What is the best way to evaluate clinical target volume for radiotherapy of brain tumors?

“Volume definition (for targets and organs at risk) is essential for the success of radiotherapy treatment planning, where it plays a crucial role in the complete eradication of the disease without toxic effects on healthy tissue.”

Alba Fiorentino^{*1}, Piernicola Pedicini¹, Rocchina Caivano¹
& Vincenzo Fusco¹

Over the last few decades, the goal of understanding dosing and protection of surrounding normal tissue during radiotherapy (RT) has improved. To date, technological development in RT has been focused on achieving a better definition of the tumor/target to increase the therapeutic efficacy.

Volume definition (for targets and organs at risk [OAR]) is essential for the success of RT treatment planning, where it plays a crucial role in the complete eradication of the disease without toxic effects on healthy tissue. Computed tomography (CT) remains the only imaging modality used for dose calculation in RT treatment planning, despite the existence of other imaging modalities, such as MRI and PET, which are important in the detection of the target.

Several studies have analyzed the importance of the definition of tumors and OAR [1–6], and the impact of various CT slice thicknesses on the identification of clinical target volume (CTV) has been assessed in terms of volume and dose reconstruction algorithms for RT planning [7,8].

However, all of the RT processes are based on CT, so slice thickness affects

not only the CTV, but also OAR definition, quality of reconstructed images in all planes (sagittal, coronal and axial), digitally reconstructed radiographs, treatment planning system beam's-eye view and the dose–volume histogram. Moreover, as RT techniques are more sensitive to geometric uncertainties due to their sharper dose gradients around the target volume and OAR, or severe hypofractionations, such as intensity-modulated RT (IMRT), stereotactic RT or brachytherapy, the volume definition becomes much more important [9,10].

The Photon Treatment Planning Collaborative Work Group recommended a CT slice thickness in the range of 3–5 mm for the head and 5–10 mm for the body to obtain an accurate definition of the inferior and superior borders of the CTV, this suggests that further studies in the CT slice thickness optimization are required [11].

A CT scanner has the availability of different slice thicknesses (from one- to several millimeters); it is, therefore, useful to choose the optimum slice thickness for treatment planning based on the tumor localization, with respect to the treatment purpose (palliative or curative). Larger slice thickness may miss part of the considered

“...it is clear that owing to the aggressiveness of brain tumors and the role of the brain, the issue concerning the correct way to delineate the radiotherapy target of brain tumors should remain a key focus...”

¹IRCCS CROB, Radiotherapy Oncology Department, via San Pio 1, 85028, Rionero in Vulture (Potenza), Italy

^{*}Author for correspondence: Tel.: +39 0972 726480; alba.fiorentino@hotmail.it

organ tissue, whereas smaller slice thickness helps to capture more tissues of a given organ, although it is not always necessary.

A phantom study conducted by Somigliana *et al.*, which used spherical volumes, showed that for targets less than 1.5 cm in diameter, it is reasonable to acquire CT images with the smallest thickness available [12]. For 3D conformal RT treatment planning, the authors also recommended a 4- and 8–10-mm CT slice thickness for targets 1.5–3 cm and greater than 4 cm in diameter, respectively. Another phantom study showed that for 3D conformal RT treatment planning of brain tumors, a CT slice thickness of 2.5 mm is essential for a tumor volume less than 25 cc, while a CT slice thickness of 5 mm is optimum for a tumor volume greater than 25 cc [7]. The phantom studies reported in the literature have been conducted in terms of partial volume effect, radiographic contrast and accuracy of CT volume reconstruction [7,12–14].

Considering the lack of patient data in the literature about this issue, in our institution, a computational study was conducted to investigate the impact of CT slice thickness on the dose coverage of the target volume in patients affected by primary or metastatic brain tumors. This anatomical site was selected because, based on the tumor size, all RT techniques can be used for brain tumors (from conformal RT to stereotactic RT or IMRT) with different purposes (palliative or curative).

Thus, for six patients, six target volumes were delineated with different sizes (2.5, 4, 10, 25, 50 and 100 cm³) and copied slice by slice on the CT at various slice thickness (1, 2, 4, 6 and 10 mm) for each patient. The target volumes, from 2.5 to 25 cm³, were contoured simulating small or large brain metastases treatable with stereotactic techniques, while the others represented primitive brain tumors, such as high-grade gliomas, treatable with 3D conformal or IMRT techniques [15]. RT plans were made optimizing the dose coverage of the target without taking into account any OAR.

The data show that the estimated size of the target volumes was reduced when the CT slice thickness was increased. This volume reduction was not significant between 1- and 2-mm CT slice thickness and no differences in terms of dose target coverage were found. Differences in terms of volume were significant between 1 and 10-mm CT slice thicknesses for all the target volumes. This result highlights that 10-mm CT

should not be used. RT slice thicknesses such as 4 and 6 mm should not be used for small CTVs (up to 10 cm³) due to the loss of volume definition and relative target coverage. However, for larger volumes, 4- and 6-mm CT slice thickness could be used independently. Overall, it was found that a greater CTV were less affected by the choice of CT slice thickness.

In conclusion, small targets (up to 25 cm³), such as those typically treated with stereotactic techniques, require the option of very small slice thickness (1–2 mm), for targets larger than 25 cm³, such as those treatable with 3D conformal RT or IMRT, 4–6-mm CT slice thickness could be used, while 10-mm CT slice thickness should never be used.

Imaging plays a key role in RT treatment planning, which has a direct impact on tumor volume delineation as well as the final treatment outcome, but the accuracy of RT tumor volume definition depends not only on CT slice thickness in brain tumors, but also on the use of other imaging modalities, such as MRI and PET [16].

In high-grade gliomas, the introduction of CT simulation increased the CTV definition accuracy, although the MRI superiority, and postoperative T1-weighted MRI should be preferred for planning purposes [17]. Several studies showed the significant increase of volume when fusion CT/MRI was used to delineate the targets ($p < 0.001$) [16,18,19]. A recent analysis conducted on 120 target volumes (delineated both on CT and fusion CT/MRI images) and 30 RT plans, showed that in the target volume delineation for the glioblastoma RT plan, fusion CT/MRI was preferred. When the CTV was contoured on CT only, the healthy tissue included in the CTV was only 8% and this did not increase the risk of side effects, however, CT was only insufficient in the tumor delineation; in fact, 20% of target volume delineated on MRI was missed (mean: 49 cm³) and not covered by radical RT dose [16].

Rieken *et al.* investigated volumetric size and uniformity of O-(2-[¹⁸F]fluoroethyl)-L-tyrosine-PET/CT- versus MRI-derived tumor volumes of 41 glioma patients. Results showed that combined modality-derived volumes were significantly enlarged: MRI missed 17% of target delineated by O-(2-[¹⁸F]fluoroethyl)-L-tyrosine-PET/CT [20].

Overall, it is clear that owing to the aggressiveness of brain tumors and the role of the brain, the issue concerning the correct way to

“Imaging plays a key role in radiotherapy treatment planning, which has a direct impact on tumor volume delineation as well as the final treatment outcome...”

delineate the RT target of brain tumors should remain a key focus owing to the risk of missing the target and increasing toxic effects.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a

financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

- Dutreix A. When and how we can improve precision in radiotherapy? *Radiother. Oncol.* 2, 275–292 (1984).
- Mah K, Van Dyk J, Keane T, Poon PY. Acute radiation-induced pulmonary damage: a clinical study on the response to fractionated radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* 13, 179–188 (1987).
- Determination of Absorbed Dose in a Patient Irradiated by Beams of X or Gamma Rays in Radiotherapy Procedures*. International Commission on Radiation Units and Measurements, Bethesda MD, USA (1976).
- Mijnheer BJ, Batterman JJ, Wambersie A. What degree of accuracy is required and can be achieved in photon and neutron therapy? *Radiother. Oncol.* 8, 237–252 (1987).
- Schlegel W, Bortfeld T. A new approach for improved tumor volumetry. Presented at: *Proceedings of the XIIIth International Conference on the Use of Computers in Radiation Therapy*. Heidelberg, Germany, 22–25 May 2000.
- Jansen EP, Dewit LG, van Herk M, Bartelink H. Target volumes in radiotherapy for high-grade malignant glioma of the brain. *Radiother. Oncol.* 56, 151–156 (2000).
- Prabhakar R, Ganesh T, Rath GK *et al.* Impact of different ct slice thickness on clinical target volume for 3D conformal radiation therapy. *Med. Dosim.* 34, 36–41 (2009).
- Prionas ND, Ray S, Boone JM. Volume assessment accuracy in computed tomography: a phantom study. *J. Appl. Clin. Med. Phys.* 11(2), 3037 (2010).
- Pedicini P, Caivano R, Fiorentino A *et al.* Comparative dosimetric and radiobiological assessment among a nonstandard RapidArc, standard RapidArc, classical intensity-modulated radiotherapy, and 3D brachytherapy for the treatment of the vaginal vault in patients affected by gynecological cancer. *Med. Dosim.* 37(4), 347–352 (2012).
- Pedicini P, Strigari L, Caivano R *et al.* Local tumor control probability to evaluate an applicator-guided volumetricmodulated arc therapy solution as alternative of 3D brachytherapy for the treatment of the vaginal vault in patients affected by gynecological cancer. *J. Appl. Clin. Med. Phys.* 14(2), 4075 (2013).
- Three-dimensional photon treatment planning. Report of the Collaborative Working Group on the evaluation of treatment planning for external photon beam radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* 21, 1–265 (1991).
- Somigliana A, Zonca G, Loi G, Sichirollo AE. How thick should CT/MR slices be to plan conformal radiotherapy? A study on the accuracy of three-dimensional volume reconstruction. *Tumori* 82, 470–472 (1996).
- Plewes DB, Dean PB. The influence of partial volume averaging on sphere detectability in computed tomography. *Phys. Med. Biol.* 26, 913–919 (1981).
- Berthelet E, Liu M, Truong P *et al.* CT slice index and thickness: impact on organ contouring in radiation treatment planning for prostate cancer. *J. Appl. Clin. Med. Phys.* 4, 365–373 (2003).
- Caivano R, Fiorentino A, Pedicini P, Califano G, Fusco V. The impact of computed tomography slice thickness on the assessment of stereotactic, 3D conformal and intensity-modulated radiotherapy of brain tumors. *Clin. Transl. Oncol.* doi:10.1007/s12094-013-1111-4 (2013) (Epub ahead of print).
- Fiorentino A, Caivano R, Pedicini P, Fusco V. Clinical target volume definition for glioblastoma radiotherapy planning: magnetic resonance imaging and computed tomography. *Clin. Transl. Oncol.* 15(9), 754–758 (2013).
- Farace P, Giri MG, Meliado G *et al.* Clinical target volume delineation in glioblastomas: pre-operative versus post-operative/pre-radiotherapy MRI. *Br. J. Radiol.* 84, 271–278 (2011).
- Thornton AF Jr, Sandler HM, Ten Haken RK *et al.* The clinical utility of magnetic resonance imaging in 3-dimensional treatment planning of brain neoplasms. *Int. J. Radiat. Oncol. Biol. Phys.* 24, 767–775 (1992).
- Lattanzi JP, Fein DA, McNeeley SW *et al.* Computed tomographymagnetic resonance image fusion: a clinical evaluation of an innovative approach for improved tumor localization in primary central nervous system lesions. *Radiat. Oncol. Investig.* 5, 195–205 (1997).
- Rieken S, Habermehl D, Giesel FL *et al.* Analysis of FET-PET imaging for target volume definition in patients with gliomas treated with conformal radiotherapy. *Radiother. Oncol.* doi:10.1016/j.radonc.06.043 (2013) (Epub ahead of print).