



Spotlight

Is reducing irradiated margins key to improving outcomes for radiotherapy?

Opening opinion: Yes

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For the **International Commission on Radiation Units and Measurements Report** see *JICRU* 2010; **10**: Report83

For more on the **impact of radiotherapy protocol compliance on cancer outcomes** see *J Clin Oncol* 2010; **28**: 2996–3001

For more on the **over-reduction of margins** see *Int J Radiat Oncol Biol Phys* 2009; **74**: 388–91

For more on **study of directional dosing towards the heart** see *Int J Radiat Oncol Biol Phys* 2018; **102**: 434–42

For more on **margin-less treatment planning systems** see *Phys Med Biol* 2013; **58**: 3563–80

Medical practice is full of uncertainties and the delivery of radiotherapy to treat cancer is no exception. These uncertainties are accounted for by adding margins to ensure effective radiotherapy delivery. Cancers are imaged, delineated, and margins added: the gross tumour volume is first expanded with a margin to produce a clinical target volume (CTV) to account for invisible tumour spread, and then to the planning target volume (PTV) to account for tumour movement during the course of treatment. The planning system then automatically shapes the radiation dose to focus on the PTV, while avoiding surrounding healthy organs. The process requires user-defined dose requirements (ie, dose constraints) for the PTV and surrounding healthy organs.

According to the International Commission on Radiation Units and Measurements Report 83, which is the most recent photon radiotherapy report from 2010, PTV is “the recommended tool to shape absorbed-dose distributions to ensure that the prescribed absorbed dose will actually be delivered to all parts of the CTV with a clinically acceptable probability...It surrounds the representation of the CTV with a margin...”.

We argue that margins are no longer the best tool to shape dose distributions to account for uncertainties in radiotherapy delivery in an era of modern radiotherapy treatment; instead, smarter tools are needed. Tumour movement generally no longer limits treatment accuracy. The introduction of image-guided therapy, which uses CT or MRI scans taken immediately before treatment, has caused a step-change improvement in the accuracy of treatment delivery. As a result, tumour motion can be corrected at every radiotherapy fraction. Despite this practice, there is no evidence to suggest that omitting margins is now possible, while some data even show detrimental effects of observer and clinical practice variation in the era of small margins.

Medical or biological uncertainties currently restrict the accuracy of radiotherapy treatment, and these uncertainties cannot be safeguarded against with the use of margins. For example, tumour delineation is affected by poor visibility of tumour boundaries. This

imaging limitation leads to unavoidable inter-observer and intra-observer contouring variation for which no margin equation is known and is frequently ignored. Additionally, dose requirements are uncertain and evidence for them is typically based on now obsolete forms of radiotherapy, such as two-dimensional planar radiotherapy. Ignoring these uncertainties can lead to poorer outcomes with improved accuracy because margins are over reduced. When it comes to radiotherapy treatment, small changes in treatment delivery can have big effects on outcomes; for example, one study showed that a very small directional shift of the dose towards the heart had a significant effect on survival for patients with lung cancer. In short, our knowledge of radiotherapy dose requirements is incomplete.

Clinical trials of radiotherapy guide major treatment choices such as prescription dose. However, the high number of dose requirements used in modern radiotherapy treatment planning hinders their evaluation in clinical trials. Using big data analysis, knowledge of factors such as tumour spread or normal tissue toxicity can be gathered. Nevertheless, planning parameters derived from such data are, and will remain, of insufficient quality. For instance, small numbers of events or the incomplete understanding of confounding factors will lead to models with many uncertainties. In our opinion, these uncertainties must be acknowledged and quantified; in other words, all treatment planning parameters must have error bars.

Smarter tools that account directly for these uncertainties during treatment planning are being developed and should become the new standard of care for radiotherapy. Imagine a treatment planning system where the planner specifies the required probability of tumour control and the maximum acceptable probability of damage to the surrounding organs that is based on clinical expectations. The system would optimise treatment (ie, shape the distribution of the radiation dose) to the required probability on the basis of pre-inputted parameters. Such systems have been proposed, but the current models are not judged robust enough for clinical use. We propose including error bars on all parameters used in radiotherapy treatment planning that explicitly convey that our knowledge (ie, dose requirements or the precise shape of the target volume) is incomplete. Planning systems based on probability assessments have been realised in research settings for uncertainties about the patients’ position, but have yet

to be developed for medical and biological uncertainties. The enormous advantage would be that even incomplete evidence (eg, data from small trials) could be used—the error bar would just be bigger. Such planning systems can incorporate medical knowledge to create treatment plans in a safe and rational way, which is compatible with the evidence to date.

In conclusion, modern radiotherapy must be planned smarter by moving away from margins to deal with uncertainties that are implicit to radiotherapy treatment. Uncertainties must be acknowledged and embraced to allow for the so-called continuous aggregation of marginal gains, and the future of radiotherapy must involve probabilistic planning.

Counter opinion: No

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Radiotherapy is a four-dimensional geometrical challenge. For modern radiotherapy planning, gross tumour volume (GTV) is pictured before treatment using CT scanning fused with anatomical and functional imaging. To account for microscopic tumour spread, a safety margin is added to the GTV and corrected for anatomical boundaries to determine the clinical target volume (CTV). Finally, systematic and random errors occurring during the fractionated course of radiotherapy are corrected for by adding another safety margin. Together, these measures constitute the planning target volume (PTV).

Over the past two decades, advances from planar x-ray-based 2D and 3D-radiation treatment planning, in which plans are only calculated from pretreatment imaging, have resulted in an increasingly accurate definition of planning treatment volume and improved local tumour control. However, radiation oncologists are currently faced with the burden of additional information on changes of the irradiated volume during treatment, since modern linear accelerators are equipped with on-board, x-ray-based imaging. Integrated magnetic resonance-linear accelerators (MR-LINAC) have become commercially available, allowing for real-time intra-fractional imaging during radiotherapy. On the basis of these images, radiation oncologists have started modifying target tumour volumes that change appearance during treatment. I argue that any changes to the target volume done during radiotherapy should be done extremely cautiously, since we should not jeopardise the excellent outcomes that have been achieved by modern radiotherapeutic methods.

Radiotherapy without quality assurance could lead to detrimental outcomes, as reported by the phase 3 TROG

02.02 trial, which showed the crucial importance of radiotherapy quality on chemoradiotherapy outcomes for patients with head and neck cancer. In a secondary analysis, it turned out that poor radiation treatment plans drastically affected freedom from locoregional failure and possibly led to negative study results.

Most certainly, daily pretreatment or even intra-fractional imaging allows for the reduction of random setup errors, and thus the planning treatment volumes are reduced. This smaller target volume reduces the dose to surrounding normal tissues and the organs at risk. Therefore, imaging might even allow for increased radiation dose while maintaining the complication probability for normal tissue. However, although this proposal sounds logical and highly appealing, changing the target volumes during treatment has only been studied in localised prostate cancer and a few other tumour sites. One recent study in patients with head and neck squamous cell carcinoma (HNSCC) showed that acute side-effects of radiation were reduced by shrinking the PTV margin when using daily cone-beam CT imaging, with freedom from locoregional failure and overall survival outcomes remaining unchanged. Previous research in patients with non-small-cell lung cancer (NSCLC) reported increased freedom from locoregional failure with identical incidence of severe pneumonitis in patients treated with image-guided radiotherapy and reduced PTV margins compared with radiotherapy according to current clinical practice. These preliminary results support the idea of reducing planning treatment volume margins, even though these margins need to be calculated by each treating centre and for each body site.

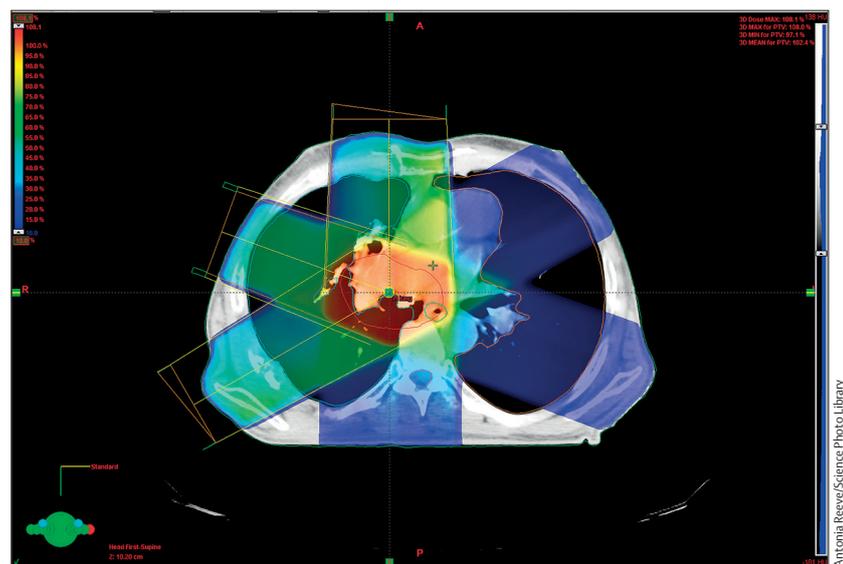
What about the GTV and CTV? With the increasing availability of daily imaging methods, radiation oncologists are tempted to adapt and reduce the GTV

EGCT declares no competing interests.

For more on **reducing PTV with cone beam CT** see *Radiother Oncol* 2019; **130**: 25–31

For more on the **uncertainties of the clinical target volume** see *Clin Transl Radiat Oncol* 2017; **3**: 1–8

For more on the **disagreement between HNSCC and NSCLC experts** see *Acta Oncol* 2019; 1–8



and subsequently add those CTV and PTV margins, which have been chosen pretherapeutically. Since the GTV is visible on imaging, I fully agree with wanting its reduction. However, as opposed to GTV and the PTV, little is known about microscopic tumour extension, or in other words, the clinical target volume, before treatment and even less is known during treatment. Additionally, experts in the fields of HNSCC and NSCLC disagree regarding the GTV and CTV prior to and during radio(chemo)therapy. Therefore, I believe that PTV margins could be altered in experienced treating centres, capable of measuring the required positioning margins. Additionally, more information is urgently needed on microscopic tumour extension, particularly during treatment. Only by finding out more information can we be certain that CTV reduction is feasible and does not lead to clonogenic tumour cells receiving insufficient dose, possibly resulting in local failure. Since tumour cell density decreases with increasing distance from the GTV,

probabilistic planning approaches resulting in reduced doses towards the periphery of the CTV and thus PTV could well be explored.

The considerations I have discussed so far have been about highly conformal photon-based radiotherapy. However, charged particles are increasingly being used in radiotherapy and their implication towards margins needs to be discussed. Proton therapy is characterised by steep dose gradients, which are used to avoid irradiating normal tissues. Still, plans for proton treatment are made on the basis of the CTV. Thus, adapting the CTV of diffusely infiltrating tumours treated by proton beam therapy could lead to even lower radiation doses than with photons and thus potentially to worse outcomes.

Therefore, I firmly believe that we ought to treat patients, in whom we adapt margins for either photons or protons or do probabilistic planning, in prospective (registered) studies to evaluate both tumour control and toxicity, as well as possible sites of local failure.