J Neurosurg Pediatrics 2:331–338, 2008

Intracranial teratomas in children: the role and timing of surgical removal

Clinical article

Rémy Noudel, M.D.,[1] Mathieu Vinchon, M.D., Ph.D.,[2] Patrick Dhellemmes, M.D.,[2] Claude Fabien Litré, M.D.,[1] and Pascal Rousseaux, M.D.[1]

[1]Department of Neurosurgery, Maison Blanche Hospital, University of Reims; and [2]Department of Pediatric Neurosurgery, Roger Salengro Hospital, University of Lille, France

Object. In this study, the authors report their experience with the surgical treatment of intracranial teratomas with an emphasis on the indications for delayed resection after oncological treatment.

Methods. The authors retrospectively reviewed the cases of 14 children with intracranial teratomas. The mean age at diagnosis was 10.5 years (range 2 days–18 years), and 11 patients were male. The final histological analysis revealed pure mature teratoma in 5 cases, mixed teratoma with germinoma in 3 cases, and nongerminomatous malignant germ cell tumor in 6 cases. Thirteen patients underwent tumor resection, and these patients were divided into 2 subgroups according to the timing of surgery. In Group A, 10 patients underwent resection as the primary treatment because no tumor markers were detected in 4 patients, a teratomatous component was revealed on biopsy sampling in 3 patients, and a large tumor volume in 3 patients. In Group B, 3 patients underwent removal of residual pure mature teratoma after oncological treatment.

Results. Seven of the 8 patients (87.5%) with pure mature teratomas or with mixed teratoma and germinoma are currently alive (mean follow-up of 9 years); the eighth patient died of postoperative meningitis. Two of the 6 patients (33%) with mixed nongerminomatous malignant germ cell tumors died of tumor progression regardless of the timing of surgery.

Conclusions. The results of this study support the belief that microsurgical removal is the only effective treatment for intracranial teratomas. Surgery may be performed as the primary therapy when there is evidence of a noninvasive teratoma, and as a secondary therapy if there is only a partial response to neoadjuvant therapy or if progression is observed in mixed malignant germ cell tumors. *(DOI: 10.3171/PED.2008.2.11.331)*

Key Words • brain tumor • germ cell tumor • growing teratoma syndrome • pediatric neurosurgery • teratoma

Intracranial GCTs are morphologically analogous to the germinal neoplasms that arise in the gonads, mediastinum, or retroperitoneum. Their presence is relatively rare in adult patients, and account for only 0.5–1% of all intracranial tumors in adults in Europe and the US,[18,41] with an unexplained higher frequency in Japan and Taiwan (1.8–5%).[18,25,28,32] Intracranial GCTs are more common in children, making up 15% of childhood intracranial tumors in Japan and 7% in the West. Approximately 90% of GCTs occur in patients younger than 20 years old, with a peak incidence at 11 years of age.[18,19,21,25,28,32]

According to the World Health Organization classification[23] and the germ cell theory,[40] intracranial GCTs are divided into 5 histological subtypes of increasingly malignant behavior: germinomas, teratomas, ECs, yolk sac tumors, and choriocarcinomas. These last 3 are considered NGMGCTs and typically secrete the oncoproteins AFP and hCG.[8,21,23] Mixed intracranial GCTs are not rare, representing 25–32% of intracranial GCTs.[21,32,39] In fact, only germinomas and teratomas are likely to be encountered as pure tumor types.[18,21,32,39] This increases the risk of sampling error, which is especially serious in diagnosing intracranial GCTs because the treatment and prognosis are conditioned by the most malignant component.[18,36] Although germinomas and NGMGCTs usually respond to chemotherapy and/or radiation therapy,[4,20,21,32] these treatments have little or no effect on the teratomatous component, and complete excision has been

Abbreviations used in this paper: CSF = cerebrospinal fluid; EC = embryonal carcinoma; ETV = endoscopic third ventriculocisternostomy; GCT = germ cell tumor; hCG = human chorionic gonadotropin; NAT = neoadjuvant therapy; NGMGCT = nongerminomatous malignant GCT.

shown to be the sole curative treatment for mature teratomas.[9,18,21,32,36] In consequence, several authors have advocated the surgical removal of a residual mature teratoma tissue after NAT for mixed intracranial GCTs.[14,15,17,25,33,44]

We report on our experience with intracranial teratomas in children to investigate the role of resection in the treatment of intracranial GCTs that have a histologically confirmed teratomatous component.

Methods

Between May 1980 and February 2007, 30 children with intracranial GCTs underwent treatment at our institution. Sixteen patients had pure germinomas and were excluded from this study. The 14 patients described here harbored histologically confirmed teratomas or mixed GCTs with a teratomatous component.

The pretreatment diagnosis was based on histopathological analysis of tissue obtained either from surgical biopsy or resection, or on the results of serum and CSF tumor markers (AFP and hCG) to classify tumors in accordance with the World Health Organization classification.[23]

Therapeutic modalities consisted of open surgery for tumor removal, oncological treatment (radio- and chemotherapy), and CSF diversion, including the use of ventriculoperitoneal shunts, external ventricular drains, or ETVs. These procedures were often performed on an emergent basis because of life-threatening hydrocephalus.

The indications for tumor resection were the presence of teratomatous components identified on biopsy sampling and/or no detectable tumor markers, or large, poorly tolerated tumors with a severe mass effect. Adjuvant therapies were administered as part of the primary treatment according to the current oncological protocols and based on each child's histopathological diagnosis. The 13 patients who underwent tumor resection were divided into 2 subgroups according to the timing of tumor removal: Group A comprised 10 patients who received surgery as a first-line treatment, and Group B consisted of 3 patients who underwent resection for residual teratoma after NAT.

Each patient underwent clinical and radiological follow-up, and serum titers of tumor markers were monitored in patients who had tested positive initially. In patients with tumor progression or relapse, additional treatments such as a "second-look" surgery or an appropriate salvage therapy were considered on a case-by-case basis.

Results

The characteristics of the 14 patients are summarized in Table 1.

Clinical Findings

The mean age at diagnosis was 10.5 years (126.5 months) and ranged from 2 days to 219 months; 11 of the 14 patients were male. Nine patients had tumors located in the pineal area, 4 in the suprasellar region, and 1 harbored a bipolar lesion (Case 9). The sex predilection related to tumor location was striking—all pineal tumors occurred in male patients and 3 of 4 suprasellar tumors arose in female patients. The pretreatment clinical signs are detailed in Table 2.

Neuroimaging and Histopathological Examinations

Craniospinal MR imaging was performed in 13 patients, and CT scanning in 1 patient who received treatment in 1980. The radiological appearance of these lesions was heterogeneous in all patients with an association of solid and cystic components suggestive of a teratomatous component in 10 cases (Fig. 1) and calcifications in 4 cases. Four patients had heterogenous tumors that strongly enhanced with contrast addition (Cases 3, 6, 8, and 14).

Tumor marker levels were available in all patients, with positive titers of AFP and/or hCG in 6 cases (Cases 3, 6, 8, 10, 11, and 14). Histopathological tissue analysis was also performed in all 14 patients. The teratomatous component was identified on primary examination in 12 patients and on residual removal after NAT in 2 patients in whom a pure germinoma or choriocarcinoma was initially diagnosed (Case 9 and 14, respectively). The final diagnosis—based

TABLE 1

*Summary of patient characteristics**

Case No.	Age (mos), Sex	Tumor Location	Tumor Markers	Histological Diagnosis			1st Tx & Response	2nd Tx & Response	3rd Tx & Response	Current Status, FU (mos)
				Method	Initial	Secondary				
1	128, M	pineal	none	R	MT	none	R, partial	NAT, partial	—	DF, 292
2	61, M	pineal	none	stereo	MT	MT	R, total	—	—	died of sepsis, 1
3	159, M	pineal	AFP & hCG	stereo	IT	IT	R, total	NAT, total	—	DF, 166
4	140, M	pineal	none	stereo	IT	G & IT	R, partial	NAT, partial	chemo, partial	stable residue, 136
5	92, M	suprasellar	none	R	MT & G	scar tissue	R, partial	chemo, partial	SR, total	DF, 132
6	219, M	pineal	AFP & hCG	endosc	MT & EC	MT	chemo, partial	SR, total	NAT, partial	died of DP, 28
7	10, M	pineal	none	R	MT	none	R, total	—	—	DF, 83
8	154, M	pineal	AFP	R	MT & EC	none	R, total	NAT, total	chemo, partial	died of DP, 10
9	207, M	both	none	endosc	G	MT	chemo, partial	R, total	SR, total	stable, 65
10	203, M	pineal	AFP & hCG	R	IT	none	R, total	NAT, total	—	DF, 23
11	171, F	suprasellar	AFP & hCG	R	IT	none	R, total	NAT, total	—	DF, 24
12	103, F	suprasellar	none	R	MT	none	R, total	NAT, total	—	DF, 34
13	2 days, F	suprasellar	none	endosc	MT	none	—	—	—	stable, 22
14	125, M	pineal	hCG	endosc	CC	MT	NAT, partial	R, total	—	DF, 10

* CC = choriocarcinoma; chemo = chemotherapy; DF = disease free; DP = disease progression; endosc = endoscopy; FU = follow-up; G = germinoma; IT = immature teratoma; MT = mature teratoma; R = resection; SR = second resection; stereo = stereotactic.

TABLE 2

*Summary of pretreatment signs and symptoms in 14 patients with GCTs**

Tumor Location	No. of Patients	ICH	Coma	Oculomotor Disturbance	Visual Deficiency	Endocrinological Signs	Behavioral Changes
pineal	9	9	1	7	1	2	1
suprasellar	4	1	1	—	2	3	1
bipolar	1	1	—	1	—	—	—
total	14	11	2	8	3	5	2

* ICH = intracranial hypertension.

both on the histological examination and the tumor marker levels—was pure mature teratoma in 5 patients (Cases 1, 2, 7, 12, and 13) and mixed teratoma with malignant component in 9 patients. Among the mixed teratomas, there were 6 NGMGCTs (Cases 3, 6, 8, 10, 11, and 14) and 3 germinomas (Cases 4, 5, and 9). Among the 6 tumors initially diagnosed on a biopsy and then surgically verified, only 2 (33%) had a good correlation with the histological results obtained at resection (Cases 2 and 3).

Surgical Procedures

Cerebrospinal fluid diversion procedures were performed in 12 patients as follows: 3 underwent ventriculoperitoneal shunt placement, 2 received external ventricular drains, and 7 patients underwent ETV. Seven biopsies were performed—3 via a stereotactic approach and 4 at the time of an endoscopic procedure.

Thirteen patients underwent ≥ 1 open surgical procedure, as follows: 6 via an occipitotranstentorial approach, 4 via a transfrontal-transventricular approach, 2 via a subfrontal supraoptical approach, and 1 via a supracerebellar-infratentorial route. Ten patients underwent only 1 open surgical procedure. Two patients required a second operation: 1 patient harbored a pineal tumor of a consistency that was too hard to be resected via a transtentorial approach and required a transfrontal-transventricular route (Case 3), and the other patient had a mixed germinoma and teratoma in the suprasellar region that was initially subtotally resected and he underwent a "second-look" surgery for removal of residual tumor on the floor of the third ventricle after chemotherapy (Case 5). One patient with an initially diagnosed bipolar germinoma (Case 9; Fig. 2) required 3 consecutive surgical interventions after chemotherapy—a transfrontal-transventricular approach was performed for residual removal of a mature teratoma, and then 2 recurrent cystic metastatic mature teratomas were removed within the posterior fossa. Overall, resection was complete for 10 patients (7 in the primary resection and 3 after the residual removal) and subtotal in 3 patients.

One patient (Case 13) has not yet undergone resection because she was a newborn at admission with good clinical tolerance after CSF circulation was restored by endoscopic fenestration of the cyst and ETV. Monitoring examination results show a stable tumor 26 months after the initial diagnosis.

Surgical Complications

After open surgical removal, 1 patient (Case 2) with a mature teratoma died of meningitis in the early postoperative period, and 2 patients awoke with delay and have moderate mental and motor deficiencies (Cases 1 and 3). Three patients experienced transient neurological worsening of preexisting oculomotor disturbances after an occipitotranstentorial approach for pineal region tumors. One patient needed reoperation to remove a textiloma in situ (Case 12). One stereotactic biopsy was complicated by intratumoral and ventricular bleeding (Case 3), requiring an emergent external ventricular drainage and an open surgical approach for total removal that resulted in a good neurological outcome.

Oncological Results

Excluding the patient who died of sepsis, 11 of the 13 remaining patients (84%) are currently alive with no evidence of disease progression after a mean follow-up of 79 months (range 10–292 months), but with a persisting stable tumor in 3 patients. Seven of the 8 patients with pure mature or mixed teratomas with germinoma (87.5%) are alive and disease free. Two of 6 patients with NGMGCT (33%) died because of disease progression: 1 patient from Group A (Case 8) and 1 patient from Group B (Case 6).

Group A comprised 10 patients managed with surgical resection as a primary treatment, as follows: 3 patients (Cases 2–4) because a preoperative biopsy had diagnosed

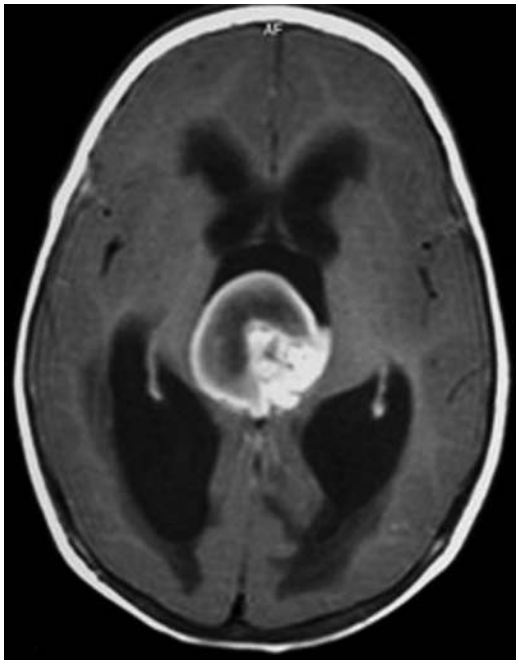

FIG. 1. Case 7. Axial Gd-enhanced MR image showing a pure mature teratoma in the pineal region, with the typical association of a solid and a cystic component and well-defined margins.

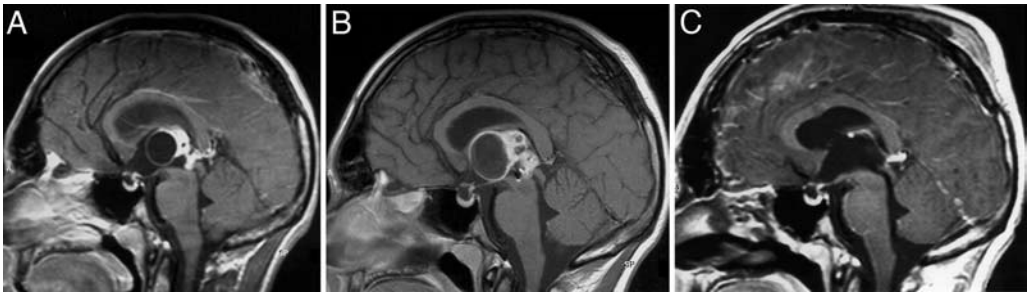

FIG. 2. Case 9. Sagittal T1-weighted MR images with Gd enhancement. A: Initial image showing a peripherally enhancing tumor in the pineal region with a large cyst bulging into the third ventricle and a synchronous, small suprasellar contrast-enhanced lesion. Both lesions were identified as germinomas on neuroendoscopic biopsy sampling. B: Image obtained 4 months after diagnosis, demonstrating tumor progression despite 3 cycles of chemotherapy. C: Postoperative MR image showing total surgical removal of the lesion (achieved via a transfrontal transventricular route).

a teratoma; 4 patients because they tested negative for the presence of tumor markers (Cases 1, 5, 7, and 12); and 3 patients because of a large tumor volume (Cases 8, 10, and 11). In Group A, 2 patients died; 1 because of the progression of a malignant secreting component leading to leptomeningeal dissemination (Case 8; Fig. 3), and the other (who had a pure mature teratoma) because of postoperative sepsis (Case 2). The 8 remaining patients are alive and 7 are free of disease after a mean follow-up of 114 months.

In Group B, 3 patients (Cases 6, 9, and 14) with pineal tumors received NAT as a primary treatment and then underwent resection of a residual tumor. One patient (Case 9) was initially diagnosed with bipolar germinoma and treated with NAT, but progression of the cystic part of the lesion required surgical removal of the tumor, which proved to be a mature teratoma (Fig. 2). Two metastatic recurrences occurred consecutively in the posterior fossa, requiring 2 surgical procedures more. The patient is currently alive with a stable cystic lesion in the posterior fossa 65 months after initial diagnosis. One patient (Case 14), initially diagnosed with a choriocarcinoma, received NAT leading to complete normalization of hCG levels, but residual tumor revealed on MR imaging 4 months later required surgical removal of a mature teratoma with no evidence of disease 10 months after diagnosis. The third patient (Case 6) had a mixed NGMGCT (ECs and mature teratomas) that responded to NAT with normalization of the AFP levels and underwent complete residual removal of a mature teratoma, but spinal relapse of the EC component led to death by tumor progression 28 months after diagnosis (Fig. 4).

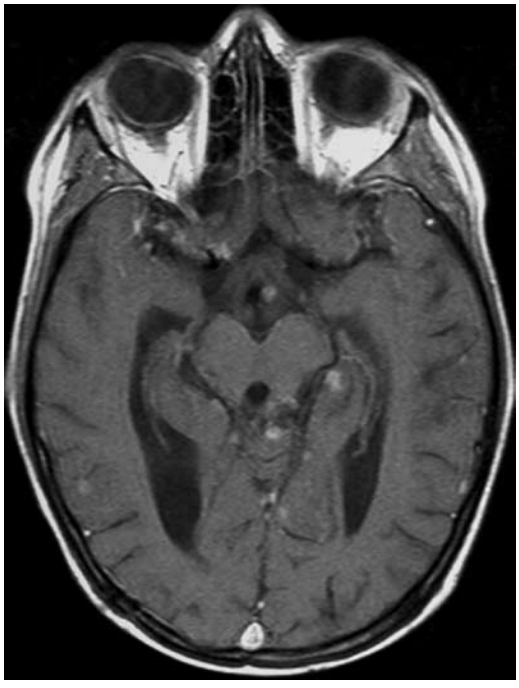

FIG. 3. Case 8. Axial Gd-enhanced MR image obtained in a 12-year-old boy showing leptomeningeal dissemination of the embryonal carcinoma component of a mixed, malignant, secreting intracranial GCT.

Final Outcome

Among the 11 surviving patients, 8 have had a normal life and attended school. Three patients have visual or oculomotor disturbances and 3 have panhypopituitarism that existed prior to surgery and require hormonal replacement. The 2 patients (Cases 1 and 3) who suffered the more severe postoperative complications of delayed awakening exhibit moderate mental deficiencies and require special education.

Discussion

Diagnostic and Therapeutic Features of Intracranial GCTs

Intracranial GCT are a heterogenous group of rare cerebral neoplasms[18,21,41] including 5 different histological subtypes combined within mixed tumors in 25–32% of cases.[21,32,39] Therefore, pathological investigation of the tumor sample is mandatory before initiation of therapy, especially because there is a choice between surgical and nonsurgical treatment options.[5,11,14,18,21,27,31,32,36,39,41] Although less differentiated tumors such as germinomas are usually highly sensitive to NAT with no need for surgical intervention,[20,21,32] pure mature teratomas, arising from the differentiated cells of the embryonic tridermal plate, are known to respond poorly to NAT, and microsurgery alone can be curative.[5,9,14,25] With an overall 10-year survival rate of 92%, germinomas and mature teratomas belong to the good prognosis group in the classification of Matsutani and colleagues,[32] while secreting lesions typically have a very

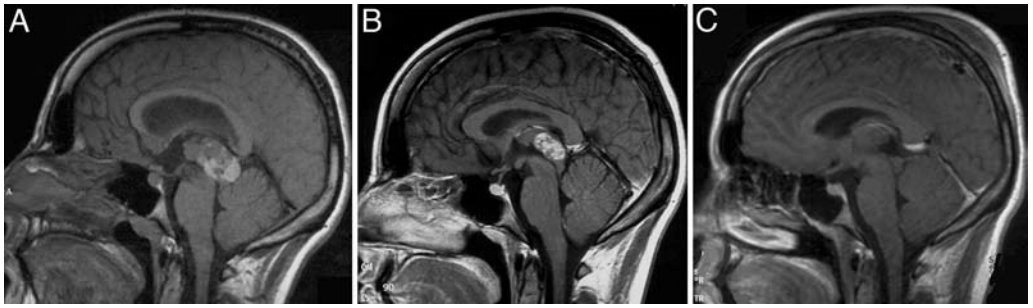

FIG. 4. Case 6. Sagittal T1-weighted MR images with Gd enhancement. A: Initial image showing a heterogenous tumor in the pineal region diagnosed as a mixed mature teratoma with EC after neuroendoscopic biopsy. B: Image obtained 8 months later showing a partial response obtained after 4 cycles of chemotherapy with a stable residual tumor. C: Postoperative image after complete resection of the residual tumor via an occipitotranstentorial approach. Final histological examination of the surgical specimen revealed pure mature teratoma.

poor outcome with < 30% of a 3-year survival rate when NAT protocols are followed.[2,24,31,32,37,44,46] The results in the present study are consistent with those in previous reports: patients with a pure teratoma or mixed intracranial GCT composed of germinoma and teratoma experienced a 10-year survival rate of 87.5%, whereas 2 of 6 patients (33%) with mixed teratoma and NGMGCT rapidly died of disease progression (Table 1).

In cases of teratomas, which account for 18–20% of all intracranial GCTs,[18,21,31,32] a pretreatment biopsy for diagnosis could be avoided if typical clinicoradiological features are identified. These are not secreting tumors and MR images typically show nonhomogenous images of mixed intensity and heterogenous contrast enhancement with frequent large cysts and areas of calcification (Fig. 1).[7,32,48] The characteristics of young age, male predominance, and pineal preferential location are also cardinal features,[11,21,32,41] as in the present study: tumors in 9 patients (64.3%) arose in the pineal region and clear radiological signs of teratoma were seen in 10 patients (71%). All of our patients were within the first 2 decades of life, and we observed a male-to-female ratio of 3:1. The 3 cases of pure mature teratoma occurred in younger patients at 0, 10, and 61 months of age. The identification of these elements of noninvasive diagnosis is crucial because biopsy sampling is risky and does not always yield a good specimen in cases of teratomas.[12,27,35,36] The reliability of noninvasive diagnostic tools is particularly illustrated in Case 9 in our study. In this patient, neuroradiological findings strongly indicated the presence of a teratoma (Fig. 2), later confirmed at surgery, despite the fact that neuroendoscopic biopsy had initially diagnosed the lesion as a pure germinoma.

Indications for Surgical Removal of Intracranial Teratomas

Complete microsurgical removal has been shown to be the only curative treatment for pure teratomas.[8,9,14,25,29,32,33,44] The use of resection as the only therapy avoids both the particularly high risks of stereotactic biopsy in the pineal region and the adverse effects of adjuvant therapies, especially in prepubescent patients.[11,18] Matsutani et al.[32] reported a 10-year survival rate of 92.9% in patients with pure mature teratomas who underwent surgical excision only, and a 10-year survival rate of 71% in patients with malignant teratomas who underwent extensive surgery followed by radiation therapy and no chemotherapy. In the present study all patients with pure mature or immature teratomas who underwent resection as the sole therapy are alive and free of disease at a mean follow-up of 9 years, with the exception of 1 patient who died of meningitis. Radical treatment is strongly advocated for intracranial teratomas because malignant transformations are not rare,[9,23] and have been reported in 4 of 27 cases of teratomas by Matsutani et al.,[32] and 6 of 7 patients with pure teratoma in Hoffman and colleagues'[18] study.

In addition, open surgery is the only way to obtain an accurate histological diagnosis because teratomas are frequently a component of mixed tumors.[11,14,18,21,27,31,32,36,39,41] Determination of the tumor type based on biopsy risks misdiagnosis if there are other tumor components that were not sampled and that require a specific treatment,[26,27,32,36] whereas resection[3,11,17,18,41] provides a large sample of the tumor,[41] minimizing the risk of missing some component.[32] Furthermore, stereotactic biopsy in the pineal region carries a particularly high risk of bleeding complications, nearly 21%,[12] with an overall mortality rate of 1.3–1.8% and a severe persistent morbidity rate of 0.8–4.5%,[10,12,27,36] increasing with harder, mature teratomas that resist needle penetration.[36] Neuroendoscopic biopsy is therefore indicated because sampling is performed under visual control.[6,34] The obstructive hydrocephalus can be managed with ETV, and the cysts managed by opening and fenestration.[6] Neuroendoscopic biopsy is characterized by the lowest level of accuracy because of the small quantity of biopsy material extracted.[47] In the present study, mixed intracranial GCTs were present with a high rate of 64.3%. Seven biopsies were performed—3 via a stereotactic approach and 4 via an endoscopic approach. Good histological correlation was achieved in only 2 (33%) of 6 surgically verified cases. The identification of the teratomatous component was delayed until surgical removal of the residual tumor after NAT in 2 patients in Group B (Cases 9 and 14; Fig. 2). Such cases of malignant GCTs for which there is no histological evidence of teratoma on the initial examination, but in which the patients have normalized tumor marker levels after NAT and require removal of residual mature teratoma after NAT, have been described both extra- and intracranially.[14,25,44] This phenomenon is called "growing teratoma syndrome."[16,29,30,33,45] The growth of a mature teratoma after NAT could be related to the chemoresistance of a benign

component within a mixed malignant GCT or result from paradoxically increasing growth as the cellular competition from the malignant element disappears.[29,38]

The prognosis of mixed teratomas varies widely depending on the nature of the most malignant component. However, even secreting components may benefit from aggressive surgery because cytoreductive intervention will improve the response to adjuvant therapy and allow lower doses to be used.[8,11] In addition, the poor prognosis of mixed malignant, secreting, intracranial GCTs improves with the combination of NAT followed by removal of residual teratoma when the patient tests negative for tumor markers.[1,4,14,15,17,24,25,30,33,37,44] In 3 recent studies,[14,25,44] the 5-year survival rate was increased to 70–100% for intracranial malignant GCTs treated with NAT first, followed by residual removal of a mature teratoma or scar tissue. In the present study, we also identified 2 cases of growing teratoma syndrome (Cases 9 and 14; Fig. 2) arising from a germinoma and a choriocarcinoma. Both patients are currently alive with no evidence of disease progression 17 months later.

Finally, resection can lead to decompression of adjacent structures, thus obviating the need for shunt placement in cases of pineal region tumors, or relieving compression of the optic pathways in cases of suprasellar tumors.[19]

Surgical Approaches to Intracranial Teratomas

Like their extracranial counterparts, intracranial teratomas tend to arise at the midline: 81–95% are located along an axis from the suprasellar cistern to the pineal region.[21,32] Despite this critical location in deep-seated regions of the brain, the refinements of microsurgical techniques within the past 30 years have made open surgical approaches to these regions safe procedures with a low morbidity rate (< 10%) and no operative deaths.[3,11,14,18,26,32,41–43] Our results emphasize the recent advances in microsurgical techniques. We performed 17 open surgical procedures. All incidences of death and complications related to open surgery in our patients occurred in the 3 patients who underwent surgery prior to 1992: 1 patient died from postoperative meningitis, and 2 patients with delayed postoperative awakening suffered permanent mental deficiencies. In our more recent cases, only 3 patients sustained transient neurological deterioration.

Given the higher prevalence of these lesions in the pineal location, the occipitotranstentorial and infratentorial supracerebellar approaches are preferentially utilized for surgical removal of intracranial teratomas.[3,15,22,26,42,43] The choice of approach depends on the lesion's size and precise location within the pineal area, and its relationship to the ventricular system, the median line, and the splenium.[3,15] A careful analysis of the morphological features and relationships of the tumor on MR imaging is decisive for determining the surgical approach. Magnetic resonance angiography focusing on the deep veins may be helpful in this respect. The supracerebellar approach is indicated for small- or medium-sized tumors located in the midline and below the galenic system and the splenium of the corpus callosum, but used to be performed with the patient in a sitting position,[3,42,43] while the occipitotranstentorial approach used currently is preferred for larger tumors extending laterally and superiorly above the tentorium and is advantageous because it adds no risk of air embolism.[15,26] A better field of view in the superoinferior direction allows an easier access to lesions at the superior cerebellar surface or with downward extension toward the fourth ventricle.[26] Retraction of the occipital lobe is almost unnecessary if an adequate amount of CSF is aspirated from the interhemispheric and ambient cisterns. Therefore, the latter technique was primarily used in the present study (6 cases): all surgeries were performed with the patient in the prone position, allowing total or subtotal removal of most pineal teratomas. We performed a transventricular approach in 2 cases of large pineal tumors of hard consistency extending anteriorly into the third ventricle (Cases 3 and 9). Indications for the transfrontal and subchoroidal approaches are the tumor's extension into the posterior and middle part of the third ventricle, and when an anterior portion reaches near the foramen of Monro region, as was true of the lesion in Case 9. The tumor was located entirely within the third ventricle, with the cystic part roofed by the foramen of Monro and the solid portion located strictly anterior to the quadrigeminal plate and below the splenium. Either of the preferred approaches to the pineal region in this case would have led to a partial resection, with a high risk of injury to the corpus callosum and the deep venous system. The obstructive hydrocephalus with considerable enlargement of the foramen of Monro bilaterally allowed a wide surgical exposure with a transfrontal transventricular route leading to complete surgical removal with no complications in this case (Fig. 2).

Limits and Timing of Resection

Mature teratomas are typically firmly adherent to neighboring tissues,[7,32] especially in cases of repeated surgery. Gamma Knife radiosurgery has been successfully applied as an alternative treatment in higher risk patients in 3 cases of residual or recurrent intracranial GCT without elevated tumor markers.[7] Given these preliminary results, the strategy of planned combined micro- and radiosurgical treatment of large intracranial teratomas should be considered either as a first therapeutic option or for recurrent or growing residual tumors, avoiding the risks related to attempting resection of small and adherent tumor pieces. The patient in Case 9 in our series could also benefit from Gamma Knife surgery for a recurrent metastatic teratoma in the posterior fossa.

The strong curative value of resection in cases of mixed teratoma with malignant component must be modulated by 3 predictive factors.[12,14,15,25,44] The main oncological prognostic factor is determined by the initial histological diagnosis: NGMGCT components are associated with a poorer outcome than germinoma[32,44] and require an aggressive pre- and postoperative chemotherapy and radiotherapy regimen. Case 6 is particularly illustrative: despite complete excision of residual mature teratoma tissue after chemotherapy for an initially diagnosed EC, the patient eventually died of progression of the malignant component. Another negative prognostic factor is the absence of complete normalization of tumor marker levels when the residual tumor is removed. Weiner et al.[44] suggested that delayed surgical removal of residual tumor should only be

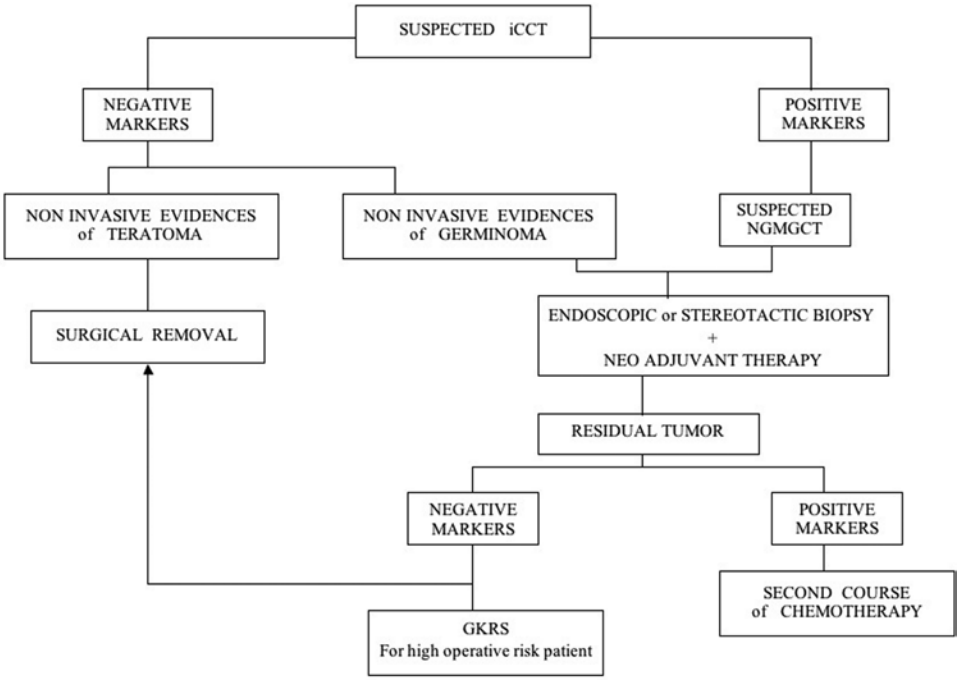

FIG. 5. Flowchart of management suggestions for diagnosis and treatment of intracranial GCTs (iCCT). GKRS = Gamma Knife radiosurgery.

performed when tumor markers have returned to normal levels. Kochi and colleagues[25] consider the presence of viable tumor cells within residual tumor tissue as a source of recurrence or progression; authors of previous extracranial studies have recommended their excision.[13]

In the context of delayed surgery, it appears to be of great value to check for evidence of preoperative dissemination on MR imaging and to assess serum tumor markers. If the markers have normalized, then surgical intervention should be undertaken as soon as possible to reduce the delay between the end of NAT and surgery, thus avoiding tumor regrowth in the interval.

Conclusions

Our results support the notion that surgical removal is the only curative treatment for intracranial teratomas because of their chemo- and radioresistance. Surgery may be performed as a first-line therapy when the results of noninvasive diagnostic investigations suggest the presence of a teratoma, or after oncological therapy for removal of residual tumor, improving the prognosis of patients with mixed malignant GCTs. In cases of mixed GCT, however, the final outcome depends on the oncological status at the time of surgery. Several conditions should then be taken into consideration and are summarized in a flowchart in Fig. 5.

Because of the high rate of mixed tumors and the poor correlation between histological biopsy tissue sampling and the results of surgical tissue examination, both pathological diagnosis and treatment of intracranial teratomas can be performed optimally through a single procedure at the time of an open surgical approach. Magnetic resonance imaging analysis will be the determining factor in choosing the surgical approach, even if the occipitotranstentorial route is preferred because of a wider exposure. The complication rate can be reduced by the use of modern microsurgical techniques, and is acceptable when surgical removal is the only available treatment.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References

1. Aprikian AG, Herr HW, Bajorin DF, Bosl GJ: Resection of postchemotherapy residual masses and limited retroperitoneal lymphadenectomy in patients with metastatic nonseminomatous germ cell tumors. **Cancer 74:**1329–1334, 1994
2. Baranzelli MC, Patte C, Bouffet E, Portas M, Mechinaud-Lacroix F, Sariban E, et al: An attempt to treat pediatric intracranial αFP and βHCG secreting germ cell tumors with chemotherapy alone. SFOP experience with 18 cases. Societe Francaise d'Oncologie Pediatrique. **J Neurooncol 37:**229–239, 1998
3. Bruce JN, Stein BM: Surgical management of pineal region tumors. **Acta Neurochir (Wien) 134:**130–135, 1995
4. Buckner JC, Peethambaram PP, Smithson WA, Groover RV, Schomberg PJ, Kimmel DW, et al: Phase II trial of primary chemotherapy followed by reduced-dose radiation for CNS germ cell tumors. **J Clin Oncol 17:**933–940, 1999
5. Calaminus G, Bamberg M, Baranzelli MC, Benoit Y, Cordero di Montezemolo L, Fossati-Bellani F, et al: Intracranial germ cell tumors: a comprehensive update of the European data. **Neuropediatrics 25:**26–32, 1994
6. Chernov MF, Kamikawa S, Yamane F, Ishihara S, Kubo O, Hori T: Neurofiberscopic biopsy of tumors in the pineal region and posterior third ventricle: indications, technique, complications, and results. **Neurosurgery 59:**267–277, 2006
7. Chiu CD, Chung WY, Hung-Chi Pan D, Wong TT, Shih YH, Lee LS: Gamma knife radiosurgery for intracranial mature

teratoma—long-term results and review of literature. **Surg Neurol 65:**343–351, 2006
8. Cho BK, Wang KC, Nam DH, Kim DG, Jung HW, Kim HJ, et al: Pineal tumors: experience with 48 cases over 10 years. **Childs Nerv Syst 14:**53–58, 1998
9. Cushing B, Perlman EJ, Marina NM, Castleberry RP: Germ cell tumors, in Pizzo PA, Poplack DG (eds): **Principles and Practice of Pediatric Oncology, ed 4.** Philadelphia: Lippincott Williams & Wilkins, 2002, pp 1091–1113
10. Dempsey PK, Kondziolka D, Lunsford LD: Stereotactic diagnosis and treatment of pineal region tumors and vascular malformations. **Acta Neurochir (Wien) 116:**14–22, 1992
11. Edwards MS, Hudgins RJ, Wilson CB, Levin VA, Wara WM: Pineal region tumors in children. **J Neurosurg 68:**689–697, 1988
12. Field M, Witham TF, Flickinger JC, Kondziolka D, Lunsford LD: Comprehensive assessment of hemorrhage risks and outcomes after stereotactic brain biopsy. **J Neurosurg 94:**545–551, 2001
13. Fizazi K, Tjulandin S, Salvioni R, Germa-Lluch JR, Bouzy J, Ragan D, et al: Viable malignant cells after primary chemotherapy for disseminated nonseminomatous germ cell tumors: prognostic factors and role of postsurgery chemotherapy—results from an international study group. **J Clin Oncol 19:**2647–2657, 2001
14. Friedman JA, Lynch JJ, Buckner JC, Scheithauer BW, Raffel C: Management of malignant pineal germ cell tumors with residual mature teratoma. **Neurosurgery 48:**518–523, 2001
15. Hancq S, De Witte O, Brotchi J: [Pineal region surgery. Experience in 22 patients.] **Neurochirurgie 48:**14–24, 2002 (Fr)
16. Hanna A, Edan C, Heresbach N, Ben Hassel M, Guegan Y: [Expanding mature pineal teratoma syndrome. Case report.] **Neurochirurgie 46:**568–572, 2000 (Fr)
17. Herrmann HD, Westphal M, Winkler K, Laas RW, Schulte FJ: Treatment of nongerminomatous germ-cell tumors of the pineal region. **Neurosurgery 34:**524–529, 1994
18. Hoffman HJ, Hotsubo H, Hendrick EB, Humphreys RP, Drake JM, Becker LE, et al: Intracranial germ-cell tumors in children. **J Neurosurg 74:**545–551, 1991
19. Hoffman HJ, Yoshida M, Becker LE, Hendrick EB, Humphreys RP: Experience with pineal region tumors in childhood. **Neurol Res 6:**107–112, 1984
20. Jenkin RDT, Simpson WJK, Keen CW: Pineal and suprasellar germinomas. Results of radiation treatment. **J Neurosurg 48:** 99–107, 1978
21. Jennings MT, Gelman R, Hochberg F: Intracranial germ-cell tumors: natural history and pathogenesis. **J Neurosurg 63:** 155–167, 1985
22. Kanno T: Surgical pitfalls in pinealoma surgery. **Minim Invasive Neurosurg 38:**153–157, 1995
23. Kleihues P, Burger PC, Scheithauer BW (eds): **Histological Typing of Tumors of the Central Nervous System, ed 2.** Berlin: Springer-Verlag, 1993
24. Kobayashi T, Yishida J, Ishiyama J, Noda S, Kito A, Kida Y: Combination chemotherapy with cisplatin and etoposide for malignant intracranial germ-cell tumors. An experimental and clinical study. **J Neurosurg 70:**676–681, 1987
25. Kochi M, Itoyama Y, Shiraishi S, Kitamura I, Marubayashi T, Ushio Y: Successful treatment of intracranial nongerminomatous germ cell tumors by administering neoadjuvant chemotherapy and radiotherapy before excision of residual tumors. **J Neurosurg 99:**106–114, 2003
26. Konovalov AN, Pitskhelauri DI: Principles of treatment of the pineal region tumors. **Surg Neurol 59:**250–268, 2003
27. Kreth FW, Schatz C, Pagenstecher A, Faist M, Volk B, Ostertag CB: Stereotactic management of lesions of the pineal region. **Neurosurgery 39:**280–291, 1996
28. Kuratsu J, Ushio Y: Epidemiological study of primary intracranial tumors: a regional survey in Kumamoto Prefecture in the southern part of Japan. **J Neurosurg 84:**946–950, 1996
29. Lee AC, Chan GC, Fung CF, Leung SY, Lau YL: Paradoxical response of a pineal immature teratoma to combination chemotherapy. **Med Pediatr Oncol 24:**53–57, 1995
30. Logothetis CJ, Samuels ML, Triade A, Johnson DE: The growing teratoma syndrome. **Cancer 50:**1629–1635, 1982
31. Matsutani M, Sano K, Takakura K, Fujimaki T, Nakamura O: Combined treatment with chemotherapy and radiation therapy for intracranial germ cell tumors. **Childs Nerv Syst 14:** 59–62, 1998
32. Matsutani M, Sano K, Takakura K, Fujimaki T, Nakamura O, Funata N, et al: Primary intracranial germ cell tumors: a clinical analysis of 153 histologically verified cases. **J Neurosurg 86:**446–455, 1997
33. O'Callaghan AM, Katapodis O, Ellison DW, Theaker JM, Mead JM: The growing teratoma syndrome in a germinomatous germ cell tumor of the pineal gland: a case report and review. **Cancer 80:**942–947, 1997
34. Oi S, Shibata M, Tominaga J, Honda Y, Shinoda M, Takei F, et al: Efficacy of neuroendoscopic procedures in minimally invasive preferential management of pineal region tumors: a prospective study. **J Neurosurg 93:**245–253, 2000
35. Pecker J, Scarabin JM, Vallee B, Brucher JM: Treatment in tumors of the pineal region: value of the stereotaxic biopsy. **Surg Neurol 12:**341–348, 1979
36. Regis J, Bouillot P, Rouby-Volot F, Figarella-Branger D, Dufour H, Peragut JC: Pineal region tumors and the role of stereotactic biopsy: review of the mortality, morbidity, and diagnostic rates in 370 cases. **Neurosurgery 39:**907–914, 1996
37. Robertson PL, DaRosso RC, Allen JC: Improved prognosis of intracranial nongerminoma germ cell tumors with multimodality therapy. **J Neurooncol 32:**71–80, 1997
38. Sano K: Pathogenesis of intracranial germ cell tumors reconsidered. **J Neurosurg 90:**258–264, 1999
39. Schild SE, Haddock MG, Scheithauer BW, Marks LB, Norman MG, Burger PC, et al: Nongerminomatous germ cell tumors of the brain. **Int J Radiat Oncol Biol Phys 36:**557–563, 1996
40. Schild SE, Scheithauer BW, Haddock MG, Wong WW, Lyons MK, Marks LB, et al: Histologically confirmed pineal tumors and other germ cell tumors of the brain. **Cancer 78:**2564–2571, 1996
41. Shokry A, Janzer RC, Von Hochstetter AR, Yasargil MG, Hedinger C: Primary intracranial germ-cell tumors. A clinicopathological study of 14 cases. **J Neurosurg 62:**826–830, 1985
42. Stein BM: Surgical treatment of pineal tumors. **Clin Neurosurg 26:**490–510, 1979
43. Stein BM, Bruce JN: Surgical management of pineal region tumors. **Clin Neurosurg 39:**509–532, 1992
44. Weiner HL, Lichtenbaum RA, Wisoff JH, Snow RB, Souweidane MM, Bruce JN, et al: Delayed surgical resection of central nervous system germ cell tumors. **Neurosurgery 50:** 727–734, 2002
45. Yagi K, Kageji T, Nagashiro S, Horiguchi H: Growing teratoma syndrome in a patient with a non-germinomatous germ cell tumor in the neurohypophysis: case report. **Neurol Med Chir (Tokyo) 44:**33–37, 2004
46. Yamagami T, Handa H, Takeuchi J, Niijima K, Furakawa F: Choriocarcinoma arising from the pituitary fossa with extracranial metastasis: a review of the literature. **Surg Neurol 19:**469–480, 1983
47. Yamini B, Refai D, Rubin CM, Frim DM: Initial endoscopic management of pineal region tumors and associated hydrocephalus: clinical series and literature review. **J Neurosurg 100 (5 Suppl):**437–441, 2004
48. Zimmerman RA, Bilaniuk LT, Wood JH, Bruce DA, Schut L: Computed tomography of pineal, parapineal and histologically related tumors. **Radiology 137:**669–677, 1980

Manuscript submitted August 15, 2007.
Accepted March 31, 2008.

Address correspondence to: Rémy Noudel, M.D., Department of Neurosurgery, Maison Blanche Hospital, University of Reims, Reims, France. email: remynoudel@yahoo.fr.