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Internal carotid artery stenosis and risk of cerebrovascular ischemia following stereotactic radiosurgery for recurrent or residual pituitary adenomas

Stylianos Pikis[1] · Adomas Bunevicius[1] · Jason Sheehan[1]

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Abstract

Purpose To evaluate the incidence of internal carotid artery (ICA) stenosis and cerebrovascular accident in a series of patients treated with stereotactic radiosurgery (SRS) for recurrent or residual pituitary adenoma.

Methods All patients treated with single fraction SRS in our institution for recurrent or residual non-functioning-, growth hormone- and ACTH-secreting pituitary adenomas were retrospectively identified and reviewed. A comprehensive literature review to identify studies reporting on ICA steno-occlusive disease following SRS for pituitary adenomas and compare the risks of carotid stenosis and ischemic stroke in the SRS treated group to the general population figures.

Results 528 patients [312 women and 216 men; median age at SRS 46 years old (range 12–80 years)] treated with SRS at our institution met study inclusion criteria. Mean clinical and radiologic follow-ups were 68.87 (SD ± 43.29) and 55.99 months (SD ± 38.03), respectively, and there were no clinically evident cerebral ischemic events noted. Asymptomatic, post-SRS, ICA stenosis occurred in two patients. A total of eight patients with ICA steno-occlusive disease following pituitary adenoma radiosurgery have been reported. Two of them suffered from ischemic stroke with however excellent recovery.

Conclusion As compared to the general population, SRS for pituitary adenomas does not seem to confer appreciable increased risk for ICA steno-occlusive disease and ischemic stroke. However, post-SRS radiation vessel injuries do occur and physicians should be aware about this rare event. Prompt identification and management according to current guidelines are essential to prevent ischemic strokes.

Keywords Adenoma · ICA stenosis · ICA occlusion · Pituitary · Radiosurgery · Stroke

Introduction

Pituitary adenomas account for 10–20% of all primary brain tumors [1, 2] and have been demonstrated to occur in up to 20% of the general population [2]. They are broadly classified into two groups. Functioning pituitary adenomas comprise tumors that secrete excessive amounts of normal pituitary hormones and depending on the hormone secreted they present with a variety of different clinical syndromes. The second group consists of non-secretory or non-functioning pituitary adenomas [2]. They account for approximately 30% of all pituitary tumors and typically present with symptoms due to compression of adjacent structures [2]. Surgical resection via trans-sphenoidal approach represents the most effective initial treatment for most patients with pituitary adenomas particularly in those patients presenting with pituitary apoplexy or deteriorating visual function. However, long-term tumor control rates with surgical resection alone vary from 50 to 90% [1, 2] and are dependent on factors such as tumor type, size and location, the presence of invasion, and follow-up duration [1].

Stereotactic radiosurgery (SRS) has been established as a generally safe and effective treatment modality for recurrent and residual pituitary adenomas [1–4]. The most common adverse radiation events of SRS for pituitary adenoma are new onset anterior pituitary insufficiency occurring in 21% to 58.3% [3–6] of cases, visual deficits and other transient or permanent palsies of the cavernous sinus cranial nerves in 3–9% of the patients [3–5]. More rare complications of SRS for recurrent or residual pituitary adenomas include brain

✉ Jason Sheehan
jsheehan@virginia.edu

[1] Department of Neurosurgery, University of Virginia Health System, Charlottesville, VA 22908, USA

parenchymal radiation injury, radiation induced neoplasms [2] and clinically evident [8, 9] or asymptomatic [10–12] internal carotid artery stenosis or occlusion.

In this study, we evaluate the incidence of internal carotid artery stenosis ≥ 50% and cerebrovascular accident (CVA) in a series of patients treated with SRS for recurrent or residual pituitary adenoma. In addition, we review the literature to identify other studies reporting on ICA steno-occlusive disease following SRS for pituitary adenomas and compare the risks of carotid stenosis and CVA in the SRS treated group compared to general population figures.

Materials and methods

Patient population and inclusion criteria

We retrospectively identified and reviewed all patients treated with single fraction SRS using the Gamma Knife (Elekta AB, Stockholm, Sweden) in our institution for recurrent or residual non-functioning, growth hormone- and ACTH-secreting pituitary adenomas from 1989 to 2019.

The study was approved by the IRB. All data were prospectively collected and analyzed retrospectively. Patients were included if they underwent radiosurgical planning with MRI and if they had at least one post-SRS MRI to evaluate for intracranial ICA changes. Also, we included patients who were treated only with single session, frame based SRS. Patients treated with CT based planning, hypofractionated SRS, or those without at least one follow up MRI were excluded from the study.

Data collected included patient demographics, previous treatments (endoscopic or microsurgical resection and radiation), procedure details (prescription dose, treated volume) and tumor control rate. Pre-procedural brain MRIs were reviewed and compared with surveillance brain MRIs to identify patients with new, post-procedural intracranial ICA stenosis or occlusion. Time from SRS to ICA stenosis or occlusion was documented. Intracranial ICA stenosis was defined as luminal stenosis ≥ 50% and critical ICA stenosis was defined as luminal stenosis luminal stenosis ≥ 70%. Non-visualization of the whole or of a segment of the intracranial ICA on post-contrast enhanced brain MRI was defined as ICA occlusion. Ischemic stroke was defined according to the Stroke Council of the American Heart Association/American Stroke Association updated definition of stroke for the twenty-first century [15].

Literature review

In addition, on November 20, 2020, we performed a comprehensive literature review of the Pubmed/MEDLINE database to identify relevant studies reporting on ICA stenosis following SRS. We searched the following terms "Radiosurgery" AND "Internal carotid artery stenosis" OR "pituitary adenoma" AND "stroke" and limited the search to English language articles for a search period of 10 days to 20 November 2020. We identified 32 articles that met the search criteria of which 27 were removed following title/abstract review. (Supplemental Fig. 1). Studies reporting the incidence, prevalence and risk factors of asymptomatic intracranial artery steno-occlusive disease were also identified.

Stereotactic radiosurgery approach and follow-up

Our treatment protocol for SRS delivery has been previously described [2, 7]. In brief, SRS was performed using the Gamma Knife device (Elekta AB, Stockholm, Sweden). For the purposes of this study, we included only patients treated with single fraction, frame based approach. Patients were typically followed at 6 month intervals for the first 2 years and yearly thereafter until year 5 and then every 2 year for the remaining time. Follow-up evaluations included clinical and radiologic assessments. Radiologic assessments included contrast enhanced and non-enhanced T1 and T2 weighted MRI sequences using a pituitary protocol. The MRI studies were reviewed by a neuro-radiologist and neurosurgeon for any potential changes in the cerebrovascular structures and for evidence of brain ischemia or infarction.

Results

Patient and tumor attributes

A total of 528 patients [312 women and 216 men; median age at SRS 46 years old (range 12–80 years)] were managed with SRS for a recurrent or residual pituitary adenoma. Of these tumors, 236 (45%) were non-functioning, 158 (30%) were growth hormone secreting and 134 (25%) were ACTH secreting pituitary adenomas. Prior to GKRS 515 (98%) and 11 (2%) of the patients underwent resection of the adenoma via trans-sphenoidal surgery and craniotomy, respectively. Adjuvant radiation therapy was previously used in 27 (5%) patients (Supplementary Table 1).

At the time of SRS, the mean tumor volume treated was 3.63 cm3 (SD ± 2.96 cm3). Median prescription dose for nonfunctioning pituitary adenomas was 20 Gy (range 12–25 Gy) and for functioning pituitary adenomas it was 25 Gy (range 10–30 Gy).

Follow-up

Mean clinical and radiologic follow-up were 68.87 (± 43.29) and 55.99 months (SD ± 38.03) respectively. There were no clinically evident cerebral ischemic events noted during follow up. Asymptomatic, post-SRS, ICA stenosis was noted in two patients. The incidence of ICA stenosis per 1000 patient-years in our cohort was 0.70 (95% Confidence Interval 0.12–2.33).

Illustrative Case 1

The patient is a 49 year old female with a 12 year history of Cushing's disease. Endocrinology evaluation revealed elevated serum cortisol and ACTH levels. Brain MRI scan was significant for a right-sided pituitary macro-adenoma 1.1 cm in maximum diameter. She subsequently underwent trans-sphenoidal resection of the adenoma but did not achieve a remission following resection. Post-operatively, she was placed on mifepristone 400 mg/day with reported improvement of her symptoms. However, ten years after the operation she presented with a 12 month history of progressive headaches, hyperglycemia, hypertension, amenorrhea, and weight gain. 24 h urine free cortisol testing was elevated, and a repeat brain MRI was negative for discrete tumor recurrence. The patient underwent SRS. The treatment volume included the sella and both cavernous sinuses with a dose of 20 Gy to the 50% isodose line. The maximum dose to the cavernous segment of the ICA was approximately 35 Gy (Fig. 1). Following radiosurgery, she achieved remission with normal 24 h urine free cortisol levels. However, on the 20 and 32 month follow-up brain MRIs, she was noted to have narrowing of the left cavernous portion of the ICA (Fig. 2). At the last follow-up 32 months following SRS, she remained asymptomatic from the narrowed carotid artery.

Illustrative Case 2

The patient has been previously reported with significantly less follow up [12]. In brief, the patient is a 46 year-old female who underwent radiosurgery for persistent Cushing's disease following two trans-sphenoidal resections that had failed to achieve endocrine remission (Fig. 3). Post-SRS, she achieved remission with normal 24 h urine free cortisol levels. However, on the 12 month follow-up brain MRI, she was noted to have left cavernous ICA stenosis (Fig. 4). Since then, the patient has remained asymptomatic with excellent collateral circulation noted. The patient has been under observation with annual brain MRI's and has not required endovascular treatment. Six years following SRS, the patient was asymptomatic from the carotid stenosis and remains in endocrine remission from her Cushing's disease.

Literature review

We identified six previously published reports of ICA stenosis or occlusion following SRS for recurrent or residual pituitary adenoma [8–11] (Table 1). Including our series, there were four females and two males (median age 35 years, range from 30 to 54 years) with ICA stenosis or occlusion after SRS for pituitary adenoma. Patient demographic data were not available for two patients [10].There were six functioning and two non-functioning pituitary adenomas [8, 9]. Hormone secreting adenomas included two ACTH secreting (current cases) one Growth hormone secreting and one Growth hormone/prolactin [11] secreting (Table 1).

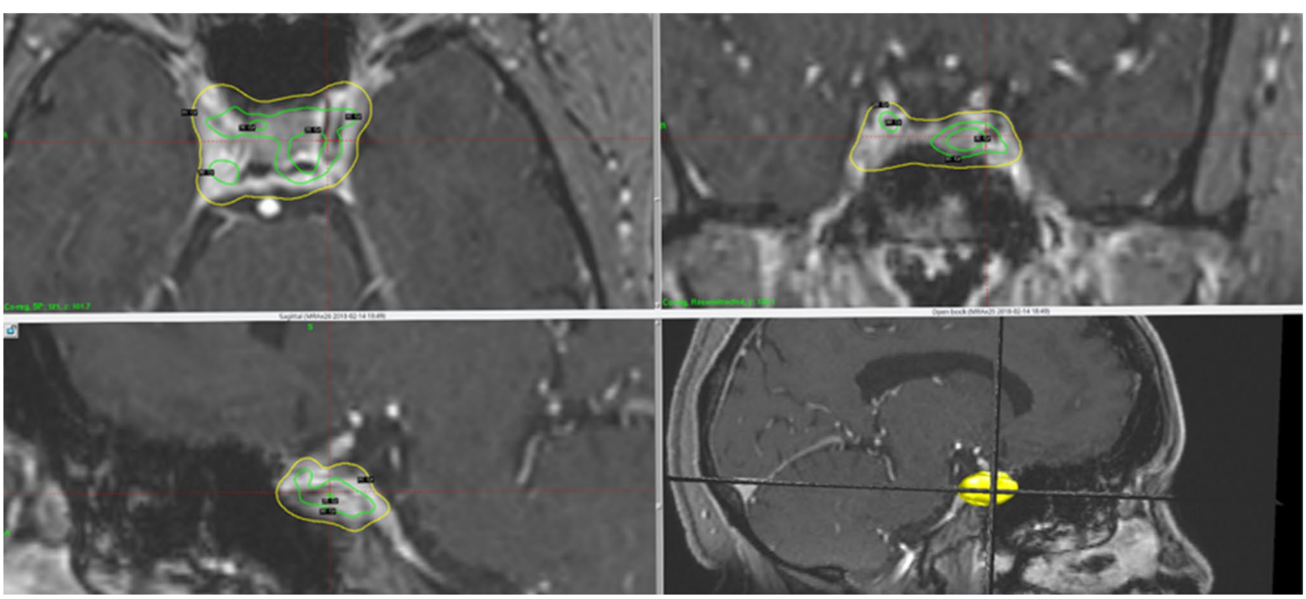

Fig. 1 Gamma Knife Radiosurgery dose plan. The yellow contour corresponds to the 20 Gy isodose line delivered to the sella and the cavernous sinus bilaterally. The green isodose lines correspond to areas receiving radiation doses of 30 (outer green) and 35 Gy (inner green). The maximum dose to the left carotid artery was approximately 35 Gy

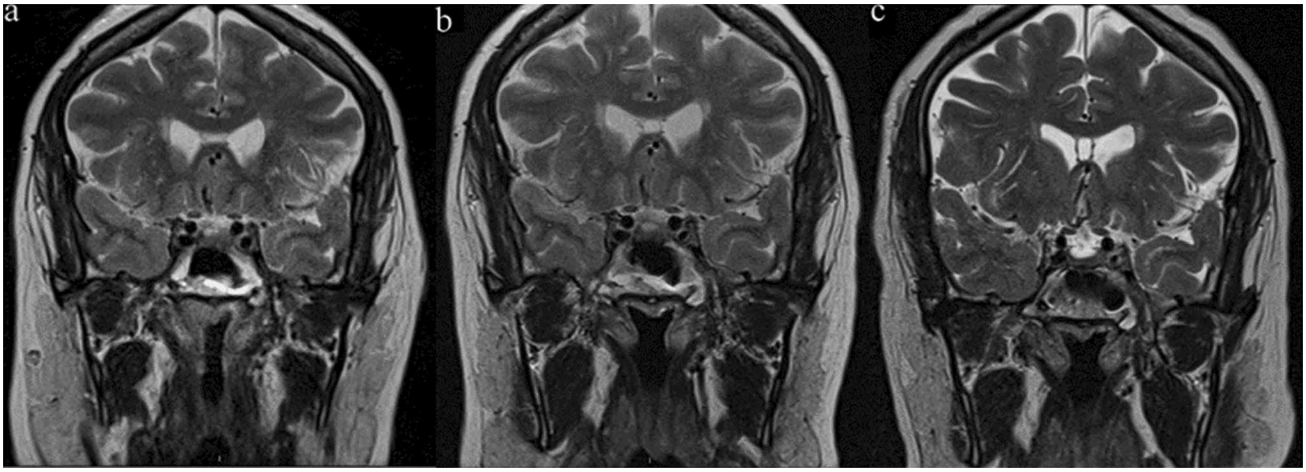

Fig. 2 T2 Weighted, coronal, brain MR Image significant for progressive decrease in size of the cavernous internal carotid artery flow void. **a** one month prior to Gamma Knife Radiosurgery, **b** at the 20 and **c** the 32 month follow-up

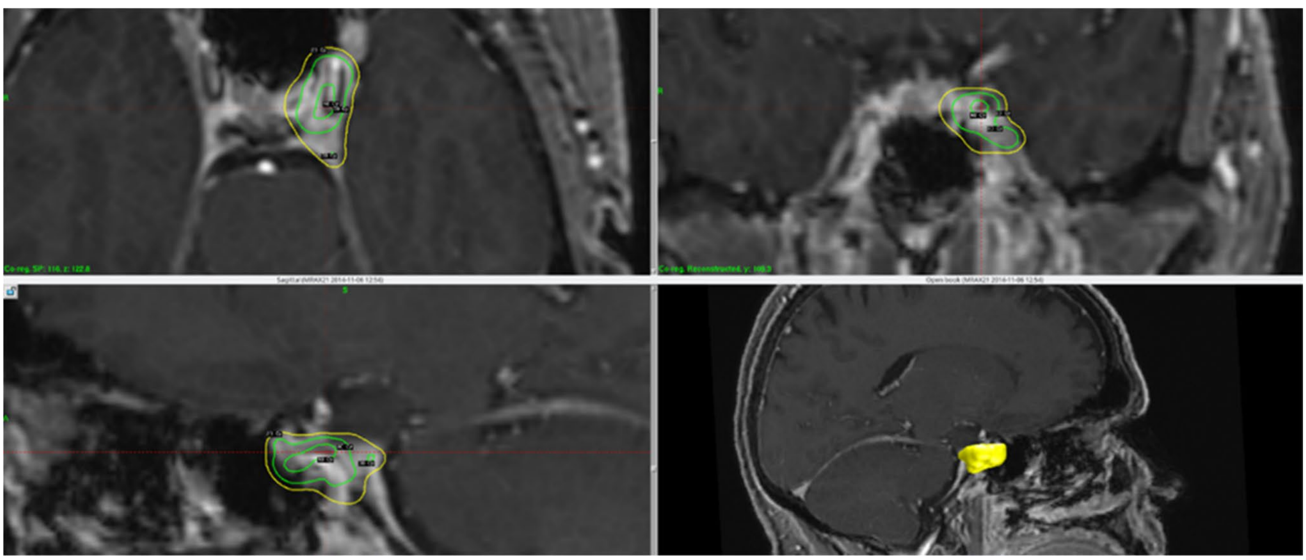

Fig. 3 Gamma Knife radiosurgery dose plan. The yellow line represents the 50% isodose line corresponding to 23 Gy. The radiation dose delivered to the left ICA corresponds to the green isodose lines and it was between 30 (outer green) and 40 Gy (inner green)

ICA stenosis was diagnosed in 5 patients and ICA occlusion in 3 patients. The median time from SRS to diagnosis of ICA stenosis or occlusion was 54 months (range from 12 to 84 months). The maximum radiation dose received by the ICA was reported for six patients and ranged from 20 to 44.7 Gy. Following SRS, follow-up data were available for four patients. The median follow-up was 40 months (range from 12 to 72 months) from SRS.

Data on clinical presentation were reported for all patients. In six patients, ICA stenosis was discovered incidentally on surveillance imaging [10, 11]. However, one patient with right ICA occlusion presented with left sided hemiparesis and left facial nerve palsy [8] and one patient with right ICA occlusion presented with ipsilateral amaurosis [9] with the later treated with balloon angioplasty due to severe right ICA stenosis [9]. The remainder of the patients were managed conservatively. There was no mortality reported with the ICA stenosis or management of this post-SRS complication. On the follow-up clinical evaluations, none of the asymptomatic patients developed new symptoms attributed to the ICA stenosis and the two patients presenting with stroke symptoms achieved full recovery (Table 1).

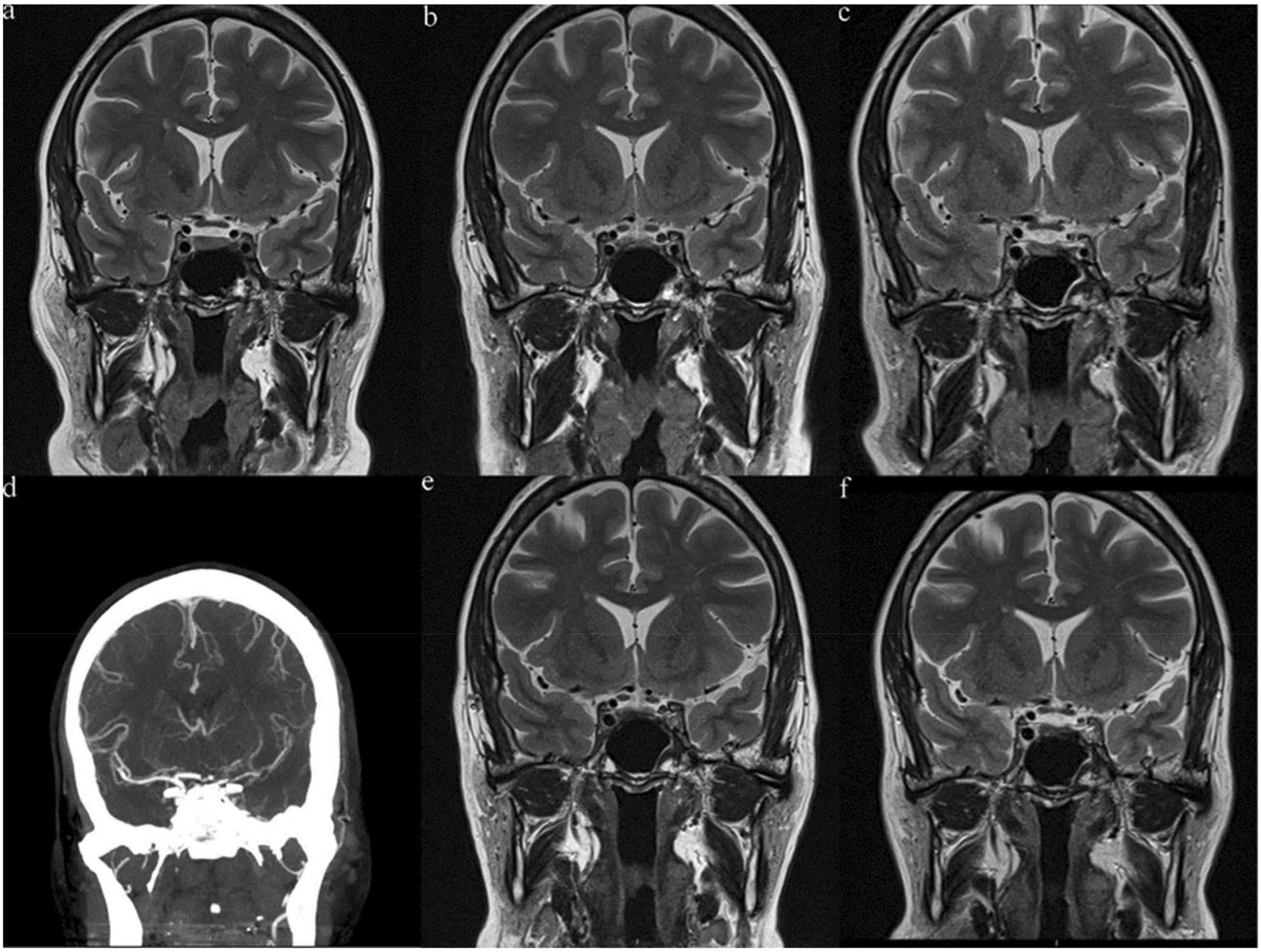

Fig. 4 Serial, coronal, T2 Weighted brain MRI **a**–**c**, **e**, **f** and **d** coronal, cerebral CT angiography at the three year follow-up time point demonstrating progression of the left ICA stenosis. **a** MR prior to radiosurgery, **b** 1-, **c** 2-, **d** 4-, **e** 5- and **f** 6-years after stereotactic radiosurgery

Discussion

Intracranial ICA steno-occlusive disease appears to be a very rare complication of radiosurgery for recurrent or residual pituitary adenoma [11]. The incidence rate of asymptomatic intracranial ICA stenosis per 1000 patient-years in our cohort was 0.70 with no patients experiencing ischemic stroke. In the general population, the reported prevalence rate of asymptomatic, large vessel, intracranial steno-occlusive disease is estimated at 3.5% to 12.9% [17, 18] and in patients with cerebrovascular insufficiency the incidence of asymptomatic ICA stenosis of > 50% was 14% in one study [19]. Intracranial vessel stenosis is associated with 3.5%/year risk of stroke and accounts for approximately 10% of all ischemic strokes [16, 18]. Traditional risk factors of ICA stenosis include African American and Hispanic descent [16], metabolic X syndrome [17], age > 65 years old [18], hypertension [18], diabetes mellitus [18, 20], and ischemic heart disease [18, 20]. ICA compression by a pituitary adenoma is a rare event. In our cohort, none of the patients suffered from ICA compression due to the pituitary adenoma prior to tumor resection or prior to SRS. In accordance to our results, Molitch et al., reported ICA compression in 1.7% (1/58) of pituitary adenomas invading the cavernous sinus and encasing the internal carotid artery [21].

The pathophysiology of cavernous, ICA steno-occlusive disease following SRS for pituitary adenomas remains unclear with two hypotheses proposed. The first theory suggests that intracranial vessel occlusion following ionizing radiation occurs due to dose-dependent DNA damage which initiates vascular endothelial cell hyperproliferation and results in narrowing of the vessel lumen [13]. To prevent post-SRS ICA radiation injury, it has been suggested to avoid hotspots exceeding 90% isodose close to the ICA and to minimize the radiation dose to the ICA [8, 9, 11]. The second hypothesis attributes intracranial ICA steno-occlusive disease following radiosurgery of cavernous sinus masses to tumor biology and tumor response to

Table 1 Literature review of internal carotid artery occlusion or stenosis following SRS for recurrent or residual pituitary adenoma

Author, year	Age/sex	Pituitary adenoma type	Max Radiation dose to ICA (Gy)	Time from SRS to diagnosis of ICA stenosis or occlusion (months)	Symptoms	ICA stenosis/ occlusion management	Follow-up (months)	Outcome
Lim et al [8], (1999)	35/M	Non-functioning	< 20	48	Lt hemiparesis, lt facial palsy	Conservative	N/R	Complete recovery
Pollock et al [10], (2002)	-	Hormone secreting	N/R	-	Asymptomatic	Observation	N/R	Asymptomatic
	-	Hormone secreting	N/R	-	Asymptomatic	Observation	N/R	Asymptomatic
Ito et al [9], (2015)	54/M	Non-functioning	20–22	60	Amaurosis	Balloon angioplasty	12	Asymptomatic
Spatola et al [11], (2016)	30/F	GH secreting	44.3	84	Asymptomatic	Observation	48	Asymptomatic
	35/F	GH/prolactin secreting	44.7	84	Asymptomatic	Observation	N/R	Asymptomatic
Current case 1	49/F	ACTH secreting	35	12	Asymptomatic	Observation	72	Asymptomatic
Current case 2	46/F	ACTH secreting	40	18	Asymptomatic	Observation	32	Asymptomatic

radiosurgery [10]. Parasellar tumors encircling the ICA may progress following SRS causing ICA luminal narrowing or occlusion by a mechanism similar to external clamping of the vessel [14]. Evidence supporting this theory comes from a study reporting nine cases of ICA steno-occlusive disease in 155 cavernous sinus meningioma treated with SRS as opposed to zero cases among 129 patients treated with SRS for GH secreting adenomas [14]. In that study, there was no association between of prescription isodose, treatment volumes, and the number of isocenters used with the risk for development of ICA steno-occlusive disease [14]. In our patients, no contact between the diseased vessels and progressive residual adenoma was noted on post-SRS imaging. Moreover, delivery of radiation doses greater than 25 Gy to human vessels has been reported to be associated with rare occlusion [13]. The maximum radiation dose to the ICAs was 35 Gy (patient one) and 40 Gy (patient two) respectively thus we speculate that radiation injury was a contributory mechanism of ICA steno-occlusive disease in our patients.

The natural history of intracranial ICA steno-occlusive disease following SRS has not been well defined yet. In our review, time from radiosurgery to diagnosis of ICA stenosis or occlusion was highly variable ranging from 12 to 84 months [11]. Presentation was also variable. One patient presented with symptoms of cerebral ischemia [8] and seven patients were asymptomatic and were diagnosed during routine follow-up neuroimaging [10, 11]. Despite management with anti-platelet medications, one of these patients developed symptoms of cerebral ischemia, and he was subsequently treated with percutaneous transluminal angioplasty [9].

In our review, prognosis of post-radiosurgery ICA steno-occlusive disease was excellent with no mortality nor permanent neurologic morbidity reported. However, due to disease rarity, specific evidence based treatment recommendations are lacking. Nevertheless, in our population of pituitary adenoma patients treated with SRS as well as those reported in the literature, the risk of ICA stenosis appears within the range reported for steno-occlusive disease within the general adult population [17–19]. According to our review, initial conservative management of ICA stenosis in post-SRS patients seems appropriate in asymptomatic patients. Endovascular treatment may be reserved for patients in whom symptoms persist or new symptoms develop despite best medical management. In our practice, we aim to reduce the annual 3.5% risk of stroke by strict management of known risk factors for intracranial vessel steno-occlusive disease such as hypertension [18], Diabetes Mellitus [18], and IHD [18, 20]. Hypertension represents a major risk factor for ischemic stroke and intracerebral hemorrhage with the risk of stroke demonstrated to increase with increasing blood pressure even in the normotensive range. It is our policy to treat hypertensive patients pharmacologically to a target BP of < 140/90 mm Hg and to manage pre-hypertensive patients with regular blood pressure monitoring. However, the optimal management of blood pressure in patients with asymptomatic or symptomatic carotid stenosis management remains a subject of debate and should be tailored to the individual patient with medical management implemented being phased in gradually [22, 23]. In addition, life style modifications according to current primary stroke prevention guidelines are recommended for all patients [24].

Limitations of our study include those inherent to its retrospective nature. Moreover, screening of patients in our cohort for intracranial ICA steno-occlusive disease with brain non-contrast/contrast enhanced MRI and not with an imaging study evaluating the cerebral vasculature may have resulted in underestimation of the true incidence of asymptomatic intra-cranial steno-occlusive disease in our study.

Conclusions

SRS for pituitary adenomas does not seem to confer an appreciable increased risk for ICA steno-occlusive disease or stroke. However, post-SRS, radiation-induced vessel stenosis can occur, and neurosurgeons should be aware about this rare event. Management depends on presentation and should be in accordance to contemporary stroke prevention guidelines.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

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