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

Cons: 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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Treating medically inoperable patients with T2N0 NSCLC central in the lung hilus by stereotactic body radiotherapy (SBRT) is a promising treatment option. Unfortunately, solid dose and volume related toxicity data are presently lacking, so that risk estimation for severe toxicities is difficult, while we simultaneously do not have evidence that such treatment would be more effective compared to conventional fractionated radiotherapy.

Why should we be concerned? Beyond the high rate of local control, the success of SBRT for peripheral lung tumors is related to a very low toxicity, as small volumes of fibrosis peripheral in the lung (a parallel structured organ) do mostly not lead to clinically relevant consequences. However, in or near the mediastinum, we are confronted with several serial organs (bronchi, large vessels, esophagus), whose small volume damage may result in clinically severe or even fatal toxicities (1). Evidence for this is found in series with conventionally fractionated radiotherapy or endobronchial brachytherapy. Although we are not completely sure that for high dose per fraction the LQ or LQL model is predictive after SBRT, such data may help to roughly assess the risk (2,3).

For conventionally fractionated radiotherapy, toxicity has been widely studied resulting in reliable models for e.g., radiation pneumonitis as a function of the mean lung dose (MLD) and the lung volume receiving more than a threshold dose (Vx). Borst *et al*. concluded that for high dose per fraction (up to 12 Gy per fraction), the linear quadratic LQ model with an α/β ratio of 3 Gy is the best method for converting the physical lung dose to predict radiation pneumonitis (4). In the context of central tumors, a recent dose escalation study published by Cannon *et al*. (5) with isotoxic planning of a 25 fraction radiotherapy regime, the prescribed dose being related to the risk of pneumonitis. A 5% rate of grade 4 and 5 complications was reported, when an EQD2 of 83 Gy (Dmax) to the central bronchial tree was exceeded. Interestingly, this dose equates to a BED10 of 100 Gy, just what would be necessary to locally control tumors by SBRT. These data do well illustrate the tightrope walk, which we face here: needing a tumor-BED sharply at the risk border to severe toxicities, there is not much room for dose inhomogeneities affecting neighboring serial normal tissues.

In general, patients with central tumors have an increased risk of dying due to a fatal pulmonary hemorrhage. Langendijk *et al*. retrospectively analyzed a large cohort

of patients treated for lung cancer to investigate whether endobronchial brachytherapy was a risk factor for fatal bleedings. He analyzed if patients were potential candidates for endobronchial brachytherapy and he selected in this way patients with central tumors. An average fatal bleeding risk of 10.8% in 938 patients, treated with RT and/or brachytherapy was reported (6). The majority of patients were treated with radical conventional RT alone (EQD2, 61.6-72 Gy). Almost half of the 840 patients had bronchoscopy-proven endobronchial tumor in the proximal airways. In this group, the incidence of a fatal bleeding was 13.1%. The multivariate analyses highlighted the presence of endobronchial tumor (central location) as a significant risk factor, as well as the fraction size of brachytherapy. When a single dose of 15 Gy brachytherapy was used, 47.8% died from massive haemoptysis. Since the large blood vessels are in close vicinity to the bronchi a high dose per fraction (single fraction of 15 Gy) had disastrous results. Beyond normal tissue damage, this may be related to simultaneous tumor invasion of both the bronchus and the vessel: in such a situation, fast tumor shrinkage without the chance for normal tissue re-organization will almost inadvertently be fatal.

The classic principle of radiation treatment is, that normal tissue tolerances are defined by an interaction of total dose, dose per fraction, overall treatment time, type of radiation and the volume treated: serial organ structure versus parallel organ structure. Although the lungs are parallel organs, bronchi and vessels are not, meaning that damage centrally will have a huge impact on the functioning of the ipsilateral lung as a whole. This might be catastrophic especially for medically inoperable patients if the lung tissue peripheral from the damage is eliminated.

Scheenstra *et al*. (7) modeled the relation between local dose and perfusion reduction in lung cancer patients with peripheral lung tumors (>2 cm distance from bronchial tree) treated with SABR. This relation showed a plateau for doses >100 Gy. The relative perfusion reduction was continuously increasing from 4 months up to 15 months after SABR caused by further development of late damage. Reperfusion was not observed. Especially in medically inoperable patients the local perfusion reduction correlates with lung ventilation and is considered to be a surrogate for pulmonary function decline.

We need to speculate whether the perfusion loss seen for peripheral tumors after SABR is also applicable to centrally located tumors. After conventionally fractionated RT we previously reported on reperfusion due to tumor shrinkage of larger and more centrally located tumors (8). So, by conventionally fractionated radiotherapy we might improve the perfusion and pulmonary function, if we treat a patient with a T2N0M0 non-small cell lung cancer located centrally in the lung hilus that compresses a large blood vessel.

In the light of all this evidence, the toxicity rates reported for SABR of central tumors appear surprisingly low. However, as can be seen in the comprehensive review by Senthi *et al*. (9), most of these data come from retrospective mono-center series or case reports. Still, fatal toxicities have been reported with deaths from fatal bleeding, esophageal ulceration and bronchial stenosis/necrosis with subsequent fatal pneumonia (3,10-17). However, due to the mainly retrospective character of the reports, the numbers of cases at risk for certain toxicity are not available. Therefore dose effect relations for toxicity models on hypo-fractionated schedules of centrally located tumors cannot be derived from these data.

Almost all data on SBRT is on medically inoperable patients. A medically inoperable patient is generally of high biological age and fragile, with reduced lung function before treatment because of COPD, intra-thoracic tumor or because they are heavy smokers. Due to the comorbidities causing inoperability, deaths e.g., caused by pulmonary reasons will not automatically be attributed to SBRT toxicity and even sudden deaths will rather be interpreted as consequences of heart disease.

With the paucity of prospective data, the low reported rates of severe toxicities from the SBRT series might also be the result of thorough patient selection in experienced centers.

The situation of a "central tumor in the lung hilus" may imply or not imply an overlap of the PTV with the central airways. The majority of patients reported with "central" SBRT may have target volumes not involving the central bronchial tree, as at least in some of the available publications, the term "central" is rather related to the neighborhood of any part of the mediastinum. Experienced centers and current clinical trial protocols apply tight dose constraints to the central airways and exclude cases with "very central tumors" (18).

Considering the potential indication for a new treatment, a high risk for toxicity would only be justified by a clearly higher effectiveness of new versus conventional treatment or by other factors leading to a clear benefit for the patient. With convincing local control data on SBRT in peripheral tumors, clinical practice has been rapidly changed in

favor of short treatment time and patient's convenience. However, to date there is only one prospective randomized trial investigating SBRT *vs*. conventional fractionation, which showed no advantage of SBRT in terms of local control and survival (19). Retrospective data from a German database furthermore showed that SBRT in central tumors if performed with reduced dose—as a potential result from toxicity concerns—may result in worse outcome as compared to peripheral SBRT (20).

Obviously, the advantages of short overall treatment time and patients convenience do also apply for SBRT in central tumors. In order to provide well established standards for safe application of this treatment, we urgently need larger databases with prospective multicenter data, where we can relate local doses and volumes to well documented toxicities. Therefore, the conduction of quality assured prospective trials with fixed inclusion criteria and thorough follow up are obligatory. The aim to evaluate the use of SBRT also for operable patients in the future furthermore stresses the need for such evidence. It is the task of us as radiation oncology community to do systematic and thorough investigations about the chances and risks of SBRT in central tumors in prospective trials. Based on validly standardized methods, the discussion with the opponents of SBRT will be much easier than on the base of retrospective data.

Overall, we think that SBRT for a medically inoperable case with a T2N0M0 NSCLC in the hilum might be an attractive option in the near future. However, in order to characterize effectiveness and toxicity profiles for future patients in a standardized setting and to elaborate clear procedures for patient selection, planning and conduction of this treatment, more prospective data must be collected before it can be recommended to the general radiation oncology community.

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Footnote

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

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