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Radiotherapy of Skull Base Meningioma: Radiological Efficacy and Tumor Volume Kinetic

Youssef Brahimi[1], Delphine Antoni[1,2], Robin Srour[3], François Proust[4], Alicia Thiery[5], Aïssam Labani[6] and Georges Noel[1,2*]

[1]University Radiation Oncology Department, Comprehensive Cancer Center Paul Strauss, France

[2]Laboratory of Radiobiology, Federation of Translational Medicine, Strasbourg University, France

[3]Neurosurgery Department, Pasteur Hospital, France

[4]Neurosurgery Department, University hospital of Strasbourg, France

[5]Epidemiology and Biostatistics Department, Comprehensive Cancer Center Paul Strauss, France

[6]Departement of Radiology, University hospital of Strasbourg, France

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Corresponding author:
Georges Noel,
Laboratory of Radiobiology, EA 3430, Federation of Translational Medicine, Strasbourg (FMTS), Strasbourg University, F-67000 Strasbourg, France,
Email: gnoel@strasbourg.unicancer.fr

ABSTRACT

Purpose: To compare 4 methods of quantitative measurements of the radiological response after irradiation of skull base meningiomas.

Methods and Materials: Radiological and clinical data from 35 patients treated between January 2009and 2014were reviewed. Most of the lesions were localized in the cavernous sinus (60%). Patients were treated either with fractionated stereotactic radiation therapy (54%) or helicoïdal tomotherapy (46%). The median delivered dose was 54.1 Gy (54 – 60). Median follow-up was 44 months (range: 24 – 77). The four methods of radiological measurements were, i/ volumes measured by serial delineation with dedicated software (software-Tumor Volume (TV)), ii/ volume calculations (calculated-TV) from the values of three diameters and iii/ measurements of the Largest Tumor Diameter (LTD), iv/ the cross product of two largest orthogonal diameters (CP).The evaluation of the overall radiological response (ORR) was based on a comparison between the quantitative measurements performed at baseline with the latest available for each patient. Among 206 MRI of follow-up of the 35 patients, 151 were suitable to reach the criteria required for this study.

Results: For the four radiological measurement techniques, there was a significant decrease between the baseline and the last follow-up values ($p < 0.05$). Partial tumor response for software-TV, calculated-TV, LTD and CP were 94%, 94%, 6%, 3%, respectively. ORR was much more marked on volumetric analyses than on LTD and CP measurements, software-ORR = -29.4% (range: -83.9 to 2); calculated-ORR = -30.3% (range: -60.1 to 8.1), LTD-ORR = -8.1 % (range: -35.4 to 2) and CP-ORR = -15.8 (range: -55.5 to 10.3), respectively. Analysis of tumor kinetics according to the four methods showed a gradual and significant decrease in tumor size from 6 months to 60 months after irradiation.

Conclusions: Radiological follow-up after irradiation of meningiomas should be based on a computerized volumetric measurement.

INTRODUCTION

The main objective of skull base meningioma treatments is to reach local control combined with neurological preservation. [1-8].Surgery with radical excision remains the reference treatment of meningiomas [9].However, for base of the skull meningiomas, surgery leads to an unsuitable morbidity rate ranging from 10 to 66.8% [4,5,10,11] and a non-acceptable mortality rate reaching up to 8.3% [5]. Even with modern surgical techniques and by high level surgery teams, Gross Tumoral Removal (GTR) of the base of the skull meningioma was gradually abandoned in favor of the Subtotal Tumoral Resection (STR) that results in less morbidity [10,11]. However, STR increases the risk of recurrence compared to GTR [4,2-14].Then, radiotherapy has been progressively more and more used and is now a well-established, safe and effective treatment both in exclusive and adjuvant treatment [15-27].The evaluation of radiotherapy effectiveness is generally measured on the clinical response of the neurological meningioma-induced impairments and the ability to obtain a radiological shrinking of the tumor. Published clinical efficacy rates varied from 20 to 67% [15,17,21-23,25,26,28].

The use of radiological imaging is fundamental to evaluate the efficacy of anti-tumor therapies and several methods to measure the tumor response has been published [29,30]. For meningiomas, depending on the chosen evaluation criteria, the radiological control can reach 95%, because, in these slow growing tumors, stabilization was often considered positively [25,28,31-34]. The radiological response is rarely detailed; there was often too much heterogeneity of the criteria to draw consistent conclusions [15-17,20,21,23,25,27,33-37]. Most of series reported clinic-radiological discordance between clinical response and tumor shrinkage [23,27,33]. There are no standardized criteria to evaluate the radiological response after irradiation of meningiomas.All criteria used in publication has been disputed. RECIST criteria could not be apply to meningiomas because of their presumed radio resistant [2,3]. 2D method using two orthogonal diameters revealed no implement compared to the previous evaluation methods [30,38,39]; a reduction of the largest diameter of at least 2mm is often unsuitable for complex shape lesions[2]. Different levels of reduction have also been proposed as radiological response criteria [27,34]. Some studies have reported that volumetric analyzes were more reliable than diameter measurements [38,40-42].The first method consists of computerized measurement of the Tumor Volume (TV) with dedicated radiotherapy software after delineation of the lesion on follow-up serial MRIs, and the second consists in calculating it from measurements of the three diameters. However, the latter is more disputable because of its approximation by considering the lesions spherical or ellipsoid [1,2,42-44]. This study was performed to analyze, by four measurement methods, the radiological response and tumor kinetic after irradiation of base of skull meningiomas. A correlation between these four radiological responses was also investigated.

MATERIAL AND METHODS

Patients characteristics

Between January 2009 and January 2014, 35 patients were treated with radiotherapy for skull base meningioma. Radiological and clinical data were retrospectively reviewed to perform a quantitative and kinetic follow-up of radiological response. Most of the patients were women (94%) and the median average age was 59 years (range: 43 – 81). Most of the lesions were located in the cavernous sinus (60%).

Patients were treated either with Normofractionated Stereotactic Radiation Therapy (NFSRT) (54.3%) and Helicoidal Tomotherapy (HT) (45.7%). The prescribed dose was 54 Gy in 30 fractions of 1.8 Gy except for one patient with histological confirmed bone invasion who received 60 Gy in 30 fractions of 2 Gy.

Follow-up

The median follow-up was 44 months (range: 24-77). The patients were reviewed at 6 months from radiotherapy completion and then every year or every two years with a clinical examination and an MRI.

Follow-up MRIs could be performed in the university or equivalent hospitals, following a relevant procedure describing the minimum required sequences or in others hospital with a less optimized set of images. All the MRIs were retrieved and transferred on a local Picture Archiving and Communication System (PACS). In total, 206 MRIs for the 35 patients were available on the PACS for the period from baseline to the longest follow-up.

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Radiological evaluations

Four methods of radiological follow-up based on quantitative measurements were tested and compared. Radiological response has been evaluated on variations of i/ volumes measured by serial delineation with dedicated software (software-TV), ii/ volume calculations (calculated-TV) from the values of three diameters and iii/ measurements of the Largest Tumor Diameter (LTD), iv/ the cross product of two largest orthogonal diameters (CP).The evaluation of the Overall Radiological Response (ORR) was based on a comparison between the quantitative measurements performed at baseline with the latest available for each patient and with each follow-up method.

Table 1: Thresholds of response according to the measurements methods.

	Software-TV$	Calculated-TV$	2D-CP*	LTD**
Complete Response (CR)	Disappearing	Disappearing	Disappearing	Disappearing
Partial Tumor Response (PTR)	> 5% of shrinkage	> 5% of shrinkage	> 50% of shrinkage	>30% of shrinkage or 2 mm decrease£
Stable Tumor (ST)	Not PTR nor PT	Not PTR nor PT	Not PTR nor PT	Not PTR nor PT
Progressive Tumor (PT)	> 5% of increase	> 5% of increase	> 25% of increase	> 20% of increase

2D-CP: 2D Cross Product; LTD: Largest Tumor Diameter; TV: Tumor Volume
$: Arbitrary current study evaluation
*: Base on WHO guidelines
**: According to RECIST
£: not used for kinetic evolution

To allow an estimation of the TV with a risk of error less than 10%, with the available software, a minimum of 5 slices was required [42]. When MRIs were not adapted to this TV measurement, the software either could not perform it, either the volume obtained was unreliable; indeed, these MRIs were not considered for the volumetric analysis. Furthermore, usable MRIs should include the axial sequences T1 gado MPR with constant and small slice thickness (maximum 5 mm) and without gap. Among the 206 performed MRIs, 151 replied to these criteria; this represents 4.3 MRIs per patient (1-6)

To perform an analysis of tumor kinetics, follow-up checkpoints were defined at 6 months from the end of radiotherapy and then every 12 months thereafter up to a limit of 60 months. MRI available at 6, 12, 24, 36, 48 and 60 months after radiotherapy completion were, respectively 17, 18, 27, 26, 16and 9. Radiological results were systematically compared with those of the baseline. The ORR and tumor kinetic were calculated in absolute and relative values. Thresholds of complete response, Partial Tumor Response (PTR), Stable Tumor (ST) and Tumor Progression (TP) for each method of measurements are summarized in (Table 1).

Volumetric measurements (Software-TV)

This method was considered as the reference method of radiological follow-up in this study [2,3,45-49]. All the MRIs have been transferred from the PACS to Artiview delineation software (Aquilab®, Loos, France). The enhancing tumor volume on T1 3D MPR sequence was delineated on each slice of all MRIs by the same operator (YB). The TV was determined by the software considering the area delineated on each slice and the slices thickness [42] (Annex 1).

Although some authors used thresholds from 10 to 20% for PTR, we assumed that a threshold at 5% of the baseline tumor volume is more relevant because we supposed that a very small shrinkage could be enough to obtain a clinical improvement of the initial symptoms. In contrast, Tumor Progression (TP) was considered in case of increased > 5% of the baseline volume for the same reason i.e. a small increase should sufficient to provoke clinical symptom.

Calculation of volumes (Calculated-TV)

Formulas were those to calculate the ellipsoid and spherical forms [1] (Annex 1). The three diameters were measured on each initial MRI and on each follow up MRI for all patients. The tumor length and width were measured on the transverse plan on the same slice to ensure a minimum of reproducibility of the measure. The height was measured either on the sagittal sections or on the coronal sections on the initial MRI. Thereafter, on follow-up MRI, the diameters were always measured on the same sections as on the initial MRI for each patient.

Variation of 2D Cross Product (CP) measure

This method used the cross product of the two largest orthogonal diameters. CR, PTR, ST, PT criteria are in (Table 2)

Variation of the Largest Tumor Diameter (LTD)

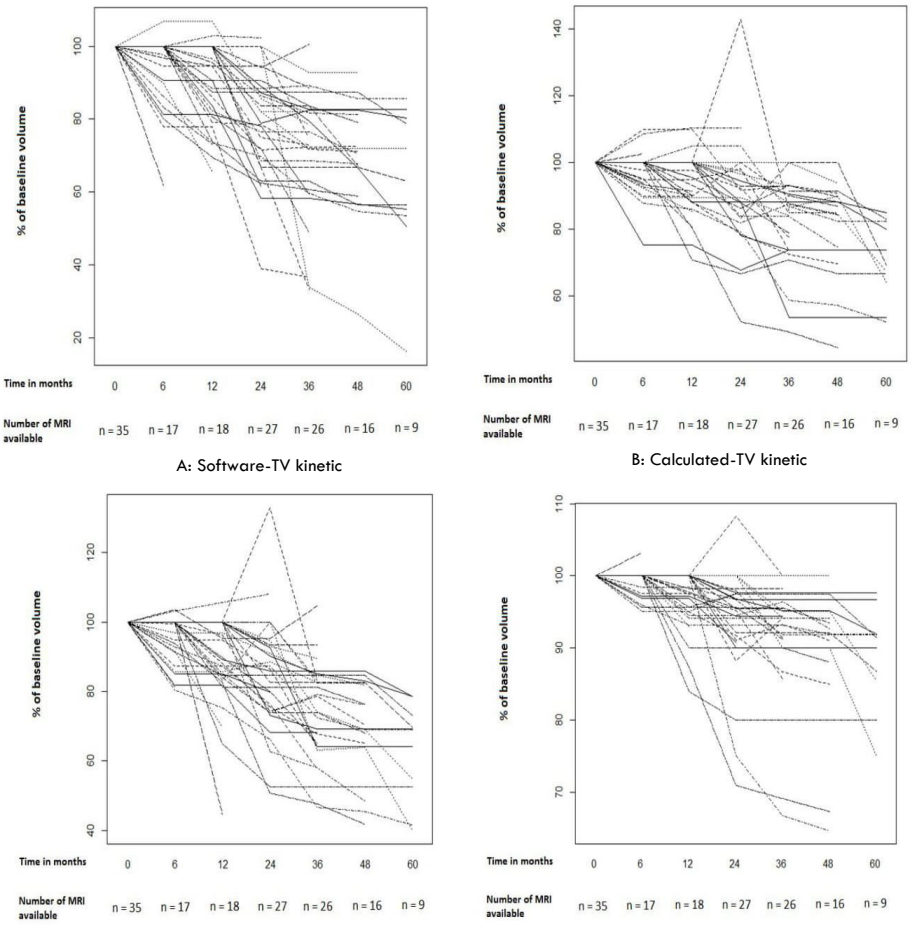
We used the RECIST criteria to measure the largest tumor diameter [30,39]

As already used, we also considered PTR for a 2 mm decrease of the LTD [24,50]. A monitoring of tumor kinetics based on variations of the LTD was also carried out and compared with the volumetric analyzes.

Table 2: Overall Radiological Response (ORR).

lues	Software TV	Calculated TV	CP of orthogonal diameters	Largest tumoral diameter
Baseline median (min - max)	9.6 ml (0.3 - 36.6)	21 ml (0.6 - 67.4)	11.4 cm² (0.7 - 34.2)	44 mm (12 - 74)
Last follow-up median (min - max)	6.8 ml* (0.1 - 26.5)	14.2 ml* (0.5 - 53)	9.3 cm²* (0.6 - 23)	40 mm* (12 - 65)
Absolutemedianchange (min - max)	-3 ml (-31 to 0)	-4.5 ml (-40.5 to 1.3)	-1.8 cm² (-16.3 to 0.6)	-4 mm (-18 to 1)
Relative medianchange (%) (min - max)	-29.4 (-83.9 - 2)	-30.3 (-60.1 - 8.1)	-15.8 (-55.5 to 10.3)	-8.1 (-35.4 to 3.2)

Significant difference between baseline and final measurements: $p < 0.05$



A: Software-TV kinetic

B: Calculated-TV kinetic

C: Cross product of orthogonal diameter kinetic

D: Largest tumor diameter kinetic

Figure 1: kinetic of meningioma according to different measurements methods.

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Statistical analysis

Comparison between baseline software-TV, calculated-TV, CP and LTD was done with a Man Whitney test. The measurements collected at each follow-up checkpoint were compared to the baseline values also with a Wilcoxon test for each radiological monitoring technique. The ORR was evaluated with a Wilcoxon test between initial and final tumor volumes and size. The results were considered significant if $p<0.05$. Correlation between baseline and ORR was expressed with the Spearman's rho coefficient.

RESULTS

For the 35 patients of the current series, the last available radiological reports concluded to 4 PTR and 31 ST. However, it was only qualitative descriptions by the radiologist, there were no quantitative tumor measures available. Furthermore, most of the comparisons were performed between the two last MRIs.

Baseline measurements

Except for the comparison between the baseline software-TV and the baseline CP ($p = 0.6$), the comparison of each group baseline measures was significantly different ($p < 0.05$). The baseline Calculated-TV was more than 2-fold elevated than Software-TV respectively 21 mL (range: 0.6-67.4) versus 9.6 mL (range: 0.3-36.6).

Overall Radiological Response (ORR)

The ORRs are summarized in the (Table 2).

Software-TV: PTR was observed in 33 patients (94%) and ST in two patients. Software-TV increased in less than 1% for one patient and 2% for the second one. Baseline and at last follow-up median software-TV were, respectively 9.6 mL (range: 0.3 – 36.6) and 6.8 mL (range: 0.1 – 26.5). The difference between the two volumes was statistically significant ($p<0.05$) with mean relative and absolute reductions of-29.4% (range: -83.9 to2) and -3 mL (range:-31 to 0), respectively ($p < 0.05$), (Table 2).

Calculated-TV: PTR was observed in 33 patients (94%) and ST and TP in two patients. The ST and TP represented respectively a 4.7 and 8.1% increase of the volume. Baseline and follow-up median calculated-TV were, respectively 21 mL (range: 0.6-67.4) and 14.2 mL (range: 0.5-53). The difference was statistically significant ($p < 0.05$) with median relative and absolute calculated-TV reductions, respectively, of 30.3% (range: -60.1 - 8.1) and -4.5 mL (range: -40.5-8.9).

Baseline calculated-TV was significantly higher than baseline software-TV ($p<0.05$).

2D Cross product (2D-CP): PTR according to the WHO criterion was observed in 1 patient (3%), ST in 34 patients (97%). The median baseline and last follow-up 2D-CP were 11.4 cm^2 (range: 0.7 – 34.2) and 9.3 mm (range: 0.6 – 23), respectively. The difference was statistically significant ($p < 0.05$) with a median relative and absolute, respectively, of -15.8% (range: -55.5 - 10.3) and -1.8 cm^2 (range: -16.3 –0.6).

Largest Tumor Diameter (LTD): PTR according to the RECIST criterion was observed in 2 patients (6%), ST in 33 patients (94%). The median baseline and last follow-up LTD were 44 mm (range: 12-74) and 40 mm (range: 12-65), respectively. The difference was statistically significant ($p < 0.05$) with a median relative and absolute, respectively, of -8.1% (range: -35.4 - 8.5) and -4 mm (range: -18 - 1).

A decrease of at least 2mm was found in 23 patients (65.7%).

Tumor kinetic

With the four radiological monitoring techniques, there was a continuous and significant decrease in volume and size of tumors from 6 to 60 months (Figure 1).

Software-TV: Six-, 12-, 24-, 36-, 48- and 60- months mean absolute reduction of software-TV were -1.03ml (SD 1.05), -2.3 ml (SD 1.8), -2.6 ml (SD 2.5), -3.9 ml (SD 5.1), -5.2 ml (SD 6.3) and -7.3 ml (SD 9.2), respectively. At each time, difference from baseline was statistically significant ($p < 0.05$). Figure 1A represents software-TV kinetics after irradiation.

Calculated-TV: Six-, 12-, 24-, 36-, 48- and 60- months mean absolute reduction of calculated-TV were -1.5 ml(SD 2.2), -4.2 ml (SD 4.5), -4.1 ml (SD 4.8), -6.8 ml(SD 7.2), -9.9 ml(SD 8.1 and, -13 ml(SD 12.7),respectively. At each time, difference from baseline was statistically significant ($p < 0.05$). At each time, difference from baseline was statistically significant ($p < 0.05$).Figure 1B represents calculated-TV kinetics after irradiation

2D Cross product (2D-CP): Six-, 12-, 24-, 36-, 48- and 60-months mean absolute reduction of 2D-CP were -0.6 cm^2 (SD 1.20), -1.5cm^2 (SD 1.7), -1.9cm^2 (SD 2.5), -2.9cm^2 (SD 3.6), -3.8cm^2 (SD 4.4) and, -5.2 cm^2 (SD 5), respectively. At each

time, difference from baseline was statistically significant ($p < 0.05$). Figure 1C represents 2D-CP kinetics after irradiation.

Larger tumor diameter (LTD): Six-, 12-, 24-, 36-, 48- and 60-months mean absolute reduction of the largest diameter were0.65 mm (SD 1.06), -2.3 mm (SD 2), -2.9 mm (SD 3.7), -3.8 mm (SD 4.3), -5.6 mm (SD 5.2)and, -5.4 mm (SD 3.9), respectively. At each time, difference from baseline was statistically significant ($p < 0.05$). Figure 1D represents LTD kinetics after irradiation.

DISCUSSION

Although clinical response rate was often high and radiological evaluation considered very satisfying, most of series reported clinic-radiological discordance between clinical response and tumor shrinkage [23,27,33]. Hypotheses to explain clinical improvement by other phenomena than tumor shrinkage has been proposed [16,27]. This clinic-radiological dissociation may reflect an underestimation of the tumor reduction and its impact on clinical efficacy. This hypothesis is also supported by the fact that, in the few studies that performed volumetric follow-up of meningiomas, tumor reduction rates are much higher than in studies that reported a radiological response simply based on a radiological description of lesions or measurements of the larger diameter, respectively 33.2% to 100% [1,2,10,45-49,51] versus 3.6% to 58% [15-17,21,25-27,31-37,52,53]. Then, it is essential to evaluate quantitatively the efficacy of a radiation therapy [45]. Radiological evaluation seems obviously, the best tool to evaluate radiation treatment [29].

Due to the slow radiological response of the meningiomas and their supposed radio resistance, some authors have suggested that RECIST criteria were not adapted to the evaluation of the tumor response in case of benign tumors [2,3]. Since 2000, the one-dimensional (1D) measurements of the RECIST criteria substituted the bi-dimensional (2D) measurements derived from the WHO criteria, after that several studies have shown that the former was more reliable and reproducible than the latter and that results were comparable in terms of tumor response [30,38,39]. Some authors proposed after irradiation of meningiomas at least 2 mm reduction of the LTD to conclude to a tumor response [24,53]. This method has also been disputed because of its unsuitability for complex shaped lesions [2].

Volumetric measurements were considered the reference of our study. Indeed, it was demonstrated that this method could detect very small variations in volumes, which other radiological methods cannot offer so precisely [40]. However, the manual delineation is very time consuming. To simplify the method, TV can be estimate from mathematical formulas that take in account the three diameters in the three dimensions of the lesion. However, these calculations have been disputed because they overestimated the TV by assuming geometric shapes to the lesions [1,43,44].

Thresholds for the volumetric have not been previously clearly defined. Some authors proposed to considered increase or decrease of 10, 15 or 20% to specify TP and PTR, respectively [1,45,47,48]. Because of the close vicinity of lots of critical organs of base of the skull meningioma, because of the onset or resolution of symptoms although the meningioma often seems not change, we considered that a very small change of volume should be responsible of clinical improvement or impairment. Thus a -5% from baseline change has been chosen to determine PTR and a +5% increase from baseline to define PT. This study is the first to compare five methods of radiological response and four methods for kinetic responses. Indeed, some authors clearly demonstrated the mathematical reasons that could explained the discrepancies between the 1D, 2D and volumetric measurement [29,38]. A 20% increasing in 1D measurement corresponds to an increase of 44% in 2D measurements whereas the threshold of progression is fixed at 25% in the WHO criteria [29,38,54,55]. Furthermore, in three dimensions, this would be equivalent to a 73% increase in tumor volume [38,55]. Thus, very small variations in diameter can be manifested by significant variations in volume.

This was perfectly demonstrated in the current study when comparing volumetric and LTD radiological response. In absolute value, the mean reduction between baseline and last follow-up LTD was -4 mm (range: -18 to 1). This was equivalent to a relative reduction of the baseline LTD of -8.1% (range: -35.4 to 3.2). In comparison, there were relative diminutions of -29.4% (range: -83.9 to 2) on software-TV and -30.3% (range: -60.1 to 8.1) on calculated-TV. This demonstrates the risk of ignoring a tumor response by the LTD method compared to the volumetric ones. The analysis of the tumor kinetics based on the follow-up of the LTD showed a significant and continuous

decrease from 6 to 60 months after the radiotherapy as well the analysis of the volumes. However, this tendency toward tumor decrease was much less marked than with the reduction of volumes, demonstrating once again that the follow-up by volumes is much more sensitive.

Because this analysis is retrospective, results could be hugely disputable. The assumed choice of a 5% variation to determine volumetric thresholds should be confirmed in future analyses of others groups.

Only one physician has performed all measurements during a short period. One could argue that a delineation performed by several physicians could improve quality of it. We considered that one delineator, well trained; multiplying the delineations of the same kind of tumor, localized in the same area, decreased the risk of heterogeneity due to the inter-observer interpretations. The number of patients and MRI analyzed in this series should be considered enough to design robust conclusions. More organized MRI sequences could have improved the number of collected and calculated data, but with 73% of suitable MRIs, representing more than 4 MRI per patients this series presented consistent data.

CONCLUSION

Manual volumetric measurements proved that radiation therapy efficacy is much betterthan the LTD can show. For patient information, manual volumetric measurements are more reliable and for scientific evaluation this method is more robust. However, it is a time-consuming method and automatic delineations should be welcome.

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ANNEXE 1

- $\text{Software-TV} = d \sum_{i=1}^{N} ai$

Software-TV = Tumor Volume determined by software, TV = the tumor volume, d is the slice thickness, N is the number of slices and ai = tumor area measured on each slice.

- $\text{calculated-TV} = 0.52 * h * w * l$

Calculated-TV = calculated tumor volume, h = height, w = weight and l = length