Neurosurgical treatment of craniopharyngioma in adults and children: early and long-term results in a large case series

Clinical article

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Object. Craniopharyngioma accounts for 2%–5% of all primary intracranial neoplasms. The optimal management of craniopharyngioma remains controversial. The authors evaluated the early results of surgery and the long-term risk of tumor recurrence in a large series of patients undergoing resection of craniopharyngiomas.

Methods. Between 1990 and 2008, 112 consecutive patients (57 male and 55 female patients with a mean ± SEM age of 33.3 ± 1.8 years) underwent resection of craniopharyngiomas at the authors’ hospital. Recurrence or growth of residual tumor tissue during follow-up was assessed using MR imaging.

Results. There were 3 perioperative deaths (2.7%). Severe adverse events were more frequent in patients who underwent operations via the transcranial route (37%) than the transsphenoidal approach (5.6%; p < 0.001). Magnetic resonance imaging showed radical resection of the tumor in 78 (71.6%) of the remaining 109 patients. Presence of residual tumor on the first postoperative MR imaging, male sex, and no postoperative radiation therapy were associated with a risk of tumor recurrence. Quality-of-life data were assessed in the 91 patients who attended the authors’ institution for follow-up visits. Among them, 8.8% patients were partially or completely dependent on others for daily living activities before surgery. This percentage increased to 14.3% at the last follow-up visit. The 5- and 10-year overall survival rates were 94.4% (95% CI 90.0%–98.8%) and 90.3% (95% CI 83.4%–97.3%), respectively.

Conclusions. Complete surgical removal of craniopharyngioma can be achieved with reasonable safety in more than 70% of patients. Recurrence of craniopharyngioma may occur even after apparent radical excision. Prompt management of residual or recurring disease by radiotherapy, repeat surgery, or a combination of both is usually successful in controlling further tumor growth. (DOI: 10.3171/2010.11.JNS10670)

Key Words • pituitary neoplasm • pituitary surgery • hypopituitarism • diabetes insipidus • craniopharyngioma

Craniopharyngioma is a histologically benign tumor arising in the sellar and suprasellar region along the path of the craniopharyngeal duct. It accounts for 2%–5% of all primary intracranial neoplasms22 and 5.6%–13% of intracranial tumors in children.20 It thus ranks as the second most frequent tumor, after pituitary adenoma, in the hypothalamic-pituitary region at any age.2 Despite its benign appearance, it can be associated with an unfavorable prognosis, due to the proximity to and relationships with vital structures.

The optimal treatment of patients with craniopharyngioma remains controversial and continues to be debated because an effective balanced protocol between aggressive therapy and reducing adverse sequelae is still lacking in both children and adults.27 Radical resection is usually considered the therapy of choice at any age for primary treatment of craniopharyngioma. This treatment is associated with the best outcome in terms of survival and recurrence-free survival.12 Nevertheless, the location and the frequent involvement of critical neurovascular structures, tumor size, calcifications, and the patient age at presentation may limit the extent of resection.5,8 Surgery also carries significant morbidity in terms of visual, hypothalamic, and endocrinological disturbances, thus potentially deteriorating the QOL of patients.12 Moreover, craniopharyngioma can also recur, despite negative postoperative brain imaging. For these reasons, many authors advocate a less aggressive surgical treatment followed by radiation therapy.6,14,18 To further elucidate the role of at-
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tempted radical resection in the treatment of craniopharyngioma, the present study retrospectively investigated the outcome after surgical treatment and the factors affecting the risk of tumor recurrence through a rigorous clinical and radiological follow-up.

Methods

Study Population

Between 1990 and 2008, 112 consecutive patients underwent resection of craniopharyngioma at the Department of Neurosurgery of the Università Vita-Salute in Milan, Italy. The diagnosis of craniopharyngioma was based on the clinical and neuroradiological picture and histopathological confirmation of the tumor. Age at surgery, sex, symptoms at presentation, hormonal data, previous treatments, neuroimaging features, surgical results, perioperative complications, recurrence, treatment of recurrence, and follow-up were prospectively collected. All patients underwent MR imaging and CT before surgery.

At each patient ambulatory visit, we collected information on disease and vital sign status, pituitary function, current or past use of hormonal substitution therapy, visual function, neurological status, and last MR imaging examination. Long-term follow-up data concerning 18 patients who did not undergo follow-up evaluation at our center were obtained by direct telephone contact with the patient or the patient’s physician. In these cases, only the relevant information on vital sign status, last MR imaging result, and hormonal substitution therapy was collected, and these patients were not included in the retrospective analysis of QOL. Standard informed consent was obtained from each patient who underwent pituitary surgery. A parent or legal guardian of patients < 18 years old gave written informed consent for the surgical procedure.

Endocrinological Evaluation

In adults, a diagnosis of hypogonadotropic hypogonadism was given in premenopausal women with amenorrhea and in men with subnormal testosterone levels. Low or normal gonadotropin levels were also required in both sexes to make the diagnosis of hypogonadotropic hypogonadism. Postmenopausal women with inappropriately low or normal gonadotropin levels were also considered to have gonadotropin deficiency. Secondary hypothyroidism was diagnosed in patients with low free-thyroxine levels and normal or suppressed thyroid-stimulating hormone concentrations. Secondary hypoadrenalism was diagnosed in patients with low morning cortisol levels, low or normal adrenocorticotropic levels, low 24-hour free urinary cortisol levels, and clinical symptoms of hypothalamic dysfunction that improved after replacement therapy with glucocorticoids. A deficit of GH secretion was established in prepubertal and pubertal children by growth arrest and in adults by the response of GH to the combined administration of arginine and GH-releasing hormone. A GH peak < 11.5, 8.0, and 4.2 μg/L in lean, overweight, and obese patients, respectively, identified patients with a GH deficit.4 Hyperprolactinemia was defined as a prolactin level > 20 μg/L in women and > 15 μg/L in men. When patients were receiving dopamine agonists, prolactin values recorded at diagnosis (if available) or after ≥ 6 months of dopaminergic washout were accepted. Diabetes insipidus was diagnosed before or after surgery in patients who had hypotonic polyuria (> 40 ml/kg body weight daily).

Visual Evaluation

An accurate ophthalmological evaluation, including visual acuity and visual field examination by computerized perimetry, was performed both before and after surgery or when clinically appropriate. The data on early postoperative results are based on an evaluation that was usually performed 2–3 months after surgery.

Neuroradiological Evaluation

All patients underwent brain MR imaging, including T1-weighted imaging with contrast administration, obtained 10 minutes after intravenous injection of 0.1 mmol/kg Gd–diethylenetriamine pentaacid (Magnevist, Berlex Labs). Tumor size was estimated by measuring the maximum anteroposterior, vertical, and horizontal diameters. Magnetic resonance imaging angiograms were obtained in select cases to evaluate the relationship with vascular structures. Computed tomography without administration of contrast was performed to verify the presence of intratumoral calcifications.

Surgical Management

The microscopic transsphenoidal and transcranial approach techniques adopted in this patient series have been previously described in detail elsewhere.19,20 Selection of the surgical approach was mainly dictated by the shape of the tumor. The transsphenoidal approach was used in patients in whom the lesion was exclusively intrasellar or in cases of intrasellar and suprasellar tumor extension with symmetrical and homogenous intrasellar and suprasellar development. The transcranial approach was selected when the tumor was exclusively suprasellar or in cases of intrasellar and suprasellar extension with asymmetrical and larger suprasellar development.

Cases with only suprasellar development, supradachyphragmatic with paraventricular development, or intraventricular development were treated using a pterional approach, or beginning in 1999 to date, a frontoorbitozygomatic approach, according to the technique we have previously described.19 The frontoorbitozygomatic approach avoids traction on the frontal lobe and allows extradural and intradural decompression of the optic nerve on the side of the approach. Moreover, after a small unilateral extension of the craniotomy toward the midline, this approach allows a unilateral interhemispheric approach to the huge retrochiasmatic tumors that extend superiorly into the third ventricle. In those cases, the dissection can be performed toward the supracallosal region, exposing the A2 segments bilaterally, after dissecting the anterior communicating artery and the chiasma. The combination of multiple access corridors, such as the prechiasmatic, opticocarotid, carotid-oculomotor, and translaminar terminalis both proximal and distal to the ante-
rior communicating artery, allows the removal of large tumors without significant traction on the frontal lobe (Fig. 1). In a single case, the interhemispheric transcallosal approach was adopted after the pterional approach to remove the residual intraventricular tumors remaining above the level of the foramen of Monro.

Radiation Therapy

When clinically indicated, patients underwent radiation treatment at our hospital. Fractionated radiotherapy was given in 25–27 fractions of 2 Gy each for a total dose of 50–54 Gy. Beginning in 1993, the Leksell Gamma Knife Unit was available in our department. Patients with craniopharyngioma were treated with a single dose of 15–18 Gy. The choice between the 2 radiation modalities was primarily dictated by the location of residual or recurrent tumor. Whenever possible, GKS was the preferred option provided that the residual or recurrent tumor was at least 2 mm away from the optic pathway.

Follow-Up and Recurrence

The first postoperative MR imaging was obtained within 4 months of surgery. Subsequent surveillance imaging studies were recommended at 6-month intervals for 2 years and then yearly or at increasing intervals depending on the radiological findings. Recurrence of the tumor during follow-up was defined as the appearance of pathological tissue on imaging studies that had not previously been detected or the growth of tumor remnants.

Quality of Life

Overall functional morbidity, including visual, neurological, hypothalamic, pituitary, and psychosocial dysfunction, was assessed using the 4-tiered classification system proposed by Wen et al. In this system, Class I includes grossly normal and independent patients who may have mild hormonal disturbances or seizures well controlled with medication. Class II includes independent patients who may have panhypopituitarism, mild to moderate visual compromise, cranial nerve deficits, or mild psychological dysfunction. Class III includes partially dependent patients who may have serious visual compromise, serious neurological deficits, learning disabilities, or poorly controlled psychological disorders. Class IV includes patients entirely dependent on others for self-care. Classification of patients was performed retrospectively before surgery and at the last follow-up visit at our center. As mentioned above, 18 patients for whom follow-up information was collected by phone were excluded from QOL measurement to preserve homogeneity of data assessment.

Statistical Analysis

Continuous data were examined for homogeneity of variance and are expressed as means ± SEM. The paired and unpaired t-tests were used to compare continuous variables within and among groups, respectively, and chi-square tabulation with Yates correction was used to compare binomial proportions. Multiple logistic regression analysis was used to determine which variables independently predicted absence of residual tumor at the first postoperative neuroimaging study. The cumulative risk of tumor recurrence was calculated according to the Kaplan-Meier method. Differences between survival curves were determined with the use of log-ranked tests. Recurrence-free survival was measured from the date of surgery to the date of tumor recurrence. Patients were censored at the date of the last neuroimaging follow-up. A Cox proportional-hazards model with adjustment of baseline characteristics was applied to examine which variables independently influenced the risk of tumor recurrence. A p value < 0.05 was considered statistically significant, and all reported probability values are 2-tailed. All calculations were performed using commercially available software (StatView 5.0, SAS Institute).

Results

Patient Characteristics

The main clinical characteristics of the 112 patients are summarized in Table 1. Mean (±SEM) patient age at surgery was 33.3 ± 1.8 years, ranging between 6 and 78 years. Childhood cases, defined as those patients < 18 years old, represented 30.4% of all cases (34 of 112 patients). Excluding age, no significant difference between childhood and adult cases was observed for any of the variables included in Table 1. Main neuroradiological characteristics are summarized in Table 2. No significant difference was observed in neuroradiological variables between children and adults, except for the presence of calcification in a higher proportion of children (84.4%) than adults (42.7%).
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**Table 1: Clinical characteristics of 112 patients who underwent operations for craniopharyngioma according to age at surgery**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Children</th>
<th>Adults</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>34</td>
<td>78</td>
<td>112</td>
</tr>
<tr>
<td>Mean age (yrs) at surgery (± SEM)</td>
<td>13.2 ± 0.6</td>
<td>42.0 ± 1.7</td>
<td>33.3 ± 1.8</td>
</tr>
<tr>
<td>Female sex</td>
<td>15 (44.1)</td>
<td>40 (51.3)</td>
<td>55 (49.1)</td>
</tr>
<tr>
<td>Adrenal function deficit</td>
<td>16 (47.1)</td>
<td>40 (51.3)</td>
<td>56 (50)</td>
</tr>
<tr>
<td>Thyroid function deficit</td>
<td>15 (47.1)</td>
<td>37 (48.7)†</td>
<td>53 (48.2)†</td>
</tr>
<tr>
<td>Gonadal function deficit</td>
<td>NA</td>
<td>59 (75.6)</td>
<td>59 (75.6)</td>
</tr>
<tr>
<td>Growth deficit</td>
<td>28 (82.3)</td>
<td>NA</td>
<td>28 (82.3)</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>7 (20.6)</td>
<td>24 (30.8)</td>
<td>31 (27.7)</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>12 (35.3)</td>
<td>30 (38.5)</td>
<td>42 (37.5)</td>
</tr>
<tr>
<td>Obesity</td>
<td>9 (26.5)</td>
<td>12 (15.4)</td>
<td>21 (18.7)</td>
</tr>
<tr>
<td>Visual deficit</td>
<td>22 (64.7)</td>
<td>63 (80.8)</td>
<td>85 (75.9)</td>
</tr>
<tr>
<td>Previous surgery</td>
<td>5 (14.7)</td>
<td>14 (17.9)</td>
<td>19 (17.0)</td>
</tr>
<tr>
<td>Transsphenoidal approach</td>
<td>10 (29.4)</td>
<td>26 (33.3)</td>
<td>36 (32.1)</td>
</tr>
</tbody>
</table>

* Values given as number of patients (%) unless otherwise indicated. Childhood is defined as < 18 years old, adulthood as ≥ 18 years old. Abbreviation: NA = not applicable.
† Information on preoperative thyroid function was not applicable in 2 adult patients: one was treated with methimazole because of coexistent hyperthyroidism, and the other was receiving L-thyroxine because of nodular goiter.

Surgery was performed via the transsphenoidal approach in 36 patients (32.1%) and the transcranial approach in 76 patients (67.9%). Histological analysis of tumor specimens confirmed the presence of craniopharyngioma in all cases. Based on morphological appearance, 104 tumors (92.9%) were classified as the adamantinomatous subtype and 8 tumors (7.1%) as the papillary subtype. Invasion of the tumor into the surrounding nervous tissue occurred in 19 patients (17.0%).

**Early Postoperative Results**

There were 3 perioperative deaths (2.7%), all occurring in patients undergoing operations via the transcranial approach. The first patient was a 65-year-old man with a large suprasellar tumor who died of untreatable electrolyte imbalance on the 3rd postoperative day. The second patient was a 43-year-old woman with a tumor extending into the retrolateral space who died 72 hours after transcranial surgery because of cerebral stroke due to the intraoperative rupture and closure of the internal carotid artery at the posterior communicating artery bifurcation, which adhered strongly to the tumor. The third patient was a 69-year-old man with a suprasellar tumor and coexisting renal insufficiency, who suffered an intracerebral hemorrhage and died on the 10th postoperative day from multiorgan failure.

Table 3 reports all the nonendocrine complications of surgery in the 109 surviving patients. Severe adverse events—those that are life-threatening, need repeat surgery, or lead to permanent neurological deficit—occurred in 29 (26.6%) of the 109 surviving patients, whereas minor nonendocrine adverse events occurred in 30 patients (27.5%). As expected, patients who underwent operations via a transcranial approach had a higher incidence of severe adverse events (37%) than patients who underwent operations via the transsphenoidal route (5.6%; p < 0.001), whereas the incidence of minor adverse events was similar in the 2 groups of patients (28.9% and 25% for the transcranial and transsphenoidal groups, respectively).

Visual function was impaired before surgery in 82 (75.2%) of the 109 surviving patients. Fifty-two (63.4%) of these 82 patients had a visual field defect only, whereas the remaining 30 patients (36.6%) also had impaired visual acuity. Visual function improved after surgery in 50 patients (61.0%), remained unchanged in 21 patients (25.6%), and worsened in the remaining 11 patients (13.4%). Among the 27 patients with preoperative normal visual examinations, 23 patients (85.2%) retained normal function, whereas the remaining 4 patients (14.8%) developed a permanent visual field defect with no impairment of visual acuity.

Changes of endocrine function after surgery are reported for each single pituitary axis. Only patients with the available relevant information both before and after surgery were included in this analysis. At baseline, normal gonadal, thyroid, adrenal, or somatotroph function was present in 18, 55, 54, and 17 patients, respectively. A new defect of the corresponding pituitary axis occurred postoperatively in 12 (66.7%), 40 (72.7%), 41 (75.9%), and 14 (82.3%) patients, respectively (Table 4). In contrast, 57, 52, 55, and 23 patients had a preoperative deficit of gonadal, thyroid, adrenal, or somatotroph function, respectively, that did not recover after surgery. Sixty-nine patients had normal urinary concentrating capacity before surgery and 21 (30.4%) retained a normal function, whereas the remaining 48 (69.6%) experienced postoperative onset of diabetes insipidus. Of the 40 patients with preoperative diabetes insipidus, 3 (7.5%) regained a normal urinary...
TABLE 3: Severe and minor nonendocrine-related complications of surgery in 109 surviving patients who underwent operations for craniopharyngioma according to the type of surgical procedure*  

<table>
<thead>
<tr>
<th>Complication</th>
<th>Transsphenoidal</th>
<th>Transcranial</th>
<th>Total</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>36</td>
<td>73</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td>severe adverse events†</td>
<td>2 (5.6)</td>
<td>27 (37)</td>
<td>29 (26.6)</td>
<td></td>
</tr>
<tr>
<td>permanent worsening of vision</td>
<td>0 (0)</td>
<td>15 (20.5)</td>
<td>15 (13.8)</td>
<td></td>
</tr>
<tr>
<td>CSF leak requiring surgery</td>
<td>2 (5.6)</td>
<td>2 (2.7)</td>
<td>4 (3.7)</td>
<td></td>
</tr>
<tr>
<td>seizure</td>
<td>0</td>
<td>3 (4.1)</td>
<td>3 (2.8)</td>
<td></td>
</tr>
<tr>
<td>hematoma requiring surgery</td>
<td>0</td>
<td>4 (5.5)</td>
<td>4 (3.7)</td>
<td></td>
</tr>
<tr>
<td>malignant neuroepithelial syndrome</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>hypothalamic derangement</td>
<td>0</td>
<td>3 (4.1)</td>
<td>3 (2.8)</td>
<td></td>
</tr>
<tr>
<td>pulmonary embolism</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>acute renal failure</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>acute lung failure</td>
<td>0</td>
<td>3 (4.1)</td>
<td>3 (2.8)</td>
<td></td>
</tr>
<tr>
<td>meningitis</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>adipsic diabetes insipidus</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>sepsis</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>minor adverse events†</td>
<td>9 (25)</td>
<td>21 (28.8)</td>
<td>30 (27.5)</td>
<td></td>
</tr>
<tr>
<td>transient worsening of vision</td>
<td>0</td>
<td>9 (12.3)</td>
<td>9 (8.3)</td>
<td></td>
</tr>
<tr>
<td>CSF leak not requiring surgery</td>
<td>7 (19.4)</td>
<td>1 (1.4)</td>
<td>8 (7.3)</td>
<td></td>
</tr>
<tr>
<td>transient electrolytic disturbances</td>
<td>2 (5.6)</td>
<td>6 (8.2)</td>
<td>8 (7.3)</td>
<td></td>
</tr>
<tr>
<td>thrombophlebitis</td>
<td>0</td>
<td>4 (5.5)</td>
<td>4 (3.7)</td>
<td></td>
</tr>
<tr>
<td>transient altered mental status</td>
<td>0</td>
<td>3 (4.1)</td>
<td>3 (2.8)</td>
<td></td>
</tr>
<tr>
<td>transient hemiparesis</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>transient oculomotor nerve palsy</td>
<td>0</td>
<td>2 (2.7)</td>
<td>2 (1.8)</td>
<td></td>
</tr>
<tr>
<td>infection</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>blood loss requiring transfusion</td>
<td>0</td>
<td>2 (2.7)</td>
<td>2 (1.8)</td>
<td></td>
</tr>
</tbody>
</table>

* Values given as number of patients (%).  
† Patients may have experienced more than 1 adverse event, both severe and/or minor.

concentrating capacity. Overall, 69 (92%) of 75, 92 (86%) of 107, 96 (88.1%) of 109, 37 (92.5%) of 40, and 85 (78%) of 109 patients had impaired gonadal, thyroid, adrenal, and somatotroph function or diabetes insipidus after surgery, respectively. Table 4 shows that the occurrence of new defects was partially dependent on the type of surgical approach: patients who underwent operations via the transsphenoidal approach had a lower risk of acquiring new pituitary defects.

The mean prolactin level decreased from 23.7 ± 3.3 μg/L to 16.5 ± 2.3 μg/L (p < 0.01), but the percentage of patients with hyperprolactinemia decreased only slightly from 33.3% to 21.3%, a nonsignificant difference.

The initial postoperative MR imaging results showed residual tumor in 31 (28.4%) of the 109 patients who could be evaluated, whereas no tumor was demonstrable in the remaining 78 patients (71.6%). Multivariate logistic regression analysis showed that previous surgery for craniopharyngioma (OR 11.1, 95% CI 2.87–42.92; p < 0.001) and maximum tumor diameter (OR [per unit increase] 1.09, 95% CI 1.02–1.17; p < 0.02) were associated with persistence of tumor residue after surgery. Other characteristics such as sex, age at surgery, diabetes insipidus before surgery, type of surgery, histological subtype, and infiltration of the surrounding nervous tissue had no association with surgical outcome.

TABLE 4: New cases of pituitary deficiency according to the type of surgical approach*  

<table>
<thead>
<tr>
<th>Pituitary Hormone</th>
<th>Transsphenoidal</th>
<th>Transcranial</th>
<th>Total</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH</td>
<td>5/5 (100)</td>
<td>9/12 (75)</td>
<td>14/17 (82.3)</td>
<td>NS</td>
</tr>
<tr>
<td>gonadotropin</td>
<td>4/7 (57.1)</td>
<td>8/11 (72.7)</td>
<td>12/18 (66.7)</td>
<td>NS</td>
</tr>
<tr>
<td>thyrotropin</td>
<td>9/18 (50)</td>
<td>31/37 (83.8)</td>
<td>40/55 (72.7)</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>adrenocorticotro-</td>
<td>10/17 (58.8)</td>
<td>31/37 (83.8)</td>
<td>41/54 (75.9)</td>
<td>&lt;0.09</td>
</tr>
<tr>
<td>pin antiadipic hor-</td>
<td>7/25 (28.0)</td>
<td>41/44 (93.2)</td>
<td>48/69 (69.6)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Only patients for whom the relevant information is available are included. Abbreviation: NS = not significant.

Tumor Recurrence

Radiation therapy after surgery was not indicated in the 78 patients who had no evidence of residual tumor on the first postoperative MR imaging. In the group of 31 patients with visible residual tumor, radiation therapy was performed in 8 cases (25.8%; 6 patients received fractionated radiotherapy and 2 were treated by single-dose GKS); was advised but not performed in 6 patients (19.4%) because of early symptomatic recurrence of the tumor necessitating another surgical procedure (5 cases, of whom 3 also underwent fractionated radiotherapy soon after the second surgery) or unrelated death (1 case); and was advised but refused by 5 patients (16.1%). In 4 patients (12.9%), residual tumor was completely removed by another surgical procedure (3 via the transsphenoidal approach and 1 via the transcranial approach). The remaining 8 patients (25.8%) were advised to undergo regular neuroradiological monitoring, leaving the choice of receiving radiation therapy until the first demonstration of tumor growth.

According to our definition, the analyses on tumor recurrence are restricted only to the 106 patients (94.6%) in whom ≥ 2 neuroradiological studies are available during follow-up. In addition to the 3 patients who died in the perioperative period, nonadherence to the scheduled neuroradiological follow-up was due to death for unrelated reasons (2 patients) or lost to follow-up (1 patient). The median follow-up duration for the 106 patients on active follow-up was 83 months (IQR 36.5–126 months), and the median neuroradiological follow-up was 67 months (IQR 30–112.5 months). In 102 patients, the observation period started after the first surgical treatment, whereas in the 4 patients who underwent another successful surgical procedure because of residual tumor, the observation period started after the second surgery. For the purpose of this particular analysis, these patients are classified in the
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A group of patients without residual tumor after surgery. Recurrence of craniopharyngioma occurred in 26 (24.5%) of the 106 patients. Figure 2 demonstrates that the risk of recurrence is higher in the 1st 3 years after surgery and then shows a plateau. The recurrence-free survival at 5 and 10 years was 75.7% (95% CI 66.7%–84.7%) and 69.3% (95% CI 58.4%–80.1%), respectively. The presence of residual tumor after surgery was the strongest predictor of late recurrence of the tumor (Fig. 3). The 5-year recurrence-free survival in patients with no residual tumor was 85.6% (95% CI 76.8%–94.4%) compared with 46.3% (95% CI 25.7%–66.8%; p < 0.001) in patients with residual tumor (Fig. 3). Cox regression analysis demonstrated that the risk of tumor recurrence was significantly associated with presence of residual tumor on the first postoperative MR imaging (HR 9.48, 95% CI 3.36–26.73; p < 0.001), male sex (HR 4.69, 95% CI 1.76–12.49; p < 0.01), and postoperative radiation therapy (HR 0.09, 95% CI 0.01–0.76; p < 0.05). Previous surgery, tumor calcification, infiltration of the nervous tissue, absence of postoperative diabetes insipidus, childhood onset, and obesity had no significant association with the risk of tumor recurrence.

Further Treatments, QOL, and Disease Status at Last Follow-Up

Twenty-four of the 26 patients who experienced tumor recurrence received further treatments. Two patients declined to undergo fractionated radiotherapy. Recurrence was treated by repeat surgery in 10 patients (via a transsphenoidal approach in 7 patients and via a transcranial approach in 3). However, 5 of these patients (3 operated on via a transcranial approach and 2 via a transsphenoidal approach) had further recurrence of the tumor and necessitated another surgical procedure followed by fractionated radiotherapy (2 cases), fractionated radiotherapy alone (1 case), GKS alone (1 case), and another transsphenoidal surgical procedure alone (1 case). Nine patients received radiotherapy after the first recurrence of craniopharyngioma; 5 patients received fractionated radiotherapy, and the other 4 received GKS. Of these 9 patients, 2 had another recurrence 14 and 48 months after fractionated radiotherapy. The first patient was further treated using GKS and the second by transcranial surgery. The remaining 5 patients were treated by surgery (3 via the transsphenoidal approach and 2 via the transcranial approach) followed by fractionated radiotherapy. At the end of the follow-up period, control of tumor growth was obtained in all patients, and there were no deaths attributable to progressive disease or to further therapy.

Data on QOL, as assessed by mean Wen score, were retrospectively collected in 91 patients both before surgery and at last follow-up. The mean score before surgery was 1.96 ± 0.05. Twelve patients (13.2%) were in Class I (grossly normal and independent patients), 71 (78%) were in Class II (patients with deficits but living independently), and 8 (8.8%) were in Class III (partially dependent patients). No patient was in Class IV (completely dependent on others for self-care). At the last follow-up visit at our center, the mean Wen score was slightly increased (2.08 ± 0.05, p < 0.02). The number of patients in Classes I, II, III, and IV was 7 (7.7%), 71 (78%), 12 (13.2%), and 1 (1.1%), respectively.

In the entire study population, there were 4 additional deaths occurring 33, 84, 108, and 161 months after surgery. The cause of death was pulmonary embolism in 1 case, car accident in 1 case, and unknown in 2 cases. All 4 patients had no visible tumor after surgery and had no recurrence of craniopharyngioma at the last neuroradiological follow-up. Figure 4 shows the overall survival of the 112 patients included in the study. The 5-year survival rate was 94.4% (95% CI 90.0%–98.8%), and the 10-year survival rate was 90.3% (95% CI 83.4%–97.3%). Sex, de-
The overall survival rates at 5 and 10 years were 94.4% (95% CI 90.0%–98.8%) and 90.3% (95% CI 83.4%–97.3%), respectively.

The age distribution of our series was similar to that reported by another center with substantial expertise in the treatment of sellar tumors, with almost one-third of the cases in the pediatric age group. We did not find any significant difference in several clinical and radiological characteristics between adults and children, except for the higher frequency of tumor calcification in the pediatric cases. Therefore, pooling the results of the 2 groups together for statistical analysis was appropriate. This does not imply, however, that tumor biology is the same in the 2 age groups.

Different from pituitary adenomas, craniopharyngiomas often need a transcranial surgical procedure because of the suprasellar and retrosellar extension of the tumor. In our series, 68% of the patients underwent operations via a transcranial procedure. In recent years, the frontoorbitozygomatic approach has become our preferred approach for the transcranial removal of craniopharyngiomas. We encountered many advantages using this approach, such as the very basal view of the chiasmatic area through a minimal unilateral frontal lobe retraction, the possibility to use multiple surgical corridors in the suprasellar area, and the possible enlargement toward the midline to combine the unilateral interhemispheric approach with the standard transsylvian route. Using this approach we were able to use multiple working corridors to remove the tumor effectively and safely.

It is well known that transcranial surgery entails a higher risk of serious side effects than transsphenoidal procedures. This fact, along with the larger extension and infiltrating nature of tumors removed via the transcranial approach, may explain the higher incidence of severe complications occurring in patients with craniopharyngiomas than in patients with nonfunctioning pituitary adenomas. The perioperative mortality in our study (2.7%) was similar to that reported in other patient series of similar size (Table 5) and was completely accounted for by patients with larger tumors treated using transcranial procedures. Among the serious side effects of surgery, worsening of visual function is particularly bothersome for the QOL of patients with craniopharyngioma. In our series, 15 patients (13.8%) had permanent worsening of visual function after surgery. Not surprisingly, this complication occurred only after a transcranial procedure and was not dependent on whether patients had normal or impaired vision before surgery. The risk of worsening vision was counterbalanced by improvement of preoperative defect in some patients, which occurred in 61% of our cases. Similar findings were reported in other series. Pituitary function at diagnosis is often impaired in patients with craniopharyngioma, independently of age at presentation, probably because the tumor originates from or strictly adheres to the pituitary stalk. Surgical removal of craniopharyngioma is associated with further impairment of pituitary function in most patients. Patients undergoing operations via the transsphenoidal approach are more likely to preserve normal pituitary function when it is not already damaged before surgery, and our data are consistent with these data. We emphasize that, at variance with surgical results in patients with nonfunctioning pituitary adenomas, pituitary function only rarely improves after surgery. Anatomical preservation of the pituitary stalk during surgery has been suggested to increase the likelihood of normal pituitary function. Another factor associated with postoperative hypopituitarism, especially in cystic tumors, is the degree of tumor removal. Simple aspiration of the fluid in the cyst does not usually compromise pituitary function, but dissection of solid tumor and capsule often leads to pituitary damage. Consistent with the views of other authors, we believe...
that complete removal of the tumor is the most effective method of preventing recurrence. Considering the attending risks of renewed treatments (see below), in both adults and children, we accept the sacrifice of the pituitary stalk to obtain radical resection, as advocated by others.3,9,22 We anticipate that pituitary replacement therapy is a very likely sequela of surgery, but it must be emphasized that patients with adequate substitution therapies may have normal life expectancy. Moreover, it has been postulated that the degree of postoperative endocrine deficits depends on the extent of tumor removal;3 but most studies did not find significant differences in pituitary function depending on whether patients had received aggressive or conservative surgical procedures.10,31,33

Radical excision of the tumor, as demonstrated by postoperative MR imaging, was achieved in 71.6% of patients, without a significant difference between children and adults. This percentage compares favorably with the results of other series using microsurgical techniques and involving more than 100 patients (Table 5). We found that the factors associated with the presence of postoperative residual tumor were previous surgery and large tumor size. Conceivably, previous surgery was an unfavorable factor because scarring and adhesions to surrounding nervous structures might decrease the possibility of radical resection. The success rate of repeat surgery was found to be markedly lower than that of primary surgery in other large surgical series.8,11,33 Moreover, perioperative morbidity and death are also increased in cases of repeat surgery.8,31,37 Large tumor size was another negative prognostic factor in our study and in previous studies.5,8,37,33

Recurrence of craniopharyngioma continues to be an unresolved problem that may affect the long-term prognosis of the patient. In our study, all patients have been followed-up exclusively using MR imaging, which can be considered the most precise neuroimaging technique to detect recurrence of the tumor. As a whole, 24.5% of the patients experienced relapse of craniopharyngioma during follow-up. The estimated 5- and 10-year recurrence-free survival rates were almost identical (75.7% and 69.3%, respectively), because, as in other surgical series,10,11,24,33,35 most relapses occurred in the 1st 3 years after surgery. This fact underscores the potential for early regrowth of craniopharyngiomas. As expected, the degree of tumor removal is a strong determinant of later recurrence. Presence of residual tumor on the first postoperative neuroimaging study was associated with late regrowth of the tumor (Fig. 3). Although there are some differences in the definitions used, most studies reported that gross-total removal of the tumor conferred a low risk of late recurrence, ranging from 0% to 26%.5,6,8,17,28,33,35 However, 2 studies13,31 found a recurrence rate of 62% and 53%, respectively, even after apparent complete removal of the tumor. Both series included only pediatric patients13 or patients younger than 25 years old,31 suggesting that young age might be a risk factor for recurrence of the tumor, independently of the degree of tumor excision. Age at surgery, analyzed both as a continuous variable or stratified as adulthood or childhood, was not an independent risk factor for tumor recurrence in our study or in other surgical series.5,7,33 However, in our study, the youngest patient was 6 years old, and we cannot exclude the possibility that younger patients might be at increased risk of tumor recurrence, as reported by others.5 Although our data are limited by the small number of patients, we confirm that radiation therapy lowers the risk of tumor growth after incomplete surgical removal. The protective effect of radiation therapy is even more evident in other series, in which the percentage of patients with residual tumor after surgery was greater than in our study.6,11,25 Sex was not a prognostic factor for recurrence in the 2 studies that analyzed this variable.11,25 whereas we found that male sex was associated with a more than 4-fold hazard risk of tumor relapse. This is a rather unexpected finding and, apart from chance alone, we have no biologically plausible explanation for this association. We believe that this association needs to be replicated in other series before we can accept it. Interestingly, no histopathological characteristic correlated with the risk of tumor recurrence. Infiltration of brain tissue by craniopharyngioma, occurring in 17% of our patients, did not portend a worse long-term follow-up result in our study. We did not systematically investigate the proliferation rate in this series, but in a previous study performed in a smaller subset of patients, we found no difference in the Ki 67 labeling index among patients who had a recurrence compared with those without it.16

Treatment of recurring craniopharyngioma remains a difficult task because previous therapies make further surgical maneuvers more hazardous and less successful. Indeed, in our series, 12 of the 26 patients with recurrent craniopharyngioma necessitated multiple treatments to obtain control of tumor growth. However, it is notable that, in our series, uncontrollable tumor growth was avoided in all patients because of an aggressive management policy including radiotherapy and/or repeat surgery.

Patients with craniopharyngioma have overall mortality rates higher than the general population.1,24,32 Our study was not sufficiently powered to assess this point. However, our estimates of overall survival rates of 94.4%
and 90.3% at 5- and 10-year follow-up, respectively, are similar to those reported by other recent patient series, and are clearly better than the rates described in older series. We did not detect prognostic factors for the long-term risk of death, but the statistical power of this analysis was very low because of the small number of deaths observed.

As improvements in therapy have led to improved long-term survival of patients with craniopharyngioma, more attention has been placed on long-term morbidity. Several different aspects of QOL have been analyzed in previous surgical series, such as neurological deficit, impairment of vision, and derangement of hypothalamic function, but no assessment tool currently exists that adequately includes the different aspects of the disease and its treatment, and none has been validated or consistently adopted in the literature. We used the scale initially proposed by Wen and coworkers because the clinical data required to form the score can be easily obtained, even retrospectively. As expected, very few patients had the lowest score, indicating grossly normal patients who live independently, both at diagnosis and at last follow-up, whereas most patients were in Class II, reflecting the high frequency of panhypopituitarism and/or mild to moderate visual compromise. The mean QOL score at last follow-up was significantly worse than at diagnosis, but the percentage of patients who were not independent in activities of daily living increased only slightly from 8.8% at diagnosis to 14.3% at last follow-up. Worsening of QOL, independently of the definition used, after treatment for craniopharyngioma is an almost universal finding in recent surgical series, and mainly reflects the long-term morbidity of therapeutic interventions and tumor recurrence. Assessing whether attempted gross-total removal or less aggressive surgery is better for the QOL of patients may be very difficult for the above-mentioned lack of uniform and complete assessment tools and for the variable and often complex track of therapeutic interventions. At first glance, the net increase of 5.5 in the percentage of patients not independent in activities of daily living increased only slightly from 8.8% at diagnosis to 14.3% at last follow-up. Worsening of QOL, independently of the definition used, after treatment for craniopharyngioma is an almost universal finding in recent surgical series, and mainly reflects the long-term morbidity of therapeutic interventions and tumor recurrence. Assessing whether attempted gross-total removal or less aggressive surgery is better for the QOL of patients may be very difficult for the above-mentioned lack of uniform and complete assessment tools and for the variable and often complex track of therapeutic interventions. At first glance, the net increase of 5.5 in the percentage of patients not independent in activities of daily living increased only slightly from 8.8% at diagnosis to 14.3% at last follow-up. Worsening of QOL, independently of the definition used, after treatment for craniopharyngioma is an almost universal finding in recent surgical series, and mainly reflects the long-term morbidity of therapeutic interventions and tumor recurrence. Assessing whether attempted gross-total removal or less aggressive surgery is better for the QOL of patients may be very difficult for the above-mentioned lack of uniform and complete assessment tools and for the variable and often complex track of therapeutic interventions. At first glance, the net increase of 5.5 in the percentage of patients not independent in activities of daily living increased only slightly from 8.8% at diagnosis to 14.3% at last follow-up.

Conclusions

In the context of the current debate about the appropriate strategy to control craniopharyngioma growth without compromising QOL, our study emphasizes that, whenever feasible, a surgical strategy aimed at gross-total resection of craniopharyngioma can achieve this goal in the majority of patients with a reasonably low risk of perioperative complications. Prompt management of residual or recurring disease by radiotherapy, repeat surgery, or a combination of both is usually successful in controlling further tumor growth.

Disclosure

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

Author contributions to the study and manuscript preparation include the following: Conception and design: Mortini, Losa, Giovanelli. Acquisition of data: Pozzobon, Acerno, Angius. Analysis and interpretation of data: Losa, Pozzobon, Barzaghi, Acerno, Weber. Drafting the article: Losa, Pozzobon, Weber, Chiumello, Giovanelli. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Losa, Barzaghi, Riva. Study supervision: Mortini.

References

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