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Cerebellar pilocytic astrocytoma: a treatment protocol based upon analysis of 73 cases and a review of the literature

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Abstract In a retrospective study of 73 patients operated on for cerebellar pilocytic astrocytomas, results of treatment, outcome and biological behaviour of residual tumour were analysed. Complete tumour resection proven by CT or MRI scans within 1 year after surgery was achieved only in 69% of cases. In 31% of cases the surgeon's opinion on the extent of surgical resection was not borne out by the result of postoperative neuroimaging. Progression of residual tumour or tumour recurrence appeared in 19% of patients, 1 patient showed metastatic spread along the craniospinal axis, and in 1 patient malignant degeneration appeared during follow-up. Stable residual tumour or regression of residual tumour was seen in 14% of patients. Outcome after surgical treatment, which was combined with irradiation in 10 patients (14%), was favourable in 80% and unfavourable in 20% of patients. This outcome of treatment was not influenced by a second operation for progression of residual tumour or recurrent tumour. Characteristics of patients with tumour progression after the first operation did not differ from those of the whole group. There were 17 reoperations for residual or recurrent tumour, 10 of which took place within 4 years after the initial surgical treatment. Surgery-related morbidity was 15% and mortality 4%. Irradiation to residual tumour in 8 patients was followed by complete regression in 1 patient, progression in 4 patients and no changes in 1 patient. For the remaining 2 patients the effect of irradiation on the residual tumour is unknown. Factors that determine the prognosis are discussed on the basis of this retrospective analysis and the data from the literature. It is concluded that optimal treatment for a cerebellar pilocytic astrocytoma does not consist solely in surgery with the aim of total tumour removal and careful tumour handling in order to avoid spread of tumour cells and subsequent metastases and additional radiation therapy in strictly selected cases, but also in posttreatment follow-up based on direct postoperative neuroimaging, preferably by MRI. An algorithm for postoperative follow-up management is presented.

Key words Biological behaviour · Pilocytic astrocytoma · Recurrence · Treatment

Introduction

The pilocytic astrocytoma was first described as a separate entity by Cushing in 1931 [8]. Other authors gave the same tumour different names: gliocytoma embryonale, spongioblastoma, classic juvenile astrocytoma and astrocytoma grade 1 (WHO classification of 1979). There is some controversy concerning the origin of the tumour cells, and whether this tumour arises from true astrocytes

or from subependymal cells called tanycytes remains unclear. However, strong agreement exists on the very good prognosis, since this tumour has a 25-year survival rate after surgical resection varying from 50% to 94%. This tumour accounts for 6% of all primary brain tumours, for 20% of all primary brain tumours in children under 15 years of age, and for 30% of all posterior fossa tumours in these children. Of all pilocytic astrocytomas, 80% have a cerebellar localization, and 20% are located in the hypothalamic region, in the cerebral hemispheres, III ventricle, optic pathways or brain stem. Treatment consists primarily in surgical resection, and in the past sometimes radiotherapy after incomplete removal.

Despite the very good prognosis, the outcome is not always favourable, mainly because of surgical morbidity and tumour recurrence. The behaviour of this tumour after complete or incomplete resection is unpredictable. The use of additional radiation therapy in the treatment remains controversial. The question as to whether all patients or only patients in whom resection has been incomplete need follow-up and how long such follow-up should be remains unanswered.

This retrospective study was undertaken to assess patient characteristics, and the features of the treatment modality and the tumour, specifically its behaviour during follow-up, that might be related to the outcome of the patient. Therefore, all data in the records of 73 patients treated for cerebellar pilocytic astrocytoma in three major neurosurgical units in The Netherlands were analysed. Based on these data and previously reported material, we established a protocol for treatment and follow-up of these patients.

Patients and methods

Medical files of 73 patients treated for cerebellar pilocytic astrocytoma between 1969 and 1990 at three University Hospitals in The Netherlands were analysed. They were screened for patient age, sex, treatment modality (surgery or surgery and radiation therapy) and duration of follow-up. The radicality of resection was estimated by analysing the surgeons' surgical reports and the results of postoperative neuroimaging. All results of neuroimaging (MRI or CT scan) performed during the period of follow-up were obtained and reviewed. They were judged on the presence or ab-sence of residual or recurring tumour. Recurring tumour is defined as the appearance of a new tumour after neuroradiologically proven total resection. The clinical status of the patient at the end of the follow-up period was used as a basis for classification in a five grade outcome scale: grade 1, no neurological deficit; grade 2, minor neurological deficit but leading normal life; grade 3, severe neurological deficit requiring special therapy or schooling; grade 4, disabled with permanent institutional stay; grade 5, death. Grades 1 and 2 are regarded as favourable, and grades 3, 4 and 5, as unfavourable. Complications of treatment were listed and regarded as directly related to surgery when they appeared within 1 month after the surgical procedure. Number and causes of deaths were listed. Archival tumour tissue was reviewed (W.M.M.).

Results

The mean age at first operation was 10.8 years. Figure 1 shows the age distribution among patients. The male to female ratio was 1.1:1. Neuroradiological follow-up, either by CT or by MRI scan, was established in 62 patients, and the duration ranged up to 20 years after the operation, with a mean of 5.3 years. The follow-up period of most of the patients was extended by interviewing the family doctor or the paediatric doctor, and is referred to as "clinical follow-up" in these cases. The duration of clinical follow-up ranged from 4 months to 26 years, with a mean of 8.2 years for all 72 patients; 1 patient died within 1 month of the operation.

Surgical complications can be divided into those occurring early, i.e. within 1 month after operation, and those occurring late. The number and nature of the surgery-related complications in the whole group are listed in Table 1.

Postoperative irradiation was administered to 10 patients (14%), 2 of whom had had total tumour removal according to the surgeon while 8 had residual tumour. Irradiation doses given were 5000–6000 rad in 6 cases, 4450 rad in 1 case, and 3180 rad in 1 case, and are unknown in 2 cases. Postirradiation follow-up of the patients irradiated for residual tumour showed progression of tumour in 4 patients, 2 of whom developed intratumoural haemorrhage requiring surgical decompression. In 1 patient the residual tumour remained unchanged and in 1 patient it regressed until it had disappeared on MRI scan 4 years after

Table 1 Early (within 1 month after surgery) and late complications related to surgery, with numbers of patients and percentages in parentheses

Surgical complications	Morbidity	Mortality
Early (10; 13%)	Postoperative blindness (4) Outcome grade 3 or 4 (4) Subdural hygroma (1)	Postoperative hematoma causing death (1)
Late (4; 6%)	Cervical kyphosis, internal fixation (1) Intraventricular hemorrhage after shuntrevision (1)	Drain dysfunction, elevated ICP leading to death (2)
Total (14; 19%)	(11; 15%)	(3; 4%)

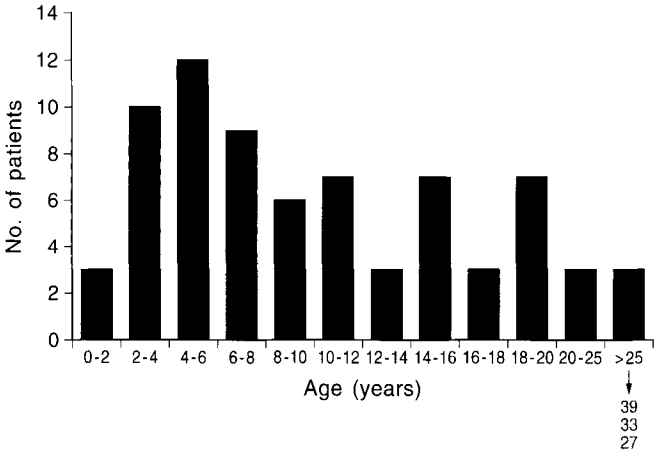

Fig. 1 Age at first operation in 73 patients treated for cerebellar pilocytic astrocytoma

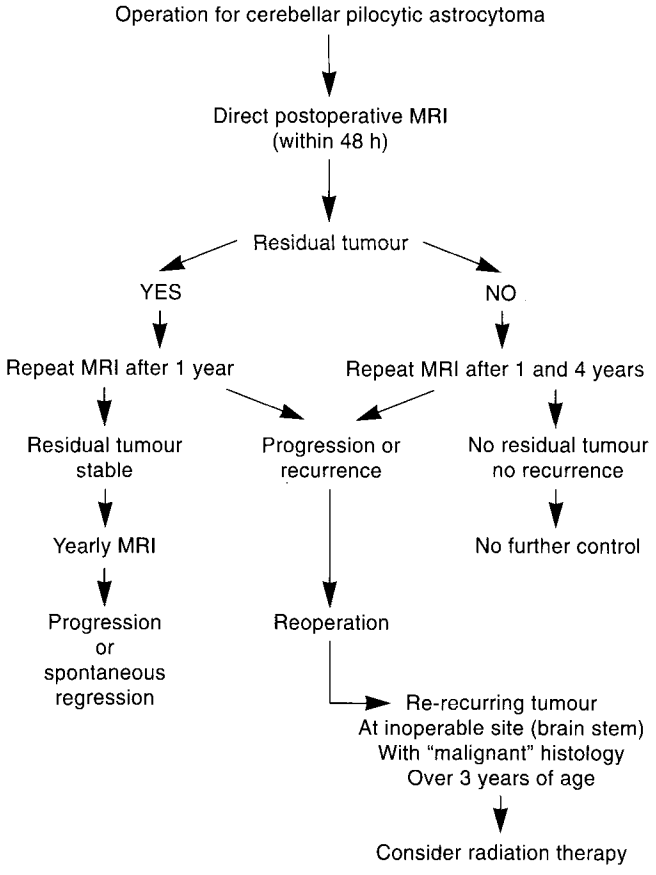

Fig. 2 Algorithm for the treatment of patients with a cerebellar pilocytic astrocytoma

irradiation. Two patients had no follow-up imaging but are alive 2 years and 12 years after surgery.

Table 2 lists the overall outcomes at the end of follow-up for the whole group. This grossly results in 80% favourable outcomes (grades 1 and 2) and 20% unfavourable outcomes (grades 3, 4 and 5).

Table 2 Outcome at end of follow-up for whole group

Grade	Patients (%)
Grade 1: No neurological deficit normal life	56
Grade 2: Minor neurological deficit, leading normal life	23
Grade 3: Severe neurological deficit, requiring special therapy or schooling	11
Grade 4: Severely disabled, permanent institutional stay	3
Grade 5: Death	7

Table 3 Comparison of the neurosurgeon's opinion of the extent of surgical resection and the result of postoperative neuroimaging (CT or MRI scans) within 1 year after surgery in 48 cases

Resection according to neurosurgeon	Result of postoperative neuroimaging
Complete: 32 cases (67%)	No tumour: 25 cases Residual tumour: 7 cases
Incomplete: 16 cases (33%)	No tumour: 8 cases Residual tumour: 8 cases

Five patients died: 1 patient in the postoperative period because of haematoma, and 4 some months or years later, 1 after malignant transformation and brain stem invasion of the tumour, and 2 because of transtentorial herniation owing to elevated intracranial pressure resulting from dysfunction of a ventriculoperitoneal shunt. One patient died from progression of optic astrocytoma, since this patient suffered from neurofibromatosis type 1. Table 3 shows a comparison of the results noted in surgical reports and the results of postoperative neuroimaging concerning extent of surgical resection. Postoperative CT or MRI scans performed within 1 year after surgery were available for 48 patients: 33 (69%) showed no tumour and 15 (31%) showed residual tumour. In 15 out of 48 cases (31%) the surgeon's opinion did not correlate with the result of neuroimaging.

In total 25 patients had residual or recurring tumour. There were 15 in whom tumour progression was detected during further follow-up, whereas in 8 patients the residual tumour remained "silent" in a follow-up period of 1–11 years (mean 4.5 years). In 2 patients the residual tumour showed regression: in 1 this was spontaneous after 10 years and in 1 it followed radiation therapy. Thus, during continued follow-up different patterns of biological behaviour of the residual tumour were seen. These patterns are listed in Table 4.

Neuroradiological follow-up demonstrated progression of residual tumour in 13 cases and true recurrence of tumour in only 2 cases. Characteristics of these 15 patients are listed in Table 5.

Table 4 Different patterns of biological behaviour as seen among 25 patients with residual or recurring tumour

Biological behaviour following surgical treatment	No. of cases
Progression of residual tumour	11
Recurrence after "total" neurosurgical tumour removal	1
Recurrence and metastatic spread along craniospinal axis	1
Progression of residual tumour with malignant transformation	1
Hemorrhage and progression of residual tumour after irradiation	1
Residual tumour without progression on follow-up imaging	8
Spontaneous regression of residual tumour	1
Regression of residual tumour after irradiation	1

Table 5 Characteristics of 15 patients with tumour progression after surgical treatment compared with results in whole group

	15 patients with tumour-progression	Whole group
Mean age at first operation	8,7 years	10,8 years
Male to female ratio	1:2	1,1:1
Outcome		
Favourable (grade 1 and 2)	80%	80%
Unfavourable (grade 3,4 and 5)	20%	20%
Resection complete	30%	69%
Resection incomplete	70%	31%
Interval between first and second operation (2 patients were operated on three times; n=17)	0,5–4 years: 10 6–7 years: 3 9–11 years: 3 17 years: 1	

The final results of neuroimaging at the end of follow-up in the whole group, including the reoperated patients, show that of 68 living patients 43 (63%) are free of tumour, and 15 (22%) still have residual tumour. For the remaining 10 patients (15%) no postoperative CT or MRI scans were available.

Discussion

Several factors might have an influence on patient outcome after treatment for a cerebellar pilocytic astrocytoma. In this group of patients these factors can be categorized in three groups: patient-related, treatment-related and tumour-related factors.

Age and sex are patient-related factors that had no predictive value for the outcome of the patient in previous studies [9, 14]. Treatment-related factors are the extent of surgical tumour removal, surgical mortality and morbidity, the effect of radiation therapy on the tumour and the side effects of irradiation. As can be seen from Table 3, the surgeon's estimation of the extent of tumour removal did not correspond to postoperative neuroimaging results in 31% of cases. This makes a postoperative scan, preferably an MRI scan obligatory to assess the patient's needs for follow-up screening. The development of better neurosurgical and neuro-anaesthesiological techniques in recent decades have led to a fall in the mortality and the morbidity of the surgical procedure. Mortality rates recorded in several studies are given in Table 6.

The effect of radiation therapy on residual tumour after surgery is disputed in the literature, the long-term prognosis of patients treated with surgery and radiation therapy apparently being no different from that of those treated with surgery alone [11, 12, 23, 24]. However, the numbers in these studies are small. On the other hand, the use of radiotherapy seems to delay or stop the progression of residual tumour [7, 9, 15, 30] but may also play a part in late recurrence with malignant transformation and in the induction of new tumours in the irradiated field, such as meningiomas and sarcomas and tumours of the parotid and thyroid glands. Some authors advocate irradiation after incomplete removal of the tumour when histological "malignant" features are present, regardless the the extent of resection [34, 36]. Irradiation is contraindicated in children under the age of 3 years because of the devastating effects it has on the developing brain, in particular intellectual impairment and dysfunction of the endocrine system.

Earlier studies have tried to identify tumour-related factors that had a predictive value on outcome [5, 13]. The laterally localized tumours and the cystic types were found to have a better prognosis than the medially localized and solid ones. Later these results were attributed to the fact that in those days such tumours were more easily completely resected [6, 9, 12, 14, 34].

Another distinction was made between a diffuse and a classic juvenile type [14, 29] on the basis of histological characteristics; the 25-year survival rate was 94% for the

Table 6 Mortality rates in several series of patients operated on for cerebellar pilocytic astrocytoma

Reference	Operated on between years	No. of patients	Mortality
[12]	1928–1980	84	10%
[24]	1916–1976	190	15%
[11]	1950–1972	89	50%
[32]	1954–1975	128	10%
[23]	?–1987	63	5%
[34]	1954–1984	100	29%
[8]	?–1931	76	18%
[18]	1955–1980	99	12,1%
[16]	1978–1993	33	6%
Present study	1969–1990	73	4%

classic juvenile, type and 38% for the diffuse type. Later studies confirmed neither the existence of these subtypes nor the difference in prognosis [23, 28]. Winston et al. [37] classified cerebellar pilocytic astrocytoma as subtypes A and B, based upon clinical characteristics retrospectively correlated to outcome. Subtype A had any of the following histological features: microcysts, leptomeningeal deposits, Rosenthal fibres and focus of oligodendroglia. Subtype B had perivascular pseudorosettes, high cell density, necrosis, mitosis, calcification and a less uniform histological pattern than subtype A. Type A had a 10-year survival rate of 94% and type B, one of 29%.

From the different possible manifestations of the biological behaviour, the progression of residual tumour, often referred to in previous studies as "recurrence", is most frequently encountered (Table 4). The incidence of "recurrence" varied in 14 larger studies from 7% to 35%, with a mean of 24% (Table 7). Whether these recurrences were new tumours after complete surgical resection or residual tumours that show progressive growth, remains unclear. In our material we found progression of tumour after operation in 21% (15 patients). However, in only 2 of those patients was there true recurring tumour, while in 13 there was progression of residual tumour. We could not identify any factors related to patients who developed progression of residual tumour or recurring tumour that were different from those related to the whole group (Table 5). The male-to-female ratio in the group with progressive tumour was 1:2 and that in the whole group, 1.1:1. Age at first operation for the tumour was lower in the group with tumour progression than in the whole group: 8.7 vs 10.8 years. Most tumour progressions were detected within 4 years after operation (10 out of 17).

The outcome in the whole group is regarded as favourable (grade 1 and 2) in 79% of patients. The outcome in the group treated for postoperative tumour progression was also favourable in approximately 80% of patients. However, complete resection during a subsequent operation was only possible in 30% of patients, whereas complete resection of the primary tumour at the first operation was achieved in 69% of cases. This means that reoperation for progressing tumour does not influence the final outcome, but patients with residual tumour do need control neuroimaging studies and will very likely need one or more reoperations.

It is important to stress that not every patient with residual tumour after operation develops tumour progression. In this group 8 patients have residual tumour that has not shown any progression during 1–11 years (mean 4.5 years) of follow-up by neuroimaging. Another 2 patients experienced regression during follow-up; 1 spontaneously and 1 after irradiation. These phenomena, stabilization of residual tumour many years after operation, even after only biopsy of a large tumour, and spontaneous regression, are well known from the literature [3, 6, 9, 11, 13, 20, 23].

Metastatic spread is mentioned in the literature in only a few cases: Eade and Urich [10] describe 5 young patients,

Table 7 Number of "recurrences" after surgical treatment in 14 previous studies

References	No. of cases	Corrected[a]	No. of recurrences	Recurrences (%)
[8]	76			30
[19]	140	93	11	12
[13]	38	34	12	35
[14]	44	44	9	21
[15]	39	38	12	32
[9]	43			35
[32]	128	125	15	12
[28]	49	49	14	29
[11]	89	44	7	16
[17]	112	112	35	31
[22]	63	59	4	7
[3]	41	41	14	34
[34]	100	71	22	31
[12]	84	66	8	12
Present study	73	72	15[b]	21

[a] Number of cases corrected for postoperative deaths and patients lost to follow-up

[b] In this study 13 cases with progression of residual tumour and 2 cases of recurring tumour

4 with a spinal and 1 with a thalamic glioma spreading via the cerebrospinal fluid. McLaughlin described four thalamic gliomas in children with cerebrospinal fluid seeding [26], Shapiro and Shulman reported 3 cerebellar astrocytomas that seeded to the spinal cord [31], Auer et al. described 1 case of benign cerebellar astrocytoma with massive craniospinal leptomeningeal spread prior to surgery [2], and Wallner et al. report 1 case of diffuse leptomeningeal seeding after four local recurrences of a cerebellar pilocytic astrocytoma over a 23-year period [36]. In another reported case leptomeningeal seeding occurred 6 years after surgery for a cerebellar pilocytic astrocytoma located in the vermis [27]. The multiple nodular metastatic lesions remained stable during a 2-year observation period. In a recent study 11 out of 90 patients with pilocytic astrocytomas at different localizations had metastatic spread along the craniospinal axis, proven by MRI studies [25]. Only 1 of these 11 patients had a primary cerebellar pilocytic astrocytoma, and it was concluded that the hypothalamic pilocytic astrocytoma was 23 times more likely to show metastatic spread than the cerebellar one. Garcia et al. report 1 patient with a spinal recurrence of a cerebellar pilocytic astrocytoma [12]. In our study 1 patient had metastatic lesions in the III ventricle and the spinal canal, detected 1 year after surgery for a cerebellar lesion together with a local recurrence, the local recurrence was extirpated and showed no different histology than the benign pilocytic astrocytoma extirpated 1 year before. In the 2-year follow-up after reoperation the metastatic lesions remained stable and were not treated since the patient had no complaints. The easier detection of spinal lesions by the more frequent use of MRI studies might show that metastatic spread of the pilocytic cerebellar astrocytoma is not as rare as for-

merly thought. In this respect careful tumour handling and intraoperative closure of the spinal canal at the foramen magnum or C1 level may be of importance to prevent the spread of tumour cells.

Malignant or anaplastic transformation is also a rare phenomenon of the cerebellar pilocytic astrocytoma. Wallner et al. [36] describe 3 patients who showed anaplastic transformation of recurring tumour. In 1 of these the primary tumour had a cerebellar localization, and this patient had undergone radiation therapy 21 years before. Kleinman et al. [21] report 1 case of malignant degeneration 48 years after partial removal and irradiation. Their literature review lists 4 more cases of malignant transformation 20–39 years after surgery, 3 of them in patients who had had radiation therapy. Five other cases have previously been described, with time intervals between surgery and malignant recurrences of 50, 21, 10 and 5 years [1, 33, 35, 38]. In all cases radiation therapy had been given in dosages of 12, 50 and 60 Gy.

In the patient in our study who was operated on twice for local recurrence of a benign pilocytic astrocytoma in a period of 2.5 years, 16 months after the last operation the tumour recurred again; then subtotal resection of a malignant ependymoma invading the brain stem was performed, but 3 weeks later the patient died. This patient had not previously been treated with radiation therapy. In the aforementioned 12 cases of malignant degeneration 10 of the patients had been treated with radiation therapy many years before. For 1 patient, in whom the malignant recurrence appeared after 20 years, the case report does not mention the use of irradiation [4, case 1]. The initial histological appearance in our patient was of a mixed type, the pilocytic astrocytoma also having areas reminiscent of subependymoma. The recurrence showed characteristics of a malignant ependymoma.

Spontaneously arising or de novo malignant transformation in pilocytic astrocytomas of the cerebellum is described in 6 cases [33]. It remains questionable whether very late malignant recurrences are the result of spontaneous tumour degeneration or of induction by the radiation therapy applied many years previously.

The literature records only 1 case of local invasive growth from a cerebellar pilocytic astrocytoma: this tumour had infiltrated the dura mater, the bone of the skull and the soft tissues of the neck and is the same tumour as described earlier, which showed metastatic spread [19].

Conclusions

In the study group of 73 patients treated for cerebellar pilocytic astrocytoma, 15 patients (21%) had tumour progression after the initial surgical treatment. The majority of these patients had postoperative residual tumour. Only in 2 patients was a true recurrence present and 1 of these also had metastatic spread of the tumour.

The surgeon's opinion of the extent of tumour resection is not very reliable, whether it is thought to have been complete or incomplete. Therefore, early postoperative neuroimaging, preferably by MRI, is indicated to establish the duration and frequency of follow-up consultations with or without imaging studies.

Tumour progression mostly appeared within 4 years after surgery. Despite its well-known benign nature, this tumour is capable of metastatic spread and malignant transformation. Steps must be taken to prevent craniospinal spread of tumour cells during the operation. Reoperation for progression of residual tumour or recurring tumour had no influence on outcome; however, total removal was only possible in 30% of cases. This means that the majority of patients with residual tumour after operation need to be subjected to the burden of periodic medical controls and neuroimaging and, possibly, reoperations for the rest of their lives. Since residual tumour may remain silent for many years, not every residual tumour needs to be operated on. In this respect a "wait-and-see" policy can be advocated. Neuroradiologically proven progression of residual tumour in the absence of clinical symptoms is, however, an indication for reoperation. The importance of aiming for total tumour removal at the first operation can not be overstressed.

Patients at risk of an unfavourable outcome or recurring tumour could not be determined by this study. Adequate postoperative follow-up is of the utmost importance; we suggest a follow-up flow-chart such as that seen in Fig. 2. In the case of total tumour removal confirmed by postoperative MRI scan, the follow-up period can be short. Such a patient can be discharged as needing no further controls after 4 years when a third MRI scan remains negative for residual or recurring tumour. When residual tumour is seen on the first postoperative MRI scan follow-up needs to be continued with MRI scans on a yearly base.

In general, radiation therapy has no place in the treatment of this tumour. However, earlier reports do suggest a benefical response of the tumour to this therapy in certain cases. The use of radiotherapy can be considered in children over 3 years of age in the case of a radiological or symptomatic re-recurrence, which means residual or recurring tumour after a second operation, in the case of a recurrence with "malignant" histological characteristics and in the case of a progressive or recurring lesion at an inoperable site, such as the brain stem.

More research is needed to determine the biological behaviour of the pilocytic astrocytoma, to find optimal treatment and to decide whether or not particular patients might be helped by radiotherapy.

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