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Original Research Article

# Cerebral infarction after fractionated stereotactic radiation therapy of benign anterior skull base tumors

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ABSTRACT

*Background:* The purpose of this study was to examine the occurrence of cerebral infarction (ischemic stroke), in a large combined cohort of patients with anterior skull base meningiomas, pituitary adenomas and craniopharyngiomas, after fractionated stereotactic radiation therapy (FSRT).

*Material and Methods:* All patients, 18 years and older, with anterior skull base meningiomas, pituitary adenomas and craniopharyngiomas, treated with fractionated stereotactic radiation, in our center, from January 1999 to December 2015 were identified. In total 169 patients were included. The prescription dose to the tumor was 54 Gy for 164 patients (97%) and 46.0–52.2 Gy for 5 patients (3%). Cases of cerebral infarctions subsequent to FSRT were identified from the Danish National Patient Registry and verified with review of case notes. The rate of cerebral infarction after FSRT was compared to the rate in the general population with a one sample *t*-test after standardization for age and year. We explored if age, sex, disease type, radiation dose and dose per fraction was associated with increased risk of cerebral infarction using univariate Cox models.

*Results:* At a median follow-up of 9.3 years (range 0.1–16.5), 7 of the 169 patients (4.1%) developed a cerebral infarction, at a median 5.7 years (range 1.2–11.5) after FSRT. The mean cerebral infarction rate for the general population was 0.0035 and 0.0048 for the FSRT cohort ($p = 0.423$). Univariate cox models analysis showed that increasing age correlated significantly with the cerebral infarction risk, with a hazard ratio of 1.090 ($p = 0.013$).

*Conclusion:* Increased risk of cerebral infarction after FSRT of anterior skull base tumors was associated with age, similar to the general population. Our study revealed that FSRT did not introduce an excess risk of cerebral infarction.



## 1. Introduction

Benign tumors of the anterior skull base include meningiomas, pituitary adenomas and craniopharyngiomas [1]. When surgery is not feasible, or as an adjuvant to surgery or therapy of tumor recurrence, highly precise stereotactic radiosurgery (SRS) or fractionated stereotactic radiation therapy (FSRT) can be utilized to focus the radiation effect on the tumor, while limiting radiation of healthy but sensitive parts of the brain, near the tumor [2]. During irradiation of tumors of the anterior skull base with close anatomical relation to structures such as the cavernous sinus and the Circle of Willis, a certain degree of collateral irradiation of these structures occurs [3,4]. Occlusion of the carotid artery or its branches leading to cerebral infarction or ischemic stroke is a potential, serious and life-threatening complication. Radiation induced cerebral infarction is well described after conventional radiotherapy of pituitary tumors [5]. More recently, several cases of cerebral infarction after single fraction stereotactic radiosurgery of cavernous sinus

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meningiomas and pituitary adenomas [6,7] have been reported. A few cases of cerebral infarction after fractionated stereotactic radiation therapy have been described [8], though the data is scarce.

The purpose of this study was to investigate the incidence and characteristics of cerebral infarction after fractionated stereotactic radiation therapy in a large cohort of patients with benign anterior skull base tumors.

## 2. Methods and patients

Patients with anterior skull base meningiomas, pituitary adenomas and craniopharyngiomas treated with fractionated stereotactic radiation therapy, in our center, during the period of January 1999 – December 2015 were included. Two patients younger than 18 years at the time of FSRT were excluded in this study. For the purpose of this study, anterior skull base meningiomas included both meningiomas in the anterior and middle cranial fossa with close relation to the carotid arteries and Circle of Willis. Patients with any intracranial malignancy at the time of treatment were excluded. In total 169 patients were included (104 women (61.5%)). There were 35 cases of cavernous sinus meningiomas and 2, 18, 3 and 13 cases of optic canal, clival/petroclival, tuberculum sellae and sphenoid wing meningiomas, respectively. Among the patients with pituitary processes 55 cases were secreting and 28 cases non-secreting pituitary adenomas and 15 cases were craniopharyngiomas. Mean age at the time of FSRT was 52 years (range 18–79). In total 135 patients (79.9%) underwent surgery before FSRT, while FSRT was the primary and only treatment in 34 patients (20.1%). Specifically, 43 (60.5%) meningioma cases, 79 (95.2%) pituitary adenoma cases and 15 (100%) craniopharyngioma cases underwent operation before FSRT. Visual outcome and tumor control of a subgroup of anterior skull base meningiomas and pituitary adenomas from this cohort, treated in the years 1999–2009, have been described elsewhere [1]. Also, visual outcome, pituitary function and tumor control of all 15 of these craniopharyngioma patients 1999–2015 have been previously reported [9].

In all cases, linear accelerators were used to deliver the stereotactic irradiation treatments; a dedicated stereotactic accelerator (Clinac 600SR, Varian Medical Systems, Palo Alto, CA, USA) was used 1999–2008, and was thereafter replaced by three NovalisTx© (Varian Medical Systems and BrainLab, Munich, Germany). Fixed circular collimators, with 0.5–3.5 cm diameter were used for the first patients and since August 2000, collimation and field shaping has been provided using micromultileaf collimators. The treatment planning was performed using a system dedicated for stereotactic radiation therapy (XKnife, RSA, USA, and BrainScan and iPlan, BrainLab and since 2012 Varian Eclipse). An individual aquaplastic mask of the head was made during the planning process and was used for all the treatments. A fusion of MRI and CT scans was used for the treatment plan, whereby the gross tumor volume (GTV) was defined. The clinical target volume was considered to be equal to the GTV. The eye balls, optic chiasm, nerves and tracts and brainstem were outlined and defined as organs at risk. The dose was prescribed to the 90% isodose contour, and the 90% isodose contour was encompassing the target volume. The prescribed tumor radiation dose was 2.0 Gy × 27 fractions for 32 patients, 2.0 Gy × 24 fractions for one patient, 2.0 Gy × 23 fractions for one patient, 1.8 Gy × 30 fractions for 132 patients, 1.8 Gy × 29 fractions for one patient, 1.8 Gy × 28 fractions for one patient and 1.8 Gy × 27 fractions for one patient, resulting in a total dose of 54 Gy for 164 patients (97%) and the remaining 5 patients (3%) with total doses of 46.0–52.2 Gy.

Cases with a clinical diagnosis of cerebral infarctions from the FSRT treated cohort were identified from The Danish National Patient Registry and verified with review of electronic and paper case notes. Clinically silent infarctions identified from MRI reviews were not considered.

Individual dose plans were reviewed, and the relationship of the area of cerebral infarction, the cavernous sinus, the internal carotid artery and/or Circle of Willis was compared with the tumor localization and radiation field, after fusion of pertinent MRI or CT with the dose plan. Two cases treated in 1999 were not evaluable in terms of radiation fields, due to server data loss that year; in all 5 of 7 cases were evaluable. Tumor control of the index cases was evaluated from baseline MRI compared with the most recent MRI or CT scan at the time of stroke, when applicable, with a change of less than 2 mm in any dimension considered stable size.

Cases of cerebral infarctions in the Danish general population were also identified from the National Patient Registry and age and year specific population data were obtained from the Statistical Bureau of Denmark. The rate of cerebral infarction in the FSRT treated cohort was compared to that of the general population, during the period January 1999 – December 2015. A case by case standardization was performed for each patient according to age and year of follow-up for analysis of the difference (see below).

## 3. Statistical methods

Statistical calculations were done using SPSS (version 24) and R (version 3.3.0). The difference between the rate of stroke in the FSRT group and the general population was analyzed by a one sample *t*-test after age and year standardization. Univariate Cox models analysis was performed with age at therapy, sex, disease type, radiation dose and dose per fraction as covariates. Competing risk analysis was performed with the Aalen-Johansen estimator [10], where cerebral infarction and death to other causes were controlled for. The Aalen-Johansen estimator, is a standard nonparametric estimator of the cumulative incidence function, in competing risks, applied to the total sample [10].

## 4. Results

Median follow-up after FSRT was 9.3 years (range 0.1–16.5). Seven of 169 patients (4.1%) developed a cerebral infarction at a median 5.7 years (range 1.2–11.5) after FSRT, at a mean age of 72 years (range 55–89); there were four females and three males (Table 1). Mean age at the time of FSRT was 52 years (range 18–79). One patient with a left cavernous sinus meningioma developed an ipsilateral frontal and a contralateral pontine infarction; one patient with a right cavernous sinus meningioma developed an ipsilateral pontine infarction (Fig. 1, Table1). Three patients with a secreting pituitary adenoma developed a left cerebral, a left cerebral and a right cerebellar infarction, respectively (Table 1). One patient with a craniopharyngioma, developed an acute right sided cerebral infarction, and two older infarctions on the left and right side, were also identified (Table 1). Thus, the occurrence of cerebral infarction after FSRT was 3 (4.2%) for meningiomas, 3 (3.6%) for pituitary adenomas and 1 (6.3%) for craniopharyngiomas (Fig. 2).

Five out of 7 patients had evaluable radiation dosimetry. All 5 received a 80–100% of the maximum dose (48–60 Gy) to what we estimated to be the vascular origins of the infarctions, while three of these patients also received lower doses (30%, 50% and 80% isodose, respectively) corresponding to the areas of infarction (Table 1). The three patients with a secreting pituitary adenoma were previously operated at 4.9, 10.2 and 22.2 months, respectively, before FSRT. The patient with a sphenoid wing meningioma was operated 2.3 months before FSRT and the patient with a craniopharyngioma was operated 23.3 months before FSRT. The two patients with a cavernous sinus meningioma had not undergone

**Table 1**
Cerebral infarction. Patient and cerebral infarction characteristics.

| Case no. | Sex (F/M) | Age (years) | Surgery before FSRT | Radiation total dose (Gy) | Years after FSRT | Tumor type | Anatomical correlates and collateral irradiation | Infarction site and vascular pathology | Presentation | Risk factors |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 55 | Yes | 54 | 9.1 | Pituitary adenoid (somatotroph) | Tumor adjacent to bilateral ICAs | Left cerebral? (CT neg.) | Right homonymous hemianopia Right arm weakness | Smoking Hypertension |
| 2 | F | 8 | Yes | 54 | 10.8 | Pituitary adenoma (corticotroph) | Tumor adjacent to bilateral ICAs | Left multiple subcortical infarction Right ICA occlusion | Expressive aphasia Dysarthria Dysphagia | Type 2 diabetes Smoking Hyperlipidemia |
| 3 | M | 69 | No | 54 | 10.4 | Left cavernous sinus meningioma | Left CS with 100% isodose line | Left frontal and right pontine | Aphasia Dysarthria Left central facial weakness | Hypertension Hyperlipidemia |
| 4 | F | 89 | No | 54 | 11.5 | Right cavernous sinus meningioma | Right CS and ICA within 90% isodoseInfarction within 50% isodose line | Right pontine Left ICA plaques | Left hemiparesis Left facial weakness Dysarthria | Hypertension |
| 5 | M | 70 | Yes | 54 | 1.2 | Craniopharyngioma | Bilateral ICAs within 90% isodose line | Right frontal and left and right internal capsule | Right hemiparesis Expressive aphasia | Hypertension Hyperlipidemia |
| 6 | F | 61 | Yes | 54 | 2.2 | Pituitary adenoid (corticotroph) | C. of Willis and basilar artery within 80% isodose line | Right cerebellar Right PICA occlusion | Double vision Nausea and vomiting | Smoking Hyperlipidemia |
| 7 | M | 81 | Yes | 54 | 1.9 | Left sphenoid wing meningioma | Left ICA within 80% isodose area Infarction within 30% isodose line | Left basal ganglia and external capsule | Right hemiparesis Expressive aphasia Dysarthria | Hypertension Atrial fibrillation |

operation and were treated primarily with FSRT. All patients had tumor control (stable or regression) on neuroimaging (MRI or CT) at the time of the stroke. Additionally, three patients who had a history of cerebral infarction, before FSRT, did not develop new cerebral infarction after FSRT, and are not considered further. One sample *t*-test showed a mean difference of 0.0013 between the age and year adjusted cerebral infarction rate for the general population and the FSRT cohort (mean 0.0048), which was not statistically significant with a t-value = 0.859 and an associated p-value = 0.423.

An Aalen-Johansen estimate of disease specific cumulative incidence of cerebral infarction following FSRT is shown in Fig. 2. Univariate Cox models analysis showed that increasing age correlated significantly with the cerebral infarction risk, with a hazard ratio of 1.090 (p = 0.013), while female sex carried a decreased risk, with a hazard ratio of 0.896 (p = 0.886). Patientś sex and age, time after treatment, tumor type, anatomical correlates and collateral irradiation, infarction site, presenting symptoms and risk factors are given in Table 1.

## 5. Discussion

Stereotactic radiosurgery (SRS) and fractionated stereotactic radiation therapy (FSRT) are highly precise image-guided irradiation therapy techniques well suited for the treatment of a variety of intracranial lesions, including benign anterior skull base tumors (1, 11). In particular, FSRT combines the high accuracy of stereotactic radiation with potentially a biological advantage of fractionated treatments which may be less toxic than radiosurgery. The therapeutic efficacy of FSRT of benign anterior skull base tumors is well established, with long-term tumor control rates reported in the range of 91–100% [11–21]. Nevertheless, side effects after FSRT occur, in particular related to visual and endocrine function [1,11,15–17,21–23].

Cerebral infarction was initially described as a complication to conventional radiotherapy of benign skull base tumors, mainly pituitary tumors. Hashimoto et al. [24] described the occurrence of ischemic stroke with a long-term follow up after conventional radiotherapy treatment, in 10 out of 139 patients with a pituitary adenoma. Flickinger et al. [5], reported 7 of 156 patients with pituitary adenomas irradiated developing ischemic stroke but the incidence was not significantly greater than the occurrence of stroke in the general population [25]. Bowen et al. reported two patients who developed symptomatic cerebral infarctions after conventional radiation therapy for pituitary adenomas [26]. Finally, Sattler et al. recently, in a large cohort of 236 patients with pituitary adenomas treated with conventional radiotherapy, identified 11 patients with post radiation ischemic stroke and found an increased risk of stroke in the cohort when compared to the general population, but not when compared to surgery only cases [27].

Also, cerebral infarction has been described after stereotactic radiosurgery for benign skull base tumors with the Gamma Knife [2,28,29,30,6,32] and LINAC [31,33].

However, with single fraction radiosurgery, the biologic effect is very different from fractionated radiation therapy and the two modalities are therefore difficult to compare.

Few cases of cerebral infarctions after fractionated stereotactic radiation therapy of benign skull base tumors have been described. Correa et al. recently reported their experience with 89 patients with cavernous sinus meningiomas, treated either with fractionated stereotactic radiation therapy or radiosurgery over a 15-year period [8]. They detected one case of total internal carotid artery occlusion, which was, however, asymptomatic [8].

More recently, Sanford et al. reported a 20% cumulative risk of cerebrovascular incidents among 50 patients with intracranial

meningiomas treated with a fractionated Proton-Photon combination therapy, with a median follow-up of 17 years. In contrast to our study, their rate of cerebrovascular incidents was significantly higher than in the general population [34].

We observed seven events of cerebral infarction after FSRT in our cohort of 169 patients, whereof all were potentially the result of the irradiation therapy, with five patients having collateral irradiation of the ICA, cavernous sinus, Circle of Willis and/or the basilar artery and branches and further two patients with potential affection of the bilateral ICAs, based on anatomical correlates.

However, in only three cases was the area of infarction within the previous field of irradiation. Also, in one case, an ipsilateral arterial occlusion was demonstrated, of the PICA, while an occlusion or plaques of the contralateral ICA were identified in two other patients. This demonstrates that the relationship between irradiation and arterial stenosis or occlusion may not be straightforward [31]. It is not clear how much radiation is tolerated by the Circle of Willis and the carotid artery, but total dose over 45–50 Gy has been related to greater risk previously [8].

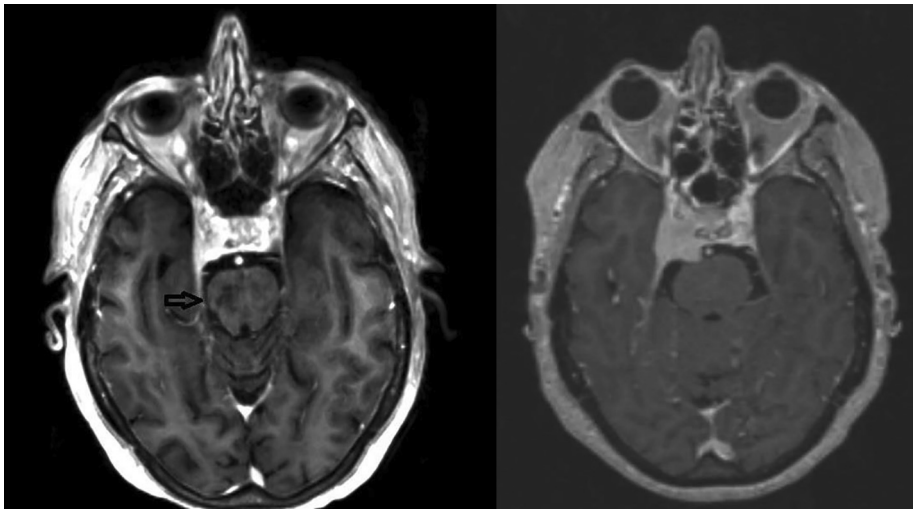

**Fig. 1.** Right sided pontine infarction 11.5 years after fractionated stereotactic radiation therapy of a right cavernous sinus meningioma abutting the pons.

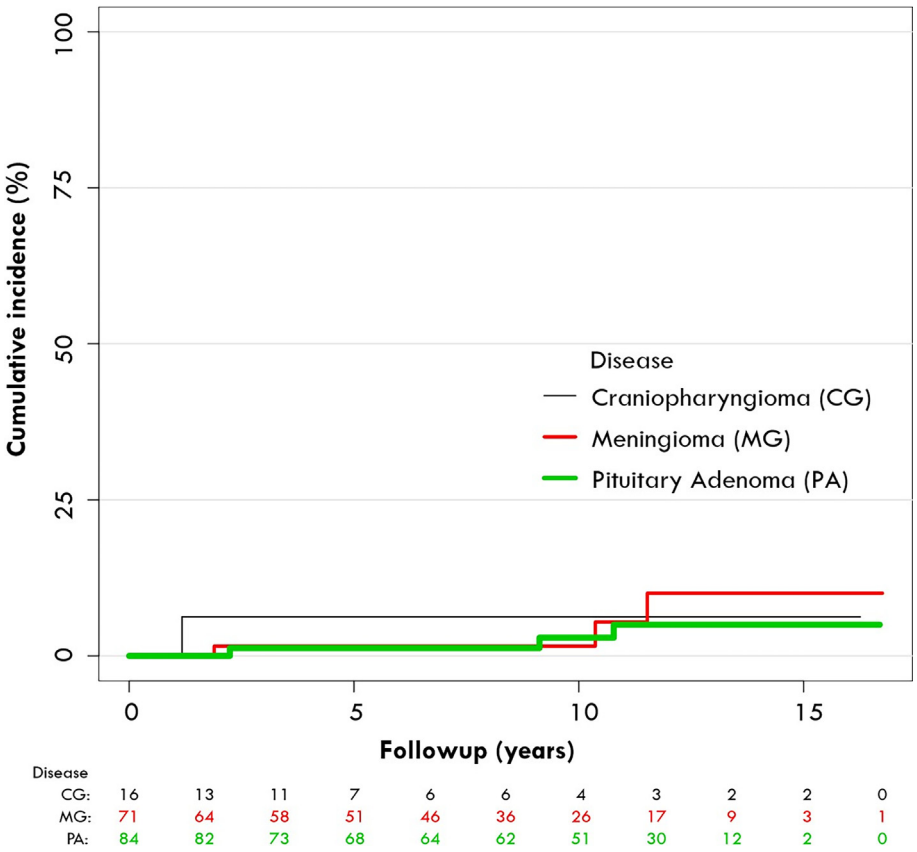


**Fig. 2.** Aalen-Johansen plot. Disease specific cumulative incidence of cerebral infarction following FSRT of craniopharyngiomas, anterior skull base meningiomas and pituitary adenomas, respectively.

As this was a national patient registry study, only patients who had received a clinical diagnosis of a cerebral infarction were included. Thus cases were not identified from a systematic review of neuroimaging studies, and it can therefore not be ruled out that a further group of patients had silent cerebral infarction after FSRT. However, cerebral infarction is primarily a clinical diagnosis, and neuroimaging findings without symptoms do not meet the criteria for a stroke diagnosis.

We compared the occurrence of cerebral infarction in FSRT treated anterior skull base tumors to that of the general population. We did not find a statistically increased rate of cerebral infarction after FSRT when compared to the general population after individual case adjustments for age and year. Our retrospective study indicates that cerebral infarction was not related to FSRT. However, it would be of interest to prospectively study if a subgroup of patients experiences an elevated risk of cerebral infarction following FSRT, i.e. patients with genetic predisposition of radiation sensitivity, diabetes, treated young age or smokers, etc.

Cerebral infarction or ischemic stroke after irradiation of skull base tumors, is usually a delayed event [2,5,6,24,26,33] and most of the patients in this study had a stroke with onset several years after FSRT.

All of the seven patients suffering a cerebral infarction in the present study, had one or more predisposing risk factors for ischemic events, most commonly smoking, hypertension and hyperlipidemia. Also, increased age was an independent risk factor in this study. The cited studies have not invariably reported there to be any predisposing risk factors, other than the radiation therapy itself, in particular for younger patients [2,33].

It has, however, been described that irradiation may accelerate the natural process of atherosclerosis [35] Radiation induced atherosclerotic changes in the vessel wall after cranial radiation therapy are usually a late event [35]. These changes affect both small, medium and large vessels. Small vessel pathology includes fibrinoid necrosis, endothelial damage, adventitial fibrosis, and perivascular lymphocytic infiltration and medium- and large-vessel pathology includes atherosclerotic plaques, calcifications, damage of the internal elastic lamina, vessel wall fibrosis and macrophages containing fat [36]. Also, the small vasa vasorum arteries may become fibrotic and contribute to the atherosclerosis of large vessels [36]. Total occlusion may result and, if there is carotid involvement, a moyamoya like disease may develop [35,36].

In summary, this is the first study evaluating the occurrence of cerebral infarction in a mixed cohort of anterior skull base meningiomas, pituitary adenomas and craniopharyngiomas, after fractionated stereotactic radiation therapy. The incidence of cerebral infarction was not high, and was not significantly greater than in the general population. Yet, when irradiating tumors of the anterior skull base, in particular cavernous sinus meningiomas and pituitary adenomas, with close relationship to the cavernous sinus, carotid artery and Circle of Willis, the risk needs to be evaluated with possible adjustments for each case.

## Disclosure statement

No potential conflict of interest is reported.

## Ethical standards

The study was approved by the Danish Data Protection Agency and was conducted according to Danish legislation, and the Helsinki II declaration. Ethical committee approval is not required in Denmark for clinical audits.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2019.02.001.

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