Clinical Neurology and Neurosurgery 187 (2019) 105560

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Gamma knife radiosurgery for pituitary spindle cell oncocytomas

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ARTICLE INFO

Keywords:
Spindle cell
Oncocytomas
Sellar
Mass
Pituitary
Transsphenoidal
Revision
Stereotactic radiosurgery
Gamma knife
Oncology

ABSTRACT

Objectives: Spindle cell oncocytomas (SCOs) are benign lesions of the posterior portion of the pituitary gland that typically come to neurosurgical attention due to compression of the sellar or parasellar structures, and headaches. Initial treatment options for SCOs include surgical resection, particularly via the transsphenoidal approach. However, given that initial resection tends to be insufficient and subsequent revision surgery carries high complication risk, adjuvant treatment modalities may appear to offer promising solutions for controlling tumor progression. This report focuses on a potential new therapeutic option for SCOs, gamma knife radiosurgery (GKRS).

Patients and methods: The authors identified all patients at one center who had a pituitary lesion treated with GKRS between 2005 and 2016. Five patients with histopathologically confirmed SCO who underwent GKRS were retrospectively identified and included in the present study

Results: The mean patient age was 52 years (range, 41–61 years). The most common presenting symptom was visual disturbance. All five patients had a history of transsphenoidal surgical resection prior to GKRS therapy. The mean tumor volume was 2.25 cm^3 (range 0.7–5.38 cm^3). The median tumor margin dose was 12 Gy (range, 12–14 Gy), and the median maximal dose was 24 Gy (range, 24–35 Gy). The median isodose was 50 (range, 40–50). No tumor volume progression was observed during radiological follow-up after GKRS (mean, 52 months; range, 36–84 months). At last follow-up, no neurological, endocrinological, or visual complications had been observed.

Conclusion: Given their highly vascular and adherent nature, SCOs can be challenging tumors to treat, in particular when they recur. In our five cases, GKRS provided excellent tumor volume control for approximately 4.3 years on average. These results suggest that GKRS is a safe and effective treatment modality for histopathologically confirmed residual SCO.

1. Introduction

Spindle cell oncocytoma (SCO) is a non-neuroendocrine tumor that arises from the posterior portion of the pituitary gland. This neoplasm was initially described by Roncaroli et al. in 2002 [1], and was added to the World Health Organization classification of central nervous system neoplasms in 2007. Clinically, the presenting symptoms are not pathognomonic and frequently include headache, visual disturbances, and endocrinopathy due to mass effect on sellar and parasellar structures [2]. Radiologically, an SCO is indistinguishable from non-functioning pituitary adenoma [1]. These tumors are extremely rare. In a recent large series of 792 patients who underwent transsphenoidal procedures for pituitary tumors, authors reported only four cases of SCO (0.51%) [3]. In total, only 46 SCO cases have been documented in the literature to date.

The initial treatment for SCO is usually transsphenoidal resection (TSR) [2]. Histopathological examination of this tumor reveals a spindled appearance, and cells with many swollen mitochondria and eosinophilic cytoplasm. Spindle cell oncocytomas exhibit immunoreactivity for epithelial membrane antigen (EMA), vimentin, S100, and galectin-3. These tumors do not secrete pituitary hormones, and they are considered benign due to their low proliferation rate and lack of invasiveness [1]. Given the high rate of SCO recurrence after initial resection, most patients require revision surgery and/or adjuvant treatment, such as radiation therapy and Gamma Knife radiosurgery (GKRS). However, the optimal management strategy for patients with residual SCO remains to be defined and there is no consensus regarding adjuvant treatments for this tumor. In this study, we evaluated the presenting features, radiosurgery parameters, and long-term radiological and

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https://doi.org/10.1016/j.clineuro.2019.105560
Received 8 August 2019; Received in revised form 5 October 2019; Accepted 6 October 2019
Available online 11 October 2019
0303-8467/

Table 1
Treatment parameters for Gamma Knife radiosurgery.

Patient No.	Tumor Volume (cm^3)	Marginal Dose (Gy)	Isodose	Maximal Dose (Gy)	Gradient	Total Shots	Beam-on-Time (min)
1	0.70	14	50	28	2.430	3	25
2	2.38	12	50	24	2.880	10	36
3	5.38	14	40	35	2.520	6	55
4	0.42	14	50	28	2.670	4	24
5	2.40	14	50	28	2.550	10	48

clinical outcomes for patients with SCO who were treated with GKRS.

2. Patients and methods

2.1. Patient series

We retrospectively reviewed all patients at our center who had had pituitary lesions treated with GKRS between 2005 and 2016. Five individuals with histopathologically confirmed SCO were identified and their cases were analyzed.

2.2. Gamma Knife radiosurgery methodology

Gamma knife radiosurgery was performed using the 4C model (between 2010 and 2012) and Perfexion model (between 2012 and 2016) of the Leksell Gamma Knife. All patients had a stereotactic frame placed under local scalp anesthetic. Stereotactic magnetic resonance imaging (MRI) was obtained to locate the target, and the images were transferred to a computer using specialized software for dose planning. In all cases, volumetric GKRS conformal target coverage was performed. The dose for each patient was selected based on our neurosurgical team's 18 years of accumulated experience with GKRS as well as the tumor's distance from critical structures and tumor volume. Details of the GKRS treatments are presented in Table 1.

2.3. Imaging assessments and clinical follow-up

After GKRS, each patient was evaluated with serial contrast-enhanced MRI at 6-month intervals for the first year, and yearly thereafter. Clinical and radiological assessments were done at each recheck. Follow-up MRI images were compared with those obtained prior to GKRS, and tumor volumes were calculated by measuring the maximal vertical, horizontal, and anteroposterior diameters of the tumor in all three imaging planes (*i.e.*, axial, sagittal, and coronal). Tumor volume control was defined as tumor progression (increase greater than 25% of lesion size at diagnosis), stable (maximum 25% change in tumor volume), or regression (decrease greater than 25%) [4].

3. Results

The patients were four men and one woman of mean age 52 years (range, 41–61 years). Patients 1, 4, and 5 presented with visual disturbance only. Patient 3 presented with visual disturbance and headache. Patient 2 exhibited loss of body hair and infertility at the time of presentation. Prior to GKRS treatment, four of the five individuals (Patients 1, 3, 4, 5) had a history of one TSR and one (Patient 2) had undergone two TSRs. After TSR, Patients 1 and 3 experienced hypothyroidism, and Patient 3 had temporary total visual loss. Patient characteristics for the five individuals are summarized in Table 2.

All five patients were histopathologically diagnosed with SCO after surgical resection. The mean tumor volume was 2.25 cm^3 (range, 0.7–5.38 cm^3). The median tumor margin dose was 12 Gy (range 12–14 Gy) and the median maximal dose was 24 Gy (range, 24–35 Gy). The median isodose was 50 (range, 40–50).

Table 2
Patient characteristics. (GKRS: Gamma Knife radiosurgery; TSR: transsphenoidal resection).

Patient No.	Age (years)	Sex	Presentation at Diagnosis	Prior Treatments History	Pre-GKRS Surgical Complications	Post-GKRS Tumor Volume Control	Post-GKRS Visual or Endocrine status	Follow-up (months)
1*	55	F	Visual impairment	TSR (x1)	Hypothyroidism	Stable	Stable	84
2	41	M	Loss of body hair - Infertility	TSR (x2)	None	Stable	Stable	51
3	61	M	Headache – visual Impairment	TSR (x1)	Hypothyroidism, temporary visual loss	Stable	Stable	47
4	50	M	Visual Impairment	TSR (x1)	None	Stable	Stable	41
5	56	M	Visual Impairment	TSR (x1)	None	Stable	Stable	36

*Patient who had repeat TSR after GKRS.

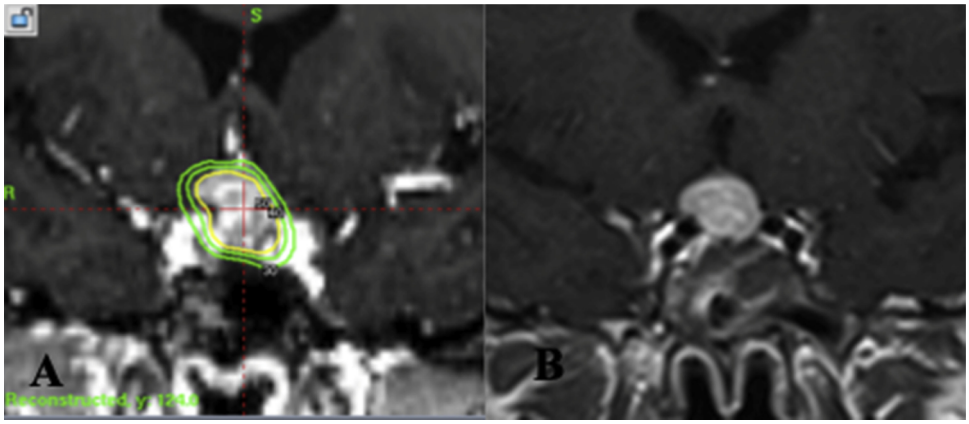

Fig. 1. Images obtained in a patient (Case 2) treated with Gamma Knife radiosurgery with 12 Gy prescribed to the 50% isodose line. **A**. Treatment planning T1-weighted MRI with contrast. **B**. T1-weighted MRI with contrast images of 3 years after Gamma Knife radiosurgery demonstrating stable tumor volume.

Table 3
Documented cases of spindle cell oncocytoma treated with radiation. (TSR: transsphenoidal resection, CKRS: CyberKnife radiosurgery, GKRS: Gamma Knife radiosurgery, TC: transcranial, RT: radiation therapy, KT: chemotherapy).

Authors and Year	Age (yrs), Sex	Radiation Therapy Type	Overall Treatment History in Chronological Order	Radiation Therapy Detail	Outcome after Radiation Therapy
Kloub et al., 2005	76, M	RT	1. TSR 2. TSR 3. **RT** 4. TSR	N/A	Growth over 7 yrs after RT
Dahiya et al., 2005	26, M	Proton Beam	1. TSR 2. TC 3. **Proton Beam**	54 Gy	Stable 7 yrs
Coiré et al., 2009	63, F	RT	1. TSR 2. TSR 3. **RT**	N/A	N/A
Borata et al., 2009	55, F	RT	1. TSR 2. **RT**	54 Gy	Growth over 10 mo. after RT
Demssie et al., **2011**	59, M	RT	1. TSR 2. TSR 3. **RT**	N/A	N/A
Ogiwara et al., **2011**	39, M	RT	1. TC 2. **RT** 3. TC 4. TSR	54 Gy	Growth over 9 mo. after RT
Fujisawa et al., 2012	68, M	RT	1. TSR 2. TC 3. **RT**	50 Gy in 25 fractions	Stable
Manoranjan et al., **2017**	60, M	RT	1. TSR 2. Bx 3. **RT** 4. TSR	N/A	Growth over 11 yrs after RT
Giantini Larsen et al., 2018	59, F	GKRS	1. TSR 2. TC 3. TSR 4. GKRS	N/A	Stable 79 mo.
	56, F	CKRS, Proton beam	1. TSR 2. TSR 3. TC 4. **CKRS** 5. TSR 6. **Proton Beam**	N/A	Growth over 9 yrs after CKRS; stable 38 mo. after Proton Beam
Witte et al., 2018	61, M	RT	1. TSR 2. TSR 3. **RT** 4. TSR 5. KT (vincristine)	45 Gy	Growth over 1 yr after RT
Guerrero-Pérez et al., 2019	60, M	GKRS	1. TSR 2. TC 3. **GKRS**	N/A	N/A
Current Study	55, F	GKRS	1. TSR 2. **GKRS** 3. TSR	14 Gy	Stable 84 mo.
	41, M	GKRS	1. TSR 2. TSR 3. **GKRS**	12 Gy	Stable 51 mo.
	61, M	GKRS	1. TSR 2. **GKRS**	14 Gy	Stable 47 mo.
	50, M	GKRS	1. TSR 2. **GKRS**	14 Gy	Stable 41 mo.
	56, M	GKRS	1. TSR 2. **GKRS**	14 Gy	Stable 36 mo.

Radiological follow-up time ranged from 36 to 84 months (mean, 52 months). All of the five patients had more than 3 years of clinical and radiological follow-up. None of the patients exhibited new neurological abnormalities, new visual field deficits, or altered endocrine status during their routine clinical visits. Radiological examinations revealed that all of the patients' tumor volumes remained stable (Fig. 1). No tumor volume progression or regression was observed.

Although one individual's tumor volume (Patient 1) was stable after GKRS, revision surgery was offered by a neurosurgeon. This patient underwent repeat TSR at a different neurosurgical center. Unfortunately, the patient died 10 days postoperatively due to surgical complications.

4. Discussion

Spindle cell oncocytoma was first described by Rancaroli in 2002, and continues to be a challenging tumor for neurosurgeons [1]. Our study analyzed the cases of five patients with histologically confirmed residual SCO who underwent treatment with GKRS. The tumor volume control rate was 100% during mean follow-up of 52 months, and no complications were observed after GKRS. This is the first report in the literature on application of GKRS for SCO, and is the first documentation of detailed GKRS parameters for treating histopathologically confirmed SCO.

Prior to this series, a total of 46 SCO cases were reported in the literature [1,2,5–34] thus, there are limited data on the specific presentations, radiological features, treatment modalities, and prognosis for these tumors. Spindle cell oncocytomas are extremely rare, non-endocrine tumors of the sella turcica. They are classified as a grade I neoplasm in the World Health Organization classification of central nervous system neoplasms. Patients with SCO frequently present with non-specific symptoms, including headache, visual disturbances and hypopituitarism [2,35]. Our five patients' presentations were in concordance with the literature. Three presented with visual disturbance, one with visual disturbance and headache, and one with endocrinopathy alone.

Surgical resection is the initial treatment for SCO. Thirty-four of the previously reported 46 patients underwent TSR, and nine underwent transcranial resection. All five of our patients underwent TSR prior to GKRS. Total or gross-total resection of SCO is associated with better prognosis; however, in most cases, this is not an achievable goal due to high vascularity and the adherent nature of the tumor [2,36]. Consequently, neurosurgeons are often only able to partial resect the tumor, especially when there is high risk of excessive bleeding and adhesion to vital structures.

The literature indicates that SCOs have high risk of progression. Eighteen (39%) of the above-noted 46 patients showed recurrence after initial resection. Recurrence time after surgery was obtained from fifteen out of 18 patients. Median recurrence time after surgery was 18 months (mean, 36 months; range, 3–132 months) in the literature. Moreover, a recent report documented metastasis of SCO in one patient years after initial surgical resection[33]. Due to recurrence, some patients with SCO require repeat surgery or adjuvant treatment after initial resection. Revision surgery for recurrent sellar and suprasellar lesions carries a high risk of complications. Recent reports describing revision surgery for recurrent pituitary adenomas have noted overall complication rates between 10% and 16% [37–40]. Additionally, other papers document complication rates of 0% to 9% for leakage of cerebrospinal fluid, 0% to 35% for new-onset diabetes insipidus, and gross-total resection rates ranging from only 49% to 63% [37–44]. Given that initial resection and subsequent repeat surgery on SCOs tend to be insufficient and carry high complication risk, adjuvant treatment modalities may offer a more promising solution for control of tumor progression.

Prior to our series, 12 of 46 previously reported patients with SCO underwent adjuvant radiation [2,8,9,11–13,16,17,22,32,33]. The literature offers no consensus regarding adjuvant treatments for residual SCOs. Eight of these 12 patients had received traditional radiation therapy, two had undergone GKRS, one had received proton beam therapy, and one had undergone both CyberKnife radiosurgery and

proton beam therapy. The radiation therapies and outcomes for past cases in the literature are detailed in Table 3.

Gamma Knife radiosurgery is a modern addition to the armamentarium of treatment modalities for primary, residual, or recurrent intracranial lesions, and offers sub-millimeter precision. In particular, GKRS has been successful for treating various sellar and parasellar tumors, including meningiomas and non-functioning adenomas, providing a high rate of tumor volume control and a low rate of complications [45,46]. Two previous reports noted no tumor progression in two patients who underwent GKRS for residual SCOs [2–32]. In our series, all five patients underwent GKRS treatment after TSR, and radiological follow-up ranged from 36 to 84 months (mean, 52 months). In all cases, tumor volume control was 100% and there was no endocrinopathy or new or further deterioration of visual function during long-term radiological follow-up. In addition, none of the patients experienced radiation-associated complications.

Our evaluation was retrospective in nature and involved a relatively small number of patients due the rareness of this tumor. However, this is the first and largest case series of GKRS therapy for histopathologically confirmed SCO to date, and offers detailed knowledge about the successful application of GKRS for this recently described tumor. Further, the follow-up period was sufficiently long to allow for informative monitoring of SCO recurrence post-GKRS.

5. Conclusion

Spindle cell oncocytomas tend to recur after initial surgery and have high complication risk during revision surgery. In this series of five SCO cases that were initially treated with TRS, GKRS achieved 100% tumor volume control and there were no new deficits or further deteriorated neurological or endocrinological dysfunction during long-term follow-up. The results suggest that adjuvant GKRS is safe and effective for patients with residual SCO after surgery.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper."

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None.

Acknowledgement

None.

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