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Original Article

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# Implications of contrast-enhanced CT-based and MRI-based target volume delineations in radiotherapy treatment planning for brain tumors

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ABSTRACT

Delineation of various target volumes using contrast-enhanced magnetic resonance imaging (MRI) and/or computed tomography (CT) constitutes the primary step for radiation therapy planning (RTP) in brain tumors. This study presents a quantification and comparative evaluation of the various clinical target volumes (CTV) and gross target volumes (GTV) as outlined by contrast-enhanced CT and MRI, along with its implications for postoperative radiotherapy of brain tumors.

Twenty-one patients of gliomas were considered for this prospective study. Peritumoral edema as CTV and residual tumor as GTV were delineated separately in postoperative contrast-enhanced CT and MRI. These volumes were estimated separately and their congruence studied for contrast-enhanced CT and MRI. Compared to MRI, CT underestimated the volumes, with significant differences seen in the mean CTV (mean ± SD: −62.92 ± 93.99 cc; $P = 0.006$) and GTV (mean ± SD: −21.08 ± 36.04 cc; $P = 0.014$). These differences were found to be significant for high-grade gliomas (CTV: $P = 0.045$; GTV: $P = 0.044$), while they were statistically insignificant for low-grade gliomas (CTV: $P = 0.080$; GTV: $P = 0.117$). The mean differences in the volumes for CTV and GTV were estimated to be −106.7% and −62.6%, respectively, taking the CT volumes as the baseline.

Thus, even though, electron density information from CT is essential for RTP, target delineation during postoperative radiotherapy of brain tumors, especially for high-grade tumors, should be based on MRI so as to avoid inadvertent geographical misses, especially in the regions of peritumoral edema.

KEY WORDS: Brain tumor, radiation therapy, target volumes, treatment planning

## INTRODUCTION

Postoperative irradiation for brain tumors is an accepted adjuvant treatment, especially for the higher grades of brain tumors.[1] Radiation portals are now restricted to partial brain irradiation (PBI) rather than whole brain. This is based on the evidences showing similar patterns of recurrence for both the treatment strategies.[2] However, with the use of PBI, it becomes important that the treatment portals be designed and placed to effectively include both residual tumor volume and the adjoining regions of brain parenchyma, which are likely to harbour microscopic disease.

Computed tomography (CT) and magnetic resonance imaging (MRI) have been the two cornerstones in the imaging of brain tumors. CT images provide valuable electron density information which is mandatory for radiation therapy dose calculations, but CT has its limitations as far as soft tissue contrast is concerned. This could lead to difficulty in accurate delineation of the tumor, peritumoral edema, and adjacent normal brain parenchyma. These targets are better demarcated through T1 contrast and T2-weighted MRI images.[1,3,4]

The International Commission on Radiation Units (ICRU)-report 50,[5] had proposed that various target volumes be delineated during the radiation therapy planning. These included, primarily, the gross target volume (GTV), representing the gross tumor, and the clinical target volume (CTV) for the microscopic presence of disease surrounding the GTV. The outlining of these target volumes could be based on the various imaging studies, namely contrast-enhanced CT or MRI. Planning target volume (PTV), defined with a margin of usually 0.5 to 1 cm surrounding the GTV or CTV, would depend on the treatment setup errors during the entire course of radiation therapy as estimated by individual departments.[2] The present study therefore, aims to carry out a comparative quantitative evaluation of the postoperative GTVs and CTVs for brain tumors, as visualized either on contrast-enhanced CT or MRI, in patients referred for postoperative adjuvant radiotherapy.

## MATERIALS AND METHODS

A total of 21 patients, histopathologically proven as glioma (all grades) and referred for postoperative radiotherapy were considered for this prospective study. All these patients were immobilized using ORFIT thermoplastic cast (ORFIT industries, Belgium) and taken up for contrast-enhanced CT and MRI with the cast *in situ*.

**CT:** The study was conducted with the patients immobilized on the flat couch of the diagnostic CT unit (Picker 5500, Picker International Inc, USA). Following contrast, axial cuts were usually taken from the vertex to the base of the skull, with a field of view (FOV) of 240 mm and a matrix size of 512 × 512. These were transferred to the radiation therapy treatment planning (RTP) workstation (Isis-3D, Technologie Diffusion, France).

**MRI:** MRI scans were taken with the standard head coil (1.5 T, Magnetom, Siemens, Germany). A custom-made Perspex™ base plate, which could fit into the standard head coil but was similar to the one used during CT acquisition, was used for fixing the cast during MRI. The images from the vertex to the base of the skull were obtained with spin-echo (SE) sequence, which has the least image distortions.[6] The conventional SE T2-weighted (TR/TE1, 2/n: 3000/12, 80/1), plain, and post-gadolinium contrast T1-weighted (1012/14/2) axial MR images were obtained using a 256 × 256 matrix size, a bandwidth of 65 Hz/pixel, and an FOV of 250 mm. The MR images were transferred to the RTP workstation for treatment planning.

Postoperative target volumes for residual GTV and CTV were drawn on contrast-enhanced CT and MRI images as per the recommendations in ICRU report 50.[5] Since all these patients had undergone prior surgery, ranging from just biopsy to subtotal resection, the residual GTV and the peritumoral edema were estimated separately for each imaging modality. The details of the delineation of various postoperative target volumes, done by an experienced neuroradiologist along with radiation oncologist on the postoperative contrast-enhanced CT and MRI, are as follows:

For phase I treatment, CTV was marked on contrast-enhanced CT as regions of brain parenchyma showing hypodensity surrounding the residual tumor with any area of adjoining mass effect. On MRI, the hyperintense region on T2W images was delineated as CTV. For the phase II treatment, the contrast-enhanced regions depicting a mass effect was considered as residual tumor (GTV) for both contrast-enhanced CT and T1W contrast studies.[7] The actual volumes (in cc) for the corresponding CTVs and GTVs were noted from the RTP workstation in contrast-enhanced CT-based and MRI based plans. A total dose of 60 Gy was delivered in two phases: 45 Gy to the CTV in phase I and 15 Gy, with reduced field sizes, to the GTV alone in phase II.

Statistical analyses were performed using SPSS statistical software for Windows, version 9.0 (SPSS Inc. Chicago, IL, USA).

## RESULTS

Patients were usually referred for postoperative radiotherapy within 2-3 weeks of the surgical procedure. Following simulation, contrast-enhanced CT and MRI were carried out at close intervals. The mean interval between surgery and postoperative CT was 29 days (median: 21 days) while with MRI it was 26 days (median: 21 days). The mean interval between CT and MRI was 3 days (median: 1 day). Most of the patients had glioblastoma multiforme and had undergone tumor decompression. The demographic details are listed in Table 1.

All the target volumes delineated in MRI were significantly larger than in CT [Tables 1 and 2]. The mean CTV, consisting of peritumoral edema volume, delineated in MRI was 180.93 cc (SD: ± 117.70) as compared to 118.01 cc (SD: ± 82.94) in CT studies. Similarly, the mean GTV, comprising hyperintense regions in contrast-enhanced T1W MRI images, was 71.64 cc (SD: ± 58.42), while it was 50.56 cc (SD: ± 37.21) in contrast-enhanced CT studies [Figure 1]. Compared to MRI, CT significantly underestimated the volumes, resulting in a mean difference between the imaging modalities (CT volume − MRI volume) of −62.92 ± 93.99 cc ($P = 0.006$) for CTV and −21.08 ± 36.04 cc ($P = 0.014$) for GTV [Table 2]. The percentage difference calculated taking the CT volume as baseline [(CT-based volume − MRI-based volume)/ CT-based volume × 100] shows that for CTV and GTV, the mean percentage differences was −106.7% (SD: ± 177.3) and −62.6% (SD: ± 131.8), respectively [Figure 2].

**Table 1: Patient demography (*n* = 21)**

| Characteristics | Distribution |
|---|---|
| Age (in years) | 42.2 ± 15.5* (range: 14-79) |
| Location of tumor | |
| Frontal:parietal:temporal:occipital | 8:3:8:2 |
| Operative procedure | |
| Biopsy:DPN:STR | 1:15:5 |
| Histology | |
| Astrocytoma:oligoastrocytoma | 19:2 |
| Tumor grade | |
| Grade I:II:III:IV | 3:2:3:13 |
| Tumor dose (Gy) | 61.1 ± 4.7 (range: 50-66) |
| Gross tumor volume (cc) | |
| CT | 50.57 ± 37.21 (range: 4.22-146.72) |
| MRI | 71.64 ± 58.42 (range: 9.78-253.97) |
| Peritumoral edema volume (cc) | |
| CT | 118.01 ± 82.94 (range: 12.43-295.55) |
| MRI | 180.93 ± 117.70 (range: 23.62-494.21) |

*Mean ± standard deviation; DPN: Decompression; STR: Subtotal resection

**Table 2: Mean difference in clinical target volumes and postoperative gross target volumes as evident on contrast-enhanced computed tomography and magnetic resonance imaging for (a) all patients, (b) grades I and II, and (c) grades III and IV**

| Volume | CECT-based (cc) (CECT) | MRI-based (cc) (MRI) | Difference (cc) CECT–MRI | *P*-value* |
|---|---|---|---|---|
| A: All patients (n = 21) | | | | |
| CTV | 118.01 ± 82.94 | 180.93 ± 117.70 | −62.92 ± 93.99 | 0.006 |
| GTV | 50.57 ± 37.21 | 71.64 ± 58.42 | −21.08 ± 36.04 | 0.014 |
| B: Grades I and II (n = 5) | | | | |
| CTV | 116.37 ± 78.14 | 239.51 ± 178.09 | −123.14 ± 117.93 | 0.080 |
| GTV | 50.07 ± 54.65 | 101.36 ± 98.10 | −51.29 ± 57.63 | 0.117 |
| C: Grades III and IV (n = 16) | | | | |
| CTV | 118.52 ± 86.84 | 162.62 ± 92.26 | −44.10 ± 80.51 | 0.045 |
| GTV | 50.72 ± 32.39 | 62.35 ± 39.96 | −11.63 ± 21.13 | 0.044 |

*Paired sample 't' test; CTV: Clinical target volume; GTV: Postoperative residual gross target volume. All volumes indicate mean ± standard deviation

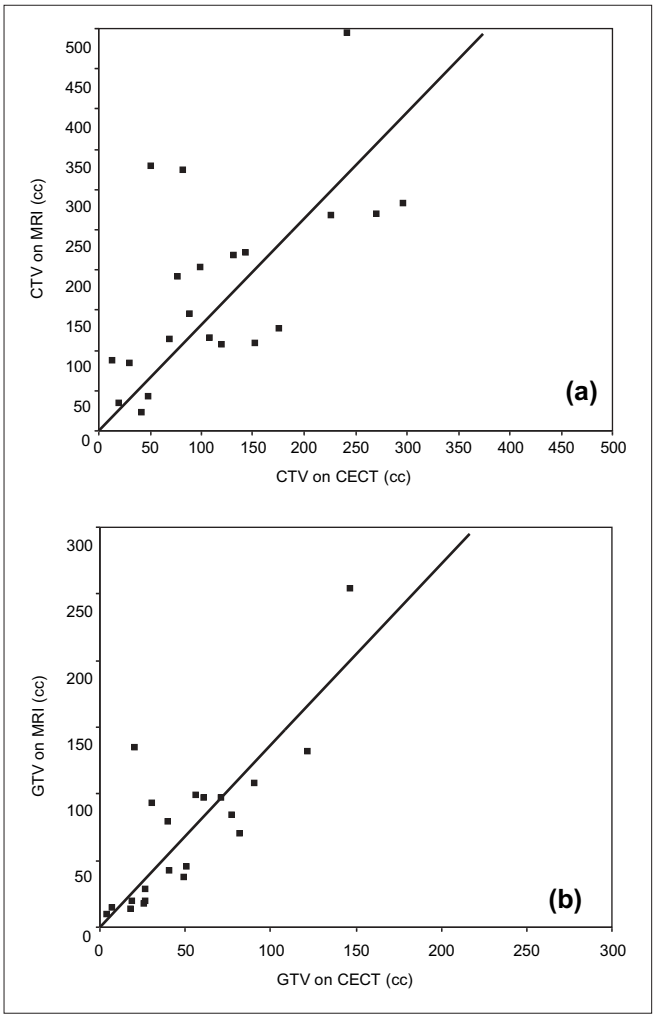


**Figure 1:** Scatter plot for the various ICRU report 50 volumes - clinical target volumes (CTV) and gross target volumes (GTV) - as estimated by contrast-enhanced CT and MRI studies. The curves fitted represent linear fit. (a) CTV: $r^2 = 0.77$, (b) GTV: $r^2 = 0.86$.

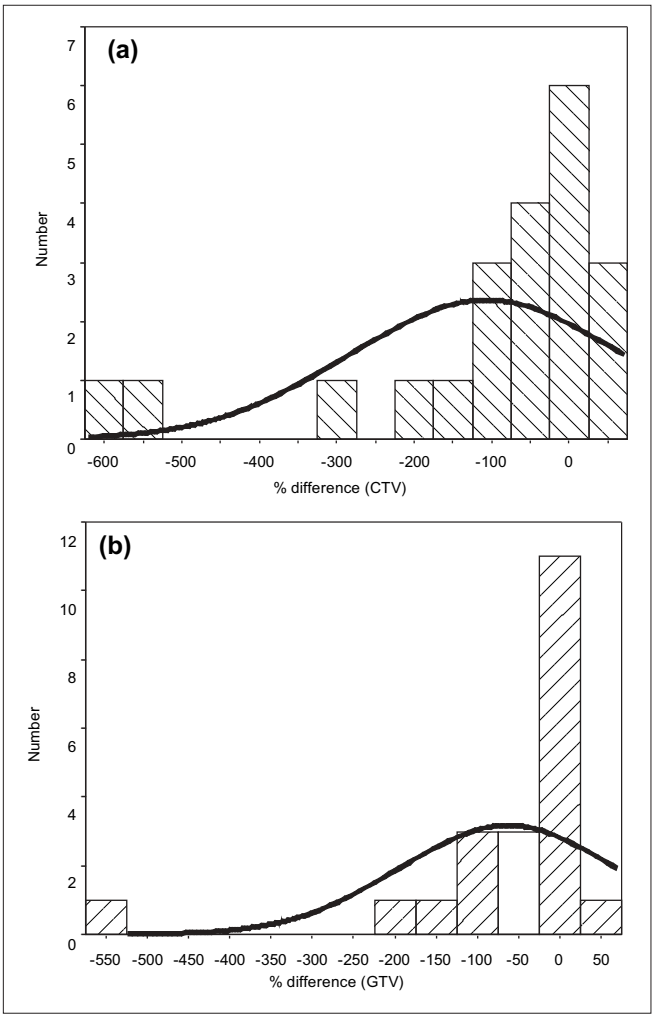


**Figure 2:** Histogram showing distribution of patients and percentage differences between contrast-enhanced CT and MRI for clinical target volumes (CTV) and gross target volumes (GTV). The normal distribution curve for the frequency distribution is also shown. (a) CTV (mean ± SD: −106.7% ± 177.3) and (b) GTV (mean ± SD: −62.6% ± 131.8).

The differences in the various target volumes were also separately evaluated for the tumors of grades I/II and grades III/IV [Table 2]. Although for each of the four target volumes evaluated, the MRI-based volumes are higher, these were significantly higher only in the higher-grade gliomas (grades III/IV).

## DISCUSSION AND CONCLUSIONS

Prior to the era of routine availability of CT and MRI, postoperative management of malignant gliomas involved whole brain irradiation. Although, various clinical trials showed a positive gain with postoperative radiotherapy in these patients, the need for accurate target localization was perhaps not felt since the radiation portals were reasonably generous in covering the entire cranial contents. However, with the gradual acceptance of PBI for malignant gliomas, accuracy in target delineation needs to be ensured. The target should include the residual postoperative tumor and a margin of usually 2-3 cm around the tumor to take care of the possibility of microscopic disease infiltration into the adjoining brain parenchyma, which has been evident from various antemortem and postmortem studies.[8-13]

Definition of target volumes could be subjective, and a number of studies have reported inter-observer and intra-observer variability.[14-19] The present study has therefore not tried to address this question of observer variability but attempted to highlight the importance of incorporation of target volumes from multiple imaging modalities.

The residual tumor volumes following surgery are perhaps best evaluated in scans carried out at 24-48 h following surgery, by which time it is possible to differentiate between the enhancing residual tumor and the postoperative changes. However, there are logistic problems involved in undertaking these scans within 24-48 h for defining the residual volume for radiation therapy. Most of these patients are still under the care of the neurosurgeons during this initial postoperative period; the patient is usually referred for radiotherapy after histopathological confirmation and once he or she is fit to be discharged from neurosurgery. Moreover, such scans for radiation treatment planning are done using immobilization casts and these can only be made after the wound has healed and when there are no dressings on the scalp that could alter the skull contours. However, during the target delineation on pre-radiotherapy CT/MRI images, all corresponding preoperative CT/MRI images are also reviewed.

The CTVs and GTVs in this study from both contrast-enhanced CT and MRI were drawn out by an experienced neuroradiologist in association with the radiation oncologist. Both these volumes were depicted larger using MRI, the difference being significantly more for the grade III and grade IV gliomas.

The implications of these volume differences could come into play during RTP. Since these patients were usually planned to receive a dose of 45 Gy to the CTV, followed by a boost of 15 Gy to the postoperative residual GTV, a difference in the corresponding volumes could result in an inadvertent geographical miss. Thus, in this group of 21 patients, the percentage difference in CTV if outlined on CT, ranged between −601 and +43% (mean ± SD: −106.7% ± 177.3) [Figure 2]. The corresponding percentage difference in GTV ranged from −571 to 29% (mean ± SD: −62.6% ± 131.8). Such an extent of uncertainty, with only CT-based planning, would be unacceptable and defeat any purposeful endeavour for dose escalation studies using various state of the art technologies such as three-dimensional conformal radiotherapy, stereotactic radiosurgery or radiotherapy, and intensity-modulated radiation therapy, all of which require accurate target delineation.[20]

Apart from anatomical target definition of brain tumors by contrast-enhanced CT and MRI, functional imaging using $^{201}$Tl-single emission photon spectroscopy (SPECT) and positron emission tomography (PET) has been able to highlight the metabolically active and viable tumor tissues within the anatomical region.[21] Even with the use of conventional MRI techniques, the limitations for demarcating the true spatial limits of tumor have been investigated and proton magnetic spectroscopy has been explored to obtain information on tumor metabolism.[22] A true representation of the target would nonetheless be an anatometabolic fusion image obtained through coregistration of images.[20,23] Thus, the present image-guided radiotherapy techniques, aided by multimodality imaging using contrast-enhanced CT, MRI, and possibly SPECT/PET, could be expected to demonstrate an improved survival as a result of more accurate target delineation, especially in certain good-prognosis subsets of patients of malignant gliomas. However, till such time as these imaging facilities, along with appropriate co-registration software, are available in most radiotherapy centers, routine RTP for brain tumors will be based either on contrast-enhanced CT or MRI.

Thus, to conclude, this study emphasizes the extent to which the CT images of operated gliomas could result in uncertainties in delineation of various ICRU-50 volumes, leading to significant geographical misses and target under dosage, especially in the case of high-grade gliomas. Since all patients included in this study have been treated based on the MRI-derived volumes, it is not possible to say as to what would have been the pattern of failures if these patients had been treated on the basis of CT-derived volumes. However, since most of the recurrences are known to be limited to the volume in and around the T2-weighted images,[2] it is necessary that a proper delineation of targets based on the MRI images should be carried out to minimize the risks of geographical misses and, thereby, enable delivery of the intended doses to the target volumes. Further refinement of these target volumes could be possible through the incorporation of the various functional images; this possibility is being currently investigated, with the hope that this would enable further dose escalation to limited volumes of metabolically viable regions of the tumor.[24]

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