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Final results of the second prospective AIEOP protocol for pediatric intracranial ependymoma

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Background. This prospective study stratified patients by surgical resection (complete = NED vs incomplete = ED) and centrally reviewed histology (World Health Organization [WHO] grade II vs III).

Methods. WHO grade II/NED patients received focal radiotherapy (RT) up to 59.4 Gy with 1.8 Gy/day. Grade III/NED received 4 courses of VEC (vincristine, etoposide, cyclophosphamide) after RT. ED patients received 1–4 VEC courses, second-look surgery, and 59.4 Gy followed by an 8-Gy boost in 2 fractions on still measurable residue. NED children aged 1–3 years with grade II tumors could receive 6 VEC courses alone.

Results. From January 2002 to December 2014, one hundred sixty consecutive children entered the protocol (median age, 4.9 y; males, 100). Follow-up was a median of 67 months. An infratentorial origin was identified in 110 cases. After surgery, 110 patients were NED, and 84 had grade III disease. Multiple resections were performed in 46/160 children (28.8%). A boost was given to 24/40 ED patients achieving progression-free survival (PFS) and overall survival (OS) rates of 58.1% and 68.7%, respectively, in this poor prognosis subgroup. For the whole series, 5-year PFS and OS rates were 65.4% and 81.1%, with no toxic deaths. On multivariable analysis, NED status and grade II were favorable for OS, and for PFS grade II remained favorable.

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Conclusions. In a multicenter collaboration, this trial accrued the highest number of patients published so far, and results are comparable to the best single-institution series. The RT boost, when feasible, seemed effective in improving prognosis. Even after multiple procedures, complete resection confirmed its prognostic strength, along with tumor grade. Biological parameters emerging in this series will be the object of future correlatives and reports.

Keywords: boost, ependymoma, grade, prognosis, surgery.

While genomic, transcriptomic, and epigenetic research has recently identified particular molecular characteristics and subtypes of ependymoma that correlate with patients' clinical features, such as age and site,[1–5] clinical trials conceived and reported to date are still based on clinically prognostic factors like the extent of resection and—for some, but not all trials—patients' age and tumor grade.[6–8] The potential for developing targeted, risk-adapted therapies based on recent biological discoveries will probably be exploited over the next few years. While we await the best stratification for the future, we report here on the results obtained in 160 consecutive children between 2002 and 2014 in the second trial on intracranial ependymoma conducted by the Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP). The therapeutic strategy was based on previously obtained results[6] and aimed to improve patient outcome, focusing particularly on the subgroups with the worst prognosis.

Materials and Methods

Patient Eligibility

Children with infratentorial or supratentorial ependymoma were eligible for the study if they met the following criteria: (i) age over 3 and under 21 years old; (ii) histologically confirmed ependymoma; (iii) no prior exposure to chemotherapy (other than steroids) or radiotherapy; (iv) normal cardiac, hepatic, and renal function; (v) Lansky score >30; and (v) more than one surgical procedure before enrollment was accepted and considered part of the design to maximize resection before adjuvant treatment. In July 2006, the protocol was amended to include diagnoses in children between 12 months and 3 years of age. A second and last amendment in April 2009 prolonged patient accrual beyond 5 years. The protocol and its amendments were approved by the AIEOP and by the independent scientific and/or ethical committees of all the 17 institutions treating the children. Parents or guardians provided written consent to the children's participation in the study.

Study Design

This was a prospective, multi-institutional, nonrandomized study. The treatments administered depended on surgical outcomes and histological grade for patients with no postoperative residual disease (Fig. 1).

Pathology Review

Histological examination was centralized for all cases before patients were assigned to any treatment arm. Subependymomas were not considered in this study. Cases were reviewed according to the World Health Organization (WHO)[9] criteria by 2 of the authors (F.G., M.A), who had already provided revision for the previous series.[6]

Treatment Regimens

All patients were to undergo maximal resection. All surgical reports were reviewed centrally. Resection was deemed complete when the neurosurgeon confirmed the absence of macroscopic residual tumor at the end of the procedure and imaging

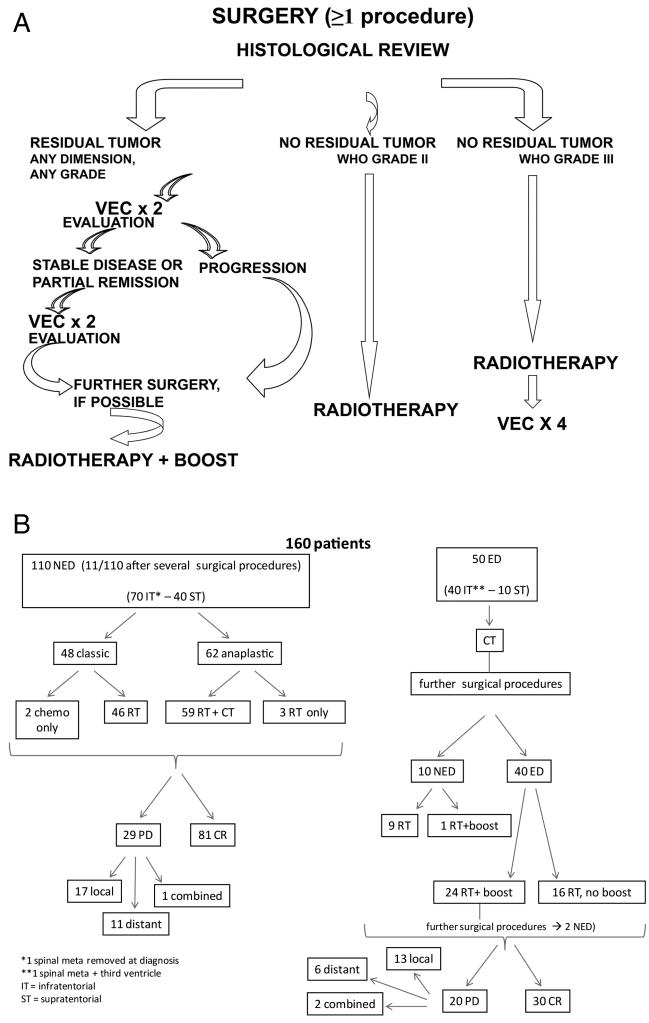

Fig. 1. (A) Treatment diagram and (B) patient flow during treatment.

documented complete/near-complete resection, essentially as it was described also in Merchant's papers on the St Jude series,[7,8] namely: gross total resection was defined as neurosurgical judgment of macroscopically complete resection and no evidence of residual tumor on MRI; near-total resection was defined as <5 mm of residual tumor in greatest dimension; and all other cases were considered as subtotal resections. Patients were then divided into 2 treatment groups by the absence or presence of visible residual disease (at least 5 mm in size) on MRI performed as soon as possible after surgery. A further stratification, identifying a third treatment arm, was applied to patients with no residual tumor, based on tumor grade (ie, WHO grade II or grade III).

(1) The aim was to start adjuvant treatment preferably within 4 weeks after surgery, but there was no time limit to begin adjuvant treatment after surgery. Three different treatment programs were adopted, depending on the extent of residual disease after surgery and on the results of upfront central pathology review, as shown in Fig. 1A. Patients achieving a gross or near-gross total excision (no evidence of disease = NED) of grade II tumors were to receive focal radiotherapy (RT) using a 3D-conformal technique, with 1.8 Gy daily up to 59.4 Gy.
(2) If patients were NED but had grade III tumors, they were also given 4 courses of vincristine, etoposide, and cyclophosphamide (VEC) chemotherapy after the same RT.
(3) Patients with residual disease (evidence of disease = ED) after surgery received a maximum of 4 VEC courses, the main aim of which was to bridge to a second-look surgery whenever possible, and received 59.4 Gy of RT followed by an 8-Gy boost in 2 fractions of 4 Gy each on any residual disease still measurable in 3 planes on MRI after chemotherapy and/or further surgery.

Since July 2006, children over 1 and under 3 years of age received the same treatment, except that the total radiation dose was lowered to 54 Gy for patients younger than 18 months, and patients with grade II tumors who were unequivocally NED after surgery could be given only 6 courses of VEC and a strict follow-up, at the local center's discretion.

The VEC regimen consisted of vincristine (1.5 mg/m^2, day 1), cyclophosphamide (1 g/m^2 infused in 1 h for 3 doses, 3 h apart, day 1), and etoposide (100 mg/m^2 infused in 2 h, days 1, 2, and 3). VEC was delivered every 3–4 weeks both before and after RT according to the general treatment plan. The use of granulocyte colony stimulating factor as a supportive treatment was optional. A central venous catheter was used to administer the chemotherapy, which was to be discontinued in the event of disease progression or unacceptable toxicity. RT was delivered using at least a 3D-conformal treatment plan and delivery technique (all intensity-modulated RT techniques, including tomotherapy and volumetric modulated arc therapy allowed). The target volumes were: the postoperative tumor bed at the primary site ± residuals after surgery for gross tumor volume (GTV); the GTV plus an anatomically confined margin of 1 cm for the clinical target volume (CTV); and a 0.3–0.5 cm geometrical expansion of the CTV for the planned target volume (PTV). The GTV had to include the edge of the resection cavity with the anatomically involved tissues, and gross residual tumor was assessed on postoperative MRI, on the sequence where it was more properly appreciated judging from its preoperative MRI features: T1 sequence ± gadolinium enhancement, T2, or (most frequently) fluid attenuated inversion recovery.

For the RT boost, the GTV coincided with all pathological tissue still measurable after surgery and chemotherapy; the CTV overlapped the GTV; and the PTV was a 0.2–0.3 cm geometrical expansion of the CTV/GTV. The boost was planned to be delivered soon after completion of the full conformal treatment.

For infratentorial tumors extending beyond the foramen magnum, the corresponding spinal cord was excluded on reaching a cumulative physical dose of 54 Gy. In all other cases, the cervical spinal cord that might be included in the PTV was excluded on reaching a cumulative physical dose of 50 Gy. Children had to be treated supine using megavoltage photons with a nominal energy ≥6 MV. Based on local policies, immobilization devices were used for all patients to ensure treatment reproducibility.

Staging and Imaging Follow-up

Disease extent at diagnosis was assessed by means of a spinal MRI and CSF cytology in all patients. If more than 4 weeks elapsed between the postoperative scan and the start of adjuvant therapy, another radiological assessment was required. For patients receiving only RT as adjuvant treatment after surgery, MRI was performed 6 weeks after RT was completed. In cases with residual disease, MRI was repeated after the first 2 courses of chemotherapy, before RT, after completing RT and before the boost, if feasible, and 6 weeks afterward. In cases undergoing second-look surgery, MRI was repeated as soon as possible after the surgical procedure. For patients with no residual disease given chemotherapy after RT, MRI was repeated after 2 courses of VEC and again 1 month after completing the treatment.

Radiological follow-up included MRI every 3 months for the first 2 years after completing the treatment, then every 4 months in the third and fourth years, and then every 6 months thereafter.

Statistical Methods

All patients were included in our analysis, regardless of whether or not they were compliant with the treatment program. The main endpoints of the study were overall survival (OS) and progression-free survival (PFS) for the whole case series. We also assessed local tumor control for the 3 treatment subgroups: (i) after conformal RT, (ii) chemotherapy and/or second-look surgery followed by RT ± boost, and (iii) chemotherapy after conformal RT. The OS time was computed as the time elapsing from the date of the first diagnostic radiological exam to the date of death due to any cause, censoring at the time of the latest follow-up for patients still alive. The PFS time was computed as the interval between the date of the first diagnostic radiological exam and the date when progression (local or distant, whichever occurred first) was identified, censoring at the latest follow-up for patients remaining in first complete remission. OS and PFS curves were estimated using the Kaplan–Meier method and compared with the log-rank test. We also separately estimated the cumulative incidence

of local and distant progression, conducting the analyses in a competing risks framework: local progression concurrent with distant progression was classified as distant progression, and the cumulative incidence curves were estimated and compared using Gray's test.[10]

Multivariable analyses were run to investigate the joint prognostic effect on OS and PFS of patient- and tumor-related characteristics, such as patients' gender and age, tumor site and grade, need for a shunt, residual tumor after first surgery, residual tumor after second-look surgery (ie, before RT), and interval between surgery and chemotherapy. For both of the endpoints investigated, the number of events (deaths or disease progressions) for each predictor variable was very low, and this hampered the reliability of the results emerging from the multivariable regression model.[11] To select the most informative variables from among the previously defined set of predictors, we therefore resorted to using "component-wise gradient boosting,"[12] as implemented in the R library "mboost,"[13] which is a machine learning method for optimizing prediction accuracy and selecting variables during the fitting process.

The association between pairs of categorical variables or between continuous and categorical variables was assessed using Fisher's exact test or the Mann-Whitney-Wilcoxon test, respectively.

Results

Patients

Between January 2002 and December 2014 (when patient accrual was stopped), 160 consecutive children with a median age of 4.9 years (range, 1–17.8 y) entered the protocol. All histological diagnoses were obtained at the local pathology service, and all tumor samples were centrally reviewed (as explained above), and treatments were tailored in the light of said review. The main characteristics of the patients in this series are given in Table 1, as a whole and by extent of resection, which was complete for 110 patients.

Tumor Location

Tumors originated supratentorially in 50 children and infratentorially in the remaining 110. At diagnosis, distant spread was identified in 2 patients with completely resected infratentorial tumors: one had further nodules in the third ventricle, the conus medullaris, and the spine at T6; the other had a cauda nodule that was removed soon after first excision of the primary tumor. Their CSF cytological examinations were negative for tumor cells, thus confirming the doubtful utility of this common diagnostic procedure.[14,15]

Extent of Resection

After initial surgery, residual tumor was documented in 50/160 (31%) children, based on combined neurosurgical reports and postoperative imaging studies.

Eleven children had achieved a complete resection after 2 surgical procedures (including the girl with the cauda metastasis). A significant association emerged between tumor location and extent of resection: residual tumor was detected in 40/110 (36.4%) infratentorial tumors, and in 10/50 (20.0%) supratentorial neoplasms ($P = .044$).

Table 1. Main patient and tumor characteristics

	Patients with NED ($N = 110$)	Patients with ED ($N = 50$)	Total Patients ($N = 160$)
Gender			
Female	46 (41.8%)	14 (28.0%)	60 (37.5%)
Male	64 (58.2%)	36 (72.0%)	100 (62.5%)
Age			
Median, y (interquartile range)	5.3 (2.8–9.3)	4.2 (2.7–7.2)	4.9 (2.8–9.1)
Under 3 y	31 (28.2%)	14 (28.0%)	45 (28.1%)
3 y or over	79 (71.8%)	36 (72.0%)	115 (71.9%)
Tumor location			
Supratentorial	40 (36.4%)	10 (20.0%)	50 (31.2%)
Infratentorial	70 (63.6%)	40 (80.0%)	110 (68.8%)
WHO grade			
Grade II/classic	48 (43.6%)	28 (56.0%)	76 (47.5%)
Grade III/anaplastic	62 (56.4%)	22 (44.0%)	84 (52.5%)
Ventricular shunt			
No	84 (76.4%)	16 (23.6%)	100 (62.5%)
Yes	26 (23.6%)	34 (68.0%)	60 (37.5%)

In 60/160 children, a permanent ventricular shunt was needed to manage hydrocephalus, and this was significantly associated with tumor location: a shunt was needed for 51/110 (46.4%) patients with infratentorial tumors, and 9/50 (18.0%) patients with supratentorial disease ($P = .001$).

Histology

Seventy-six tumors (47.5% of the sample) were defined as "classic" (WHO grade II) ependymomas, while 84 (52.5%) were "anaplastic" (WHO grade III).

The percentage of anaplastic ependymomas differed at the 2 locations: 49/110 (44.5%) tumors arising infratentorially and 35/50 (70%) of supratentorial tumors were anaplastic ($P = .004$). There was no significant difference in tumor histology between the group of NED patients, 62/110 (56.4%) of whom had anaplastic tumors, and the ED group, where 22/50 (44.0%) had the anaplastic form ($P = .173$).

Patients' Gender and Age

Gender was not significantly associated with tumor origin, extent of resection, tumor grade, or need for a shunt (data not shown).

Age was significantly associated with tumor origin: the percentage of patients with infratentorial tumors was higher among those aged <3 years (40/45 [88.9%] vs 70/115 [60.9%] patients ≥3 y old; $P = .001$). Age was also significantly associated with tumor grade ($P = .034$), the percentage of patients with grade III tumors being higher among those aged <3 years (30/45 [66.7%] vs 54/115 [47.0%] patients aged ≥3 y). The proportion of patients needing a ventricular shunt was also significantly higher among the younger patients (23/45 [51.1%] vs 37/115 [32.2%]; $P = .030$). Age was not significantly associated with the extent of resection, however ($P = .999$).

Adjuvant Treatment

Figure 1B shows the treatment diagram for the series as a whole.

Of the 110 NED children, 3 with grade III anaplastic ependymoma did not receive chemotherapy after radiation due to a local physician violating the protocol (in 2 cases) or to the patient's poor neurological conditions (in 1). Two children under 3 years of age at diagnosis with a grade II classic histology received only VEC chemotherapy after complete resection.

Of the 50 ED patients, 27 underwent further surgical procedure(s) after 1–4 courses of VEC. Number of VEC courses was not compulsory because the main chemotherapy aim, in patients with residual disease, was to bridge to second-look surgery. Complete resection was achieved in 10 cases. Another 2 patients were submitted to complete resection of tumor residuals after RT, as will be below further described.

Second-look surgery

Including second-look procedures performed soon after a first excision, before any adjuvant treatment, a total of 100 procedures were performed in 46/160 children (28.8%), with 40 patients undergoing surgery twice, 5 children 3 times, and 1 child 5 times. One of these patients had second-look surgery during RT on a cystic mass, while residual tumor was removed in 2 children 10 and 14 months after they had received the RT boost. This approach achieved an additional 23 complete resections with respect to the status after the first surgical procedure.

Of the 40 patients still with ED when their RT started, 24 had RT boosts, as per our protocol, after completing conformal RT. In one other child, a neurosurgeon prescribed the RT boost on what he contoured as an area of microscopic residual disease, even though second-look surgery had been judged complete (so this RT boost went against the protocol). Sixteen remaining children with ED did not receive the boost for the following reasons: (i) at the radiotherapist's discretion, due to a large residual tumor or anatomical constraints in 9 cases; (ii) because no residual tumor was clearly identifiable after chemotherapy in 6; and (iii) due to metastatic disease in 1.

Of the 158 patients given adjuvant radiotherapy after surgery, 140 received 59.4 Gy, another 8 children under 18 months of age at diagnosis received 54 Gy, and 8 patients received doses of 50.5–57.6 Gy, with a median of 55.8 Gy. The 2 patients with metastatic disease were treated differently. The patient with the complete resection of both the primary tumor and the spinal metastasis, who was 12 years old, received craniospinal irradiation at a total dose of 36 Gy, in 20 daily fractions of 1.8 Gy, with a boost up to 54 Gy on the primary tumor bed and up to 50.4 Gy on the secondary site. The other child, 6 years old at diagnosis, received 59.4 Gy on the primary tumor bed because the other sites were not ascertained for sure to be metastases, thereafter, when they did grow, he had surgery on the spinal nodules and received 59.4 Gy on the third ventricle metastasis and 36 Gy on the spine.

The PFS and OS of the 16 patients receiving different radiation doses on their primary tumors did not differ statistically from the other 141 patients.

Of the 2 children receiving only chemotherapy as adjuvant treatment, one was alive in continuous remission at 77 months after diagnosis, while the other had a local relapse after 19 months, was reoperated on and irradiated at the total dose of 59.4 Gy, and was alive in second remission at 118 months at the time of this report.

Treatment Toxicity

At least one neurological deficit and/or hemorrhagic or infectious episode was reported in 63/160 patients after surgery. Among those, gastrostomy or a nasogastric tube was to be put in place in 5 patients and tracheostomy in 3, while postsurgical mutism was detected in 3 cases. Adjuvant treatment began more than 6 weeks after surgery for 63/160 patients. In 36 cases, this was due to recovery from postsurgical complications, mainly low cranial nerve deficits and CSF dynamic alteration, while in the remaining 27 patients it was a referral delay. None of the patients had to abandon the adjuvant treatment due to these events. For the sample as a whole, the time elapsing between surgery and adjuvant treatment ranged from 11 to 210 days, median 42 days. This interval had no prognostic impact.

None of the children died due to adjuvant treatment.

Second-look surgery was followed by a deterioration in neurological cerebellar and lower cranial nerve function in 4/46 patients and by bleeding in 1. At the time of this report, all neurological impairments had reportedly improved.

Chemotherapy-related toxicity overlapped with the situation seen in the previous protocol when it was used before RT,[6] and did not differ when the 4 VEC schedules were administered after RT.

Progression-free Survival and Overall Survival

The median follow-up was 67 months (95% CI: 59–78 mo; interquartile range: 41–110 mo). For the whole series, the 5-year PFS and OS were respectively 65.4% (95% CI: 57.7%–74.0%) and 81.1% (95% CI: 74.6%–88.2%) (Fig. 2). The

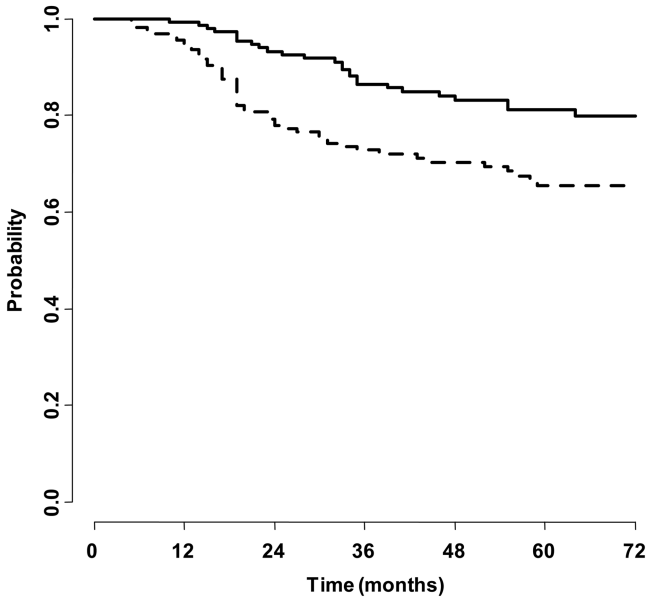

Fig. 2. Kaplan–Meier PFS and OS curves for the whole series.

5-year probability of local relapse was 20.7% (95% CI: 14.8%–29.1%) and for distant metastasis it was 13.9% (95% CI: 9.2%–21.0%). Combined relapses were detected in 3 cases, as shown by Fig. 1B.

The median time to progression was 19 months (4–103 mo), 23 months for local, and 17 months for distant relapse.

Based on the surgical results at the time of starting adjuvant treatment, the 5-year PFS and OS rates were respectively 70.8% (95% CI: 66%–75.6%) and 86.6% (95% CI: 82.9%–90.3%) for patients without residual disease, and 53% (95% CI: 39.7%–71%) and 68.6% (95% CI: 55.7%–84.6%) for patients with residual disease.

Table 2 shows the 5-year PFS and OS estimates by the different prognostic variables. Female patients had a significantly better PFS ($P = .005$) and OS ($P = .031$) than males. Having found significant results for PFS, we separately estimated the cumulative incidence of local and distant relapse. The local relapse rate was significantly lower in females (5-year cumulative incidence estimate: 3.4%; 95% CI: 0.9%–13.3%) than in males (31.8%; 95% CI: 22.9%–44.0%; $P < .0001$), while for distant metastases there was no significant difference between the 2 groups, with 16.3% (95% CI: 8.8%–30.1%) in females, and 12.4% (95% CI: 7.1%–21.7%) in males ($P = .597$).

There were no significant differences in PFS by patients' age, but the 2 groups (<3 vs ≥3 y old) differed significantly in terms of OS (Table 2). PFS did not differ significantly by tumor location either (infratentorial vs supratentorial), whereas OS did ($P = .039$). PFS was significantly better for grade II tumor patients without residual disease than for grade III tumor patients with or without residues, while the latter shared much the same PFS (Fig. 3A; $P = .025$); the OS also differed significantly between these 3 groups (see different curves in Fig. 3B; $P = .007$). Figure 1B shows the pattern of tumor relapse: there was no significant difference as regards local relapse ($P = .309$; Supplementary Fig. S1), but patients with residual disease after surgery had the highest incidence of local recurrence (5-year estimate: 28.9%; 95% CI: 17.6%–47.4%), followed by grade III tumor patients without residues (19.4%; 11.3%–33.5%) and grade II patients without residues (13.5%; 5.8%–31.7%). Distant relapses were significantly more common among patients with grade III tumors—whether they were without residues (18.7%; 10.8%–32.1%) or with residual disease (17.9%; 9.4%–34.1%)—than in grade II patients without residues (2.3%; 0.3%–16.9%) ($P = .048$). Considering grade influence on patients' PFS and OS according to tumor location, neither PFS nor OS was influenced in supratentorial tumor patients. There was instead a statistically significant difference for patients whose tumor originated infratentorially in both PFS (5-year estimate: 73.3%, 95% CI: 61.0%–88.2% if grade II; and 47.8%, 95% CI: 35.0%–65.2% if grade III, $P = .0047$) and OS (5-year estimate: 89.7%, 95% CI: 81.5%–98.7% if grade II; and 65.1%, 95% CI: 52.1%–81.4% if grade III, $P = .009$).

Considering the patients' status before RT, with a further 10 patients becoming disease free after chemotherapy and second-look surgery, the PFS and OS differed statistically between the 120 patients who were NED and the 40 who were still ED. The 5-year estimates for local relapse were 16.9%

Table 2. Kaplan–Meier PFS and OS

	PFS		OS	
	5-y Estimate (CI)	*P* (log-rank)	5-y Estimate (CI)	*P* (log-rank)
Gender		.005		.031
Female	80.3% (70.4%–91.6%)		89.3% (81.5%–97.8%)	
Male	55.8% (45.9%–67.9%)		75.7% (66.6%–86.0%)	
Age		.164		.035
<3 y	57.6% (43.1%–77.2%)		70.3% (56.3%–87.8%)	
≥3 y	67.9% (59.3%–77.8%)		84.8% (77.9%–92.3%)	
Tumor location		.116		.039
Infratentorial	60.9% (51.4%–72.2%)		77.7% (69.4%–87.0%)	
Supratentorial	73.8% (61.9%–87.9%)		88.1% (78.8%–98.6%)	
Residual disease after surgery		.025		.007
No residual grade II	84.1% (72.9%–97.0%)		97.6% (93.1%–100.0%)	
No residual grade III	61.9% (50.3%–76.1%)		79.1% (68.6%–91.2%)	
Residual, any grade	53.1% (39.7%–71.0%)		68.6% (55.7%–84.6%)	
Status before radiation therapy		.011		.001
NED	72.1% (63.8%–81.5%)		87.8% (81.5%–94.6%)	
ED	45.3% (30.9%–66.2%)		61.2% (46.5%–80.5%)	
WHO grade		.018		.031
Grade II/classic	75.3% (64.9%–87.3%)		90.5% (83.4%–98.1%)	
Grade III/anaplastic	57.0% (46.7%–69.6%)		73.3% (63.5%–84.6%)	
Ventricular shunt		.349		.019
No	68.9% (59.8%–79.4%)		85.7% (78.4%–93.6%)	
Yes	58.4% (45.5%–74.9%)		72.5% (60.6%–86.6%)	

(95% CI: 10.8%–26.4%) in NED patients and 32.5% (95% CI: 19.5%–54.0%) in still-ED patients ($P = .119$). The corresponding cumulative incidence estimates for distant metastases were 11.1% (95% CI: 6.5%–18.9%) and 22.3% (95% CI: 11.9%–41.9%) ($P = .105$).

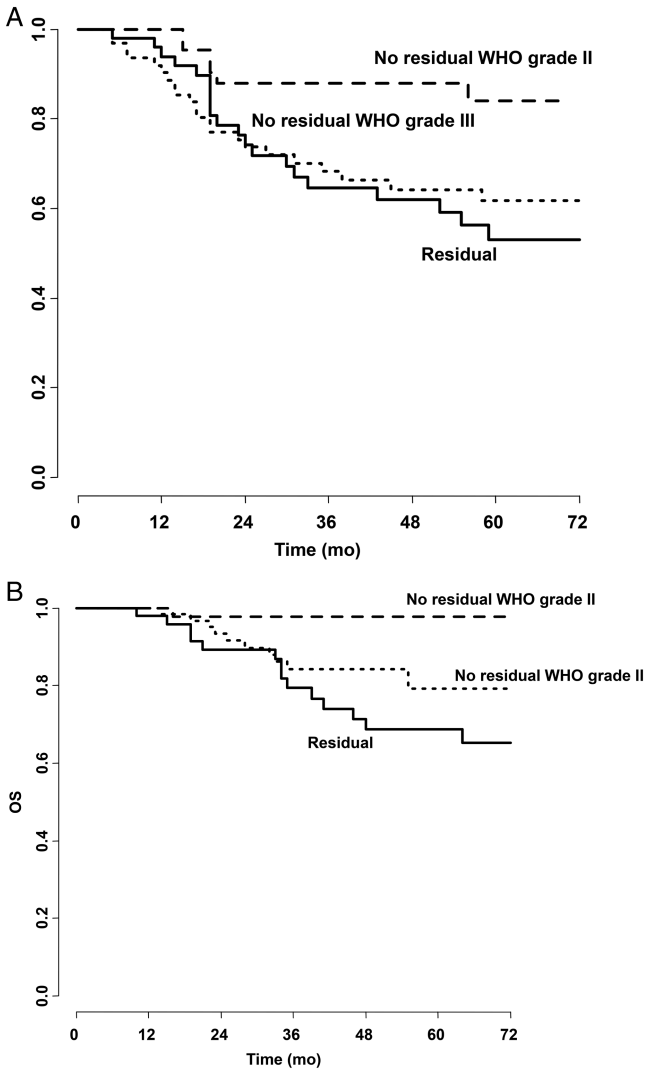

Fig. 3. (A) Kaplan-Meier PFS and (B) OS curves by outcome of first surgery.

When the 2 children who achieved NED status after RT boost were included, there were 23 patients who came to have NED after accrual thanks to multiple surgical procedures and chemotherapy; their prognoses, in terms of both PFS and OS, were much the same as for patients who had NED after a single excision (data not shown).

Among the 40 patients with ED before RT, 24 received the prescribed boost after the standard course of radiation (Fig. 1B): the 5-year estimates for PFS were 58.1% (95% CI: 39.1%–86.4%) for the latter 24 patients, and 43.0% (95% CI: 43.0%–78.6%) for the 16 not given the boost ($P = .344$), while the OS estimates were 68.7% (95% CI: 50.5%–93.4%) versus 50.2% (95% CI: 29.8%–84.6%) ($P = .346$). A WHO grade II classic ependymoma was associated with the best PFS and OS in our sample: the PFS was 75.3% (95% CI: 64.9%–87.3%) and 57.0% (95% CI: 46.7%–69.6%) for grade II and grade III tumor patients, respectively ($P = .018$); and the OS was 90.5% (95% CI: 86.8%–98.1%) and 73.3% (95% CI: 63.5%–84.6%) for grade II and grade III tumor patients, respectively ($P = .031$). The 5-year estimates for local relapse were 17.3% (95% CI: 9.6%–31.0%) in the grade II subgroup and 23.7% (95% CI: 15.6%–35.9%) for patients with ED ($P = .281$). The corresponding cumulative incidence estimates for distant metastases were 7.4% (95% CI: 3.2%–17.5%) and 19.3% (95% CI: 12.1%–30.6%) ($P = .052$). Among the 45 patients aged below 3 years at diagnosis, 16 had grade II tumors. Differently from older children, their PFS and OS were not significantly better than those of children with grade III tumors.

Table 3 shows the results of Cox's multivariate analysis, after selecting prognostic variables with the boosting algorithm. The most influential variables identified by the algorithm were the same on both of the endpoints considered, but tumor grade had the most influence on PFS, followed by gender, NED/ED status before RT, and tumor location; as for OS, the most influential variable was NED/ED status before RT, followed by tumor grade, tumor location, and gender.

Discussion

After the previous Italian experience showing quite a good prognosis for completely resected classic ependymoma,[6]

Table 3. Cox multivariate model analyses of PFS and OS

	PFS		OS	
	Hazard Ratio (CI)	*P* (Wald test)	Hazard Ratio (CI)	*P* (Wald test)
Gender		.063		.251
Male vs female	1.93 (0.96, 3.86)		1.72 (0.68, 4.37)	
Tumor location		.186		.076
Infratentorial vs supratentorial	1.59 (0.80, 3.14)		2.47 (0.91, 6.72)	
Status before radiation therapy		.058		.009
ED vs NED	1.78 (0.98, 3.22)		2.73 (1.28, 5.83)	
WHO grade		.012		.009
Grade III vs II	2.20 (1.19, 4.06)		3.03 (1.31, 6.98)	

efforts were made to improve the strategies for patients with residual disease and for the children whose prognoses remained poor even after a complete resection, that is, those with anaplastic ependymoma.[8,16] Given the renewed interest in RT in recent years, with the advent of more sophisticated RT planning and delivery techniques, allowing a dose reduction to normal tissues and improving clinical results (as described mainly in several publications by T. Merchant and colleagues[7,8]), including a reasonably satisfactory neurocognitive outcome even in the pluri-operated and the youngest children,[17] we applied the same approach to children under 3 years old.

As already reported,[18] second-look surgical procedures were undertaken on a national scale in both the first[6] and this subsequent protocol, achieving a complete resection rate of 75% without significant additional morbidity. This percentage comes very close to the 125/158 cases reported by Merchant in 2009[8] and compares favorably with other experiences,[19–21] raising hopes that a larger percentage of children may be cured. Optimal local tumor control was further pursued by using higher doses of radiation and adding hypofractionated 8-Gy boosts to local residues after surgery. At the time of writing the protocol, and more recently too, some authors were beginning to demonstrate the activity of high-dose local radiation in a few patients with residual or recurrent ependymoma. They reported achieving local control rates as high as 70%, albeit always with short follow-ups and smaller series than the one described here.[22–25] In our series, the 24 patients receiving the RT boost had a 5-year PFS higher than 58% and, for the whole group of patients with ED, it was over 53% compared with 35% in our previous report,[6] 41% for the St Jude series,[8] and <30% with the Children's Cancer Group protocol 9942,[21] which are the largest and most recent series. The difference vis-à-vis the patients achieving a complete resection persisted, however, on univariate analysis for both PFS and OS, and on multivariate analysis for OS.

We added VEC chemotherapy after RT for patients with completely resected anaplastic ependymomas, who had a worse prognosis than those with completely resected classic WHO grade II tumors in our own previous series and in those of others.[8,26] The German Hirntumoren (HIT) trials had obtained the best results in this subset of patients by using adjuvant chemotherapy with sandwich or post-RT courses.[26] Our protocol was not as successful in the 2 subgroups of patients with different tumor grades but the same surgical results: the outcome for the 2 populations remained significantly different. The role of adjuvant chemotherapy in ependymoma will only be definitively ruled out, however, after the completion of the randomized trial by the International Society of Paediatric Oncology (SIOP), which is investigating this issue.

The prognosis for children under 3 years old did not differ significantly, in terms of PFS, from that of older children treated according to the same protocol, but their OS was lower. This may be because the younger children were offered a less aggressive second treatment at relapse, whereas nowadays there is a tendency to perform further excisions and to repeat irradiation.[27–29] The use of chemotherapy-only protocols in young patients achieved very low PFS and high re-treatment rates,[19,30,31] and—barring exceptional cases—it should be abandoned, especially now that experiences of good neurofunctional outcomes after first-line irradiation have been confirmed.[8]

The better prognosis for female patients had already been noted[8,32] and correlated with a lower local relapse rate, but not with any other significant prognostic factors. A better prognosis for female patients had already been described in high-grade glioma.[33] To our knowledge, this rather peculiar difference in outcome has yet to be studied, but a correlation with still hidden biological differences between the genders has been hypothesized.

As in our previous protocol and subsequent papers,[6,20,34] we again found a strong prognostic impact of tumor grade, even on multivariate analysis. Despite inconsistency in other national series, the prognostic significance of tumor grade in our previous series was also confirmed in a multinational pathological review.[16] It is now clear that the impact of histology can emerge only if well-characterized clinical cohorts of sufficient size are selected, and relevant and reproducible histological criteria are adopted.[16,35,36] In particular, given the efforts to provide optimal adjuvant radiotherapy, it is tempting to speculate that the impact of histology detected in Italian series may relate to different radiosensitivity of WHO grade II versus grade III ependymoma.

In conclusion, in a national multi-institutional setting, and in the largest sample of ependymoma patients to be included in a prospective trial to date, we have demonstrated the feasibility of multiple surgical procedures followed by a novel radiotherapeutic approach, with a trend to outcome amelioration in children with residual disease, a patient group that carries a poor prognosis. A limitation of this study is the lack of complete observations on neurocognitive outcome, even if some evaluations have been published.[37] The recently opened SIOP trial will try, as did the previously open COG-ACNS0831 trial, to shed light on the usefulness of adjuvant chemotherapy in patients with completely resected tumors. The significance of factors repeatedly shown to be prognostic will be further analyzed in the light of genomic and molecular studies on the same series of patients in an effort to elucidate how they may be subgrouped differently, also with a view to sparing certain patient categories from adjuvant treatment.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Journal* online (http://neuro-oncology.oxfordjournals.org/).

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