INTRODUCTION

A carotid-cavernous sinus fistula is an abnormal communication between arteries and veins within the cavernous sinus [1,2]. Carotid-cavernous fistulas (CCFs) can occur spontaneously or as a consequence of trauma [3]. CCFs may be classified into four types: direct fistulas (Barrow type A) and dural, or indirect, fistulas (Barrow types B, C, and D) [1]. Direct or type A CCFs are usually of traumatic etiology and may demonstrate the classic triad of clinical symptoms (ocular bruit, pulsatile exophthalmos, and conjunctival chemosis) [4,5], although these are not always present [5]. Conversely, indirect CCFs are usually spontaneous and present with milder sequelae [6-8].

Recent progress in the field of endovascular neurosurgery has introduced multiple treatment modalities for the management of CCFs [9]. The mainstay of therapy...
for CCFs is endovascular embolization, while other treatment options, such as open surgery or radiosurgery, are still utilized as second-line or adjuvant therapeutic options [10,11].

Many previous reports concluded that Gamma Knife radiosurgery (GKRS) is a useful additional modality, and GKRS is considered an adjuvant treatment for CCF. The purpose of this preliminary report is to show the safety and clinical outcome of GKRS as the only treatment for CCFs.

MATERIALS AND METHODS

Patients

We analyzed the radiologic and clinical outcomes of nine patients with spontaneous CCFs who underwent GKRS alone with the Leksell Gamma Knife (PERFEXION; Elekta Inc., Stockholm, Sweden) at Jeonbuk National University Hospital between December 2017 and December 2020. Seven patients were female, and two patients were male (median age, 73 years; range, 46 to 86 years).

CCFs were confirmed by performing digital subtraction angiography (DSA). All nine patients were referred from endovascular specialists because of the challenges of the endovascular approach. They all underwent GKRS alone for spontaneous CCFs. The median follow-up period was 15.5 months (12 to 43 months).

Outcome data were collected through an independent medical record review and were analyzed by a neurosurgeon who did not participate in patient management and ophthalmologist. Three patients showed CCFs in the left cavernous sinus, five patients showed CCFs in the right side, and one patient showed CCFs in both sides. The indirect CCFs were developed spontaneously in all patients.

Carotid-cavernous fistula classification

CCFs were classified according to the Barrow classification system [12].

The Barrow scheme classifies CCFs based on their arterial supply: type A, direct high-flow shunt between the internal carotid artery (ICA) and cavernous sinus; type B, indirect low-flow shunt between dural ICA branches and the cavernous sinus; type C, indirect low-flow shunt between dural external carotid artery (ECA) branches and the cavernous sinus; and type D, indirect low-flow shunt between ECA/ICA dural branches and the cavernous sinus [12]. Five fistulae were Barrow type B, four were type C, and one was type D.

Radiosurgical technique

The median marginal dose irradiated to the nidus margin was 17.5 Gy (range, 16 to 18 Gy; 50% isodose line). The maximum irradiated dose ranged from 32 to 36 Gy (median, 35 Gy). The median targeted volume was 0.39 cm$^3$ (range, 0.13 to 3.05 cm$^3$). The targeted point of the CCF was the fistula site for the type B CCF and the compartment of the cavernous sinus for the types C and D CCFs.

Follow-up examination

Patients were followed every 1 to 3 months after GKRS. Follow-up magnetic resonance imaging (MRI) was performed at 3, 6, and 12 months until CCFs disappeared. The follow-up DSA was done 12 months after GKRS in accepted patients. Neurologic and ophthalmic evaluations were performed to assess clinical outcomes every 3 months. Complete resolution of symptoms was defined as there is no evidence of CCF-related symptoms.

All patients had a minimum follow-up duration of 12 months (median, 15.5 months; range, 12 to 43 months).

Ethical statements

This study was approved by the Institutional Review Board (IRB) of the Jeonbuk National University Hospital (IRB No: 2013-10-022-002). Written informed consent was obtained from the patient.

RESULTS

Overall clinical outcomes

All nine patients had chemosis, exophthalmos, ocular pain on the affected side, and diplopia at the time of GKRS. There were no patients with cranial nerve symptoms or neurological deficits. The median duration from diagnosis to treatment was 4 weeks (range, 1 to 12 weeks). Severe headache was reported by 2 patients and one patient suffered from accompanied glaucoma.

All patients responded rapidly and favorably to GKRS with an improvement of symptoms (median time to symptom improvement, 3 weeks; range, 1 to 32 weeks) (Table 1). All symptoms associated with CCFs were completely resolved without any adverse effects or recurrence.

Radiologic outcomes

Trans-femoral angiography, orbit MRI, or brain magnetic resonance angiography at 12 months after GKRS indicated that seven fistulas were obliterated, and three fistulas in the diameter of the superior ophthalmic vein (SOV) were decreased by more than
GKRS for spontaneous CCFs

Three patients with decreased SOV diameter in MRI are currently undergoing further follow-up. In our series, the time consumed for CCF obliteration, as demonstrated in any imaging modality, was predicted to be 12 months. We presented case No. 4 patient in Fig. 1.

**DISCUSSION**

The signs and symptoms of indirect fistulas are experienced gradually and are mostly comprised of chronic red eyes, ocular bruits, proptosis, and other eye conditions, such as glaucoma [13].

Treatment options for indirect CCFs include observation, intraocular pressure (IOP)-lowering agents, intermittent compression of the ipsilateral ICA or SOV, stereotactic radiosurgery (SRS), and endovascular intervention. As up to 70% of dural CCFs close spontaneously due to local thrombosis of the SOV propagating posteriorly, observation or conservative treatment techniques are not only acceptable but also are the preferred approaches to management in cases without high-risk features [3]. After the exclusion of patients deemed to be poor candidates for carotid compression therapy due to decreased visual acuity or cortical venous drainage of the fistula, the success rate of this procedure was found to be 35%, with resolution occurring between 2 weeks and 7 months after initiation [1,14].

Although a watchful waiting approach is reasonable in many patients with indirect CCF, treatment is sometimes required to pre-

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**Table 1. Patients’ profile**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Barrow type</th>
<th>Marginal dose (Gy)</th>
<th>Target volume (cm³)</th>
<th>Fistula site</th>
<th>Symptom site</th>
<th>Treatment site</th>
<th>Duration of symptom improvement after GKRS (wk)</th>
<th>Radiologic outcome after GKRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>M</td>
<td>B</td>
<td>18</td>
<td>0.4</td>
<td>Lt.</td>
<td>Lt.</td>
<td>Lt.</td>
<td>7</td>
<td>Complete obliteration at 12 mo (TFCA)</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>F</td>
<td>B</td>
<td>18</td>
<td>0.13</td>
<td>Rt.</td>
<td>Rt.</td>
<td>Rt.</td>
<td>2</td>
<td>Complete obliteration at 12 mo (MRA)</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>M</td>
<td>B</td>
<td>18</td>
<td>0.38/0.17</td>
<td>Rt.</td>
<td>Bi</td>
<td>Bi</td>
<td>4</td>
<td>Complete obliteration at 12 mo (TFCA)</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>F</td>
<td>B</td>
<td>18</td>
<td>0.26</td>
<td>Rt.</td>
<td>Rt.</td>
<td>Rt.</td>
<td>2</td>
<td>Complete obliteration at 12 mo (MRA)</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>F</td>
<td>C</td>
<td>18</td>
<td>3.05</td>
<td>Lt.</td>
<td>Lt.</td>
<td>Lt.</td>
<td>2</td>
<td>50% decreased filling at 6 mo (MRA)</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>F</td>
<td>C</td>
<td>16</td>
<td>1.64</td>
<td>Rt.</td>
<td>Rt.</td>
<td>Lt.</td>
<td>1</td>
<td>50% decreased filling at 3 mo (MRA)</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>F</td>
<td>C</td>
<td>18</td>
<td>0.9</td>
<td>Rt.</td>
<td>Lt.</td>
<td>Lt.</td>
<td>12</td>
<td>50% decreased filling at 6 mo (MRA)</td>
</tr>
<tr>
<td>8</td>
<td>86</td>
<td>F</td>
<td>C</td>
<td>18</td>
<td>0.31</td>
<td>Lt.</td>
<td>Lt.</td>
<td>Lt.</td>
<td>32</td>
<td>Complete obliteration at 12 mo (MRA)</td>
</tr>
<tr>
<td>9</td>
<td>73</td>
<td>F</td>
<td>D</td>
<td>16</td>
<td>0.74</td>
<td>Rt.</td>
<td>Rt.</td>
<td>Rt.</td>
<td>2</td>
<td>Complete obliteration at 12 mo (MRA)</td>
</tr>
</tbody>
</table>

GKRS: Gamma Knife radiosurgery, M: male, F: female, Lt.: left, Rt.: right, Bi: bilateral, TFCA: transfemoral catheter angiography, MRA: magnetic resonance angiography.

**Fig. 1.** Images of case 4. (A) Brain MRA (top) and the MRA source image (bottom) before Gamma Knife radiosurgery (red arrows point to CCF). (B) Target and dose planning image of treatment for CCF. (C) Brain MRA (top) and the MRA source image (bottom) 12 months after Gamma Knife radiosurgery (yellow arrows point to regions where the CCF has disappeared). MRA: magnetic resonance angiography, CCF: carotid-cavernous fistula.
vent long-term sequelae. Indications for intervention include uncontrollable IOP, unmitting diplopia, severe proptosis with corneal exposure, optic neuropathy, retinal ischemia, severe bruit, and cortical venous drainage from the fistulae. Endovascular treatment is the first line and maybe performed transarterial or transvenous. Similar to the embolization of direct CCFs, the embolization of dural CCFs may be accomplished using coils, acrylic glue, or Onyx, which can be used individually or in combination [15,16]. Flow-diverting stents also may be used alone or in combination with coils [3].

Endovascular embolization of dural CCFs is not always possible or effective because of challenging vascular access, risk of retrograde flow of embolic materials, or partial embolization [7]. SRS has become a reasonable alternative treatment option for dural arteriovenous fistulas (DAVFs) without concurrent fatal conditions, such as intracranial hemorrhage. SRS can be a first line therapy when embolization or surgery cannot be performed safely or when employed for residual or recurrent lesions after prior treatment.

Our results show that SRS is an effective and safe primary treatment modality for spontaneous CCFs and has high obliteration rates and a low risk of complications. The control rate and duration until symptom improvement are similar to Park et al’s report [17].

Complications after Gamma Knife radiosurgery for carotid-cavernous fistulas compared with endovascular embolization

New onset of cranial nerve palsy was not observed in our series. The cranial nerves in the cavernous sinus are generally resistant to radiation injury and tolerate up to 40 Gy in a single fraction [18].

There are few reports of radiosurgery- associated complications after SRS for DAVFs. Cifarelli et al. [19] reported that T2-weighted radiation-induced change at the perimeter of the lesion was evident in 12% of the patients. Similar to our results, Hanakita et al. [20] demonstrated that none of the patients experienced radiation-induced complications after SRS. However, that series with a median follow-up of 30 months may have underestimated the risk of late radiation-induced complications. So we think that we also need to follow up for more than an average of 36 months.

Endovascular embolization has a potential risk of neurologic deficit because of ischemic complications and migration of embolic material. Angiographic architecture and clinical presentations should be considered when selecting either embolization or SRS because embolization is usually used in patients who need immediate symptom relief, and SRS is performed in patients with relatively mild symptoms. In our series, the fastest improvement of CCF-related symptoms began a week after treatment.

In the basis of our study is that GKRS can lead safe and early responses without the embolic complications associated with endovascular treatment. Transvenous embolization affected the patients who were at risk of intracerebral hemorrhage because of venous rupture or newly developed cranial nerve palsy due to cavernous sinus embolization [21]. Cranial nerve signs after embolization may be caused by progressive thrombosis of the cavernous sinus, mass effect from the coils, or direct injury of the nerve by coils or the microwire/microcatheter [22]. Yoshida et al. [7] reported that 7% of patients showed permanent complications, and 14% of patients showed transient morbidity after transvenous embolizations. In Park’s review [23], he concluded that depending on the patient’s condition and the angiographic features of DAVFs, SRS may be an alternative and safe treatment modality for DAVFs. SRS can be performed when it is difficult to treat DAVF endovascularly or surgically or when the patient prefers a non-invasive treatment.

Our study showed that the duration until symptom relief and obliteration of CCF was relatively short period compared with the duration of arteriovenous malformation (AVM) obliteration after GKRS. The reason for this relatively short period response is a relatively small target volume and evenly irradiated maximum dose compared with AVM. In previous study described that compared with AVMs, DAVFs seem to more promptly react to SRS because the shunt size in DAVFs is smaller than that in AVMs [21,24]. The type CCFs did not show statistical significance in the duration until symptom relief and radiologic outcome in this study. However, type D CCFs took a long time compared with the other types. It is necessary to enroll more patients and variable CCF types for further study.

CONCLUSION

Although our study needs a larger patient group and long-term follow-up, GKRS can be considered a definitive and safe treatment modality for spontaneous CCF, not only an adjuvant modality. In addition, we think that, although symptoms do not improve immediately like in endovascular treatment, since symptoms improve within a relatively short duration and the risk of complications is low, GKRS can be considered a single treatment method.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This paper was supported by research funds from Jeonbuk National University.
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