In silico study of pseudoprogression in glioblastoma: collaboration of radiologists and radiation oncologists in the estimation of extent of high dose RT region

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Background and Aim. Oncologists play a vital role in the interpretation of radiographic results in glioblastoma patients. Molecular pathology and information on radiation treatment protocols among others are all important for accurate interpretation of radiology images. One important issue that may arise in interpreting such images is the phenomenon of tumor "pseudoprogression"; oncologists need to be able to distinguish this effect from true disease progression. Exact knowledge about the location of high-dose radiotherapy region is needed for valid determination of pseudoprogression according to RANO (Response Assessment in Neuro-Oncology) criteria in neurooncology. The aim of the present study was to evaluate the radiologists' understanding of a radiotherapy high-dose region in routine clinical practice since radiation oncologists do not always report 3-dimensional isodoses when ordering follow up imaging.
Methods. Eight glioblastoma patients who underwent postresection radiotherapy were included in this study. Four radiologists worked with their pre-radiotherapy planning MR, however, they were blinded to RT target volumes which were defined by radiation oncologists according to current guidelines. The aim was to draw target volume for high dose RT fields (that is the region, where they would consider that there may be a pseudoprogression in future MRI scans). Many different indices describing structure differences were analyzed in comparison with original per-protocol RT target volumes.
Results. The median volume for RT high dose field was 277 ccm (range 218 to 401 ccm) as defined per protocol by radiation oncologist and 87 ccm (range 32–338) as defined by radiologists (median difference of paired difference 31%, range 15–112%). The Median Dice index of similarity was 0.46 (range 0.14 – 0.78), the median Hausdorff distance 25 mm.
Conclusion. Continuing effort to improve education on specific procedures in RT and in radiology as well as automatic tools for exporting RT targets is needed in order to increase specificity and sensitivity in response evaluation.

Key words: pseudoprogression, RANO, glioblastoma, radiotherapy, high-dose field

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INTRODUCTION

Significant effort of the Response Assessment in Neuro-Oncology (RANO) group has led over several last years to improvement in the standardization of follow-up image evaluation for newly diagnosed glioblastoma in both clinical practice and neurooncology trials[1-3]. However, the differentiation of pseudoprogression (PsP, the self-stabilizing or resolving enhanced lesion in early postradiotherapy follow-up imaging, which mimics a progressive tumor most commonly due to inflammation related to therapy and the true tumor progression on early MRI scans remains challenging[4]. Employing rigorous RANO criteria, recent reports indicate incidence of PsP about 11–22% of glioblastoma patients undergoing standard concurrent chemoradiotherapy[5-7].

According to the original RANO criteria from 2010, the glioblastoma progression within the first 12 weeks

after completion of radiotherapy (RT) can only be determined if the majority of the new enhancement is outside of the radiation field (literally beyond the high-dose region or 80% isodose line) or if there is the pathologic confirmation of progressive disease[1]. However, radiation oncologists do not always report three-dimensional RT isodoses while ordering follow-up imaging, even for patients treated within clinical trials. Thus, we questioned the general awareness of radiologists about the spatial location of high-dose RT region, which is needed for valid differential diagnostics of early postradiotherapy MRI. Importantly, the correct evaluation of early follow-up MRI has huge consequences for decision making regarding the continuation of adjuvant treatment or enrollment into clinical trials, for example. The aim of the present study is to stimulate an interdisciplinary collaboration by discussion over definition of the RT high dose region as well as to stimulate the development of automatic tools for easy workflow in reporting parameters of RT treatment plans.

MATERIALS AND METHODS

Patients selection and definition of target volumes

Eight patients with newly diagnosed unifocal glioblastoma who were all treated by the same postoperative RT protocol were included in this study. All patients signed the informed consent allowing the usage of their clinical and imaging data for research purposes in an anonymous form. A planning brain MRI (T2/FLAIR and contrast enhanced T1 sequences) was performed before RT for a subsequent definition of target volumes according to the Radiation Therapy Oncology Group, RTOG approach[8]. The target boost volume, representing the high dose RT region for 60 Gy prescription, was defined as follows: a gross tumor volume was represented by surgical cavity plus the contrast enhancing T1 abnormality on the planning MRI scan with additional margin of 2 cm for the creation of the so-called clinical target volume, covering the location of expected or suspected microscopic disease. This 2 cm margin is reduced around natural barriers to tumor growth to as low as 3–5 mm to non-rigid barriers (brain stem, ventricles) or to as low as 0 mm to rigid barriers (bone, falx). An additional margin of 4 mm is added in all dimensions, including extent beyond bones (3D- isotropic expansion with 2D-manual corrections). With this margin, the final target volume, the so called planning target volume (PTV) is created, where the RT dose is prescribed, representing the high-dose region. This last margin is needed to accommodate all general inaccuracies to ensure delivery of prescribed dose into the clinical target volume (examples of inaccuracies are patient's immobilization and setup during a daily treatment or general inaccuracies of imaging acquisition and postprocessing including contouring). All patients were treated by the volumetric modulated arc therapy (VMAT) RT technique, an advanced form of the intensity-modulated RT, delivering the precisely-sculpted 3D dose distribution around planned volume with steep gradient of dose (80%

of prescribed dose usually within 1 cm, 50% of prescribed dose usually within 2–4 cm). This is the consecutive cohort of patients treated within the same particular clinical trial, where all patients underwent the central review of RT target volumes as well as treatment plan. This led to minimizing the well-known bias of interobserver contouring variability among radiation oncologist.

Radiologists' contouring

Four mutually blinded radiologists were given 8 MR studies (contrast enhanced T1 sequences) which were used for RT planning of 8 included patients, however, they were blinded to RT target volumes which were used in the treatment. Their task was to draw target volume for high dose RT fields – the PTV. In other words, to draw the region, where they would consider possible PsP in future follow-up MRI scans. Subsequently, radiologists contoured a structure which, in their view, represented 80% isodose line. Radiologists have different level of expertise, although all are board certified in general radiology. Except one, they all have more than ten years of experience. One has special brain imaging training, however, the other have daily routine in a cancer center.

Statistical analysis

Basic descriptive statistics were applied for the evaluation of patients' characteristics. Using the VelocityTM software (Varian Medical Systems, Palo Alto, CA), several indices were used for the evaluation of the radiologists' contour accuracy as follows: 1) the absolute and relative volume of radiologists' PTV and 80% isodose, 2) the Dice index of similarity (also called overlap index), which yields a measure of how similar two structures are by comparing the overlap and volume shared (the results is a number on a scale of 0 to 1, where 0 means that the two structures do not share any volume or overlap and a result of 1 means that the two structures are identical in volume and overlap), 3) the surface distance metrics (providing a sense of how far the two structures are from each other. The mean, standard deviation and maximum distances of the points on one surface to the nearest point on the second structure's surface was reported, all in millimeters. The maximum surface distance is known as the Hausdorff distance). The surface distance measure is particularly sensitive to the so-called "panhandle problem" in different segmentation comparison, when only one of the segmentations has a strong local deviation that doesn't necessarily take up much volume but results in a large shape difference. Median values from all 8 cases are reported separately for each radiologist.

RESULTS

The basic characteristics of 8 included patients are summarized in Table 1. With the median follow-up of 13.3 months, 5 recurred (one patient experienced PsP) and 3 patients died. The median volume of PTV and the volume of 80% isodose was 277 ccm (range 218 to 401 ccm) and

Table 1. Patients' disease and postoperative RT characteristics.

Patients' characteristics	n=8	Ref.
Age		
median, (range)	57, (26.1–63.6)	
Sex		
men (%)	4 (50%)	
Karnofsky PS		
100 (%)	3 (38%)	
90 (%)	4 (50%)	
80 (%)	1 (12%)	
Extent of resection		
GTR (%)	4 (50%)	
STR (%)	4 (50%)	
MGMT status		
Methylated (%)	3 (38%)	
IDH (R132H) status		
Mutated (%)	2 (25%)	
ATRX status		
Mutated (%)	1 (17%)	
EGFR status		
Amplificated (%)	8 (100%)	
Ki-67		
Median (range)	35 (20–70)	
RPA (Wee et al., 2017)		9
Class I (%)	1 (12.5%)	
Class II (%)	5 (62.5%)	
Class III (%)	2 (25%)	
Time to start RT (weeks)		
Median (range)	5.95, (5.1–6.1)	
Length of RT (days)		
Median (range)	42.5, (41–49)	
PTV volume (ccm)		
Median (range)	277, (218–401)	
80% isodose volume (ccm)		
Median (range)	473, (328–596)	

PS: performance status; GTR: gross total resection; STR: subtotal resection; MGMT: O6-methylguanin-DNA-methyltransferase; IDH: isocitrate dehydrogenase; R: arginine; H: histidine; ATRX: alpha-thalassemia/mental retardation syndrome X-linked; EGFR: Epidermal growth factor receptor; RPA: Recursive partitioning analysis; RT: radiotherapy; PTV: planning target volume

Fig. 1. Volumes of planning target volumes (PTV) in all 8 patients defined per protocol by radiation oncologist and by the estimate of four radiologists.

DISCUSSION

The results of this in-silico study indicate the need for higher awareness and closer collaboration of clinical radiologists and radiation oncologists during follow up of patients after glioblastoma radiotherapy. Volumes of radiologists' PTV were only 31% of original, per-protocol, volumes constructed by radiation oncologists and the median Dice index of similarity only of 0.46 (Fig. 2). Thus, with missing information or with weaker awareness about the location of the high-dose RT field, many PsP on early MRI can by mistakenly described as clear progression. This need for greater collaboration and access to treatment planning information is a valued message to the medical neuro-oncology community. Guidelines for the evaluation of PsP is an ongoing process employing advanced multiparametric imaging[4,10,11] or even introducing a conceptual shift with the proposal of post-radiation MRI examination as the baseline for subsequent response assessment[12]. Also, the RANO group is continuously developing and releasing updates of response criteria tailored for many specific situations in neuro-oncology as are the immunotherapy RANO criteria[13], criteria measuring patient-reported outcomes[14] or guidelines for clinical trial design for patients with brain metastases[15,16].

Despite the obvious assumptions about continuing education and collaboration between radiologists and radiation oncologists, the clinical utilization of RANO criteria in real-world clinical practice is still, almost 9 years after the publication of the original RANO criteria, limited. In the current survey of glioma imaging in 220 European centers (almost 60% academic centers), most respondents (60%) relied on a visual estimate of tumor size while only 27% report the usage of RANO guidance[17].

Collaborative efforts of radiologists and radiation oncologists for a routine utilization of RANO criteria represents a suitable trend related to new establishment of multidisciplinary teams with solid know-how in MR imaging as well as RT treatment planning. In the field of clinical radiology, an organ specific sub-specialization is warranted as well. Furthermore, the described collaboration represents one of the cheapest and most straightforward way of improving the care of our glioblastoma patients. A routine

473 ccm (range 328 to 596 ccm), respectively. Four patients underwent initial gross total resection resulting in no contrast enhancement on planning MRI.

Median absolute volume of PTV drawn by radiologists was 87 ccm (range 32–338), which is a paired difference of 31% (range 15–112%) of the PTV volume drawn by radiation oncologists (the analysis of pooled data from all 4 radiologists and all 8 included patients). Individual results are summarized in Fig. 1 and Table 2, together with other measured indices. The median Dice index of similarity was 0.46 ranging from 0.14 to 0.78. The median value of mean surface distance was 11 mm, SD 6 mm. The median Hausdorff distance reached 25 mm ranging from 15 to 49 mm.
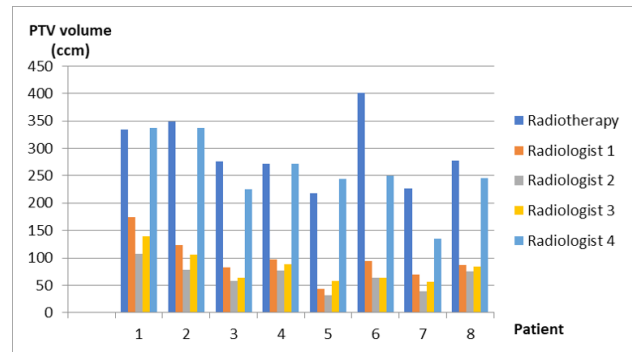
Table 2. Comparison of radiologists' view of target volume and true volumes used in RT.

	Rad 1	Rad 2	Rad 3	Rad 4	Average (Rad 1–4; pooled individual data)
PTV volume (absolute; ccm)	91	70	74	248	87
Median (range)	(44–174)	(32–107)	(56–140)	(135–338)	(32–338)
PTV volume (relative; %)	31%	22%	28%	93%	31%
Median (range)	(20–52%)	(15–32%)	(16–42%)	(60–112%)	(15–112%)
80% isodose volume (absolute; ccm)	285	224	405	518	353
Median (range)	(167–499)	(52–336)	(238–582)	(341–629)	(52–629)
80% isodose volume (relative; %)	69%	51%	100%	119%	79%
Median (range)	(44–98%)	(16–67%)	(40–119%)	(79–124%)	(16–124%)
Dice index of similarity	0.47	0.32	0.4	0.69	0.46
Median (range)	(0.34–0.65)	(0.14–0.48)	(0.27–0.56)	(0.6–0.78)	(0.14–0.78)
Mean surface distance measurement (mm)	11	14	12	7	11
Median (range)	(7–15)	(12–18)	(9–20)	(5–8)	(5–20)
SD (range)	6 (5–7)	7 (6–9)	7 (5–13)	4 (3–5)	6 (3–13)
Max surface distance measurement (Hausdorff distance; mm)	24	27	25	21	25
Median (range)	(22–31)	(25–31)	(22–49)	(15–26)	(15–49)

Rad: radiologist; PTV: planning target volume; SD: standard deviation

reporting of 3-dimensional isodoses (or at least of 95% isodose representing the high-dose RT region) by radiation oncologists would further improve the response evaluation of all cancers. Nowadays we are witnessing rapid evolution of advanced RT technology enabling more and more conformal irradiation with steep dose gradient delivered for example by the VMAT technique. The same postoperative RT technique was employed for patients included in the present study. The current RT techniques and procedures are completely different compared to those used in patients enrolled in the landmark Stupp's glioblastoma trial, the current standard of care[18,19]. Nowadays, more advanced RT techniques are available including the investigation of target definitions based on positron emission tomography imaging[20,21]. In this present study, the more accurate radiologists' estimation was for 80% isodose (the averaged volume was 79% of the original volume of this isodose region) comparing to the estimation of PTV volume (only 31% of the original PTV volume). Actually, this should be interpreted as an unrealistic estimate of the possibilities of current RT technology. In the figure 3, isodoses of the representative RT treatment plan delivered by a non-coplanar (that is with the rotation of the table on the RT treatment unit) VMAT technique show a steep dose gradient with 80% isodose within 1 cm around PTV.

Unfortunately, many different types of software are used for image visualization among radiology departments, which limits the possibilities of automatic reports of RT structures or isodoses from the most common RT treatment planning systems. Exports from these RT systems are often in a DICOM-RT (Digital Imaging and Communications in Medicine – RT) format not easily readable by a software used for general image visualization. Based on the observation from the present study, we currently established in our institution routine reporting of RT structures and 95% isodose employing on-demand script for an easy ("push one button") export from the RT planning software (Eclipse™, Varian medical systems, Palo Alto, CA, USA) into Picture Archiving and Communicating System (PACS) utilized by institutional radiologists. Technical issues will be published separately as well as the results of the subsequent interventional study whereby the diagnostic radiologists are introduced to the standard RTOG target volume approach and then allowed to contour the PTV, thus demonstrating the potential improvement with collaboration.

The limitation of this study may be the limited number of participating radiologists and the number of patients used for contouring. On the other hand, it seems sufficient to stimulate improvements in department's collaboration within our institution as well as in neuro-oncology centers within the national neuro-oncology centers network. A clear limitation is in the willingness of blinded radiology participants to be "tested" with the aim to objectify possibly worse knowledge. Yet, this may be the reason for the overall uniqueness of the present study. The other limitation lies in special contouring tools used in the RT treatment planning software which may seem not user friendly for new users. All radiologists included in the present study underwent short education about basic contouring tools.
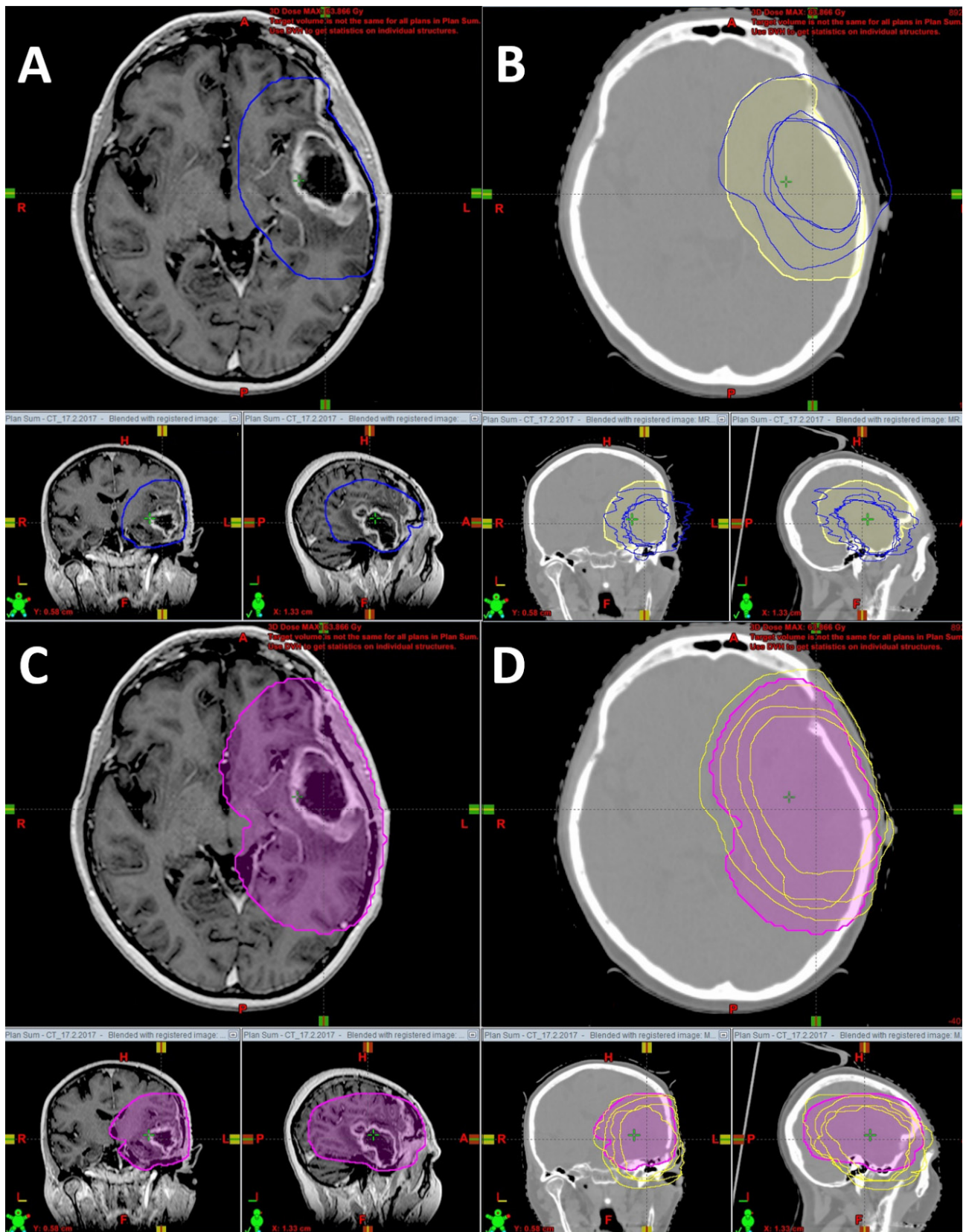
Fig. 2. Overplayed comparison of radiologists' and radiation oncologists' contours in selected representative patient. A: per protocol PTV (planning target volume). B: original PTV in yellow color, overlayed by 4 radiologists' contoure (4 blue lines). C: 80% isodose from original treatment plan overlayed by 4 radiologists' estimate (4 yellow lines on D section).
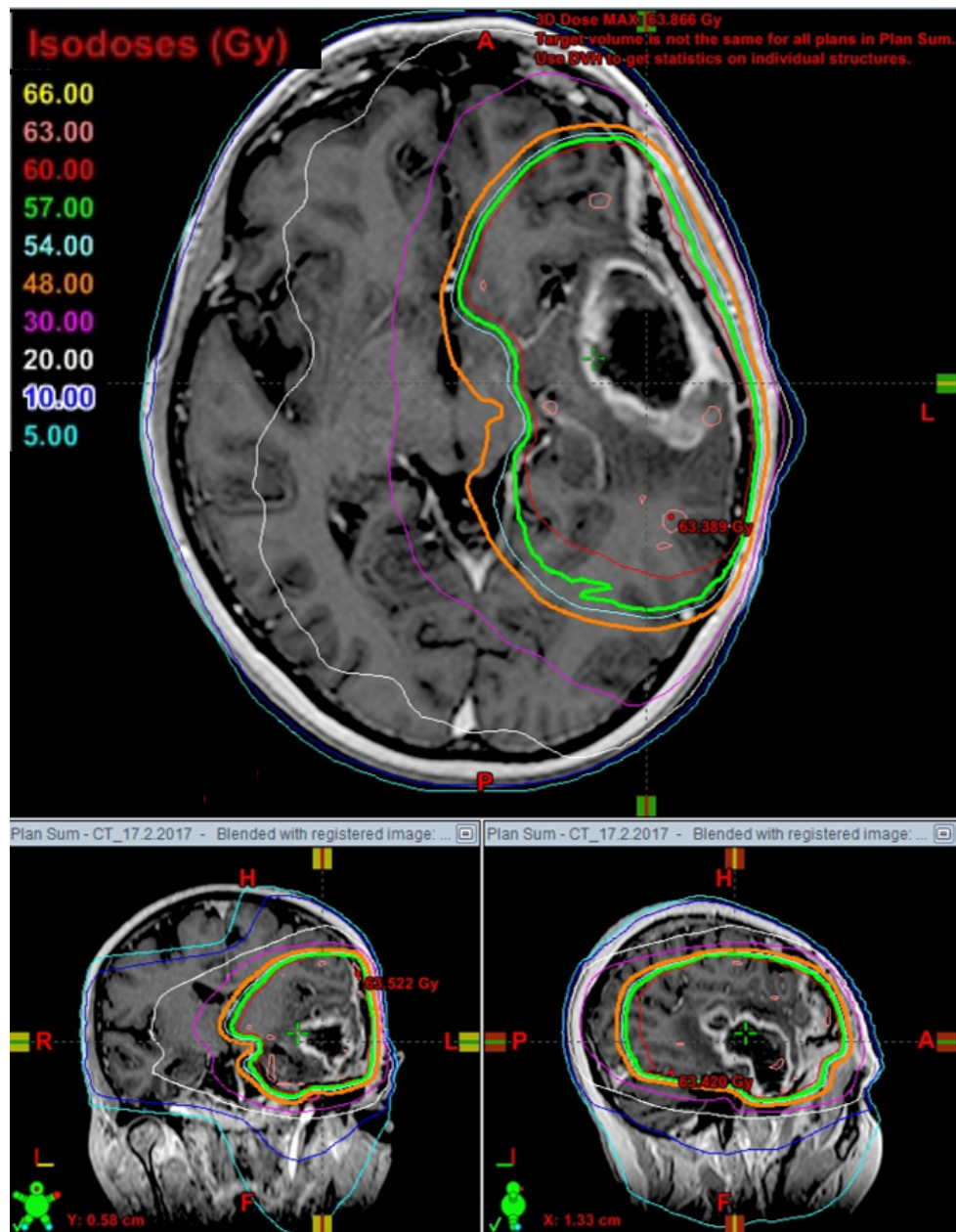
Fig. 3. Isodoses from original radiotherapy treatment plan of selected representative patient. Stronger green line represents 57 Gy (that is 95% isodose, encompassing planning target volume) and stronger orange line represents 48 Gy (that is 80% isodose).

CONCLUSION

In conclusion, the RANO criteria represent currently the ideal approach to treatment response evaluation in neuro-oncology, however still with a limited utilization in real-world daily clinical practice. The exact knowledge about the location of high-dose RT region is needed to valid determination of PsP according to the RANO criteria. Based on the observed data in this study, a close collaboration between radiologists and radiation oncologist is needed in evaluation of glioblastoma patients. This continuing effort to mutual education about specific procedures in RT and in radiology is needed also for further increase of specificity and sensitivity in response evaluation. Automatic tools for exporting of RT target volumes, or even isodoses, in a format readable by routinely used imaging software in radiology departments would be highly useful for further improvement of routine clinical practice.

ABBREVIATIONS

RANO, Response Assessment in Neuro-Oncology; PsP, pseudoprogression; MRI, magnetic resonance imaging; FLAIR, Fluid-attenuated inversion recovery; VMAT, volumetric modulated arc therapy; PS, performance status; GTR, gross total resection; STR, subtotal resection; MGMT, O6-methylguanin-DNA-methyltransferase; IDH, isocitrate dehydrogenase; R, arginine; H, histidine; ATRX,

alpha-thalassemia/mental retardation syndrome X-linked; EGFR, Epidermal growth factor receptor; RPA, Recursive partitioning analysis; RT, radiotherapy; PTV, planning target volume; Rad, radiologist; SD, standard deviation.

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