Editorial Commentary

A biologically effective dose threshold for stereotactic body radiation therapy—can we put the issue to BED?

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The phenomenon of stereotactic body radiotherapy (SBRT) radically altering worldwide practice patterns for patients with early stage non-small cell lung cancer (NSCLC) is unprecedented. A particularly notable observation from the National Cancer Database (NCDB) review by Moreno *et al.* is that SBRT utilization increased from 0.2% in 2004 to 22% in 2014 (1). The ubiquitous uptake reflects just how many patients are actually candidates for a curative-intent treatment option when that option is both effective and convenient. While the possible role of SBRT is debated for operable (or borderline operable) patients, its role for those deemed unfit for surgery is seemingly cemented. However, questions remain about the dose response relationship, and the optimal choice of regimen.

Findings from the NCDB analysis suggest that SBRT biologically effective dose (BED) intensity may be directly related to patient outcomes and that the intensity prescribed has actually decreased over time. The initial North American prospective experience from Indiana University (IU) (2), and subsequently, the Radiation Therapy Oncology Group (RTOG) 0236 study utilized "intensive" three-fraction regimens. RTOG 0236 taught us that SBRT could be safely scaled to the multi-institutional level with excellent rates of local control (LC) (3). On this trial, patients were treated with 60 Gy in three fractions, but those with lesions located in the 'central' zone near the proximal bronchial tree were excluded given that treatment of such tumors on the IU study led to an increased risk of severe and lethal toxicity. With 96% in-field control, RTOG 0236 defined an excellent standard regimen for peripheral, early stage NSCLC. A post-hoc analysis suggested that the prescribed dose should be converted to 54 Gy in 3 fractions when heterogeneity corrections are applied, as is the case for most modern treatment planning algorithms (4). It is noteworthy that the actual dose delivered can vary by 10% based on the use these corrections—a factor not accounted for in the NCDB.

Despite the impressive RTOG 0236 results, the three-fraction regimen was not universally adopted as standard of care for peripheral lesions. The acceptance of alternatives in clinical practice, including those with lower predicted BED, was likely tied to increasing recognition of rib and chest wall toxicity coupled with the availability of data that suggested less intensive regimens also produced excellent local tumor control. In fact, adverse events involving the soft tissue and rib—now accepted and appreciated as a common consequence of SBRT for peripheral tumors—were not initially envisioned when RTOG 0236 was designed. At about the same time, results from The Japan Clinical Oncology Group (JCOG) 0403 trial, which utilized 48 Gy in 4 fractions, first became available, and 3-year LC (~88% at 3 years) was comparable to the IU trial's intensive regimen (5). Similarly, a regimen of 45 Gy in 3 fractions was reported to provide excellent tumor control in a prospective European trial (6). These rates of LC appeared to be no worse, despite less intensive dose schemes.

The fact that tumor location (central *vs.* peripheral) is not identified in the NCDB also bears mentioning. Many—but not all—SBRT treatment regimens were stratified by tumor location following publication of the IU data. Starting in 2009, the RTOG enrolled patients on a phase

I/II study designed to determine if a more protracted five-fraction regimen was safe and efficacious for central tumors. This recently reported experience produced a maximum tolerated dose of 60 Gy in 5 fractions (7) with acceptable toxicity and LC approaching 90%, similar to series treating peripheral lesions. These data also suggest that LC is maintained with a lower-BED regimen, and toxicities notwithstanding, lead to outcomes similar to those with early stage tumors. The impact of centrality on survival has not been evaluated prospectively, but a systematic review detailed no discernible effect (8). Further evaluations are ongoing with regard to tumors deemed ultra-central, those notable for direct contact with proximal organs at risk.

In practice, a risk adapted approach is often utilized, where the selected dose and fractionation depends on tumor location and size, among other patient and tumor characteristics. This approach is highlighted in a large prospective database from the Netherlands (9) where a nominal dose of 60 Gy resulted in excellent local tumor control with low toxicity. Fractionation varied with tumor location: peripheral tumors received 3 fractions, central lesions received 8 fractions, and those considered very peripheral near the chest wall received 5 fractions. Tumor size is another factor often impacting the SBRT dose regimen, as studies suggest the risk of toxicity increases with increasing tumor size. Nevertheless, we believe caution should be used in reducing dose for larger tumors given concerns about compromised tumor control, where reports are conflicting (10,11).

The current NCCN guidelines support 1, 3, 4, 5, or 8–10 fraction regimens, depending on size and location (12). In general, there is consensus that central lesions should be treated with 5 or more fractions to limit the risk of severe toxicity, but little agreement exists for peripheral lesions. Given the absence of level 1 evidence, choosing a dose schedule is left to clinician judgment. While local tumor control rates appear to be consistently high regardless of SBRT regimen, a note of caution was initially raised in data from a large multicenter Japanese review suggesting poorer outcomes with SBRT regimens with a BED less than 100 Gy (13), an observation subsequently supported by others (8,14). Nevertheless, the radiation oncologist can adhere to this guideline and still choose from a large array of prescriptions.

So what are we to make of the NCDB analysis recently published in the *Journal of Thoracic Oncology*? The report included over 20,000 patients matched for clinical characteristics to strengthen a comparison between those treated with a "low" BED [100–129] and a "high" BED (>130) regimen (1). Overall survival at five years was 34% and 26% in the high and low BED groups, respectively (P=0.039), and this remained significant after multivariate analysis. The authors are to be commended on assessing a meaningful question in a very large patient population, though the results are admittedly hypothesis generating and limited by constraints of the NCDB. As noted, factors that could substantially influence choice of SBRT regimen (most notably tumor location) and variables that could influence the actual dose delivered and "real" BED (heterogeneity corrections, dose prescription method, dose calculation algorithm) are not collected in the database. Moreover, data regarding local tumor control is also not available, preventing a direct assessment of the impact of dose regimen on the primary tumor itself. Perhaps if there was a clear dose response with tumor control, the assumption that higher BED regimens resulted in improved survival, rather than a host of other factors, would be better supported.

There are at least two basic caveats in attempting to define a dose response relationship. The first being that the model most often used to evaluate BED, the linear quadratic formula (BED = nd [1+ d/(α/β)]), incorporates assumptions developed for fractionated radiotherapy regimens, and the applicability to SBRT regimens is debated. That said, it is generally accepted that a 3-fraction regimen is more intense than a 5 fraction regimen when prescribed to an equal total dose. The other confounding issue is that the actual dose delivered may differ substantially even with the same nominal dose prescription because of varied treatment planning factors including dose calculation algorithm and prescription methodology, as noted earlier. These variables are inconsistently reported in the literature, if at all, thus even large multicenter experiences are often flawed in this regard.

In fact, published outcomes of tumor control should be assessed critically too, as LC is often defined as the lack of radiographic progression, which may overestimate true local tumor sterilization. This was highlighted by the MISSILE-NSCLC trial (15), where pathologic complete response was demonstrated in only 60% of tumors resected 10 weeks after SBRT. This was unexpected, given that rates of LC in a multitude of SBRT studies approach or exceed 90%. One convenient explanation is that residual tumor on standard histologic staining may not correlate with viability, but competing risks and relatively short follow up with

SBRT series in general might obscure our view. That said, conducting prospective randomized trials with sufficient power to compare SBRT fractionation schemes is a heavy lift. A Japanese trial (JCOG 1408) comparing 42 Gy in 4 fractions *vs.* 55 Gy in 4 fractions is ongoing, but we will likely not have results for several years (accrual goal 720 patients). Even prospective trials attempting to compare conventionally fractionated radiotherapy with SBRT have not provided consistent evidence of a benefit with SBRT despite substantial differences in calculated BED—though they were relatively small studies (16,17).

The relationship between radiation dose intensity, local tumor control, and overall survival is complex. Indeed, there are precious few examples in any disease site, where altering the radiotherapy regimen results in improved overall survival. Two prime examples relate to accelerating the treatment course in locally advanced NSCLC (18) and limited stage small cell lung cancer (19). So the suggestion from the NCDB review that higher BED regimens improve survival should be critically assessed. But, interpretation of survival outcomes following SBRT presents substantial challenges, as historically, SBRT has been employed predominantly in those with pulmonary dysfunction and/or other medical comorbidity which renders them unfit for surgical resection. Overall survival is significantly influenced by underlying patient specific factors, and the majority of patients treated with SBRT die from causes other than lung cancer. While a retrospective analysis can attempt to control for prognostic factors, intangibles that influence treatment decisions cannot be captured.

Given the breadth of experience treating peripheral tumors, is the data provided in the NCDB analysis convincing enough to narrow the choice of recommended regimens based on predicted BED? With the observation that lower BED regimens have been increasingly used over the past 15 years, taken together with the expanded offering of SBRT to borderline operable patients with longer life expectancy, the answer may be a qualified "probably". A major driver to prescribe reduced BED regimens for peripheral tumors is the increased appreciation of rib and chest wall toxicity. In contrast to SBRT related complications for central lesions which can be life threatening or lethal, chest wall toxicity is generally self-limited and managed conservatively. This is not to say the risk of complications should be ignored, but perhaps be assigned lower priority in the joint decision making regarding therapeutic ratio with patients. Moreover, the vast majority of comparative data suggesting increased toxicity with intensive SBRT dose schemes emanate from retrospective studies.

As SBRT data have matured, there has been increasing awareness that although local tumor control remains high (at least by conventional radiographic measures) as patients are living longer, regional and distant relapse are not insignificant. Similar to surgical series, the rate of distant relapse appears related to tumor size and functional imaging activity, among other factors. The majority of these recurrences occur within the first two years (20). This observation has largely shifted prospective research away from dose and fractionation questions, to trials assessing the addition of systemic therapy to SBRT. Given the nature of the population, data with cytotoxic chemotherapy is limited, but several trials are ongoing investigating the use of immunotherapy as (neo)-adjuvant additions to SBRT, including the PACIFIC-IV trial evaluating adjuvant durvalumab for two years following treatment (NCT03833154), and the SWOG lead intergroup trial which evaluates induction and consolidation atezolizumab (NCT04214262).

Moving forward, it will be important to expand our view of factors that impact patient outcomes following SBRT. Data from ongoing prospective trials should aid both our understanding of the relationship between dose intensity and survival, and how it impacts toxicity and quality of life. As the prospect of adjuvant immunotherapy nears—the interrelationship of BED and immune response will warrant careful study—as will the effects on those with underlying pulmonary comorbidity. While no one paradigm, dose, or schema will be appropriate for all patients, perhaps algorithms suggesting optimal treatment according to tumor, patient, and treatment characteristics can be better defined. While the discussion about intensity thresholds will likely be ongoing—the context and priority with which we view dose intensity is sure to evolve.

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References

1. Moreno AC, Fellman B, Hobbs BP, et al. Biologically Effective Dose in Stereotactic Body Radiotherapy and Survival for Patients With Early-Stage NSCLC. J Thorac Oncol 2020;15:101-9.
2. Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest 2003;124:1946-55.
3. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
4. Xiao Y, Papiez L, Paulus R, et al. Dosimetric evaluation of heterogeneity corrections for RTOG 0236: stereotactic body radiotherapy of inoperable stage I-II non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2009;73:1235-42.
5. Nagata Y, Hiraoka M, Shibata T, et al. Stereotactic Body Radiation Therapy for T1N0M0 Non-small Cell Lung Cancer: First Report for Inoperable Population of a Phase II Trial by Japan Clinical Oncology Group (JCOG 0403). Int J Radiat Oncol Biol Phys 2012;84:S46.
6. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290-6.
7. Bezjak A, Paulus R, Gaspar LE, et al. Safety and Efficacy of a Five-Fraction Stereotactic Body Radiotherapy Schedule for Centrally Located Non-Small-Cell Lung Cancer: NRG Oncology/RTOG 0813 Trial. J Clin Oncol 2019;37:1316-25.
8. Senthi S, Haasbeek CJ, Slotman BJ, et al. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. Radiother Oncol 2013;106:276-82.
9. Lagerwaard FJ, Haasbeek CJ, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;70:685-92.
10. Parker SM, Siochi RA, Wen S, et al. Impact of Tumor Size on Local Control and Pneumonitis After Stereotactic Body Radiation Therapy for Lung Tumors. Pract Radiat Oncol 2019;9:e90-e97.
11. Verma V, Shostrom VK, Kumar SS, et al. Multi-institutional experience of stereotactic body radiotherapy for large (>/=5 centimeters) non-small cell lung tumors. Cancer 2017;123:688-96.
12. NCCN. NCCN Clinical Practice Guidelines in Oncology - Non-Small Cell Lung Cancer. Available online: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. 2020. Accessed April 30 2020.
13. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94-S100.
14. Grills IS, Hope AJ, Guckenberger M, et al. A collaborative analysis of stereotactic lung radiotherapy outcomes for early-stage non-small-cell lung cancer using daily online cone-beam computed tomography image-guided radiotherapy. J Thorac Oncol 2012;7:1382-93.
15. Palma DA, Nguyen TK, Louie AV, et al. Measuring the Integration of Stereotactic Ablative Radiotherapy Plus Surgery for Early-Stage Non-Small Cell Lung Cancer: A Phase 2 Clinical Trial. JAMA Oncol 2019;5:681-8.
16. Ball D, Mai GT, Vinod S, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. Lancet Oncol 2019;20:494-503.
17. Nyman J, Hallqvist A, Lund JA, et al. SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. Radiother Oncol 2016;121:1-8.

18. Saunders M, Dische S, Barrett A, et al. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. Radiother Oncol 1999;52:137-48.
19. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999;340:265-71.
20. Senthi S, Lagerwaard FJ, Haasbeek CJ, et al. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol 2012;13:802-9.

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