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Management of Recurrent Craniopharyngioma

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Summary

Although histologically benign, craniopharyngioma can regrow either from macroscopic remnants of the tumour left behind at operation, or even after an apparently gross total removal. Recurrence rates vary significantly in the literature, depending on the efficacy of surgical treatment and also on the growth potential of the tumour itself. The main factor influencing tumour regrowth is obviously the extent of surgical resection, as total removal carries a much lesser risk of recurrence compared to subtotal or partial resections (although in such cases radiation therapy can lower this risk significantly). Other factors involved are the duration of follow-up and patient's age at operation, as children tend to relapse more frequently than adults. Even in the "microsurgery" era, characterized by high percentages of total resections, recurrences remain high and continue to represent a major problem of craniopharyngioma treatment.

Twenty-seven children and adolescents were operated on for craniopharyngioma at the Department of Neurosurgery, Section of Pediatric Neurosurgery, Catholic University Medical School, Rome, between June 1985 and June 1997. Total tumour resection was achieved in 18 cases, subtotal in 7 and partial in 2 instances. One patient died post-operatively. Post-operative neuroradiological investigations confirmed the operative findings, although 3 children with an apparently gross total removal showed a residual non-enhancing calcium fleck adherent to the hypothalamus (which remained stable at the following examinations). Three of the 9 patients with less than total removal underwent post-operative radiation therapy. Out of the 26 surviving patients 6 presented a recurrence of their craniopharyngioma, 2 after an apparently gross total removal and 4 after a subtotal or partial resection (one of them had received radiation therapy). The diagnosis was merely neuroradiological in 5 cases, as only one child presented a clinical picture suggestive of tumour regrowth.

Surgery was the first therapeutic option in all the cases. Total tumour resection was accomplished in 3 cases, subtotal in 2 and partial in the last one. One child died post-operatively. Four of the 5 survivors received radiation therapy. All the patients are presently alive and stable (mean follow-up: 5.6 yrs). The authors conclude that surgery should be the first therapeutic option in case of recurrent craniopharyngioma and that radiation therapy should also be considered but only as adjuvant therapy.

Keywords: Craniopharyngioma; pediatric brain tumour; surgical therapy; recurrence.

Introduction

Craniopharyngioma is the most common non-glial tumour observed in infancy and childhood [1, 4, 6, 20]. Its histological pattern is one of a benign tumour composed of stratified epithelial cells derived from embryonic remnants of Rathke's pouch. Irrespective of its benign nature, craniopharyngioma often behaves as an aggressive tumour and carries an elevated risk of recurrence [1, 7, 45]. True recurrences (that is appearance of a "new" tumour after an apparently gross total removal confirmed by negative post-operative neuroimaging studies) even remote from the primary tumour site [17, 21, 25, 38, 40], should be differentiated from the "regrowth" of those parts of tumour left behind during the first operation, either voluntarily because of the risk of damaging vital structures such as optic nerves, hypothalamus, carotid artery and its main branches, or involuntarily, because inaccessible to surgical inspection. Though the judgment of the surgeon, supported by the post-operative neuro-imaging studies, may in some instances provide a reliable evaluation about the completeness of surgical removal, in several cases the differentiation between true recurrence and regrowth of the tumour remains quite theoretical, as tumour regrowth from craniopharyngioma remnants too small in size to be detected by the currently available neuroradiological tools, cannot be excluded.

The recurrence rates reported in the literature vary greatly from 0% to almost 100% [2–6, 7, 9, 10, 12–16, 18–20, 22–24, 28–30, 32–34, 39–42, 45, 46] depending on the efficacy of the surgical treatment and adjuvant therapy as well as on the growth potential of the tumour itself. On the other hand, the main factor ob-

viously influencing tumour regrowth is the extent of surgical resection at the time of the first operation. In fact, it has been repeatedly reported in the literature that a complete surgical excision, expecially when confirmed by a negative post-operative neuroradiological examination, bears a much lesser risk of tumour recurrence compared to subtotal or partial resections. In cases of incomplete tumour removal, radiation therapy plays an important role in reducing the rate of recurrences [2, 7, 9–11, 18, 26, 27, 31, 43, 44]. Another factor influencing tumour regrowth is age at operation, as children tend to relapse more frequently than adult patients [7]. Finally, it is also common experience that the recurrence rate increases with the duration of follow-up, although in many reports both tumour regrowth and recurrences tend to occur mainly in the first 3 post-operative years [7, 12–15, 29, 32, 40, 46].

Whichever the cause, recurrence represents one of the the most common complication of craniopharyngioma treatment and poses many problems as to management. In the present report we analyse the results obtained in children and adolescents operated on for craniopharyngioma with special attention to the modalities adopted in dealing with such major complication.

Patients and Method

Twenty-seven children and adolescents up to 14 year-old, affected by craniopharyngioma, have been treated at the Department of Neurosurgery, Section of Pediatric Neurosurgery, Catholic University Medical School, Rome, between June 1985 and June 1997. These patients represent about 5% of all paediatric brain tumours operated on at the same institution over the same time span. Fourteen of them were children below 10 years of age: in particular, 5 were less than 2 years old, 4 between 2 and 5 years, and 5 between 5 and 10 years. The remaining 13 patients were adolescents ranging in age from 10 to 14 years. Nineteen were males, 8 females.

The craniopharyngioma was purely intrasellar in 2 cases, and infundibular in the remaining 25, with variable growth patterns: towards the anterior cranial fossa, pushing back the chiasm and optic nerves, in 10 patients, and mainly "retrochiasmatic" with predominant growth into the 3rd ventricle in the other 15; in 3 of the latter patients there was also a significant growth towards the posterior fossa, with apparent invasion of the clivus in one of them. The first and mainly unique therapeutic approach was surgery in all the cases. Two children with purely intrasellar craniopharyngiomas underwent radical resection by means of a transsphenoidal approach. In the other 25 patients the tumour was resected through a right frontotemporal craniotomy. Four of these 25 patients underwent staged operations in order to achieve the most complete tumour removal, in 2 cases by means of two separate craniotomies and in the other 2 by means of transsphenoidal resection followed by craniotomy. Surgical excision was judged as total in 18 cases, subtotal in 7 cases and partial in 2 cases, on the grounds of the surgical evidence during the operation as well as of the post-operative CT and MRI findings.

It is worth noting that in 3 of the 18 children with an apparently gross total tumour removal, the post-operative neuro-imaging studies documented a residual, non-enhancing calcium fleck adherent to the hypothalamus. Repeated neuroradiological investigations showed stable size of these lesions and consequently, for the aim of this analysis, we did not consider them as residual tumour also agreeing with what is suggested in the literature [14, 15]. One girl died post-operatively as a consequence of a fulminating meningoencephalitis complicated by thrombophlebitic occlusion of the intracranial venous sinuses, which occurred 48 hours after an apparently successful excision of the craniopharyngioma by the transsphenoidal route. In all the cases the histological examination documented an adamantinomatous variant.

One patient died approximately 3 years after the operation, mainly as a consequence of the hypothalamic imbalance, although the dismal outcome was prompted by a severe head trauma with subacute subdural haematoma. Three of the 9 patients who underwent less than total tumour removal, aged 6 years or more, received standard external radiation therapy in order to reduce the chance of recurrence.

Following the completion of treatment the 26 survivors were closely followed-up with repeated neurosurgical, neuroradiological, endocrinological, and ophthalmological examinations. In particular, post-operative neuroradiological surveillance consisted of an early post-operative CT scan within 1 week from the operation, and thereafter of CT and/or MRI studies performed every 6 months for the first 2 years and yearly thereafter. The neurosurgical follow-up paralleled the neuroradiological one, with periodical evaluations every 6 months for the first 2 post-operative years, and every year thereafter. The ophthalmological follow-up consisted of an early post-operative assessment of the visual function (including the study of the visual field) and once a year thereafter, apart from particular cases which required closer monitoring. Finally the endocrinological follow-up consisted also of an early assessment of the hormone deficiency residual to the operation, with the consequent indication for hormone replacement. The assessment was repeated approximately 6 months later, and once a year thereafter.

The duration of follow-up observation in the 26 surviving patients ranged from 6 months to 11.5 years (mean 5.6 years).

Results

Six out the 26 patients surviving the operation for craniopharyngioma showed a reappraisal of the tumour growth from 6 months to 6 years (mean 29 months) after completion of the initial treatment. However, considering separately tumour "regrowths" from true "recurrences", respectively 4 and 2 cases, tumour relapsed 6 to 28 months (mean 13 months) after the operation in those children who had an initially incomplete resection of their craniopharyngioma (2 subtotal and 2 partial); only one child with partial resection had received complementary radiation therapy and was the one who relapsed latest. On the contrary, the remaining 2 patients with an apparently gross total removal at the first operation and initially negative post-operative CT scan, relapsed much later than the former, respectively 4 years and 7 months and 6 years

after the operation. The overall recurrence rate in this series was 23.1%. However, when considering distinctly cases with total and less than total resection, recurrence rates are 11.1% (2 out of 18) for total resections, and 28.5% (2 out of 7) and 100.0% (2 of 2) respectively in case of subtotal or partial resections.

All these patients were males. Their age at relapse ranged between 4 and 16 years. At that time all patients but one showed a stable and relatively good clinical condition. From the endocrinological point of view one child was normal. Five children had diabetes insipidus, lasting from the operation, which was adequately treated by means of desmopressin (DDAVP), and varying degrees of pituitary dysfunction, which was complete in 3 cases, and limited to GH in the other two. As to the ophthalmological work-up, 3 children did not exhibit any visual deficit. On the other hand, the remaining 3 patients had more or less severe deficits in their visual function, which was complete in one of them. Two of these latter children also exhibited a reduction in visual field in the visually impaired eye. However, it is worth noting that only one child (who became amaurotic in the right eye) showed a progression in visual impairment, whereas the other 2 children had stable visual deficits which had remained unchanged since the early post-operative assessment. Two patients presented with a mild partial 3rd cranial nerve deficit, and one with a left sided hemiparesis which was improving under physiotherapeutic treatment over the last months prior to the diagnosis of recurrence. Only one child had the clinical manifestations of increased intracranial pressure, and was the only case where the clinical condition suggested a return of the disease.

Actually in all but this one child, the diagnosis of tumour recurrence was obtained on the mere basis of a positive CT and/or MRI study demonstrating tumour regrowth or recurrence. In 3 of the 4 patients with persistent tumour after the first operation, the direction of the tumour regrowth was mainly suprasellar/ ''retrochiasmatic'' (with extension into the posterior fossa in one) (Fig. 1), and supra/intrasellar in the remaining one. The last 2 patients with an initially negative post-operative CT scan, had their recurrence respectively in the suprasellar region, beneath the right optic nerve and chiasm, in one case, and within the posterior 3rd ventricle in the other one (Fig. 2). These recurrences were mainly cystic in 4 cases, and mainly solid in the other two. Two children with obstructive hydrocephalus had already been treated with a ventriculo-peritoneal shunt, which was poorly functioning in one case.

As far as treatment is concerned, the decision to reoperate on these children was taken on the grounds of the documented tumour regrowth (at least 2 consecutively positive imaging studies) without waiting for the appearance of clinical manifestations, in 5 cases. Surgery was the main and first therapeutic approach in all the cases. One child with a large suprasellar cystic recurrence underwent cyst drainage and intracystic injection of Bleomycin as initial treatment. Another patient with a large, mainly cystic recurrence protruding into the sellar cavity, was first treated by the transsphenoidal route. Subsequently both of them underwent craniotomy and tumour excision. The other 4 patients underwent craniotomy and tumour excision as first and only surgical treatment. The pre-existing fronto-temporal craniotomy was utilized in 5 instances, whereas the recurrence within the 3rd ventricle was removed by means of an interhemispheric transcallosal approach. In all the patients undergoing re-opening of the previous craniotomy the arachnoidal adhesions made it particularly difficult, or even precluded in some instances, the development of a safe plane of dissection, particularly around the main arterial trunks of the circle of Willis and the optic pathways. Gross calcifications, mainly near or around the main arterial branches, heavily limited the surgical maneuvers.

Despite the difficulties experienced in tumour dissection, a total resection was achieved in 3 cases, subtotal in 2, and partial in the last one. Total resection, in particular, was achieved in the two patients with late recurrences and initially negative neuro-imaging studies, and in one child with a huge, mainly cystic recurrence, who was blind in the right eye, which permitted a more aggressive removal of the residual tumour. This last child underwent the operation in a very poor clinical condition and died 3 weeks postoperatively, as a consequence of the hypothalamic damage which resulted in incontrollable hydro/ electrolytic imbalance. Such death corresponds to a surgical mortality of 16.6%.

Surgical morbidity was significant as 5 out 6 patients showed various post-operative complications (All patients experienced post-operative hydro/ electrolytic imbalance which was, however, successfully managed by means of DDAVP in 5 of them. In one case the medication could be stopped approximately 4 months after surgery, whereas the remaining 4 patients are still under medication. As to the pitui-

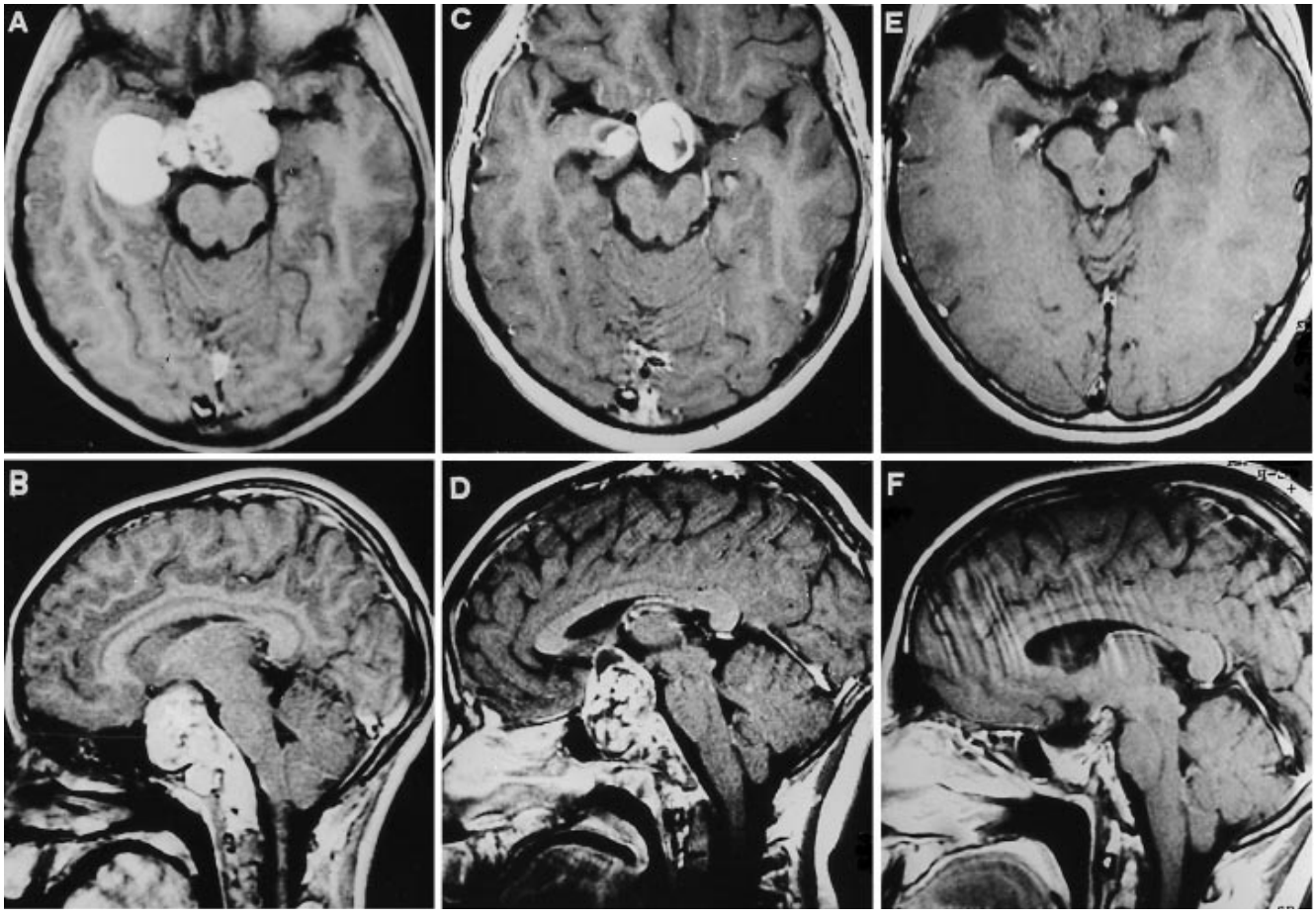

Fig. 1. Eleven-year-old boy presenting with growth retardation, decrease in visual acuity and visual field impairment. Pre-operative T1-weighted axial and sagittal MR scans (A, B) demonstrate a huge tumour mass which occupies the sella turcica and the suprasellar cistern; the tumour also extends into the right temporal fossa and into the posterior fossa with an apparent invasion of the clivus. After craniotomy and near total resection of the suprasellar and temporal components of the tumour (adamantinous craniopharyngioma) no adjuvant therapy was given. About twelve months later, control MRI (C, D) demonstrates a suprasellar regrowth of tumour, and further invasion of the midline bone structures. A further subtotal resection of the cranipoharyngioma was performed, followed by standard radiation therapy. The last control MRI (E, F) obtained three years and a half following completion of the treatment, shows only a small residual mass in the interpeduncular cistern and an apparent disappearance of the tumour infiltrating the clivus

tary function, no significant modification was detected in the 3 patients with pre-operative panhypopituitarism, whereas those who had only GH deficiency pre-operatively, developed complete pituitary deficit. The visual function which was already impaired in 3 patients, further deteriorated in 2 of them, including the one who died. Two patients developed CSF leak from the nose, in one case following transsphenoidal surgery, in the other after craniotomy with extensive drilling of the anterior clinoid to gain access to the pituitary fossa. These CSF leaks were complicated by meningitis in the case first approached by the transsphenoidal route, and by pneumocephalus in the other. Both patients, however, recovered from these complications.

Four of the 5 surviving patients, aged 9 years or more (3 with incomplete and 1 with an apparently gross total tumour removal) received radiation therapy. All patients but one are alive and in stable good clinical condition. Four of these five patients are under endocrinological medication for their pituitary/hypothalamic deficits, and 2 are still receiving anti-epileptic medication. Follow-up ranges from 2 to 12 years, with a mean of 5 years and 6 months. Neuro-imaging studies show stable intracranial pictures. In particular, no residual tumour is seen in the 2 patients with total removal (although one of them shows a tiny, non-enhancing calcium fleck near the hypothalamus); likewise, stable calcified masses are present in the 3 subjects with less than total removal.

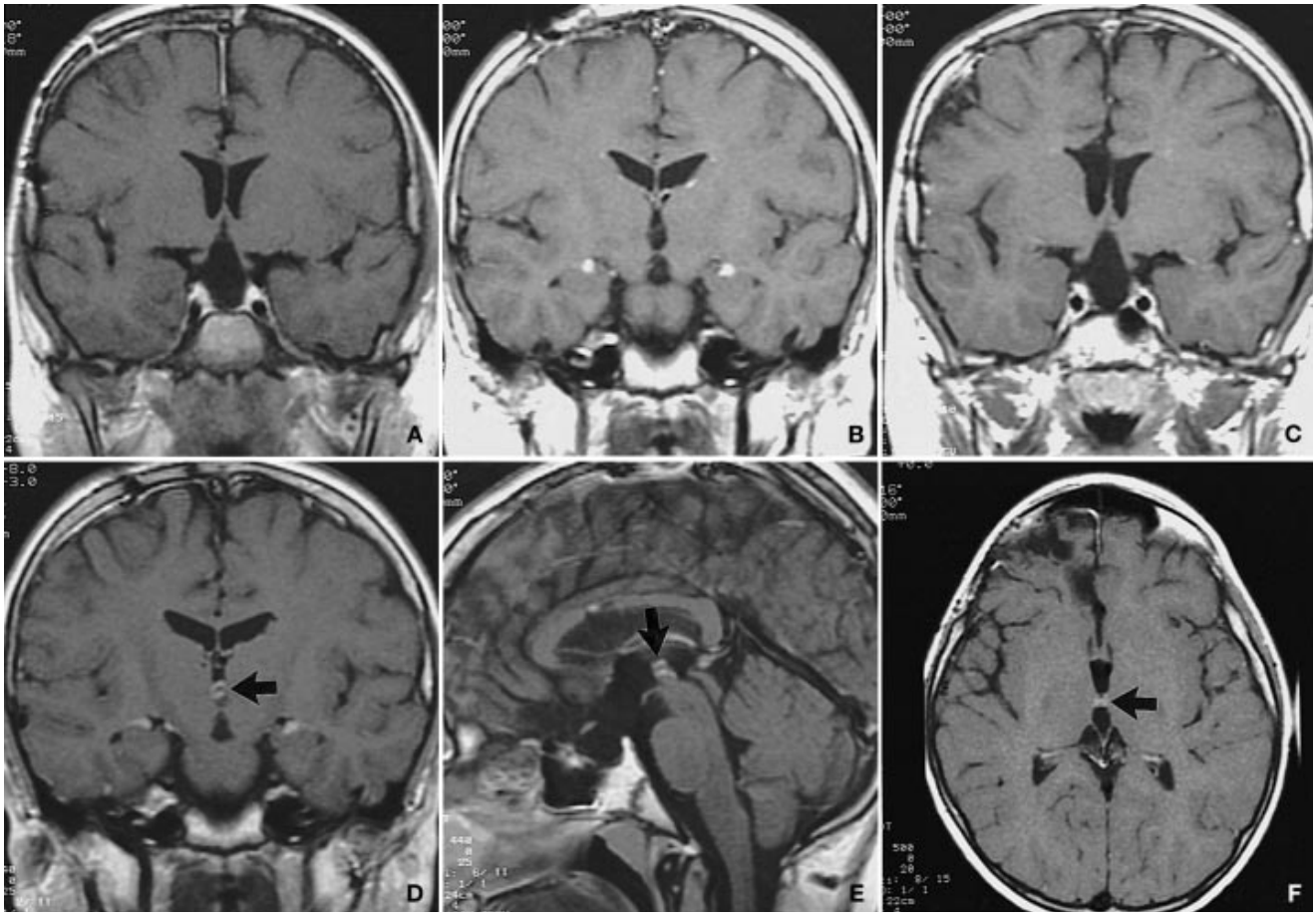

Fig. 2. Four-year-old boy affected by cranioparyngioma. About 6 months after craniotomy and the apparently gross total removal of an infundibular craniopharyngioma, coronal contrast-enhanced MRI (A, B) confirms the radicality of surgical excision. After repeated negative post-operative investigations, the last MRI obtained about 4 years after the operation (C, D: coronal; E: sagittal; F: axial) demonstrates a small enhancing tumour recurrence, with a central hypo-intense area, which occupies the posterior part of the third ventricle. Post-operative findings include empty sella trucica and a defect in the anterior floor of the third ventricle (namely a third ventricular-cisternostomy)

Discussion

Although histologically benign [1], craniopharyngioma has a considerable potential of regrowth if even small remnants of the tumour capsule are left behind at operation. This may happen because these fragments lay in areas not accessible to surgical inspection as, for instance, the inferior aspect of the optic nerves and chiasm and mainly the hypothalamus and 3rd ventricle, from which the tumour is detached by applying gentle, blind traction (which cannot avoid the capsule breaking off and fragments being left behind). Theoretically this problem should be dealt with, at least in part, by utilizing more sophisticated operative equipment which allows for a better view of the operative field even in ''blind'' areas, in order to remove the tumour as radically as possible. Actually, the introduction of the operating microscope and allied surgical aids has greatly increased the surgeon's ability to perform a safe gross total removal of most craniopharyngiomas [13–15, 19, 20, 33, 35, 39–41, 46]. Moreover, extended surgical approaches (as, for instance, the bifrontal or extended fronto-temporal) can help avoid missing any part of the tumour out of the surgical inspection.

However the main reason for more or less conspicuous portions of the neoplasm being left behind at the first operation, is the objective difficulty faced by the surgeon when separating the tumour capsule from the surrounding vascular and nervous structures which occupy the suprasellar region (and the fear of damaging them when attempting radical tumour excision). This situation is translated by the more or less high rate of incomplete tumour removals present in all the series in

the literature (which obviously corresponds to the surgeon's confidence with this pathology) [14, 18–20, 33, 40, 46].

The risk or recurrence has been repeatedly underlined in the literature. Matson was the first to attempt and to accomplish safe gross total resection of craniopharyngioma in children since the early '50s [22]. An analysis of the long-term results in his series done by Katz in 1975 [16], revealed more than 40% total recurrences, although only 26% were those occurring after total resection. Other reports published between 1970 and early '80s, which refer to patients operated on in the ''pre-microsurgery'' era, give recurrence rates ranging between 30% and 50% [3, 5, 6, 12, 15, 16, 23, 27–29, 31–33, 37], with only a few authors reporting better results. More recent publications which analyse the results of treatment of craniopharyngioma in the ''microsurgery'' era, show a tendency to a reduction in these figures, with many authors reporting recurrences in less than a fifth of the patients [4, 7, 14, 18–20, 24, 35, 40–42, 45, 46].

The main reason for this decline in tumour recurrence is represented by the introduction of the operating microscope which has increased the percentage of total resections at the first operation. Data from the literature confirm the importance of radical surgery. In fact, extrapolating from the total the recurrence rates in case of total resection, they are presently below 20% in most cases [5, 6, 13, 14, 18–20, 24, 28, 33–35, 39–41, 45, 46], with some authors reporting figures of about 10% [20, 24, 34, 40, 45, 46].

Nevertheless, even in the ''microsurgery'' era recurrences still represent a major problem. Also in our experience, when considering separatedly the 18 cases in whom a total resection was performed, 2 children (11.1%) relapsed over a 5.6 year mean follow-up period. As radicality of tumour removal is so important, it is obvious that subtotal or partial resections carry a much higher risk of recurrence (from 50% to almost 100%). In such cases, however, post-operative radiotherapy plays a fundamental role in lowering the risk of relapse to percentages which closely parallel that of total resection [2–5, 7, 10–12, 26, 27, 29–32, 37, 40, 43, 44]. Radiation therapy, however, carries the risk of damaging the hypothalamus and the optic pathway, as well as of producing a secondary moya-moya disease. For this reason in most paediatric neurosurgical centers it is not performed routinely on children operated on for craniopharyngioma. This was also our policy as we reserved this treatment for only 3 of the 9 patients who received partial or subtotal resections, aged 6 years or more. Also in our experience this complementary treatment reduced significantly the percentage of the recurrences as only 1 of the 3 patients submitted to complementary radiotherapy experienced tumour regrowth (33.3%) whereas as many as 3 of the 6 who did not receive it, relapsed (50.0%).

Beside the completeness of tumour removal (and/or the utilization of radiation therapy in case of incomplete resection) another factor which greatly influences the recurrence rate is the duration of the follow-up. In fact, although many reports suggest that up to 75%–85% of recurrences occur within the first 3 post-operative years [7, 12, 14, 29, 32, 39, 45, 46], it is also well documented that the longer the follow-up, the more recurrences are recognized. For this purpose, Hoffman first reported in 1977 [15] an initial 0% recurrence rate in his series of totally resected craniopharyngiomas. Following reports by the same author, however, documented an increased recurrence rate with elongation of the mean follow-up, respectively of 16% with a 2.6 years mean follow-up [13], and of 28% with a mean follow-up of 4.8 years [14].

Craniopharyngioma recurrences have been also correlated to the histology. An exhaustive anatomopathological study performed by Adamson [1] on the surgical specimens of Yasargil's series demonstrated that no recurrence was associated with the squamous papillary variant (which is found only in adults), whereas all the recurrences were associated with the most frequent adamantinomatous variant (which is the only kind of craniopharyngioma observed in children). In particular, 9% of totally resected craniopharyngiomas in children in his series relapsed. The same author [1] commented on the presence of small islets of tumour cells inside the gliotic brain surrounding the tumour in case of adamantinomatous craniopharyngioma, and attributed to them the responsibility for recurrences. The same opinion is shared by many other authors [7, 14, 15, 28, 42]. On the contrary, others [33, 41, 45] are against this point of view and in fact attribute to this gliotic reaction a fundamental role in allowing safe tumour dissection; in their opinion it is more likely that recurrences originate from small remnants of the tumour capsule within the adventitia of the main vessels at the cranial base, rather than from the supposed infiltration of the hypothalamus.

Our two cases which recurred after total resection can be explained on the basis of remnants of the tumour capsule, respectively behind the optic nerve and

within the 3rd ventricle (in the case of a retrochiasmatic craniopharyngioma previously approached by opening the lamina terminalis). Both these children had received growth hormone replacement following operation. The question as to whether hormone replacement might play a role in influencing tumour regrowth is presently overcome by increasing clinical evidence that deny this possibility [7, 8].

As far as treatment is concerned, we favour treating all cases of recurrent craniopharyngioma surgically, provided that the clinical condition does not prevent such possibility. Obviously, small residual calcified non-enhancing lesions which remain unmodified at follow-up, are not to be considered as recurrences and in fact are not treated. Surgery should be considered as the first choice of treatment among therapeutic modalities for recurrent craniopharyngiomas, although it is generally more difficult than the first operation. In fact, arachnoid adherences make it difficult, if not precluding it altogether, as the development of a safe plane of dissection is very problematical. In particular, an "aggressive" initial operation which eliminated the gliotic envelope of the tumour, can represent a limiting factor when trying to perform a second gross total resection [16, 35, 39, 40, 45, 46]. This was also our experience as the total resection of the tumour was possible in only 2 of 5 patients undergoing re-opening of the previous craniotomy (in the third patient total excision was achieved by a different route); however, in one of them the presence of a blind eye facilitated the resection. As reported in the literature, attempts to perform a radical surgical excision in case of recurrent craniopharyngioma are hampered by an increased risk of major complications, including death [5–7, 14, 16, 18, 22, 34, 39, 40, 44–46]. Our surgical fatality was certainly related to the poor general condition of the child, although the role of an excessively "aggressive" surgical attitude cannot be excluded.

Our limited experience with intracavitary Bleomycin [36] seems in agreement with that of others who utilize this technique routinely as a preparatory step prior to craniotomy, because of the sclerosing properties of this antibiotic, which makes the tumour capsule more resistant and consequently facilitates its detachement from the surrounding nervous and vascular structures.

Although we did not utilize radiation therapy as the first treatment in any of our children with tumour recurrence, we favour its use after an incomplete surgical removal. In such regard, in fact, it is worth noting that radiotherapy not only influences the occurrence and precocity of the recurrence in case of incomplete resection, but it is also effective in reducing the tumour growth potential [2–5, 10–12, 26, 27, 29–32, 43, 44]. Actually, our case with clivus invasion (Fig. 1), was definitively managed by means of radiation therapy.

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Comment

The authors analysed 27 cases of craniopharyngioma with total tumour resection in 18, subtotal in 7, and partial in 2 cases and their recurrences which were found to be 6 out of 26 (23.1%).

The message is "Surgery should be the first therapeutic option in case of recurrent craniopharyngioma and that radiation therapy should also be considered, but only as adjuvant therapy". I agree with this statement and also with the definition that true recurrence should be preserved for cases with total resection confirmed by neuro-imaging. I agree as well that sometimes this definition is too theoretical, because there is no definite MRI detection of tiny tumour remnants.

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