significant for the high BED arm (HR 0.96, P=0.032).

The authors are to be commended for reporting the largest matched cohort to date investigating SBRT dose escalation in early stage NSCLC, employing appropriate statistical rigor to their analysis and controlling for potential available confounders that are coded for in the NCDB. These findings also serve to ballast four other retrospective multi-institutional and population-based database reports demonstrating improved cancer control and survival outcomes with BED_{10} in the ranges ≥125–150 Gy, especially for larger tumor volumes (>3 cm or T2 stage) (7-10). It

appears that, when feasible and safe, dose escalation beyond BED_{10} of 130 Gy seems to be supported by the currently available retrospective experience. It should be noted that consistently lacking in these reports are availability of toxicity data, particularly related to dose.

The significant limitations inherent in comparative efficacy utilizing large dataset analysis, and specifically the NCDB, warrant some scrutiny before we can adapt a strategy that uniformly maximizes BED_{10}. Implicit confounding that cannot be accounted for in the data elements available in the NCDB may in fact influence survival analysis, despite the statistical rigor employed. For example, tumor size and lobe location are coded elements and did not predict survival or influence the High BED improved overall survival effect on multivariate analysis, but tumor location in respect to critical central thoracic, mediastinal or chest wall anatomy is not a coded element and may in fact confound. Tumor centrality as defined by the RTOG (within 2 cm of the proximal bronchial tree or abutting the mediastinal/pericardial pleura), ultra-centrality (often defined as tumor abutting mainstem bronchus or carina, trachea, esophagus, great vessels or brachial plexus), or very peripheral tumor locations that overlap the chest wall/ribs influence dose fractionation decisions often leading to lower BED regimens in the interest of sparing normal tissues (11,12). Treating tumors in these critical locations likely drives the shift in SBRT dose regimens patterns of care the authors were able to document over the analysis time period. As the authors clearly demonstrated the significant decline over time of the 60 Gy in 3 fraction regimen and the rise in utilization of 5–10 fraction regimen coincides with the publications of key reports showing worsening toxicity with 3 fraction courses for central lung tumors (11-13).

By analyzing the dose fractionations utilized in the high BED *vs.* low BED arms one is able to infer that patients included in the high BED_{10} (>130 Gy) arm, likely had fewer central and ultra-central tumor since the majority (71%) were treated with 3 fraction regimens which are discouraged by multiple consensus guidelines and the NCCN in the timeframe of the analysis (14). When developing dose fractionation regimens and planning radiation delivery in these critical locations, achieving higher equitoxic BEDs comes at the cost of normal tissue toxicity and is often not possible or requires significant tradeoffs of BED, requiring clinical judgment in terms of prioritizing target coverage *vs.* organs at risk (15). In addition to tumor size, central tumor location represents an independent risk factor for occult mediastinal metastases, perhaps portending a more biologically aggressive course after completion of SBRT (higher rates of mediastinal, and/or distant metastatic dissemination) (16). Potential imbalance in the number of patients with central/ultra-central tumors between the high and low BED_{10} stratified arms may in turn influence the survival analysis.

Even when considering peripheral tumors, the report's premise that higher BED leads to better local control translating into better survival is relatively untested. For example, a systematic review of published prospective SBRT studies does not provide convincing evidence of differences in freedom from local progression in this higher range of EQD2 doses (17). Since the NCDB does not provide cancer specific recurrence endpoints it is also difficult to conclude that the survival gains between the high and low BED arms was clearly secondary to lung cancer specific improvements.

The authors note that their findings are consistent with published randomized trials, but that additional prospective investigation is necessary before we conclude that higher BED_{10} improves survival. Clearly this is a critical point in light of the multitude of factors that influence patient outcomes when treating early stage NSCLC with SBRT such as delivery technique (conventional linear accelerator based *vs.* robotic platforms), various respiratory motion management strategies (compression, gating or tracking), Image Guided Radiation techniques (fiducial based *vs.* volumetric imaging vs kilovoltage based imaging), treatment planning considerations around calculation algorithm (pencil beam *vs.* convolution superposition or Monte Carlo), delivery scheduling (consecutive *vs.* nonconsecutive days), tumor location (central *vs.* peripheral) as well as emerging literature showing overall poor agreement between results of population based observational studies and subsequent RCTs (18-20).

What will ultimately be required is prospective randomization comparing dose escalated BED_{10} beyond 130 Gy in peripheral T1–T2 lesions with strict inclusion criteria, radiation delivery quality assurance and normal tissue dose constraints. If clear cancer specific and/or survival gains can be demonstrated with dose escalation in this patient population, prescriptions for treating tumors near higher risk anatomical locations or frailer patients can then be tailored to maximize BED while respecting normal tissue constraints (i.e., 8–15 hypo-fractionated stereotactic delivery) (21). In addition, knowing if dose escalation above BED of 130 Gy improves OS, would critically inform currently accruing and planned randomized trials comparing SBRT to primary surgical management in

medically operable patient populations.

Prospective investigation of dose escalation must also be done in synchrony with evolving systemic immuno-oncology (IO) strategies in patients receiving SBRT for early stage NSCLC, since regional and distant metastatic recurrence is an important competing risk that influences overall survival in this patient population (22). Several clinical trials currently accruing are assessing integration of either adjuvant, post-SBRT PD1 inhibition with durvalumab (PACIFIC 4, NCT03833154) or concurrent and adjuvant integration of PDL1 inhibition with atezolizumab (SWOG S1914, NCT04214262) (23,24). Potential synergy between the immunomodulatory effects of SBRT and check-point inhibition may show this to be a viable strategy and therefore Lower BED fractionation regimens that may be sub-ablative but optimize immune effects and abrogate potential overlapping toxicity profile of IO (i.e., pneumonitis) may need to be explored.

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