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CLINICAL INVESTIGATION **Brain**

HYPERFRACTIONATED RADIOTHERAPY AND CHEMOTHERAPY FOR CHILDHOOD EPENDYMOMA: FINAL RESULTS OF THE FIRST PROSPECTIVE AIEOP (ASSOCIAZIONE ITALIANA DI EMATOLOGIA-ONCOLOGIA PEDIATRICA) STUDY

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Purpose: A postsurgical "stage-based" protocol for ependymoma was designed.

Methods and Materials: Children were given: (*1*) focal hyperfractionated radiotherapy (HFRT) if with no evidence of disease (NED), or (*2*) 4 courses with VEC followed by HFRT for residual disease (ED). HFRT dose was 70.4 Gy (1.1 Gy/fraction b.i.d.); VEC consisted of VCR 1.5 mg/m^2 1/w, VP16 100 mg/m^2/day × 3, CTX 3 g/m^2 d 1. When feasible, second-look surgery was recommended.

Results: Sixty-three consecutive children were enrolled: 46 NED, 17 ED; the tumor was infratentorial in 47 and supratentorial in 16, with spinal metastasis in 1. Of NED patients, 35 of 46 have been treated with HFRT; 8 received conventionally fractionated radiotherapy, and 3 received no treatment. Of the 17 ED patients, 9 received VEC + HFRT; violations due to postsurgical morbidity were as follows: HFRT only (2), conventionally fractionated radiotherapy (3) + VEC (2), and no therapy (1). Objective responses to VEC were seen in 54%; objective responses to RT were seen in 75%. Overall survival and progression-free survival at 5 years for all 63 children were 75% and 56%, respectively; for the NED subgroup, 82% and 65%; and for the ED subgroup, 61% and 35%, respectively. All histologies were centrally reviewed. At multivariate analysis, grading, age, and site proved significant for prognosis.

Conclusions: HFRT, despite the high total dose adopted, did not change the prognosis of childhood ependymoma as compared to historical series: New radiotherapeutic approaches are needed to improve local control. Future ependymoma strategies should consider grading when stratifying treatment indications. **© 2004 Elsevier Inc.**

Childhood ependymoma, Adjuvant therapy for ependymoma, Hyperfractionated radiotherapy in ependymoma.

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INTRODUCTION

Ependymoma accounts for 10% of childhood central nervous system tumors, with half the cases presenting in children below 3 years of age, and 10% to 15% as spinal tumors (1–3). Most of our knowledge derives from single-institutional series spanning many years, so it is not surprising that the conclusions of some reports are partially in conflict. Some of the many questions still under debate concern the optimal radiotherapy volumes, doses, and techniques; the usefulness of chemotherapy as adjuvant treatment; and the prognostic impact of histologic grading, patient's age, tumor site, and persistent hydrocephalus (4–7). In 1993, based on a retrospective national survey that enabled a relatively large series of ependymomas to be collected (5), a prospective single-arm study was launched with treatment stratification based on the completeness of surgical resection. Moreover, the effects of postoperative hyperfractionated radiotherapy (HFRT) were to be investigated in all patients, along with the possible role of a chemotherapy schedule containing cyclophosphamide, etoposide, and vincristine administered in children with postoperative residual disease before irradiation. Between October 1993 and May 2001, this observational protocol accrued 63 pediatric patients, and the results achieved are reported in this article.

METHODS AND MATERIALS

Patient eligibility

Children with posterior fossa or supratentorial ependymoma fulfilling the following criteria were eligible for the study: (*1*) age over 3 years and below 21; (*2*) histologically proven ependymoma; (*3*) no prior exposure to chemotherapy (except for steroids) or radiotherapy; (*4*) normal cardiac, hepatic, and renal function; (*5*) a Lansky score exceeding 30; (*6*) more than 1 surgical operation was accepted to maximize resection before adjuvant treatment. This protocol was approved by the Italian Association for Pediatric Hematology-Oncology and by the scientific and ethical committees of each institution treating the children. Children's parents or guardians provided written consent for participation in the study.

Pathology review

Histologic centralization was performed for all cases.

Ependymoblastoma, mixopapillary ependymoma, and subependymoma were not included in this study.

The cases were reviewed according to the World Health Organization criteria (8) by one of the authors (F.G.) with no information about the clinical course. For the purposes of the analysis, ependymomas were divided into Grade 2 and Grade 3 lesions, i.e., classic and anaplastic ependymoma. Grade 2 ependymoma was defined according to the microscopic features described by Wiestler *et al.* (8). Anaplastic features were defined as increased cellularity, cytologic atypia, and microvascular proliferation. Necrosis, although more frequently observed in anaplastic lesions, was not uncommon in classic Grade 2 neoplasms. Figure 1 shows the most relevant aspects of the adopted criteria.

Surgery and staging

All patients were to undergo maximal surgical resection. All operative reports were reviewed centrally. Resection was deemed complete when the neurosurgeon confirmed the absence of residual tumor at the end of the procedure, and imaging documented complete/near complete resection, according to the guidelines of the International Society of Pediatric Oncology (9), namely R1 (no visible tumor on early postoperative CT or MRI with and without contrast

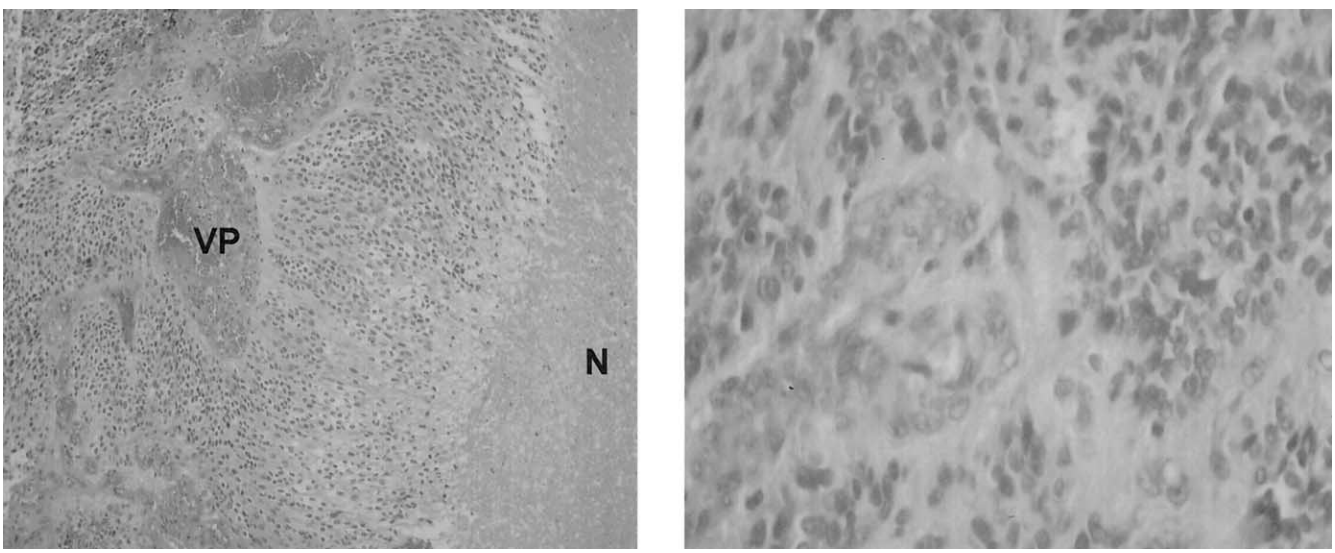

Fig. 1. (Left) Anaplastic ependymomas characterized by high cellularity and vascular proliferation (VP); necrosis (N) was not a requisite for anaplasia (H&E staining 100× power fields). (Right) Anaplastic ependymoma; focal vascular proliferation in a high cellularity area (H&E staining 400× power fields).

injection) and R2 (rim enhancement at the operation site). Patients were thereafter divided into two treatment groups according to the absence or presence of visible ($\geq$1.5 cm^2) residual disease before or after contrast enhancement on CT scan or MRI performed as soon as possible after surgery. Disease extent at diagnosis was assessed by means of a spinal MRI and cephalo-spinal fluid cytology. If more than 4 weeks had elapsed between postoperative scan and the beginning of adjuvant therapy, a new radiologic evaluation was required.

Magnetic resonance imaging evaluation was repeated after the first two courses and at the end of chemotherapy, if prescribed, before radiotherapy, and 6 weeks after its end. Tumor response evaluation followed International Society of Pediatric Oncology criteria (9), but disease reduction inferior to 50% (minor response) was included also in the amount of objective responses. Partial remissions and minor responses were defined altogether as volume reduction.

Radiologic follow-up included MRI every 3 months for the first 2 years after treatment, every 4 months for the third and the fourth year, and then every 6 months.

Treatment regimens

Adjuvant treatment was intended to be started within 4 weeks of surgery and followed two different treatment programs, according to extent of disease after surgery. Patients with postsurgical evidence of residual disease measuring at least 1.5 cm^3 received 4 monthly cycles of chemotherapy followed by HFRT, whereas children with no residual disease were given HFRT alone. Chemotherapy consisted of the vincristine, etoposide, cyclophosphamide (VEC) regimen, with vincristine (1.5 mg/m^2, Day 1; repeated on Days 8, 15, and 22 of the first and third course), cyclophosphamide (1 g/m^2 infused in 1 h for 3 doses, Day 1), and etoposide (100 mg/m^2 infused in 2 h, Days 1, 2, and 3). The use of granulocyte colony-stimulating factor as supportive treatment was optional. A central venous catheter was required for the administration of chemotherapy. MRI evaluation was repeated after the first 2 courses, before radiotherapy, and 6 weeks after its end. Chemotherapy was discontinued if disease progression or unacceptable toxicity occurred. Radiotherapy was delivered to a volume including the preoperative tumor extent plus a margin of 2 cm in all directions. The prescribed total dose of radiation was 70.4 Gy in 64 fractions of 1.1 Gy administered twice daily with a minimum 6-h interval between fractions, for a total of 32 treatment days. For tumors extending below the foramen magnum, the total dose to the spinal cord was maintained below 55 Gy. Children had to be treated with high-energy photon beams. Immobilization devices, according to local policies, were required for all patients to guarantee treatment reproducibility. Two-dimensional or three-dimensional computerized treatment plans to optimize dose distribution around the target volume were strongly recommended. Craniospinal irradiation was given exclusively in the case of proven distant spread and never for prophylactic purposes.

Statistical analyses

This observational protocol was stopped to accrual on May 2001, when the target number of 60 patients was reached. The major end points of the study were to estimate overall survival (OS) and progression-free survival (PFS) rates for the entire case series and for the two subgroups of patients with and without disease after surgery. In addition, local tumor control after high-dose HFRT was assessed, as well as tumor response to the adopted chemotherapy regimen.

All patients were included in the analysis according to the "intention to treat principle," regardless of whether they were compliant with the planned treatment program.

Overall survival rates were estimated using the Kaplan-Meier product-limit method from the day of the first radiologic diagnostic examination up until death, or to the date of the latest follow-up visit for patients who were still alive. PFS rates were estimated from the day of the first radiologic diagnostic examination up to the time of progression or the date of the latest follow-up visit for patients remaining in first complete remission (CR) (10).

The null effects hypothesis concerning the differential effect of some prognostic factors in univariate analysis was tested by means of the log–rank test (11), and all p values were two-tailed. In addition, the joint effects of the prognostic indicators—extent of residual disease and classes of age, tumor site, ventricular shunt, and grading—were investigated by a Cox regression model (12) using a backward selection procedure that retained only the variables that reached the conventional significance of 5% level. The null hypothesis of the regression analysis was tested by Wald test (13). The relative risks were estimated as hazard ratios (HR).

Follow-up data were updated as of December 31, 2002.

RESULTS

Patients

Between October 1993 and June 2001, 66 consecutive children entered the first Italian Association for Pediatric Hematology-Oncology cooperative protocol for the treatment of intracranial ependymoma. All histologic diagnoses were performed at the local pathology service, but all tumor samples were centrally reviewed by one of the authors (F.G.). Three patients were excluded because of misdiagnosis (glioblastoma multiforme in 2 patients and primitive neuro-ectodermal tumor [PNET] in 1 patient).

This group of 63 eligible patients represented an annual accrual rate of 9.3 patients, corresponding to more than 70% of all children in Italy from this age group with intracranial ependymoma.

The main characteristics of the patients are described in Table 1.

Tumor location

The tumor originated supratentorially in 16 children and in the posterior fossa in the remaining 47. In an examination

Table 1. Patient characteristics

Characteristics	Patients without residual disease (46)	Patients with residual disease (17)	Total (63)
Supratentorial	12	4	16
Infratentorial	34	13	47
Grade 2	32	11	43
Grade 3	14	6	20
Over 6 years	29	6	35
Under 6 years	17	11	28
No ventricular shunt	36	8	44
Ventricular shunt	10	9	19

of this latter group of patients, the tumor was described as adhering to the cerebellopontine angle in 27 cases and intraventricular in 17, whereas in another 3, the surgeon reported being unable to identify the origin of the tumor. At diagnosis, distant spread was found in only 1 patient with a completely resected supratentorial tumor and a spinal node located at D7. In another 2 patients, the tumor extended from the supratentorial site to the posterior fossa in 1, and from the posterior fossa to D7 in the other.

Extent of resection

After surgery, residual tumor was documented in 17 of 63 (27%) children, as assessed by combined neurosurgical reports and postoperative imaging studies.

In 16 of 46 completely resected cases, the posterior fossa tumor had reached the spine at C2.

Three children achieved complete removal of the tumor through 2 (2 cases) and 3 (1 case) operations. No significant correlation was found between tumor location and the extent of resection: Residual tumor was detected in 13 of 47 (28%) of the infratentorial tumors and in 4 of 16 (25%) of the supratentorial neoplasms.

In 19 of 63 children, a permanent ventricular shunt was needed to manage hydrocephalus. This occurred more frequently in patients less than 6 years of age (13/28 or 46%) than in older children (6/35 or 17%, $p < 0.04$).

Histology

All slides were centrally reviewed, and 43 tumors were defined as "classic" (Grade 2) tumors (68%), whereas 20 (32%) were "anaplastic" (Grade 3) according to the World Health Organization classification (8). When the reviewed diagnoses were compared with the original ones, the tumor was downgraded in three cases from Grade 3 to Grade 2 ependymoma. Concordance therefore reached 95%.

The percentage of anaplastic tumors differed at the two locations: 12 of 47 (25%) tumors arising in the posterior fossa and 8 of 16 (50%) supratentorial tumors were anaplastic. There was no difference between the group of patients completely resected, where 14 of 46 (30%) had anaplastic tumors, and the group with residual disease, where 6 of 17 (35%) had anaplastic tumors.

Treatment feasibility and compliance

We examined whether the treatment guidelines had been applied correctly. The interval between surgery and adjuvant treatment (HFRT and VEC) ranged between 23 and 130 days with a median of 41 days. This interval was not statistically different between the group of patients without (range, 24–130 days; median, 48 days) and the group with (range, 23–130 days; median, 35 days) residual disease after surgery. In some patients, a longer interval was needed to ameliorate postsurgical conditions before any adjuvant treatment was delivered; in one child included in the study, no adjuvant treatment was possible, because he suffered a basilar vein thrombosis soon after surgery and remained comatose for 73 months. Another 8 children had major postsurgical sequelae: 6 needed a permanent tracheostomy, accompanied by a percutaneous gastrostomy in 1 case; 1 suffered from iatrogenic diabetes insipidus and 1 from monolateral deafness. The scheduled chemotherapy was not adopted in 3 patients, based on the local physician's judgment that the patients' performance status was too poor, and modified (delivering oral VP16 for 4 monthly courses) in 1 child with a hematologic syndrome (protein C deficiency).

Radiotherapy was not administered to 4 of 63 patients. In 2 cases, poor postsurgical conditions prevented any adjuvant treatment; in the cases of 2 children with nonanaplastic supratentorial ependymomas, the local physician decided that surgical resection had been adequate. In 46 of 59 children, the prescribed HFRT was administered. In 13 children, a conventional fractionation (1 fraction a day, conventionally fractionated radiotherapy [CRT]) was adopted. In 2 cases, the parents refused hyperfractionation; in the patient with spine metastasis, craniospinal irradiation at 36 Gy was adopted, whereas the boost at the primary site followed the HFRT schedule at a total dose of 70.4 Gy. In the remaining 10 cases, there were logistic problems, mainly because of the young age of the patients requiring general anesthesia, in the delivery of 2 fractions per day. The median dose of CRT to tumor bed was 54 Gy.

Compliance in patients without residual tumor

When this subgroup of 46 patients is considered in detail, the main treatment violations consist of (*a*) the adoption of a CRT schedule in 8 cases, and (*b*) the omission of any adjuvant radiotherapy in another 3 cases.

The 3 children who did not receive radiotherapy were a boy with a tracheostomy and 2 children with completely resected Grade 2 supratentorial tumors, mentioned earlier, whose local oncologist decided to omit irradiation. Overall, 35 of 46 children (76%) without residual disease were correctly treated with HFRT, including 4 children who received also VEC for referral center decision.

Compliance in patients with residual tumor

As already mentioned, the proposed chemotherapy schedule was applied in full in 12 of 17 cases. In 3 children, no chemotherapy was delivered, because of postsurgical complications. In 1 child, a different schedule (oral VP16) was used, because of a preexisting protein C deficiency; in 1 patient, the second course was suspended as a result of inappropriate ADH secretion and a disturbed cardiac rhythm. One patient received 8 VEC courses for massive postsurgical residual disease. HFRT was given to 11 patients, whereas 5 were treated with CRT; 1 was not irradiated at all, because he was comatose. In all, 9 of 17 (53%) children fully complied with the protocol guidelines.

Of the 12 patients evaluable for the effect of radiotherapy—being 1 in CR after VEC and 3 after second-look surgery, as will be detailed in a further paragraph—6 had CR and 3 volume reduction (objective responses, 9/12), 1 had stable disease, and 2 revealed tumor progression at the first radiologic reevaluation.

Response to chemotherapy

We report here the response evaluated after the first 2 courses and after all the four scheduled courses. All 13 of 17 patients with residual disease treated with VEC were evaluated for tumor response to chemotherapy with MRI as scheduled. Seven of 13 had tumor volume reduction after the first two courses, and the response continued to be appreciable after the subsequent two courses, reaching a CR in 1 of 13. Five had stable disease during the first two courses and after the whole chemotherapy phase; 1 had progressive disease after the first two courses. The objective response rate was 54% (95% confidence interval [CI], 25%–81%).

Chemotherapy toxicity

In all, 48 complete 3-day chemotherapy courses were administered to 13 patients. The weekly administrations of vincristine after the first day of the first and third courses amounted to 94 of 130, and 12 of 94 were reduced to 75% of the full dose, because of peripheral neurotoxicity. Another 12 of 94 (13%) doses of weekly vincristine were reduced, because of prior severe constipation or peripheral neuropathy. Neutropenia Grade 4 NCI/CTC was reported after 11 courses, which required precautionary or therapeutic hospitalization in 9 of 11 patients; Gram+ bacteriemia was documented in only 1 patient. Seven platelet transfusions were required for piastrinopenia Grade 4 in 2 patients, and 27 packed red cell transfusions were given to 8 patients. Inappropriate antidiuretic hormone secretion and postvincristine intestinal ileum complicated the second chemotherapy course in 1 patient. None of the patients suffered toxic death after chemotherapy.

Second-look surgery

Five of the 17 patients with residual disease underwent resurgery for potentially resectable tumor after chemotherapy. Second surgery was performed after two courses in 1 patient and after all the scheduled chemotherapy in the other 4 children. Three patients consequently became disease free: In 2 cases, the tumor location was supratentorial; in 1, a spinal metastatic nodule was resected. In 2 other cases (1 stable disease after 4 courses, 1 tumor progression), the neurosurgeon achieved only a cytoreductive surgery. None of these resections was followed by permanent morbidity.

Overall survival and progression-free survival

The median follow-up of the survivors in this series was 5 years (range, 1.5–9 years). The PFS rate for all patients at 5 years was 56% (95% CI, 41%–70%) with a rate of 65% (95% CI, 49%–82%) for patients without residual disease and 35% (95% CI, 10%–61%, $p = 0.05$ [Fig. 2]) for patients with residual disease after surgery.

The OS rate for the whole series at 5 years was 75% (95% CI, 62%–88%), being 82% for patients without residual disease (95% CI, 68%–97%) and 61% (95% CI, 36%–86%, $p = 0.03$ [Fig. 2]) for patients with residual disease after surgery.

A total of 23 patients have relapsed so far at a median time of 21 months from diagnosis. Of the 12 relapses occurring in children without residual disease after surgery, 4 were local recurrence only (4 in the posterior fossa, and 1 was supratentorial). Seven relapses were outside the original site, namely in the dorsal spine (3 cases), lateral ventricle (2), basal nuclei (1), and frontal lobe (1). One local failure in the posterior fossa was accompanied by synchronous dissemination with s.c. and cervical spine nodules. Ten of the 11 children with residual disease recurred locally, 1 in the cauda. Overall, 8 of 23 (35%) relapses were remote, corresponding to 13% of the whole patient population. Table 2 analyzes relapses according to patients' characteristics, revealing a trend toward distant relapses in patients without residual disease after surgery. Mean time to local and distant failure was 25 and 22 months, respectively. The treatment protocol did not include a strategy for relapse, so salvage therapy followed the local pediatric oncologists' indications. Eleven of the 23 relapsing patients are still alive, 3 of 11 in second or further remission. Median survival after relapse is 15 months, with a range from 1 to 34 months.

Survival analyses

The results of the univariate analyses of PFS and OS are listed separately in Table 3 for the entire case series. In the entire case series, residual disease after surgery and Grade 3 were associated with a significantly higher risk of both relapse and death, whereas ventricular shunting influenced only progression-free survival, and age <6 years negatively affected overall survival. Figure 3 depicts the PFS and OS for patients with classic (Grade 2) and anaplastic (Grade 3) tumors, showing that anaplastic tumors are at significantly higher risk of both disease progression ($p = 0.0008$) and death ($p < 0.0001$). Of note, the presence of anaplasia was able to negatively influence treatment outcome in children both with and without residual disease after surgery.

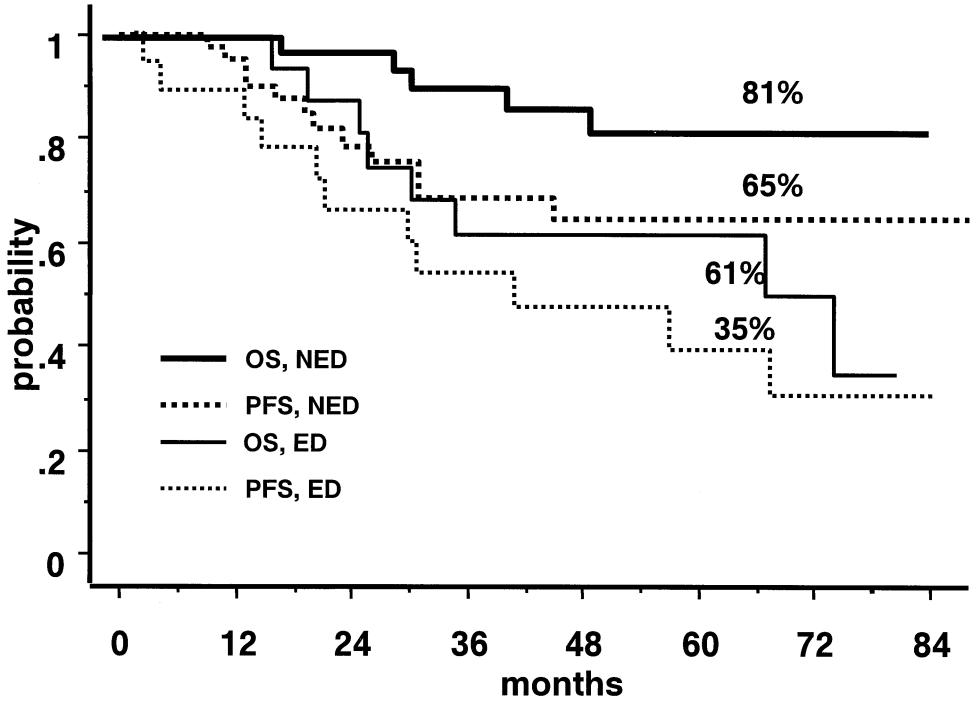

Fig. 2. Overall survival (OS) and progression-free survival (PFS) at 5 years for patients without (NED) and with (ED) evidence of residual disease

The final model of the regression analysis revealed that PFS was significantly affected by the presence of anaplastic subtype (HR: 4.9, 95% CI, 2.1–11.5; $p = 0.002$) and tumor located in the posterior fossa (HR: 4.2, 95% CI, 1.22–14.3; $p = 0.02$). The presence of anaplastic subtype influenced significantly OS (HR: 8.2, 95% CI, 2.4–27.8; $p = 0.0008$), as did age <6 years (HR: 3.8, 95% CI, 1.2–13.9; $p = 0.05$). In both models, the presence of residual disease showed only a nonsignificant trend ($p = 0.11$ and $p = 0.13$, respectively) for a higher risk of both disease progression and death.

Table 2. Main characteristics in relapsed patients

Characteristics (23)	Local failure (14)	Distant failure (8)	Local + distant (1)
Patients without residual disease (12)	4	7	1
Patients with residual disease (11)	10	1	0
Grade 2 (11)	8	3	0
Grade 3 (12)	6	5	1
Over 6 yr (9)	4	4	1
Under 6 yr (14)	10	4	0
No ventricular shunt (12)	6	5	1
Ventricular shunt (11)	8	3	0
Supratentorial (3)	3	0	0
Infratentorial (20)	11	8	1

DISCUSSION

The management of intracranial ependymoma is still a controversial topic in pediatric neuro-oncology and may range among institutions from surgery alone to a combination of surgery, radiotherapy, and chemotherapy (2, 3, 7, 14–16). The lack of uniformity is partially justified by the disappointing results reported by the majority of series. The 5-year survival for children with ependymoma ranges between 30% and 50% with a worse prognosis for patients with residual disease after surgery. In many series reported so far, the annual accrual rate does not exceed 3 to 8 patients, and this paucity contributes to uncertainties regarding the optimal treatment.

The main challenge in treating ependymoma is local relapse, which accounts for the vast majority of failures. Ependymoma has consequently been considered a “surgical disease” where completeness of excision can be reached in about half of the cases (3, 5, 6, 14). After reviewing and reporting on an Italian series of 92 children treated over 17 years, we were retrospectively able to identify the presence of residual disease as the only prognostic factor at multivariate analysis. Overall survival was 70% for patients who were disease free after surgery and 57% for patients who had residual disease; PFS was 32% and 11%, respectively (5).

The present protocol was therefore designed with two different treatment strategies for patients with and without residual disease. The addition of radiotherapy for all patients was based mainly on historical data that left many questions still unanswered (3, 7, 17). Considering the results

Table 3. Five-year overall survival and progression-free survival rates for all patients (*p* values are two-tailed according to log–rank test)

	n	%PFS (95% CI)	*p*	%OS (95% CI)	*p*
Residual disease after surgery					
Absent	46	65 (49–82)	0.05	82 (69–97)	0.031
Present	17	35 (10–61)		61 (36–86)	
Age					
>6 years	35	64 (45–83)	0.07	85 (70–100)	0.02
<6 years	28	46 (25–68)		64 (43–84)	
Site					
Supratentorial	16	76 (52–99)	0.08	84 (63–100)	0.24
Infratentorial	47	48 (30–65)		71 (55–87)	
Ventricular shunting					
No	44	66 (50–82)	0.05	78 (62–94)	0.08
Yes	19	36 (11–60)		68 (45–91)	
Grading					
Grade 2	43	66 (50–83)	0.0008	87 (76–99)	<0.0001
Grade 3	20	30 (5–55)		40 (10–69)	
Total	63	56 (41–70)		75 (62–88)	

Abbreviations: PFS = progression-free survival; OS = overall survival.

reported by Vanuystel and Brada (18), concluding that the risk of spinal seeding was uninfluenced by the extent of radiotherapy volume (local vs. craniospinal radiotherapy), we opted for local radiotherapy, which has become a standard postoperative treatment in the majority of institutions (14, 19, 20) Hyperfractionated radiotherapy was adopted in the attempt to increase the chances of local tumor control in both treatment groups throughout the delivery of a higher total dose (70.4 Gy) as compared with conventional treatments (54–56 Gy), without increasing late damages on normal brain tissues. The preliminary results reported by Needle *et al*. on a monoinstitutional series of 19 patients were indeed very favorable, with a PFS of 72% at 5 years after systemic chemotherapy and HFRT at a total dose of 72 Gy (21).

As for chemotherapy, the only randomized study published to date, which adopted vincristine and lomustine, concluded that this regimen did not improve survival (22). Among other drug combinations, the "8 in 1" regimen, MOPP and etoposide-carboplatin, have been disappointing (3, 23), whereas the best response rate so far has been reported by Duffner *et al*. with the Pediatric Oncology Group (POG) "baby brain" protocol (24): The combination of vincristine plus cyclophosphamide, alternating with eto-

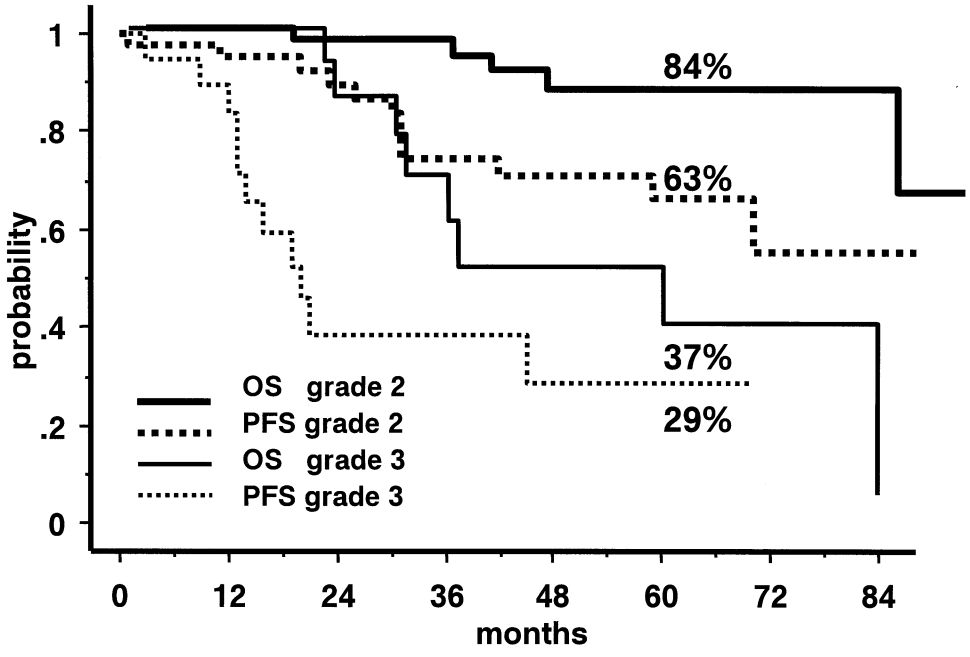

Fig. 3. Overall survival (OS) and progression-free survival (PFS) at 5 years for patients with Grade 2 and Grade 3 subtypes.

poside and cisplatin, obtained an objective response of 48%. In said study, moreover, delaying radiotherapy until after quite a long chemotherapy schedule (12–24 months) did not seem to interfere with the outcome of radiotherapy. We have adopted a schedule with a higher dose of cyclophosphamide, aiming to improve dose intensity and thus overcoming the chemoresistance of ependymoma (4) and obtaining a better local control in children with residual disease.

Our series compares fairly well with the largest reported so far, with an annual accrual rate of over 9 patients, even excluding children below 3 years of age (1, 3, 5, 7, 17).

The tumors completely or nearly resected amounted to more than 70%, and this proportion is among the highest currently reported (17). This difference in comparison to other series can be explained by the strong inclination among neurosurgeons to remove the tumor completely, much of the disease prognosis being dependent on optimal excision (26). The goal of complete tumor removal was therefore pursued, with even second-look resections being adopted either after an early postoperative scan or later on, after chemotherapy and before radiotherapy. This approach is, in other authors' opinions as well as ours, wiser than a single "heroic" and probably more harmful surgery that can lead to severe sequelae (27–29). In our series, 4 children received no therapy after surgery, because of "first-line" surgical morbidity, whereas none of the 8 second-look operations were complicated by sequelae. Ventricular shunting was necessary in about 30% of patients to manage hydrocephalus, even in the presence of complete resection. The number of shunts directly correlated with the patient's age, being more numerous in children under 6 years old. When dealing with ependymoma, complete resectability depends on the skill of the operator, of course, but also on the characteristics of the tumor itself (27, 30, 31): In fact, infratentorial ependymoma in more than 50% of cases (32, 33) (54% in our series) involves the cerebellopontine angle intimately related with the cranial nerves. Finally, the resectability of ependymoma may reflect also a favorable tumor biology determining a noninfiltrating growth pattern (17, 30, 34).

One-third of the tumors were classified as Grade 3 or anaplastic. In the literature, the histologic distribution is very heterogeneous, with some series containing a high percentage of anaplastic tumors (6, 17), especially if they include children below 3 years of age, whereas other series reported only Grade 2 tumors (21, 25, 34, 35). In our series, a centralized review of the specimens revealed a good consistency among pathologists (95%).

When we considered patients who received chemotherapy, whose activity in patients with evidence of disease was one of the end points of the strategy adopted, our results documented a potential role of VEC in ependymoma with an objective response rate reaching 54%. The role of chemotherapy in newly diagnosed ependymoma remains a matter of debate, however. As Duffner *et al.* (24, 36, 37) have already pointed out, the real question is related not to the chemo-sensitivity of this tumor, which we and other authors have identified (38–40), but to the curative capability of chemotherapy, because children with ependymoma tend to develop progressive disease after several years, in striking contrast to other pediatric tumors, which usually recur early. Most studies employing chemotherapy, however, have contributed little to our understanding of the activity of the drugs adopted, because the drugs were used soon after radiotherapy (16, 21, 43), or regardless of the presence of measurable disease (5, 22). A recent hypothesis, also stemming from the issue of the "baby" protocols (6, 37), is that chemotherapy could facilitate a subsequent second surgical approach, not only because of reduction or stabilization of tumor volume, but also for the time left to the recovery from postsurgical morbidity (4, 23, 41) and maybe because the residual tumor becomes more circumscribed and amenable to resection (28), i.e., less infiltrating vital structures.

Radiotherapy achieved a response in 9/12 evaluable patients. These results confirm the effect of radiation treatment in ependymoma (42) and also in the presence of residual disease. Local failures have not been prevented by adopting the hyperfractionated schedule, however, or by delivering a high total dose in the vast majority of cases. Despite several studies supporting a dose–response relationship in radiation therapy for ependymoma (19, 25, 27), the schedule we adopted has not dramatically improved local control compared to historical series, especially in patients with residual disease and anaplastic histology.

Thirteen percent of all patients relapsed outside the radiotherapy fields; in 7 of 8 of these cases, the primary tumor had been completely resected. Isolated metastatic relapses have been reported by other authors in 3% to 15% of cases (3, 14, 24, 43), despite the adoption of craniospinal radiotherapy (15, 16) and despite different total radiotherapy doses and fractionations (44–46).

An infratentorial origin and age less than 6 years were associated with a worse prognosis. These clinical features are recognized as risk variables, regardless of tumor malignancy and extent of resection, by other authors, as well (15, 29, 45, 47). In our series, age correlated with the need for ventricular shunting, maybe as a result of the more difficult surgical approach in smaller patients, because of a "plastic" tumor growing peripherally, displacing or involving vessel and nerve structures in the subarachnoid space (32, 33, 48).

Anaplastic subtype and posterior fossa origin indicated higher risk of relapse and death. The standard grading criteria for ependymoma in the literature are controversial, and their prognostic significance remains debatable (1, 5, 7, 14, 24, 46). In a recent comment on histologic classification and prognostic criteria, Packer (49) observed that the lack of an accepted grading system prevents any conclusions as to the histologic features that are more prognostic. In our series, histologic grading was the most powerful prognostic indicator: Grade 2 tumors obtained a PFS of 66% and an OS of 87%, whereas anaplastic ependymoma reached only 29% and 37% for PFS and OS, respectively. The same pathologic criteria, adopted in a recent paper by Merchant *et al.* on a

retrospective series, revealed the same prognostic impact of grading (50).

The different prognostic criteria adopted in the classification of risk categories for intracranial ependymoma have contributed in the past to determining very different treatment approaches in the few prospective studies published so far. There are patients whose treatment has been tailored according to tumor grade, resulting in more aggressive strategies being adopted for the anaplastic histotype (16); other patients are treated according to the tumor's site of origin (2, 34) or the patient's age at diagnosis (6, 24). Some children are treated on the basis of surgical results, as they are in our series (27). It may be that each of these approaches determines a different trend in the natural history of the disease or, more probably, that we are dealing with different diseases, all grouped under the same name, ependymoma. We would argue that, based on what molecular biology has revealed for other pediatric cancers, e.g. acute leukemia or neuroblastoma, cytogenetic and molecular biology studies might disclose new features of this tumor. With that event, we will be able to consider new, more reliable features for modeling more satisfactory treatment strategies, in addition to the various clinical and histologic aspects already outlined, for intracranial ependymoma.

We conclude that, to the best of our knowledge to date, surgery remains the main treatment tool for ependymoma, but it should be modeled in a prospective setting to suit the patient's neurologic conditions, in one or more operations, to avoid losing the chance to implement subsequent treatment for the morbid effects of surgery. VEC chemotherapy could be more widely explored, considering its at least partial efficacy in the small series of patients that we have treated. VEC features a substantial lack of severe toxicity and the possibility of rendering a second surgical approach more successful in terms of patient morbidity, though this result has been proven in only a minority of patients. The VEC schedule, like other chemotherapy regimens adopted so far, is not, however, the key to the cure of ependymoma. As for radiotherapy, HFRT does not seem to have had a determinant therapeutic impact as compared to historical controls. New radiotherapy treatment techniques such as three-dimensional conformal radiotherapy may allow the delivery of high radiation doses focused to small volumes while sparing significantly the surrounding normal brain and improving the therapeutic ratio; therefore, patients with poor prognosis should benefit from the application of these techniques (19, 42, 46).

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