Controversies in the Management of Intracranial Germinomas

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Intracranial germinomas are uncommon tumors. In the past, patients have traditionally been diagnosed with a trial of focal radiotherapy without biopsy. If the tumor was radiosensitive, it was presumed to be a germinoma.

Introduction

Intracranial germinomas are rare and account for 1% of all intracranial tumors in the Western hemisphere. In Japan, intracranial germinomas are more common, comprising 4% of all central nervous system neoplasms. Approximately, two-thirds of germinomas arise in the pineal gland region and one-third in the suprasellar region.[1] Multiple midline tumors defined as 2 or more separate tumors arising in the pineal, suprasellar or parasellar regions, can occur.[2] Intracranial germinoma develops most frequently in young adolescents; males are more likely to be affected than females.

Histologically, germinomas are identical to testicular seminomas or ovarian dysgerminomas. On light microscopy, germinomas are composed of large, monotonous round primitive cells with eosinophilic cytoplasm and vesicular nuclei intermixed with small lymphocytes; placental alkaline phosphatase staining is positive.[3]

Signs and symptoms at presentation depend on the location of the tumor. For pineal region lesions, headaches, papilledema, nausea, vomiting and lethargy may occur secondary to obstruction of the posterior third ventricle and aqueduct of Sylvius. Parinaud’s syndrome (inhibition of upward gaze, diminished pupillary response to light with preservation of accommodation) may occur when the tumor compresses the midbrain tegmentum and quadrigeminal plate. Hypothalamic and pituitary dysfunction may occur with suprasellar germinomas; these may include diabetes insipidus, growth failure, and delayed or precocious puberty.

The work-up of patients with intracranial germinoma includes a computed tomographic scan (CT) of the brain with contrast. Magnetic resonance imaging (MRI) with gadolinium will further delineate the tumor’s extent and location. Magnetic resonance imaging of the spinal axis or myelogram, in addition to cerebrospinal fluid (CSF) cytology, is performed because of the possibility of tumor spread. Cerebrospinal fluid and serum alpha fetoprotein (AFP) and human chorionic gonadotropin (HCG) are evaluated since an elevated AFP rules out a pure germinoma and may be secondary to an endodermal sinus tumor (yolk sac tumor). Mild to moderate elevation of HCG (< 2000 mIU/mL) may be associated with germinoma with syncytiotrophoblastic giant cells. Significantly high elevation of HCG is seen in non-germinomatous germ-cell tumors, specifically, choriocarcinoma. Because disease outside the CNS is rare, other systemic work-up is not warranted unless the patient is symptomatic.

Diagnosis

Is Tissue Diagnosis Necessary?
Tumors of the pineal region are in close proximity to various vascular and brain structures.[4] In earlier reports, operative mortality after direct surgery and/or biopsy ranged from 30% to 70% with a morbidity of 65%.[5,6] Because surgery and biopsy were associated with a high mortality and morbidity, many institutions utilized a trial of 2,000 cGy radiation therapy to a local field as a means of [radiodiagnosis] and treatment. (Computed tomographic scans of the brain in patients with pathologically verified pure germinoma have shown marked tumor response to a trial dose of ≤ 2,000 cGy.[7,8] If the tumor was radioresponsive, the tumor was thought to be a germinoma, and further treatment included craniospinal irradiation to a dose of 3,000 cGy. If the tumor was radioresistant or slow to respond, further radiation to a local field or surgical resection was sometimes suggested.
At present, most clinicians would recommend obtaining a tissue diagnosis. In one large multi-institution study conducted in France, stereotactic biopsy for tumors of the pineal gland
between the years 1975 to 1992 resulted in a mortality of 1.3%, morbidity of 0.8%, and diagnostic yield of 94%. Improvements in microsurgical techniques and open biopsy are also associated with low mortality and morbidity. Some investigators prefer an open biopsy because of the possibility of a sampling error in a heterogeneous tumor.

Tissue diagnosis of a pineal or a suprasellar lesion is imperative in the management of the patient's disease. Because the majority of those affected are children and adolescents, radiation therapy can be avoided in those with benign lesions. Craniospinal irradiation and chemotherapy is indicated in patients with primitive neuroectodermal tumors (PNET), whereas local irradiation and chemotherapy after maximal surgical resection is used for those with high-grade gliomas.

In one series, histologic verification of pineal and suprasellar region lesions showed that 61% were germ-cell tumors, 15% were pineoblastomas (PNETs of the pineal gland), 17% were gliomas, and 7% were benign tumors. Of the germ-cell tumors, approximately two-thirds were pure germinomas and one-third non-germinoma germ-cell tumors. Furthermore, pineoblastomas and some nongerminomas may shrink with a trial of radiotherapy and may be mistaken for a pure germinoma. Thus, because of the wide spectrum of histologies and different treatments, we advocate obtaining tissue diagnosis, especially since current neurosurgical techniques are associated with minimal morbidity.

What is the Incidence of CSF Cytology Positivity?

The positivity rates of CSF cytology in patients with intracranial germinoma vary considerably (range, 0% to 100%). The wide variation in incidence may be attributed to the fact that the majority of series have included radiographic or non-histologically verified germinomas. Table 1 shows recent reports of histologically verified germinomas and the incidence of CSF cytology positivity: the incidence varies from 7.7% to 17.6%. There does not seem to be a higher incidence of subarachnoid seeding with suprasellar lesions.

In one study of 42 patients, 16 with a histologic and 26 with a clinical/radiologic diagnosis, the CSF cytology was positive in 52%. The authors noted that the method of detection (wet film, membrane filter cytocentrifugation, millipore filter/cell culture) may influence CSF cytology positivity, with those detected by cytocentrifugation having a higher positivity rate.

Surgical Management

Is CSF Shunting Contraindicated?

Children with germinomas may present with hydrocephalus secondary to occlusion of CSF pathways by tumor. The use of ventriculo-peritoneal (VP) shunts has been successful in alleviating symptoms from increased intracranial pressure. There has been some concern regarding the use of VP shunts because of the possibility that tumor cells from the brain may spread to the abdomen. In a review of the literature, Rickert found 35 VP shunt-related abdominal metastases from pediatric brain tumors. The most common type of tumor implicated was germinoma, followed by medulloblastoma.

In a review of 25 cases of pineal region tumors treated at Stanford University, Fuller and colleagues noted that only 1 of 15 patients who had VP shunt placement developed abdominal metastases. In another study, the risk of tumor seeding via a shunt catheter was 3.8%. In conclusion, although there have been reports of tumor seeding via shunts, the risk of such an occurrence is small and should not be a contraindication to shunting a patient.

What is the Role of Radical Resection?

Surgical debulking is a critical part of the treatment of many pediatric brain tumors, such as gliomas and PNETs. In general, radical resection of these tumors offers the patient a better chance of cure. Because nearly all germinomas are curable with radiation therapy and/or chemotherapy, the question arises as to whether radical resection offers any additional benefit.

In a retrospective study of 29 patients who underwent surgery for germinoma, 16 had a biopsy performed, 5 had a partial resection, and 8 had a gross total resection. The majority received chemotherapy and radiation therapy after the planned surgery. There was no significant difference in outcome related to the extent of surgery. Transient surgical complications were observed in 5 patients who underwent partial or total resection of the tumor, whereas none of the 16 patients in whom biopsy specimens were obtained experienced complications.

The authors concluded that the primary goal of surgery should be to obtain sufficient tissue for histologic examination. Radical resection of intracranial germinomas offers no benefit over biopsy since all patients still require radiotherapy and/or chemotherapy.
As mentioned above, some physicians prefer open surgical biopsy to stereotactic biopsy in order to obtain sufficient tissue to minimize the likelihood of missing a mixed germ cell tumor.

**Radiotherapeutic Management**

**Radiotherapy Volume**
One of the most frequently debated questions in the radiotherapeutic approach to germinomas is what volume to treat when radiotherapy is used alone. Table 2 summarizes the results of treatment using craniospinal irradiation in selected series. The results with craniospinal irradiation are excellent, as demonstrated by 10 year relapse-free survival rates of approximately 90%.\[20,22,29-31\] Perhaps the strongest data in support of routine craniospinal irradiation for all patients with intracranial germinoma comes from an early report by Sung et al.[32] Of 14 patients with biopsy-proven germinoma who did not receive spinal irradiation, 6 developed spinal metastases. Linstadt et al analyzed the literature prior to 1988 and estimated that spinal failures rates are 8% and 23% with and without spinal irradiation, respectively.[16] More contemporary series indicate that the risk of spinal failure is low even without spinal irradiation. Table 3 demonstrates the incidence of spinal failure in patients with histologically verified germinomas who did not receive prophylactic spinal irradiation.[16,19,21,22,33] The risk of spinal failure was low at approximately 9%. In patients receiving radiotherapy to the tumor plus margins alone (involved field), Haddock et al showed 4 spinal recurrences in 11 patients.[21] In contrast, a report from Dattoli et al showed only 1 spinal recurrence in 10 patients treated with involved-field radiation alone.[19] When only the whole brain was irradiated, the spinal recurrence rate ranged from 0% to 10%.

Concern regarding the use of craniospinal irradiation has been attributed mainly to the late effects of radiotherapy. Delayed skeletal growth, impaired neurocognitive skills, hypothyroidism and other hormonal deficiencies, and gonadal dysfunction can occur as a result of craniospinal irradiation. From the standpoint of late toxicity, involved-field radiotherapy would obviously be the treatment of choice, but when used alone this technique may be associated with a high risk of intracranial recurrence.

In a report from Northern Japan, four of eight patients who received involved-field radiotherapy had an intracranial failure outside of the radiotherapy port.[22] The 10-year relapse-free survival rates of patients receiving craniospinal irradiation and involved-field radiotherapy were 90% and 22%, respectively. Mayo Clinic researchers reported a 45% rate of intracranial recurrence at 5 years in patients receiving less than whole-brain irradiation.[21] The actuarial 5- and 10-year disease-free survival rates were 29% and 0%, respectively, for those treated with involved-field radiotherapy and 94% for those given whole-brain and craniospinal radiotherapy.

We advocate the use of whole-brain radiotherapy followed by a tumor boost when radiation is used alone. Proponents of craniospinal irradiation argue that disease-free survival is slightly better than with whole-brain irradiation; furthermore, the late effects on the spine would be nil to minimal because most children treated with craniospinal irradiation are adolescents and will be affected less than are younger children.

Craniospinal irradiation, at best, offers approximately a 10% to 15% advantage if one relies on Linstadt’s pre-1988 analysis. However, the risk of spinal relapse in more contemporary series is < 10% (Table 3). We would continue to recommend craniospinal radiation when there is evidence of a multiple midline germinomas, positive CSF cytology, or neuraxis dissemination on MRI of the spine or myelogram. The use of predominantly whole-brain fields followed by a tumor boost has resulted in excellent survival.[22,34,35]

**Radiation Dose**
Because intracranial germinomas are histologically similar to seminomas, they are very radiosensitive and highly curable with radiation. In fact, pathologic complete response with a dose as low as 1,600 cGy has been reported.[36] Earlier data, however, have shown a dose response at approximately 5,000 cGy. Kersh et al found a 78% survival rate in germinoma patients who received \( \geq 5,000 \) cGy to the primary tumor, as compared with a 58% rate in those given \(< 5,000\) cGy.[37] The Columbia-Presbyterian experience showed a 10% rate of intracranial failure with a \( \geq 5,000 \) cGy to the tumor, compared to a rate of 47% when doses from 3,800 to 4,500 cGy were used.[33] Abay et al demonstrated an increasing local control rate with radiotherapy dose.[38] The local control rates for doses \(< 3,000\) cGy, 3,000 to
3,999 cGy, 4,000 to 4,999 cGy, and ≥ 5,000 cGy were 33%, 57%, 78%, and 88%, respectively. Investigators reasoned that because extragonadal germ-cell tumors required a higher dose than their testicular seminoma counterparts, the same held true for intracranial germinomas. Also, earlier data were problematic due to a large proportion of histologically unverified pineal region and suprasellar tumors. Furthermore, if, in the pre-CT era, involved fields were used, failures may have been due to inadequate volume coverage rather than inadequate dose.

More recent data advocate 4,000 to 4,500 cGy to the primary tumor when radiotherapy is used alone.[22,29,30] A study from the Joint Center of Radiation Therapy showed no dose response at the 5,000-cGy level.[39] The authors also analyzed the literature and found 19 patients treated with less than 4,650 cGy; of the 11 patients treated with whole-brain irradiation followed by a tumor boost, none had local failures. Researchers from the University of Kyoto recommend a dose-tumor size schema in the radiotherapeutic approach to germinomas.[30] For tumors < 2.5 cm, 2.5 to 4.0 cm, and > 4 cm, the recommended doses are 4,000, 4,500, and 5,000 cGy, respectively.

For patients with CSF positive cytology, Shibamoto et al recommend a 2,000 to 2,400-cGy craniospinal dose. With such a dose to the remainder of the entire neuraxis, the outcomes of patients with positive and negative cytology were similar.[24]

Chemotherapy

Chemotherapy Alone

Because testicular cancer is effectively treated with chemotherapy, some investigators have tried the same agents to treat recurrent intracranial germ-cell tumors.[2,40,41] Chemotherapy was later explored as primary treatment or in combination with radiotherapy for primary intracranial germinomas. The possibility of eliminating radiation is compelling especially in treating children and young adults because of the possibility of neurohormonal and cognitive deficits associated with radiotherapy.

In a report from the First International Central Nervous System Germ Cell Tumor Study, Balmaceda and colleagues studied the effect of carboplatin (Paraplatin), etoposide, and bleomycin (Blenoxane) on intracranial germ-cell tumors.[42] The study employed four cycles of carboplatin, etoposide, and bleomycin; patients who had a complete response (CR) received two further cycles, whereas those with less than a CR had two additional cycles intensified with cyclophosphamide (Cytoxan, Neosar). The treatment plan allowed for irradiation of patients who did not achieve a CR after four cycles. At a median follow-up of 31 months, CRs were achieved in 37 (82%) of 45 evaluable germinomas. Twenty patients (54.1%) with germinoma who achieved a CR later relapsed. Almost all of the patients were salvaged with radiation therapy or a combination of radiotherapy and chemotherapy.[42,43] The authors concluded that a certain subset of patients were successfully treated with chemotherapy alone; however, they recommended that chemotherapy-only regimens for CNS germ-cell tumors be used only in a clinical trial setting.

Neoadjuvant Chemotherapy Followed by Radiotherapy

Some investigators have used neoadjuvant chemotherapy to determine whether radiation dose and volume can be minimized.[23,44-49] At Memorial Sloan-Kettering Cancer Center, Allen et al treated 11 germinoma patients with neoadjuvant cyclophosphamide or a modified multidrug regimen consisting of vinblastine, bleomycin, cyclophosphamide, and cisplatin (Platinol).[44] Seven patients had disseminated neuraxis disease. Ten germinoma patients had a CR after two cycles of chemotherapy; the other patient had a partial response (PR). The planned dose of radiotherapy was reduced from a mean tumor dose of 5,500 to 3,310 cGy and from a mean craniospinal dose of 3,600 to 2,620 cGy in the 10 patients who had a CR. Ten patients remained disease-free at a median follow-up of 47 months.

In a multi-institutional study, Allen and colleagues treated 11 germinoma patients with normal HCG titers with neoadjuvant carboplatin.[45] Four patients had multifocal disease. If a CR was observed after two cycles of carboplatin, radiation doses to the involved field and craniospinal axis were lowered from 5,000 to 3,000 cGy and from 3,600 to 2,100 cGy, respectively. If less than a CR was observed, two additional courses of chemotherapy were given, after which response was evaluated. Patients with less than a CR required full radiotherapy doses. Seven patients had a CR to chemotherapy; 10 of 11 patients remain in continuous remission for a median follow-up of 25 months.

The Europeans have also explored the possible use of neoadjuvant chemotherapy.[46,47] In 1988, the French Society of Pediatric Oncology (SFOP) began a study of vinblastine, bleomycin, and
cisplatin or carboplatin with 3,000 cGy of local-field irradiation; this pilot study of five patients resulted in three failures. The protocol was then modified: the carboplatin dose was increased, ifosfamide (Ifex) and etoposide were substituted for vinblastine and bleomycin, and the radiation dose to the involved field was increased to 4,000 cGy. Overall survival at 4 years is 100% and event-free survival is 93.3% with a median follow-up of 32 months.

At the University of Hokkaido, Sawamura et al treated six patients with solitary pure germinoma using three to four cycles of cisplatin and etoposide (EP regimen) followed by 2,400 cGy of involved-field radiotherapy.[23] Eleven patients with HCG-secreting, multifocal or disseminated germinomas received four to five cycles of ifosfamide, cisplatin, and etoposide (ICE regimen) followed by 2,400 cGy of involved-field radiotherapy. Craniospinal fields were employed in the three patients with disseminated germinoma. At a median follow-up of 24 months, 94% of patients are alive without recurrence.

Matsutani et al treated seven germinoma patients with three courses of either carboplatin or cisplatin combined with etoposide followed by involved-field radiation (3,000 cGy).[48] All patients had a CR following chemotherapy alone. At a median follow-up of 4.3 years, all patients are alive without recurrence.

In summary, neoadjuvant chemotherapy has a high likelihood of producing a CR. Radiation doses can be reduced. Involved-field radiotherapy combined with chemotherapy results in an excellent outcome.

**Conclusions**

The management of patients with germinoma is evolving. Tissue diagnosis is important and can be safely achieved with current stereotactic and microsurgical techniques. Radiation therapy has a proven record of long-term cure and is the gold standard to which all new treatments should be compared. Radiation therapy has undergone considerable changes, with reduction in field sizes and doses. A proportion of patients can be cured with chemotherapy alone. The use of neoadjuvant chemotherapy and involved-field radiotherapy is promising, especially in younger children.

**References:**


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