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Technical Report

Comparative Analysis of Recurrent Glioblastoma Target Contours via ^{11}C-Methionine, ^{68}Ga-Prostate-Specific Membrane Antigen Positron Emission Tomography, and Magnetic Resonance Imaging: Implications for Precision Radiotherapy Planning

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Purpose: Glioblastoma (GBM) recurrence poses challenges in radiation therapy treatment planning because reirradiation has limited leeway needed for precise target delineation. Although effective radiotracers are emerging for treatment planning, comparisons of ^{11}C-methionine positron emission tomography (MET-PET), ^{68}Ga-prostate-specific membrane antigen PET (PSMA-PET), and magnetic resonance imaging (MRI) for contouring recurrent GBMs are lacking in the literature. This case study aimed to highlight the differences and similarities in target contours delineated from 3 examinations, aiming to raise doubts about the adequacy of current radiation therapy planning practices.

Methods and Materials: A 37-year-old female patient with recurrent Isocitrate dehydrogenase (IDH)1/2 wild-type GBM underwent MRI, MET-PET, and PSMA-PET scans. Target delineations were performed, and volumes were compared using the Dice similarity coefficient, conformity index, and overlap volume, considering different planning target volume margins.

Results: We found that MET-PET and MRI volumes showed superior agreement compared with PSMA-PET across all similarity parameters, indicating a more marked discrepancy between PSMA-PET and other modalities. Increasing planning target volume

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margins demonstrated progressive convergence in intervolume discrepancies. Notably, PSMA-PET delineated larger volumes extending beyond MRI-based volumes.

Conclusions: MRI alone may not suffice for target delineation in recurrent GBMs. PET imaging modalities offer complementary insights. Combined PET-MRI guidance could improve tumor boundary detection in target delineation for reirradiation. Prospective trials are necessary to ascertain its impact on patient outcomes.

Introduction

Glioblastoma (GBM) is a highly malignant cancer associated with a median survival ranging from 7.5 to 17 months.[1] Recurrence is frequent, despite maximal safe resection followed by chemoradiation therapy as per the Stupp protocol.[2] Limited therapeutic options exist in such cases, including reresection, reirradiation (re-RT), second-line systemic therapy, or participation in clinical trials.[3] Reresection might not always be feasible when tumors extend into eloquent areas or closely approach critical structures (eg, optic pathway), making re-RT the final local therapy option. However, re-RT poses safety concerns because of the risk of radionecrosis from cumulative radiation doses and potential damage to organs at risk (OARs), such as the optic pathway or brainstem.[4]

In this challenging scenario, achieving optimal tumor control while minimizing radiation-related adverse effects is crucial, considering the scarcity of further effective treatments. Delineating the borders of recurrent tumors as precisely as possible becomes paramount, making the identification of new positron emission tomography (PET) radiotracers (eg, ^{11}C-methionine [MET] and ^{68}Ga-prostate-specific membrane antigen [PSMA]) alongside standard magnetic resonance imaging (MRI) helpful for aiding radiation oncologists in contouring.[5-7]

MET-guided therapy has demonstrated efficacy in improving survival for both patients with newly diagnosed and those with recurrent GBM, showing superiority over MRI-based therapy in the latter cohort.[8,9]

PSMA, initially identified as specific to prostatic cancer cells, has unveiled new frontiers in GBM managements as a potential radiopharmaceutical technique.[10,11] Beyond aiding in external beam radiation therapy contouring, PSMA can be loaded with therapeutic radioisotopes such as [^{177}Lu] to selectively deliver cytotoxic radiation to GBM cells via the bloodstream.[12] Although more evidence is awaited, PET imaging can be a valuable tool in GBM treatment planning for radiation oncologists, ensuring effective response monitoring even in ambiguous cases.[13]

This case study aimed to highlight the differences and similarities in target contours delineated from 3 examinations (MRI, MET-PET, and PSMA-PET), seeking to stimulate research in the field of re-RT for recurrent GBMs.

Methods and Materials

To exemplify the issue discussed in this paper, we selected an illustrative case that underscores how the present findings may impact the general practice of contouring recurrent GBMs.

An index case for illustrative purposes

A 37-year-old woman with a history of surgically resected and chemo-irradiated left frontotemporal Isocitrate dehydrogenase (IDH)1/2 wild-type GBM diagnosed in September 2021 and reresection at first recurrence in January 2023 demonstrated poor response to temozolomide, which was administered as per the Stupp protocol and subsequently rechallenged. Further resection was deemed unsuitable at the second recurrence diagnosed by MRI in October 2023. The patient underwent 2 PET scans: one with 470.9 MBq of ^{11}C-MET and the other with 136.9 MBq of ^{68}Ga-PSMA, respectively. The PET scans and T1-weighted gadolinium-enhanced MRI sequences were rigidly fused using Velocity software by Varian v.3.2.1, employing a 1.25-mm slice thickness computed tomography simulation for radiation therapy planning in the Eclipse Treatment Planning System (v.13.7.14, powered by Varian). Subsequently, separate target delineations were performed, as depicted in Fig. 1 and described below.

Target contouring

The MRI-gross tumor volume (GTV) was defined as the region of contrast enhancement on the T1-weighted MRI sequence, as shown by Combs et al.[14] The maximum standard unit value for MET and PSMA were 11.29 and 4.15, respectively. The MET-GTV was the biological tumor volume (BTV) automatically segmented using a threshold of 1.5 times the mean cerebellar uptake (2.25 in our case), as described by Lee et al.[15] In contrast, the PSMA-GTV demonstrated clearer delineation as a BTV because of an excellent tumor-to-background ratio (4.11),

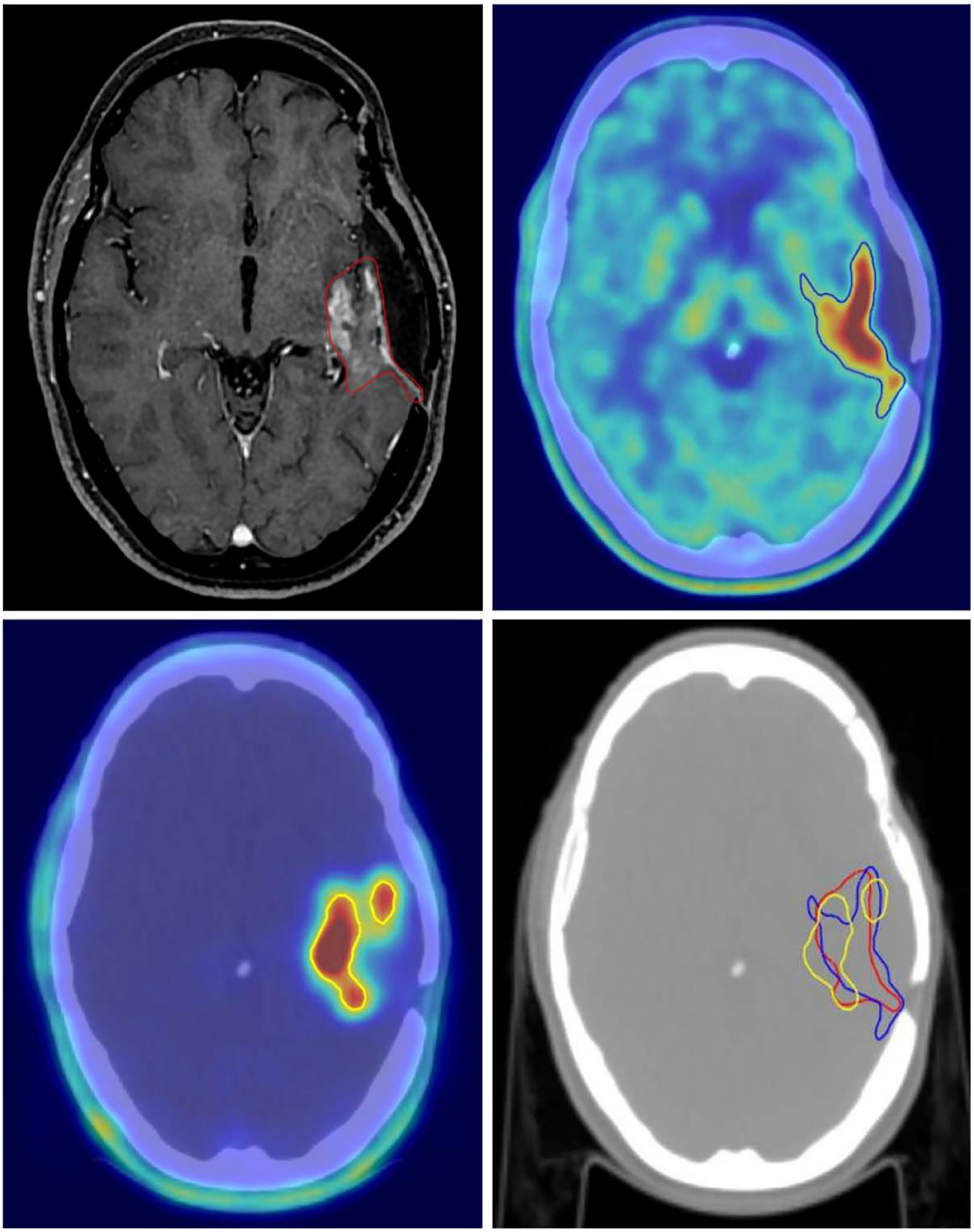


Figure 1 Delineation of the gross tumor volume on different images, as seen in a case of recurrent glioblastoma. Top left, magnetic resonance imaging (tumor in red); top right, ^{11}C-methionine positron emission tomography (tumor in blue); bottom left, ^{68}Ga-prostate-specific membrane antigen positron emission tomography (tumor in yellow); bottom right, superimposition of all 3 contours on simulation computed tomography (CT). All 4 images represent the same slice. Minimal variations in shape between the red contour outlined on the magnetic resonance imaging (top left box) and the one displayed in the CT simulation (bottom right box) are due to a slightly different tilt of the skull in the 2 examinations, which was thus sliced with a minimally different orientation. This does not alter the reliability of our results and only serves to explain why the rear red tail appears stockier in CT simulation than in magnetic resonance imaging.

resulting in distinctly sharp tumor margins, and corresponded to the region of interest automatically segmented by the GE HealthCare Volume Share 5 − Advantage Workstation 4.6 based on the default threshold value of 42% of maximum standard unit value. For each imaging, we created 3 clinical target volume (CTV) expansion scenarios based on variability in institutional practices. These 3 scenarios included an expansion of the GTV by 0, 3, or 5 mm, which was then trimmed to exclude anatomic barriers to tumor growth (eg, skull bones, ventricles, and OARs). The latter 2 CTVs were subsequently expanded by 1 mm to create a planning target volume (PTV). Therefore, in the 0-mm scenario, GTV, CTV, and PTV represent the same volume. Acknowledging the absence of a consensus on the margins around the GTV for recurrent GBMs, the 3 examined CTV + PTV expansion margin combinations (0 + 0 mm, 3 + 1 mm, or 5 + 1 mm) were derived based solely on prevailing practice patterns to assess how such expansions influence the outcomes of this investigation. PTV margins vary depending on the stereotactic equipment available at each center. For example, Gamma Knife does not require PTV expansion. In our center, we are equipped with a TrueBeam Novalis STx supported by ExacTrac (Varian Medical Systems, CA), which allows all setup corrections greater than 0.5 mm, so that a 1-mm expansion easily encompasses all residual positional uncertainties. This guided our choice to test these 2 PTV margins (0 and 1 mm). However, larger PTV margins may be used depending on institutional practices and equipment.[16]

The resultant set of target volumes from each imaging scan was compared with the other 2 based on the following parameters.

Target comparison

The established target volumes were paired by CTV + PTV expansion margin combinations (0 + 0 mm, 3 + 1 mm, or 5 + 1 mm) and compared using Boolean operators to determine the overlap volume and Dice similarity coefficient (DSC), as described by Şahin et al,[17] and the conformity index (CI) according to Van't Riet, adapted from the dosimetric plan evaluation.[18] Additionally, the DSC was calculated for the entire triplet of target volumes ($DSC_{overall}$). These metrics yield values between 0 and 1, where values closer to 1 indicate better volume matching. Finally, any portions of PET-based GTVs extending beyond the 3 MRI-CTVs were recorded.

Ethical issues

Ethical approval from the relevant review committee was waived because of the observational nature of the study. Informed consent was obtained from the participants included in the study.

This article does not involve any studies conducted on animals by the authors. All procedures carried out in this study adhered to the ethical standards set by the institutional and/or national research committee, following the 1964 Helsinki Declaration and its subsequent amendments or equivalent ethical standards.

Results

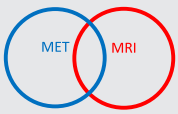
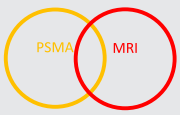
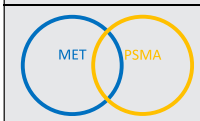
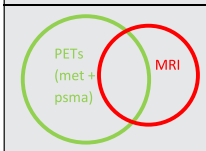
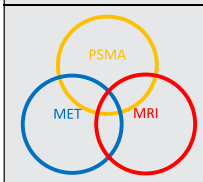
The results of the intervolume comparisons in the case study are summarized in Table 1. From the values of the overlap volume, all less than 1, it is clear that no volume completely encompasses the other. MET-PET and MRI volumes had superior agreement with each other, compared with that between MRI and PSMA-PET, as indicated by consistently higher values across all similarity parameters for MET-PET compared with PSMA-PET, irrespective of the considered PTV margins (first and second sets of comparison parameters). Consequently, a significant disparity existed between MET-PET and PSMA-PET volumes (third set), which persisted when comparing their amalgamation with MRI volumes (fourth set). It is worth noting that values of only 0.1 and 0.31 for CI and DSC, respectively, reflect a huge mismatch and low similarity between the PSMA-GTV and MRI-GTV. The corresponding values in the comparison between the MET-GTV and MRI-GTV were higher (0.36 and 0.59). There was also poor agreement between the MET and PSMA volumes (third set), thus negatively influencing that between the merged volume of the 2 PETs and the MRI volume (fourth set).

The similarity parameters exhibited improvement with increasing PTV margins (from left to right), ie, as their relative length encountered anatomic barriers and OARs (eg, ventricles, skull bones, and optic pathways) increased. This happened even when considering the $DSC_{overall}$ (fifth set). Notably, Table 2 highlights how much PSMA-GTV and MET-GTV extended beyond each MRI-CTV (GTV_{PSMA_LESS} and GTV_{MET_LESS}). The first was considerably larger than the second, contributing substantially to the larger amount when merging them ($GTV_{PETs\_LESS\_UNION}$). GTV_{PSMA_LESS} was nonnegligible even outside the $CTV_{MRI\_5\ mm}$ (0.1 cm^3), unlike the corresponding GTV_{MET_LESS} (0.005 cm^3).

Discussion

To our knowledge, this is the first case study investigating the discrepancies in target contours of recurrent GBM using MET, ^{68}Ga-PSMA-PET, and MRI. Notably, all 3 imaging modalities accurately identified the site of recurrence, but the extent and shape of the identified regions

Table 1 Intervolume comparisons between magnetic resonance imaging, ^{11}C-methionine positron emission tomography, and ^{68}Ga-prostate-specific membrane antigen positron emission tomography scans in the illustrative case with recurrent glioblastoma

Intersection types	Nomenclature for volumes on different imaging techniques and related similarity parameters	GTV	$PTV_{CTV\_3\ mm}$	$PTV_{CTV\_5\ mm}$
	V_{MRI}	26.9	74.3	96.1
	V_{MET}	20.2	61.9	80.4
	V_{PSMA}	14.9	49.3	67.3
	V_{PETs}	28.1	76.1	96.6
	$V_{MET\cap MRI}$	14	52.7	70.9
	CI	0.36	0.6	0.65
	OV	0.69	0.85	0.88
	DSC	0.59	0.77	0.8
	$V_{PSMA\cap MRI}$	6.4	35.7	51.9
	CI	0.1	0.35	0.42
	OV	0.43	0.72	0.77
	DSC	0.31	0.58	0.64
	$V_{MET\cap PSMA}$	6.6	35.1	51
	CI	0.14	0.4	0.48
	OV	0.44	0.71	0.76
	DSC	0.38	0.63	0.69
	$V_{PETs\cap MRI}$	16.3	57.6	76.7
	CI	0.35	0.59	0.63
	OV	0.61	0.78	0.8
	DSC	0.59	0.77	0.8
	$DSC_{overall}$	0.67	0.83	0.86

The columns show 3 different target contouring settings: gross tumor volume (GTV; 0 + 0 mm in the main text), planning tumor volume ($PTV_{CTV\_3\ mm}$; 3 + 1 mm in the main text), and $PTV_{CTV\_5\ mm}$ (5 + 1 mm in the main text). In the rows, there are the absolute and intersection volumes and the corresponding similarity parameters for the comparison of each pair. V_{MRI}, V_{MET}, V_{PSMA}, and V_{PETs} are for the target volumes (Vs) contoured on the MRI, MET-PET, PSMA-PET, and the latter 2 combined, respectively. $V_{X\cap Y}$ is for the intersection Vs, as exemplified by the schematic representation on the left side. All Vs are expressed in cubic centimeters, whereas the similarity parameters are nondimensional. The Dice similarity coefficient (DSC) is also provided for the triplet (fifth set).

Abbreviations: CI = conformity index; CTV = clinical target volume; MET = ^{11}C-methionine; MRI = magnetic resonance imaging; OV = overlap volume; PET = positron emission tomography; PSMA = ^{68}Ga-prostate-specific membrane antigen.

varied. This challenges the reliance solely on MRI for guiding contour delineation in recurrent GBMs, which might suffice during the initial Stupp phase but may prove insufficient in recurrent scenarios. In the initial radiation course, GTV-to-CTV margins are considerably wider than those in re-RT (1-2 cm vs 0 to 0.3-0.5 cm) because of the necessity to irradiate edema around the surgical cavity and fewer concerns regarding radiation tolerability.[19] Consequently, in Stupp treatment planning, minor variations in GTV contours based on different images can likely be accommodated within a larger CTV, minimizing the risk of missing subclinical disease. Şahin et al[17] observed that among patients with newly diagnosed GBM undergoing postoperative radiation therapy, PSMA-based BTVs significantly differed from MRI-based GTVs. Although BTVs initially appeared larger than GTVs, this distinction became insignificant when applying the same CTV margin that encompassed the peripheral edema.[17]

Table 2 Subtraction of gross tumor volumes delineated by ^{11}C-methionine, ^{68}Ga-prostate-specific membrane antigen, and their union from the corresponding whole by cropping the amount extending inside the magnetic resonance imaging CTVs.

PET GTVs extending outside the MRI contours	GTV_{MRI}	$CTV_{MRI\_3\ mm}$	$CTV_{MRI\_5\ mm}$
GTV_{MET_LESS} (cm^3)	2.6	0.1	0.005
GTV_{PSMA_LESS} (cm^3)	7	1.1	0.1
$GTV_{PETs\_LESS\_UNION}$ (cm^3)	8.8	1.1	0.1

The GTV_{MET_LESS} and GTV_{PSMA_LESS} are determined on a case-by-case basis as the amount of MET-GTV and PSMA-GTV extending outside the GTV_{MRI}, $CTV_{MRI\_3\ mm}$, and $CTV_{MRI\_5\ mm}$. The $GTV_{PETs\_LESS\_UNION}$ derives from the union of GTV_{MET_LESS} and GTV_{PSMA_LESS}. All values are expressed in cubic centimeters (cm^3).
Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; MET = ^{11}C-methionine; MRI = magnetic resonance imaging; PET = positron emission tomography; PSMA = ^{68}Ga-prostate-specific membrane antigen.

Similarly, our findings indicate progressive convergence of intervolume discrepancies with increasing PTV margins because of consistent cropping of each target from natural boundaries and OARs. Although MET uptake by GBM needs to be balanced against normal brain cortex uptake, PSMA, with its clearer tumor borders against healthy brain background, offers easier target delineation. However, in the case described here, the PSMA-based contour significantly diverged from the MET-based one, as evidenced by a very low $CI_{MET \cap PSMA}$ (0.14). This suggests that the 2 PET images complement each other and can provide mutual benefits.

MRI is a morphologic examination, whereas PET provides insights into tumor activity, whose extent can exceed morphologic boundaries as in the present case and also change the surgical approach. Hirono et al[20] proved that MET-guided supratotal resection of primary GBMs achieved better survival than MRI-based gross total resection without worsening neurocognitive performance. Re-RT of recurrent GBMs also produced better survival

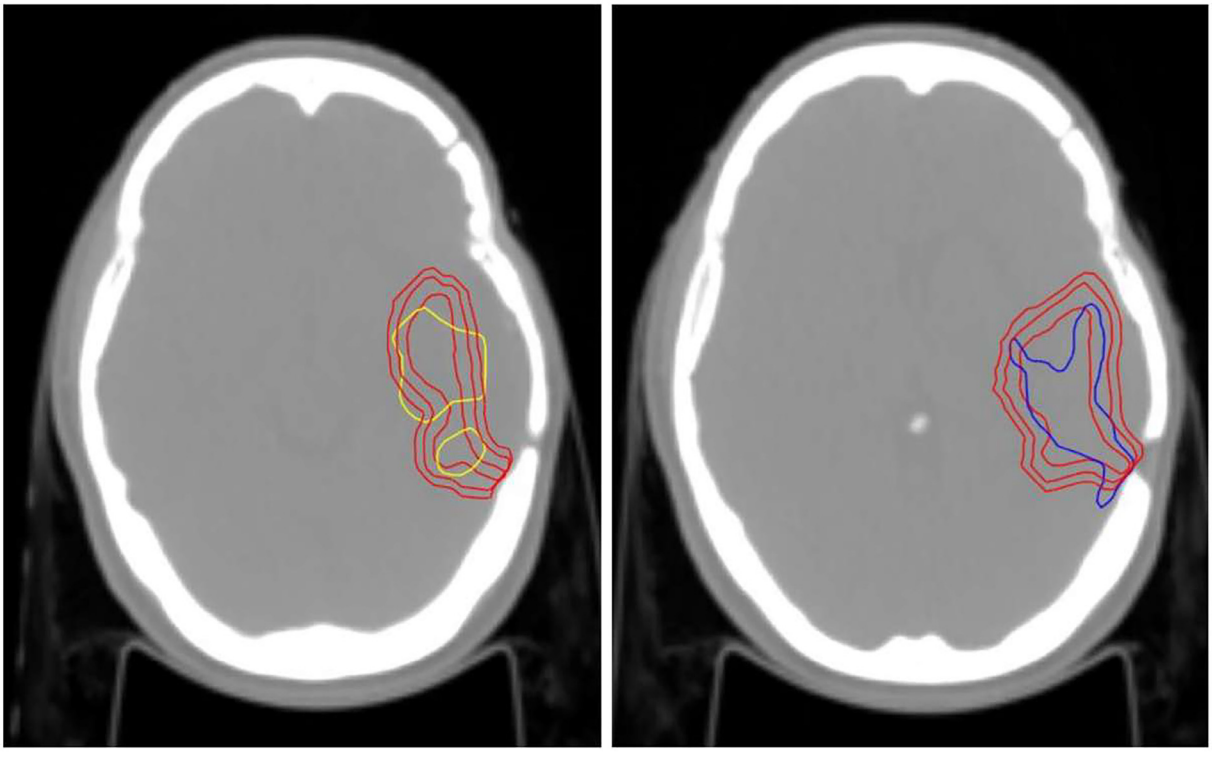


Figure 2 Relationship of gross tumor volumes delineated by ^{68}Ga-prostate-specific membrane antigen on the left (in yellow) and ^{11}C-methionine positron emission tomography on the right (in blue) with magnetic resonance imaging (MRI) target contours, as seen in a case of recurrent glioblastoma. The red contours represent gross tumor volume_MRI (the smallest and innermost red contour), $CTV_{MRI\_3\ mm}$ (the intermediate red), and $CTV_{MRI\_5\ mm}$ (the outermost red). The 2 images represent different slices, independently chosen to highlight the divergence of each positron emission tomography contour with MRI. CTV = clinical target volume.

outcomes when guided by MET-PET rather than MRI.[9] MET is an essential nutrient for the metabolism of GBM cells, and its uptake correlates with their proliferation.[21] On the contrary, PSMA is not taken up directly by GBM cells but by the tumor neovasculature that supplies them, possibly reflecting a slightly different spatial distribution compared with MET.[22] It becomes evident that enhancing the MRI-based RT planning with metabolic information deriving from the above 2 PETs may have some relevant implications, as already demonstrated in surgery planning.[8,20] Re-RT represents a critical situation, and its refinement is particularly important to maximize disease control while limiting adverse events. Given the lack of consensus in defining the optimal CTV contour,[16] we merged the GTVs obtained from the 3 examinations and expanded the resulting GTV to CTV by a margin of 3 mm. For the PTV, an additional margin of 1 mm was added. Notably, treating only the GTV_{MRI} in the present case would have missed significant portions of both GTV_{MET} and GTV_{PSMA}, the latter remaining substantial even when considering $CTV_{MRI\_5\ mm}$ (Table 2 and Fig. 2). The theoretical risk of increased radionecrosis because of a larger final target resulting from merging the target volumes delineated on the 3 different images emphasizes the urgency to establish the superior contouring procedure to effectively balance the risks and benefits of re-RT. The functional boundaries provided by PET imaging could usefully complement the morphologic ones delineated on MRI without any of the 3 examinations actually prevailing over the other 2. Large prospective trials are necessary to clarify whether the delineation method for recurrent GBM significantly impacts survival outcomes.

Conclusions

This study underscores the limitations of relying solely on MRI for delineating target volumes in recurrent GBMs. The findings demonstrate significant variations in target contours derived from MRI, MET-PET, and PSMA-PET imaging modalities. Although each accurately identifies the recurrence site, they depict diverse extents and shapes of identified regions. The study raises the question of whether incorporating MET-PET and PSMA-PET alongside MRI for target delineation in recurrent GBMs may have clinical relevance. It first reveals that MET-PET diverges significantly from PSMA-PET. Notably, treating only MRI-based target volumes may miss substantial portions identified by MET-PET and PSMA-PET, highlighting the need for a comprehensive approach using multiple imaging modalities to improve delineation. The observed discrepancies between imaging modalities and the potential risk of increased target volumes from their combination emphasize the urgency of establishing optimal delineation methods that effectively balance risks and benefits in re-RT scenarios. In summary, relying solely on MRI for recurrent GBM target delineation might be inadequate, especially with minimal margins. Integrating MET-PET and PSMA-PET scans into clinical practice shows promise but warrants further specialized investigations to determine their role in improving target delineation and treatment outcomes.

Disclosures

None.

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