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Original Article

The last decade's experience of management of central neurocytomas: Treatment strategies and new options

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ABSTRACT

Background: The purpose of the presented work is to evaluate the last decade's experience in surgical management of central neurocytoma (CN) and elucidate on the treatment strategies and new options.

Methods: The current series consists of the remaining 125 patients (70 females and 55 males) operated on during the past decade from 2008 to 2018. Most tumors were resected through transcortical (n = 76, 61%), or transcallosal (n = 40, 32%) approaches. In 5 (4%) patients with predominantly posterior location of the tumor, non-dominant superior parietal lobule approach was utilized. Both approaches (transcortical + transcallosal) were used in 4 (3%) of cases. Seven consecutive patients with large CN underwent prophylactic intraventricular stenting to prevent hydrocephalus.

Results: Gross total resection was achieved in 45 patients (36%), subtotal resection (STR) in 40 (32%) cases. After surgery, 63 (50%) patients had neurocognitive problems, including disorientation, attention deficit, global amnesia, short-term memory deficits, and perceptual motor and social cognition problems. A total of 26 patients (21%) had postoperative hemorrhage in the resection bed. Obstructive hydrocephalus was noted in 25 (20%) patients. The entrapment of the occipital and/or temporal horns was observed in seven cases. None of the seven patients with prophylactic intraventricular stents required shunting.

Conclusion: Although high rates of gross total or STR can be expected, the mortality and morbidity remain significant even in the modern neurosurgical era. Prophylactic intraventricular stenting in patients with large posteriorly located tumors with hydrocephalus may prevent ventricular entrapment and shunting. The main risk factors for recurrence are presence of residual disease and Ki-67 index over 5%. Recurrent symptomatic tumors should be treated surgically, whereas asymptomatic progression can be managed with stereotactic radiosurgery. Both treatment modalities are associated with low risk of complications and high tumor control rates.

Keywords: Central neurocytoma, Postoperative complications and outcomes, Radiosurgery, Stereotactic radiotherapy, Surgical resection

INTRODUCTION

Central neurocytoma (CN) was described as a distinct clinicopathologic entity by Hassoun *et al.* in 1982.[18] CN account for <1% of all central nervous system (CNS) neoplasms.[33] It is suggested that CN might be an embryonal tumor originating from the multipotent germinal

matrix cells located in the lateral ventricles.[2] CN is biologically benign lesions composed of small uniform cells with round nuclei and perinuclear halos. Mitotic figures are rare.[17] This tumor may be associated with a relatively favorable prognosis.[24-54] Patients with CN may present with a wide variety of symptoms, primarily related to the long-standing intracranial hypertension and obstructive hydrocephalus. Maximally aggressive surgical excision is a widely accepted mainstay of treatment. According to the literature, it can be achieved in only 50–60% of the patients.[24-41] Surgical challenges are the result of the deep location, frequently large size at presentation, and high vascularity.[41]

The largest clinical series included 438 patients by Rades and Schild 92 cases by Qian *et al*., 84 by Konovalov *et al*., and 63 cases by Wang *et al*.[24,41,43,51] Early publications described high rate of complications and low resection rates. In the original series of Hassoun *et al*. and subsequent report by Nishio *et al*., only 50% of the patients had gross total resection (GTR).[19,38] In the last decade, however, a higher number of patients underwent more radical resections, ranging from 71% to 91% with acceptable morbidity.[8,23,41] In this manuscript, the authors systematized the results of surgical treatment of CN in the past decade from 2008 to 2018. The main focus of this largest surgical series of patients with CN to date is the analysis of anatomy and location of the tumor, proper selection of surgical approaches, and evaluation of outcomes.

MATERIALS AND METHODS

A total of 250 patients with CN were operated on at our institution from 1992 to 2018. The current series consists of the 125 patients (70 females and 55 males) operated on during the past decade from 2008 to 2018. The patients' age ranged from 14 to 66 years (median 30 years). The study was approved by the Research and Ethics Committee. The charts, radiographic data, and surgical records were retrospectively reviewed. The following data were extracted and analyzed: age, sex, clinical presentation, radiographic characteristics of the lesions, including size, location, and relationship with surrounding anatomical structures, enhancement pattern, intraoperative findings, extent of resection, perioperative complications, and causes of mortality. All patients had their first postoperative brain magnetic resonance imaging (MRI) 3 months after surgery, followed by annual MR studies, unless clinically indicated otherwise.

The extent of tumor resection (ETR) was defined as (1) GTR, when complete removal without any obvious residual was achieved, (2) subtotal resection (STR), when small residual nodular enhancement, or linear enhancement of the resection bed, indistinguishable from the residual tumor was present, and (3) partial resection (PR), when more than 10% of the tumor was seen on postoperative MRI. The estimation of the EOR was reported by the staff neuroradiologists based on the postoperative MRI 3 months after surgery. All patients underwent neuropsychological and psychiatric evaluation by the staff psychologist and psychiatrist.

Statistical analysis

To establish the effect of clinical factors on overall survival, a Kaplan–Meier analysis was performed. A log-rank test (logarithmic rank test) and a Chi-square test were used to assess differences between the two groups forming the Kaplan–Meier curves in analysis 2 (e.g. complete or incomplete resection) to identify the validity of differences between the analyzed groups and obtain of risk ratio (RR). A single-factor regression analysis, all significant factors for which $P < 0.05$ was included in the multi-factor regression analysis (Cox Proportional Hazards Model), was used to assess the prognostic role of different factors. Assessment of recurrence was performed by multifactorial regression analysis with RR and 95% confidence interval. Differences were considered valid at $P < 0.05$. Statistical analysis was performed using the program "MedCalc" (version 19.6).

Clinical presentation

Symptoms associated with raised intracranial pressure (ICP) were the most common clinical presenting findings in this series. Seventy-eight patients (62%) had evidence of papilledema. The extent of papilledema was graded according to the Frisen grading system.[41] Fundoscopic evaluation was performed preoperatively and postoperatively in each patient.[13]

Fifteen patients (12%) presented with hemiparesis. Memory changes were noted in 40 patients (32%). Psychiatric and cognitive problems were documented in 28 patients (22%). Clinical findings are presented in more detail in [Tables 1 and 2].

Preoperatively, 76 patients had a Glasgow coma scale (GCS) of 14–15, whereas 49 patients had GCS of 12–13.

Radiographic characteristics

All 125 patients underwent an MRI of the brain with utilization of the standard brain tumor protocol with contrast. In 83 patients (66%), the tumor was isointense to the brain cortex on T1-weighted images. On T2 images, CN was seen as heterogeneous lesions with multiple small hypointense cyst-like areas, which were noted in 69% of the patients. About 60% of the neoplasms were larger than 4 cm in maximum diameter. The largest mass had the longest linear dimension of 8.0 cm. CN showed considerable anatomical variability in their location within the ventricular system.

Based on the tumor size, we propose the following classification: Group I: small tumors (<2 cm); Group II:

medium size (2–4 cm); Group III: large (4–6 cm); and Group IV: giant (>6 cm). According to the location, the tumors can be classified into Group A: anterior (located in the anterior horns); Group B: medial (located in the body of the lateral ventricle); Group C: posterior (in the trigonum and the occipital horn); and Group D: extensive (involving several parts of the lateral ventricles or casting them) [Figure 1]. The numbers of patients in each group are summarized in [Table 3]. In 30 patients, the tumor was extending into the third ventricle. In Group A patients, tumor extension onto the third ventricle was observed in 8 of 43 cases; in Group B patients, in 12 of 54; and in 10 of 17 patients in Group D.

Indications for surgery

Our approach was to recommend surgical resection in all symptomatic patients with radiographic findings of intraventricular mass suggestive of CN. Surgery was contraindicated in patients with significant comorbidities, in whom general anesthesia and potentially, prolonged surgery was felt to be risky. In the absence of major comorbidities and contraindications to general anesthesia, we recommend maximally safe resection of even very large and giant tumors, as surgery can be the patients' only chance for survival. In patients harboring tumors with very significant infiltrative component, surgical indications are not straightforward. In such instances, operative treatment may be considered on a case by case basis with the main objectives to establish tissue diagnosis, achieve maximally safe debulking and palliation.

Table 1: Clinical presentation of 125 patients with CN.

Signs of increased ICP (chronic headaches, nausea, and vomiting)	78 (62%)
Memory decline	40 (32%)
Psychiatric and cognitive problems	28 (22%)
Hemiparesis and hyperreflexia	15 (12%)
Visual field cuts	2 (1.7%)
Double vision due to abducens nerve palsy	2 (1.7%)
Seizures	8 (6%)

ICP: Intracranial pressure, CN: Central neurocytoma

Table 2: Papilledema in patients with CN according to the Frisen grading system.

Papilledema	***n***
Normal Optic Disc	47 (38%)
Minimal Degree of Edema	11(9%)
Low Degree of Edema	16 (12%)
Moderate Degree of Edema	21 (16%)
Marked Degree of Edema	14 (11%)
Severe papilledema with atrophy and hemorrhages	30 (24%)

CN: Central neurocytoma

Surgical treatment

Surgical approaches

Most tumors in our series were resected through transcortical (n = 76, 61%), or transcallosal (n = 40, 32%) approaches. In five (4%) patients with predominantly posterior location of the tumor, non-dominant superior parietal lobule approach was utilized.

Anterior frontal transcortical approach is used in patients with (1) CN located predominantly in the anterior horn and the body of the lateral ventricle, (2) medial tumors with lateral extension, and (3) large CN with lateral extension, as well as tumors spreading to the contralateral side, but only when ventriculomegaly was present. In patients with very large tumors, casting most of the lumen of the lateral ventricle, the craniotomy window had to be shifted more anteriorly to achieve a favorable angle of attack along the main axis of the neoplasm.

Transcallosal approach was preferred exposure in (1) patients with medial or unilateral location of the tumor without significant lateral extension and (2) small to medium size medial tumors in both ventricles. The main advantages of this approach were optimal visualization of the tumor in both lateral ventricles and elimination of risks associated with cortical transgression. Although the risks of transcallosal approach include injury to the parasagittal veins and subsequent venous infarct,[23,36] we did not encounter any

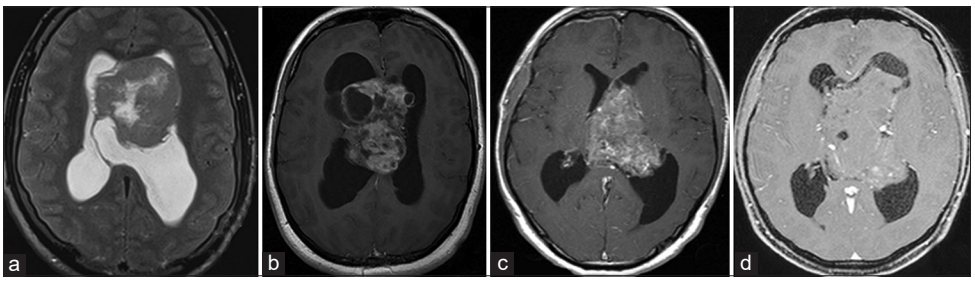

Figure 1: CN (a) limited to the frontal horn of the left lateral ventricle, (b) medial tumor, (c) posterior location, and (d) very large CN casting the lateral ventricles. CN: Central neurocytoma.

Table 3: Classification of CN based on the size and location.

Size	Number of patients	Location	Number of patients
Group I: small (<2 cm)	19 (15%)	Group A: anterior (in the anterior horns)	43 (34%)
Group II: medium (2–4 cm)	31 (25%)	Group B: medial (in the body of the lateral ventricle)	54 (43%)
Group III: large (4–6 cm)	58 (46%)	Group C: posterior (in the trigonum and occipital horn)	11 (9%)
Group IV: giant (> 6 cm)	17 (14%)	Group D: extensive (involving several parts of the lateral ventricles, or casting them)	17 (14%)
Total	125	Total	125

CN: Central neurocytoma

large bridging cortical veins in the surgical field in any of the 40 patients operated on through this approach. In 25 patients with asymmetrical location of the tumor, we opened up the corpus callosum most often between pericallosal arteries or lateral to the ipsilateral pericallosal artery. The size of corpus callosotomy depends on the size of the tumor, but never larger than 2 cm in our series. Typically, the callosotomy was carried out in the anterior or middle part of the body of the corpus callosum, depending on the location of the major bulk of the tumor. If severe hydrocephalus is present, this approach allows the removal of tumors located more posteriorly, in the body of the lateral ventricle and if the lesion involved both lateral ventricles.

In four cases of giant tumors casting the lateral ventricles and extending into the third ventricle, we used combined approaches: three patients were operated on through transcortical and transcallosal approaches, and in one case, through bilateral transcortical approach.

Microsurgical nuances

We found that positioning of the patient on the operating table with maximum utilization of gravity, adequate brain relaxation and wide tumor exposure are critical to successful removal of CN. In 35 patients, the surgeons reported relatively soft consistency of the tumor, which allowed an efficient utilization of regular suction and ultrasonic aspirator. Multiple tumor vessels were coagulated within the parenchyma of the tumor. We tried to avoid or minimize the use of coagulation on the walls of the lateral ventricles to minimize the risk of normal brain damage. Securing the bleeding from the hypertrophied ependymal vessels was frequently challenging. The ependymal feeders commonly have very thin and frail walls and continue to bleed, even as they retract into the normal brain. Local hemostatic agents, such as gelfoam soaking wet in thrombin and oxidized cellulose were helpful. When the anterior-inferior aspect of the tumor is mobilized, it is important to visualize the foramina of Monro and carefully preserve the fornices. In 30 patients, the tumors were extending into the third ventricle. In these cases, we did not encounter any serious adhesions between the tumor and the walls of the third ventricle. The surgeons were able to mobilize and aspirate the tumor through the foramen of Monro without the need to widen the transforaminal exposure. Thalamostriate veins were preserved in all patients, including 12 cases, when the tumor was densely adherent to them, utilizing sharp dissection. In eight cases, a very thin layer of tumor was left on the thalamostriate veins to preserve them. Septal veins were either unidentifiable, or sacrificed in all cases, as neoplasms invaded septum pellucidum. When the tumor invaded choroid plexi, we tried to preserve their largest draining veins until the very end of resection. Their early sacrifice could contribute to significant intraoperative hemorrhage that resulted in challenging hemostasis during removal of the posterior pole of the tumor. We attempted maximally aggressive resection, as bleeding into the residual mass can result in potentially life-threatening sequela of postoperative intraventricular hemorrhage and even casting of the ventricular system with blood, resulting in obstructive hydrocephalus. To prevent obstructive hydrocephalus, microsurgical fenestration of the septum pellucidum was performed in almost all cases [Figure 2].

Ventriculostomy catheter was left in 85 (68%) of the patients. Seven most recent consecutive patients with large CN underwent prophylactic intraventricular stenting to prevent hydrocephalus between the anterior and posterior horns of the lateral ventricles or between the lateral and third ventricles. Early postoperative brain computed tomography (CT) (within 3 h of surgery) was performed in all cases to rule out acute postoperative changes, such as hemorrhage and hydrocephalus.

Neuromonitoring of somatosensory evoked potentials (SSEP) and motor evoked potentials (MEP) was utilized in 82 patients with posteriorly located, extensive tumors, and tumors infiltrating the walls of the lateral ventricles. In addition, continuous subcortical stimulation was performed during tumor resection. The authors did not monitor patients with smaller and anteriorly located neoplasms.

RESULTS

Extent of resection

In this series of 125 patients, GTR was documented in 45 (36%), STR in 40 (32%), and PR in 40 (32%) of patients.

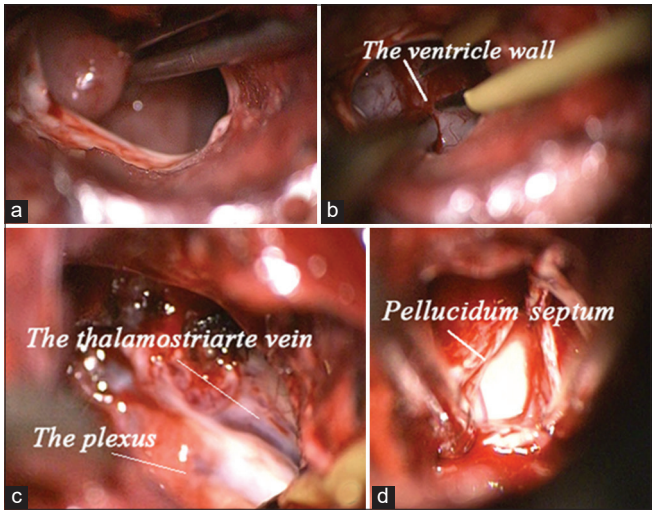

Figure 2: Basic principles of microsurgical resection: (a) in most cases, the tumor is relatively soft, which allows an efficient use of the regular suction and ultrasonic aspiration; (b) multiple tumor vessels are coagulated in the parenchyma of the tumor. The use of coagulation on the walls of the side ventricles should be avoided or minimized; (c) if the tumor is located in the lower part of the anterior horn, it is important to visualize and release the foramen of Monro by removing the tumor through it without the need to expand the transforaminal exposure while preserving the fornix. Thalamostriate vein and the vein of the choroid plexus should be preserved; (d) septum pellucidotomy is performed to interconnect the ventricles.

Further analysis of the relationship of the preoperative tumor volume and the EOR demonstrated that GTR/STR was achieved in 100% of patients with tumors <2.0 cm in largest diameter, in 69% of the patients with tumors measuring 2–4 cm, in 66% with tumors measuring 4–6 cm, and in only 50% when lesions were larger than 6 cm [Table 4].

In patients with anterior tumors (Group A), aggressive resection (GTR and STR) was achieved in 65% of cases (28 out of 43 patients). In patients with medial tumors (Group B), aggressive resection (GTR and STR) was achieved in 74% (40 out of 54) of patients. In Group C patients (posterior tumors), 64% (7 from 11) had aggressive resection. In patients with extensive tumors (Group D) GTR/STR was possible in only 56% of cases (9 out of 16 patients) [Table 5].

Even with neuromonitoring, 22 of 82 patients with large posterior infiltrating lesions developed either worsening of the weakness, or new motor deficits. Interestingly, only 15 of 22 patients had documented decrease in the amplitudes of SSEP and MEP. Further resection of the periventricular and/or thalamic parts of the tumor was stopped in each case when alarming electrophysiological changes occurred, if hemostasis was adequate.

Table 4: Size of the tumor and extent of resection.

Group/Size of the tumor	GTR	STR	GTR+STR	PR	Total
Group I: small (<2 cm)	16	3	19 (100%)	-	19
Group II: medium (2–4 cm)	15	7	22 (69%)	9 (31%)	31
Group III: large (4–6 cm)	12	23	35 (66%)	23 (34%)	58
Group IV: giant (>6 cm)	2	7	9 (50%)	8 (50%)	17
Total	45 (36%)	40 (32%)	85 (68%)	40 (32%)	125

GTR: Gross total resection, STR: Subtotal resection, PR: Partial resection

Postoperative complications

Hemorrhagic complications

A total of 26 patients (21%) were found to have postoperative hemorrhage in the resection bed. In all cases, the bleeding was associated with residual tumor. Postoperative hematomas were more common in patients with large or giant tumors (n = 22). Radiographically, the volume of hemorrhage was comparable with, or larger than the volume of the original tumor in all cases. We found that 85% of the bleeds (n = 22) occurred within the first 24 h after surgery. Only three patients were stable enough to manage conservatively, whereas in 19 cases, surgical revision and evacuation of the intraventricular hematoma with resection of residual tumor were performed within 24–48 h postoperatively. In addition, four patients experienced second rebleeding on postoperative days 3–5 (after the first revision). These patients were operated on again within 4–6 days after craniotomy for tumor removal. In the group of 19 patients who had to undergo an emergent evacuation of the hematoma due to significant mass effect, brain shift and/or herniation, two patients died and two were discharged in persistent vegetative state.

Further analysis of hemorrhagic complications and their relationship with the type of approach and location of the tumor showed that hematomas most commonly occurred after transcortical approach (16 of 76 patients/64%), followed by combined approach (2 of 4 patients/50%), and less commonly, after transcallosal approach (8 of 40 patients/31%). Postoperative hematomas were most common in group C (3 of 11 patients/27%), followed by Group A (9 of 43 patients/21%); Group D (3 of 17 patients/18%); and Group B (8 of 54 patients/15%).

Subdural collections

Three patients developed acute postoperative subdural hematomas and one patient was diagnosed with subdural

Table 5: Location of the tumor, surgical approach, and extent of resection.

Surgical approach	Group A: anterior tumors (*n*=43)		Group B: medial (*n*=54)		Group C: posterior (*n*=11)		Group D: extensive (*n*=17)		Total
	Tot (GTR/STR)	PR	Tot (GTR/STR)	PR	Tot (GTR/STR)	PR	Tot (GTR/STR)	PR	
Anterior transcallosal	8 (5/3)	4	20 (11/9)	8	-	-	-	-	40
Anterior transcortical	20 (12/8)	11	20 (11/9)	6	6 (3/3)	3	6 (1/5)	4	76
Posterior transcortical	-	-	-	-	1 (1/0)	1	1(0/1)	2	5
Combined	-	-	-	-	-	-	3 (1/2)	1	4
Total	28 (17/11)	15	40 (22/18)	14	7 (4/3)	4	10 (2/8)	7	125

GTR: Gross total resection, STR: Subtotal resection, PR: Partial resection

hygroma 8 days after craniotomy. None of them required surgical evacuation.

Impaired CSF circulation and absorption

Hydrocephalus

Obstructive hydrocephalus was noted in 25 (20%) patients. In 80% of the cases progressive worsening of ventriculomegaly occurred acutely, on postoperative days 2 and 3. In 19 cases, the external drain was placed. Consequently, 14 of the 19 patients with external drain ended up with ventriculoperitoneal shunt. Shunting procedures for obstructive hydrocephaly were performed in a delayed fashion (10–35 days after the first surgery), once CSF had become visually clear. In 5 of 14 patients who underwent shunt placement, the procedure was performed on postoperative days 30–35 due to meningitis, which was treated with IV vancomycin until CSF analysis became normal and cultures negative. We did not observe any mortality or significant morbidity related to CSF infection.

Interestingly, although we did not establish any clear correlation between the extent of resection and development of hydrocephalus, over 50% of hydrocephalus cases occurred after STR and PR of the tumor. In 15 patients after GTR, the occlusion was at the level of the foramina of Monro due to direct obstruction by the blood clots. In 10 patients after PR, the obstruction was related to the presence of both, "strategically placed" residual tumor tissue in the vicinity of the foramina of Monro and blood clots. Hydrocephalus developed in 17 patients after transcortical approach, five patients after transcallosal approach, two patients after combined approach, and in one case after tumor resection through the superior parietal lobule.

Entrapment of the occipital and/or temporal horns

A unique complication was encountered in Group C patients (with posteriorly located tumors): the entrapment of the occipital and/or temporal horns. This problem occurred in a total of 7 of 11 patients in Group C. Once the high risk of entrapment was realized, all seven subsequent patients were prophylactically stented to establish connection between the posterior-inferior aspects of the lateral ventricles and the rest of the ventricular system.

In three of seven patients, the intraventricular stents extended through the foramina of Monro and the aqueduct [Figure 3]. Intraventricular stenting was performed with utilization of the ventricular catheter, trimmed to achieve desired length. In all cases, surgeons added several side holes to minimize the chances of occlusion. The stents were not anchored. There were no incidents of stent occlusion, malfunction, or migration. None of the patients after stenting required shunt placement or any other type of revision surgery.

Neurological outcome

All postoperative patients experienced early neurological and cognitive worsening to some extent. In half of the patients (n = 62, 50%), the symptoms were mild, included increased somnolence, decreased level of activity, sensorimotor agitation, and anxiety, and improved within the 1st postoperative week. The other 63 patients had a more complicated course, characterized by significant disorientation, attention deficit, global amnesia, short-term memory deficits, and perceptual motor and social cognition problems. In 22 (of 63 patients in this group), the neurocognitive problems remained permanently. All 28 patients (22%), who presented with neurocognitive deficits before surgery, were found to have further neurocognitive decline [Table 6]. Postoperative GCS score distribution among the alive patients was 14–15 in 51 cases, 12–13 in 62, and 9–11 in seven patients.

Analysis of the postoperative complications and tumor location revealed the following relationships: patients with anteriorly located lesions (type A and/or B) were more likely to have memory and cognitive disturbances, whereas patients with posteriorly located and extensive tumors (type C and/or D) were prone to have signs of pyramidal tract damage (i.e. hemipares) and speech disturbance. Among the 11 patients with posteriorly located tumors (types C), partial

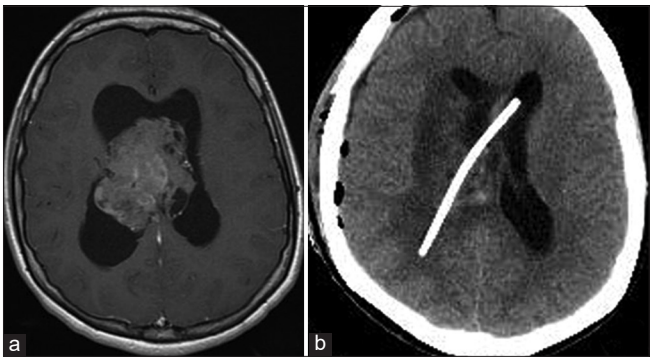

Figure 3: (a) Preoperative MRI (T1 with contrast) showing the tumor involving both lateral ventricles; (b) postoperative brain CT after resection of recurrent neurocytoma and stenting of the left lateral ventricle: the longer stent extends from the occipital horn of the right lateral ventricle to the frontal horn on the left; the shorter stent connects the right frontal horn and the body of the lateral ventricle. MRI: Magnetic resonance imaging, CT: Computed tomography.

hemianopsia was diagnosed in two. After surgery, these patients and two others developed complete hemianopsia on formal visual field evaluation [Table 7].

Mortality

Five patients (4%) died in the early postoperative period. All deaths were related to hemorrhage into the residual tumor, with resultant mass effect and compression of the brainstem. Two patients underwent revision within 24 h of surgery. Although some improvement of the brainstem function was noted after decompression (i.e. hemodynamic stabilization), their neurological status remained extremely poor. In one patient, postoperative hemorrhage was complicated by sepsis and subsequent multisystem organ failure that ultimately lead to expiration.

Tumor recurrence

CN's are slowly growing tumors. Therefore, only patients with long-term follow up were selected for analysis of data on recurrence. After surgical treatment from 2008 to 2018, 84 patients with CNs were followed for 2–10 years (mean 6 years). Of those 84 patients, 26 (30.2%) were found to have tumor recurrence within 12–96 months after surgery; in 19 cases after incomplete resection, and in seven cases after GTR. Two-year progression-free survival (PFS) was documented in 94% and 5-year PFS in 73% of the patients [Figure 4].

The multivariate analysis of factors potentially affecting the recurrence rate revealed that the EOR and the range of Ki-67 proliferative index were associated with the most significant impact [Figure 5 and Table 8]. Five-year PFS was 90% after GTR and only 65% after subtotal and partial resection ($P < 0.05$). In patients with Ki-67 index <5%, 83% experienced 5-year PFS versus only 40% in patients with Ki-67 index ≥5% ($P < 0.05$). The Kaplan–Meier estimator curve illustrating the PFS in relation to Ki-67 index is provided in [Figure 6].

Table 6: Clinical presentation of 125 patients with CN before and after microsurgery.

Clinical manifestation	Before surgery	After surgery
Memory decline	40 (32%)	62 (50%)
Other psychiatric and cognitive disturbances	28 (22%)	32 (27%)
Signs of increased ICP	78 (62%)	-
Upper motor neuron signs (hemiparesis and hyperreflexia)	15 (12%)	22 (18%)
Double vision due to abducens nerve palsy	2 (1.7%)	4 (3.6%)
Visual field loss	2 (1.7%)	4 (3.6%)
Speech disorders	-	11 (9%)
Overall number of patients	125	120 alive patients

ICP: Intracranial pressure, CN: Central neurocytoma

Table 7: Comparison of the nature of postoperative complications with tumor localization and lateralization.

Clinical presentation	Group A: anterior (*n*=43)	Group B: medial (*n*=54)	Group C: posterior (*n*=11)	Group D: extensive (*n*=17)
Memory decline	23	27	2	10
Other psychiatric and cognitive disturbances	6	14	1	11
Upper motor neuron signs (hemiparesis and hyperreflexia)	0	7	7	8
Double vision due to abducens nerve palsy	0	0	0	4
Visual field loss	0	0	2	2
Speech disorders	0	2	4	4

Management of recurrent tumors

Continuous observation

Of 26 patients with recurrent CN's, eight cases were managed conservatively with serial imaging studies because the documented increase in size of the recurrence was ≤2 mm in each case and Ki-67 index ≤5%. None of the patients in this subgroup showed any further increase in the tumor size.

Table 8: The multivariate analysis of factors potentially affecting the recurrence rate: the EOR and the range of Ki-67 proliferative index were associated with the most significant impact.

Covariate	b	SE	Wald	*P*	Exp (b)	95% CI of Exp (b)
Ki_67	2.3250	0.4337	28.7427	<0.0001	10.2265	4.3710–23.9262
Max_diameter	0.8698	0.4062	4.5850	0.0323	2.3864	1.0764–5.2909
EOR	1.2911	0.4115	9.8430	0.0017	3.6369	1.6234–8.1476

EOR: Extent of resection, SE: Standard error, CI: Confidence interval

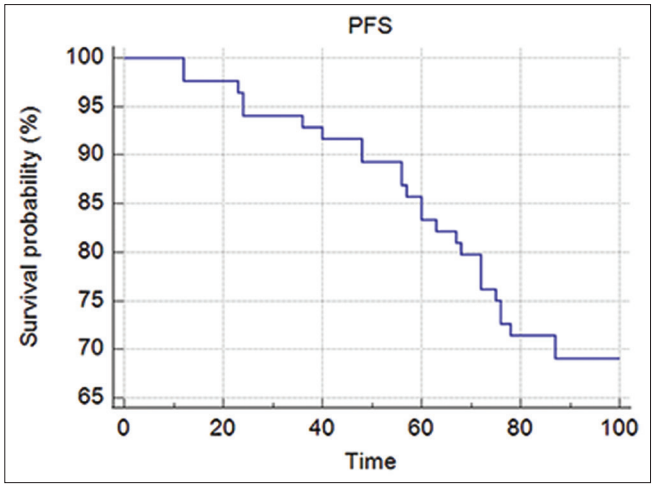

Figure 4: Progression-free survival.

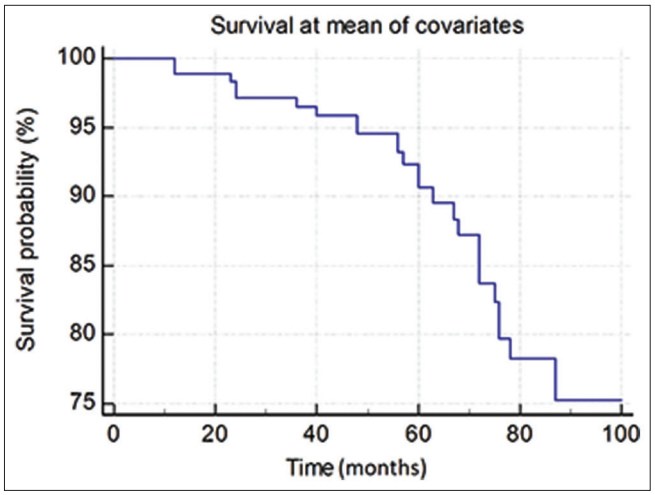

Figure 5: Survival function at mean of covariates.

Repeat surgical resection

Seven patients were diagnosed with significant postoperative radiographic tumor progression associated with mass-effect, hydrocephalus, and/or development of neurological deficits. They subsequently underwent repeat craniotomy for resection of recurrence. In five of these cases, GTR was achieved, 82% of patients in this subgroup improved

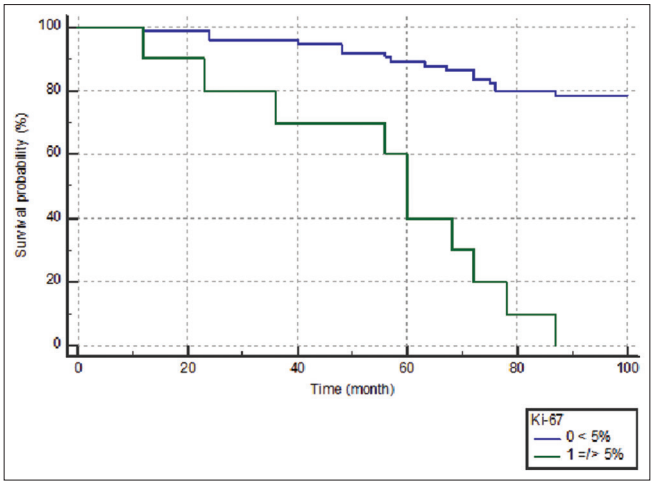

Figure 6: Progression-free survival and Ki-67 values (P<0.05).

neurologically and cognitively or remained unchanged. None of the patients experienced surgical complications. The authors impression was that repeat surgeries were less technically challenging, as the lesions were smaller than in the first surgery and tended to be less vascular. In all cases, the lesions were well defined with clearer borders than in the original procedures. The images of one of the illustrative cases are depicted in [Figure 7].

Radiation therapy

Eleven patients were found to have significant interval enlargement of the tumor on follow-up MRI. They did not have evidence of increased ICP/mass effect, or impaired CSF circulation/hydrocephalus. These patients were felt to be good candidates for radiation therapy (XRT). The choice of XRT methods depended on the volume of residual tumor and the extent of tumor spread in the ventricular system. The XRT techniques are summarized in [Table 9].

All 11 patients with recurrent CN treated with XRT demonstrated satisfactory results over the mean follow-up of 2.5 years. The tumor decreased in size in 4 patients and remained stable in 7 [Figure 8].

None of the patients had evidence of radiation-induced damage to the surrounding tissues on follow-up MRI. Eight

Table 9: XRT techniques, dosage and fractionation used in patients with recurrent CN.

Type of XRT	Tumor Volume, cm^3	Mean Volume, cm^3	Total radiation dose, Gy	Marginal dose, Gy	Fractionation	XRT machine	Number of patients
SRS radiosurgery	0.5–4.5	0.3	-	10–16	Single fraction	Cyber Knife®	2
						Gamma Knife®	1
Hypofractionated XRT	2.7–11.7	8.8	21.0–27.5	-	7 Gy × 3; 5.5 Gy × 5	Cyber Knife®	3
Standard fractionated XRT	12.0–62.0	35.0	54	-	1.8 Gy × 30; 2 Gy × 27	Novalis®	3
						TrueBeam®	2

XRT: Radiation therapy, CN: Central neurocytoma, SRS: Stereotactic radiosurgery

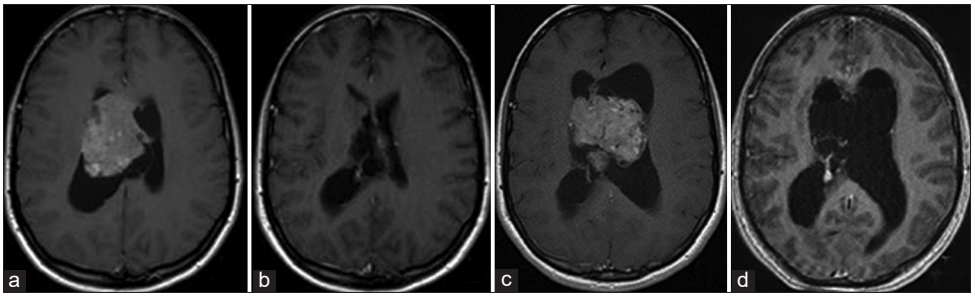

Figure 7: (a) Preoperative MRI of the tumor with Ki-67 index >5% (T1 with contrast); (b) T1 MRI with contrast 6 months after surgery, with evidence of GTR of the tumor; (c) T1 MRI with contrast 3 years after surgery showing large recurrent tumor; (d) immediate postoperative T1 MRI with contrast demonstrated GTR of the lesion. MRI: Magnetic resonance imaging, GTR: Gross total resection.

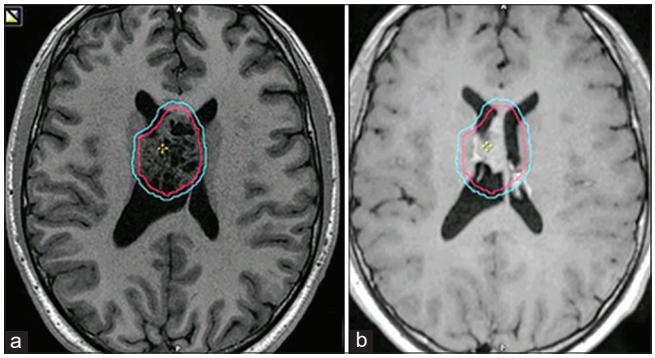

Figure 8: Illustrative case of the XRT plan in a patient after standard fractionated treatment to the recurrent tumor (a), total dose of 57.6 Gy; T1 MRI 12 months after XRT demonstrated significant decrease in size of the tumor (b) XRT: radiation therapy, MRI: magnetic resonance imaging.

patients treated with XRT developed clinically significant problems with CSF circulation and/or absorption. In two cases of communicating hydrocephalus shunt placement was performed 6 and 12 months after XRT respectfully. The remaining six patients developed entrapment of the temporal and/or occipital horns of the lateral ventricles. This complication was observed when the tumor extended into the posterior body and/or trigonum of the lateral ventricles. The ventricular entrapment was discovered on neuroimaging studies between 6 and 18 months after XRT. These patients were managed with either endoscopic or open microsurgical membrane fenestration or lysis of intraventricular adhesions with successful restoration of normal CSF circulation in all cases [Figure 9]. We did not observe any cases of pseudoprogression.

DISCUSSION

CN is biologically benign, slowly growing neoplasms with an overall favorable chance of survival. CN is most common in young adults, potentially most productive age group (between ages of 20 and 40 years).[20,36,54]

Our literature search identified close to 500 reported cases of CN. The largest clinical series to date was by Rades and Schild with 438 cases (365 adults and 73 pediatric patients). Interestingly, 87 patients in this series were found to have atypical CN.[43] Other large series included 92 patients by Qian *et al.*, 84 and 115 patients by Konovalov *et al.*, and 63 cases by Wang *et al.*[24,25,41,51]

These series are summarized in [Table 10].

Early reports including our recent publication described high rates of complications and low resection rates.[24] In the original series of Hassoun *et al.* and subsequent report by Nishio *et al.* only 50% of the patients had GTR.[19,38] In the

Table 10: The most representative series of patients with neurocytomas and the results of surgical treatment.

Author	Year	*n*	Radical resection	Hydrocephalus	Shunt	Postoperative neurologic symptomatology	Mortality
Qian *et al*., 2012 [41]	2012	92	65 (71%)	62%	14%	40%	3 (2.5%)
Konovalov *et al*., 2006[24]	2006	84	11+48 (13+58%) (GTR+STR)	33 (40%)	14 (17%)	17 (21%)	10 (12%)
Wang *et al*., 2018[51]	2018	63	34 (54%)	25 (40%)	-	14 (22%)	5 (8%)
Chen *et al*., 2016[8]	2016	32	29 (91%)	3 (9%)	1 (3%)	6 (19%)	0
Kim *et al*., 2013[23]	2013	58	42 (88%)	10 (17%)	-	14 (24%)	1 (2%)
Hallock *et al*., 2011[17]	2011	19	10 (53%)	-	-	16%	5%
Present series	2020	125	45+40 (68%) (GTR+STR)	25 (20%)	14 (11%)	22 (18%)	5 (4%)

GTR: Gross total resection, STR: Subtotal resection

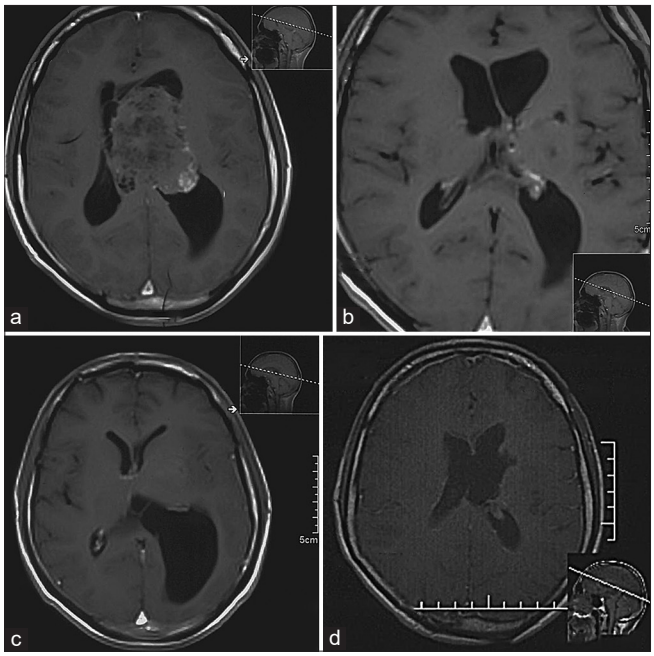

Figure 9: (a) CN involving both lateral ventricles before and (b) after surgery; (c) entrapment of the occipital horn of the left lateral ventricle (6 months after surgery); (d) follow-up MRI 6 months after open microsurgical lysis of intraventricular adhesions, showing successful interval decompression of the trapped ventricle. CN: central neurocytoma, MRI: magnetic resonance imaging.

last decade, however, a higher number of patients underwent more radical resections, ranging from 71% to 91% with acceptable morbidity.[8,23,41]

This was probably due to earlier detection of tumors by neuroimaging, improvements in microsurgical techniques and introduction of routine image-guidance and intraoperative MRI.[2] Nowadays, maximal safe resection has become the standard first line of treatment in patients with CN. The main objectives of surgery are to provide tissue for diagnosis, decompress the brain and treat hydrocephalus.[34,47]

Challenges related to the tumor location and size

CN is characterized by their deep intraventricular location and ample blood supply from the choroidal arteries. Other factors include their large size at presentation and early involvement of such critical structures as thalami and fornices.[8,19,23,26,29,34,36,38,51] The current consensus is that aggressive resection is not recommended if the tumor infiltrates the fornices, thalami, or encases the large intraventricular veins.

Many authors noted strong correlation between the EOR and tumor recurrence.[1,39,42,50] However, due to the mechanism of the tumor growth with wide infiltration of the ventricular walls, GTR might be challenging in many cases, and safely possible only in smaller and better circumscribed lesions.

Our GTR rate is lower than in the largest published series up to date by Chen *et al*.[8] It is felt to be mainly due to larger size of the lesions at presentation in our report. In the present study, 69 of 125 patients (55%) presented with large or giant tumors. The mean tumor size was 5.2 cm, compared to 4.8 cm reported by Chen *et al*. We demonstrated a very strong relationship between the size and the extent of resection of the tumor. GTR/STR was achieved in 100% of patients with tumors <2.0 cm in largest diameter, in 69% of tumors measuring 2–4 cm, in 66% of tumors measuring 4–6 cm, and in only 50% when lesions were larger than 6 cm. In five cases, we utilized endoscopic assistance, primarily to visualize residual tumor in the ventricular system. Despite successful use of the 0° and 30° scopes and adequate magnification, in three cases the surgeons failed to differentiate tumor from normal tissue. Overall, our experience with endoscopic assistance was not felt to be clearly advantageous.

Although aggressive resection should be an ideal goal, Leenstra *et al*. reported no difference in overall outcome in patients after GTR and STR.[26] Other authors recommend a more conservative resection combined with stereotactic radiosurgery (SRS) as a method of choice to minimize the treatment related risks. The combined approach provides excellent long-term control of this biologically low-grade neoplasm.[20]

Choice of the approach

The choice of the surgical approach depends on three factors: (1) location of the tumor, (2) size, and (3) extent of hydrocephalus.[20,31,41] Transcortical approach through the premotor cortex was used in the majority of our patients. This approach is advantageous in cases associated with significant ventriculomegaly and asymmetrically located tumors occupying large portions of the lateral ventricles. Transcallosal approach is preferable in centrally located tumors in the anterior parts of the lateral ventricles. In rare cases of giant CN, a combined approach might be necessary. Various combinations of transcallosal and transcortical and bilateral transcortical approaches can be utilized. Thorough analysis of preoperative imaging studies can be very helpful in selecting the best approach. Kim *et al*. found no difference in the extent of resection and the actuarial overall survival between the surgical approaches.[23] However, there was a difference in functional outcomes, especially in the risk of cognitive deficits and seizures, that were more common after transcortical resection. Therefore, if feasible, interhemispheric transcallosal route should be the approach of choice, as it provides the least disruptive anatomical corridor associated with smaller risk of approach related complications.[8]

The ipsilateral interhemispheric posterior parieto-occipital approach and the posterior interhemispheric transfalcine transprecuneus approach can be utilized to resect tumors located in the trigonum and the occipital horn of the lateral ventricle. These approaches provide a wider surgical corridor, which leads to minimal retraction, sparing of the optic radiation, temporal, and parietal cortices and early access to the arterial feeders. The disadvantages include significant ipsilateral hemispheric retraction; long working distance; and risk of injury to contralateral hemisphere.[5,11,30] To prevent damage to the critical visual fibers in patients with very posteriorly located CN, the ipsilateral interhemispheric posterior parieto-occipital and the posterior interhemispheric transfalcine transprecuneus approaches can be considered a reasonable alternative to the trans-superior parietal lobule approach.[40]

Prevention and management of complications

Most CN series report high incidence of complications, including hemorrhage, obstructive hydrocephalus, neurological deficits, seizures, and cognitive deficits.[8,19,22-24,38,45,51] Lubrano *et al*. reported 66% complication rates in their multicenter study. The main causes of postoperative disability were motor deficits and/or aphasia, memory problems (29%), and hydrocephalus (26%).[29] Higher complication rates in early publications might be related to larger size of the tumor, likely due to delayed patient diagnosis in the previous decade.[15,19,36,38,45] In our series, most significant complications were associated with hemorrhage and/or hydrocephalus. Postoperative hemorrhage is probably the most life-threatening complication. We agree with the observation of Chen *et al*. that difficult hemostasis and frequent hemorrhagic complications in CN can be explained on the basis of abundant blood supply with presence of multiple pathologic vessels without smooth muscle cells and well-developed network of cavernous venous structures.[8] Hematomas typically form in the residual tumor and frequently require revision of craniotomy and evacuation. Eighteen of the 26 patients with life-threatening hematomas in our report were operated on emergently. The morbidity and mortality in this group of patients were very high: two of them died and two were discharged in persistent vegetative state. We also noted that none of the patients operated on in a delayed fashion, that is, 4–6 days after the hemorrhage, or after the first emergent revision, died. In fact, all of them improved after hematoma evacuation. These findings support our previous observation that delayed evacuation of hematoma (i.e. after stabilization of the clot) may be beneficial in selected stable patients and can lead to somewhat easier hemostasis.[24] Analysis of the hemorrhagic complications revealed that postoperative hematomas occur twice as frequent after transcortical approach, compared to transcallosal. This finding might be related to the fact that transcortical approach is typically selected for larger tumors that also tend to be more infiltrative with more robust blood supply from the surrounding periventricular white matter. We did not find any correlation between the occurrence of hematoma in the resection bed and location of the tumor. Chaves *et al*. reported resection of a giant pediatric CN after successful preoperative embolization, which supposedly resulted in smaller blood loss.[7] The patients in our series did not receive preoperative embolization.

Obstructive hydrocephalus is another dangerous complication, especially if develops acutely in the early postoperative period. Soliman suggested that tumor remnants and blood clots are the main causes of obstruction of the CSF pathways.[47] We concur with this observation. The incidence of early postoperative hydrocephalus in the current study (20%) is almost half the incidence in the historic series and comparable to the results reported in the modern studies.[8,19,38,51] Seven patients in this series were found to have entrapment of the occipital and/or temporal horns. All these patients belonged to Group C, harboring

posteriorly located tumors. Prophylactic intraventricular stenting appears to be beneficial in eliminating the risk of entrapment and subsequent shunting. The authors consider stenting a more physiological and less invasive procedure, as the CSF flows across the stent in both directions, as opposed to unidirectional flow toward the shunt, and then outside of the cranium. This is probably a pathophysiological basis for essential absence of cases of stent occlusion in this series. However, if CSF resorbtion is impaired, stenting alone may be insufficient. The authors acknowledge the small number of patients who underwent stenting and recommend a judicious use of this technique in selected cases of large posteriorly located tumors with intraventricular obstruction.

Postoperative hydrocephalus was twice as common after transcortical resection (22.3%) as after transcallosal resection (12.5%). The difference is likely also related to the larger volume and extent of ventricular involvement in patients undergoing transcortical resection. In addition, transcallosal approach allows better visualization and decompression of both foramina of Monro and the third ventricle.

Long-term management

Between 2008 and 2016, the authors utilized the 2008 World Health Organization (WHO) classification. After 2016, the new WHO classification has been used.[27,28] Ki-67 index was established in all patients to determine proliferative activity. Ki-67 index has become a very useful parameter in prognostication and evaluation of tumor response to treatment.[10,25,48] In our series of 25 patients with disease progression, 14 (56%) had Ki-67 index ≥5%. This factor was found to be statistically significant on multivariate analysis ($P < 0.05$). Conversely, low Ki-67 index (<5%) combined with aggressive tumor resection was found to be associated with longer PFS.

Patients with recurrent CN could be considered candidates for repeat microsurgical resection or XRT. Seven of 16 patients in this series, with radiographic and symptomatic progression underwent repeat microsurgical resection. Most of them (86%) had a GTR of the tumor with good results, which proves that repeat surgical resection remains safe and effective long-term management strategy.

XRT was reserved for the patients with radiographic progression without evidence of increased ICP and/or hydrocephalus. The high efficacy of various forms of XRT was demonstrated in several publications with adequate long-term tumor control rate exceeding 80%.[9,48] The largest series of CN treated with XRT up to date, is a report of 42 consecutive cases treated with SRS, by Karlsson *et al*. in 2012.[21] The majority of their patients underwent SRS to the tumor remnants after STR. About 91% and 81% tumor control rates were achieved at 5 and 10 years, respectively.[3,4,12,14] The results of SRS in patients with CN's are summarized in [Table 11].

Our data and review of the literature demonstrate that the use of various XRT modalities in recurrent CN cases is safe and associated with high tumor control rates. Rare cases of hemorrhage, edema, and radiation necrosis are typically self-limited and not associated with major negative clinical sequela. In patients with obstructive hydrocephalus, who would otherwise be considered good candidates for XRT, surgical CSF diversion (using microsurgical approaches, shunting, and/or stenting) should be performed before irradiation. Although we did not observe tumor pseudoprogression in our series, this condition was described in the literature. Pseudoprogression is associated with benign course and managed conservatively.

Table 11: The results of SRS in patients with CN's in the literature.

Author	*n*	Type of equipment	V (ml)	Max dose (Gy)	Follow-up (months)	Tumor control rate (%)	Complications
Yamanaka *et al*., 2016 [52]	36	Gamma Knife®	4.9	15.0	54.5	94	Hemorrhage-2; Radiation necrosis-1
Monaco *et al*., 2015[34]	8	Gamma Knife®	5.5	14.6	63.3	100	None
Kim *et al*., 2013[22]	20	Gamma Knife®	11.0	15.4	103	85	Edema-1
Karlsson *et al*.,2012[21]	42	Gamma Knife®	12.0	13.0	73	95	None
Genc *et al*., 2011[14]	22	Gamma Knife®	13.4	16.4	36	95	Hemorrhage-1
Yen *et al*., 2007[53]	7	Gamma Knife®	6.0	16.0	60	100	Alopecia-1, Edema-1, Radiation necrosis-1
Martin *et al*., 2003[32]	4	Novalis®	3.2	16.5	33	100	None
Anderson *et al*., 2001[3]	4	Gamma Knife®	7.0	17.0	17	100	None
Bertalanffy *et al*., 2001[4]	3	Gamma Knife®	3.9	12.8	60	100	None
Cobery *et al*., 2001[12]	4	Gamma Knife®	14.8	10.5	44	100	None

SRS: Stereotactic radiosurgery, CN: Central neurocytoma

Rarely, CN can spread along the CSF pathways. Goyal *et al*. described a case of periventricular atypical neurocytoma after STR. The patient in this report underwent adjuvant focal radiotherapy and subsequently developed local and spinal leptomeningeal recurrence treated with salvage chemotherapy. The disease continued to progress, and the patient was offered comfort measures.[16] Fortunately, we did not observe this phenomenon in our series.

A literature review of 19 atypical cases with malignant behavior showed MIB-1 LI above 2% in 12 of 14 cases, and above 10% in those progressing within a year.[35] Seventeen patients had craniospinal dissemination. However, craniospinal irradiation was given to only three patients after documented craniospinal dissemination.[6,37,49] Rades and Schild, after an extensive review of 438 patients, including 87 atypical CNs, with a minimum follow-up of 1 year, gave treatment recommendations for various CN subgroups. No adjuvant therapy is required after GTR. After STR, adjuvant radiation improves survival in atypical lesions in adults but not in children, while local control improves across all subgroups. Adults need doses exceeding 54 Gy while doses above or below 50 Gy have comparable outcomes in children. Authors recommended adjuvant RT doses of 50 Gy in children, 50–54 Gy in typical CN, and 56–60 Gy in atypical CN.[43]

In addition to leptomeningeal dissemination, other unusual cases of CN spreading all the way down into the fourth ventricle[44] and association of CN with other neoplasms, such as pituitary adenoma[46] have been described, none of which occurred in our patients.

Limitations of the study and future directions

Our study has several limitations: (1) the retrospective nature of the study introduces the possibility of selection bias and biased post hoc data analysis, especially when most surgeries were performed in one institution by the senior neurosurgeon; (2) since utilization of the intraoperative MRI was suggested to be associated with higher extent of resection, it could be advantageous to use this technique to better evaluate its impact (if any) on the surgical outcomes.

Most of these limitations could be successfully addressed in future prospective cohort studies. However, given the infrequency of this diagnosis, conduction of the large prospective studies of CN may encounter significant logistical and temporal difficulties. Therefore, creation of prospective multi-institutional databases could become a more practical approach. Continuous refinement of microsurgical techniques, utilization of new technology, such as intraoperative MRI and judicious use of multimodality treatment may lead to further improvement in the outcomes, reduce morbidity and mortality.[8,17,23,41,51]

CONCLUSION

CN remains surgically challenging lesion. The results of this series are comparable to the results reported in previous studies. Although high rates of GTR or STR can be expected, the mortality and morbidity remain significant even in the modern neurosurgical era, regardless of the approach. Large size of the tumor, presence of hydrocephalus and preoperative neurological or cognitive deficits are associated with lesser extent of resection and poorer outcome. Prophylactic intraventricular stenting in patients with large posteriorly located tumors with hydrocephalus may prevent ventricular entrapment and shunting. Early diagnosis and continuous refinement of microsurgical techniques along with judicious use of multimodality treatment may positively impact the outcomes.

Despite an overall favorable prognosis, up to a third of the patients experience disease progression and recurrence. The main risk factors for recurrence are presence of residual disease and Ki-67 index over 5%. Recurrent symptomatic tumors should be treated surgically, whereas asymptomatic progression can be managed with SRS. Both treatment modalities are associated with low risk of complications and high tumor control rates.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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