

HEMANGIOBLASTOMA OF THE POSTERIOR FOSSA

THE ROLE OF MULTIMODALITY TREATMENT

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ABSTRACT - The authors made a review of a series of patients with hemangioblastomas of the posterior fossa treated between 1973 and 1993. A total of 32 patients were analyzed with 24 patients receiving resection, 8 patients receiving radiosurgery and 2 patients receiving conventional radiotherapy. The mortality in the patients with a resection was considered acceptable with 2 deaths (8%) and with a morbidity of 3 patients (12.5%). A review of the literature suggests that conventional radiotherapy with high doses (45-60 Gy) may have a role in the post-operative control of hemangioblastomas and in some cases could be employed even before the resection in order to facilitate the surgery. The radiosurgical treatment is regarded like adjuvant. Poor results were obtained with radiosurgery in large tumors where low doses (less than 20 Gy) were used. Because of the rarity and complexity of these tumors, mainly when associated with von Hippel-Lindau disease, a multicenter study could be useful with the assessment of the optimal utilization and combination of these treatment modalities.

KEY WORDS: hemangioblastoma, treatment, radiosurgery, radiotherapy.

Hemangioblastoma da fossa posterior: papel do tratamento multimodal

RESUMO - Os autores fazem revisão de uma série de pacientes com hemangioblastomas da fossa posterior tratados entre 1973 e 1993: 32 pacientes foram analisados com 24 deles recebendo ressecção, 8 recebendo radiocirurgia e 2 recebendo radioterapia convencional. A mortalidade dos pacientes submetidos a ressecção foi considerada aceitável com 2 mortes (8%) e com morbidade de outros 3 pacientes (12,5%). A revisão de literatura sugere que a radioterapia convencional com altas doses (45-60 Gy) pode ter um papel no controle pós-operatório dos hemangioblastomas e em alguns casos pode ser empregada mesmo antes da ressecção com o objetivo de facilitar a cirurgia. O tratamento radiocirúrgico é considerado coadjuvante. Resultados ruins foram obtidos com a radiocirurgia em tumores grandes em que doses baixas (menos que 20 Gy) foram utilizadas. Devido a raridade e complexidade destes tumores, principalmente quando associados com a doença de von Hippel-Lindau, um estudo multicêntrico pode ser útil na avaliação da combinação e otimização dessas modalidades de tratamento.

PALAVRAS-CHAVE: hemangioblastoma, tratamento, radiocirurgia, radioterapia.

Hemangioblastomas (HBLs) of the posterior fossa are relatively rare, benign tumors comprising 1.1 to 2.5% of all intracranial neoplasms in major surgical and pathological series^{3,7,52}. They can occur either in a "sporadic" or "isolated" form or like one of the components of the von

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Hippel-Lindau disease (vHLD), an autosomal dominant condition with almost complete penetrance and variable expression^{12,13,22,23,30-32,49}. Posterior fossa HBLs are related to vHLD in up to 43% of cases^{21,25,36,47}. In vHLD, nervous system HBLs are often associated with other disorders such as angiomas of retinae (HBLs of the retina), renal and adrenal tumors^{2,7,10,15,17,19,25,32,33,39}. Despite awareness and improvements in HBL screening within vHLD^{1,4,9-11,16,27,34,41,42} as well as further refinement in our knowledge of the genetic constitution of the disease^{6,12-14,20,23,26,30,31,35,43,44,48-50}, mainly because of critical brain location and a tendency to recur, these tumors still pose a challenge for the neurosurgeon. Posterior fossa HBLs and renal cell carcinomas are the main cause of death in vHLD patients with a median life expectancy of approximately 40 to 50 years^{15,19,25,32}.

After review of our surgical series of 24 patients operated on between 1973 and 1991 and adding 8 patients that had radiosurgery between 1989 and 1993, we suggest that a multimodality approach including resection, conventional radiotherapy and radiosurgery should be employed to manage these difficult lesions.

MATERIAL AND METHODS

We reviewed the records of 24 patients that had a resection of a posterior fossa HBL at the University of Pittsburgh Medical Center (1973-1991). In this series only 2 patients had previous surgery. In addition, we managed 8 patients with Gamma-Knife radiosurgery (1989-1993). All the radiosurgery patients had prior surgeries (7 of 8 from other institutions). Two of the 24 patients that received resection at our institution also received conventional radiotherapy. We were unable to obtain a long-term follow-up in these patients (resection series) because of the long span of time of the series. The 8 patients of the radiosurgery series had a proper follow-up albeit short.

RESULTS

SURGICAL SERIES

Twenty five resections were performed on 24 patients and 25 tumors (Table 1). One patient had two resections (a vHLD case). In 9 patients concomitant ventriculostomy was used. Thirteen patients (54%) were male and 11 (46%) female (age range, 24-70 years). The mean age at surgery was 46 years. The two vHLD cases were 24 and 36 years old respectively. Patients were symptomatic for a median of 3 months before surgery with a range of 0.5-60 months. Diagnostic cerebral angiography was used in 22 (92%) patients, including one where it was the only diagnostic imaging test used, all other patients also had a CT scan. Six patients (25%) had MRI examinations. The mean preoperative Karnofsky score was 80 (range, 50-90). In the immediately postoperative period, 15 patients (62.5%) had improvement in their neurological condition and Karnofsky grade. In 4 patients (17%) there was no change, 3 (12.5%) were worse and 2 (8%) died. One patient died from a hematoma after intra-operative coagulopathy and the other, 4 months after resection of a large brainstem tumor. Only 2 (8%) patients in a group of 24 had a known diagnosis of vHLD at the time of surgery, but only 8 of the 22 "sporadic" HBL patients had appropriate screening for vHLD, reflecting a lack of awareness for that condition (mainly in the beginning of the series).

Afterwards we were able to identify at least 2 new cases of vHLD making the incidence of this disease in this series of 17%.

RADIOSURGICAL SERIES

All 8 patients in this series had at least 1 previous posterior fossa surgery with a total of 12 craniotomies (Table 2). Only 1 had a previous surgery in our institution. Two patients had also craniotomies for supra-tentorial HBLs. We had 4 males and 4 females. The youngest patient was 28 years old and the oldest was 75 years old. The mean age at treatment was 49 years. Six patients (75%) had a radiosurgical treatment for a symptomatic tumor and 2 patients (25%) had an asymptomatic new growth or residual tumor. For the planning, 4 patients had a head CT scan, 3 had an MRI and 1 had both examinations. At the time of treatment, 3 cases (37.5%) were considered vHLD cases but again, not all the patients had a proper screening prior to radiosurgical procedure.

Table 1. Surgical results.

Patient no. & initials	Surgery date	Sex	Age at surgery	Localization	Size	Type	No. of resections	Results
1 CRS	10-03-73	M	29	Left hemisphere	Large	Cystic	1	Improved
2 AC	01-28-76	M	38	Left hemisphere	Medium	Cystic	1	Improved
3 DS	11-19-76	M	34	Vermis	Medium	Mixed	1	Improved
4 ER	01-10-78	F	54	Left hemisphere			1 + shunt	Improved
5 JR	02-05-79	M	51	Right hemisphere			1 + shunt	Improved
6 EH	03-24-80	F	57	Left hemisphere			1	Improved
7 WAF	05-28-81	M	55	Left hemisphere	Large	Cystic	1	Improved
8 JJ	06-12-81	M	37	Left hemisphere	Medium		1 + shunt	Improved
9 DAS	01-13-82	F	24	Brain stem (+ spinal cord)	Small	Solid	1 + shunt + spinal surgery	Worse
10 JRM	01-23-82	M	29	Right hemisphere			1	Improved
11 CC	05-04-82	F	65	Right hemisphere				Worse
12 HMS	01-17-83	M	68	Left hemisphere	Large	Cystic	1	Improved
13 SB	12-13-84	F	55	Left hemisphere	Large	Mixed	1	Improved
14 TMB	02-14-85	M	30	Right hemisphere			1	Improved
15 NA	09-17-85	F	34	Brain stem		Solid	1 + shunt	Same
16 LEC	10-08-86	F	70	Vermis	Large	Mixed	1	Same
17 LLB	01-19-87	M	59	Vermis	Large	Solid	1 + shunt	Worse
18 JB	05-12-87	F	61	Brain stem	Large	Solid	1 + shunt	Death
19 RL	02-29-88	F	57	Right hemisphere	Large	Mixed	1 + shunt (1 previous surgery in another hospital)	Death
20 LJJ	07-29-88	F	39	Left hemisphere	Medium	Cystic	1	Improved
21 DJM	02-12-90	M	46	Left hemisphere		Cystic	1	Improved
22 RS	06-11-90	F	59	Right hemisphere		Cystic	1 + shunt (2 previous in other hospital)	Same
23 CMW	09-05-90	M	34	Left hemisphere		Cystic	1	Same
24 RPB	04-17-91	M	32	Left hemisphere		Solid	2	Improved

Tabela 2. Radiosurgical treatment.

Case	Age, Sex	Signs, Symptoms	Location	Prior Treatment	Volume (mm ³)	Dosimetry (min/max) Gy	Survival (months)	Progression Free Survival (months)	Imaging (months)	Additional Treatment	Outcome
1	46 F	HA, dizziness	Medulla, C1	Resection	(520), (50)	(16/32) (15/30)	18	18	No f/u	Chemo for breast CA	Dead (breast CA)
2	30 F	Ataxia	Medulla, cerebellum	Resection	(879), (335)	(20/40) (20/40)	24	24	No change (24)	—	Stable
3	53 M	Ataxia, HA CN V, VII, IX, X	CPA	Resection (2)	(8792)	(14/35)	33	10	50% increase bleed (35)	Resection thoracic tumor	Dead of tumor bleed
4	74 F	Ataxia, dementia	Cerebellum	Resection VPS	(5296)	(15/30)	19	7	No change (7)	—	Dead of tumor
5	32 F	Intact	Cerebellum	Resection (3), VPS	(2826)	(20/40)	26	26	Decreased, new cerebellar lesion (26)	—	Stable
6	28 M	Ataxia, diplopia	CPA	Resection (2), VPS	(3203)	(17/34)	20	18	Increased (18)	Resection	Repeat OR
7	75 M	Intact	Cerebellum	Resection	(10532)	(14/28)	15	10	Increased (15)	Scheduled for resection	Repeat OR
8	56 M	Ataxia, diplopia, CN IX, X	CPA	Resection	(7850)	(13/26)	37	8	Increased (8)	Resection	Repeat OR

HA, headache; CN, cranial nerve; CPA, cerebellum-pontine angle; VPS, ventriculo-peritoneal shunt; OR, operation (resection).

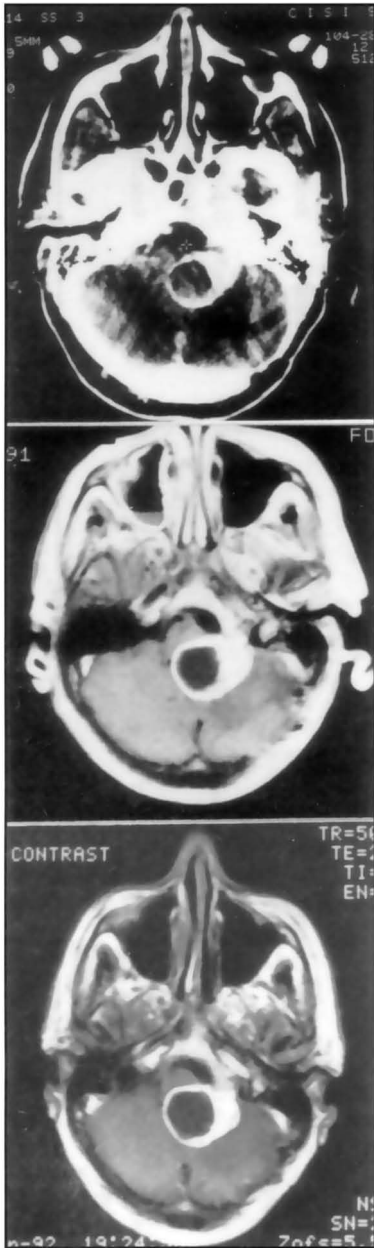


Fig 1. Case 8. A, CT scan with contrast at the time of radiosurgery. B, MRI T1 weighted with gadolinium at 3 months showed slight increase in size of the cyst portion. At that time patient had only episodes of vomiting. C, MRI at 8 months showed increase in cyst size. Because of progressive symptoms the patient had a new (partial) resection.

The pre-operative Karnofsky grade of the patients were in the range of 50 to 90 with a mean of 80. So far, despite the short follow-up, our best results had a radiosurgical dose at margin of 20 Gy. Our two more recent cases had lower doses, one because the cerebellum-pontine angle (CPA) location of the tumors and the other because of the large volume (cases 7 and 8). Three cases had new resections (one partial) after the radiosurgery and the residuals tumors have been stable since then (Fig 1).

DISCUSSION

THE ROLE OF SURGICAL RESECTION

Despite the absence of a capsule, HBLs are histologically and biologically benign lesions^{5,37,40,52}, correspondingly, surgical treatment should be curative and microsurgical resection is the method of choice for symptomatic tumors^{5,36-38,47,51}. The goal is the removal of the mural nodule in cystic lesions, or the entire tumor when solid³⁸. Usually, one tries to remove the lesion "en bloc" like an AVM (arteriovenous malformation) and aims to keep the dissection plane outside the tumor in order to minimize bleeding^{37,38,51}. Sometimes, because some tumors are intimately attached to the brain stem or cranial nerves, only a partial resection can be obtained. Even "gross total" resections can be followed by recurrence in 3 to 10% of cases³⁷. In recent series^{21,36,47} the reported morbidity and mortality was low (Table 4), but like any tumor that can recur, long-term follow-up must be performed to evaluate the overall management result. It is expected that in reoperations the morbidity and mortality rates will be higher than in the original surgery⁴⁷. There is no doubt that the ideal treatment is surgery but to avoid repeated resections for recurrences or new growths or even to treat asymptomatic cases found in screening for vHLD (if judged necessary to treat asymptomatic HBLs) the adjuvant techniques of conventional radiotherapy and radiosurgery need to be assessed.

Another surgical technique, imaged-guided stereotactic aspiration of growing, symptomatic tumors cysts can provide clinical improvement, but cyst re-expansion often occurs over time⁵.

RADIOSURGERY FOR HEMANGIOBLASTOMAS OF THE POSTERIOR FOSSA

At the present time there is little information on the results of radiosurgery for HBLs, most of it published in abstract format. Despite the small number of cases and the short follow-up, our series is adding more information to this scarce data. At the present, there is no prospective study about the natural history and growth

Table 3. Results of series when conventional XRT was used after resection.

Series/ Year	Years	No. of Patients	Overall Survival	Survival High Dose 45-50 Gy	Local Control Dose	Complications
Sung, 1982	1950-1976	29	5 years 70.9% 10 years 40.5% 15 years 16.9%	5 years 90.5% 10 years 56.5% 15 years 56.5%	Not available	Not available
Smalley, 1990	1963-1983	27	5 years 85% 10 years 58% 15 years 58%	Not available	> 50 Gy 57% < 50 Gy 33%	2

Table 4. Comparison of recent surgical series.

Author/ Year	Years	# of Cases/ Tumors	vHLD incidence	Morbidity	Mortality
Symon, 1993	23 (1968-1990)	51/104	22 (43%)	3 (5.8%)	2 (3.9%)
Neumann, 1989	10 (1976-1986)	36/39	10 (23%)	4 (11.1%)	2 (5.5%)
Huson, 1986*	13 (1972-1985)	19/20**	8 (42%)	2 (10.5%)	1 (5.2%)
Georg, 1996	18 (1973-1991)	24/25	4 (17%)	3 (12.5%)	2 (8.3%)

*One original case reported was an autopsy case.

** Presumed from the case reports.

patterns of these lesions but in general, they have a slow growth with a benign behavior^{37,52} and in that way only with a long follow-up accurate statements can be made about different treatments. The rich vascularity of these lesion make them similar to true AVMs, otherwise, not only endothelial cells are present but also pericytes and the stromal or interstitial cells that are major components in the tumoral tissue^{37,40,52}. Therefore, the biological effect of the radiation in the different types of tumor cells could provide or preclude the desired result. Currently, the appropriate radiosurgical dose has been based in our experience with the treatments of AVMs and benign tumors like meningiomas and acoustic neuromas^{8,28,29}. The location of the lesion prevents a more liberal use of irradiation according with our previous experiences^{24,28}. Despite the poor initial results demonstrated in our series, a better understanding about the proper selection of patients, dose/results and the possible association of radiosurgery and conventional radiotherapy was obtained. At the present we are still at the beginning of a learning curve in the respect of HBLs and radiosurgery but we remained convinced of a coadjuvant role of this technique in the multimodality treatment of these lesions.

A cooperative multicenter projective study assessing the multimodality treatment is proposed in this paper.

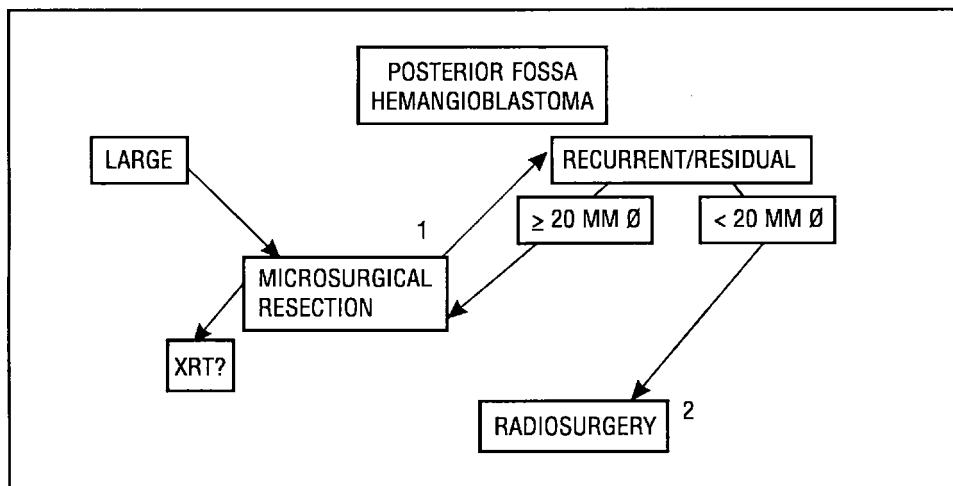
CONVENTIONAL RADIOTHERAPY FOR HBLs OF THE POSTERIOR FOSSA

Because of the relatively rare occurrence of these lesions, few data in this issue were obtained in the English language literature^{3,18,45,46}. In two retrospective series with overall good results^{45,46} there are indications for better survival rates and local control using high doses of radiation, in the range of 45-60 Gy (Table 3). With these more aggressive protocols survival rates around 60% were found at 10 and 15 years. Few complications were cited. The use of fractionated external beam radiotherapy (XRT) was recommended mainly for partially excised tumors or recurrences but also for microscopically or clinically suspect margins. Another possible use of radiation therapy is the planned preoperative irradiation in difficult cases with the objective to diminish tumor vascularization and with surgery postponed for some months^{18,45}. The capacity of XRT to prevent the growth of asymptomatic lesions or even to prevent the appearance of new growths in vHLD cases is not

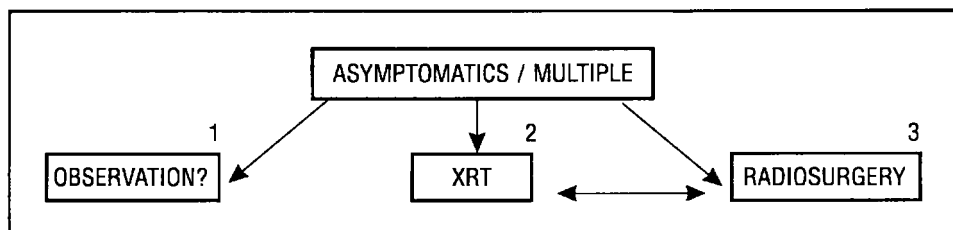
known. Currently at our institution (Pittsburgh) we are using a protocol for the combined use of XRT and radiosurgery in the treatment of brain metastases. Whether this combined use of these two techniques can be also of value in the prevention and control of HBLs (especially in vHLD) remains to be studied.

CONCLUSION

Despite the progresses in the radiological diagnosis and in the genetics of vHLD the treatment of HBLs still needs refinement or an alternative to microsurgical resection alone. Deep brain stem tumors and large cystic ones can pose difficulties for safe open surgery. Recurrences necessitating repeated resections increase risks and costs. In our surgical series with several surgeons, the overall results can be considered good. Perhaps both patients that died post-operatively after resection of large tumors could have benefit from pre-operative conventional radiotherapy. In our radiosurgical series, a better selection of patients (patients with good Karnofsky grades and small tumors) had lead to better results, despite the short term follow-up so far obtained. The lack of appropriate screening for vHLD was not only reflected in our surgical series but also in our radiosurgical series where most of the patients were referred from other institutions. Finally, we propose these following flow charts with our current suggestions regarding the multimodality treatment of HBLs.



1. Microsurgical resection should be ideally used as primary treatment for small HBLs located on the surface (cerebellum); 2. Deep located, small HBLs are dealt preferably by radiosurgery.



1. Observation alone make HBLs more difficult to treat after their growth; 2. Although not entirely proved, XRT could prevent new growths, specially in vHLD cases; 3. Radiosurgery can be the ideal way to treat multiple small, deep seated HBLs and can be used as a boost to XRT.

Acknowledgement - The authors would like to thank Dr. Ailton Melo for his review of this article.

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