

#### Editor's note:

In the era of personalized medicine, a critical appraisal new developments and controversies are essential in order to derived tailored approaches. In addition to its educative aspect, we expect these discussions to help younger researchers to refine their own research strategies.

#### Controversies on Lung Cancer: Pros and Cons

## Pros: should a medically inoperable patient with a T2N0M0 non-small cell lung cancer central in the lung hilus be treated using stereotactic body radiotherapy?

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### Introduction

The view that surgery represents the only curative treatment for non-small cell lung cancer (NSCLC) still prevails today. Perhaps the greatest achievement of stereotactic body radiotherapy (SBRT) has been to challenge this, providing a platform to promote radiotherapy as an effective curative treatment that should be considered alongside surgery (1). The impact of this is clearest when considering population-based outcomes from national cancer registries. In the Netherlands, the widespread implementation of SBRT has increased radiotherapy utilization, decreased the proportion of patients left untreated and as a consequence improved NSCLC survival (2). The logistic benefits of SBRT courses over conventional radiotherapy has clearly played a role in this, providing a treatment option for the elderly or those with significant comorbidities who might not otherwise be offered curative treatment. These patients represent the fastest growing population of lung cancer patients (3) and a proportion will have central tumors for which conventional radiotherapy is infeasible. The primary argument as to whether to use SBRT for central tumors rests with maintaining population survival gains and weighing the risks of harm against those of not offering curative treatment.

### Why are there concerns using SBRT for central tumors and should there be?

It is clear that SBRT for central tumors represents a higher risk clinical scenario, with little prospective evidence compared to SBRT for peripheral tumors (4). Toxicity concerns first came to light when Timmerman defined 'central' and found SBRT for lesions within 2 cm of the bifurcation of lobar bronchi were 11 times more likely to result in severe toxicity, including death (5). However one needs to consider the limitations of applying such data to SBRT treatments delivered almost 10 years go. In the Timmerman report, SBRT occurred without 4DCT simulation, inhomogeneity-corrected dose calculation or daily soft-tissue based image guidance. Independently each of these factors may contribute to an increased risk of toxicity. The radiotherapy dose of 66 Gy in 3 fractions (used for T2 tumors) significantly exceeds that which is routinely used today or that is required for optimal local control (4). In addition to this, the scoring of toxicities may have overestimated the risk of death. Four of the six potentially 'SBRT-related' deaths were due to bacterial pneumonia, a common occurrence in a population with a median age of 70 years, an FEV1 less than 40% predicted and a smoking

history of at least 20 pack years with frequent continued smoking. Concerns regarding the use of SBRT for central tumors were again brought to the fore when the *New England Journal of Medicine* reported a case of fatal airway necrosis using 50 Gy in 5 fractions with modern SBRT techniques (6). The report is important in that it highlights that death is possible and caution is required, but as with any case series, it provides no insight into the relative risk compared to treating peripheral tumors. The weight of such evidence, an unplanned subgroup analysis and case report, needs to be placed into context and have clinicians ask; does this justify denying my patient potentially curative treatment, when SBRT represents their only option.

### Is there evidence to support using SBRT for central tumors?

There are limited prospective reports of SBRT outcomes for central tumors. Xia *et al.* reported outcomes for nine central tumors using an SBRT schedule of 50 Gy in 10 fractions delivered by gamma-knife system (7). Local control at 3 years was 93% (entire stage II cohort) and central tumors did not result in any grade 3 or higher toxicities. After longer follow-up, the 22 patients with central tumors Fakiris *et al.* originally reported on were found to have an overall survival and severe (grade 3-5) toxicity risk that was the same as that of peripheral tumors (8). Bral *et al.* reported on a prospective cohort of 40 patients, 17 of which were central tumors and treated to 60 Gy in 4 fractions (9). They found tumor location did not predict local control, patterns of relapse or overall survival. Although they found 20% of patients developed grade 3 pulmonary toxicity, and this was associated with central location ( $P=0.06$ ) and PTV size  $>65$  cc ( $P=0.02$ ), central tumors were significantly larger than those peripherally located on average (67 *vs.* 42 cc,  $P=0.0009$ ). Taremi *et al.* prospectively assessed 108 patients, 20 of which had central tumors. Although they did not assess the impact of tumor location on toxicity, they reported no grade 4 or 5 events (10). Videtic *et al.* prospectively investigated quality of life after SBRT in 21 patients, including 12 with central tumors treated with 50 Gy in 5 or 10 fractions (11). They found no grade 3 or higher toxicity or change in global quality of life and these did not correlate with tumor location.

When faced with elderly patients with central NSCLC, the majority of clinicians already feel there is sufficient evidence to utilize SBRT. A recent pattern of care study found more than 80% would use SBRT, the vast majority

outside a clinical trial protocol, even if conventional radiotherapy was an option (12). The consequence of this has been increasingly robust retrospective evidence to support the use of SBRT. A recent systematic review found 20 reports of outcomes in more than 500 central tumors following SBRT (4). None of the included studies found central location predicted worse survival. In addition, SBRT related mortality was found to be dose-related, with a 2.8% (16/563) risk overall and a 1.0% (2/204) risk when an SBRT schedule with a  $BED_3 < 210$  Gy was utilized. This approximates to dose fractionations of 50 Gy in 5 fractions or 60 Gy in 8 fractions. Since then, Mangona *et al.* identified 79 patients with central tumors and matched them to 79 patients with peripheral tumors (13). When baseline differences were accounted for using propensity-matched analysis, central tumors had the same toxicity profile as those peripherally located, with respective grade 3 or higher toxicities of 3% *vs.* 7% ( $P=0.48$ ). Using a SBRT scheme of 48 Gy in 4 fractions for tumors  $<3$  cm, 60 Gy in 5 fractions for tumors  $>3$  cm and respecting their institutional organ at risk constraints (which were published), the 2-year incidence of grade 4 and 5 toxicity was  $<1\%$ . Furthermore, Park *et al.* used logistic regression modeling in a cohort of 111 central and 140 peripheral NSCLC with a median follow-up of 31 months (14). On multivariate analysis tumor location did not impact survival, local control or toxicity.

### Putting risks into context and patient-centeredness

As surgery is regarded to be the standard of care treatment for NSCLC, the mortality following lung cancer surgery can be considered the accepted benchmark against which to consider SBRT-related toxicity. Mortality following surgery at 30 days ranges between 1.1-5.4% and increases up to three-fold to 2.7-9.5% at 90 days (15). Surgical risks are even higher for central tumors as these necessitate complex bronchoplastic and/or angioplastic procedures that may ultimately be converted to pneumonectomy (16,17). For such patients, 30-day mortality is almost 5% and the risk of operative complication approaches 30%. In contrast, when SABR-related mortality occurs, the time to event is approximately 7.5 months (range, 5-12.5 months) (4). Put this into context and consider, that elderly patients who are not offered curative treatment have a median survival of approximately 6 months (2). In an area where literature can be interpreted variably, is continually evolving and often dependent on individual clinician's willingness to administer SBRT, the decision as to whether SBRT should

be offered to central NSCLC needs to be patient centered, accounting for individual patient preferences (18). Arguing against using SBRT, risks clinicians assuming ‘paternalistic authority’ and continues to underestimate the level of involvement patients want in their treatment decisions (19).

## Conclusions

The overall quality and extent of literature to guide treatment of central NSCLC with SBRT is limited. Reports against the use of SBRT have significant limitations and appear outweighed by the body of evidence supporting SBRT, which suggest the risk of mortality and morbidity are acceptable with more protracted SBRT courses, in particular 60 Gy in 8 fractions. European experts seem to agree, as this fractionation will be robustly tested in the phase II setting without dose finding (20).

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## Footnote

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

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