Management of primary intracranial germinomas: diagnostic surgery or radical resection?

YUTAKA SAWAMURA, M.D., NICOLAS DE TRIBOLET, M.D., NOBUAKI ISHII, M.D., AND HIROSHI ABE, M.D.

Department of Neurosurgery, University of Hokkaido School of Medicine, Sapporo, Japan; and Department of Neurosurgery, University Hospital, Lausanne, Switzerland

Because intracranial germinomas are readily curable with radiation and chemotherapy or radiation therapy alone, the role of radical surgery has become debatable. This study assesses the optimum degree of surgical resection for intracranial germinomas.

Twenty-nine patients who underwent surgery for germinoma were retrospectively analyzed (male/female ratio 27:2, median age 18 years). Among these 29 patients there were 10 solitary pineal, seven solitary neurohypophyseal/hypothalamic, and 12 multifocal or disseminated tumors. Biopsy samples were obtained in 16 patients (stereotactically in eight, transtentorially in four, and via frontotemporal craniotomy in four). Partial resection was attained in five patients (via a frontotemporal approach in three and occipitotransiently in two). Gross-total resection was achieved via an occipitotransdentorial route in eight patients with pineal masses. After surgery, 10 patients were treated with radiotherapy alone, and 19 received radiation and chemotherapy; complete remission was achieved in all 29 patients. The overall tumor-free survival rate was 100% at a median follow-up period of 42 months. There was no significant difference in outcome related to the extent of surgical resection. Postoperative neurological improvement was seen in only two patients, whereas transient postoperative complications, mainly upgaze palsies, were observed in six. One patient experienced a slight hemiparesis, bringing the surgical morbidity rate to 3% (one of 29).

It is concluded that radical resection of intracranial germinomas offers no benefit over biopsy. The primary goal of surgery should be to obtain a sufficient volume of tumor tissue for histological examination. If there is strong evidence of germinoma on radiological studies, biopsy samples should be obtained. When a perioperative histological diagnosis of pure germinoma is made during craniotomy, no risk should be taken in continuing the resection.

KEY WORDS • central nervous system • intracranial germ cell tumor • germinoma • surgery

GERMINOMA is a rare neoplasm in the central nervous system of children and young adults. It is a malignant primary neoplasm that can be cured by conventional radiation therapy alone or by reduced-volume and field irradiation in combination with chemotherapy. Therefore, the role of surgery in the management of intracranial germinomas has become debatable.

Germinoma is one of the subcategories of intracranial germ cell tumors, which encompass a variety of histological subtypes. In contrast to pure germinomas, the germ cell tumors that include a component with highly malignant histological findings, such as embryonal carcinoma, choriocarcinoma, yolk sac tumor, or other types of cancer, have an extremely poor prognosis. However, definitive diagnosis to predict histological findings and malignancy of these germ cell tumors cannot be achieved even with modern imaging techniques; germinomas are indistinguishable from certain other types of primary brain tumors. Because management of patients with germ cell tumor should be planned precisely according to histologically and biologically determined malignancy, diagnostic surgery is indispensable when there is evidence of an intracranial germ cell tumor on radiological studies.

Surgical debulking is part of the treatment for intracranial malignant brain tumors such as gliomas. A radical resection of the neoplasm generally offers a better prognosis for the patient. However, radical resection of germinoma carries a certain risk of surgical morbidity, because these tumors occur in eloquent areas of the brain such as the neurohypophysis or the pineal region. Because nearly all germinomas are curable with adjuvant therapy, the question arises as to whether germinomas should only be biopsied or radically removed when possible. Although there have been a number of reports presenting the results of surgical treatment of germinomas, which were included in a series of pineal region tumors or intracranial germ cell tumors, no report has focused on the extent of surgery and its effect on outcome in patients with histologically pure intracranial germinomas. It is uncertain to what extent partial or total resection of a germinoma contributes to local control of the tumor.

This study was conducted to define the optimum degree of surgical resection for intracranial germinomas. We review our experiences with newly diagnosed patients with...
Surgical management of germinoma in the era of magnetic resonance (MR) imaging and discuss the role of surgery in combination with postoperative adjuvant therapy.

Clinical Material and Methods

Patient Population

Twenty-nine patients with primary intracranial germinomas who underwent surgery either at the University Hospital of Hokkaido or Centre Hospitalier Universitaire Vaudois in Lausanne between 1985 and 1995 were included in this analysis. There were 27 males and two females ranging from 9 to 36 years of age, with a median age of 18 years at surgery (Table 1). Patients who had a preoperative provisional clinical diagnosis of germinoma, but a final histologically determined diagnosis of another brain neoplasm, were not included in this study.

All patients had exhibited clinical evidence of a germ cell tumor, including germinoma, before surgery. Prior to admission to our institutions, only one patient had undergone surgery, chemotherapy, or radiation therapy. This one patient had a medium-sized pineal mass, had undergone a stereotactically guided biopsy procedure, was diagnosed with a pineocytoma, and was afterward referred to us for radical resection of the pineal tumor.

Tumor Types and Locations

The tumors and their locations included 10 solitary pineal, seven solitary neurohypophyseal/hypothalamic, 11 multifocal, and one disseminated lesion (Table 1). Multifocal germinoma was defined as tumor involving the pineal gland, the hypophysis, hypothalamus, optic chiasm, or anterior half of the lateral ventricle wall, but no evidence of cerebrospinal fluid (CSF) seeding. Dissemination was defined as evidence of CSF seeding on MR imaging with or without evidence on CSF studies. Among 17 solitary tumors, the maximum diameter of the mass was less than 2 cm (small) in one case, between 2 and 3.5 cm (medium) in 11 cases, and greater than 3.5 cm (large) in five cases.

Serum levels of human chorionic gonadotropin (HCG)-β and α-fetoprotein were routinely examined. The levels of α-fetoprotein were normal in all patients, and six patients showed elevated values of HCG-β in less than 100 ng/ml of serum.

Surgical Management

Although there are no definitive criteria for surgical management of germinomas, the strategies were the same in both institutions. A radical removal was planned only for solitary pineal tumors. Neurohypophyseal lesions, multifocal lesions, or disseminated disease were treated with biopsy or partial removal.

Results

Approaches and Extent of Surgery

Biopsy specimens were obtained in 16 patients by means of stereotactic guidance in eight, a transsphenoidal approach in four, and a frontotemporal craniotomy in four (Table 2). Partial resection was attained in five patients via a frontotemporal route in four and occipitotranstentorially in one. Gross-total resection was achieved in eight patients who had a pineal mass via the occipitotransventorial route.

Among 10 solitary pineal masses, gross-total resection was achieved in eight patients whose tumors were small or medium sized. The remaining two patients had large pineal masses; one underwent an 80% partial resection and the other a biopsy. The patient with a preoperative histological diagnosis of pineocytoma on a previous stereotactic biopsy study underwent a gross-total resection.

Among seven solitary mass lesions in the hypothalamic/neurohypophyseal region, biopsy specimens were obtained transsphenoidally in four patients, and partial removal using the pterional approach was achieved in three patients.

Among 11 patients with multifocal masses, stereotactically guided biopsies were performed in six, and biopsy specimens were obtained via a frontotemporal craniotomy in four. Another patient with multifocal tumors separately located in the pineal and neurohypophyseal regions underwent gross-total resection of the medium-sized pineal mass, but a tiny neurohypophyseal mass was left. The extent of surgery in this patient was estimated as a partial resection (Table 2).

<table>
<thead>
<tr>
<th>Location</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>solitary pineal</td>
<td>10</td>
</tr>
<tr>
<td>solitary hypothalamic/neurohypophyseal</td>
<td>7</td>
</tr>
<tr>
<td>multifocal</td>
<td>11</td>
</tr>
<tr>
<td>disseminated</td>
<td>1</td>
</tr>
<tr>
<td>size of 17 solitary tumors</td>
<td></td>
</tr>
<tr>
<td>small (&lt;2 cm)</td>
<td>1</td>
</tr>
<tr>
<td>medium (2–3.5 cm)</td>
<td>11</td>
</tr>
<tr>
<td>large (&gt;3.5 cm)</td>
<td>5</td>
</tr>
<tr>
<td>hydrocephalus</td>
<td>17</td>
</tr>
<tr>
<td>elevated serum HCG-β</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Site</th>
<th>Biopsy Route</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stereo-</td>
</tr>
<tr>
<td></td>
<td>tactic</td>
</tr>
<tr>
<td>solitary pineal</td>
<td>1</td>
</tr>
<tr>
<td>solitary hypothalamic/neurohypophyseal</td>
<td>0</td>
</tr>
<tr>
<td>multifocal</td>
<td>6</td>
</tr>
<tr>
<td>disseminated</td>
<td>1</td>
</tr>
<tr>
<td>total</td>
<td>8</td>
</tr>
</tbody>
</table>

* GTR = gross-total resection; STR = subtotal resection.
† One pineal mass was totally resected, leaving a small neurohypophyseal mass.
One patient with a disseminated tumor that filled the entire ventricular area, including the fourth ventricle, was diagnosed by means of a stereotactically guided biopsy obtained from the anterior horn of the lateral ventricle.

Seventeen patients had symptomatic obstructive hydrocephalus, and nine of these patients underwent ventricular drainage before removal of their tumors. Only one patient required ventriculoperitoneal shunt placement.

**Postsurgical Definitive Diagnosis**

Perioperative histological examination by frozen section with hematoxylin and eosin stain was performed in 15 patients who underwent craniotomy or transsphenoidal biopsy. All of these perioperative histological examinations indicated germinoma with a typical two-cell pattern arrangement, results that were consistent with the final histological diagnosis by permanent section.

Twenty-six tumors were found to be pure germinomas on histological examination. Immunohistochemical studies in the remaining three patients, who had elevated levels of serum HCG-β, revealed scant syncytiotrophoblastic giant cells positive for HCG-β.

**Surgical Complications**

Obstructive hydrocephalus due to a pineal mass resolved in all of the eight patients who underwent gross-total removal. Postsurgical improvement of diplopia was seen in two patients. Otherwise, no remarkable improvements of neurological, ophthalmological, or endocrinological deficits were observed immediately after surgery.

Transient surgical complications were observed in five patients who underwent partial or total resection of the tumor. Four patients with Parinaud’s sign preoperatively showed transient worsening of the upward gaze palsy after craniotomy, but all subsequently improved to at least better than preoperative status. Another patient suffered an epileptic seizure after tumor removal via an occipito- transtentorial approach. Sixteen patients in whom biopsy specimens were obtained experienced no complications.

Tension pneumocephalus caused by ventricular over-drainage occurred in one patient immediately after craniotomy, although the resection of the tumor itself was uneventful. The pneumocephalus resulted in left hemiparesis, and the patient had persistent slight hemiparesis. Impairment of endocrinological or visual function related to surgery was not evident. Thus, the overall persistent surgical morbidity rate was 3% (one of 29) in this series.

**Postsurgical Adjuvant Therapy and Primary Response**

All 29 patients were given postsurgical adjuvant therapies, which varied with each patient. Radiation therapy was administered to all patients. Ten patients received radiation therapy alone, with total tumor dosages ranging from 45 to 50.4 Gy in daily fractions of 1.8 Gy.

Chemotherapy was administered to 19 patients before, during, or after radiation, using various combinations of agents including cisplatin, etoposide, carboplatin, methotrexate, Adriamycin, and cyclophosphamide. Seventeen patients received preradiation chemotherapy followed by a reduced dose (24 Gy) of radiation therapy.

Three courses of chemotherapy followed by radiation therapy invariably eradicated postsurgical residual germinoma. When evaluated 1 month after completion of the adjuvant therapies, all 21 patients who underwent a partial removal or a biopsy achieved a complete remission, with complete disappearance of the tumor on neuroimaging studies and normalized levels of serum HCG-β (Table 3).

The overall primary response rate to the adjuvant therapies was therefore 100% (21 of 21 patients). No maintenance chemotherapy was administered.

**Final Outcome**

The median and mean follow-up period for all 29 patients were 42 months and 44.5 months, respectively. The median follow-up period for the patients in whom a biopsy was obtained was 43 months, 44 months for partial resection, and 39 months for total resection (Table 3).

Recurrence was found in only one patient; thus, the recurrence rate during the observation period was 3.4%. This patient underwent gross-total resection of a solitary pineal germinoma and experienced recurrence 38 months postsurgery. However, this patient has achieved a second complete remission and has been free of tumor for 20 months. Thus, the tumor-free survival rate was 100% at the end of the study. There was no significant difference in outcome related to the extent of surgical resection.

**Discussion**

Despite the variation in adjuvant therapy, it is clear that radical resection of intracranial germinomas offered no benefit over biopsy. Because management strategies for intracranial germinomas are greatly dependent on accurate histological diagnosis of individual tumors, the primary goal of surgery should be to obtain a sufficient volume of tumor tissue for histological examination.

Stereotactically guided biopsy, with a 0 to 1.6% morbidity rate, provides a safe method of sampling tissues. However, researchers have found that pathological diagnosis of a small specimen taken from a larger tumor may be erroneous when a mixed germ cell tumor including germinoma is encountered. None of 16 biopsy samples in our series was diagnosed incorrectly. All tumors were eradicated by adjuvant therapy, and all patients were tumor free at the last follow-up examination.
Surgical management of germinoma

With advanced MR imaging and the use of immunohistochemical studies, a diagnostic error of stereotactic biopsy should not occur. When there is strong radiological evidence of germinoma, a stereotactic biopsy should be performed. If a mixed germ cell tumor is mistakenly interpreted as “pure germinoma” on biopsy, two cycles of chemotherapy can eliminate at least the germinoma component. After that, a second-look surgery will be feasible to resect the chemoresistant residual tumor.

Open surgical resection provides a larger sample for histological diagnosis than does stereotactic biopsy, thus facilitating adequate treatment. However, the surgeon should keep in mind that intracranial germinomas are curable with appropriate adjuvant therapy. Therefore the goal of treatment should be tightly focused on the reduction of posttreatment sequelae. In this regard, radical resection is not recommended, particularly if the germinoma originates from the neurohypophyseal, hypothalamic, or both regions. Biopsy samples of these tumors, which are histologically infiltrative to the optic pathway as well as the hypothalamus, should be obtained.

In addition, for small suprasellar germinomas confined strictly to the optic pathways and inferior part of the hypothalamus without involvement of the hypophysis, we prefer an open biopsy using a frontotemporal craniotomy to stereotactic biopsy, which may injure these critical structures. A biopsy of the tumor involving the hypophysis can be obtained via the transsphenoidal route.

A surgical resection with sufficient bulk reduction in a solitary mass may enhance the efficiency of adjuvant therapy, especially for malignant germ cell tumors. However, this seemed inappropriate for pure germinomas because this study found no significant difference related to the extent of resection.

We removed tumors in the pineal region using radical resection because nongerminomatous germ cell tumors preferentially involve this region and because approxi- mately one-third of pineal tumors such as pineocytoma or mature teratoma are benign and surgery alone can be curative. Pineal germinomas can be approached safely and effectively using currently available microsurgical techniques. Nevertheless, potential complications of radical resection, even if minor and transient, cannot be neglected, as we found. The most common complications seen with the infratentorial–supracerebellar approach include impairment of extraocular movements, altered mental status, and ataxia. On the other hand, complications of the occipitotransventricular approach include impairment of extracerebral movements and hemianopsia. When a perioperative histological diagnosis of pure germinoma is made during craniotomy, no risk should be taken in pursuing the resection.

No matter what the degree of surgical resection, patients diagnosed with pineal germinoma must be given adjuvant therapy. Only a course of nonintensive chemotherapy, such as small doses of cisplatin and etoposide, can dramatically reduce the size of residual germinoma and finally allow adjuvant radiotherapy to eradicate the tumor. There is no sound reason to attempt complete removal of a pineal germinoma after resection of sufficient volume of tissue for perioperative histological diagnosis. Near the end of a complete removal of a pineal germinoma, we often encountered a residual mass adherent to the aqueduct, the superior colliculus, and the posterior thalamus. Stopping the procedure at this point may reduce the complication rate significantly.

To reduce complications after radiotherapy, proper application of craniospinal irradiation is vital. Recently, some authors have suggested that prophylactic craniospinal irradiation is not necessary when no other lesions are detected by complete diagnostic craniospinal neuroimaging. Considering the associated morbidity in children before puberty and the significant late effect on cognitive function in young adults, craniospinal irradiation should be administered only to patients with disseminated germinomas. With modern diagnostic work-up and appropriate radiation techniques for individual tumor extension, disseminated relapse of germinoma rarely occurs.

Shunt placement should be avoided because of the potential for peritoneal metastasis. Tumor spreading via a shunt occurs rarely, but it is generally lethal. In our series, only one patient had a ventriculoperitoneal shunt placed for an adhesive aqueduct stenosis after partial resection of a pineal germinoma. In the other cases, gross-total resection of a pineal mass or postsurgical chemotherapy resolved the obstructive hydrocephalus. Germinomas can be remarkably reduced in size either by a single course of chemotherapy or by low-dose radiotherapy. When a biopsy is performed in a patient with obstructive hydrocephalus, promptly administered chemotherapy can immediately resolve symptoms of increased intracranial pressure, usually within several days in our recent experience. During the course of chemotherapy in the immediate postsurgical period, ventricular drainage controls the hydrocephalus, and the need for shunt placement is obviated.

Conclusions

Radical resection of intracranial germinomas offers no benefit over biopsy. The primary goal of surgery should be to obtain a sufficient volume of tumor tissue for histological examination. If there is strong radiological evidence of germinoma, a biopsy should be performed. When a perioperative histological diagnosis of pure germinoma is made during craniotomy, no risk should be taken in pursuing the resection.

References

6. Committee of the Brain Tumor Registry of Japan: Incidence of...
40. Y. Sawamura, et al.