



Delivering safe and effective stereotactic body radiation therapy for patients with centrally located early stage non-small cell lung cancer

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Stereotactic body radiation therapy (SBRT) combines accurate anatomic targeting of a tumor with the precise delivery of high doses of radiation per fraction in an attempt to ablate the tumor while sparing surrounding normal tissues (1). SBRT has been described in the treatment of lung cancer since the mid-1990s (2). The initial uses of lung SBRT were in patients with early-stage non-small cell lung cancer (NSCLC) who were medically inoperable or refused surgery, but it has also emerged as an effective treatment option for medical operable NSCLC patients (3,4), patients with early stage SCLC (5), and patients with parenchymal metastasis from lung and other malignancies.

Prospective data on the treatment of NSCLC with SBRT dates from as early as 2005, when McGarry *et al.* (6) described results of a phase I trial treating tumors with up to 72 Gy in 3 fractions. The Indiana University group subsequently noted that treatment of centrally located tumors in 3 fractions was associated with increased toxicities and even death from treatment, and the investigators concluded that such high doses per fraction likely should not be used for tumors near the central airways due to the risk of excessive toxicities (7). That study observed grade 3 to 5 toxicity in 14 of 70 patients and noted 2-year freedom from severe toxicity of only 54% in central tumors, compared to 83% for peripheral tumors. They defined central tumors relative to a “zone of the proximal bronchial tree”, which

was a 2 cm uniform expansion from the proximal bronchial tree (PBT), termed the no-fly zone (NFZ) for treatment with SBRT. It was in this setting of heightened awareness of excess toxicities in the treatment of central lung tumors that the NRG Oncology RTOG 0813 trial was conceived.

Many definitions have been used to describe “central” lung tumors, and more recently “ultra-central” lung tumors. RTOG 0813 was designed over a decade ago when relatively little was known about the nature of risk in central lung tumors. Of note, the study defined central tumors more generously than the initial definition by Timmerman *et al.* (7) as those not only within or touching the NFZ, but also those with a planning target volume (defined as the gross tumor volume plus margin for intrafraction respiratory motion plus a margin for setup variations and uncertainties) touching the mediastinal or pericardial pleura (8). Other investigators at the time took an even broader view, defining a central tumor as being “within 2 cm of the bronchial tree, major vessels, esophagus, heart, trachea, pericardium, brachial plexus, or vertebral body, but 1 cm away from the spinal canal” (9). Now, many investigators consider a central tumor to be that which fits the original Indiana definition of within or touching the NFZ, without the additional mediastinal or pericardial pleural qualifier, and this is the definition that was adopted in the 2017 ASTRO Evidence-Based Guideline for SBRT

of early-stage NSCLC (10).

There is not a uniformly accepted definition for “ultra-central” tumor. RTOG 0813 did not define such an entity in the study protocol. The Executive Summary of the 2017 ASTRO Evidence-Based Guideline for lung SBRT does not address or define ultra-central tumors (10). Concern about central tumor treatment increased following the 2012 publication of a case report describing fatal central-airway necrosis in a patient who received a relatively conservative dose of 50 Gy in 5 fractions for a central NSCLC that was located very close to the right mainstem bronchus (11). A subsequent retrospective report in 2015 was an early such report to describe a cohort of “ultra-central” tumors and defined this higher risk subset of central tumors as those that directly abut the central airway (trachea and proximal bronchial tree) (12). Other retrospective publications have used the same definition (13), but some defined ultra-central differently, such as Tekatli *et al.* who include tumors that may or may not abut central structures but have a planning target volume that overlaps the trachea or main bronchi (14).

As RTOG 0813 accrued and results matured, many institutions published their experiences using SBRT for central lung tumors. Two large, modern institutional series from Yale University (15) and University of Pennsylvania (16) did not show a difference in tumor control or toxicity with SBRT for central versus peripheral tumors. A systematic review of SBRT for central lung tumors published in 2013 corroborated prior individual reports that showed improved local tumor control when the biologically effective dose of radiotherapy at an alpha/beta ratio of 10 (BED_{10}) was sufficiently high (17). Namely, a BED_{10} greater than or equal to 100 Gy achieved a local control of 85% compared to 60% with BED_{10} less than 100 Gy. The rate of grade 5 toxicity with SBRT for central tumors was 2.8%, and the median time to death following SBRT was 7.5 months. Grade 3 or 4 toxicity was noted in 8.6% of patients. This systematic review was limited by heterogeneity, being comprised of 20 studies, most of which included fewer than 25 cases of central early-stage NSCLC and defined “central” in a variety of ways. Despite this limitation, the finding of improved local control with $BED_{10} \geq 100$ Gy was taken to heart by many in the field, setting 10 Gy \times 5 ($BED_{10} = 100$ Gy) as a potential minimum effective dose for central tumors when delivered in 5 or fewer fractions.

Investigators at MD Anderson Cancer Center published their updated central SBRT experience in 2014 (18). They treated 100 patients with primary T1–2N0M0 or locally recurrent NSCLC in a central location, defined as within

2 cm of the bronchial tree, trachea, major vessels, esophagus, heart, pericardium, brachial plexus, or vertebral body. SBRT was delivered to 50 Gy in 4 fractions ($BED_{10} = 112.5$ Gy) or 70 Gy in 10 fractions ($BED_{10} = 119$ Gy). Local control at 3 years was excellent at 96.5%, and toxicity was reasonable, with most common toxicities being chest wall pain (13% grade 2) and radiation pneumonitis (11% grade 2, 1% grade 3). Of note, there were only 23 patients with tumors within 2cm of the bronchial tree, and for the 21 of those who received 50 Gy in 4 fractions, the median distance to bronchial tree was 1.4 cm. As such, this study was limited in its ability to ascertain toxicities for ultra-central tumors.

Our experience at Memorial Sloan Kettering Cancer Center (19) was updated in 2016 and reported fatal complications for several patients with ultra-central tumors (13). One hundred eight patients were treated with central lung tumors defined by RTOG 0813 criteria. The treatment dose ranged from 45 Gy in 5 fractions (most commonly delivered) to 60 Gy in 3 fractions. Local control at 2 years was limited at 77.4% (13), likely owing to the standard use of 45 Gy in 5 fractions ($BED_{10} < 100$ Gy) for central tumors prior to the 2013 systematic review by Senti *et al.* (17). Notably, there were 18 patients treated with ultra-central tumors in this cohort, and 4 of those patients (22%) experienced mortality attributed to SBRT. No grade 5 toxicity was observed in non-ultra-central tumors ($n=0/90$). Notably, 3 of the ultra-central grade 5 toxicities occurred at a dose of 45 Gy in 5 fractions which delivered a BED_{10} lower than was delivered in RTOG 0813, whereas the fourth occurred at 50 Gy in 5 fractions. Two of the patients received anti-VEGF therapy before and after SBRT, which may have contributed to the observed toxicities. We concluded that ultra-central tumors appear to represent a special subset of central tumors for which additional caution should be taken when utilizing SBRT in five or fewer fractions.

Prospectively, a phase I/II trial central SBRT led by investigators at Washington University in St. Louis was published in 2018 (20). They defined a central lung tumor using the NFZ as well as tumors within 5 mm of mediastinal pleura or parietal pericardium. In phase I of the trial, they treated central tumors in 23 patients with 5 fractions using dose levels of 9, 10, 11, or 12 Gy per fraction. The only acute adverse events were 2 patients in the 10 Gy arm with grade 3 lung toxicities unrelated to SBRT. The only local failure occurred in a patient treated in the 9 Gy arm. The investigators decided to proceed with the 11 Gy dose

level for phase II of the study because, although 12 Gy was technically the maximum tolerated dose (MTD), there was longer follow up in the 11 Gy phase I arm, and the investigators preferred not to risk having worse late toxicity with 12 Gy. Fifty-one patients were treated in the phase II portion to 55 Gy in 5 fractions. Of note, tumor size was relatively large, with the majority greater than 3 cm and 16% greater than 5 cm. Despite this, local control at 2 years was 85%. Acute grade ≥ 3 toxicities occurred in just 6% of patients. Late toxicities were more substantial, with rates of grade 3 and 4 toxicities being 27% and 12%, respectively. Most late toxicities were pulmonary in nature. One patient suffered a late grade 5 toxicity (fatal hemoptysis) 17 months following SBRT. This publication did not report on the distance from the tumor to the PBT or other central structures, so ultra-central data are not available. The authors concluded that SBRT for central tumors with 11 Gy \times 5 fractions yield very good local control but is associated with severe late toxicities in some patients.

The multi-institutional RTOG 0813 trial (8) was initiated around the same time as the single-institution Washington University trial (20) and is similarly a prospective phase I/II study. Its phase I/II design was structured seamlessly to facilitate immediate accrual to the MTD, thus allowing many patients to be treated at or near the MTD without requiring extended periods of study closure for toxicity assessment. Patients enrolled on RTOG 0813 had medically inoperable stage T1–2N0M0 central NSCLC. Treatment was delivered with SBRT in 5 fractions over 1.5–2 weeks with dose levels of 10, 10.5, 11, 11.5, and 12 Gy per fraction. Dose limiting toxicity (DLT) was defined as a grade ≥ 3 pre-defined adverse event attributable to SBRT that occurred within 1 year of treatment. MTD was the dose level that produced the greatest DLT probability up to 20%.

The trial accrued 120 patients, 100 of whom were evaluable, and 71 of whom were treated at the two highest dose levels. Local control at 2 years for dose levels of 11.5 and 12 Gy per fraction were 89.4% and 87.9%, respectively. The MTD was 12 Gy per fraction, which was associated with a DLT probability of 7.2%. Across dose levels, there were 5 total DLTs that occurred within 1 year of therapy. Only 1 DLT was grade 5 (1%), and this occurred at the 10.5 Gy per fraction dose level. The authors conclude that the study provides high quality data that SBRT for central lung tumors delivered in 5 fractions is safe and effective.

There are many strengths to the RTOG 0813 trial, and the investigators are to be highly commended for diligent

completion of such an important study. Thanks to the seamless study design, many patients were treated at high dose levels, which maximizes the robustness of the efficacy and toxicity data at high doses. It should be noted that while local control rates in the two highest dose levels were excellent, rates of local control were high across all dose levels. Local control at 2 years was greater than 85% in all dose groups, a finding that is in keeping with the local control reported in the Washington University study at a dose level of 11 Gy per fraction. Furthermore, treatment across dose levels was well tolerated, with only 5 DLTs in the first year of follow-up.

It is worth noting that RTOG 0813 reported on the probability of toxicity rather than the absolute toxicity rate. The probability was determined using an a priori assumption that toxicity would be greater as dose increased, and Monte Carlo simulations were used to assist with probability calculation. As such, the toxicity probabilities do not match exactly with the absolute toxicity rate. Although it was argued by some that the dose levels above 10 Gy per fraction produced toxicity rates that could be interpreted as unacceptably high, the RTOG 0813 authors responded that while their threshold of 20% DLT used to determine MTD is high, the observed toxicity was much less than that in all dose cohorts (21). Furthermore, randomized data will be difficult to obtain in this setting, as any trial design would need to account for a great deal of heterogeneity regarding central tumor location and resulting organs at risk, in addition to other stratification factors. No such randomized trials are currently planned.

Two areas that would benefit from additional exploration are the ultra-central subset of central lung tumors and particularly large centrally located tumors. RTOG 0813 reported that few of the patients enrolled had ultra-central tumors, but the definition of ultra-central that the investigators used was not described in the protocol or publication. Appropriately, no subset analysis of ultra-central tumors was performed, likely because it was not pre-specified and with small numbers it would be difficult to exact meaningful conclusions. Recent data suggest that excess mortality from SBRT in ultra-central tumors may be related to synergistic toxicity from antiangiogenic agent exposure (22). Future prospective data focusing on ultra-central tumors, or perhaps a combined analysis of existing prospective data sets containing ultra-central tumors (inclusive of RTOG 0813), would be informative to describe and determine toxicities in this interesting group. Milder hypofractionation regimens like 7.5 Gy \times 8 fractions, 7 Gy

×10 fractions, or 4 Gy ×15 fractions could also be considered in patients with ultracentral lesions in an attempt to reduce toxicities compared with SBRT regimens delivered in five or fewer fractions. Additionally, as SBRT is increasingly being used to treat large, node-negative patients with NSCLC (23), the findings of RTOG 0813 might provide guidance on the optimal treatment for these patients. While RTOG 0813 excluded patients with tumor sizes >5 cm, other reports have shown that SBRT to these large tumors can be safe and effective, without differences in toxicity rates for central versus peripheral tumors (24). Based on the safety and feasibility findings of 11–12 Gy fractional doses in RTOG 0813, larger tumors might particularly benefit from dose escalation above 10 Gy ×5 since they have a more precipitous decline in local control over time compared with smaller tumors when treated to BED₁₀ of just 100 Gy (25).

Overall, along with other prospective and retrospective data, RTOG 0813 is the most comprehensive evidence to date demonstrating that treatment of central lung tumors with SBRT can be carried out safely and effectively. These findings suggest that for patients with centrally located early stage NSCLC, there is no longer a need to resort to conventional radiation fractionation over six to eight weeks or to surgery in a very high operable risk patient, and that SBRT should be considered the standard treatment approach in this population. While greater than three fractions should be used, specific SBRT and hypofractionation treatment dose and fractionation should be personalized on a case-by-case basis and should take into account the specific features of each individual tumor. As central tumors in general still carry greater treatment risk than peripheral tumors, all SBRT treatment should be carried out in accordance with the ASTRO evidence-based guideline for SBRT of early-stage NSCLC (10) and ideally at a high-volume center.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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