



Long-term volumetric analysis of vestibular schwannomas following stereotactic radiotherapy: Practical implications for follow-up

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ABSTRACT

Background and purpose: Transient tumor swelling is a well-known phenomenon following radiotherapy for vestibular schwannomas (VS). We analyzed the long-term volumetric changes of VS after LINAC radiosurgery, in order to determine a time interval during which a true tumor progression can be distinguished from a pseudoprogression.

Methods: Among 63 patients with VS treated by one fraction or fractionated radiotherapy, we selected 52 of them who had a minimal follow-up of 5 years. Maximal axial diameter and three-dimensional tumor volume were measured on each MRI scan. Volume changes were interpreted using different error margins ranging from 10 to 20%. Patients were categorized according to the tumor evolution pattern over time.

Results: Median follow-up was 83 months. One tumor (1.9%) remained stable and 26.9% had continuous shrinkage. Applying an error margin of 13%, a transient tumor enlargement was observed in 63.5% of patients, with a first peak at 6–12 months and a late peak at 3–4 years. A true progression was suspected in 4 (7.7%) patients, tumor regrowth starting after the 3rd or 4th year post-treatment. Only one patient required salvage radiotherapy.

Conclusion: Transient swelling of VS following radiotherapy is generally an early phenomenon but may occur late. In the first 5 years, a true tumor progression cannot be differentiated from a pseudoprogression. A significant tumor expansion observed on 3 sequential MRI scans after the 3rd year may be suggestive of treatment failure. Long-term follow-up is therefore mandatory and no decision of salvage treatment should be made until the 6th year.

1. Introduction

During decades, microsurgery or observation were the only management modalities of vestibular schwannomas (VS). In the '90 s, stereotactic radiosurgery (SRS) has emerged as a reliable treatment option for small-to-medium-sized tumors. Fractionated or hypofractionated stereotactic radiotherapy (FSRT) was also proposed for larger schwannomas. Radiotherapy is generally safe and effective, with a tumor control rate above 93% and a minimal morbidity [1].

While the radiological follow-up after a surgical tumor resection is unambiguous, interpretation of serial magnetic resonance imaging (MRI) following radiotherapy remains a matter of debate. Transient tumor enlargement, also called pseudoprogression, and loss of central

contrast enhancement were described in 5–74% of patients in the first three years after SRS [2–26]. These well-known phenomena are of no or little relevance for the patient, since they are rarely symptomatic. It is therefore critical to distinguish a transient swelling from a true tumor progression to avoid unnecessary salvage surgery or repeat radiotherapy.

Several studies showed that transient tumor enlargement usually peaks at 6 months after SRS and resolves in 12–18 months [4,6,8–10,12,13,16,18,20,21,23,24]. But its resolution may require years for some patients. On the other hand, true progression seems to occur between 2 and 5 years after SRS and no later than 10 years [12]. Based on these data, the classical follow-up schedule includes MRI at 6 and 12 months, then annually for 4 years and then every 2 or 3 years

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until 10 years. However, the optimal imaging interval and the need for early imaging are still controversial. In most of the studies, the minimal follow-up did not exceed 2 years and data on very long-term evolution (greater than 5 years) are lacking.

Moreover, changes in tumor size may be subtle and below the error margin related to the volumetric technique, the MRI sequences or the inter-observer variations. Historically, 2D interpolated measurement of tumor volume was used in the majority of studies [2–4,7,9–11]. More recent data showed that 3D volumetric analysis was more accurate to define tumor shrinkage or progression [27,28].

The present study aims to describe more precisely the long-term volume changes of VS treated by SRS or FSRT with a linear accelerator (LINAC), using an MRI-based 3D volumetric assessment with a minimal follow-up of 5 years, in order to determine a time interval during which a true tumor progression can be ascertained.

2. Materials and methods

2.1. Patient population

We retrospectively reviewed the data of 63 consecutive patients treated in CHU UCL Namur with LINAC stereotactic radiotherapy for VS between 2008 and 2015. We selected patients having a minimal follow-up of 5 years and at least 5 post-treatment MRI scans. Ten patients were lost to follow-up and were excluded from the study. Another one died during the follow-up. Fifty-two patients were finally included in the study. Two of them had undergone a previous partial tumor resection. All tumors were sporadic.

2.2. Radiotherapy procedure

Head fixation was performed with stereotactic thermoplastic masks (Brainlab, Feldkirchen, Germany), except between January 2008 and June 2010 for SRS when invasive head ring was used. Stereotactic planning computed tomography (CT), post-gadolinium 3D T1-weighted and T2 gradient-echo MRI were coregistered in iPlanRT Image software (Brainlab) for gross tumor volume (GTV) and surrounding organs at risk (OAR) delineation. The planning target volume (PTV) margin was 0–1 mm. Marginal dose prescription (at the 70% isodose) and schedule depended on PTV size and brainstem vicinity: 12 Gy (SRS) or 50.4 Gy by 1.8 Gy (FSRT). Treatments were planned with non-coplanar arcs of 6 MV photons with iPlanRT dose (Brainlab) or Eclipse (Varian, Palo Alto, CA, USA). Treatments were delivered on a modified Varian Clinac 2300-CD (2008–2010) and from June 2010 with a dedicated Novalis-TX. All treatments were delivered with a short corticoids prophylaxis.

2.3. Volumetric measurement

Radiological and clinical evaluations were performed at 6, 12, 24, 36, 48 and 60 months, and then biennially. Tumors were measured on contrast-enhanced T1-weighted MRI sequence and sometimes also on T2 gradient-echo sequence, with a slice thickness of 0.5–2 mm. 3D volumetric analysis was made using slice-by-slice manual contouring with the dedicated software iPlan (Brainlab). Maximal axial tumor diameter was also calculated. All volume measurements were performed by the same observer (OF) and were reviewed by a second neurosurgeon (TG). Post-treatment volume variations were expressed as a percent change relative to the pre-treatment volume.

Based on the tumor radiological behavior over time, patients were classified in four categories: (1) stable volume, (2) continuous tumor shrinkage, (3) transient tumor swelling or pseudoprogression and (4) true tumor progression. Pseudoprogression was defined as a significant volume increase at any time followed by a continuous tumor shrinkage, whether the tumor volume returned to the initial value or remained larger at the end of the follow-up. True progression was considered in case of continuous tumor growth after 3 years, eventually following a

transient swelling or regression.

As proposed by some authors [29], we defined a significant change in tumor volume as a 13% variation from baseline. In order to assess the influence of the potential measurement error, pseudoprogression rates were also calculated with thresholds of 10% and 20% for 3D volumetric measurements and of 2 mm for maximal diameter. In addition, an individualized percentage of error (1–13%), depending on the tumor volume and MRI slice thickness was used, according to the algorithm developed by Snell [30].

New clinical symptoms (loss of useful hearing, facial paresis, facial spasm, vertigo and dizziness, trigeminal neuropathy, tinnitus) were systematically recorded at each follow-up. Tone and speech audiometry was also performed with the same frequency. Serviceable hearing was defined as a Gardner-Robertson score I or II.

2.4. Statistical analysis

The presence or the absence of pseudoprogression was analyzed in function of four factors : age, initial tumor volume, necrosis and type of treatment (SRS or FSRT). Chi-squared tests and t-tests were used. Pseudoprogression ratio, i.e. the division of the maximal volume by the initial volume, was also characterized by the same four factors, using t-tests and linear models. Kaplan-Meier method was used to estimate the median time for 50 % of the patients to fall below the initial volume. All tests were performed with the R software, version 4.0.1 (R Foundation for Statistical Computing, Austria).

3. Results

Patient demographics are summarized in Table 1. The median age was 54 years (range 22–78). Median follow-up was 83 months and maximal follow-up 122 months. Seventy five percent of patients had a last MRI at 6–7 years, 10% at 8–9 years and 8% at 10 years. Overall, 403 MRI scans were analyzed, with a median of 7 MRI per patient (range 5–9). Mean baseline tumor volume was 0.69 ml in the SRS group and 3.21 ml in the FSRT group. Twenty-nine % of tumors were classified as Koos grade 1, 58% as grade 2 and 13% as grade 3. There was no purely cystic tumor.

Based on the 3D volumetric measurements with an error margin of 13%, patients were categorized as follows : one tumor (1.9%) was stable (group 1), 14 (26.9%) had continuous shrinkage (group 2), 33 (63.5%) harbored a pseudoprogression followed by a shrinkage (group 3) and 4 (7.7%) had a true progression (group 4). Volumetric curves for the four groups are depicted in Fig. 1 and distribution of groups according to the radiotherapy schedule was listed in Table 2. Globally, the mean tumor volume increased at 6 months and then decreased steadily (Fig. 2). Percentage of patients having a tumor larger, stable or smaller at each time compared with the pre-treatment volume is represented in Fig. 2.

In the group 2, the mean decrease in volume at 5 years was 45% (41% for SRS and 55% for FSRT). In the group 4, three tumors progressed following a pseudoprogression (bimodal pattern) and one tumor grew after an initial volume decrease. Three of these patients were treated with SRS and one with FSRT. Pre-treatment tumor volume in this group ranged from 0.43 to 1.72 ml. The onset time of true progression

Table 1
Pre-treatment patient and tumor characteristics.

Variable	SRS	FSRT	Total
n	42	10	52
Median age (yr)	55 (29–78)	53 (22–65)	54 (22–78)
Male/female	22/20	3/7	25/27
Dose (Gy)	12	50.4 (28x)	
Baseline tumor volume (ml)	0.69	3.21	1.17
Baseline necrosis (%)	18 (43%)	5 (50%)	23 (44%)
Median follow-up (m)	83	79.5	83
Prior surgical resection	2	0	2

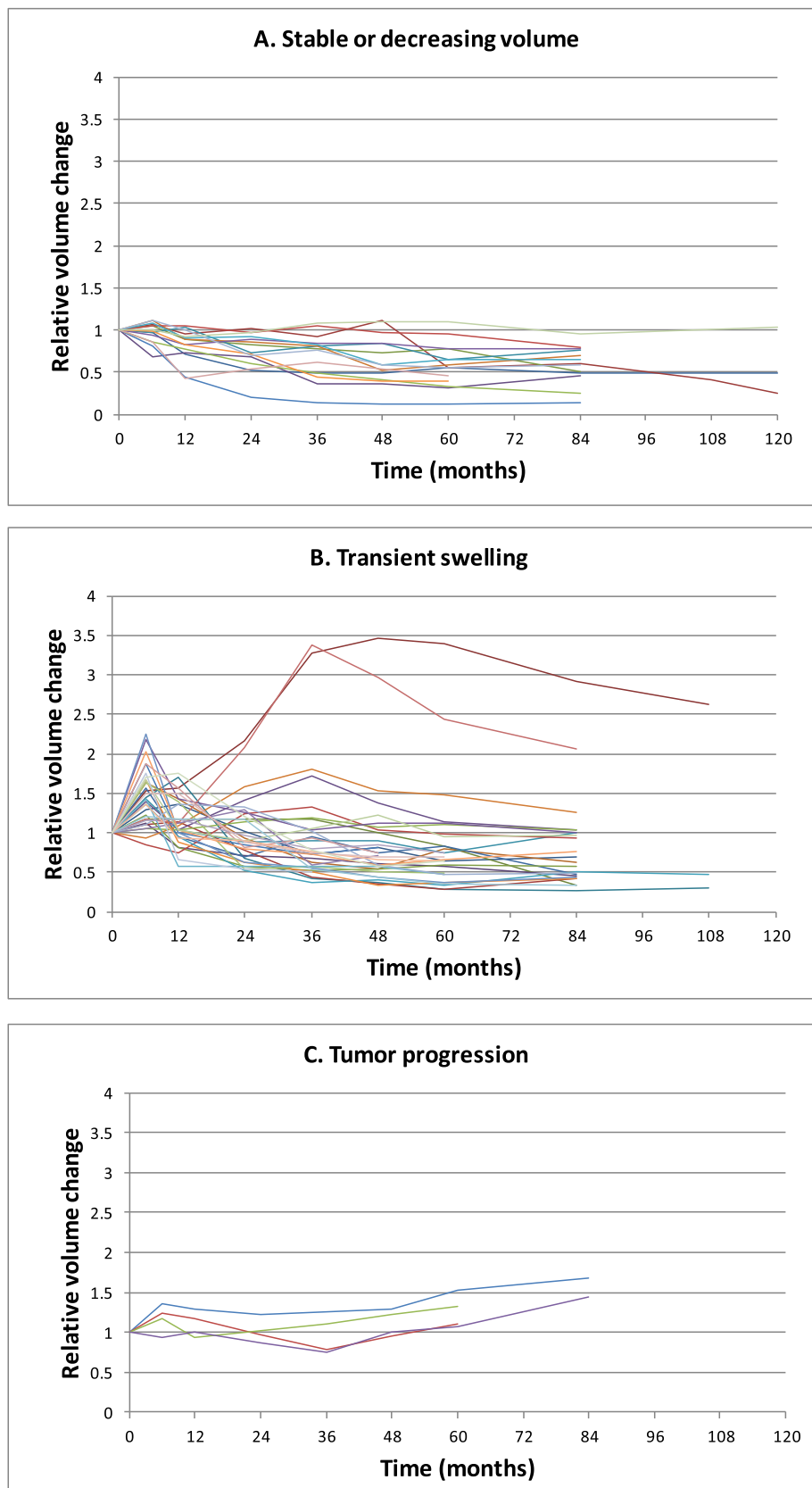


Fig. 1. Graphs showing volumetric changes over time by pattern category: (A) stable or decreasing volume (groups 1 and 2), (B) transient swelling (group 3) and (C) tumor progression (group 4). Curves are plotted as volume changes relative to pre-treatment volume.

Table 2

Distribution of evolution pattern categories according to the radiotherapy scheme, based on 3D volumetry with an error margin of 13%.

Pattern	SRS	FSRT	Total
Stable tumor (group 1)	2,4%	0%	1,9%
Continuous shrinkage (group 2)	23,8%	40%	26,9%
Pseudoprogression (group 3)	66,7%	50%	63,5%
Tumor growth (group 4)	7,1%	10%	7,7%

was 36 months for two patients and 48 months for the two others. Three tumors had a loss of central contrast enhancement at 6 months. Only one patient, treated with SRS, required salvage radiotherapy because of a 95% volume increase between the fourth and sixth year. The three other patients exhibited a tumor expansion of 37, 39 and 43% at the end of the follow-up. Tumor progression was confirmed whatever the selected threshold, except for the axial diameter measurement applying an error margin of 2 mm.

In the pseudoprogression group (group 3), the peak of transient swelling occurred at 6 months for 64% of patients and at 1 year for 17%. Six patients (17%) demonstrated a late tumor enlargement with a peak at 3 or 4 years (4 following SRS and 2 after FSRT). The mean tumor volume increase was 64% (range 13–246%). At 5 years, the mean volume was reduced by 25% after SRS and remained 25% larger than the pretreatment one following FSRT (overall, 17% decrease). The median time to resolution of transient swelling was 2 years. No significant correlation was found between transient tumor swelling occurrence or magnitude and patient age ($p = 0.78$ and 0.45 respectively), tumor volume ($p = 0.34$ and 0.28), central necrosis ($p = 0.56$ and 0.078) or radiotherapy fractionation scheme ($p = 0.75$ and 0.93).

The rate of pseudoprogression varied largely depending on the measurement method and the selected margin of error. Using a 3D volumetric measurement with a cutoff of 10%, 13% or 20%, or a 1D axial diameter measurement with a relative threshold of 13% or an absolute variation of 2 mm, we obtained pseudoprogression rates of 75%, 69%, 58%, 33% and 33% respectively. Applying the algorithm from Snell [30], this rate was 73%.

Among patients responding to radiotherapy (groups 1 to 3), 89.6% had a tumor volume equal or smaller at 5 years compared to baseline. After 5 years, changes in tumor volume were still observed in 12 of 39 patients (30.8%).

Loss of central contrast enhancement was observed in 44% of patients before treatment and in 83% following radiotherapy. This phenomenon was maximal at 6 months. The median time to resolution was

2 years. All the patients recovered a homogeneous tumor enhancement at 5 years (Table 3). For the six tumors exhibiting a late pseudoprogression, loss of contrast enhancement was not synchronous with the peak of enlargement.

Loss of serviceable hearing was detected in 39.5% of the 38 patients who had a pre-treatment useful hearing (36.7% after SRS and 50% after FSRT). Facial paresis was observed in 3 patients (11.1%) (House-Brackmann grade 1) and facial spasms in 10 patients (19.2%). The spasms occurred between 6 and 12 months and spontaneously disappeared between 12 and 24 months after treatment. Transient vertigo or dizziness was noted in 5 patients (9.6%) and trigeminal neuropathy in 8 patients (15.4%). Tinnitus was reported by 7 patients (13.5%). These adverse events were seen in all pattern categories both after SRS and FSRT. The small number of events did not allow a statistical analysis.

4. Discussion

During the last three decades, many studies focused on the radiological evolution of VS following radiosurgery [2–26]. Most of them had a short minimal follow-up of 1–2 years, so that long-term data were extrapolated from Kaplan-Meier curves. Only two studies included a minimal follow-up of 5 years [3,20]. Long-term evolution remains therefore unclear.

In all the studies, a transient tumor swelling (“pseudoprogression”) was described, but with a large variation of occurrence rates, ranging from 4.7 [3] to 74% [13]. On the other hand, the rates of true progression reported in the literature fluctuate between 4 and 19% [4,6–8,24], and up to 13.6% of patients underwent a salvage treatment [31]. This disparity can be explained by differing observation periods, but also the method of tumor volume measurement (2D or 3D) and the criteria used to differentiate pseudoprogression from true progression.

Table 3

Percentage of tumors losing central contrast enhancement, depending on time and fractionation scheme.

Central necrosis	SRS	FSRT	Total
Baseline	43%	50%	44%
6 m	86%	70%	83%
1 y	55%	50%	54%
2y	10%	20%	12%
3 y	2%	10%	4%
4 y	0%	10%	2%
5 y	0%	0%	0%

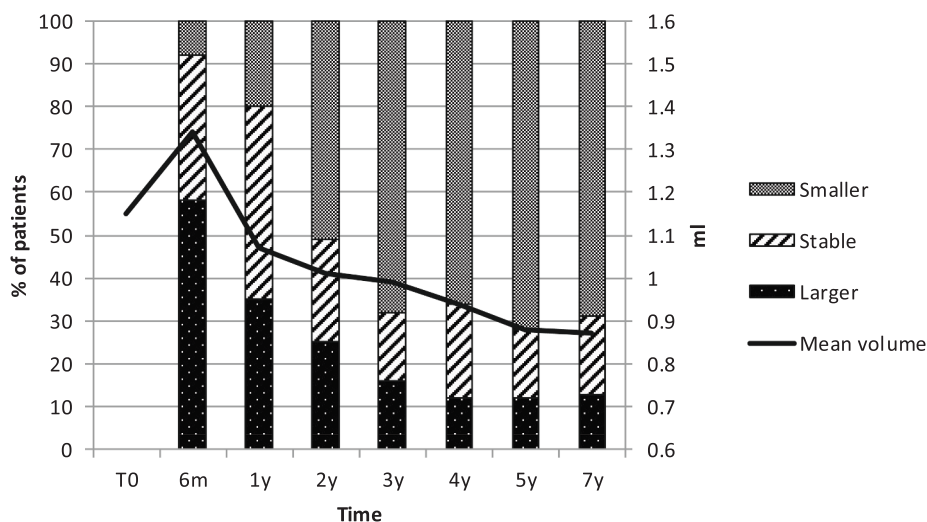


Fig. 2. Graph demonstrating the percentage of tumors with a smaller, stable or larger volume at each follow-up time, compared to the pre-treatment volume. The continuous curve shows evolution of the mean tumor volume for all groups.

Salvage treatment is usually triggered by a fast tumor growth, a persistent slow growth or the onset of new neurological symptoms. But the threshold of tumor volume increase and the time interval during which a progression can be ascertain are still a topic of ongoing debate. However, these informations are critical to avoid unnecessary salvage therapies.

This study confirms the relativity of the definition of pseudoprogession, which is mainly influenced by the volume measurement method. The rates of transient tumor swelling we observed ranged from 33 to 75%, depending on whether the tumor enlargement was calculated on 1D or 3D volumetric assessment and also on the selected measurement error percentage. With equal and comparable criteria, our data are close to those of other studies [15,32]. For most patients, the time of peak expansion seems constant between 6 months and 1 year. Of note, two patients had a late and marked transient tumor swelling, peaking at 3 or 4 years and then resolving very slowly. This second peak was also mentioned by Breshears and Matsuo [20,24]. The mean transient tumor enlargement ranges from 23 to 75% in the literature [10,11,13,16,20,24], with a maximal increase of 800% [23]. The time to resolution of tumor expansion in our series was similar to other studies. Breshears [24] reported a median time to resolution of 2.4 years with 90% of cases completely resolving by 6.9 years and Meijer noted a median time to swelling regression of 2.8 years [12]. Overall, 55–72% of patients had a smaller tumor volume than the pretreatment one at 5 years [3,11,20,24]. In addition, 27–30% of patients had a stable tumor at that time.

In 4 patients, a treatment failure was suspected because of a slow tumor growth between years 4 to 7, occurring after an initial regression or transient swelling. Only one patient exhibited a sufficiently significant enlargement to justify a reirradiation. In all these patients, tumor progression was detected with 3D volumetric measurement as well as with the maximal axial diameter measurement, regardless of the selected cutoff. Conversely, we did not find any continuous growth pattern in the current study.

We observed a transient loss of central contrast enhancement in 83%, that is in the range of 54 to 93% reported in the literature [4,5,7,8,10,11,17,20,25]. In most cases, it was maximal at 6 months and occurred concurrently to a transient tumor swelling. However, in the six patients exhibiting a late tumor enlargement at 3 or 4 years, the loss of contrast was seen only between 6 months and 1 year, suggesting different physiopathological mechanisms for these phenomenons. On the other hand, 3 of the 4 tumors classified as progressive temporarily lost central enhancement. As also mentioned by several authors, this indicates that loss of contrast enhancement represents an early effect of radiation and is not necessarily predictive of tumor control [17]. The mechanisms underlying changes in contrast enhancement and pseudoprogession are still poorly understood [33].

In the majority of studies, no significant relationship was found between the radiological response to treatment and patient- or treatment-related factors such as age, tumor volume, pretreatment tumor growth, radiation dose or schedule [4,6,8,12,13,16,18,20,21,34]. In particular, the rate of pseudoprogession seems similar following Gamma Knife (4,7 to 74%) and LINAC radiotherapy (14,3 to 63,6%) [3,13,14,20]. A few authors noted, however, a significant correlation between transient swelling and tumor volume [9,18] or loss of contrast enhancement [5], tumor volume and loss of enhancement [22], or treatment failure and tumor volume [24,35]. A relationship between onset of new cranial neuropathies (V, VII and VIII) or hydrocephalus and tumor enlargement was suspected in three studies [13,18,23] but was not observed in two others [16,25]. In our study, we found no significant difference in occurrence of these phenomena between radiotherapy schedules.

Several authors also proposed to categorize the patients according to the radiological evolution pattern over time [4,8,10,16,17,20,24]. These classifications generally comprise 3–5 groups including transient tumor enlargement, stable volume, continuous shrinkage, persistent growth or bimodal evolution. Based on the graphical representation of volumetric

data, they are mainly interesting to identify a true, long-term tumor progression and to decide on a salvage treatment. However, assigning a patient to one of these categories can be difficult because the volume changes are sometimes subtle and are dependent on the selected error margin. Moreover, volume modifications may persist over the long term. Matsuo [20] described changes in 64% of cases after 5 years and 33% after 10 years. Most of the tumors continued to shrink but a transient swelling was still observed late in rare cases. Consequently, no conclusion should be drawn from the curves until the fourth or fifth year post-treatment.

In the future, new MRI sequences or post-processing algorithms, such as arterial spin labeling, diffusion coefficient mapping or radiomics, could have a potential interest in differentiating tumor growth from effects of radiation [36,37].

Lastly, this study carries several limitations, in particular its retrospective nature, heterogeneity of the population in terms of fractionation schemes and the small sample size limiting statistical analysis. Some inaccuracy of volume measurements due to variations in MRI sequences and slices thickness could also induce biases, especially for small tumor volumes.

5. Practical considerations and conclusion

Transient tumor enlargement after radiotherapy is quite frequent. The patient should be informed of this indolent phenomenon. The serial volumetric data should be recorded in the patient file as graphical curves, with the aim to differentiate from treatment failure. Contrast-enhanced T1-weighted scan is the MRI sequence of choice for the follow-up. Because the volume measurement error increases exponentially with the slice thickness [30], only thin slices (2 mm or less) should be used. In routine clinical practice, measurement of the maximal axial tumor diameter provides sufficient information in most of situations [15,32]. In case of doubt on the evolution pattern, 3D volume calculation should be done.

Yearly MRI is recommended during the first 5 years in order to categorize the evolution profile. Since pseudoprogession is of no or little clinical relevance, a first MRI at 3 or 6 months seems not useful, except for large VS. If the tumor is stable or smaller at 5 years than initially, with or without a transient enlargement, only one or two scans are required up to 10 years. In contrast, if the tumor volume remains larger than the pretreatment one, annual monitoring should be continued.

The closest attention must be paid to the fourth year MRI, because a slight increase in volume at that time point may indicate a possible treatment escape. In this case, we recommend to obtain 3 sequential yearly MRI showing a persistent growth before ascertaining a treatment failure. Consequently, no decision of salvage therapy should be made until the 6th year post-treatment. Caution is required in case of large tumors or onset of new symptoms.

On the other hand, no clear recommendation has emerged from the literature concerning the error margin to be applied for measurement of the tumor volume. In the majority of studies, this threshold ranged from 10 to 20% [8,12,16,29,32], but was often empirical or based on internal calculation. Conversely, several criteria proposed by some authors to define tumor progression are not valid and should no longer be used (volume increase of more than 20% once, any growth after 3 years, no return to the pretreatment volume following a transient swelling). In the same way, only the trend of volume variation over time is indicative for treatment response rather than an absolute volume change compared to the previous value.

Due to these uncertainties related to the post-radiotherapy radiological evolution, the “wait and scan” conservative approach remains the management of choice for small and asymptomatic VS, according to the recent EANO guidelines [38].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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