TREATMENT OF CENTRAL NEUROCYTOMAS

Marc C Chamberlain, M.D.
Department of Neurology
USC/Norris Cancer Center

Marc C Chamberlain, M.D.
Department of Neurology
USC/Norris Cancer Center
1441 Eastlake Ave., Suite 3459
Los Angeles, CA 90033-0804
Phone: (323) 865 – 3945
Fax (323) 865 – 0061
E-mail: chamberl@usc.edu

Text Pages: 16
Table Pages: 0

ABSTRACT:

Central neurocytomas (CN) are uncommon tumors of the CNS representing approximately 0.1-0.5% of all primary CNS tumors. Patients most often present with symptoms of increased intracranial pressure (headache, nausea/vomiting, diplopia) due to obstructive hydrocephalus. Rarely, CN may present with a hemorrhage. CN are intraventricular tumors with a predilection for arising in either the lateral or third ventricles. CT or MR cranial imaging demonstrates a circumscribed mass in the ventricles, frequent calcification and moderate contrast enhancement. Surgery provides definitive treatment, as little evidence exists as to response of these tumors to either radiotherapy or chemotherapy. Histopathology reveals a homogenous neoplastic cell population with neuronal differentiation, frequent calcification, occasional perivascular pseudorosettes and infrequent mitoses. Uncommonly, anaplastic variants of CN (malignant CN) are encountered and are distinguished by frequent mitoses, necrosis and endothelial cell proliferation. Following complete resection, CN have a favorable prognosis usually obviating the need for either radiotherapy or chemotherapy.

INTRODUCTION:

Hassoun first described central neurocytomas (CN) in 1982[1]. He characterized two tumors that were neuronal by electron microscopy but which resembled oligodendroglioma rather than medulloblastoma by light microscopy. Hassoun stressed the relatively mature appearing neuronal population of tumor cells and the benign clinical course. These tumors were contrasted with the malignant intraparenchymal neuroblastoma and from benign ganglion cell tumors, two other tumors of neuronal origin. Hassoun further suggested that these intraventricular tumors arise from neuroblasts of the septum pellucidum germinal matrix.

Since Hassoun's original description, more than 150 cases of CN have been described confirming the core characteristics of the tumor[1-20]. The widespread use of the synaptophysin immunoreaction and electron microscopy has lead to an increased recognition and diagnosis of CN. These main features of CN include:

1) lateral ventricle location, 2) occurrence in young adults, 3) characteristic radiological findings (see below), 4) resemblance to oligodendroglioma or ependymoma on light microscopy, 5) a neuronal cell origin seen on electron microscopy and by immunohisto-chemistry, and 6) a favorable prognosis with benign biological behavior. However, there are several reports of atypical aspects of CN and which occur in 10-20% of most cases series [2,4,7,13,18]. These variations include: 1) a non-central location (usually either extraventricular or spinal), 2) occurrence in older patients, and 3) a malignant variety manifested biologically by early recurrence and progression to death.

CLINICAL PRESENTATION:

The majority of patients are young (medium age 23; range 15-72 years) and present with an etiologically non-specific syndrome of raised intracranial pressure (ICP) [5,6,9,10]. Patient presentation is either acute or sub-acute (median clinical course 6-7 months) during which time; the symptoms of ICP rapidly escalate. Headaches are the dominant symptom and are initially nonspecific and diffuse in nature. Over time headaches increase in frequency and intensity. Many patients are either awakened by or upon awakening from sleep with headache. Subsequently, new symptoms are added with nausea and vomiting next most frequent. In patients presenting with progressive headaches associated with nausea or vomiting, the classic trial of cerebral hypertension is realized. At this juncture, patients often complaint of visual impairment due either to papilledema (corresponding symptom: visual obscuration) or abducens palsy (corresponding symptom: diplopia).

Additionally, patients may complain of lightheadedness, impaired mentation and gait instability. When initially seen, patients are felt to have a benign headache syndrome and may be considered to have migraine if nausea or vomiting is part of the symptom complex. However, progressive daily headaches with or without other symptoms should always raise the suspicion of increased ICP warranting cranial neuroradiographic examination. Rarely, patients with CN will present with focal or lateralized symptoms such as hemiparesis or partial seizures. These individuals will have evidence of either intraparenchymal disease or hemorrhage [a presentation seen in perhaps 3% of all

patients with CN] as contrasted with the majority of patients discussed above whom has evidence of obstructive hydrocephalus due to an intraventricular tumor [20]. .

NEURORADIOLOGY:

CT brain imaging demonstrates an intraventricular tumor (lateral ventricle more often than third ventricle), which are round and well circumscribed [2,5,6,9,10,14]. The tumors are iso- to slightly hyperdense with smooth margins and with small low-density areas. Calcification is present in approximately 50% of all CN. The tumors are often attached to the septum pellucidum and invariably evidence of obstructive hydrocephalous is seen. Post- contrast CT images show relatively homogenous contrast enhancement of the tumor.

MR brain imaging demonstrates a mass which is either isointense (most common pattern) or hyperintense compared with cerebral cortex on T_1- and T_2- weighted images [2,3,5,9,14]. Homogenous enhancement is seen in all tumors within which are multiple, small signal void areas. These hypointense regions represent blood vessels (serpiginous signal-void areas), calcification (punctate signal-void areas) or cysts and are seen in 25%, 50% and >80% of CN respectively . The tumor demarcation, site of attachment and extent of tumor are demonstrated more clearly by MR as compared to CT.

Cerebral angiography in the majority of CN demonstrates a homogenous vascular staining with either a choroidal (anterior or posterior) or lenticulostriate feeding artery. Typically no draining vein is visible [5,9,10].

Other intraventricular tumors such as oligodendroglioma, ependymoma and meningioma are neuroradiographically similar and would be included in the differential diagnosis.

However, CN is suggested by the combination of intraventricular localization, clear tumor demarcation and attachment to the septum pellucidum or lateral wall of the lateral ventricle.

The role of metabolic brain imaging such as FDG-PET or MR spectroscopy, is not defined at the present time.

NEUROPATHOLOGY:

By light microscopy**,** CN are composed of a uniform cell populated with round and occasional polygonal cell contours and central round nuclei with a fine chromatin pattern [1,2,4,5,8-10,14]. Cell cytoplasm is clear to eosinophilic and is uniform in appearance. Mitotic figures, capillary proliferation, pleomorphism or necrosis are infrequent. The isomorphic tumor cell population are often gathered into groups creating the so called comb architecture similar to that observed in oligodendrogliomas and each group is bound by capillaries or very thin bands of connective tissue. Occasionally tumor cells are arranged about wide round fibrillary patches giving rise to a pseudorosette formation similar to that observed in ependymomas. Numerous amorphous or laminated microcalcifications are observed. Generally, CN are well demarcated from the adjacent brain.

By immunohistochemical examination, CN demonstrate a distinctive pattern characterized by strong positivity for neuron specific enolase and synaptophysin and absence of staining to glial fibrillary acidic protein and neurofilament protein [2,4,5,8-10,14].

By electron microscopy, CN tumor cell nuclei are round to oval in shape with euchromatin [2,4,5,8-10,14]. The cytoplasm contains parallel microtubules and membrane-

bound electron-dense or electron-lucent core neurosecretory granules. Well-defined synapses are not observed.

An aggressive variant of CN, sometimes referred to as a malignant CN, occurs in 10-20% of most case series [2,4,7,18]. Evidence of anaplasia (nuclear pleomorphism, endothelial proliferation, necrosis and frequent mitotic figures) may be seen but correlates poorly with clinical outcome. Alternatively, a measure of tumor proliferation has been utilized in an attempt to better predict biological behavior of CN [3,11,18].

The proliferative potential of CN has been evaluated by immunoreactivity to proliferating cell nuclear antigen (PCNA), silver colloid staining for nucleolar organizing regions. (AgNORs), DNA flow cytometry and Ki-67 labeling index utilizing MIB-1 antibody [3,11,18].

In general, PCNA staining is less than 1% in CN. Diploidy is seen in all tumors by flow cytometry with a mean proliferation index of 7.8% (range 5.1- 9.6%). KC-67 labeling index varies (range 0.4-11.2%) 38-60% of tumors having indices greater than 2%. Clinical outcome correlates with the Ki-67 labeling index (LI) in that >60% of patients with LI> 2% recur versus <20% of patients with LI<2% [3].

In a recent paper examining proliferative potential of CN utilizingMIB-1 labeling index, 36 cases were subdivided into two subpopulations [18]. 54% of patients [22 patients] had LI < 2% and amongst whom, 2 recurred. This group of patients (low LI) had a 22% chance of recurrence over a 10-year epoch. 46% of patients [14 patients] however had LI > 2% and 6 of these patients recurred over the observation period [63% chance of relapse over a 10-year follow-up]. In addition, vascular proliferation but not necrosis correlated with LI [markedly more common in tumors with high LI]. The paper concludes that the

proliferative potential of CN varies considerably and progression-free survival correlates with LI. The authors suggest that the term atypical CN be used for tumors displaying either LI > 2% or vascular proliferation and perhaps treatment [for example the inclusion of radiotherapy] should be modified for this group.

TREATMENT:

Surgery:

A consensus has evolved that attempted gross total resection with complete tumor removal is the treatment of choice for CN [2-19]. The surgical approach is dependent upon the tumor location and operator experience and preference. Most often, an anterior interhemispheric transcallosal route is used though transfrontal or other transcortical surgical approaches to the tumor may be utilized.

Notwithstanding the goal of complete tumor resection, this is not achievable in upwards of 50% of patients either because of extent of disease, adherence of tumor to adjoining structures or hemorrhage. Therefore, the management of subtotally resected tumors is frequently seen in clinical practice. Re-operation much as is done for partially resected ependymomas, juvenile pilocytic astrocytomas or low-grade gliomas has not been reported through would appear rational (authors opinion). Re-operation is always a consideration should tumor recur.

Radiotherapy:

At present there is no compelling evidence to suggest radiotherapy is beneficial in the treatment of patients with CN [1,5]. Notwithstanding the uncertainty of radiotherapy, a majority of series has utilized radiotherapy postoperatively irrespective of whether a partial or complete excision was accomplished [2-5,9-10,15]. Reports in the literature have

commented upon the occasional neuroradiographic response following radiotherapy in partially resected CN leading in part to the enthusiasm for application of radiotherapy. The histopathological features of CN such as neuronal differentiation, low mitotic activity, absence of vascular endothelial proliferation and tumor necrosis would suggest a relative resistance to ionizing radiation. Kim, in the only study to evaluate the role of routine postoperative radiotherapy, compared eight patients receiving radiotherapy to seven patients not receiving radiotherapy and otherwise matched with respect to extent of surgical resection [15]. No difference was noted with respect to quality of life (by means of the Karnofsky performance status) or survival.

Also not clearly defined is the role of radiotherapy in patients with the malignant variant of CN [2]. Most authors however advocate adjuvant radiotherapy to this aggressive variant regardless of whether a complete or incomplete resection has been performed.

Finally, the majority of authors also advocate treating recurrent CN with radiotherapy regardless of whether a resection is performed [2-5,9-10,15].

When radiotherapy has been administered, either whole brain or involved-field treatment volume is given utilizing a standard fractionation schedule and to a total tumor dose of 50-55 Gy.

The role of stereotactic radiotherapy in the treatment of CN as for example gamma knife radiotherapy or LINAC radiosurgery, is in addition unclear.

Chemotherapy:

The role of chemotherapy in treating CN has been limited to patients with recurrent CN of only three small case series involving one, two and three patients respectively have been reported [12-14]. In all three series, chemotherapy utilized one of two platinum-based

regimens (carboplatin + VP-16 + ifosfamide or cisplatin + VP-16 + cyclophosphamide). Of the six patients so treated, no response data regarding chemotherapy was given in two patients. Amongst the remaining four patients, one patient received chemotherapy without surgery and demonstrated a partial response, which was sustained for 22 months. Following tumor recurrence, the patient was treated with re-operation followed by radiotherapy. In the remaining three patients (all treated at time of recurrence), one patient had a complete response (duration of response 36 months) and two patients had stable disease (duration of response 15 and 18 months).

Therefore, any recommendations regarding chemotherapy in the treatment of CN, are based on four patients in whom there was one complete response, one partial response and two stable disease patterns with a medium duration of response at 20 months (range 15-36 months). Consequently, recommendations regarding CN and chemotherapy must be viewed as limited and preliminary.

OUTCOME:

A majority of patients (>70%) can be expected to be long-term survivors and probably cured of their disease. However the benign outcome predicted in earlier series is not consistently realized. Features that predict for tumor recurrence and death due to progressive disease are high proliferative indices (see neuropathology section), early disease recurrence and disseminated disease with or without CSF spread of disease. However, none of these features aside from disseminated disease necessarily preclude re-operation with or without radiotherapy. The literature suggests a significant proportion of such patients (>50%) may have long-term durable responses.

In that recurrences have been reported as late as eight years after initial surgery, cranial MR imaging every 6-12 months (or in the rare instances of spinal cord CN, spinal MR imaging) would appear well advised (author's opinion). However, no formal recommendations regarding follow-up are available in the literature.

CONCLUSIONS:

The natural history of CN is poorly defined. CN may behave both in a benign and malignant manner complicating formal recommendations regarding treatment. In addition, as the biologic spectrum of CN is characterized, it has become apparent that these tumors may occur in locations other than the lateral or third ventricles and, in addition, CN may be seen in adults greater than 40 years of age. Nonetheless, for a newly diagnosed CN, complete resection has been advocated and felt to result in the best

long-term prognosis. In the event of CN recurrence, the majority of recurrences are local and re-resection with or without radiotherapy results in long-term survivorship.

The role of both radiotherapy and chemotherapy in the treatment of CN is unclear and suggests that cooperative groups utilizing randomized clinical trials offer the best means by which to evaluate the non-surgical treatment of CN.

EXPERT OPINION

Given the present uncertainties regarding therapy as discussed above, a definitive statement as to how to manage CN necessarily should be couched in humility. With this caveat, the author feels that an attempt at complete resection should be undertaken when the diagnosis of CN is entertained. In patients presenting for second opinion following prior incomplete resection, a consideration for re-operation and complete resection is suggested. In all instances following surgery, neuropathology should provide a MIB-1 LI/Ki-67 as the largest pathological series clearly documents two subpopulations of CN based on a LI cutoff value of < or > 2%. In patients with low LI [< 2%], surgery and follow-up as discussed above is appropriate. In patients with LI >2%, involved-field radiotherapy would seem rationale. Recurrent disease is best managed by re-operation and if residual disease remains or the LI is > 2%, treatment with radiotherapy if not previously administered should be considered. Chemotherapy is best reserved for patients having failed both surgery and radiotherapy and though platinum-containing regimens have been utilized, other agents such as cyclophosphamide, VP-16 and temozolomide might be utilized as well.

FIVE-YEAR VIEW

The evaluation and treatment of CN are unlikely to improve pending creation of a brain tumor consortium with particular interest in CN. Without randomized clinical trials involving sufficient numbers of patients, definitive statements as to the management of CN will remain a subject of debate and controversy. In particular, the role of radiotherapy and chemotherapy could easily be clarified by randomized clinical trials. The use of experimental therapeutics such as stereotactic radiotherapies and investigational chemotherapy in the treatment of CN would next be addressed following clarification of the role of standard therapies such as external beam radiotherapy.

REFERENCES

Papers of special note have been highlighted as:

- of interest
- of considerable interest

1. Hassoun J, Gambarelli D, Grisoli F, Pellet W, Salamon G, Pelissier JF. Central neurocytomas. An electron microscopic study of two cases. Acta Neuropathol (Berl) 56: 151-156, 1982.

* Initial description of the entity

2. Yasargil M, Gazi A, von Deimling K, von Valavanis A, Wichmann A, Wiestler W, Otmar D. Central neurocytoma: Histopathological variants and therapeutic approaches. J Neurosurg 76:32-37, 1992.

** A key paper describing the standard treatment approach

3. Kim DG, Kim JS, Ghi JG, Park SH, Jung HW, Choi KS, Han DH. Central neurocytoma: proliferative potential and biological behavior. J Neurosurg 84:742-747,1996.

4. Eng DY, DeMonte F, Ginsberg L, Fuller GN, Jaeckle K. Craniospinal dissemination of central neurocytoma. J Neurosurg 86:547-552, 1997.

5. Louis DN, Swearingen B, Linggood RM., Dickersin GR, Kretschmar C, Bhan AK, Hedley-Whyte ET. Central nervous system neurocytoma and neuroblastoma in adults-report of eight cases. Journal of Neuro-Oncology 9: 231-238, 1990.

6. Townsend, J. J., Seaman, J. P. Central neurocytoma – a rare benign intraventricular tumor. Acta Neuropathol (Berl) 71: 167-170, 1986.

7. Tatter SB, Borges LF, Louis DN. Central neurocytomas of the cervical spinal cord. J Neurosurg 81:288-293, 1994.

8. Becker LE. Central neuronal tumors in childhood: relationship to dysplasia. Journal of Neuro-Oncology 24: 13-19, 1995.

9. Kim DG, Chi, JG, Park SH, Chang KH, Lee SH, Jung HW, Kim HJ, Cho BK, Choi KS, Han HH. Intraventricular neurocytoma: clinicopathological analysis of seven cases. J Neurosurg 76:759-765, 1992.

10. Nishio S, Tashima T, Takeshita I, Fukui M. Intraventricular neurocytoma: clinicopathological features of six cases. J Neurosurg 68:665-670, 1988.

11. Mackenzie, IRA. Central Neurocytoma: Histologic Atypia, Proliferation Potential, and Clinical Outcome. Cancer 85(7): 1606-1610, 1999.

12. Dodds D, Nonis J, Mehta M, Rampling R. Central neurocytoma: A clinical study of response to chemotherapy. Journal of Neuro-Oncology 34: 279-283, 1997.

13. Brandes AA, Amista P, Gardiman M, Volpin L, Danieli D, Guglielmi B, Carollo C, Pinna G, Turazzi S, Monfardini S. Chemotherapy in Patients with Recurrent and Progressive Central Neurocytoma. Cancer 88(1): 169-174, 2000.

* The best paper describing the role for chemotherapy

14. Ashkan K, Casey, Adrian TH, D'Arrigo C, Harkness WF, Thomas DGT. Benign Central Neurocytoma. Cancer 89(5): 1111-1120, 2000.

15. Kim Dg, Paek SA, Kim IH, Chi JG, Jung H-W, Han DH, Choi KS, Cho BK. Central Neurocytoma: The Role of Radiation therapy and Long Term Outcome. Cancer 1997; 79: 1995-2002.

* The best paper describing the role for radiotherapy

16. Sgouros S, Carey M, Aluwihare N, Barber P, Jackowski A. Central Neurocytoma: A Correlative Clinicopathologic and Radiologic Analysis. Surgical Neurology 49(2): 197-204, 1998.

17. Metellus P, Alliez JR, Dodero F, Hassoun J, Alliez B. Central Neurocytoma: 2 case reports and review of the literature. Acta Neurochirurgia 142(12): 1417-1422, 2000.

18. Soylemezoglu F, Scheithauer BW, Esteve J, Kleihues P. Atypical Central Neurocytoma. J Neuropath Exp Neurol 56(3): 551-556, 1997.

** The best paper to describe proliferative capacity as a measure of tumor prognosis

19. Cabiol J, Acebes JJ. Central Neurocytoma: A Reappraisal. Crit Rev Neurosurg. 6: 309-315, 1996.

20. Okamura A, Goto S, Sato k, Ushio Y. Central Neurocytoma with hemorrhagic onset. Surgical Neurology 43(3): 252-255, 1995.

KEY ISSUES:

- Central neurocytomas is an uncommon neuronal tumor of the central nervous system most often of young adults and located in the lateral ventricle
- Gross total resection of the tumor is associated with the best long-term prognosis
- The role for radiotherapy and chemotherapy is unclear
- 10-20% of neurocytomas behave aggressively and may be predicted based on MIB-1 LI > 2% or presence of vascular proliferation
- Randomized clinical trials are necessary to clarify the role of radiotherapy and chemotherapy in treatment of CN