

Central Neurocytomas: A Comprehensive Review with Special Emphasis on the Role of Gamma Knife Stereotactic Radiosurgery

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Abstract

Central Neurocytomas (CNs) are uncommon tumors of central nervous system, arising from neuronal cells. Mostly these tumors are intraventricular and commonly occurs at the level of the "Foramen of Monro". However, recently cases of "Extraventricular Neurocytoma" have also been reported. Typically, CNs are associated with favorable outcome. Best long term prognosis, in terms of local control and survival is achieved by maximal safe surgical resection, which is considered as ideal therapeutic option. However, management of recurrent or residual CNs remains controversial. Treatment options for patients with recurrent or residual CNs includes reoperation, radiotherapy or chemotherapy. Use of conventional radiotherapy in recurrent or residual CNs is associated with long term complications in the form of cognitive abnormalities and risk of developing secondary malignancies. Recently, Gamma Knife Radiosurgery is used in patients with recurrent or residual CNs as an alternative treatment option to conventional radiotherapy. Studies have reported that Gamma Knife Radiosurgery provides safe and effective alternative treatment option for recurrent or residual CNs, by eliminating the long term side effects of conventional radiotherapy. However, these are based on results of limited number of studies, with small sample sizes, with no control groups. Randomized control trials or larger studies are required to confirm the effectiveness of Gamma knife Radiosurgery in recurrent or residual CNs. This paper reviews the findings of case series and case reports that contribute to the effectiveness of Gamma knife Radiosurgery in CNs.

Keywords: Central neurocytoma; Treatment; Gamma knife

Introduction

Central neurocytomas (CNs) are unusual tumors of the central nervous system, characterized by midline intraventricular location particularly at the level of "Foramen of Monro" [1]. It was first described by Hassoun et al. [2], in 1982, who reported two cases of Central neurocytomas and defined these tumors as a different pathological entity. In 1993, Hassoun et al. [2], reviewed the literature of 127 cases of CNs and summarized the epidemiology, clinical presentation and histopathological features. Since the original description by Hassoun et al. [2], there has been a steady increase in recognition of this entity. However, despite their increased recognition, CNs remain rare neoplasms of the central nervous system. Generally, the incidence of this tumor is only 0.25-0.5% of all brain tumors [2,3].

Epidemiology and Clinical Presentation

CNs predominantly occurs in young adults (between the ages of 20 and 40 years), with a mean age at presentation being 29 years, with no clear preponderance of either sex [2]. Largely CNs are midline lesions spanning the lateral and third ventricles, often in relation to the "Foramen of Monro" and arising from the neuronal cells of septum

pellucidum, fornix, or walls of the lateral ventricles [2]. Patients typically present with signs and symptoms of obstructive hydrocephalus in the second and third decades of life [3]. Schild et al. [3], in his study of 27 patients with CNs regarding the presenting symptoms, most of the symptoms were attributed to increased intracranial pressure secondary to obstructive hydrocephalus, found that 93% of patients had headache, 37% had visual changes, and 30% had nausea and vomiting. Less frequently, patients complained of lethargy (11%), balance problems (11%), and tinnitus (7%) [3].

Imaging

Typical imaging features of central neurocytomas are as follows [4], plain Computed Tomography scan shows an iso to slightly hyperdense mass in the lateral ventricle with moderate postcontrast enhancement with hypodense areas corresponding to cystic degeneration. On CT 50% demonstrate calcification and evidence of obstructive hydrocephalus. Magnetic resonance imaging shows an inhomogeneous mass, isointense on T1 weighted image, isointense or hyperintense on T2 weighted image with moderate to strong postcontrast enhancement (Figures 1-3).

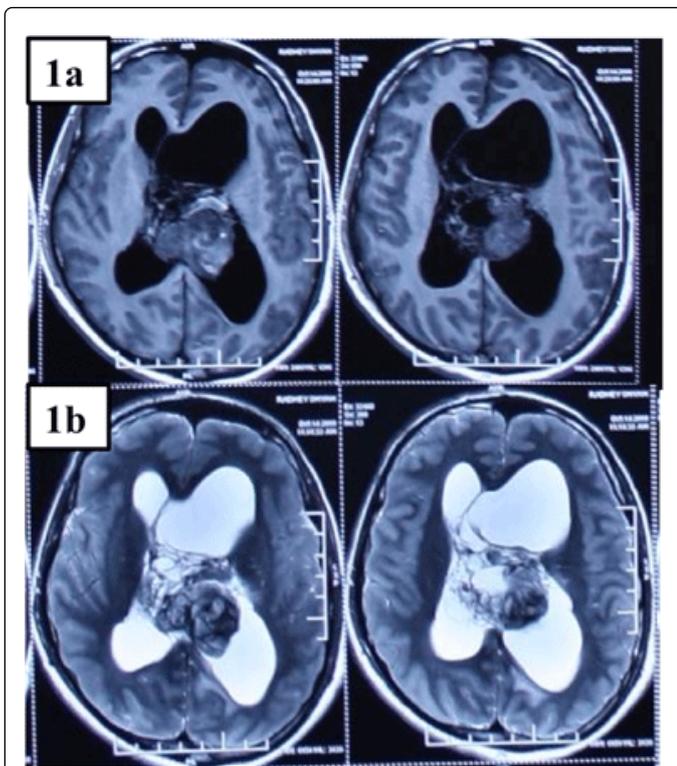


Figure 1: T1 and T2 weighted MRI axial sections showing a large hypo to isointense intraventricular lesion extending into both lateral ventricles with ventriculomegaly.

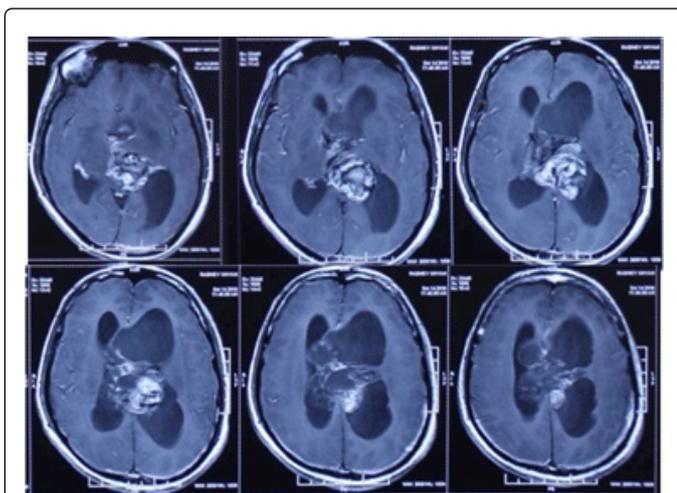


Figure 2: Post contrast axial sections showing heterogenous contrast enhancement in the intraventricular lesion located in the lateral ventricles

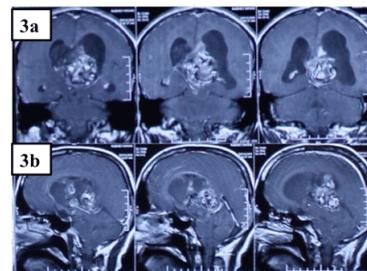


Figure 3: Post contrast coronal (a) and sagittal (b) sections showing the heterogenously enhancing intraventricular lesion

Neuropathology

Grossly Neurocytomas are generally greyish in color, well circumscribed, lobulated, resembling the grey matter, with areas of hemorrhage and cystic degeneration and calcifications [5]. On light microscopy these tumors are composed of uniform, small-to-medium-sized cells with rounded nuclei, finely stippled chromatin (“salt and pepper” chromatin) and inconspicuous nucleoli, along with scant cytoplasm, resembling “fried-egg” appearance of oligodendroglioma [5]. On electron microscopy these tumors shows high degree of neuronal differentiation containing parallel arrays of microtubules, with both clear core vesicles and dense core granulations in their terminations. Though intermediate filaments and synapse formation are seen, but these are not essential for diagnosis [5]. On immunohistochemistry vast majority of neurocytomas have been diagnosed on the basis of synaptophysin immunoreactivity alone, even without ultrastructural evaluation [5]. Strong immunostaining for synaptophysin has been recognized as the most appropriate and consistent diagnostic marker (Figure 4). CNs also shows positivity for Neuron specific enolase, however, positivity of Glial fibrillary acidic protein (GFAP) is variable [5].

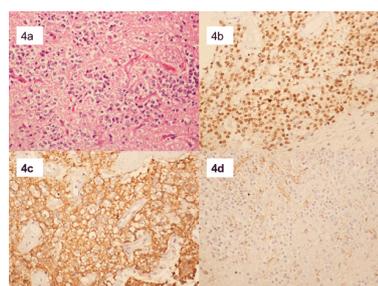


Figure 4: Photomicrograph showing monophasic population of oligodendroglia like cells in a fibrillary background (a, H&E×200), immunohistochemistry staining for NEU N1 and synaptophysin showing diffuse positivity (b and c, ×200), the cells are immunonegative for GFAP (d, H&E×200)

Treatment Options, Strategies and Outcome

Many clinical studies show that gross total resection (GTR) confers long term control for the CNs [3,6,7]. Schild et al. [3], analysed 32 patients with CNs retrospectively with a median follow up of 4.7 yrs

and reported a 5-year local control and survival rate of 100% and 80% after GTR, without adjuvant therapy. The 5-year local control rate was 70% for patients undergoing subtotal resection (STR). The 5-year local control rate was 100% for patients who received RT after STR compared with 50% for those who did not. Kim et al. [6], retrospectively analyzed 15 cases of central neurocytoma, over a period of 13 yrs, with a median follow up of 52 months and showed

that 2 out of 5 patients with GTR without RT recurred, two patients with GTR and RT remained stable, three patients with STR without RT were stable, five patients with STR and RT were stable. They concluded that radiotherapy appeared to have an effect on tumor control and reduce the chances of recurrence. Various studies quoting the use of primary and secondary Gamma Knife Radiosurgery in central neurocytoma have been summarized in Table 1.

Authors	No. of pts	GK as primary or secondary	Dose of GK,Gy	Follow up period (months)	Pre-GK tumor volume, ml	Post GK tumor volume, ml	Clinical outcome	Recurrence	Complication
Schild et al. [3]	1	NA	15	-	NA	No change at 13 months	-	-	-
Pollock et al. [21]	1	Secondary (recurrent)	18	34	2.7	Reduced	Good	No	None
Bertalanffy et al. [8]	3	Secondary (recurrent)	9.6-19	12-60	0.6	0.25	Good	No	None
					5.9	2.3	Good	No	None
					5.2	3.1	Good	No	None
Anderson et al. [14]	4	Secondary(recurrent)	16-20	12-28	1.7-12.3	Reduced	Good	No	None
Cobery et al. [17]	4	Residual-3 Recurrent-1	9-13	12-99	6.5	3.5	Good	No	None
					13	3.6	Good	No	None
					29	5.4	Good	No	None
					10.5	2.5	Good	No	None
Tyler-kabara et al. [16]	4	Primary-2 Residual-1 Recurrent-1	14-20	38-53	7.9	Reduced significantly	Good	No	None
					4.2				
					0.33				
					1.3				
Hara et al. [18]	1	Residual	20	12	5.7	80% reduction at 2months	Good	No	None
Kim et al. [15]	13	Residual-7 Primary-6	9-20	6-96	4.6-36.4	0.4-12.1	Good	No	None
Ali Genc et al. [19]	22	Residual & recurrent	16.4	36.7	0.7-68.9	6-unchanged 15-decrease in size 1-increased in size	Good	No	None
TOTAL	53	Primary-8, secondary-45							

Table 1: Summary of reports for Central Neurocytoma treated with Gamma Knife Radiosurgery

Leenstra et al. [7], retrospectively analysed 45 patients with CNs with a median follow-up was 10.0 years showed that the 10-year overall survival and local control rate was 83% and 60%, respectively. Patients whose tumor had a mitotic index of <3 (per 10 high-power fields) experienced a 10-year survival and local control rate of 89% and 74%, respectively, compared with 57% (p=0.040) and 46% (p=0.14) for patients with a tumor mitotic index of ≥ 3. The 10-year survival and local control rate was 90% and 74% for patients with typical tumors

compared with 63% (p=0.055) and 46% (p=0.41) for those with atypical tumors. A comparison of gross total resection with subtotal resection showed no significant difference in survival or local control. Postoperative RT improved local control at 10 years (75% with RT vs. 51% without RT, p=0.045); however, this did not translate into a survival benefit.

Bertalanffy et al. [8], retrospectively analysed 14 patients over a period of 17 years and out of the 14, 2 patients (14%) died postoperatively and one patient had a malignant course (7%). In the remaining 11 patients, one patient with an incompletely resected CN had disease progression after 37 months but at the time of last follow-up had had a stable disease for 10 years. In addition, the authors reported 5 patients with disease recurrence, occurring at a median gap of 67 months after surgery (range, 51-79 months after surgery), all of which occurred after complete surgical resection was performed and concluded that, CNs appear to have a higher tendency to recur during long-term follow-up than previously reported, even after complete resection. Chemotherapy can be useful for recurrent or residual CNs that cannot be resected and have been irradiated, but long term responses have not been reported regarding the use of chemotherapy [9-11].

Paek et al. [12], reported the long-term outcome following conventional radiation therapy (RT) in six cases of CNs. Between 1985 and 1992, six patients were treated with RT for residual tumors or for prevention of recurrence after surgery. The median follow-up period of radiological and clinical status were 171 (range: 128-229) and 202 months (range: 165-227), respectively. Tumors disappeared in three and reduced in three patients at the last follow-up. One mortality occurred due to radiation necrosis and another with radiation induced malignancy occurred. White matter degeneration and cortical atrophy were noticed with slow progression of performance deterioration in two patients. They concluded that conventional RT seemed to effectively control residual CNs after surgery. However, more sophisticated radiation techniques should be applied to minimize the long term sequelae of radiation therapy.

Rades et al. [13], reviewed 121 patients with CNs over a period of 8 years and concluded that the results of both conventional radiotherapy and stereotactic radiosurgery (SRS) were similar, however, SRS is a reasonable alternative to conventional therapy in selected patients. Since most neurocytomas are located close to the fornix, septum pellucidum, corpus callosum and little is known about the radiation tolerance of these structures, therefore use of conventional radiotherapy has been criticized because of well known long term side effects on cognitive function and also development of secondary malignancies. Stereotactic radiosurgery potentially avoids these side effects with its rapid dose fall off effect at the target edges and local control of tumor growth [14].

There are a few case reports and small case series indicating the effectiveness of stereotactic radiosurgery treatments for residual neurocytomas with similar results as conventional radiotherapy but without any serious side effects. Kim et al. [15] reported complete disappearance of tumor mass at 36 months and no side effects after LINAC based.

SRS. Tyler-Kabara et al. [16] reported four patients in their case series who underwent gamma-knife radiosurgery with good results. Cobery et al. [17], found that GKS resulted in 48, 72, and 81% volumetric decreases in three patients treated by subtotal tumor removal, and a 77% decrease in volume one patient with a recurrent tumor. In a case report by Hara et al. [18], rapid mass shrinkage of a subtotally resected CN was noticed two months after radiosurgery. Ali Genc et al. [19], in their study comprising of 22 patients with recurrent or residual neurocytomas treated with GKRS has shown that tumor decreased in size in 15 patients, in 6 patients tumor size remained unchanged and in 1 patient size of the tumor increased.

Asymptomatic lateral ventricular tumors have been found incidentally during routine medical checkups. The management of such asymptomatic cases remains controversial. Study done by Ali Genc et al. [19] recommends surgical resection for tumors larger than 3 cm in diameter. For patients with intraventricular tumors smaller than 3 cm, or for patients with large tumors that are not amenable to surgery and in patients who are at high risk for surgery (i.e., advanced age, other medical conditions), this study recommends a stereotactic biopsy. Once central neurocytoma is confirmed, GKRS can be advised. For symptomatic tumors and asymptomatic but large (3 cm) lesions, surgery can be curative. However, local recurrence after radiologically shown total resection might occur [20,21]. As a result, patients with gross total resection should be closely followed. Current practice is to repeat cranial MRI every three months in the first year, every six months in the second year and yearly thereafter [19]. However, when total resection is not achieved, further treatment should be based on the MIB1 LI of the tumor [19]. Subtotally resected tumors with an MIB1 LI >2% should be immediately treated by GKRS. On the other hand, subtotally resected tumors with an MIB1 LI <2% may either be treated by GKS or followed until the first sign of progression [19].

Conclusions

Generally CNs have a favorable prognosis. In cases with MIB1 LI >2% ,the clinical course can be more aggressive. The primary therapeutic modality remains surgery. However, in asymptomatic patients with tumor <3 cm, GKRS can be advised after stereotactic biopsy confirmation of neurocytoma. A safe maximal resection confers the best long-term survival and local control. In cases of a subtotal resection, standard external beam radiation can be added or radiation can be delayed until tumor progression occurs. But conventional radiotherapy is associated with long term side effects. So residual tumor or recurrences can be treated with more conformal radiation or focused radiosurgery using Gamma Knife. Various studies have shown effectiveness of GKRS in recurrent or residual neurocytomas. GKRS is an effective and safe alternative therapy for residual or recurrent CN. Further studies are needed to find out the long-term outcomes and optimal GKRS dose for CN.

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