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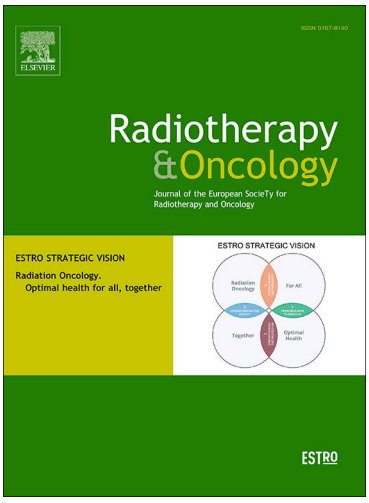

Technical Note

FET PET-based target volume delineation for the radiotherapy of glioblastoma: A pictorial guide to help overcome methodological pitfalls

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FET PET-based target volume delineation for the radiotherapy of glioblastoma: A pictorial guide to help overcome methodological pitfalls

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Abstract (unstructured, max. 50 words)

PET is increasingly used for target volume definition in the radiotherapy of glioblastoma, as endorsed by the 2023 ESTRO-EANO guidelines. In view of its growing adoption into clinical practice and upcoming PET-based multi-center trials, this paper aims to assist in overcoming common pitfalls of FET PET-based target delineation in glioblastoma.

Key words:

Glioblastoma; FET PET; PRIDE trial (NOA-28; ARO-2024-01; AG-NRO-06; NCT05871021; treatment planning; biological tumor volume (BTV)

Highlights (3-5 bullet points):

- Methodological pitfalls of FET PET-based target delineation may hamper accurate radiation delivery to glioblastoma, potentially resulting in over- or undertreatment.
- Current clinical guidelines acknowledge the evolving role of PET for the radiotherapy of glioblastoma but come short in providing specific technical guidance on how to overcome PET-related methodological pitfalls.
- This technical note aims to provide procedural assistance on how to specifically address common pitfalls of FET PET-based radiotherapy-planning in glioblastoma and includes a pictorial guide.
- In view of ongoing and upcoming prospective multi-center trials using FET PET-based target definition for the radiotherapy of glioblastoma, the proposed steps may enhance standardization of target volume delineation across study sites.

Introduction

Accuracy of radiation technologies continues to improve and warrants precise definition of target volumes [1]. For the radiation therapy of glioblastoma, *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) positron emission tomography (PET) has shown clinical usefulness in addition to magnetic resonance imaging (MRI) and it is increasingly used for pre-therapeutic target definition, as acknowledged by the current 2023 ESTRO-EANO guidelines and by the PET/RANO Group [1-4]. The use of FET PET imaging in glioblastoma enables to depict the biological tumor volume (BTV) that complements information on lesion extent and on areas potentially susceptible for

radiation boost delivery, thus directly impacting on target volume definition [5-9]. Along with the increasing clinical application of FET PET, several ongoing or upcoming prospective multi-center trials in the context of radiotherapy of glioblastoma incorporated FET PET-based target delineation in their study design [10-13]. While interdisciplinary consensus reports and current nuclear medicine practice guidelines provide extensive methodological information including metrical parameters on how to semi-automatically delineate active glioblastoma tissue on PET [4, 14, 15], a pictorial guide on how to potentially overcome common pitfalls in FET PET-based target volume definition is currently lacking. As underscored by recently published preliminary results of the ongoing Australian FET PET-based multi-center "FIG study" (TROG 18.06), there appears to be an unmet need to improve accurate implementation of PET-based target volume delineation into radiotherapy practice: Protocol violations regarding FET PET analysis were found in 34.7% of cases with the primary reason of resubmission being BTV over-contouring [16].

Therefore, this technical note aims to provide specific guidance using a pictorial approach to address common pitfalls of FET PET-based radiotherapy-planning in glioblastoma, relevant to everyday clinical practice. Further, the proposed methods may enhance standardization of target volume delineation across study sites of ongoing and upcoming prospective multi-center trials involving FET PET-based target volume delineation in glioblastoma. Specifically, this paper serves as guide to define targets for boost delivery as part of the PRIDE trial (NOA-28; ARO-2024-01; AG-NRO-06).

Common pitfalls of FET PET-based target volume delineation

Although clinical application of FET PET is mostly straightforward, various methodological challenges may complicate image interpretation including pitfalls in target volume delineation. Experienced nuclear medicine readers may be trained to overcome these issues, hence difficult cases should always be approached in collaboration with nuclear medicine specialists. Yet, we identified common pitfalls that may be worth of increased awareness and propose how to address them in a pictorial guide. The selected major challenges of FET PET-based target volume delineation covered by this technical note include:

1) Quantitative assessment of FET uptake in the cerebral background,
2) Application of target-to-background ratios (TBR) as a threshold for semi-automatic tumor delineation,
3) Exclusion of intra- or extra-cerebral non-tumoral structures from the biological tumor volume (BTV).

The aim of this technical note is to specifically assist radiation oncologists in the use of FET PET imaging for treatment-planning of radiotherapy in glioblastoma – a broader review on general challenges, limitations and pitfalls of PET and advanced MRI in patients with brain tumors has recently been published by the PET/RANO Group [17].

Practical guide

1) Assessment of background activity

Tumor delineation on FET PET relies on cutoffs that are defined by a selected target-to-background ratio (TBR), i.e., a ratio in relation to the mean FET uptake in the healthy-appearing brain ("background activity") on 20 min static PET image acquisition obtained 20 min after tracer injection [15]. Therefore, appropriate quantitative assessment of FET uptake in the healthy-appearing cerebral background is crucial for generating a reliable BTV according to current standards. An underestimated cerebral background activity would lead to an underestimated threshold and ultimately to an overestimated BTV (vice-versa, an overestimated cerebral background activity would lead to an underestimated BTV). The recommended approach for background activity assessment is to place six adjacent large crescent-shaped regions-of-interest (ROIs) in the brain hemisphere opposite to the target lesion [18]. The mean standardized uptake value (SUV_{mean}) of those joint ROIs is defined as the background activity.

A first common pitfall in this context would be to inadvertently include areas of high FET uptake into the background ROIs, including either intraaxial structures such as the basal ganglia, extraaxial structures such as vessels or muscles, or even tumoral lesions (e.g., in case of bihemispheric disease). A second pitfall would be to include a high proportion of areas with inherently reduced tracer uptake, these include the ventricular system, cysts, or resection cavities. All areas of substantially abnormal increase or decrease of FET uptake must not be included in the background ROIs. Take care not to include a high proportion of white matter as compared to grey matter as this will lead to underestimated background activity. In sum, for background activity assessment we recommend to strictly adhere to the current procedural standards as published [15, 18]. A condensed illustration of common pitfalls along with the correct approach of background activity assessment on FET PET is shown in **Figure 1**.

2) Application of target-to-background ratios (TBR) serving as threshold for BTV definition

An interdisciplinary Response Assessment in Neuro-Oncology (RANO) expert panel recently recommend defining PET-positive disease using a TBR threshold of 1.6 (PET RANO 1.0, [14]). This must be considered an important step to promote standardization and reproducibility in clinical trials. However, the pathology-controlled evidence for a 1.6 TBR threshold is limited [19], as also acknowledged by the PET RANO 1.0 authors. In addition, various circumstances can generally complicate semi-automatic tumor delineation on PET. Despite the important aim for reproducibility in PET-based response assessment, it is therefore essential to understand that a 1.6 TBR threshold has not to be strictly applied for pre-therapeutic BTV definition under all circumstances: Instead, in the case of contradictory or clearly conflicting clinical evidence regarding tumor extent, it is legitimate to opt for a different approach of BTV contouring, e.g. using the also widely published 1.8 TBR threshold that has also been chosen for the feasibility analysis of the PRIDE trial [12, 15].

Although not typically noted on FET PET images in clinical routine, a potential pitfall for semi-automatic BTV delineation using a fixed TBR threshold is a significantly increased FET uptake of non-neoplastic origin immediately adjacent to the tumoral site. Apart from individual peculiar factors such as clinically relevant post-operative local infection, in our experience, an interval of less than 14 days from the date of

surgery to the PET scan generally makes a reactive contribution to such increased FET uptake appear more likely. Also, a less focal and continuously circular uptake pattern along the resection cavity and/or a lower uptake intensity compared to areas with high suspicion of active tumor tissue can be indicators of a reactive FET uptake, e.g. in case of co-existent inflammatory processes or postoperative changes [17]. Thus, the use of a higher TBR threshold, e.g., a cutoff of 1.8 × mean background activity, may enable to semi-automatically include likely suspicious areas in the BTV while sparing areas of confluent reactive FET uptake. Also, a higher threshold may spare normally increased FET uptake of unaffected brain structures. Examples are illustrated in **Figure 2**. Yet, histology-correlated evidence to support such a pragmatical approach in general is insufficient. Literature on the underlying pathophysiological causes for non-neoplastic increased FET uptake include several factors such as postoperatively increased perfusion, blood-brain-barrier break-down or inflammatory processes [17, 20]. The determination of whether such an increased uptake on early-postoperative PET images is associated with an actual tumor remnant or instead reactive processes remains difficult, and reactive uptake may (especially in cases of high uptake intensity) mask co-existent residual tumor. The most important step regarding this pitfall is to be aware of it at all. When interpreting FET PET results, make note of the patient's history and additional clinical information, e.g., the time interval between the PET scan and surgery or other prior treatments. Although this is only a simplification for the interpretation and definition of the target volume definition, as a rule of thumb, the glioblastoma volume on contrast-enhanced T1-weighted MR images will not exceed the BTV on PET, and the latter will most likely not exceed the tumor volume on FLAIR/T2-weighted MR images, while they not necessarily show a complete or near-complete spatial overlap [21]. This approximation is most suitable for newly diagnosed cases. At recurrence, contrast-enhancing areas without increased FET uptake frequently occur and are indicative of post-therapeutic changes. In general, it is important to ensure that the information from the FET PET is compatible with the MRI sequences mentioned above. When using (semi-)automated tools for BTV delineation in case of multifocal disease, make sure that inclusion of multiple lesions is allowed on the software tool used. In individual inconclusive cases with perceived major uncertainties about the BTV extent due to suspected reactive FET uptake, e.g., when the PET has been performed shortly after surgery, one may consider performing a short-term follow-up PET scan prior to irradiation.

Several further pitfalls could arise when choosing PET parameters outside the technical specifications as published in the current procedural guidelines [15]. E.g., BTVs may vary depending on the recorded emission time frame chosen for the PET image analysis [22]. A pictorial demonstration of these technical specifications is beyond the scope of this paper; they are usually not in the direct responsibility of the treatment-planning radiation oncologist. Software assistance devices including artificial intelligence tools are currently under development and will potentially enable a fully automated brain tumor detection, less prone to intra- and interobserver variability [23, 24].

3) <u>Exclusion of intra- or extra-cerebral non-tumoral structures from the biological tumor volume (BTV)</u>

As touched upon above, certain normal structures of the brain and its surroundings show an increased FET uptake above the cerebral background activity. Therefore, they are prone to be inadvertently included in the BTV. This is even more evident, when using semi-automatic approaches for target delineation on PET, e.g., threshold-based contouring as implied in the current guidelines [15]. If not intended to be an actual target of irradiation (e.g., in case of tumor infiltration), these non-neoplastic structures of increased FET uptake must be excluded from the BTV, no matter which technical approach of contouring is chosen (e.g., threshold-based). The structures at risk in terms of overcontouring on FET PET commonly include (but are not limited to) caudate nucleus, cavernous sinus, pineal gland, putamen, sigmoid sinuses, superior sagittal sinus, temporal muscles, and thalamus [25]. Examples are illustrated in **Figure 2**.

To overcome this pitfall, the pivotal step is to directly correlate areas of increased FET uptake to the corresponding findings on MRI. Also, once a BTV has been generated, its plausibility should be double-checked in direct correlation to the MRI. The morphological information on MRI will in most cases allow for a prompt allocation of increased FET uptake to unaffected structures, e. g. the pineal gland or an extracerebral muscle. It may sound trivial, but this step is mandatory to be performed at the first place when assessing the actual PET images, i.e., before generated contours are exported to a radiation planning software. If not done so, especially BTV overcontouring with the inclusion of intracerebral unaffected structures might be overseen. Yet, it remains difficult to demarcate active tumor tissue from immediately adjacent sites of normally increased FET uptake that are indeed susceptible for tumor-infiltration. In those cases, along with the MRI correlation, it may help to assess the likelihood of a potential infiltration by performing a side-by-side comparison of the FET uptake: If the uptake of the normal structure is equal to the contralateral side and shows no suspicion on MRI, an infiltration is unlikely, and it may therefore be excluded from the BTV. However, again, there is insufficient histology-correlated evidence to support such a pragmatical approach in general. Further, irregularly shaped lesions as well as lesions adjacent to resection cavities or cysts may be at risk for overcontouring when performing (semi-)automatic tumor delineation, depending on the software tool and settings used. In those cases, make sure to check for plausibility of the BTV in correlation to MRI. Whenever an area of normal FET uptake has been identified to be inadvertently included in the BTV, it can simply be cropped out using the precisely overlayed MRI as the anatomical reference.

Discussion

This technical note is intended to raise awareness on selected common pitfalls of FET PET-based target volume delineation in glioblastoma. It proposes solutions on how to potentially overcome these pitfalls, relevant to everyday clinical practice of radiation oncologists. Of note, this paper is not intended to replace established guidelines, nor has it been developed in a process initiated or driven by professional societies. We would like to emphasize that the validity of the methods shown has not been proven by prospective studies but, rather, they represent expert opinions and may encourage to generate further evidence in this clinically evolving field.

CRediT authorship contribution statement

Adrien Holzgreve: Conceptualization, Methodology, Validation, Writing – original draft, Visualization, Project administration, Funding acquisition. **Alexander Nitschmann**: Formal analysis, Investigation, Writing – preliminary draft, Visualization – conceptualization. **Sebastian H. Maier**: Writing – review & editing. **Marcel Büttner**: Writing – review & editing. **Stephan Schönecker**: Writing – review & editing. **Sebastian Marschner**: Writing – review & editing. **Daniel F. Fleischmann**: Writing – review & editing. **Stefanie Corradini**: Resources, Writing – review & editing. **Claus Belka**: Resources, Writing – review & editing. **Christian la Fougère**: Resources, Writing – review & editing. **Raphael Bodensohn**: Resources, Writing – review & editing. **Nathalie L. Albert**: Conceptualization, Writing – review & editing. **Maximilian Niyazi**: Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest:

The authors declare no conflicts of interest related to this work. Authors of this paper participated in the development of guidelines and/or served in committees of professional societies related to the topic of this publication. Of note, this paper is not intended to replace established guidelines, nor has it been developed in a process initiated or driven by professional societies.

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Figures:

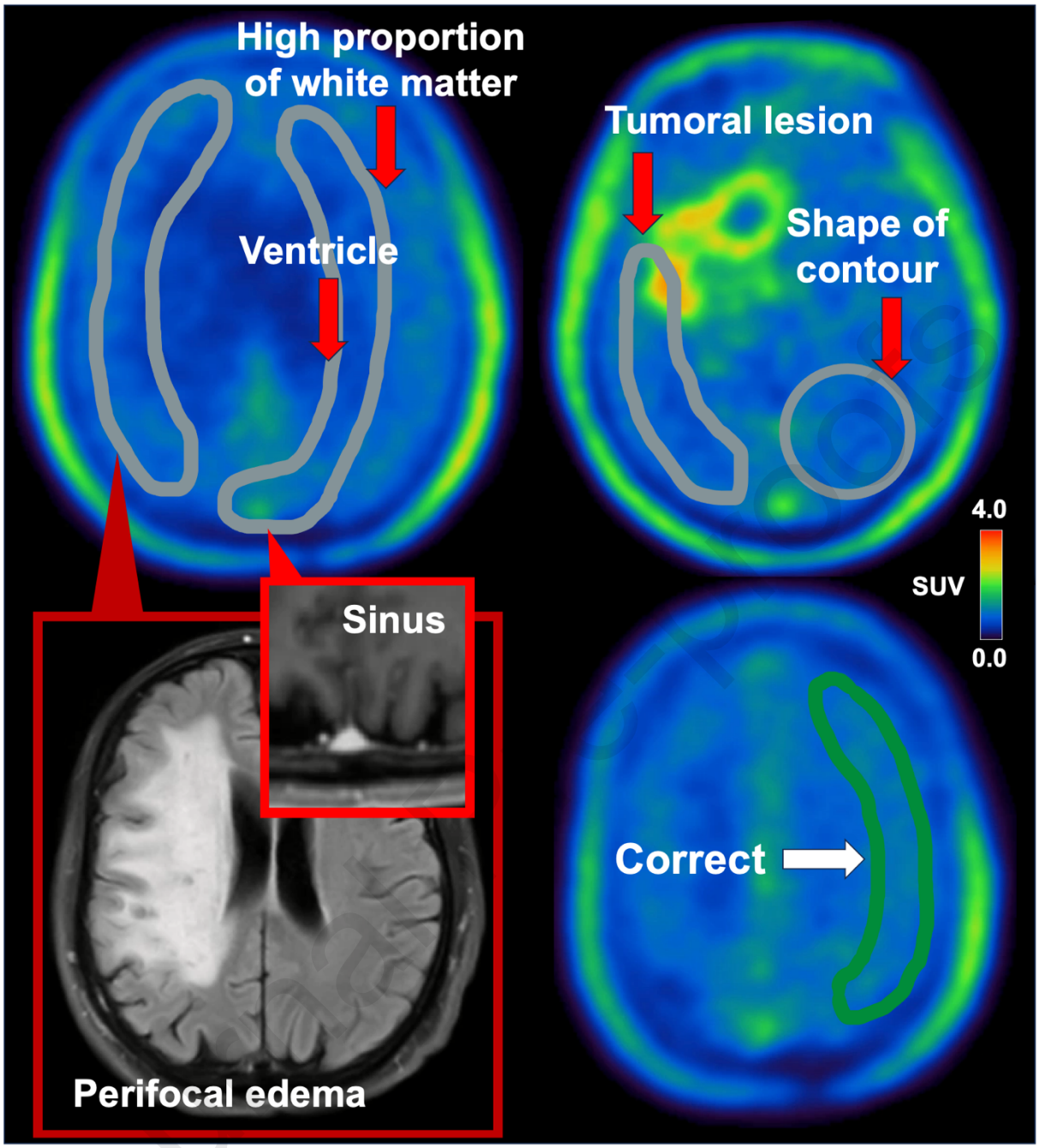

Figure 1. Background activity assessment on FET PET. 63-year-old patient with a right frontotemporal glioblastoma, IDH-wildtype CNS WHO grade 4 status post chemoradiotherapy and 6 cycles of adjuvant temozolomide until 9 months ago. Current MRI (performed 14 days prior to FET PET imaging) showed multiple areas of progressive contrast enhancement and an increase of the perifocal edema especially on the right frontal side. FET PET was performed to differentiate areas of tumor progression from treatment-related reactive changes. Red arrows and arrowheads indicate errors in contouring the regions-of-interest for background activity assessment. SUV = standardized uptake value.

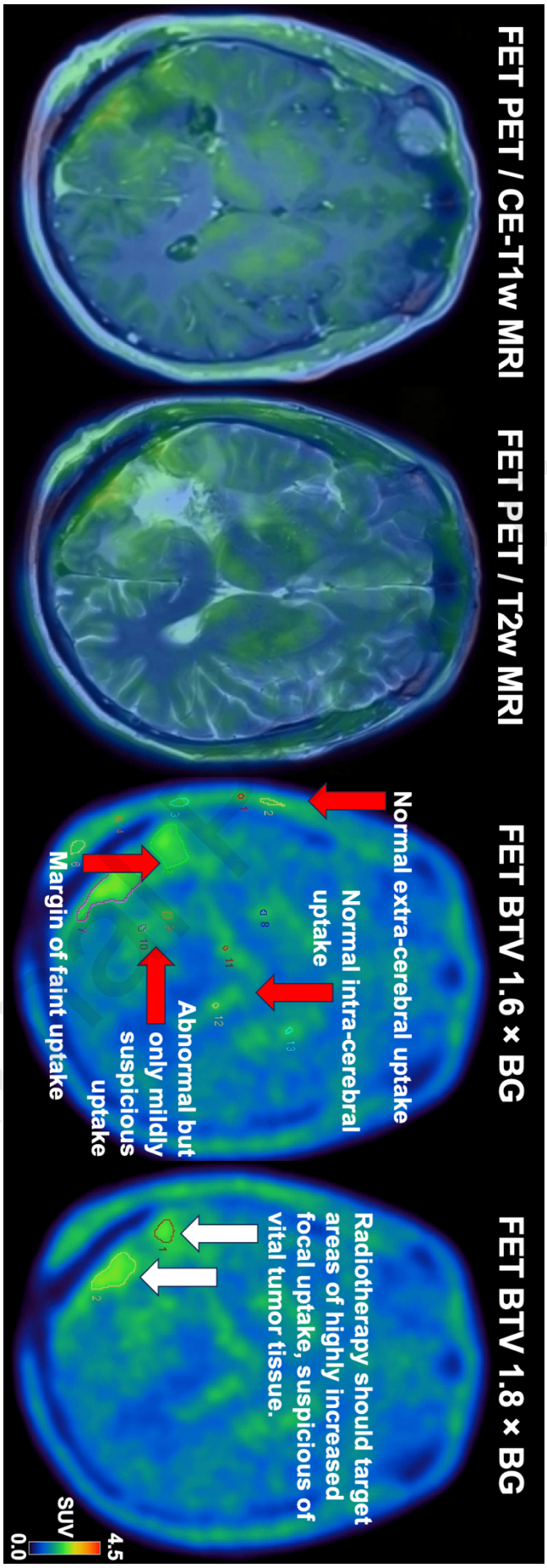

Figure 2. Semi-automatic tumor delineation on FET PET using a TBR threshold. 55-year-old patient with a newly diagnosed glioblastoma, IDH-wildtype CNS WHO grade 4. FET PET has been performed 18 days after surgical resection of a right temporoparietal lesion. Red arrows indicate areas that must be excluded from the target volume. In this case, a TBR threshold of 1.8 × BG on FET PET was favorable to plan radiotherapy of tumor remnants. CE = contrast-enhanced, w = weighted, BTV = biological tumor volume, BG = background, SUV = standardized uptake value.

Declarations

Manuscript: “FET PET-based target volume delineation for the radiotherapy of glioblastoma: A pictorial guide to help overcome methodological pitfalls”

by Adrien Holzgreve et al.

CRediT authorship contribution statement

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