



Surgical treatment of brainstem cavernomas using diffusion tensor imaging and diffusion tensor tractography

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ABSTRACT

Introduction. The aims of this study were to assess the prognosis of patients after a single haemorrhage from the cavernoma, and also in the case of rehaemorrhage, and to determine the indications for surgical treatment of brainstem cavernomas.

Material and methods. The study included a group of 35 patients with brainstem cavernomas, 23 women and 12 men aged 27 to 57 years (mean age 38.4). Up to 2005, MRI perfusion-weighted imaging/diffusion-weighted imaging had been carried out in 13 surgically treated patients. From 2005 onwards, the other 22 patients also underwent MRI diffusion tensor imaging and diffusion tensor tractography (DTI/DTT). DTI/DTT assessed the course of long fibre tracts. The course of the corticospinal tract, medial lemniscus and transverse pontine tracts was entered into the neuronavigation system. The surgical approach and the safe entry zone were determined based on the DTI/DTT.

Results. Our study showed that rehaemorrhage from a cavernoma depends on its size and volume. However, it is not related to its location. Based on the modified Rankin scale, the results of treatment of our patients after the first haemorrhage were better compared to the assessment after another haemorrhage. Complete resection was performed in 32 cases (91%) and partial resection in the remaining three (9%). Two patients underwent another surgery after several years due to partial resection. One patient presented with another haemorrhage after three years. New deficits developed postoperatively. Already existing deficits were exacerbated, but gradually resolved. Symptoms of cerebellar dysfunction and cranial nerve injury (including respiratory disorders) were the most difficult to resolve.

Conclusions. Patients with brainstem cavernomas should undergo surgical treatment after their first haemorrhage, especially in the case of a large cavernoma.

DTI/DTT should be used to determine the trajectory to the cavernoma, particularly to the deep cavernoma, and to determine the safe entry zone.

Total resection of the cavernoma should be performed even where this means that reoperation is required.

Key words: cavernous malformation, brainstem, surgical treatment, haemorrhage

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Introduction

Surgical treatment of brainstem cavernomas is a serious challenge in neurosurgery. These procedures carry a significant risk of postoperative disability. On the other hand, if

these patients do not undergo surgery, they may be at risk of haemorrhage with a serious prognosis. The prevalence of brain cavernomas varies between 0.4% and 0.8% [1, 2], of which 10–35% are located in the brainstem [3, 4]. Neurological deficits are due to a haemorrhage from the cavernoma.

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However, these symptoms gradually resolve. Neurosurgical intervention is usually not performed after the first haemorrhage. Rehaemorrhage poses the greatest risk to the patient. According to various authors, recurrent haemorrhage rates range from 4.5% [5] to 30% [6]. Due to rebleeding, the patient's condition is more severe, significant neurological deficits occur, and full recovery is impossible. Improvement is slower and less spectacular. Therefore, the question arises as to whether patients should undergo surgery after the first haemorrhage to avoid an unfavourable clinical course. Different studies have reported significantly worse results of surgical treatment after the second hemorrhage compared to surgery after the first event [7, 8].

Classical surgical and skull-base approaches are used for surgery for brainstem cavernomas [6]. To avoid postoperative disability, preoperative diffusion tensor imaging (DTI) and diffusion tensor tractography (DTT) are most commonly applied during surgery. These neuroimaging techniques in the neuronavigation system allow determination of the surgical trajectory and brainstem entry point [9, 10].

The aims of this study were to: (1) determine the prognosis of patients after a single haemorrhage from the cavernoma, and also in the case of rehaemorrhage; (2) to assess whether the size of the cavernoma and its volume affect the occurrence of recurrent haemorrhage; (3) to examine whether the use of DTI/DTT during surgery prevents limb deficits and whether it affects the prognosis on the modified Rankin Scale (mRS); (4) to determine whether neurological deficits before and after surgery tend to resolve over time; and (5) to determine the indications for surgical treatment of brainstem cavernomas.

Material and methods

The study included a group of 35 patients with brainstem cavernomas, 23 women and 12 men aged 27 to 57 years (mean age 38.4). Only MRI perfusion-weighted imaging/diffusion-weighted imaging had been carried out in 13 surgically treated patients before 2005. From 2005 onwards, MRI also included DTI/DTT in the other 22 patients. DTI/DTT assessed the course of long fibre tracts using the classification by Kovanlikaya [12]. All the surgical procedures were performed using the neuronavigation system, which was applied to determine the location of the cavernoma and the course of the corticospinal tract, medial lemniscus and transverse pontine tracts (DTI) in order to preserve the continuity of the tract.

The choice of surgical approach and safe entry zone was determined by the location of the cavernoma and the result of the course of the corticospinal tract, medial lemniscus, medial longitudinal fasciculus, and the inferior, middle and superior peduncle cerebellar tracts, as measured by DTI. Motor evoked potential (MEP) obtained with transcranial electrical stimulation (TES) was used. The localisation of the nuclei of nerves VII, IX, X and XII within the fundus of the fourth ventricle was established by direct electrical

stimulation (DES). Somatosensory evoked potentials (SSEPs) were monitored. The monitoring system was the same as the one presented in a paper published in 2018 on the surgical treatment of brainstem gliomas [13]. The extent of resection was confirmed by contrast enhanced MRI performed within three days of surgery.

The following surgical approaches were used to remove the brainstem cavernomas: suboccipital — 19 (54%); subtentorial telovelar — 8 (23%); infratentorial, supracerebellar — 6 (17%); subtemporal, transtentorial — 1 (3%); and peritrigeminal — 1 (3%). After the surgical procedure, patients were transferred to the intensive care unit. The clinical status of patients before and after surgery and in the last follow-up was assessed based on mRS [14].

Ethical approval was not necessary for the preparation of this article as it concerns a retrospective analysis.

Statistical analysis

The distribution of quantitative variables was verified by a Shapiro-Wilk test. The median was used to describe quantitative variables with non-normal distribution. A Mann-Whitney U-test was used to assess differences between variables. Fisher's test was used to check the prevalence of a single haemorrhage or rehaemorrhage in the groups with a favourable or unfavourable mRS. A chi square test with Yates's correction for small size groups was used to assess intergroup differences for independent qualitative variables. Spearman's rank coefficient was used to determine the correlation between qualitative features. Statistical analysis was performed using STATISTICA 12 software, and $p < 0.05$ was considered significant.

Results

Seventeen patients presented with a single haemorrhage, and 18 with rehaemorrhage. Table 1 sets out the neurological signs on admission, immediately after surgery, and at the last follow-up visit.

Table 1 shows that neurological deficits were exacerbated postoperatively in some patients with such deficits. New neurological deficits were also found. Treatment and rehabilitation resulted in a gradual resolution of limb deficits, observed before and after surgery. Similarly, superficial and deep sensation disturbances were also reduced. Cerebellar disorders were less likely or even impossible to resolve. Cranial nerve deficits can resolve, although such resolution is a very slow process. In the case of postoperative respiratory disorders, resolution can sometimes take several weeks.

Preoperative DTI showed the influence of the cavernoma after the haemorrhage on the course of the fibre tracts in the brainstem (Tab. 2).

Table 2 sets out the number of patients diagnosed with deviation, deformation or interruption of fibre tracts. From the main fibre tracts in the brainstem, corticospinal tract (CST) injury was observed in 82% of cases. Changes in the

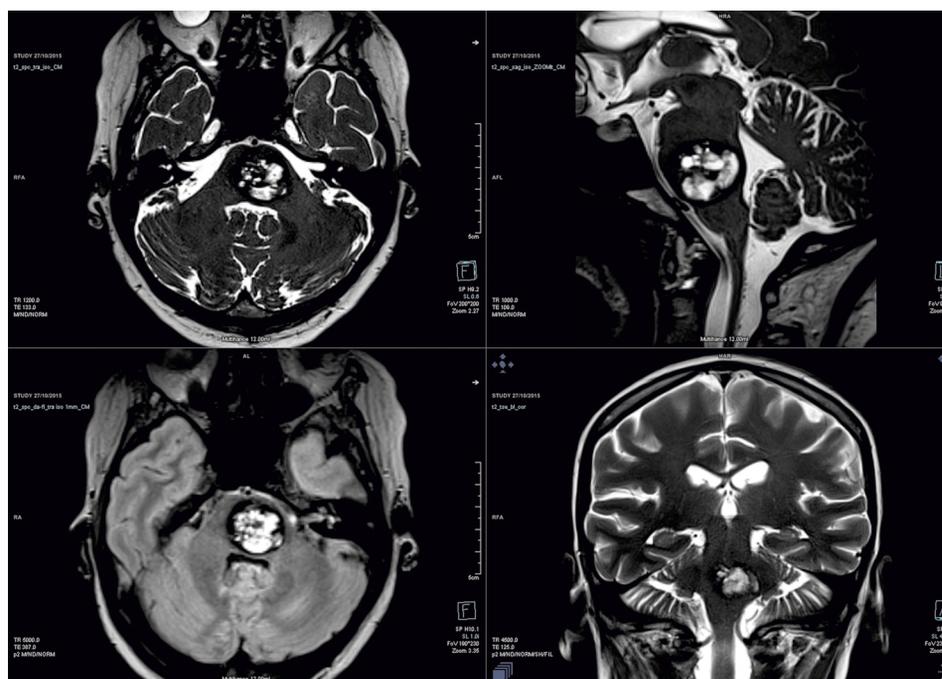
Table 1. Neurological signs of patients with brainstem cavernomas before surgery, after surgery, and at last follow-up visit

Total: 35 patients	Neurological signs		
	Before surgery	After surgery	Last follow-up visit
Motor deficits	12 (34%)	21 (60%)	6 (17%)
Sensory disturbances	16 (46%)	18 (51%)	7 (20%)
Cerebellar involvement	11 (31%)	12 (34%)	9 (26%)
Cranial nerve deficits	14 (40%)	22 (63%)	8 (23%)

Table 2. Classification of fibre tract changes in DTI

Fibre tract changes in DTI*	CST	ML + MLF	ICP	SCP	MCP
Normal	4	5	13	14	15
Deviated	11	11	7	6	2
Deformed	7	6	1	1	5
Interrupted	0	0	2	1	0

*22 patients accomplished DTI investigation

**Figure 1.** T2-W MRI: Cavernoma of pons; AP dimension: 2.42 cm; volume: 7.96 cm³. Patient after two haemorrhages

course of the medial lemniscus (ML) and the medial longitudinal fasciculus (MLF) were observed in 77%, in the inferior cerebellar peduncle (ICP) in 45%, in the middle cerebellar peduncle (MCP) in 32%, and in the superior cerebellar peduncle (SCP) in 36%.

Total resection of the cavernoma was performed in 32 cases (91%), with partial resection in the other three (9%). Two patients underwent reoperation due to partial resection. One patient presented with rehaemorrhage after three years. This is of crucial importance, as subtotal resection can be related to another severe haemorrhage [15]. Establishing the trajectory

and the safe entry zone are the most important elements of determining eligibility for surgery.

MRI of a patient with cavernoma of the pons with the trajectory to the tumour based on this imaging technique is shown below (Fig. 1, 2).

Based on the imaging results (Fig. 1, 2), the trans-fourth ventricle approach was the best option during surgery for the cavernoma. Figure 3 shows the postoperative T2-weighted MRI (sagittal section).

Total resection of the vascular malformation was performed as shown on the follow-up MRI on day 2 postoperatively.

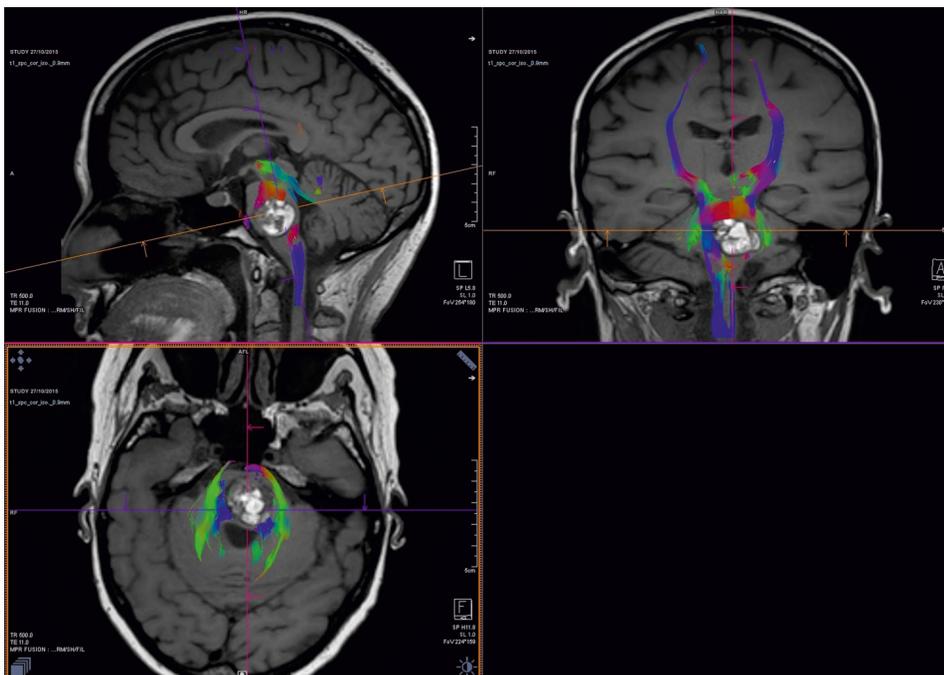


Figure 2. DTI/DTT: Cavernoma of pons (subependymal location; fourth ventricle of brain). Corticospinal tracts and medial lemniscus are located laterally to cavernoma

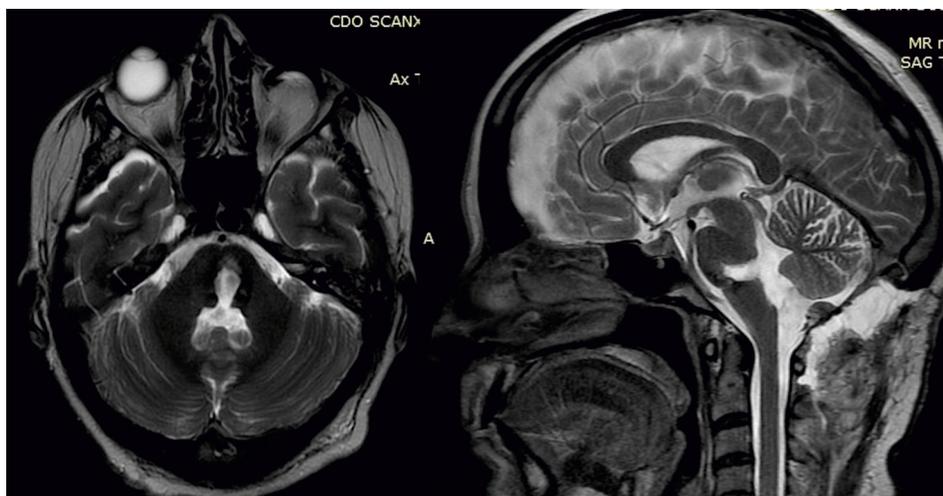


Figure 3. T2-W MRI: Complete resection of cavernoma of pons

Table 3 shows the prognosis of patients after a single haemorrhage or rebleeding depending on the location, size and volume of the cavernoma.

Table 3 shows that rehaemorrhage did not depend on the location of the cavernoma in the brainstem. Cavernomas in patients with recurrent haemorrhage were significantly larger compared to those that occurred in patients with a single haemorrhage. Also, the volume of cavernomas that caused recurrent haemorrhage was statistically significantly higher than in the case of a single haemorrhage. The number of patients with a good prognosis in the group of patients with a single

haemorrhage was higher compared to the number of patients with rebleeding. This difference was statistically significant.

Figures 4 and 5 illustrate the relationship between the rehaemorrhage from the cavernoma and its size and volume.

As shown in Figure 4, the larger the cavernoma, the higher the risk of rebleeding.

As shown in Figure 5, the larger the volume of the cavernoma, the higher the risk of rebleeding.

Table 4 shows the prognosis of patients based on the modified Rankin Scale (mRS) after a single haemorrhage and recurrent haemorrhage.

Table 3. Prognosis of patients with single haemorrhage and rebleeding from brainstem cavernoma

Location	Single haemorrhage	Rebleeding	P-value
Midbrain	3 (43%)	4 (57%)	0.087
Pons	8 (31%)	13 (69%)	
Medulla oblongata	6 (86%)	1 (14%)	
Lesion size, AP cm, median	1.21 (0.74–2.07)	1.91 (1.00–3.95)	0.008
Volume [cm ³], median	1.38 (0.40–5.29)	4.03 (0.42–22.64)	0.040
Favourable mRS (0–2)	14 (61%)	5 (39%)	0.002
Unfavourable mRS (3–6)	3 (13%)	13 (87%)	

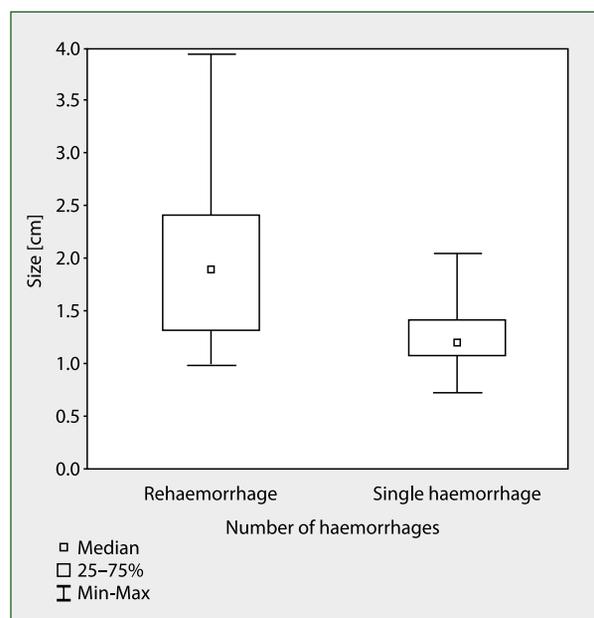
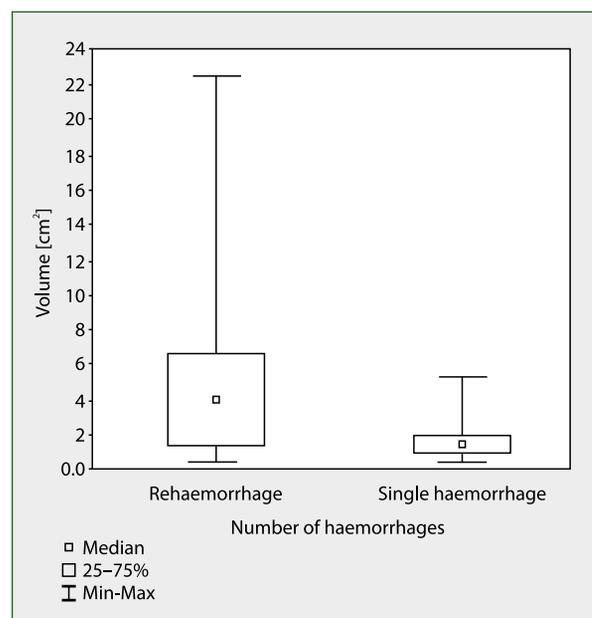

Figure 4. Prevalence of haemorrhage from brainstem cavernoma depending on its size

Figure 5. Prevalence of haemorrhage from brainstem cavernoma depending on its volume

Table 4. Patient prognosis based on modified Rankin Scale (mRS) in group of patients after single haemorrhage and in those who underwent surgery after two haemorrhages

	Median score on modified Rankin Scale		P-value
	Single haemorrhage	Recurrent haemorrhage	
Before surgery	1.88	1.96	0.176
At last follow-up visit	1.63	2.37	0.001

The clinical status of the patients after hospital admission was not significantly different. During the last follow-up visit, a significant difference was found in mRS score between patients with a single haemorrhage and patients with rebleeding ($p = 0.001$); (Spearman rank coefficient test).

During the last follow-up visit, scores of 1 and 2 were predominant in the group of patients with a single haemorrhage. There were no patients with scores of 4, 5 or 6.

During the last follow-up visit, patients with rebleeding with a score of 3 (mRS) were predominant. There were also patients with scores of 4 and 6 on mRS.

Figure 6 shows the graphical illustration of that relationship.

We then assessed whether the use of DTI/DTT during surgery significantly affected the prognosis of patients on mRS (Tab. 5).

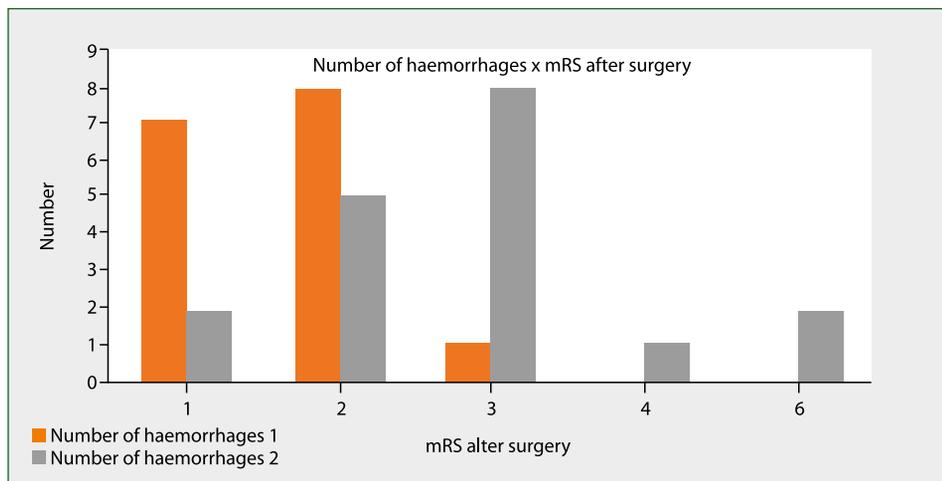


Figure 6. Prognosis of patients after a single haemorrhage and rehaemorrhage based on modified Rankin Scale

Table 5. Prognosis of neurological status of patients with brainstem cavernous malformations based on preoperative diffusion tensor imaging (DTI)

	DTI/DTT group	Control group	P-value
Mean mRS score, median			
Before surgery	1.96	2.25	0.330
After surgery	2.37	2.13	0.702

There were no significant differences between the group that underwent preoperative DTI and patients who did not undergo this examination in respect of their prognosis based on the mRS.

We also conducted analysis to check how preoperative DTI affected the postsurgical resolution of limb deficits. The numbers of patients with limb deficits before surgery and during the last follow-up visit were as follows: with DTI — 10/22 (53%) and 1/22 (5%) respectively; with no DTI — 7/13 (44%) and 5/13 (31%), respectively. Postoperative limb deficits were significantly less prevalent in patients with preoperative DTI compared to patients in whom DTI was not performed preoperatively.

Discussion

The questions of whether and when patients after hemorrhage from the brainstem cavernoma should undergo surgery remain open to discussion.

However, it should be borne in mind that the risk of rebleeding from a brainstem cavernoma is higher than from those cavernomas located in other parts of the central nervous system [16]. Deep cavernomas are more frequently the cause of haemorrhage [17]. Based on a very large number of patients having undergone surgery, different authors have suggested that surgery should be performed after the first haemorrhage within 6–8 weeks following the event [7, 18, 19]. This especially applies to patients in whom haemorrhage resulted in the

occurrence of new neurological deficits [20, 21]. Treatment results of patients after the first haemorrhage from a cavernoma are better than treatment results after rebleeding [8, 19].

Based on treatment results of 1,390 patients with brainstem cavernomas in neurosurgical centres worldwide, Gross et al. indicated that patients should be surgically treated after the first haemorrhage with cavernomas pial representation [22].

The following are crucial for patient prognosis: the size and volume of the cavernoma, whether this malformation crosses the midline or whether it is accompanied by vascular malformation, and whether the location of the cavernoma is subarachnoid or subependymal [7, 8, 19]. The use of DTI/DTT is the best option to determine the trajectory to the cavernoma and the safe entry zone. This technique determines the course and location of long fibre tracts [9, 10, 23]. In 2010, Cao et al. showed that the use of DTI for surgical treatment of brainstem lesions improved patient condition as measured by the Rankin scale [24]. Similarly, Ulrich et al. reported that the preoperative and postoperative DTI- fibre accuracy was associated with the neurological findings [25].

In another study, DTI FT was used to determine the location of the facial nerve during surgery on an acoustic neuroma [26]. This examination, although it accurately determined the position of this nerve during the operation, did not prevent postoperative paresis of the facial nerve. This is because the function of the facial nerve after the surgery depends on its continuity and blood supply. The aim is to avoid traumatization of the VII and VIII nerves during the procedure.

Long-term follow-up of patients who underwent surgery due to brainstem cavernomas has shown that the patient's condition gradually improved postoperatively, that no risk of rehaemorrhage was found, and that their quality of life improved. However, a postoperative follow-up MRI is necessary to assess the completeness of resection. Another surgery is indicated in a case of non-radical surgery [15].

Since 2005, surgical procedures have been performed in our department with the use of a neuronavigation system and DTI/DTT. Suboccipital, telovelar and infratentorial supracerebellar approaches were used most frequently for surgery for brainstem cavernomas. The approach adopted depended on the location of the cavernoma and the course of CSTs, ML and ponto-cerebellar pathways was established based on DTI/DTT. This allowed for a relatively precise access which meant that monitored fibre tracts could be unaffected in the neuronavigation system. The use of DTI/DTT in determining the surgical access to brainstem cavernomas has been described by Januszewski as more accurate than the two-point technique [27]. Only the course of CSTs, ML and ponto-cerebellar transverse tracts was entered into the neuronavigation system, which allowed a significant reduction mainly in locomotor disability and sensation disorders after surgery.

Preoperative DTI/DTT showed that CSTs, ML and MLF were mostly injured after haemorrhage from the cavernoma. Damage to long fibre tracts in the inferior, middle and superior peduncles was found in approximately 33% of patients who underwent preoperative DTI/DTT. Similar changes in the course of these fibre tracts were found preoperatively by Flores et al. [9].

The prevalence of postoperative limb deficits was related to the use of DTI/DTT, which was established by making a comparison between patients in whom DTI/DTT was performed during surgery and the group that underwent surgery without DTI/DTT. Other studies have found that a lack of preoperative DTI/DTT significantly correlates with a higher prevalence of postoperative limb deficits [10, 27].

Faraji et al. demonstrated that the use of DTI/DTT during surgery did not correlate with deficits reported postoperatively [28]. However, slightly different results have been presented by other neurosurgeons [24, 25].

In our patients, large size and large volume cavernomas were more likely to cause rebleeding compared to smaller cavernomas. Patient prognosis was better when the subjects underwent surgery after the first haemorrhage, which aligns with the conclusions of other authors [1, 8, 18]. The location of cavernomas in different parts of the brainstem did not affect the occurrence of rebleeding in our patients.

In the group of patients who underwent surgery in our department, preoperative neurological deficits were found in 31–51% of patients, and in 34–64% postoperatively, depending on whether these were motor, sensory or cerebellar deficits or were related to cranial nerve injury. The neurological condition of patients deteriorated postoperatively in most

cases. Subsequently, neurological status gradually improved. During the last follow-up visit, we found that motor and sensory disorders usually resolved. Cerebellar-related disorders regarding ataxia, tremor and balance disorders were less likely to resolve. Cranial nerve deficits showed a tendency to resolve, but over a much longer period. During the last follow-up visit, 17–26% of patients presented with neurological deficits. Zaidi et al. reported that 53% of patients presented with new or worsened neurological deficits postoperatively. However, gradual improvement was observed. Zaidi et al. observed permanent postoperative deficits in 35% of patients from a group comprising 367 patients [7].

The prognosis of patients based on the mRS who underwent surgery in our department with the use of DTI/DTT, as against those without this imaging technique, did not differ statistically significantly, and this is in accord with the results of Flores et al. [9].

Based on their follow-up of 71 patients who underwent surgery for brainstem cavernomas, Dukatz et al. demonstrated that their quality of life improved gradually following surgical treatment [29]. As many as 87% of patients were able to pursue the same professional activity as before surgery, and 82% of patients reported feeling good or better after surgery.

Conclusions

Patients with brainstem cavernomas should undergo surgical treatment after the first haemorrhage, especially in the case of a large size cavernoma.

DTI/DTT should be used to determine the trajectory to the cavernoma, particularly to the deep cavernoma, and to determine the safe entry zone.

Total resection of the cavernoma should be performed even where this means that reoperation is required.

Postoperative neurological deficits gradually resolve or decrease.

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