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COMMENTARY

The role of technology in clinical trials using stereotactic body radiotherapy

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ABSTRACT

Stereotactic body radiotherapy is a highly technology-driven treatment modality. The wider availability of in-room imaging and advanced radiotherapy delivery techniques has led to more institutions offering stereotactic ablative therapy (SABR). While some technological challenges remain, the crucial point for the next generation of SABR clinical trials is that today's technology is used correctly and close to its optimal potential for accuracy. The credentialing procedure of SABR needs to be extensive, but this investment will benefit the trial itself, the patients and the professionals involved.

COMMENTARY

Radiotherapy is a highly technology-driven treatment modality for patients with cancer, and few treatments are as technology intensive as stereotactic procedures. Yet, technological advances can move slowly: it took over 15 years from the first intracranial stereotactic treatment in the mid-1970s[1] to using the same approach in the thorax and abdomen.[2] From its introduction, pioneers of this stereotactic body radiotherapy [recently also called stereotactic ablative therapy (SABR)] were aware of the challenges of interfraction and intrafraction motion mainly due to respiration. The stereotactic body frame introduced by Lax et al[3] had the dual purpose of providing patient and tumour immobilization as well as an innovative way to transfer the information of the tumour position from the pre-treatment CTs to the treatment couch.

Today, in-room imaging has made the verification of patient (and target) position easier and more efficient. Faster treatment deliveries (volumetric-modulated arc therapy) have also resulted in a more comfortable procedure, accessible to patients who are frailer. External reference frames have been replaced by chest boards and vacuum fixing technology. In addition to the reliability of the treatment, its cost efficiency has made it a viable alternative to surgery for new patient groups, such as patients with Stage 1 non-small-cell lung cancer.[4]

A typical lung SABR treatment in 2005 involved three-dimensional (3D) planning CT with fluoroscopy, daily treatment CTs (on rail if available, otherwise in a separate room) and a stereotactic body frame, possibly with abdominal compression to reduce respiratory tumour motion. Today, four-dimensional CT and daily cone-beam CT are widely available and constitute the state of the art in thoracic and abdominal treatments, together with robotic treatment units (such as the CyberKnife) that feature tumour tracking. These imaging capabilities, along with improvements in dose calculation software, have translated into a more reliable delivery of the dose to the tumour and have enabled confirming a clear relationship between prescribed dose and local control for Stage I non-small-cell lung cancer.[5,6] The wider availability of technology has led to more and more institutions offering SABR: treatments are reaching the community hospital setting and are no longer limited to large academic centres.

While minimal technological requirements are definitely needed to ensure a certain quality and consistency of outcome amongst institutions participating in a clinical trial, this does not necessarily mean that a multi-institutional trial should enforce a uniform technological approach. A careful selection of technological approaches is necessary to achieve a balance between ensuring a high quality of treatment delivery and allowing the desired number of institutions to enter the trial. For example, the new Lungtech trial[7] will allow for gating and tracking as alternatives to a more common "internal target volume" approach. The already accruing Radiation Therapy Oncology Group 1112 (NTC01730937) allows for treatment delivery using 3D conformal radiotherapy, intensity-modulated radiotherapy or protons for primary liver cancer. These modalities will lead to different dose

distributions to organs at risk (OARs). However, this can also be an advantage if one of the end points of the trial is to investigate toxicity: variations in dose distributions may provide a spread in data points on which to build a dose–response relationship.

Can technology improve SABR treatments further? Undoubtedly, some technical challenges remain in ensuring the highest geometric accuracy in treatment delivery, and solutions may be worthwhile for the short SABR treatment schemes where inaccuracies during one fraction cannot easily be compensated in the remaining fractions. Adaptive radiotherapy (ART) to cope with anatomy deformations, particle therapy for reduction of OAR dose delivery and management of intrafraction motion are sophisticated novel technologies attracting most attention. ART has shown advantages for liver SABR in a simulation study,[8] and particle therapy has been investigated for limited numbers of patients.[9] Tomosynthesis is a promising technique where 3D images can be reconstructed over a limited range of acquisition angles (*i.e.* a short acquisition time):[10,11] when it becomes clinically available, it would offer a pragmatic way of monitoring the position of the target during treatment delivery. Tumour motion tracking for coping with intrafraction motion has been commercially available for two decades. While previously limited to dedicated treatment machines such as the CyberKnife[12] and the Vero,[13] tumour motion tracking has recently been delivered on a standard C-arm gantry linear accelerator.[14] Although ART, particle therapy and advanced intrafraction motion management may improve treatment accuracy, there is no clinical evidence that they should constitute a technological requirement to deliver a high-quality SABR treatment, or a condition for participation in clinical trials.

So what is the next technical frontier in clinical trials on SABR? The most likely answer is: quality assurance (QA). Clinical trial QA is frequently underrated because it is a time-consuming, often tedious process compared with routine clinical practice, and it increases the level of documentation. As such, it might discourage some clinical investigators. Yet, a recent systematic review highlighted the importance of clinical trial QA and the link between protocol violations and treatment outcome:[15] in these (non-SABR) trials, the rate of major radiotherapy deviations ranged from 11% to 48%. According to the authors, these deviations may have masked the potential benefits of the treatments investigated but may also have adversely affected the outcome of individual patients. Considering the high doses delivered in SABR in only a few treatment fractions, we argue that a thorough QA programme should be of high priority in SABR clinical trials.

Recent SABR clinical trials have embraced this high level of pre-trial as well as prospective QA with central reviews of the treatment plans delivered at each institution: these can include external audit of the output of the linear accelerator (*Tr*ansarterial Chemoembolization with Drug-*Eluti*ng Bea*d*s versus Stereotactic Body Radiation Therapy for hepatocellular carcinoma "TRENDY" NCT02470533), central review of the dose distributions before treatment start (TRENDY), central approval of the planning target volume margin calculation recipe (TRENDY) and information about the frequency of essential quality control checks of image guidance and respiratory control equipment ("RAS01" NCT01233544). As an example, the RAS01 trial not only requires the use of "daily image-guided radiotherapy", it asks for documentation about the periodic verification of the concordance of the planning isocentre with the delivery isocentre ("Winston–Lutz" tests) and the imaging isocentre, as this directly affects the accuracy of the dose delivery. An overview of SABR QA has recently be presented by Solberg et al[16] and suggests that high-quality QA instruments are needed to allow high-quality thresholds in the accreditation of centres interested in trial participation. For example, because of the high demands on geometrical accuracy, the distance-to-agreement parameter in dosimetric γ-analyses should be within 2 mm, preferentially 1 mm as opposed to the standard of 3 mm in non-SABR treatments.

There are still many challenges in SABR clinical trials which technology cannot directly address. The lack of standards in normalization and prescription of the heterogeneous dose distribution is perhaps the clearest example, and guidelines on this point are being developed. More detailed reporting on dose distributions not only in the tumour but also in the OARs is essential to be able to compare results. The present state-of-the-art technology (four-dimensional CT, cone-beam CT, tracking etc.) is not SABR specific and is now widely available: the crucial point for the next generation of SABR clinical trials is that this technology will be used correctly and close to its optimal potential for accuracy. The credentialing procedure of SABR needs to be extensive, but this investment will benefit the trial itself, the patients and the professionals involved. The ultimate goal is to achieve a robust trial, with patients treated following predefined criteria for planning and delivery and reported outcomes that can be compared and/or validated in other patient groups.

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