Radiotherapy for subependymal giant cell astrocytoma: time to challenge a historical ban? Case report and review of the literature.

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Abstract

Background Subependymal giant cell astrocytoma is a deep-seated benign but life-threatening brain tumor that occurs in patients with the tuberous sclerosis complex. Resection is the traditional treatment and expert opinion is strongly against the use of radiotherapy. Systematic epidemiological studies, however, demonstrate high rates of complications and recurrences. The need for efficient non-surgical treatment is best illustrated by the considerable enthusiasm about the activity of the mTOR inhibitor everolimus in reducing tumor volume. Unfortunately regrowth is frequent after dose reduction or cessation and continued tumor control requires continued administration of the drug, leading to concerns about its metabolic and immunosuppressive side effects and cost of treatment. Results We successfully treated a case with growing bilateral subependymal giant cell astrocytoma with fractionated stereotactic radiotherapy before everolimus became available. After a follow-up of 8 years, everolimus was administered for renal angiomyolipoma and the patient was followed up until 13 years after radiotherapy. Successive MRI's demonstrated an 80% volume reduction after radiotherapy that further increased to 90% during everolimus administration. In order to review the basis for the strong expert opinion against radiotherapy, we performed an exhaustive literature study regarding efficiency, potential dangers and side effects of radiation. 1298 article references and 780 full-text articles in search of evidence for contra-indicating radiotherapy. Varying short-term tumor control of single-fraction radiosurgery were described in a total of 13 cases. Only in two published cases the radiation dose of fractionated radiotherapy was mentioned. A single publication mentions an induced secondary brain tumor 8 years after total brain irradiation. Conclusion There is no evidence for contra-indicating fractionated radiotherapy in subependymal giant cell astrocytoma. Our experience demonstrates that these tumors, as other benign intracranial tumors, responds slowly to radiotherapy and suggests that fractionated stereotactic radiotherapy holds promise to consolidate responses obtained with mTOR inhibitors avoiding regrowth after cessation. This combined treatment would avoid costs and complications of long-term treatment with everolimus and deserves to be studied as a definitive non-surgical treatment.

Background

Subependymal giant cell astrocytoma (SEGA) is a non-invasive WHO grade I glioma that occurs in 20% of tuberous sclerosis complex (TSC) patients, usually in the first two decades of life (1). They are located mainly in the periventricular area and are bilateral in 20% of the cases (1). SEGA most frequently occurs in patients with accompanying features of TSC which is an autosomal dominant neurocutaneous disorder caused by mutation in the TSC-1 or TSC-2 genes that involves brain, skin, eyes, lung, liver and kidneys. Only 38 cases of SEGA have been described in patients without other clinical features of TSC, but in 7 out of 9 cases in which molecular analysis was performed, a mutation of TSC-1 or TSC-2 was still detected in tumor tissue (2). Brain involvement of TSC consists of delayed neurocognitive development and growth of benign tumors that are classified into intraparenchymal hamartomas and subependymal nodules. The latter can demonstrate accelerated growth and are then called SEGA, although they remain histologically identical to subependymal nodules (3). SEGA have been shown to be

responsible for 25% of the excess mortality in TSC patients (4) by causing hydrocephalus and sudden death.

The standard treatment of symptomatic SEGA is complete surgical removal. The only alternative treatment option as of today, pharmacological treatment with everolimus, has been approved by both the European Medicines Agency and Food and Drugs Administration only when curative resection is not possible.

Recently, research has shifted to pharmacological treatment, as mTOR inhibitors like everolimus were shown to induce significant responses and a multicenter, randomized, placebo-controlled phase 3 trial (EXIST-1), demonstrated that at least 35% of patients had at least 50% reduction in SEGA volume after 9.6 months of treatment with everolimus (5).

While fractionated stereotactic radiotherapy (FSRT) is a standard treatment modality in the treatment of other low-grade gliomas (UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on September 30, 2016), no experience with FSRT in the treatment for SEGA has ever been reported. There appears to be in broad consensus that no form of irradiation should be used for this indication and, if at all mentioned as a treatment, it has been described as 'ineffective' (6), 'proved inefficient' (7) and it is claimed that "logically, some kind of radioresistance should be observed" (8). In the recommendations report of the 2012 International Tuberous Sclerosis Complex Consensus Conference it is stated (unreferenced) that there is a lack of responsiveness to radiotherapy (9). In the same report, as in many others, concern is expressed about potentially increased risk in TSC of developing secondary malignancies due to radiotherapy and chemotherapy.

We report about a case of bilateral SEGA that the referring neurosurgical team decided not to operate and that was irradiated before mTOR inhibitors became available. During a follow-up of nearly 8 years, we observed a dramatic volume reduction of both tumors and when everolimus was started for angiomyolipomas of the kidneys the SEGA volume further decreased.

Motivated by this favorable outcome, we decided to accurately document the volumetric response of the tumor to radiotherapy and later to everolimus, to conduct a systematic review of literature concerning irradiation of SEGA and to review the rationale behind the consensus against the use of radiotherapy in the treatment of SEGA.

Results

Case report

We present a female patient with TSC, diagnosed since childhood based on the typical skin lesions combined with delayed psychomotor and intellectual development. At the age of 10y, bilateral periventricular hamartomas had been observed on brain CT's. The clinical diagnosis of TSC was subsequently confirmed by the demonstration of a mutation in the TSC2-gene.

The patient was referred to our neurosurgical department at the age of 22 years for cranial disease progression with increased behavioral changes, including aggression and headache, before everolimus was in use for treatment of SEGA. A wait-and-scan approach had been adopted for about 3 years and the volume of both SEGA doubled during that time. As she then suffered from signs of increased intracranial pressure due to obstructive hydrocephalus, a ventriculoperitoneal drain was placed and symptoms improved rapidly. Due to the presence of bilateral tumors, the absence of sufficient ventricular dilation to facilitate endoscopic resection and the compromised neurocognitive status, the referring neurosurgeons were reluctant to perform bilateral transfrontal surgery and asked radiotherapeutic advice.

At that time very limited data was available concerning radiotherapy for this indication, but it was felt that it was reasonable and safe to prescribe a fractionated stereotactic radiotherapy to a dose of 30 × 2 Gy to the gross tumor volumes with a 2 mm PTV margin.

This treatment was well-tolerated, did not require prophylactic corticotherapy and did not cause acute side effects.

We followed the tumor response through volumetric assessment through slice by slice delineation of GTVs on 1 or 2 mm T1 gadolinium-enhanced MRI in the 17 pre- and post-radiotherapy MRI's done over more than 16 years (Fig. 1). A slow tumor regression was observed in the first year, but in the second year after radiotherapy the response accelerated and continued until nearly 8 years after radiotherapy, when their volume had decreased by 72 and 82%.

At that point in time, everolimus (2.5 mg/d) was started to treat growing bilateral renal angiomyolipomas. Remarkably, the residue of the larger SEGA still responded dramatically to everolimus (Fig. 2) with again a 50% reduction of its remaining volume within one year, while the speed of volume reduction of the smaller tumor did not seem to be influenced by the drug (Fig. 1). After a follow-up of 13 years after radiotherapy and 5 years of everolimus, both tumors had a residual volume of less than 10%. We never observed signs of increased tumoral or peritumoral inflammation or edema nor did the patient at any time have seizures.

Review of the Literature

In order to find publications relevant to the efficacy and toxicity of irradiation of SEGA, we used Endnote X7 to search and collect via Pubmed and UpToDate using the search terms: 'treatment of SEGA', 'radiotherapy in SEGA', 'SRS in SEGA', 'treatment of tuberous sclerosis complex', 'radiotherapy treatment in low grade astrocytomas', etc. All freely accessible plus institutionally subscribed as well a selection of charged-access full-text articles were downloaded and their textual contents was indexed. In a second step, the article references were screened for the terms 'radiotherapy', 'induced tumors', 'malignant tumors'. Secondary references were added to the database and processed the same way as the originally found references. Reviews about secondary radiation-induced brain and cranial tumors in general were added to the database as well. Specific attention was given to potential traces of reports containing data

about irradiated SEGA and about high-grade brain tumors in TSC patients. The database was locked on 1-02-2018 containing 1298 article references and 780 full-text articles.

Finally, all database fields as well as the indexed content of all full-text articles were used to find reports on SEGA that had been irradiated, malignant brain tumors in TSC patients and radiation-induced tumors in TSC patients.

Tumor control with radiosurgery and radiotherapy

There are no publications specifically addressing SEGA response after fractionated radiotherapy and the only data we found was in publications with a different focus. Consequently, elementary data like dose, fractionation, criteria for response and follow-up time were often missing. In some publications, SEGA and other low-grade gliomas astrocytomas have been pooled. Nevertheless, we found reports containing information of 34 SEGA patients having received some form of irradiation (Table 1). Seven cases received fractionated adjuvant radiotherapy after complete resection, so no response could be assessed other than absence of recurrence in all 7 (10). Fourteen were single fraction SRS (Gamma Knife) and in 6 of those SEGA (3 in one single publication) tumor control was unsatisfactory.

Table 1

Reported results of radiotherapy and radiosurgery for SEGA

Author (Year)	Resection	FU (m)	Irradiation type	Treated/ Responded	Dose (Gy)	Criteria
Kapp (1967)	P	156	X-Ray	1/1	N.S.	Clinically well
Sinson (1994)	P	24	N.S.	0/1	N.S.	N.S.
Park (1997)		12	GK SRS	2/2	6–25	Volume – 70 / -80%
Matsamura (1998)	P	96	RT	1/1	50	No growth
Sharma (2004)	N.S.	N.S.	RT	7/N.S.	N.S.	1 recurred 22y later
Wang (2006)		67	GK SRS	0/3	15	No growth
Henderson (2009)		48.2	GK SRS	1/3	12–20	N.S.
Park (2011)	P	73	GK SRS	4*/6	11–20	N.S.
Jiang (2011)	C		RT	7/7	N.S.	No recurrence
	P	16	RT	1/2	N.S.	N.S.
Gagliardi (2017)		N.S.	GK SRS	1/N.S.	N.S.	N.S.
Azam (2017)		12	RT	1/1	50.4	No growth
Present study		150	RT	2/2	60	volume – 80%

*: one patient with formation of enlarging cyst was scored as non-reponder and was salvaged by repeat SRS

The dose of fractionated radiotherapy was mentioned only in two publications: 25 × 2 Gy and 28 × 1.8 Gy respectively) after which the SEGA did not further grow during 8 years resp. 1 years of follow-up (11, 12). In a very early publication fractionated X-rays were used, no evolution was noted after 13y of follow-up (13).

Taken together, it is clear that SEGA can respond to irradiation, but the broad range of doses and fractionations, the lack of detail in the reports and the far too short follow-up do not permit to draw firm conclusions about radiosensitivity of SEGA. One publication describing responses to Gamma Knife SRS suggests that, in comparison to pilocytic astrocytomas, SEGA does appear to be less sensitive since all 3 SEGA and none of the 5 pilocytic astrocytomas recurred (14).

Malignant and potentially radiation induced intracranial tumors in TSC

One single published case of a radiation-induced glioma in a TSC patient was found. He had been treated in 1987 with whole-brain radiotherapy (20 × 2 Gy) plus boost of 5 × 2 Gy with opposing lateral 8 × 9 cm fields (11). A glioblastoma developed 8 years after radiotherapy in the temporal lobe, likely in 50 Gy region. The irradiated SEGA did not grow during these 8 years. This article was referenced 28 times (Web of Science, retrieved 9-1-2017) and none of the referencing manuscripts mentioned other cases of induced malignant brain tumor. A case of a potentially radiation-induced meningioma was mentioned by Shepherd et al. as the cause of death of a patient 19 years after radiation (15).

Seven more malignant gliomas were reported in TSC patients that never received therapeutic radiation (16–22).

An article specifically looking at the incidence of malignant tumors in TSC patients examined 240 patients over 14 years and concluded that there was only an increased risk in renal cancer but not of intracranial tumors (23)

Discussion

While complete resection has abundantly been acknowledged as the first line treatment of SEGA, complete and safe surgical removal can be problematic (24, 25). This is perhaps best illustrated by epidemiological studies that provide an unbiased view on real-life efficiency, safety and cost of treatment. A study looking at three large US national healthcare claims databases examined the outcomes of SEGA surgery among TSC patients who underwent SEGA surgery between 2000 and 2009 (26). In 48.9% of the patients postoperative complications were registered. The postoperative diagnosis of 'SEGA' in 100% of the cases and high reoperation rates suggests that many patients had incomplete resection, regrowth or contralateral regrowth. The authors concluded that alternative therapeutic strategies should be considered. Even when safe and complete removal is possible, the tissue damage that is inevitable in surgery, especially for bilateral deep-seated tumors, may lead to neurocognitive decline that could negate part of the positive neurocognitive effects of mass reduction and resolution or prevention of hydrocephalus.

Because of problems associated with surgery as first-line treatment for SEGA, the discovery of activity of the immunosuppressive drug everolimus against SEGA (published in 2006, (27)) was met with considerable enthusiasm. Within 6 years a multicenter randomized trial was published demonstrating that at least 35% of the patients had a 50% or more reduction in SEGA volume after 2y of treatment (5). In a subsequent report of the same patient cohort that received at least one dose of everolimus either initially or after cross-over from the control arm, results and toxicity were reported up to almost 5y of treatment (28, 29). The median change in SEGA volume after 12 months was − 37.8% and this did not improve much, staying below − 50%, during continued treatment (29). This somewhat disappointing

observation is especially remarkable because 30% of the cases were cross-overs from the placebo arm and thus may still have been in the initial response rather than the extended phase of response to everolimus. In line, the majority of responses occurred within the first few months, the mean time to response was a short 5.32 months and no further responders were counted beyond approximately 2.5 years. Of the 13 patients that progressed, 5 had first responded to treatment. Toxicity was significant with 36% G III and 4.5% G IV serious adverse events ascribed to treatment, leading to discontinuation in 9.9% of patients.

It should be noted that everolimus was developed as an immunosuppressant and appears to have a cytostatic rather than a cytotoxic effect, and that perhaps life-long treatment may be necessary. Indeed, SEGA usually grow back after cessation of everolimus (27, 30, 31) and control of epilepsy may dramatically depend on continuation of the drug (32). Attention to long-term toxicity is justified because of metabolic (dyslipidemia, hypertriglyceridemia) (33, 34), multiple CYP3A4/PgP-mediated drug interactions and immunosuppressive side effects that can be life-threatening (35). While no direct carcinogenic risk of everolimus in the standard 2-y carcinogenicity bioassays could be detected, these assays are known to be unreliable for immunosuppression-associated carcinogenicity (36) and the product monograph of Certican (Novartis Pharmaceuticals Canada Inc), one of the brand names of everolimus, specifically warns for "increased susceptibility to infection and the possible development of malignancies such as lymphoma and skin cancer" (37).

The cost of life-long treatment may be a problem as well, especially in developing countries (38). These concerns have motivated some authors to perform resections to avoid having to continue the drug even during significant and ongoing responses to mTOR inhibitors (38). Others studied dose-reduced maintenance therapy after at least 12 months of standard dosing and concluded that SEGA volumes need to be closely monitored during reduced-dose maintenance everolimus therapy because the majority of SEGA increased in size, and that patients who did not have a significant response to standard doses should not be recommended for dose reduction (39) .

Irradiation, whilst being a standard modality in the treatment of pilocytic astrocytoma historically appears to have been banned from the treatment options in SEGA. We found very little data to support the strong and widespread expert opinion against the use of fractionated stereotactic or indeed, any other form of irradiation in the treatment of SEGA. A single case of radiation-induced glioblastoma after whole brain radiotherapy has been systematically cited as an argument against the use of radiation, even when modern conformal radiation techniques are known to decrease the radiation burden to the healthy brain tissue by several orders of magnitude.

Because TSC patients do not have an a priori increased risk of malignant intracranial tumors there is no theoretical argument to suggest they may be more susceptible to intracranial tumor induction.

It could be argued that highly conformal radiotherapy techniques would not reduce the risk that the SEGA itself might become malignant. Indeed, in G I pilocytic astrocytomas a few cases have been described that are consistent with radiation as a cause of malignant degeneration (40). However, spontaneous

malignant transformation has been described as well (41–46) and it is likely that the selection of tumors to receive radiotherapy may have induced an adverse bias. In G II gliomas, it is well-known that in fractionated radiotherapy actually delays malignant transformation. Furthermore, clinically malignant behavior of SEGA itself appears to be exceedingly rare and only three cases have been mentioned in publications, none of them after therapeutic radiation (47–49).

The bilateral SEGA's that we have treated, before everolimus was in use, with FSRT to a dose of 30 × 2 Gy reacted slowly and progressively over a period of 8 years and decreased to 20% of their original volume. Such slow responses are common in in low-grade or benign intracranial tumors, and have previously led to incorrect conclusions about 'radioresistance' of e.g. meningioma.

Remarkably, after the start of everolimus for extracranial manifestations of TSC, rapid acceleration of the volumetric response of the larger SEGA occurred, suggesting that the irradiated SEGA may not have been fully inactivated by radiation and that the response of SEGA to everolimus likely involves different and perhaps complementary mechanisms of cell kill, potentially involving apoptosis, as has been described in in vitro experiments and xenografts (50).

While in our patient radiation was delivered as the initial treatment for SEGA, followed by everolimus, opposite sequencing of these treatments could be more advantageous. First, the response to everolimus appears to be faster than to radiotherapy and could thus be more effective to avoid or perhaps even treat volume-dependent complications such as hydrocephalus. Second, a smaller radiation target would decrease radiation burden to the surrounding healthy brain.

There is abundant data describing radiosensitising effects of mTOR inhibitors on in vitro and in vivo on non-TSC mutated cells. Any radiosensitising effect of mTOR inhibitors is particularly relevant to the question of whether these drugs should be continued or not during consolidation radiotherapy. mTOR inhibitors could potentially be particularly effective radiosensitisers in SEGA but, on the other hand, would likely radiosensitise healthy tissues as well. The mechanism of mTOR radiosensitisation, however, involves enhanced apoptosis that should not increase the risk of induction secondary tumors.

While extremely intriguing, it may be too early to specifically explore the concept of simultaneous mTOR inhibition and irradiation for SEGA, but whether mTOR inhibitors have administered or not during radiotherapy of SEGA should clearly be documented and reported as it may have a significant effect on the optimal dose of radiation.

The dose that we have delivered is higher than the 50-54Gy in 25–30 fractions that would be conventional in other G I gliomas and many other benign tumors. This had at the time been motivated by an anticipated absence of toxicity and by the theoretical reduction of radiosensitivity in TSC due to a potentially activated PI3 K/Akt/mTOR pathway (51). The few published results of non-fractionated SRS that were published later on appear to confirm the somewhat reduced radiosensitivity of SEGA compared to pilocytic astrocytomas. This is in line as well with our own observation of an acceleration of tumor response of the larger SEGA after starting everolimus.

Conclusions

Surgical resection is currently the treatment of choice for SEGA and both American and European drug agencies approve treatment by everolimus only when resection is not possible.

There is, however, a unmet need for a non-surgical treatment option for a subset of SEGA, as illustrated by the considerable enthusiasm about the mTOR inhibitor everolimus. Quite reliable and rapid responses are indeed the rule when initiating this treatment, inasmuch that it has been used even in patients with hydrocephalus. The drug, however, has a cytostatic rather than a cytotoxic effect and to maintain tumor control maintenance treatment, perhaps life-long, is necessary, leading to concerns about continued patient exposure to its immunosuppressive action and metabolic side effects as well as ac cumulated cost of therapy.

Irradiation appears to have been banned from the therapeutic arsenal for SEGA without good reason and has never really been studied. The long-term favorable outcome of the bilateral SEGA that we have treated with FSRT demonstrates that these tumors do respond slowly and progressively to fractionated radiotherapy, similar to other low grade intracranial tumors. Moreover, the further response of one of the SEGA to intercurrent everolimus administration suggests an additive effect of radiation and the drug that could be clinically exploitable. Indeed, responses to everolimus are particularly rapid and the reduced tumor volume facilitates radiotherapy and reduces the risk for complications and side effects and risks to levels not comparable to those of total brain irradiation. Patients that do not require continued systemic treatment for other manifestations of the tuberous sclerosis complex could potentially stop the drug after consolidation with FSRT.

Patients without hydrocephalus that require multiple or bilateral open surgeries may be a population in which induction treatment with everolimus followed by fractionated stereotactic radiotherapy may be an alternative to surgery.

List Of Abbreviations

SEGA: subependymal giant cell astrocytoma; TSC: tuberous sclerosis complex; FSRT: fractionated stereotactic radiotherapy; SRS: stereotactic radiosurgery; mTOR: mammalian target of rapamycin; GTV: gross tumor volume; PTV: planning target volume; CTV: clinical target volume

Declarations

Ethics approval and consent to participate: Approval of the Ethics Comitty ('Comissie Medische Ethiek' O.G. 016°) was obtained to collect data for his retrospectieve study.

Consent for publication: the patient agreed and signed a declaration to do so. This declaration together with the manuscript was submitted tot he local Ethics Comitty (O.G. 016 ref. 2019/442) that agreed to publication.

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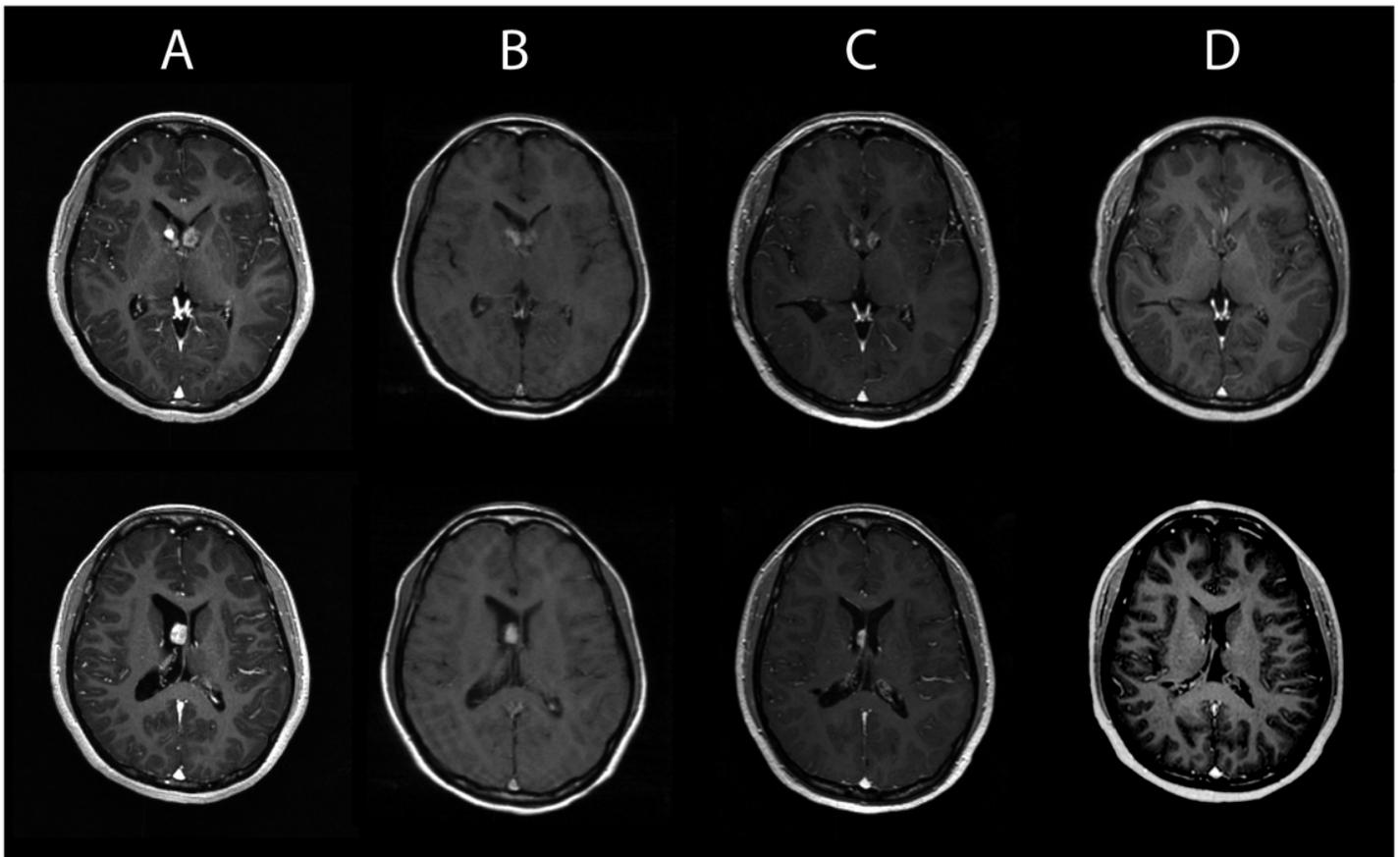
Figures

Figure 1

MR imaging Legend: Contrast-enhanced T1 MR slices at the maximal transsectional surface of the two SEGA (rows) at different time points (columns). At start of radiotherapy (A), 4.3y after radiotherapy (B), after 7.6y after radiotherapy, immediately prior to start of everolimus (C) and after 12.5y of total follow-up (D).
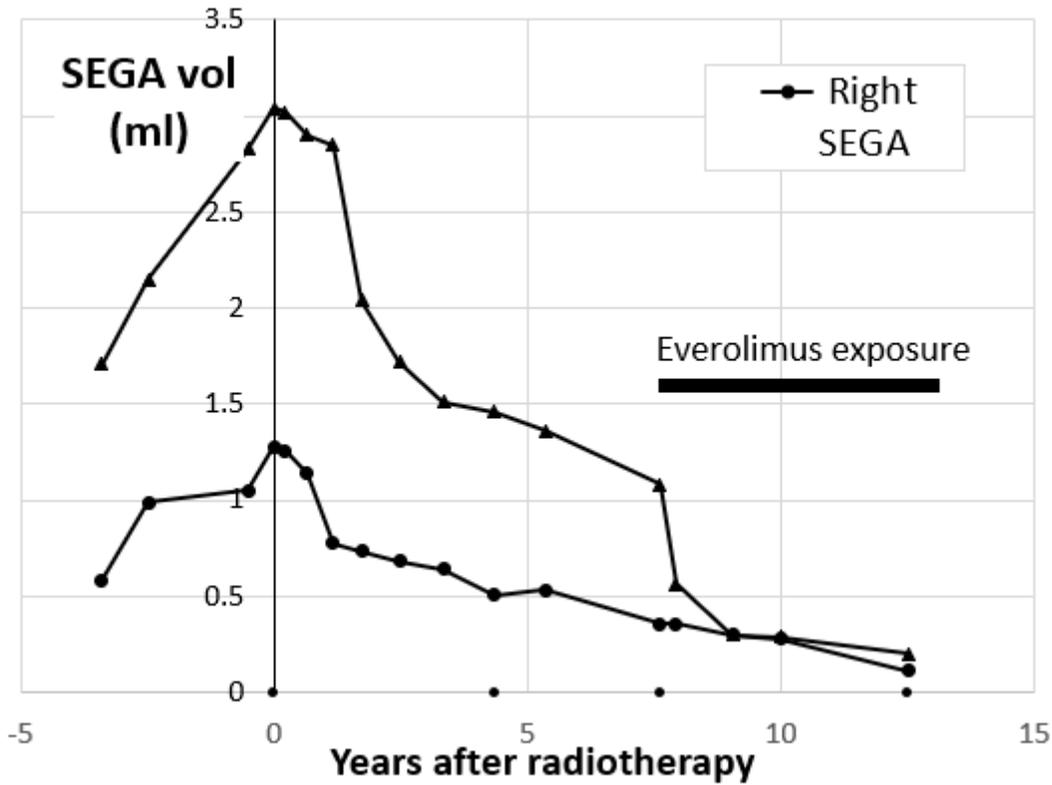

Figure 2

Volumetric evolution Legend: Volume of the two SEGA during wait-and-scan, post-radiotherapy and everolimus exposure. The time points A-D correspond to the MR slices shown in Fig. 1.