Surgical management of primary central nervous system germ cell tumors

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A review

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The successful treatment of children with a primary CNS germ cell tumor can be greatly influenced by the neurosurgeon involved in the diagnostic and therapeutic care of these children. Variability in surgical philosophies no doubt exists due to the relatively infrequent incidence of these tumors, a lack of consensus regarding diagnostic and therapeutic approaches, and the advent of recent surgical innovations. Many of these issues were discussed at the Second International Symposium on Central Nervous System Germ Cell Tumors through presented abstracts and invited presentations. The neurosurgical aspects of these proceedings are summarized here in an effort to present the agreed-upon and debated issues that may confront the pediatric neurosurgeon. (DOI: 10.3171/2010.5.PEDS09112)

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Neurosurgical intervention for the patient with a primary CNS GCT may be required for diagnostic sampling, tumor cytoreduction, or hydrocephalus treatment. Advances in diagnostic imaging, navigational guidance, endoscopic technology, biochemical profiling, and neoadjuvant chemotherapy have had a significant impact on the surgical strategy for these patients. Within the past decade endoscopic techniques such as tumor biopsy, tumor removal, and third ventriculostomy have been integrated into the surgical treatment of patients with primary CNS GCTs. The evolution of conventional microsurgical techniques coupled with high-resolution imaging and navigational guidance has resulted in a progressive decline in associated morbidity. Thus, principal sites of CNS GCTs, namely the suprasellar and pineal regions, which have been historically considered as ominous surgical undertakings, are now approached with morbidity rates in accordance with most other intracranial sites. This feature affords the opportunity to reassess the value of aggressive resection of tumor at the time of diagnosis or following induction chemotherapy. This latter approach of second-look surgery is intended to remove residual tumor that is unresponsive to radiotherapy or chemotherapy. These contemporary issues were recently presented by the authors at the Second International Symposium on Central Nervous System Germ Cell Tumors and are highlighted in the following sections.
Advances in Neurosurgical Management

Technological advances in endoscopic equipment have resulted in reduced endoscope dimensions, brighter illumination, and compatible instrumentation. These features have allowed the field of neuroendoscopy to burgeon with a noticeable impact on certain neurological disorders. The success of endoscopic surgery, however, remains strongly dependent on disciplined patient selection, using the appropriate technique, and the endoscopic experience of the neurosurgeon.

Several unique features of CNS GCTs create a very appealing opportunity to employ endoscopic therapy. Diagnostic sampling for CNS GCTs is frequently all that is needed due to the high response rates of GCTs using neoadjuvant radiation or chemotherapy, thus refuting a need for extensive tumor resection at the time of presentation. Endoscopic tumor biopsy for GCTs is a natural extension of endoscopic surgery given that these tumors are situated in and around the ventricular compartment. The anatomical feature of surrounding CSF offers a natural medium for light and image transmission. The appeal of a minimally invasive approach is furthered by the typical deep and central locations for many of these tumors, positions that can be challenging for conventional surgical techniques. An additional benefit of endoscopic tumor biopsy is the ability to simultaneously perform an ETV. Endoscopic third ventriculostomy is established as an advantageous treatment alternative compared with ventriculoperitoneal shunting in selected patients with noncommunicating hydrocephalus.11,12,15 The patient with noncommunicating hydrocephalus due to a posterior third ventricular or pineal region tumor is an ideal candidate for ETV. Adding only several additional minutes to the surgical procedure, ETV is easily integrated at the time of tissue biopsy.7,29,32 Endoscopic biopsy also allows a safe alternative to lumbar puncture for CSF sampling in the patient with noncommunicating hydrocephalus.

Initial reports indicated a modest rate of diagnostic accuracy with endoscopic tumor biopsy, but subsequent assessments have shown diagnostic yields as high as 90%—98%.3,29,32,37,40 A representative case of endoscopic tumor biopsy of a pineal region tumor is shown in Fig. 1. Although it is simpler in patients with large ventricles, endoscopic biopsy has been shown to be safe and effective in patients without hydrocephalus through the integrated use of stereotactic guidance and other technical modifications.38

Tissue sampling of primary CNS GCTs should be governed by the requisite need for biopsy. Serum and CSF markers should be measured if possible. The absence of both serum and CSF AFP is mandatory in the diagnosis of pure germinoma. More controversial is the level of either serum or CSF β−HCG, which is used to exclude a pure germinoma.8 Because it is known that pure germinomas can include syncytiotrophoblastic cells, some secretion of β−HCG is occasionally found. Although a β−HCG level up to 50 mIU/ml is considered by most to be consistent with a secretory germinoma, some investigators have shown no change in patient outcome when patients with β−HCG levels as high as 200 mIU/ml are included in germinoma therapy trials.10 For tumors with biochemical testing indicating an NGGCT (AFP > 0 mIU/ml and β−HCG > 50 mIU/ml), there is no convincing rationale for tissue sampling because the treatment approach is not altered. Furthermore, there is the possibility of misleading information from tissue sampling in a biochemically proven NGGCT due to the high frequency of mixed tumor types.23 Given the recent emphasis on biological and genetic profiling of primary CNS GCTs, the rationale for tissue sampling may expand to include NGGCT.20

A theoretical concern with endoscopic tumor biopsy unique to patients with primary CNS GCT is the potential risk of iatrogenic tumor dissemination.14,44 This anxiety is justified given the common utilization of limited radiation fields and frequent subtotal tumor resection. The rare but documented occurrence of peritoneal dissemination of GCT through ventriculoperitoneal shunts further supports this concern.13,19,28,45 Additionally, case reports have identified cerebral dissemination along both proximal shunt catheters and endoscopic paths.3,35 Thus it is logical to speculate that patients undergoing simultaneous tumor biopsy and ETV may be at an increased risk of distant failure. Whether rates of distant failure will differ in such patients will be the topic of future prospective studies, but initial patient series suggest no higher rate of CSF dissemination.22 A common misconception regarding endoscopic tumor surgery is that patient morbidity is increased due to uncontrolled hemorrhage. However, endoscopic tumor biopsy is rarely associated with complications or catastrophic hemorrhage.21

Intraventricular endoscopic surgery offers an unprecedented opportunity to inspect the ependymal surface for direct or distant tumor dissemination. This ability has recently been shown to offer a potentially more sensitive appraisal of tumor spread than is available with contrast-enhanced MR imaging.5,30,44 An example of germinoma dissemination noted at the time of endoscopic tumor biopsy is shown in Fig. 2. Given the importance applied to metastatic staging and the strong influence on selecting the best therapeutic alternative, diagnostic endoscopic ventriculoscopy may play an increasingly important role in the treatment of patients with primary CNS GCT.

Complete tumor removal has been shown to be possible using both an endoscopically assisted or primary en-
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The high response rates of pure germinoma in combination with the previously noted morbidity of surgical removal appropriately tempered past enthusiasm for resection in the management of these tumors. Because these tumors typically lie in deep midline regions, such as the pineal region and the suprasellar cistern, and are in close proximity to critical brain structures, surgery traditionally has been considered to have inordinate risk for seemingly limited benefit. However, current microsurgical techniques, aided by the development of high-resolution imaging, navigational guidance, and advanced endoscopic procedures, make resection of these lesions relatively safe in experienced hands. Extrapolating the morbidity rates from contemporary series for approaches to the suprasellar and pineal region, it is logical to reconsider aggressive cytoreductive surgery for pure germinoma. This reappraisal is only logical if it can be shown that aggressive resection of pure germinoma has an oncological benefit compared with current treatment paradigms. Cytoreductive surgery may play a role in the future in chemotherapy-only strategies, in which radiation therapy is minimized to avoid neuropsychological sequelae or in regions of the world where it is not readily available.

To analyze this issue, pooled data from the First, Second, and Third International Central Nervous System Germ Cell Study Groups were analyzed.17,18,26 All patients were initially treated with neoadjuvant chemotherapy without radiation. Upfront radiation therapy was avoided to limit neurocognitive sequelae and because of its limited availability in other countries. Sixty-six histologically and biochemically proven pure germinomas were studied. The average age of the patients was 14 years, and they were followed for an average of 6 years. Fourteen of these patients had multifocal disease and were excluded from this analysis. Of the remaining patients, those who had less than 1.5 cm² of residual disease prior to the initiation of adjuvant therapy had better outcomes than those with a larger residual tumor, with recurrence rates of 38% versus 65%, respectively. This was found to be true regardless of tumor location. These results are still not as good as those noted in other series in which upfront radiation therapy is employed. Thus, at this time, treatment should include adjuvant radiation and no role for aggressive cytoreduction. However, these results do suggest that treatment paradigms that rely primarily on chemotherapy might be more efficacious if the tumor burden is less.

An additional rationale for aggressive resection of CNS pure germinoma is the purported increase in diag-

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**Fig. 2.** Example of germinoma dissemination noted at the time of endoscopic tumor biopsy. A and B: Sagittal (A) and coronal (B) postcontrast MR imaging scans obtained in an adolescent patient with a pineal region tumor. Endoscopic third ventriculostomy and tumor biopsy were planned for a presumed germinoma. C: Endoscopic view from a right anterior approach with a view into the third ventricle. Ependymal deposits (arrow) believed to be disseminated tumor are situated on the lateral margin of the foramen of Monro.
nostic accuracy. Many tumors classified as germinomas have been shown to contain nongerminomatous elements upon further evaluation. It is often these nongerminomatous elements that are resistant to therapy, confounding any analysis of treatment outcomes. It is unknown if a more aggressive resection of CNS germinomas would improve outcome from the standpoint of more accurate diagnostic interpretation or reduced tumor burden.

Although not currently considered the standard of care, the role of resection in CNS germinomas warrants further investigation. Recurrence rates as high as 10–15% using current treatment regimens, coupled with the potential for improved functional outcome through reduced treatment-related morbidity, raises the possibility of incorporating different surgical strategies. This paradigm shift will admittedly be difficult to study in future cooperative studies given the current success in patients with newly diagnosed pure germinoma.

Second-Look Surgery

Using induction chemotherapy, radiographic and biochemical responses are typical for marker-positive NGGCT (β-HCG > 50 mIU/l and/or AFP > laboratory standard of approximately 8–12 ng/ml in serum and > 1.5 ng/dl in CSF). However, biochemically silent residual disease following induction chemotherapy poses a diagnostic challenge and is a critical issue in treatment. Prior experience in the treatment of systemic GCTs revealed that residual radiographic abnormalities after initial chemotherapy often implied fibrosis-related changes or teratoma. Observation alone in this situation would result in radiographic progression in many situations, an entity referred to as the growing teratoma syndrome. In the case of residual or progressive radiographic abnormality without biochemical abnormality, it was found that patients could be rendered long-term survivors using delayed, second-look surgery.

This experience in systemic GCTs suggested that the ideal CNS GCT candidate for delayed or second-look surgery would be the patient who presented with marker-positive NGGCT, and who also harbored a mature teratoma within this mixed tumor that became evident only after initial treatment with chemotherapy. The NGGCT elements within the tumor would respond to chemotherapy, yet the follow-up MR imaging scan would reveal a residual enhancing mass. Resection would be then be used, for the first time in this protocol, to treat this residual lesion. This approach is unique in neurosurgical oncology and represents a new paradigm for the role of resective surgery in CNS neoplasia. A representative case of such an approach is demonstrated in Fig. 3.

A number of published reports substantiate the approach of using second-look surgery to completely eradicate these tumors completely, a second-look operation should be considered. Illustrating this point is a recent review of 126 patients enrolled in 2 international, multicenter, clinical CNS GCT trials. Of 10 patients who were treated with delayed resection, 5 were found to have teratomas (3 mature and 2 immature) and 5 had necrosis/scar tissue at delayed resection. Similarly, Friedman et al. identified 6 patients out of 16 treated at their institution who were treated in this fashion, 5 of whom harbored teratoma and 1 necrosis/scar. Similarly, another report found that of 10 patients with NGGCT who were initially treated with chemotherapy, 5 underwent second-look surgery. Four of these patients had pathologically confirmed teratoma and 1 had fibrotic tissue.

Despite the success of this overall approach, some valid questions remain. The exact timing of delayed surgery remains to be determined. Importantly, it has been found that delayed resection should certainly be avoided in patients in whom tumor markers have not normalized completely, due to the finding that these patients appear to progress despite second-look surgery. More problematic is the scenario of a near-total radiographic response, normalized or decreasing markers, and no symptoms after initial chemotherapy. In this particular scenario, it is reasonable to assume that the likely diagnosis is necrosis and/or scar, and avoiding second-look surgery may be desirable. Alternatively, the presence of any residual radiographic abnormality may imply the presence of dormant malignant GCT elements that have resisted therapy. One might consider the following strategy: in the setting of an enlarging lesion with normalized markers, the diagnosis is likely teratoma, and delayed resection should be performed; with an asymptomatic lesion that is stable or diminishing in the presence of normalized tumor markers, avoiding delayed surgery would be preferable because the likely diagnosis is necrosis/scar; and if markers are not completely normalized, persistent NGGCT and/or immature teratoma is most likely, and delayed surgery should be avoided. One potential limitation of using such a strategy is in the case of NGGCTs that do not have elevated...
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markers. If it is conceivable that advanced molecular or imaging techniques will contribute to a higher specificity of diagnosing CNS GCT types, thus defining more accurately when surgical intervention is warranted.

Lastly, the initial rationale driving the use of secondlook surgery in CNS GCTs was to complete the response initiated by chemotherapy, and thereby avoid additional intensive treatment, such as radiation therapy and/or chemotherapy. However, other risk factors such as the presence of tumor dissemination may be equally important in determining whether further therapy may be necessary. A recent illustrative case involved an 8-year-old girl who initially presented with headaches, polydipsia/polyuria, and fatigue, an enhancing suprasellar lesion, serum and CSF β-HCG > 100 IU/L, and positive CSF neuraxis dissemination. Although the markers normalized completely after initial chemotherapy, a residual radiographic mass was detected. She underwent a resection for tissue that was pathologically confirmed as necrosis and scar formation. Four years later, however, a routine MR imaging scan revealed a left basal ganglia GCT recurrence, confirmed by stereotactic biopsy. Thus, despite the secondlook surgery confirming no active tumor, it is possible that she relapsed due to unrecognized microscopic dissemination or multifocal tumor.

Contemporary Clinical Trials

The rarity of intracranial GCT has significantly hindered identifying optimal therapeutic and surgical approaches. Cooperative groups have thus led the charge in clarifying some issues pertaining to the treatment of children with CNS GCT. Current cooperative group trials are aimed principally at defining the role of chemotherapy (adjunctive with dose reduction or avoidance of radiation therapy) and the appropriate field (involved field, periventricular, craniospinal, and others) and optimal dose of radiation therapy. Some of these trials have incorporated important surgical objectives. The recently closed COG study (ACNS0122) had a secondary aim: to evaluate the correlation between biochemical markers and tumor removed with second-look surgery in patients with NGGCT. It is expected that this study, encompassing about 100 children, will support the concept of second-look surgery in the setting of residual tumor with a complete biochemical response. The results from the most recent International Society of Pediatric Oncology study (SIOP CNS GCT96) strengthened the requisite need for preoperative biochemical assessment, by showing that significant numbers of children underwent unjustified tumor resections or tissue sampling. Most recently, the COG study ACNS0232 had a primary intent to compare germinoma treatment using radiation alone with chemotherapy followed by response-based radiation therapy. Notably, that study included 2 neurosurgical objectives based on a better understanding of the role of endoscopic neurosurgery in the management of these children: the true risk of CSF dissemination with simultaneous ETV and tumor biopsy, and a comparison between endoscopic observations and MR imaging in indentifying metastatic disease. This study (ACNS0232) closed due to poor patient accrual and highlights the dire need for study approval and member participation. No doubt future cooperative studies will integrate similar neurosurgical aims.

Conclusions

The surgical management of primary CNS GCT has evolved coincident with the introduction of advanced technology including microsurgical dissection, endoscopic neurosurgery, and navigational guidance. These surgical techniques have since been applied to a minimally invasive and less morbid approach to the patient with either a newly diagnosed CNS GCT, or for secondlook surgery following neoadjuvant chemotherapy. The decrease in surgical morbidity paralleling an enthusiasm for reducing the adverse effects of irradiation may justify a critical reappraisal of radical removal of pure germinoma. These important topics need to be addressed by integrating surgical questions into the design of future cooperative studies.

Disclosure

Mark M. Souweidane is a paid consultant for Aesculap. Author contributions to the study and manuscript preparation include the following. Conception and design: Souweidane, Krieger, Weiner, Finlay.

References


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