Stereotactic Radiation Therapy for medically inoperable centrally located Non-Small Cell Lung Carcinoma

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SUMMARY: Radiation therapy techniques for Non-Small Cell Lung Carcinoma has evolved in recent years. Stereotactic technology allows delivery of high doses in a fewer number of fractions to very precise tumour targets. Treatment-related morbidity and mortality for centrally located lung cancers had proven significant, especially for tumours abutting critical mediastinal structures. Modern clinical trials however are now open and are assessing the safety and efficacy of stereotactic radiation therapy for such tumours. This article describes these and the evidence supporting this sophisticated technology for such anatomically difficult tumours.

Lung cancer is the leading cause of cancer death worldwide with a crude incidence in the European Union of 52/100,000 per year and a disease-related mortality of 47/100,000 per year. Non-Small Cell lung cancer (NSCLC) accounts for approximately 80% of these cases. The five-year survival of patients with NSCLC is poor (16%), mainly due to such patients being diagnosed at advanced stages. However, if lung cancer can be detected and treated at an earlier stage, the outcome and survival rates are more favourable with five-year survival rates approaching 77%.

The current recommendation for standard of care in small volume tumours is surgical resection in medically fit patients, consisting of lobectomy or pneumonectomy accompanied by a systematic mediastinal lymph node sampling. For this patient population with early stage smaller volume disease, surgery offers the potential of local tumour control in up to 96% of patients. However, approximately one quarter of patients are medically inoperable because of co-existing morbidities or poor general condition, mostly the result of a long smoking history, concurrent chronic obstructive pulmonary disease and coronary artery disease.

When best supportive care and no curative treatment are offered to these patients, overall survival (OS) is low. The 5-year OS was reported to be only 9% in untreated stage I NSCLC, which is partly a result of advanced age and comorbidities in many of these cases. However, cancer specific survival (CSS) was also low in this group at 16% after 5 years, suggesting that the majority of untreated patients die of their lung cancer despite early stage of disease and despite the high competing risk of death due to comorbidities. These numbers clearly indicate the need for a curative treatment option in medically inoperable patients with early stage NSCLC.

Conventionally fractionated external beam radiotherapy (EBRT) has historically been the standard of care for medically inoperable NSCLC with prescribed doses of usually 60 Gy – 66 Gy delivered at 2 Gy per fraction. This moderate irradiation regimen resulted in a local failure rate of approximately 50% and it is local failure, not distant, that has been shown to be the most frequent pattern of disease recurrence. Still, conventional EBRT resulted in OS and CSS superior to best supportive care, though it is clearly still an insufficient treatment with CSS rates of only approximately 30% after 5 years.

In the mid-1990's, after encouraging success in the treatment of cerebral malignancies, the concept of highly precise stereotactic radiation therapy was adapted from the central nervous system to the body. With this technique, only the primary tumour was targeted and precise tumour localisation combined with techniques reducing tumour motion allowed small safety margins. These small volumes were treated with fewer number of fractions and escalated irradiation doses. Since then, the technique of image guided (IG) – stereotactic body RT (SBRT) also known as stereotactic ablative body radiotherapy (SABR) was developed. This aspect of therapy uses daily CT imaging to localise precisely the tumour position and its proximity of critical structures. Daily adjustments to the treatment plan can then be made to account for changes in tumour position.

Several prospective phase II studies summarised in Table 1, reported high local tumour control rates and low rates of toxicity. Population studies have indicated that the introduction of SABR has also been associated with improved OS. The superiority of SABR over conventional EBRT for such early stage lung cancers has been confirmed in a recently published randomised trial in terms of local control (14% vs 31%) and freedom from local treatment failure improvement in the SABR group (HR 0.32, 95% CI 0.13 -0.77, p=0.0077).

The safety of SABR for peripheral NSCLC and its associated low toxicity profile has been demonstrated consistently and exists even in potentially higher-risk patients with advanced age, severe COPD and very poor

Table 1: Studies on SABR in NSCLC (Stage I)

	No. of Patients and Follow-Up	RT Dose	Local Control	Overall Survival
(Nagata *et al.*, 2005)	45 30 months	12 Gy x 4 fractions	98% @median 30 months	75% @3 years
(Baumann *et al.*, 2009)	57 35 months	15 Gy x 3 fractions	92% @3 years	60% @3 years
(Fakiris *et al.*, 2009)	70 50 months	20-22 Gy x 3 fractions	88% @3 years	43% @3 years
(Ricardi *et al.*, 2010)	62 28 months	15 Gy x 3 fractions	88% @3 years	51% @3 years
(Timmerman *et al.*, 2010)	54 34 months	18 Gy x 3 fractions	98% @3 years	38% @3 years
(Bral *et al.*, 2011)	40 16 months	60 Gy in 3-4 fractions	84% @2 years	52% @2 years

pulmonary function. Any curative approach except for SABR in these cohorts is therefore extremely difficult or even impossible via so-called conventional approaches.

The available data have been criticised as a certain percentage of tumours had no histological confirmation of malignancy and the diagnoses relied heavily on imaging. The main reason for this is due to the high risk of potentially life-threatening complications that may occur even during small biopsy procedures as these patients have such poor medical condition. However, it has been shown that outcomes remain similar in biopsy-proven cohorts compared to non-biopsied cases. Unfortunately, randomised studies, which look to investigate the efficacy of SABR versus resection prospectively, face problems of slow recruitment. Nevertheless, SABR may in the future open an alternative curative treatment option, e.g. for patients in a moderate-to-high perioperative risk category.

The irradiation doses used in SABR were most frequently adopted from the phase I dose escalation trial used by McGarry et al (2005). Here the maximum tolerated dose was 3 fractions of 22 Gy per fraction in T2 tumours. Since then, the majority of studies and centres used a fractionation of 3 x 20 Gy for stage I NSCLC.

Using this fractionation schedule Timmerman et al (2006) reported relatively high toxicity after SABR with doses of 3 x 20-22 Gy and 6 patients may potentially have SABR related mortality. In 5 of these patients, deaths were from respiratory causes: 1 fatal haemoptysis, which was associated with a local recurrence, and 4 infectious pneumonias; the sixth patient died of complications from a pericardial effusion. These deaths occurred after a median of 10.4 months following SABR (range 1-20 months). These toxicities occurred in tumours located in a central location defined as within 2 cm from the proximal bronchial tree (Figure 1). By differentiating the peripheral tumours from the central ones (within 2 cm distance from the proximal bronchial tree), it could be shown that the 2-year incidence of toxicity grade ≥ 3 was 17% and 46% after SABR for peripherally and centrally located stage I NSCLC, respectively.

The major difference between peripherally and centrally located NSCLC is the spatial relationship to critical normal tissues (Organs At Risk). For peripherally located tumours, the pulmonary tissue around the target is the only relevant critical organ at risk and is well known to show a parallel radiobiological behaviour, which has been successfully reproduced in SABR. In fact, ablation of a small pulmonary volume around the tumour has been shown to have a negligible influence on post-SABR pulmonary function.

In terms of radiobiology, the function of "parallel organs" (e.g. lung, liver, bone marrow) is not severely compromised as long as a small subvolume is damaged by radiation, leaving the majority of the organ intact. In contrast, severe damage to a subvolume of "serial organs" (e.g. spinal cord, bowel, large vessels) will lead to significant loss of function of the organ. Unlike for peripheral lesions, several serial organs at risk need to be considered in SABR of centrally located targets - large bronchi, blood vessels, the oesophagus and the heart. It is to these structures that significant treatment related toxicity can occur, and escalated hypo-fractionated irradiation doses might pose a potential risk in SABR.

The observation of severe toxicity after SABR treatment of centrally located NSCLC was confirmed by two subsequent studies: Grade 5 toxicity was observed in 1 out of 17 patients after treatment with 60 Gy in 4 fractions (Bral et al., 2011) and in 1 out of 9 patients after irradiation with 48 Gy in 4 fractions delivered on consecutive days (Song et al., 2009). Based on these published experiences, central tumour location was an exclusion criterion for the majority of subsequent prospective and retrospective studies.

However, in contrast to the above-mentioned studies, other groups have reported safe SABR treatment for centrally located targets. Some recent publications with moderate fractionation schemes have shown relatively low toxicity rates with toxicity comparable to peripheral NSCLC.

LungTech, a multi-centre EORTC phase II central lung trial (opened in 2014) has put forward an 8-fraction regime of 7.5 Gy per fraction for central lung tumours. The justification of the fractionation takes into consideration all the literature findings of different fractionation schedules at the time of opening, citing the most favourable clinical results have been published for the 8-fraction regime to date.

On the other hand, NRG-RTOG 0813 (opened in 2009 and completed in 2013) is a multi-centre North American central lung trial aimed to determine a maximum tolerable dose of a SABR schedule for 5 fractions. Five fractions were chosen, as it was short practical schedule suitable for patients with comorbidities. It was also within the American reimbursement criteria for SABR fractionation. This study started with a 10 Gy dose level using a continuous reassessment methodology escalating subsequent levels by 0.5 Gy up to a max of 12 Gy. Data from the primary endpoint of the phase 1 portion of the study indicated a relatively low rate of serious toxicity on the highest dose level with 7.2% rate of dose-limiting toxicity (DLT). They concluded that the higher does could be delivered with acceptable toxicity and produce outcomes similar to patients with peripheral disease. Phase II efficacy results are based on the patients treated at the two higher dose levels. The median follow-up was 33 months for the 11.5 Gy/# cohort and 29.8 months for the 12 Gy/# cohort. Late grade three or higher toxicities attributed to SABR were two grade five toxicities for the 11.5 Gy/# cohort and in the 12 Gy/# cohort, three grade three toxicities. Two-year local control in the 11.5 Gy/# cohort was 89.4% and in the 12 Gy/# cohort was 87.7%. In summary, the toxicity in the 71 patients treated at the two highest dose levels in this trial was acceptable and the local control and outcomes data comparable to SABR results in peripherally located early stage NSCLC.

There is even less evidence describing outcome for higher risk centrally located NSCLC or ultracentral tumours. In these patients there is significant

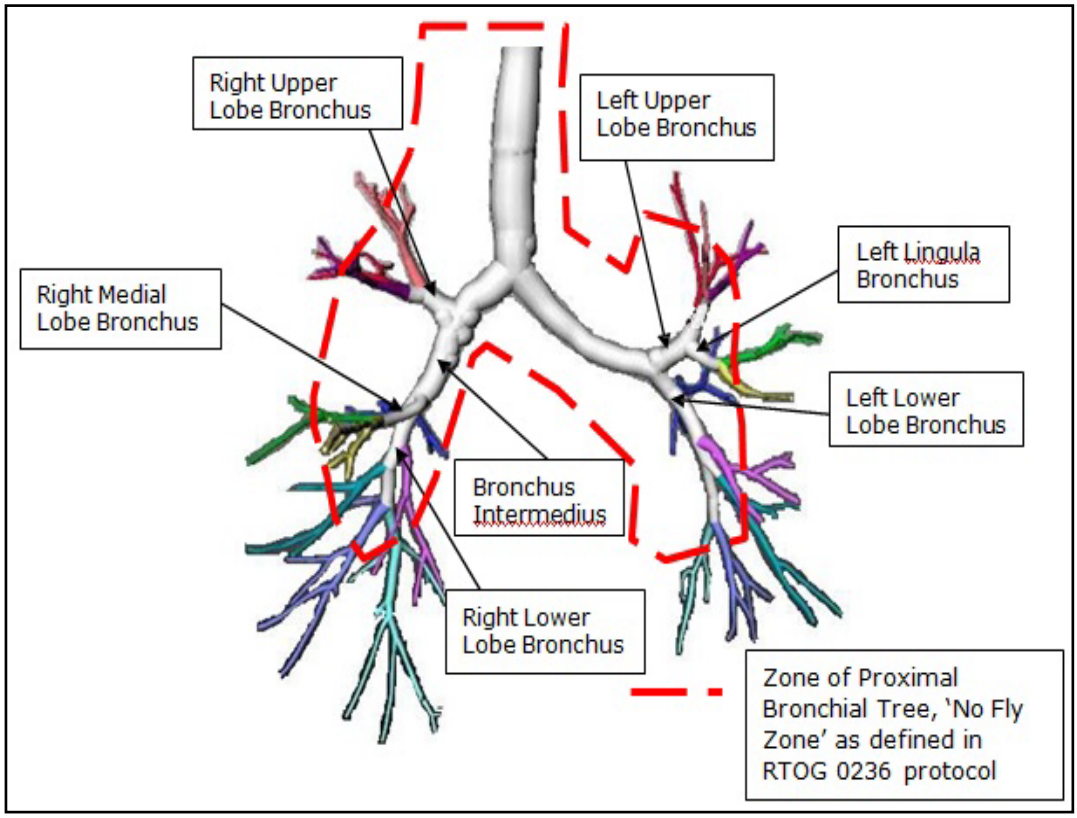

Figure 1: 'No Fly Zone' of the Proximal Bronchial Tree

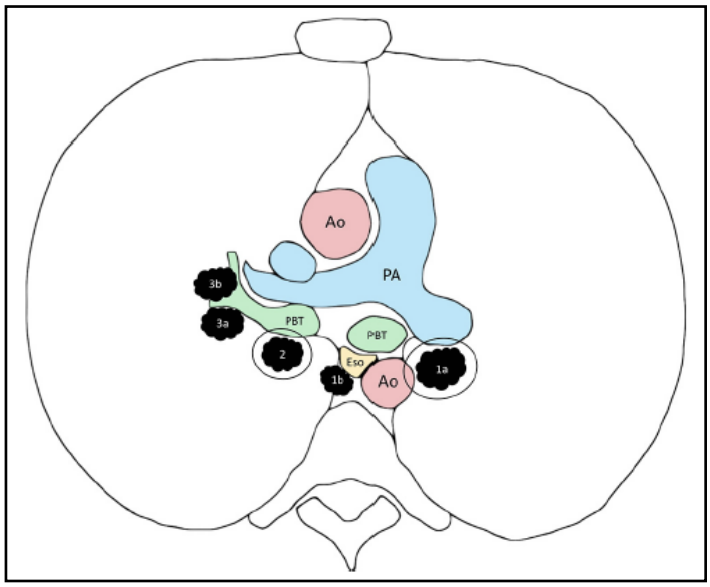

Figure 2: Illustration of the most common definitions of ultra-central among studies. Ao, aorta; PA, pulmonary artery; PBT, proximal bronchial tree; Eso, esophagus. 1a, volumeexpansion on tumor involves non-PBT central strustures (aorta, pulmonary vessels or esophagus); 1b, tumor abuts non-PBT central structures; 2, volume expansion on tumor involves the PBT, 3a: tumor abuts the PBT; 3b, tumor directly invades the PBT.

overlapping of the target with the main central airway or mediastinal structures. (Figure 2)

A systematic review of published studies of SABR for such ultracentral lung cancers reported median grade ≥3 toxicity of 10% (0 – 50%) which was most commonly pulmonary haemorrhage and treatment-related mortality was 5% (0 – 22%). High risk features for SABR related mortality included gross endobronchial disease, a high maximum dose to the proximal bronchial tree ≥ 180 Gy3 and use of peri-SABR bevacizumab, antiplatelet or anticoagulant use. Local control was high at 2 years was 92% (57 – 100%). Consequentially, major international collaborative groups do not recommend the use of SABR for ultracentral lung cancers outside of a clinical trial.

There are currently two trials preparing to investigate this. SUNSET is a Canadian study attempting to determine the maximum tolerated dose for ultracentral NSCLC. This is based on the anatomic definition of ultracentral where the PTV touches or overlaps with the central bronchial tree, oesophagus, pulmonary vein or artery. The second is the Cancer Trials Ireland sponsored SOURCE LUNG (Stereotactic Ablative Radiation Therapy Of UltRacentral Non-Small CEll LUNG Cancer) phase II CTRIAL-IE 18-33 study.

A key and novel concept of CTRIAL-IE 18-33 SOURCE LUNG is that the definition of an ultracentrally located tumour is not considered from an anatomical perspective as mentioned previously and used in other trials. The definition proposed by our group is based on organ at risk dose volume histogram safety constraints as those who are not fulfilling the conservative hybrid safety constraints of the LungTech and RTOG 0813 studies with full dose coverage. Patients with anatomically defined central lung tumours whereby the conventional central lung safety constraints are not met will be defined as ultracentral and deemed eligible for this study. Figure 3 is a pictorial demonstration showing the high radiotherapy dose in colour wash undercovering the target (red line) but protecting the central airway (yellow arrow).

Using the most up to date imaging and delivery of SABR to the central lung, the goal for this study is to determine the safety of the 8 x 7.5 Gy treatment regimen on the basis of the rate of ≥ Grade 3 treatment-related adverse events occurring between the start of RT and one year post-RT, which are possibly, probably or definitely related to treatment.

For this study, patients with central tumours not fulfilling the conservative hybrid safety constraints of the central lung trial while achieving full dose coverage will be entered into this single arm non-randomised study. Organ at risk constraints must still be respected but an intentional lower minimum dose will be allowed, using dose intensity modulation. These minimums are chosen to represent at least an equivalent biological effective dose to the RT standard fractionation of 60 Gy in 30 fractions.

Secondary objective of this study include:

1. To estimate freedom from local failure, local failure-free survival, disease-free survival and metastasis-free survival rates.
2. To estimate OS.
3. To evaluate post treatment response and outcomes using CT and PET
4. To assess acute toxicities
5. To assess late toxicities
6. To assess time to onset of acute and late ≥ Grade 2 and ≥ Grade 3 toxicities
7. To assess tolerability and feasibility of treatment
8. To assess pulmonary function changes
9. To evaluate change from baseline in quality of life at 6 months post-treatment
10. To determine overall survival in patients who become ineligible (if safety constraints cannot be met) for the trial following registration

Based on the results of previous retrospective studies, it is expected that at most 38% patients will experience a ≥ Grade 3 treatment-related adverse events (TxR-AE) by the end of 1 year after completion of treatment. In the first stage, 91 evaluable patients will be accrued. If there are 35 or fewer ≥ Grade 3 TxR-AEs in these 91 evaluable patients, the study will be stopped, and it will be concluded that the regime is not unsafe. If there are 43 or more ≥ Grade 3 TxR-AEs in 91 evaluable patients, the study will be stopped, and the conclusion will be made that the regime is not safe. Otherwise, 87 additional evaluable patients will be accrued for a total of 178 evaluable patients. The conclusion will be made that the regime is not safe if 78 or more TxR-AEs are observed in 178 evaluable patients.

This Irish trial, due to commence accrual in 2020, has enormous potential to influence international practice and answer a current unknown in terms of safety and efficacy. This is turn will provide patients with potentially superior treatment to the current standard.

https://clinicaltrials.gov/ct2/show/NCT04375904

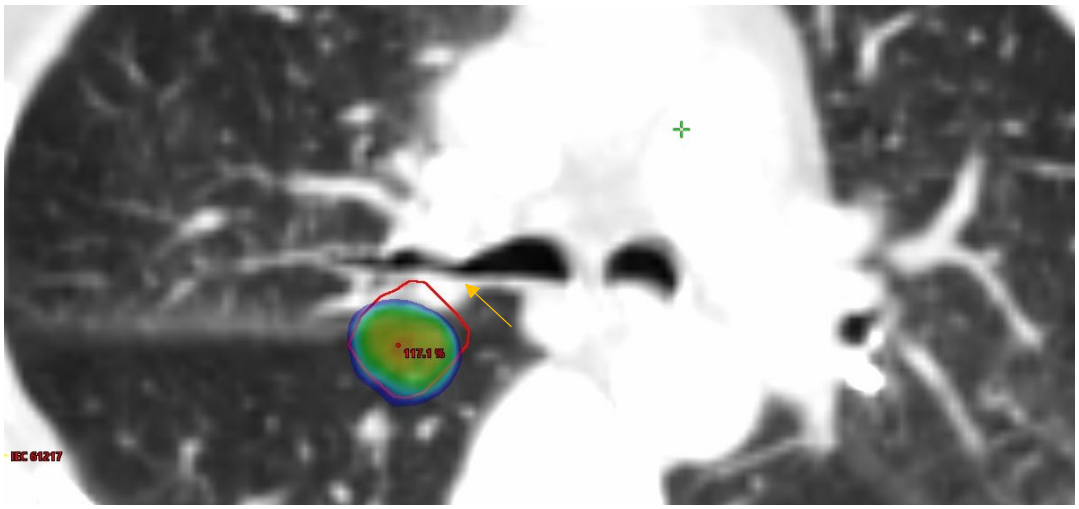

Figure 3