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Intraventricular neurocytomas

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Background

Epidemiology and clinical presentation

A review of 385 reported neurocytoma cases [1–96] shows that, in general, central neurocytomas (CNCs) are well-differentiated intraventricular tumors that affect young adult men and women equally. Most commonly, CNCs occur in the anterior portion of the lateral ventricle around the foramen of Monro and can attach to either the septum pellucidum or the lateral wall of the ventricle [19,58,71,97]. Whereas 75% of cases occur in patients between the ages of 20 and 40 years [15,28,98], CNC occurring in patients 18 years of age or younger [3,5,14,19,32,36,42, 44,58,68,69,71,74,76,78,88,94] and in patients 50 years of age or older [3,4,7,19,40,44,45,53,69, 76,78,93,99] have been reported. The term *extraventricular neurocytoma* is used to describe histologically similar tumors not found in intraventricular locations [43]. Extraventricular locations include the occipital lobe [8,22,54,72], parietal lobe [3,22,54], frontal lobe [8,22,24,58,96], temporal lobe [8,9,22,58], thalamus [8,72,100], hypothalamus [8,22,69], cerebellum [7,17], pons [77], spinal cord [3,12,18,44,47,79,82,83], cauda equina [81], retina [52], and pelvis [101] as well as mature cystic teratoma of the ovary [102]. Cases of neurocytoma have previously been reported as intraventricular oligodendroglioma, differentiated cerebral neuroblastoma [34,95], primary cerebral neuroblastoma [64,103,104], and intraventricular neuroblastoma [105].

A review of the available data from clinical reports has provided some insight into common signs and symptoms associated with CNC. The clinical presentation usually involves signs and symptoms of increased intracranial pressure (ICP) of a few weeks to several months as a result of noncommunicating hydrocephalus. As shown in Table 1, reported symptoms include headache, visual disturbance, motor disturbance, altered mental status, sensory disturbance, seizure, dizziness, and nausea or vomiting without associated headache. Not all reported cases of CNC include a detailed clinical history, however. Table 1 also reports signs elicited on physical examination; however, this analysis is limited by the lack of detailed information in some reports. Other authors have reported headache, nausea and vomiting, and visual disturbance as the most common symptoms, with papilledema present in most patients [46,69]. Signs like ataxia [32,42, 46,58,69,94], altered level of consciousness [16, 46,62,69,87,91], hemiparesis [16,32,40,46,63], and seizures [3,8,22,42,46,58,63,89] were less common. Patients presenting with intraventricular hemorrhage (IVH) [12,23,37,62,76,84,91] and sudden death [4] have also been reported. In addition, many cases have been discovered incidentally in patients undergoing neuroimaging for unrelated reasons [15,22,32,58,87,91]. Neurologic examination often yields no focal neurologic findings other than those caused by increased ICP [46].

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Table 1
Signs and symptoms

Signs and Symptoms	No.	%
HA	178/202	88.1
N/V without HA	2/202	1.0
Dizziness	4/202	2.0
Visual disturbance	51/202	25.2
Altered mental status	22/202	10.9
Seizure	9/202	4.5
Motor disturbance	40/202	19.8
Sensory disturbance	14/202	6.9
Papilledema	46/51	90.2

Abbreviations: HA, headache or reported as signs and symptoms of increased intracranial pressure; N/V, nausea and/or vomiting without headache. Dizziness includes dizziness or vertigo; visual disturbance includes blurring, diplopia, decreased acuity, intermittent vision loss, photophobia, blindness, or abducens nerve palsy; altered mental status includes altered level of consciousness, loss of memory, apathy, disorientation to mild dementia, loss of concentration, mood swings, syncope, personality change, depression, psychosis, irritability, or mental change; motor disturbance includes spasticity of extremities, hemiparesis, hemiplegia, atrophy, clonus, hypotonia, increased DTR, imbalance, left hemisyndrome, gait disturbance, ataxia, loss of balance, weakness, pyramidal signs unsteady gait, or gait dysfunction; sensory disturbance includes pain, paresthesia, left hemisyndrome, hemihypaesthesia; seizure includes all types of seizures and papilledema includes unilateral and bilateral types. *Data from* references [1–8,10,11,14,15,18, 23,26,27,29,31,33,34,39,41,42,45,56–58,62–66,68,70,71, 74–76,82,85,87,89,91,93,95,96,99,104,108,114, and 118].

Neuroimaging

CT/MRI/angiography

Appropriate diagnostic imaging studies for patients with CNC may include CT, MRI, or angiography. Relative to the brain parenchyma, CNC appears as a well-circumscribed, isodense, hyperdense, or mixed isodense/hyperdense mass with slight to moderate contrast enhancement on CT examination. Noncommunicating (obstructive) hydrocephalus is often present. Calcifications and cyst-like areas may also be seen on CT images. Compared with the surrounding white matter, T1-weighted and proton-weighted images typically appear isodense. T2-weighted images appear heterogeneous with areas of calcification and cysts appearing hyperintense and the tumor appearing isointense to hyperintense. Variable enhancement with gadolinium is common, reflecting the heterogeneous vascularity of CNC (Fig. 1). For tumor localization and visualization of the attachment site, MRI is preferred [15,46,97,106]. Angiography has also been used to assess vascularity; however, the results are nonspecific, ranging from avascular [3,36,40,71] to highly vascular [40,46,53,85]. Feeding arteries are reported to include anterior choroidal [1,15,40, 53,71,76], posterior choroidal [1,31,40,53,57,87], lenticulostriate [40,53], and branches of pericallosal arteries [40,53].

Magnetic resonance spectroscopy/single photon emission computed tomography/positron emission tomography

Magnetic resonance spectroscopy (MRS) [33,35,38,54,94], single photon emission computerized tomography (SPECT) [35], and positron emission tomography (PET) [35,53,85] have all been used in preoperative evaluation. The experience using these modalities is limited, however, and there is no consensus on the characteristics of CNC. Many investigators suggest that prominent glycine and choline with low N-acetyl aspartate (NAA) peaks are characteristic markers of CNC on MRS [33,38,94]. Others have found an increased choline peak and decreased NAA signal but failed to consistently find the 3.55-ppm peak characteristic of glycine [35,54]. SPECT analysis shows increased uptake of ^{201}T on delayed images, indicating a high activity of sodium potassium triphosphate on cell membranes. PET analysis has demonstrated decreased O_2 extraction fraction, cerebral metabolic rate of O_2, and cerebral metabolic rate of glucose in CNC. Cerebral blood flow and blood volume were increased in three of four cases, correlating with the angiographic findings in these patients [53]. The authors suggest that CNC metabolism is more oxidative than that of other brain tumors and that a decreased rate of glucose metabolism may predict a favorable prognosis [52]. Further study is necessary to determine whether these combined findings are truly characteristic of CNC.

Pathologic examination

After reviewing such factors as presenting symptoms, patient age, and location of the tumor, a focused differential diagnosis for CNC includes subependymoma, astrocytoma, ependymoma, intraventricular meningioma, intraventricular oligodendroglioma, and subependymal giant cell astrocytoma [43,46,58,79,97]. Adding information from imaging studies usually narrows the differential diagnosis to intraventricular meningioma,

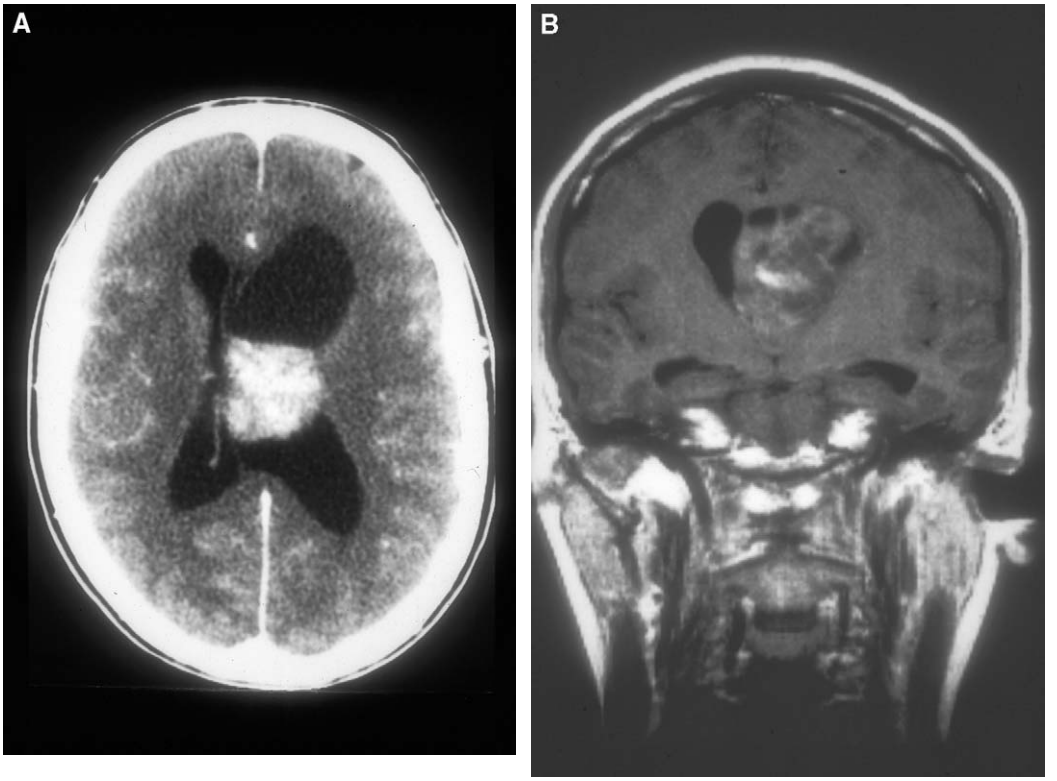

Fig. 1. (*A*) Axial CT image with contrast. (*B*) Contrast-enhanced coronal T1-weighted MRI. (*C*) Axial T1-weighted MRI. (*D*) Sagittal T1-weighted MRI.

ependymoma, and CNC. A definitive diagnosis requires tissue analysis with light microscopy, immunohistochemistry, and, in some cases, ultrastructural examination.

Light microscopy

On light microscopy, CNC appears similar to oligodendroglioma (Fig. 2). Clinically, they can be distinguished based on their location. CNCs are typically intraventricular and centrally located, whereas oligodendrogliomas arise more peripherally. Light microscopy shows a honeycomb architecture with uniform small round cells with central nuclei and clear cytoplasm dispersed within a fibrillary stroma. The chromatin typically has a salt and pepper appearance. Microcalcifications or microcysts may be present, and mitoses, endothelial proliferation, and necrosis are rare [15, 43,46,98,106]. The presence of neuroblastic rosettes and nuclei with a ganglionic appearance is suggestive of neurocytoma; however, immunohistochemistry or electron microscopy is required to confirm the diagnosis [46].

Immunohistochemistry

The hallmark characteristic of CNC is positivity for synaptophysin, a calcium-binding membrane protein of presynaptic vessels. In addition, CNC is usually positive for neuronal specific enolase (NSE) and negative for glial fibrillary acidic protein (GFAP) and neurofilament protein (NFP) (Fig. 3A) [15,43,46,51,98,106]. These characteristics differentiate CNC from oligodendroglioma and ependymoma.

Ultrastructural features

Ultrastructural examination is only required in the diagnosis of CNC if synaptophysin is lacking or equivocal or if extraventricular neurocytoma is suspected. CNC shows neuronal differentiation, microtubules, dense core and clear vesicles, and abortive or typical synapses (see Fig. 3B) [15,27,28,46,51,98,106]. Occasional mitochondria,

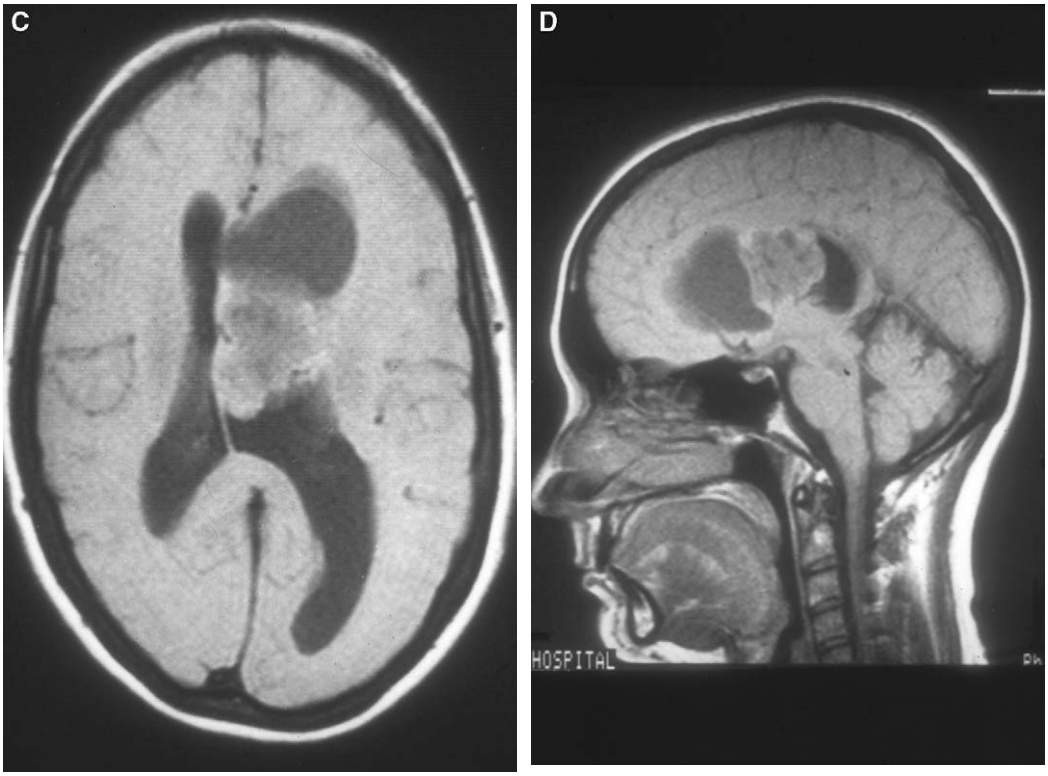

Fig. 1 (*continued*)

moderate free ribosomes, and variable endoplastic reticulum may also be present [15,43,46,98].

Histogenesis/genetics

CNC is thought to be derived from bipotential progenitor cells from the subependymal plate that are capable of neuronal and glial differentiation [30,89,93,97,107]. Indeed, on cell culture, CNC differentiates into neuronal and glial cells [30,89]. In addition, CNC is capable of ependymal differentiation [75]. CNCs are genetically distinct from oligodendrogliomas and neuroblastomas, as evidenced by a lack of association with specific 1p and 19q loss of heterozygosity and rarity of N-myc amplification [75].

Atypical neurocytoma

Atypical neurocytomas are a rare variant of CNC, with cellular pleomorphism, mitotic activity, necrosis, or vascular proliferation (Fig. 4) [3,19,54,62,71,73,77,92,108–111]. Although most CNCs appear as uniform small round cells on light microscopy, atypical CNCs may show peri-

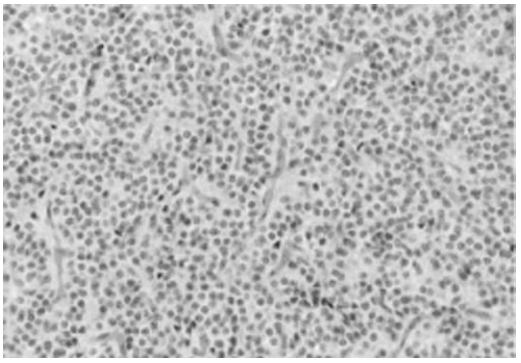

Fig. 2. Histological stain of a central neurocytoma demonstrating sheets of monomorphic pale cells with small delicate capillaries in the background. The tumor cells have round uniform nuclei with fine chromatin and inconspicuous nucleoli. There is no evidence of necrosis or mitotic activity. (*From* Anderson RC, Elder JB, Parsa AT, Issacson SR, Sisti MB. Radiosurgery for the treatment of recurrent central neurocytomas. Neurosurgery 2001;48(6):1231–8; with permission.)

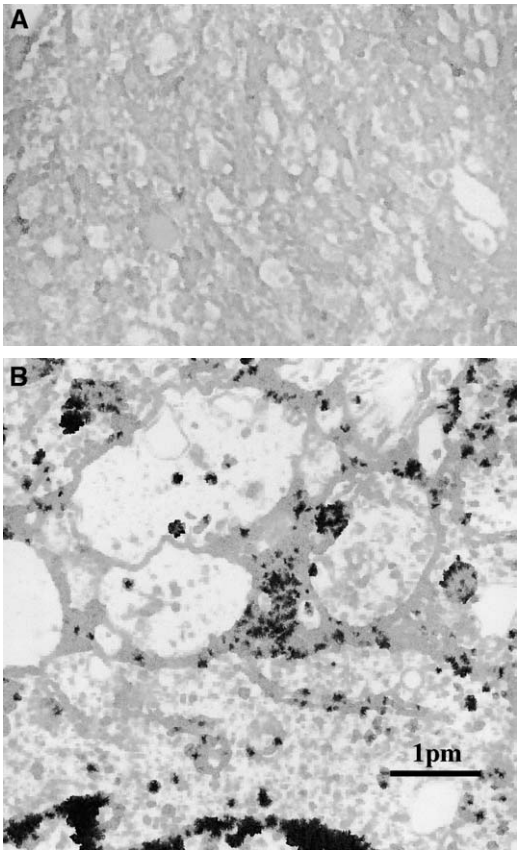

Fig. 3. (*A*) Central neurocytoma showing immunoreactivity for synaptophysin (synaptophysin immunohistochemistry, original magnification × 20). (*B*) Electron microscopy of central neurocytoma. The tumor cells have round nuclei and clear cytoplasm. The cytoplasm contains microtubules, dense core vesicles, and synapses (*) (original magnification × 10,500). (*From* Hara M, Aoyagi M, Yamamoto M, Maehara T, Takada Y, Nojiri T, et al. Rapid shrinkage of remnant central neurocytoma after gamma knife radiosurgery: a case report. J Neurooncol 2003;62(3):269–73; with permission.)

vascular pseudorosettes, neuropil islands, multinucleate cells, or ganglion cells. Mitotic activity can be as high as 30 mitoses per high-power field, and evidence of necrosis may range from focal to extensive. Although the correlation between histologic atypia and proliferation potential in atypical CNC was poor [110], vascular proliferation showed a significant correlation with the MIB-1 labeling index (LI) ($P = 0.0006$) [77]. It is unclear how the histology of atypical CNC relates to biologic behavior. Although elevated proliferation potential correlates with poor outcome, histologic grade does not seem to have prognostic value [77,110].

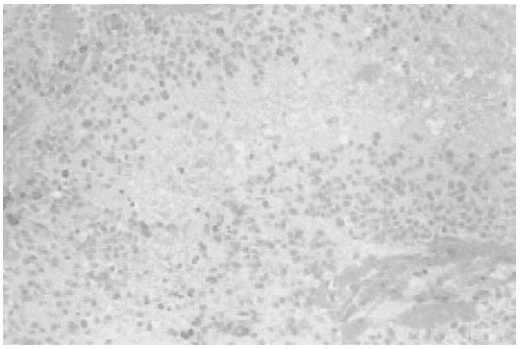

Fig. 4. Central neurocytoma with atypical histologic features, including necrosis, vascular endothelial proliferation, and cellular pleomorphism (hematoxylin-eosin, original magnification × 10). (*From* Mackenzie IR. Central neurocytoma: histologic atypia, proliferation potential, and clinical outcome. Cancer 1999;85(7): 1606–10; with permission.)

Treatment

Overview

Treatment strategies for CNC are based on retrospective case series (Table 2), case reports, and analysis of pooled data. There are no randomized clinical trials and few prospective studies. In many earlier reported cases, initial management may have been based on a diagnosis that was revised on retrospective review [40,42,46,65,67,68,70,71,89].

Most authors agree that, when possible, complete tumor resection for symptomatic CNC is the treatment of choice [19,40,44,46,60,70,96]. The addition of adjuvant radiation therapy (RT) in the immediate postoperative period is controversial. Some authors routinely use RT after subtotal tumor resection (STR) [1,5,19,39,46,59,89]. Although some have used RT after gross total resection (GTR) as well [3,7,15,19,27,32,40,45,53, 58,70,96], several authors state that RT after GTR is not indicated [3,5,27,41,46,56,57,64,70,71,90]. Given the potential for long-term radiation side effects, some advocate for adjuvant RT only for recurrent or progressive CNC [24,46,57], because the subependymal and subventricular zone is sensitive to radiation. More recent reports of stereotactic radiosurgery address the concerns of

Table 2
Larger case series

n	MIBY labeling index	Location	Primary treatment	Recurrence	Average months to recurrence (range)	Radiation	Timing of RT	Average FU in months (range)	Local control	Survival rate	Outcome	Reference
4	Not reported	3 LLV, 1 LLV/3rd	4 CTR	4/4	17.25 (9–25)	GKS, 16–20 Gy to tumor margin	4 salvage	20.25 p GKS, 54.5 p CTR	0% p initial surgery, 100% p GKS	100.0%	Returned to work with full fxn, 3/4 neurologically nl, 1/4 on dilatin for postoperative seizure	[2]
9	3.6375	9 intraventricular	6 ITR, 3 CTR, 3 RT	2/9	6–18	55 Gy (2 adjuvant, 1 salvage for asymptomatic progression)	2 adjuvant, 1 salvage	45.33 (6–89)	83.30%	91.7%	7 KPS 100, 1 KPS 50, 1 died secondary to hemorrhage	[3]
4	Not reported	3 LLV, 1 BLV	1 CTR with GKS for recurrence, 3 ITR/GKS	1/4	53	GKS, 9–13 Gy (3 adjuvant, 1 salvage)	3 adjuvant, 1 salvage	44 (12–99)	100%	100.0%	3 asymptomatic, 1 neurologically intact	[11]
18	Not reported	2 3rd, 3 3rd/LV, 2 CC, 1 CC/SP, 8 FOM/LV, 2 SS	4 biopsy/VPS/RT, 7 CTR, 7 ITR, 1 chemo, 7RT	8/18	NS	NS	7 adjuvant	46.4 (6–84)	44.40%	83.0%	2 dead, tumor recurrence; 7 alive, no tumor recurrence; 6 alive, tumor recurrence; dead no tumor recurrence; 1 dead 4 days after surgery; 1 dead, 2 years after surgery	[19]
10	1.9 (0.1–5.6)	Not reported	8 ITR/RT, 1 ITR, 1 ITR/RT then CTR	1/10	At least 12	5 RT, 26–50 Gy whole brain, 20–32 Gy local, 1 RT, 50 Gy whole brain, 4 RT, 50–60 Gy local	9 adjuvant, 1 salvage	90 (23–160)	100%	100.0%	10/10 no evidence or recurrence	[20]
6	Not reported	2 LLV, 1 midline, 3 LLV/3rd	NS	NS	NS	NS	NS	15 (0.5–36)	NS	100.0%	2 asymptomatic, returned to work; 1 mild residual hemiplegia; 1 behavioral, cognitive, and dexterity problems; 1 short-term memory deficit; 1 recovering well after surgery	[23]

15	9 proliferating cell nuclear antigen < 1%	5 RLV, 1 LLV, 2 BLV, 2 BLV/3rd, 1 RLV/3rd, 1 LLV/3rd, 3 NS	7 CTR, 8 ITR 7 RT	2/15	8–21	6 RT, 50.4–59.8 Gy, 1 RT, 54.6 Gy/21 Gy spine, 1 radiosurgery with recurrence 1 with 14 Gy with recurrence, then refused Tx, reoperation 10 years later	7 adjuvant, 2 salvage	66.1 (18–168)	75% surgery only, 100% surgery/RT	100.0%	12 KPS 100, 1 KPS 90, 1 KPS 90 before suicide, 1 KPS 60	[39, 40]
7	Not reported	2 BLV, 3 LLV, 1 LLV/3rd, 1 RLV	3 CTR, 4 ITR, 2 RT	n	NA	60 Gy	Adjuvant	52.7	NS	87.5%	2 KPS 100, 3 KPS 90, 1 KPS 80, KPS 0 (died 1 day after surgery)	[41]
8	Not reported	7 LV, 1 3rd	2 stereotactic Bx/RT, 5 stereotactic Bx/RT/chemo	1/8	15	50 Gy whole brain (180 cGY × 5–6 weeks)	Primary	78 (15–108)	88%	86.0%	1 lost to follow-up; 5 asymptomatic, employed, KPS > 90; 1 shunt surgery at 9 years after initial RT, employed, KPS > 90; 1 died as a result of shunt dysfunction at 5 years after initial RT	[42]
5	Not reported	3 RLV, 2 LLV/3rd	1 ITR, 2 ITR/VPS/RT, 2 ITR/VPS/chemo/RT	n	NA	1, RT, 52.5 Gy to tumor, 3 RT, 54.0 Gy to tumor/30 Gy to axis	Adjuvant	23.5 (11–78)	NS	100.0%	5 alive and well	[44]
15	1.9 (0.1–6)	15 ventricular	2 Bx/obs, 8 CTR, 5 ITR, 5 RT	n	NA	NS	NS	72.8 (13–255)	71.40%	93.3%	1 lost to follow-up, 10 alive and well, 3 asymptomatic recurrence, 1 died at 1 month	[45]
5	Not reported	2 LLV/3rd, 1 LLV, 1 BLV/3rd, 1 BLV	3 CTR, 2 ITR	n	NA	NA	NA	NS (up to 50)	NS	80.0%	1 recovered with slight hemiparesis at 5 y, 1 lost to FU p 3 months, 1 died after surgery, 2 totally recovered after surgery	[46]
4	Not reported	2 RLV, 2 LLV/3rd	1 Bx/obs, 2 CTR, 1 ITR, 1 RT	n	NA	50 Gy	Adjuvant	50.25 (4–135)	80%	100.0%	2 no recurrence, 2 no regrowth	[53]
8	Not reported	6 LLV, 1 BLV/3rd, 1 BLV	6 ITR, 2 ITR, 3 RT	NS	NS	NS	3 adjuvant	120.5 (67.2–181.2)	NS	100.0%	3 KPS 100, 2 KPS 90, 2 KPS 70, 1 KPS 50	[58]

Table 2 (*continued*)

n	MIBY labeling index	Location	Primary treatment	Recurrence	Average months to recurrence (range)	Radiation	Timing of RT	Average FU in months (range)	Local control	Survival rate	Outcome	Reference
4*	Not reported	2 LV, 1 BLV/3rd, 1 LV/3rd	2 ITR, 2 ITR, 3 RT	n	NA	NS	3 adjuvant	81.75 (15–227)	100%	100.0%	KPS 100, 90, 80, 50; 5/6 no recurrence	[60]
7	6 <1%	2 BLV, 2 RLV, 3 LLV	2 GTR, 4 STR, 1 Bx*N*PS/RT, 2 RT	n	NA	NS	3 adjuvant	10–122	100%	85.7%	5 alive, asymptomatic; 1 death; 1 alive with considerable neurologic deficits	[99]
32	Not reported	10 LLV, 10 RLV, 11 BLV, 1 hypothalamus	5 GTR, 5 GTR/RT, 14 STR, 8 STR/RT	NS	NS	11 RT, 48.6–61.2 Gy to tumor bed, 2 RT, 30–36 Gy to craniospinal axis for adjuvant RT	13 adjuvant, 3 salvage	56.4 (28–184)	79%	81.0%	NS	[70]
6	Not reported	1 RLV, 1 LLV, 1 SS	3 ITR, 2 RT	1/3	9	NS	1 salvage at 9 mo	30, 34 ys, 10	66.70%	66.7%	1 died at 10 mo, 1 alive at 34 y, 1 alive at 2.5 ys, shunt after surgery	[71]
20	0.75 (0.1–3)	10 RLV, 4 LLV, 4 LLV, 1 LLV/3rd, 1 3rd	14 CTR, 6 ITR, 15 RT	n (4 lost to FU)	NA	40–60 Gy over 6 weeks	Adjuvant	32 (6–72)	100%	75.0%	15 alive, 5 died after surgery as a result of IVH	[74]
36	3.4 (0.1–21)	36 LV	34 CTR, 1 stereotactic Bx/RTCTR for residual, 1 biopsy/RT	8/36	27.75 (4–73)	2 RT, 34–60 Gy whole brain/20–30 Gy spine, 6 RT, 6.8–55 Gy	7 adjuvant, 1 primary, 3 salvage	46.9 (0.5–204)	NS	89.7%	29 alive, 4 NS, 1 dead with cerebral edema after surgery, 1 dead with massive IVH 6 weeks after surgery, dead with brain stem infarct 1 month after recurrence noted at 4 months	[78]
4	Not reported	1 LLV, 1 LV/3rd, 1 3rd/hypothalamus, 1 3rd/thalamus	2 biopsy/GKS, 1 CTR, 1 ITR × 2/GKS	1/4	48	GKS, 14–20 Gy to tumor margin, 28–40 Gy maximum	2 primary, 1 salvage, 1 adjuvant	45.75	100% p GKS	100.0%	No neurologic, visual or, endocrine problems; employed; well, no new neurologic problems, no new clinical symptoms	[88]
5	Not reported	1 BLV, 2 LLV, 1 RLV/3rd, 1 LLV/3rd	2 CTR, 3 ITR, 2 RT	1/5	18	Dose not recorded	1 salvage, 3 adjuvant	109.2 (12–150)	50% surgery, 100% surgery/RT	100.0%	3 with memory disturbance, all tumor-free, 3 results good	[89]

10	Not reported	2 LV, 4 SP, 1 CC, 4 FOM	NS	1/10	24	NS	NS	NS	NS	NS	NS	[98]
7	Not reported	6 LV, 1 LV/ 3rd/4th	6 CTR, 1 ITR, 1 RT	3/7	36, 38, 72	54 Gy, 50 Gy salvage	1 adjuvant, 1 salvage	61.8 (5–143)	50%	100.0%	6 returned to work; 1 residual hemiparesis; 3 shunt at 2 mo, 1 mo and 1 y; 1 asymptomatic recurrence, obs	[96]

* Cases 4 and 6 included in reference 113.

Abbreviations: LV, lateral ventricle (otherwise not specified); LLV, left lateral ventricle; BLV, bilateral lateral ventricles; RLV, right lateral ventricle; 3rd, third ventricle; 4th, fourth ventricle; SP, septum pellucidum; CC, corpus callosum; FOM, Foramen or Monroe; FU, follow up; NS, not specified; NA, not applicable; BX, biopsy; Obs, observation; p, post. *Data from* Meningiomas 1991:569–81.

radiation side effects; however, long-term follow-up data are lacking [2,6,11,36,48,65,88]. Chemotherapy has also been used in a limited number of cases [7,14,18,42,44,71,88]. Outcome measures used to assess efficacy of therapeutic interventions include local control, time to progression or recurrence, survival, and functional performance.

Although most patients with intraventricular tumors present with symptoms of obstructive hydrocephalus, the advent of CT and MRI has increased detection of asymptomatic tumors [15, 22,32,53,60,87,91]. Management of patients with asymptomatic CNC is largely unexplored in the published literature. Indications for treatment usually include signs and symptoms caused by the tumor. Consequently, a practical approach to patients harboring an intraventricular tumor with characteristic features of a CNC may be to delay intervention until symptoms occur [58]. By extension, judicious observation may be appropriate for patients with asymptomatic recurrence or progression.

Given that initial management in many CNC patients was based on an incorrect diagnosis [2, 3,14,40,42,46,60,65,68,89,90,93], there is no clear management or treatment paradigm for primary, recurrent, or progressive CNC in the literature [36]. In addition, long-term follow-up for patients is not standardized. The following section discusses treatment management for symptomatic CNC, including prospective observation, surgery, RT, radiosurgery, and chemotherapy for primary and recurrent CNC.

Observation

Because the indications for surgery usually include signs and symptoms caused by the tumor [58], one approach to asymptomatic tumor management is observation with close follow-up. One of the first reported cases of CNC was initially treated with a ventriculoperitoneal shunt (VPS), followed by observation for an unspecified period [27]. The patient later underwent biopsy and GTR after symptomatic progression. Mackenzie [45] has reported two cases of CNC that were observed after biopsy, and both patients are alive and well with no progression at 35 and 255 months of follow-up, respectively. The MIB-1 LI for these biopsies showed MIB-1 LIs of 0.1% and 1.8%, respectively. Giangaspero and colleagues [22] have reported one case of a parietal neurocytoma discovered incidentally after biopsy. This patient had stable disease at the 6-month follow-up examination but showed progression at the 26-month follow-up examination. The LI of this tumor was 1% to 1.5%. Mineura and colleagues [53] also have reported one case of CNC discovered incidentally after biopsy. No progression was noted at the 51-month follow-up examination. Yasargil and colleagues [96] have reported two cases of asymptomatic recurrent CNC 3 and 6 years after GTR. The patients were observed and were alive and well at last follow-up at 58 and 92 months, respectively.

Takao and colleagues [82] have reported a case of CNC that was observed after biopsy because of pregnancy. STR was performed 11 months later because of symptomatic progression. As the result of postoperative MRI revealing residual tumor with spinal cord dissemination, the patient underwent RT (66 Gy, cone technique, extended field at 40 Gy, reduced field at 20 Gy, with use of limited field size for a final boost of 20 Gy to the tumor bed and 46 Gy to the spinal cord, 2 Gy/d, 4 fractions per week), resulting in a decrease in tumor size and stable disease at the 3-month follow-up examination. Agranovich and colleagues [1] have reported a case of CNC that presented as IVH on imaging and was followed with serial CT scans because the patient declined surgery. After subsequent biopsy and MRI 3 years later because of symptomatic progression, the patient received RT (50 Gy in 25 fractions over 5 weeks, isocentric technique [6.5 cm $\times$ 5 cm, 7 $\times$ 5 field size] with a 6-MV energy linear accelerator [LINAC]) and was asymptomatic with stable tumor size at the 3-year follow-up examination.

Because of the benign clinical course of CNC, prospectively observing patients after biopsy until symptomatic progression of the tumor may be a reasonable approach. The MIB-1 LI may help to stratify patients into high-risk and low-risk groups. Observation may also play a role in tumor management after asymptomatic progression or recurrence; however, this approach should be used with caution, because recurrent tumors demonstrate proliferation that may indicate a more clinically aggressive tumor (Table 3).

Acute management

Because many patients present with symptoms of increased ICP, acute management may necessitate the use of temporizing measures before a more definitive treatment is administered. Treatment of acute noncommunicating

Table 3
Observation

Primary treatment	Recurrence or progresson	Months to recurrence or progression	Treatment for recurrence or progression	Follow-up in months	Outcome	Reference
Observation with CT patient refused surgery	y	36	Stereotactic biopsy and GTR	36 p GTR	Asymptomatic	[1]
VPS/observation	y	Not stated	Stereotactic biopsy and RT	Not stated	Alive, no recurrence	[27]
Biopsy/observation	n	—	—	35 p biopsy	Alive and well	[45]
Biopsy/observation	n	—	—	255 p biopsy	Alive and well	
Biopsy/observation	n	—	—	51 p biopsy	No regrowth	[53]
Biopsy/observation us a resulted pregnancy	y	11	STR/RT	3 p STR/RT	Alive and well	[82]
GRT	y	36	Observation asymptomatic	58 p GRT	Returned to work, asymptomatic recurrence	[96]
GRT	y	72	Observation asymptomatic	92 p GTR	Returned to work, asymptomatic recurrence	

Abbreviations: GTR, gross total resection; n, no; RT, radiation therapy; STR, subtotal resection; VPS, ventriculoperitoneal shunt; y, yes; p, post.

hydrocephalus on an emergent basis through extraventricular drain placement [11,14,15,27,42,46,62,71], intravenous steroids [32,63,68], and hyperosmolar therapy [68] has been reported in cases of CNC.

Surgical treatment

Improvements in neuroanesthesia, surgical techniques, and postoperative care have helped to decrease morbidity and mortality after resection of deep brain tumors. Therefore, aggressive resection of tumor should be attempted when possible [70,106]. The goal of neurosurgery is complete tumor removal with minimal morbidity [15]. Complete tumor resection for patients is the treatment of choice [19,40,44,46,58,70,96]; however, this may not be possible given the vascular nature of the tumor [38,39,57] or adherence to adjacent structures [40,58]. GTR is achieved in only one third to one half of cases [28,40,70]. Particular care should be taken to avoid damage to the fornices [37,56,58,89]. The surgical approach is variable, depending on the tumor location, size, and surgeon preference. Transcallosal, transcortical, transventricular, and combined approaches have all been used with success (Table 4). Because of the fact that most CNCs arise in the septum, the fornices and thalami are pushed inferiorly by large tumors. The key to determining a safe plan for resection is identification of the ependymal surface of the floor of the ventricle anterior and posterior to the tumor. The choroid plexus and ependymal veins can then be used as guides for dissection along the inferior aspect of the tumor.

Surgical resection: gross total resection versus subtotal resection

Because of the benign nature of the disease, GTR and STR have resulted in a stable long-term outcome. After GTR, disease-free survival has been reported up to 12.5 years [41]. Similarly, after STR, stable disease has been reported up to 18.5 years [45]. Recurrences have been reported after STR and GTR, however [18,39,40,72,96]. There is an inherent bias in the STR group, because those tumors may be more extensive.

In a retrospective review of 32 cases of patients who received multimodality therapy, Schild and colleagues [70] compared GTR $\pm$ RT and STR $\pm$ RT and found a 5-year local control rate of 70% for patients after STR $\pm$ RT compared with 100% for patients after GTR $\pm$ RT (log rank rest of Kaplan-Meier product limit method projection, $P = 0.08$). Adjuvant conventional external beam RT in initial treatment ranged from 48.6 to 61.2 Gy in 180- to 200-cGy fractions delivered to the tumor bed in 11 patients. Two patients received adjuvant craniospinal and whole-brain

Table 4
Surgical approaches

Surgical approach	No. patients	References
Transcallosal	31	[5, 11, 14, 15, 26, 35, 39, 63, 74, 76, 85, 88, 89, 91, 96]
Transcortical	30	[1, 7, 14, 15, 32, 35, 36, 40, 43, 46, 53, 62, 68, 71, 75, 82, 88, 89]
Transventricular	1	[57]
Combined	17	[2, 7, 31, 40, 53, 60, 63]
Biopsy	28	[7, 14, 19, 28, 30, 42, 45, 53, 78, 82, 88, 99, 105, 108]
Not specified	194	[3, 6, 10, 11, 19, 20, 23, 27, 30, 33, 41, 44, 45, 48, 58, 60, 65, 70, 78, 85, 87, 93–95, 99]

irradiation using 30 to 36 Gy. In addition, 3 patients received RT (50.4 Gy in 28 fractions to the tumor bed, 30 Gy in 15 fractions to the craniospinal axis with a boost to a total dose of 60 Gy in 30 fractions to the tumor bed, and 15 Gy in 1 fraction with stereotactic gamma knife surgery [GKS]) as a part of salvage therapy for tumor progression. The 5-year survival rate was 77% for patients after STR ± RT compared with 90% for patients after GTR ± RT (log rank rest of Kaplan-Meier product limit method projection, $P = 0.44$). After GTR without postoperative RT, the 5-year local control and survival rates were 100% and 80%, respectively. This case series demonstrates a trend for better local control with GTR versus STR and raises the question of the need for adjuvant RT after GTR.

Rades and Fehlauer [112] have reported a 3-year local control rate of 95% after GTR and 55% after STR in a retrospective analysis of 310 CNC cases. At 5 years, local control rates were 85% after GTR and 46% after STR (log rank rest of Kaplan-Meier projection, $P < 0.0001$). Median time to progression was 36 months after GTR and 20 months after STR. The 5-year survival rates were 99% after GTR and 86% after STR (log rank rest of Kaplan-Meier projection, $P = 0.0028$). These data show that GTR yields significantly better local control rates and survival than STR. In addition, no differences of surgery-related morbidity were reported between the two groups.

When possible, GTR is the treatment of choice because overall local control and survival are high. In addition, functional outcome after GTR and STR using the Karnofsky performance scale [35] or other scales seems to be high [40,42,112]. Because many CNC reports are from the pathologic literature, however, postoperative and long-term follow-up data were not always described in detail. Complications, such as hydrocephalus requiring VPS placement [2,27,71,96], mild cognitive defects [40,89], transient hemiplegia or hemiparesis [11,15,16,32,46,68] meningitis [27], hemorrhage [43,78], and death [41,43,46,70,78], after surgery have been noted, but most patients have an uncomplicated postoperative course (Table 5).

Surgery for recurrence/progression

CNC can recur or progress, and some authors have reported their experience with repeat surgery [2,10,78,96]. Over the years, the small but demonstrated risk of morbidity associated with surgery has provided the impetus to pursue alternative treatments for recurrence. Accordingly, surgery for recurrence or progression has decreased in frequency over the years as other therapeutic options have become available [40,62,71].

Stereotactic biopsy

In cases where initial treatment does not include surgical resection, a tissue biopsy must be obtained to establish a definitive diagnosis. Although histologic atypia has not been shown to correlate with clinical outcome [39,40,99], proliferation potential has been correlated to prognosis. Evaluation of proliferation potential using the MIB-1 LI can be used to guide further therapy. MIB-1 is a monoclonal antibody that is more durable than the original Ki-67 antibody and is used as a nuclear proliferation marker. Nuclei positive for MIB-1 are easier to count than nuclei positive for proliferating cell nuclear antigen (PCNA), and the results are comparable to those of bromodeoxyuridine (BUDR) analysis (Fig. 5) [51].

In a retrospective case series evaluating proliferation potential using the MIB-1 LI, Soylemezoglu and colleagues [78] reported that tumors with an MIB-1 LI greater than 2% (39% of cases) have a significantly greater chance of relapse (63%) over an observation period of 150 months compared with cases with a lower MIB-1 LI (22% relapse) (χ^2 test of Kaplan-Meier analysis using one degree of freedom, $P = 0.08$). An MIB-1 LI

Table 5
Postoperative complications within the first 3 months

	No.	%
After gross total resection (n = 127)		
None	108	85.0
Death	8	6.3
Transient hemiparesis	1	0.8
Persistent hemiparesis	6	4.7
Shunt within 1 month	2	1.6
Meningitis	1	0.8
Cognitive dysfunction	5	3.9
Comatose <3 weeks	1	0.8
Decreased vision	2	1.6
After subtotal resection (n = 99)		
None	85	84.8
Death	3	3.0
Transient hemiparesis	2	2.0
Persistent hemiparesis	4	4.0
Hydrocephalus	3	3.0
Cognitive defect	4	4.0
Decreased vision	1	1.0
Seizures	1	1.0
Extradural hematoma	1	1.0
After biopsy (n = 28)		
None	28	100

Cognitive dysfunction includes memory disturbance, confusion, neuropsychologic dysfunction, cognitive defection stupor.

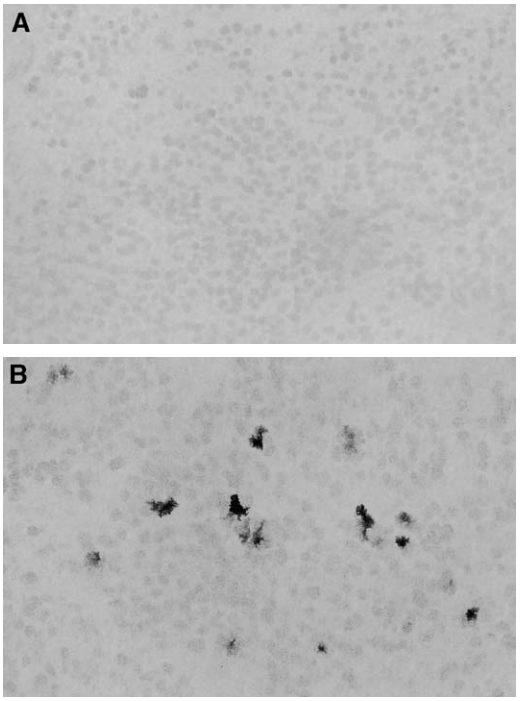

Fig. 5. (*A*) MIB-1 labeling index (LI) of 0.6% (MIB-1 immunohistochemistry, original magnification×20). (*B*) MIB-1 LI of 6.0% (MIB-1 immunohistochemistry, original magnification×20). (*From* Mackenzie IR. Central neurocytoma: histologic atypia, proliferation potential, and clinical outcome. Cancer 1999;85(7): 1606–10; with permission.)

greater than 2% showed a close correlation with the presence of vascular proliferation ($P = 0.006$, test not specified) [78]. The MIB-1 LI is particularly useful, because only cells in G_0 show no immunoreactivity to MIB-1 [78]. Accordingly, the MIB-1 LI may help to predict the clinical outcome of CNC [20,45,74,78].

Radiation therapy

The histopathologic features of CNC, such as neuronal differentiation, low mitotic activity, absence of vascular endothelial proliferation, and lack of tumor necrosis, suggest a relative resistance to ionizing radiation [96,113]. CNC has been shown to respond to RT, however.

The effect of RT on CNC has been explained by Kim and colleagues [40], who suggest that RT causes hyalinization of arterioles feeding the tumor rather than by lethal reproductive damage or induction of apoptosis in tumor cells. CNCs are hypervascular tumors, as demonstrated by angiography and enhancement on MRI and CT. The decrease in tumor size after RT is often not immediate; rather, it usually occurs 1 year after RT. This interval is similar to the that of changes of small to medium-sized vessels reported in arteriovenous malformations after radiosurgery [6,9,40,113].

RT is associated with acute, subacute, and delayed central nervous system (CNS) toxicities. Acute toxicities include transient worsening of symptoms usually caused by peritumoral edema, nausea, vomiting, alopecia, and dermatitis. These effects usually subside within the first 4 to 6 weeks after completing RT. Subacute toxicity of neurologic deterioration in the 6 to 12 weeks after therapy may be attributed to changes in capillary permeability or transient demyelination. Delayed CNS toxicities may include parenchymal or focal necrosis with associated impairments of recent memory, abstraction, problem solving, and learning ability [111,114]. There is also a small risk of iatrogenic tumor development after RT [111].

Toxicities caused by RT correlate with the volume of brain irradiated and dose [113,114].

Conventional radiation therapy

As primary therapy after biopsy. Conventional RT has been used as a primary treatment after biopsy in a limited number of cases. Ishiuchi and Tamura [30] have reported a patient who received RT using 50 Gy (dosing schedule not specified) after biopsy and was free of tumor for 23 years, the longest reported disease-free follow-up period. This patient subsequently underwent GTR and had no evidence of disease at last follow-up. Kulkarni and colleagues [42] have reported a case series of eight patients who underwent stereotactic biopsy followed by conventional whole-brain RT at a total dose of 50 Gy in 180-cGy fractions for 5 to 6 weeks. Six of these patients had an initial diagnosis of oligodendroglioma and later also received chemotherapy with lomustine (seven to nine doses, total dose not specified). The remaining two patients received no other treatment and were asymptomatic at 36 and 105 months, respectively. Follow-up CT examination showed decreased or no contrast enhancement as well as a decrease in tumor size. Figarella-Branger and colleagues [19] have reported four cases of ventroperitoneal cerebrospinal fluid (CSF) diversion and biopsy followed by RT (dose not specified). Two of these patients were alive with residual tumor at 6 and 7 years. The other two patients died after 11 months and 2 years of follow-up. Louis and colleagues [44] have reported one case of biopsy followed by 43.2-Gy RT to the tumor (dosing schedule not specified). This patient received no other therapy and was alive and well at 54 months of follow-up. Soylemezoglu and colleagues [78] reported two patients who received RT (55- and 34-Gy whole-brain RT plus 20-Gy spinal RT, respectively [dosing schedule not specified]) after biopsy. One patient underwent surgery for residual tumor soon after, whereas the other underwent surgery 4 years later. Brandes and colleagues [7] have reported one case of RT (limited field RT with 54.4 Gy in 30 fractions) after stereotactic biopsy of a tumor initially diagnosed as an oligodendroglioma. A partial response of a greater than 50% reduction in tumor size was achieved, and the patient had stable disease for 5 years. This patient later received chemotherapy for recurrence. Although conventional RT as a primary therapy has been used with success in the initial treatment of CNC, the experience is limited and the reported follow-up data are brief. If the tumor is small and patients are closely observed for tumor progression, focal RT after biopsy may be a possible treatment option in centers that lack stereotactic radiosurgery.

Role of radiotherapy after gross total resection. Rades and Fehlauer [112] have reported that the 3-year local control rate showed no statistical difference between GTR (95%) and GTR/RT (96%) (RT dose not specified). Similarly, local control at 5 years showed no statistical difference between these two groups (85% for GTR and 89% for GTR/RT). Data from Schild and colleagues [70] support these findings and demonstrate that GTR resulted in 5-year local control and survival rates of 100% and 80%, respectively. Median time to progression was 36 months after GTR and 39 months after GTR/RT with 5-year survival rates of 99% for GTR and 95% for GTR/RT (dose not specified by patient). Although the number of patients in the GTR/RT group was small ($n = 35$), these data suggest that RT should not be used as an adjuvant in patients after GTR, because there is no proven benefit.

Role of radiotherapy after subtotal resection for treatment of residual tumor. Schild and colleagues [70] have reported that among patients who underwent STR, the 5-year local control rate was 100% for patients who received postoperative RT and 50% for patients who did not (log rank rest of Kaplan-Meier product limit method projection, $P = 0.02$). The 5-year survival rate after STR also showed a trend for longer survival in patients who received postoperative RT (88%) compared with patients who did not (71%) (log-rank rest of Kaplan-Meier product limit method projection, $P = 0.3$). Brown and colleagues [9] also found that crude local control rates for STR versus STR/RT (48.6–61.2 Gy in 180–200 cGy fractions or 59-Gy median dose) were 62% and 100% (two-tailed test, $P = 0.0008$), respectively. In a larger study, Rades and Fehlauer [112] have reported a 3-year local control rate of 55% compared with 89% among patients who underwent STR and STR/RT, respectively. At 5 years, local control rates were 46% for STR and 83% for STR/RT (log rank rest of Kaplan-Meier projection, $P < 0.001$). Median time to progression was 20 months after STR and 34 months after STR/RT; however, 5-year survival rates were 86% for STR and 90% for STR/RT and showed no

significant difference between groups. Overall survival was good in both groups, and postoperative radiation improved local control but not survival. Rades and Fehlauer [112] argue that the benefit seen in local control is enough to warrant the use of postoperative RT in all patients undergoing STR. Schild and colleagues [70] offer an alternative approach and suggest that observation until progression may spare approximately 50% of patients with STR related potential radiation toxicity. Kim and colleagues [40] have reported that at their institution, because of the benign clinical course of CNC and potential for delayed radiation toxicity, routine postoperative radiation is not given even after STR.

We concur with many clinicians who believe that adjunctive RT should not be routinely administered after STR of CNC [5,11,24,27, 41,46,57,58,61,64,71,90,93]. The decision to use adjunctive RT for residual tumor can also be based on the MIB-1 LI. Because certain aspects of histologic atypia do not necessarily correlate with clinical outcome [39,40,99], the MIB-1 LI currently seems to be the best predictor of proliferative potential. Hence, the MIB-1 LI may help to predict the clinical outcome of CNC [3,77,110]. The time to progression may be prolonged in tumors with a high MIB-1 LI treated with adjuvant RT [7].

Prophylactic radiation therapy. If RT is pursued, most clinicians agree that only the tumor bed and directly adjacent areas should be included in the treatment field [9,70]. Prophylactic radiation of the spinal cord and total brain has been reported in earlier cases [20,27,40,42,44,56,70,78]; however, the rationale for prophylactic RT was either not stated, based on a diagnosis that was later changed [40,42], or the result of a diagnosis of atypical neurocytoma [20,78]. At this time, prophylactic RT is not indicated for CNC because of the benign nature of CNC and risk of radiation toxicity [112].

Radiation dosing. The experience with radiation dosing is varied. Rades and colleagues [115] studied the optimal radiation dose in a retrospective analysis of patients receiving conventional RT after STR. Their analysis included 52% of the reported cases and 11 unpublished cases from their institutions with a minimum follow-up of 12 months. The cases were divided into group A (40–53.6 Gy [n = 42]) and group B (54.0–62.2 Gy [n = 47]), with a 10-year local control rate of 65% for group A and 89% for group B (log rank rest of Kaplan-Meier projection, $P = 0.0066$). The median time to recurrence was 26 months in group A and 96 months in group B, although a significant difference in the 10-year survival rate was not found. Therefore, the optimal minimal dose with high chance of local control is the equivalent dose in 2-Gy fractions of 54 Gy or greater. This dose seems to result in better local control and longer time to recurrence. Late toxicity after radiation is tolerable if the total radiation does not exceed 60 Gy [112]. The risk of severe toxicity at 5 years is 5% if up to one third of the brain receives 60 Gy. Therefore, using a target volume including only the preoperative tumor and a 2-cm margin is recommended [115]. The optimal dose for RT for patients with CNC seems to be 54 to 60 Gy.

Radiation therapy after recurrence or progression. RT has been used with success after tumor progression or recurrence. Cases of RT after recurrence are often part of larger case series and are often combined with other therapy. Yasargil and colleagues [96] have reported a case of asymptomatic recurrence 38 months after initial GTR that was treated with GTR/RT with recurrence (50 Gy, dosing schedule not specified). Follow-up at 37 months after completing RT showed no recurrence. Valdueza and colleagues [89] have reported a case of recurrence noted 18 months after STR treated with GTR/RT (dose not specified). Follow-up 4 years later showed no tumor recurrence. Dodds and colleagues [14] have reported a case of GTR/RT (54 Gy in 30 fractions over 6 weeks using a shrinking field technique with 5-MeV X-rays) following recurrence after chemotherapy. No radiation toxicity was noted, and no recurrence was present on CT 5 years after completing RT. Kim and colleagues [40] have reported a case of recurrence 21 months after GTR. The patient began RT and received 14 Gy (dose schedule not specified) before refusing to complete the course. This patient was lost to follow-up until 10 years later, when he underwent reoperation for tumor progression. Schild and colleagues [70] have reported two patients who received RT (50.4 Gy in 28 fractions to the primary tumor bed, 30 Gy in 15 fractions to the craniospinal axis, with boost to total dose of 60 Gy in 30 fractions to the tumor bed) following recurrence after STR. Brandes and colleagues [7] have reported one case treated with chemotherapy and RT (39.6 Gy in 22 fractions to the craniospinal axis plus a boost of 14.4 Gy in 8 fractions on

T8) following recurrence 3 years after GTR. No radiation toxicity was noted, and the patient was in complete remission at the 36-month follow-up examination.

Not all cases of RT for recurrent or progressive CNC have shown a positive outcome. Mineura and colleagues [53] have reported a case of RT with 60 Gy (dosing schedule not specified) following progression 4 months after STR. At the 3-month follow-up examination, the tumor showed continued progression, but subsequent follow-up data were not reported. Ashkan and colleagues [3] have reported a case of asymptomatic progression 29 months after STR treated with 55 Gy (dosing schedule not specified) for a tumor with an MIB-1 LI of 11.2%, with no further follow-up data reported. Sgouros and colleagues [71] describe two cases of RT (dose and schedule not specified) following recurrence 12 months and 9 months after STR, which resulted in death at 5 years and 10 months later, respectively. The first patient responded well initially, but the tumor continued to progress; the second patient deteriorated while receiving RT, so it was discontinued. Only one of these cases reported the MIB-1 LI; therefore, the true characterization of these tumors is unclear. More classic CNC tumors seem to show a positive response to RT for recurrent or progressive CNC. The determination of whether RT is beneficial in treating atypical neurocytomas requires further study, however.

Stereotactic radiosurgery

GKS or LINAC stereotactic radiosurgery can deliver a high dose of radiation with a steep drop off, thereby limiting the unnecessary exposure of surrounding brain tissue, which results in a decreased risk of side effects. The goals of radiosurgery are long-term local control, maintenance of neurologic function, and prevention of new neurologic deficits [6,109]. Although not the goal, tumor volume reduction often occurs. The effects of GKS and LINAC radiosurgery on tumor control are thought to be similar [36,110].

CNCs seem to be ideal targets for stereotactic radiosurgery [6,36,58]. Depending on their size and location, CNCs are often surrounded by CSF and are well demarcated from the adjacent brain. Patients undergoing stereotactic radiosurgery typically are discharged the same day of the procedure and experience few side effects [2,6,36,65]. The experience of treatment of CNCs with stereotactic radiosurgery is limited, but early reports are encouraging (Table 6) [2,6,11,36,65].

Gamma knife surgery

As primary therapy. Tyler-Kabara and colleagues [88] have reported two cases of GKS as primary therapy (two 14-mm isocenters and two 8-mm isocenters, 15-Gy marginal dose and 30-Gy maximum dose; one 8-mm isocenter and one 4-mm isocenter, 20-Gy marginal dose and 40-Gy maximum dose) after biopsy. Both patients are well 40 and 42 months, respectively, after the procedure, with a reduction in tumor size noted on follow-up imaging. Javedan and colleagues [108] have reported a case of third ventricular CNC treated with GKS (18 Gy at the 50% isodose line, five isocenters) after endoscopic biopsy and third ventriculostomy. No adverse side effects were reported, and the patient was neurologically intact with minimal shrinkage of the tumor on imaging 25 months after the procedure. Further study and longer term follow-up data are needed to evaluate GKS as a primary treatment option after biopsy.

For residual tumor (adjuvant). Cobery and colleagues [11] have reported three cases of GKS (3–23 isocenters, 30%–50% isodose level, 9- to 13-Gy peripheral dose) as adjuvant therapy for residual tumor after STR. All three patients tolerated the procedure well and demonstrated a reduction in tumor size (48%, 72%, and 81%) on follow-up imaging at 99, 23, and 42 months after the procedure, respectively. Hara and colleagues [26] have reported a case of GKS (20-Gy marginal dose and 40-Gy maximum dose, 50% isodense gradient) after STR with a marked decrease in tumor size 2 months after GKS, which remained unchanged after 1 year. The response to GKS as adjuvant therapy is encouraging. As with conventional RT, the MIB-1 LI should play a role in the timing of therapy for residual tumor. The robust effect on tumor volume coupled with a low risk of radiation toxicity makes GKS an attractive alternative to conventional RT, however.

For recurrence. Bertalanffy and colleagues [6] have reported three cases of GKS (3–27 isocenters, 30%–60% isodose line, 9.6- to 16-Gy marginal dose) for asymptomatic tumor recurrence 5 to 6 years after GTR. The MIB-1 LIs were 2.4%, 7%, and 8.7%, respectively. No patient developed new neurologic deficits after GKS. In all three cases, follow-up imaging (1, 2, and 5 years, respectively) showed a reduction in tumor volume.

Anderson and colleagues [2] have reported four cases treated using GKS (multiple isocenters with combinations of 8-, 14-, and 18-mm collimators, 16–20 Gy to target area) for evidence of recurrence

Table 6
Stereotactic radiosurgery and outcome

Primary treatment	Recurrence in months	Radiation	Timing of radiation	Initial size in cc cubic centimeters	Follow-up MRI	Follow-up in months	Outcome	Reference
GTR	9	GKS, 16 Gy	Salvage at 9 months	6.2	Decrease in tumor size	14 p GKS, 24 p GTR	4/4 returned to work with full fxn	[116]
GTR	25	GKS, 16 Gy	Reoperation with GKS salvage at 25 months	12.3	Decrease in tumor size	28 p GKS, 83 p GTR	3/4 neurologically nl, 1/4 on dilantin for postoperative seizure	
GTR	21	GKS 20, Gy	Reoperation with GKS salvage at 21 months	1.7	Decrease in tumor size	12 p GKS, 84 p GTR	1/4 on dilantin for post operative seizure	
GTR	14	GKS, 16 Gy	Salvage at 14 months	7.9	Decrease in tumor size	27 p GKS, 27 p GTR		
GTR × 2	60–72	GKS, 12.5 Gy	Salvage at 5 to 6 years	0.6	58% decrease in tumor size after GKS	12 p GKS	Died us a result of cardiac failure caused by pericarditis 1 year p GKS, 2/3 returned to work, 3/3 no new neurologic problems, 1/3 had persistent abducens palsy and visual impairment	[6]
GTR		GKS, 13 Gy		5.2	40% decrease in tumor size after GKS	60 p GKS		
GTR × 2		GKS, 9.6–16 Gy		5.9	61% decrease in tumor size after GKS	24 p GKS		
STR/GKS	—	GKS, 9 Gy	Adjuvant 8 months later	6.5	48% decrease in tumor size	99 p GKS	Neurologically intact	[11]
STR/GKS	—	GKS, 13 Gy	Adjuvant 18 months later	13	72% decrease in post op tumor	23 p GKS	Asymptomatic	
STR/GKS	—	GKS, 10 Gy	Adjuvant	29	81% decrease in tumor size	42 p GKS	Asymptomatic	
GTR	53	GKS, 10 Gy	Salvage at 53 months	10.5	77% decrease in tumor size	12 p GKS	Asymptomatic	

STR/GKS	—	GKS, 20 Gy	Adjuvant	5.7	2, 4, 6, 8, 10, and 12 months after GKS, tumor shrank at 2 months	12	Neurologically intact	[26]
STR/GKS	—	GKS, dose not stated	Adjuvant	Not stated	Shrinkage of tumor at 21 months	21 p GKS	No progression, shrinkage of tumor, KPS full	[35]
STR	Not	GKS, 15 Gy	Salvage	Not stated	Stable disease	13	Stable disease	[70]
Biopsy/GKS	—	GKS, 15 Gy	Primary	4.2	Significant decrease in tumor size at 40 months	50 p GKS	No new neurologic problems	[89]
STR × 2/ GKS	—	GKS, 14 Gy	Adjuvant	7.9	Complete regression at 18 months	53 p GKS	No new clinical symptoms	
Biopsy/GKS	—	GKS, 18 Gy	Adjuvant	Not stated	Minimal decrease in tumor size at 25 months	25 p GKS	Normal neurologic examination	[8]
GTR/ radiosurgery	72	Radio-surgery, 50 Gy	Adjuvant	Not stated	Complete remission p initial Tx, 6 years later recurrence	87 mo p radiosurgery	Stable disease no progression (received chemo 72 months p radiosurgery)	[7]
GTR	8	Radio-surgery	Salvage at 8 months	1.2	6 months p radiosurgery	10 p radiosurgery, 18 p GTR	KPS 100	[40]
GTR	36	Radio-surgery 18 Gy	Salvage at 3 years	2.7	Significantly smaller tumor p radiosurgery	34 p radiosurgery	Neurologically intact	[65]
STR	12	LINAC, 17.5 Gy	Salvage after 6 months of observation	Not stated	Decrease in tumor size at 6 months p LINAC, disappeared by 36 months p LINAC	51 p LINAC	Neurologically intact	[36]
STR/RT	144, 36, 36	30 Gy at presentation/ 50 Gy at recurrence 2/ LINAC at recurrence 3	Adjuvant and salvage	Not stated	Not stated	60 p LINAC, 240 p initial ITR	Alive with disease	[30]

Abbreviations: chemo, chemotherapy; fxn, function; GTR, gross total resection; KPS, Karnofsky performance scale; LINAC, linear accelerator; nl, normal; p, post; RT, radiation therapy; STR, subtotal resection; Tx, therapy.

on MRI 9 to 14 months after GTR and reoperation for recurrence. At the 12- to 28-month follow-up examinations, all tumors demonstrated a reduction in tumor size and the patients have all returned to their previous employment with full function. Tyler-Kabara and colleagues [88] also have reported two patients treated with GKS (five 14-mm isocenters, 14-Gy marginal dose and 28-Gy maximum dose; three 8-mm and two 4-mm isocenters, 16-Gy marginal dose and 32-Gy maximum dose) following recurrence after surgery. Both patients remain well, and follow-up imaging demonstrates complete regression at 53 months and marked tumor regression at 38 months, respectively, after the procedure.

An additional three cases have been reported in the literature. One patient treated with GKS (nine isocenters, 18-Gy marginal dose and 36-Gy maximum dose) following asymptomatic recurrence 3 years after GTR experienced no adverse side effects and was neurologically intact at the 34-month follow-up examination with a decrease in tumor size noted on MRI [65]. Another patient treated with GKS (29 isocenters, 50% isodose level, 10-Gy peripheral dose) for asymptomatic recurrence 53 months after GTR remained asymptomatic following the procedure, and follow-up imaging at 12 months showed a 77% reduction in tumor volume [11]. The third patient was treated with GKS (15 Gy in 1 fraction [dose not otherwise specified]) for tumor progression after STR, and follow-up imaging at 13 months showed stable disease [70].

Overall, the reported response of CNC to GKS is favorable, with 15 of 16 cases demonstrating a reduction in tumor size and 1 of 16 cases showing stabilization of disease. Most patients tolerated GKS without complication and were discharged the next day. These reported cases describe GKS as the primary therapy and treatment of residual tumor or asymptomatic tumor recurrence identified on neuroimaging. Because the follow-up period after GKS is limited, future study is needed to demonstrate the long-term efficacy of this treatment modality.

Linear accelerator. Treatment of CNC using LINAC radiosurgery is limited to three cases in the literature. Maruyama and colleagues [48] have reported a patient with CNC treated with LINAC radiosurgery (10-MV photons with multiple-arc noncoplanar method, 50% isodose line, 24 Gy to central target) after STR. Radiographic follow-up at 6 months showed no change in tumor size. Kim and colleagues [36] have reported a patient with CNC who showed residual tumor on MRI 6 months after resection. Because the patient was asymptomatic at the time and the residual tumor was small, the patient was observed for 6 months. After tumor progression on follow-up imaging, LINAC radiosurgery (three 2-cm isocenters, 70% isodose line, 17.5-Gy marginal dose and 25.0-Gy maximum dose) was initiated. Imaging at 6 months after LINAC radiosurgery showed a decrease in tumor size and complete disappearance by 36 months. At 51 months of follow-up, the patient was neurologically intact with no signs of recurrence on MRI. Ishiuchi and Tamura [30] have reported a patient treated with LINAC radiosurgery (dose not specified) following ventricular dissemination after repeated surgery and RT. At 5 years after LINAC radiosurgery, this patient was alive with disease. Although the experience with LINAC radiosurgery in the treatment of residual or progressive CNC is limited, these three cases demonstrate a favorable response.

CyberKnife. The frameless image-guided stereotactic radiosurgery used with the CyberKnife (Accuray, Sunnyvale, California) is a recently developed technology that may be used in the future to treat CNC. This device couples an X-band LINAC to a computer-controlled robotic arm that aligns the radiation beams with the target based on frequent input from the radiographic tracking system. Paired orthogonal high-resolution digital images are coregistered with digitally reconstructed radiographs from preoperative CT images to provide spatial positioning with six degrees of freedom. The CyberKnife automatically adjusts for patient movements of up to 1 cm. In phantom testing, the second-generation CyberKnife system demonstrates high accuracy, with a spatial error of 1.1 ± 0.3 mm, which is comparable to frame-based radiosurgical systems, such as GKS and LINAC systems [116,117]. This technology is untested in the treatment of CNC to date; however, the successful use of the CyberKnife in treating other benign tumors [110] suggests a possible role for this technology in treating CNC.

Chemotherapy

Chemotherapy is an appealing alternative to radiation for CNC, because these patients tend to be younger and, as a result, more susceptible to the long-term side effects of radiation. Incorporation of chemotherapy into treatment strategies

involves several challenges: (1) inherent or acquired mechanisms of resistance, (2) effective drug delivery, and (3) altered drug metabolism caused by interactions with anticonvulsants and steroids. Chemotherapeutic regimens often involve combining drugs with different mechanisms of action and nonoverlapping toxicities. Some chemotherapeutic agents may also cause radiosensitization. In general, histopathologic grade plays a key prognostic role in choosing a chemotherapy regimen [21]. The goal of adjuvant chemotherapy is to consolidate tumor reduction after surgery and decrease the probability of recurrence [21]. Limiting systemic toxicity, such as myelosuppression and end organ and tissue damage, is also important [7,21].

The experience with CNC and response to chemotherapy is limited and is often used as a part

Table 7
Chemotherapeutic regimens

Primary treatment	Chemo	Recurrence in months	Follow-up in months after chemo	Outcome
GTR/RT, stereotactic	Adjuvant salvage etoposide (40 mg/m^2/d days 1–4), cisplatin (25 mg/m^2/d days 1–4), cyclophosphamide (1000 mg/m^2/d day 4), five cycles	72	15	Stable disease maximum result 8 months after chemo, no progression
Stereotactic biopsy/RT	Same as above, five cycles	60	18	Stable disease, no progression
GTR	Same as above, three cycles	38	36	Complete remission for 36 months
Shunt, cells for cytology, STR/chemo	Adjuvant four cycles of carboplatin (500 mg/m^2 days 1 and 2 of week 1), etoposide (100 mg/m^2 days 1–3 of weeks 1 and 3, and ifosfamide (3 g (m^2 days 1–3 of week 3)	22	96	Full-time employment, no progression
Stereotactic Bx/RT/chemo	Adjuvant loumustine, seven doses[a]	—	60	Died because of shunt dysfunction at 5 years after initial RT
Stereotactic Bx/RT/chemo	Adjuvant loumustine, nine doses[b]	15	15	Lost to follow-up
Stereotactic Bx/RT/chemo	Adjuvant loumustine, seven doses[a]	—	108	Shunt surgery at 9 years after initial RT, employed, KPS >90
Stereotactic Bx/RT/chemo	Adjuvant loumustine, eight doses[b]	—	90	Asymptomatic, employed, KPS >90
Stereotactic Bx/RT/chemo	Adjuvant loumustine, nine doses[a]	—	114	Asymptomatic, employed, KPS >90
Stereotactic Bx/RT/chemo	Adjuvant loumustine, seven doses[a]	—	96	Asymptomatic, employed, KPS >90
STR/VPS/chemo/RT	Adjuvant cytoxan, cisplatin[b]	—	14	Alive and well
STR/VPS/chemo/RT	Adjuvant cytoxan, cisplatin[b]	—	11	Alive and well
2 GTR/RT/chemo	Adjucant cisplatin plus lomustine[b]	Not stated	Not stated	Not stated
2 STR/RT/chemo	Adjuvant lomustine alone[b] Adjuvant lomustine plus carmustine[b] Adjuvant vincristine, lomustine, prednisone[b]			

Abbreviations: Bx, biopsy; chemo, chemotherapy; GTR, graps total resection; KPS, Kurnofsky performance scale, RT, radiation therapy; STR, subtotal resection; VPS, ventroperitoneal shunt.

[a] Schedule not specified.

[b] Dose and schedule not specified.

of multimodality therapy (Table 7). Dodds and colleagues [14] described a patient who received primary chemotherapy for a tumor that later was diagnosed as CNC. Because the tumor was largely inoperable and some mitotic activity was present in initial smear preparations, a trial of chemotherapy was started. Four cycles of carboplatin (500 mg/m^2 on days 1 and 2 of week 1), etoposide (100 mg/m^2 on days 1–3 of weeks 1 and 3), and ifosfamide (3 g/m^2 on days 1–3 of week 3) were given before chemotherapy was stopped because of decreasing renal function. Follow-up CT 1 month after completing chemotherapy showed regression of the tumor, with a decrease in the solid component and a corresponding increase in the cystic component. This patient underwent successful STR and RT 22 months later because of progression. At last report, the patient was back to neurologic baseline with stabilization of disease. This case demonstrates a potential benefit of chemotherapy. Because chemotherapy was used in combination with surgery and RT, however, the individual contribution of chemotherapy cannot be assessed.

Brandes and colleagues [7] have reported three cases in which patients received chemotherapy (etoposide, 40 mg/m^2 on days 1–4; cisplatin, 25 mg/m^2 on days 1–4; and cyclophosphamide, 1000 mg/m^2 on day 4 [repeated every 4 weeks]) for recurrent or progressive CNC. Two patients showed recurrence on MRI 5 to 6 years after STR and RT. These patients received five cycles of chemotherapy and achieved a 40% to 60% reduction in tumor size. One patient showed recurrence on MRI 3 years after GTR. This patient received three cycles of chemotherapy and later received RT, resulting in complete regression of the tumor. At last follow-up, all three patients had maintained their clinical response over 15 to 36 months.

Schild and colleagues [70] also described four patients who received chemotherapy after STR or GTR followed by RT. Chemotherapy regimens (doses not specified) included lomustine alone; cisplatin plus lomustine; lomustine plus carmustine; and vincristine, lomustine, and prednisone. Kulkarni and colleagues [42] have reported six patients who received chemotherapy with lomustine (dose not specified) after stereotactic biopsy and RT as the result of an initial diagnosis of oligodendrocytoma. Patient-specific outcome data were not reported, however, and the contribution of chemotherapy alone could not be meaningfully assessed. In these two studies combined, all patients maintained local control as documented by follow-up CT or MRI, except for one patient who showed subependymal spread [42,70]. Sgouros and colleagues [71] have reported only a temporary reduction in tumor size associated with carboplatin (dose not specified) in one patient, however.

Although these reported cases suggest the potential benefit of chemotherapy in the treatment of CNC, surgery and RT have shown a proven benefit in larger cohorts of patients. If RT and surgery are not appropriate or possible, chemotherapy in the setting of clinically aggressive behavior or a high proliferation index may be considered [14]. Of note, none of the reports describing chemotherapy for patients with CNC used the MIB-1 LI to assess proliferation potential before treatment. The limited data concerning long-term prognosis after chemotherapy may warrant further study.

Follow-up

There is no established standard for follow-up of CNC, but most clinicians include components of postoperative imaging to determine if there is residual tumor, serial neuroimaging at variable intervals, and regular clinical examinations. In the sole reported prospective follow-up study, patients were clinically evaluated three times per month initially and twice yearly thereafter [3]. Some studies suggest a yearly clinical examination [11,96] or a clinical examination at 6 months after surgery [15], whereas others suggest a regular clinical examination without specifying a time period [14,88]. Most authors recommend serial imaging; however, the interval varies from yearly [6,10,11], to biennially [57], to twice a year initially [59] and then gradually building up to once every other year, to periodically with the interval unspecified. Evaluation of postoperative outcome also varies (Table 8); however, the use of a validated scale, such as the Karnofsky performance scale [118], should be a goal of all practitioners.

Other factors, such as type of treatment, high MIB-1 LI, presence of a VPS, and older patient age, may modify the follow-up intervals. When patients are left with residual tumor after STR or biopsy, more frequent initial follow-up may be warranted. In tumors with a high MIB-1 LI, closer follow-up should be instituted because of the higher likelihood of recurrence [78]. Patients with a VPS may also need closer follow-up because of the high failure rate over time [13,38,92,119]. Several deaths as a result of shunt failure have been reported in patients with CNC

Table 8
Outcome measures

Outcome measure	No. patients	References
Survival	181	[1–7, 10, 11, 14, 15, 18, 19, 20, 23, 26, 27, 31, 35, 36, 40–46, 53, 56–58, 60, 62–65, 68, 70, 74, 78, 82, 85, 87–89, 94–96, 99, 104, 108]
Shunt failure	5	[27, 42, 70]
Local control (recurrence, progression, stable disease)	153	[2–4, 6, 7, 10, 11, 14, 15, 18, 19, 20, 26, 27, 30, 31, 35, 36, 40, 42, 45, 53, 57, 58, 60, 62, 63–65, 68, 70, 78, 82, 85, 87–89, 94–96, 99, 104]
Change in neurologic examination	26	[1, 2, 5, 6, 11, 15, 23, 25, 36, 46, 57, 65, 68, 88, 96, 99]
Functional description[a]	98	[1, 2, 5, 6, 10, 14, 15, 23, 35, 40–42, 44, 45, 56, 58, 60, 63, 68, 96, 99]

[a] Includes Karnofsky performance scale score, ADL, well, employment status.

with a VPS [42,70]. A reasonable postoperative management strategy may include immediate postoperative imaging to confirm GTR or STR, followed by repeat imaging between 3 and 6 months and then yearly for at least 5 years. With no tumor recurrence, longer intervals between follow-up imaging may be considered. The goal of follow-up should be early identification of recurrent or progressive CNC.

Given that most patients present with signs and symptoms of noncommunicating hydrocephalus, long-term treatment of hydrocephalus is an important consideration. Surgery to debulk the tumor is often sufficient for relief of outlet flow obstruction. Some patients may still require shunt placement as a part of the postoperative treatment of hydrocephalus, however. A review of the literature shows that 27 of 303 patients underwent VPS placement (type not specified) as part of the management of CNC. For those cases reporting the timing of CSF diversion, shunt placement usually occurred either at surgery or within the 4-month postoperative period (17 of 20 cases). Shunt-related complications included infection (2 of 27 cases) or death (5 of 27 cases). Third ventriculostomy to treat noncommunicating hydrocephalus has been described in only 1 patient [108].

Management paradigm

Based on the literature, CNC usually follows a clinically benign course, with most symptoms caused by increased ICP as a result of noncommunicating hydrocephalus. In general, appropriate management of patients with CNC results in a favorable clinical outcome; however, more aggressive variants have also been reported. The clinical treatment and outcome for reported cases of CNC for which detailed information was available.

Initial treatment should be based on symptoms rather than on incidental findings on neuroimaging. Emergent treatment and evaluation of noncommunicating hydrocephalus should include CT imaging and standard therapy, such as intravenous steroids, hyperosmolar fluids, and extraventricular drain (EVD) when indicated. Nonemergent cases may also undergo initial CT imaging. MRI is necessary to characterize the tumor better and to localize the attachment within the ventricle.

In all cases, biopsy is necessary to establish a definitive diagnosis. The MIB-1 LI should also be determined so as to establish the risk of progression or recurrence. Large tumors are best treated with surgery to debulk the tumor and attempt GTR. Smaller tumors may be treated with biopsy followed by radiosurgery or conventional RT if the MIB-1 LI is not greater than 2%. With an MIB-1 LI greater than 2% or with severe neurologic symptoms, surgery is recommended. After radiosurgery or RT, patients should be evaluated with neuroimaging at least every 6 months for the first 2 years and should also have regular clinical examinations to monitor for recurrence and assess the efficacy of treatment.

For patients undergoing surgery for large tumors or tumors with a high proliferation index, complete tumor resection should be the goal when possible. Immediate postoperative imaging should be performed to evaluate the extent of tumor resection. Tumors with a high MIB-1 LI should also receive adjuvant radiosurgery or RT. After these treatments, patients should be clinically and radiologically followed for recurrence or progression. Patients with low MIB-1 LI tumors should also be observed for recurrence or progression. The follow-up interval depends on the presence of a VPS, patient age, and amount of residual tumor. If symptomatic recurrence or progression does occur, patients may be treated

with radiosurgery, RT, or reoperation. If malignant behavior is suspected, reoperation is favored. Otherwise, RT and radiosurgery seem to have less associated risk and morbidity. Clinical and radiologic follow-up for symptomatic recurrence should resume after treatment.

Summary

The literature to date on the treatment of CNC reflects an evolution of clinical practice in neuro-oncology. The advent of sophisticated tools, such as MRS and molecular pathology, has facilitated more efficient diagnosis of CNC. Decreased morbidity associated with surgical intervention has resulted in better outcomes in patients undergoing resection of CNC. Prospective monitoring of treated patients with MRI coupled with judicious use of radiosurgery will likely further decrease treatment-related morbidity.

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