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Intracranial ependymoma

Patterns of failure after radiotherapy for pediatric patients with intracranial ependymoma

Fatima Tensaouti [a,*], Anne Ducassou [b], Léonor Chaltiel [c], Stéphanie Bolle [d], Xavier Muracciole [e], Bernard Coche-Dequeant [f], Claire Alapetite [g], Valérie Bernier [h], Line Claude [i], Stéphane Supiot [j], Aymeri Huchet [k], Christine Kerr [l], Elisabeth le Prisé [m], Anne Laprie [a,b], On behalf of the radiotherapy committee of the French Society for Childhood Cancer (SFCE)

[a] *Toulouse NeuroImaging Center, Université de Toulouse, Inserm, UPS;* [b] *Department of Radiation Oncology;* [c] *Department of Biostatistics, Institut Claudius Regaud, Institut Universitaire du Cancer de Toulouse – Oncopole;* [d] *Department of Radiation Oncology, Institut Gustave Roussy, Paris;* [e] *Department of Radiation Oncology, CHU La Timone, Marseille;* [f] *Department of Radiation Oncology, Centre Oscar Lambret, Lille;* [g] *Department of Radiation Oncology, Institut Curie, Paris;* [h] *Department of Radiation Oncology, Centre Alexis Vautrin, Vandoeuvre, Nancy;* [i] *Department of Radiation Oncology, Centre Léon Bérard, Lyon;* [j] *Department of Radiation Oncology, Institut de cancérologie de l'ouest, Nantes;* [k] *Department of Radiation Oncology, CHU Bordeaux;* [l] *Department of Radiation Oncology, Institut régional du Cancer Montpellier-Val d'Aurelle; and* [m] *Department of Radiation Oncology, Centre Eugène Marquis, Rennes, France*

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ABSTRACT

Purpose: To investigate the patterns of failure after radiotherapy for pediatric intracranial ependymoma and their correlation with dose parameters.
Methods: Between 2000 and 2013, 206 patients were treated in France. MRI scans at relapse were registered to the original planning CTs for topographic analysis of failure patterns. To compare relapse patients (RP) with non relapse patients (NRP), several dose parameters were derived from dose volume histograms.
Results: Over a median follow-up of 53.8 months, 84 patients presented with relapse. Topographic analysis showed 50 patients with local relapse in the radiation field, 6 in the edge of field, 6 locoregional outside the field, 10 in the spine, 5 supratentorial and 7 local and distant. The median coverage, target coverage and homogeneity indices did not differ significantly between RP and NRP. The median volume of in-field relapse was 1.25 cc [0.11, 27], with a median dose of 57.83 Gy [50.04, 61.69].
Conclusions: Local relapse in the tumor bed and the higher dose regions was the predominant pattern of failure. Improving coverage of the target volume and increasing the dose to the high radioresistant regions, taking into consideration other clinical and biological pronostic factors, may be an effective way of reducing local failures.
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Ependymomas (70% infratentorial and 30% supratentorial) are the third most common type of brain tumor in children [1]. They arise from the cells lining the ventricles and central canal within the spinal cord.

The first step of ependymoma treatment is maximum safe resection, to remove as much of the tumor as possible. Adjuvant radiation therapy is recommended for older children, even in the case of gross total resection [1–4]. Chemotherapy may be used to delay radiation in infants and very young children.

Until the 1990s, craniospinal irradiation was used in patients with high-grade and infratentorial tumors [5,6], but research has shown that local-field treatment can be used without compromising local control and outcome of ependymomas [7,8]. Intensity-modulated radiation therapy (IMRT) and proton therapy have thus been used in the treatment of ependymoma in an effort to spare surrounding normal tissues from high doses of radiation and improve local control [9,10].

The high relapse rate of these tumors prompted us to investigate patterns of relapse in a large series of patients treated with different radiation therapy techniques, and their correlation with dose parameters.

Methods

Patient selection

Two hundred and two patients with intracranial ependymomas diagnosed between 2000 and 2013 were included in a large retrospective French study approved by the national French ethics

* Corresponding author at: CHU Purpan, Pavillon Baudot, Place du Dr. Joseph Baylac, 31024 Toulouse Cedex 3, France.
E-mail addresses: fatima.tensaouti@inserm.fr, tensaouti.f@chu-toulouse.fr (F. Tensaouti).

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committee. Inclusion criteria included presence of histologically proven, localized intracranial ependymoma, age at diagnosis ⩽25 years, adjuvant radiotherapy (RT) treatment, and sufficient follow up after RT.

Patients' dosimetry plans were retrieved, along with the clinical and imaging data, and all the pathological reports were carefully reviewed. Tumor grade was determined using the standard WHO criteria. Fig. 1 provides a patient inclusion chart with details of the data available in DICOM format.

Identification and analysis of relapse

The T1-weighted (T1-WI) magnetic resonance imaging (MRI) sequences obtained at relapse without and with contrast enhancement (CE) were co-registered with the original planning CT for topographic analysis of the relapse, to determine whether the local recurrence was in the primary tumor bed or not. Radiation fields were also reviewed to determine whether the recurrence was inside or outside the RT field.

Evaluation of the plans

Clinical target volume (CTV) and planning target volume (PTV) margins were extracted, and several International Commission on Radiation Units and Measurements (ICRU) indices [10], including homogeneity (HI), coverage (CO), and target coverage (TCO), were derived from the dose volume histograms by analyzing the treatment plans of patients with and without relapse after RT.

Each plan was transferred to Artiview software v2.8 (Aquilab SAS, Lille, France). Plan quality was assessed according to the criteria of the ICRU 83 report: near-minimal ($D_{98\%}$), near-maximal ($D_{2\%}$) and median ($D_{50\%}$) doses, and HI [10]. Other parameters we analyzed included mean dose (D_{mean}), CO and TCO [11]. All evaluation indices were based on volume definition, described as follows:

$$\mathrm{HI} = \frac{D_{2\%} - D_{98\%}}{D_{50\%}} \text{ optimum} : 0$$

$$\mathrm{CO} = \frac{D_{\mathrm{near\_min}}}{D_R} \text{ optimum} : 1$$

where $D_{\mathrm{near\_min}}$ is the near minimum dose in the target, and D_R the reference dose.

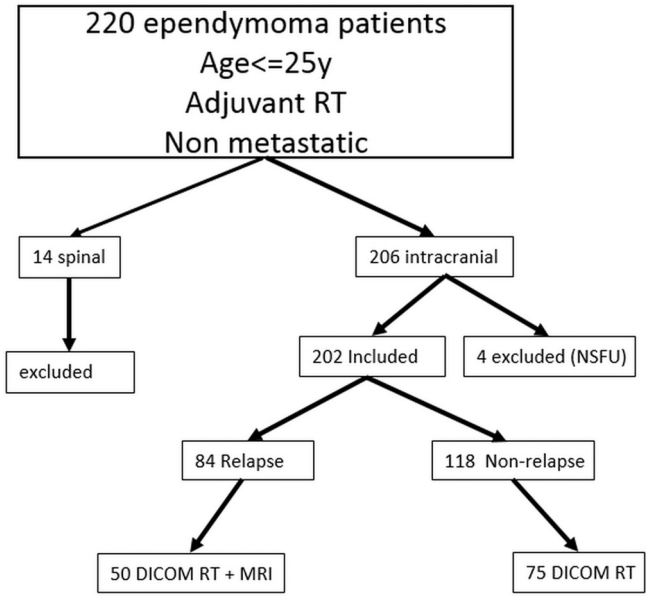

Fig. 1. Patient inclusion chart. NSFU = not sufficient follow up.

$$\mathrm{TCO} = 100 \times \frac{V_{S,R}}{V_S} \text{ optimum} : 100\%$$

where $V_{S,R}$ is the target volume covered by the reference isodose.

Evaluation of the patterns of relapse

There were performed in patients with initial treatment DICOM RT data available and available MR sequences at relapse.

Statistical analysis

Data were described by the usual statistics. Qualitative variables were summarized as frequencies and percentages for each category, and continuous variables as medians and ranges. Differences between groups were assessed using Chi-square or Fisher's exact test for qualitative variables and Mann–Whitney test for continuous variables.

All survival times were calculated from the date when RT began. Overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan–Meier method, using the following first-event definitions: local relapse, distant relapse or death for disease-free survival (DFS), and death for OS. Patients relapse free or alive were censored at the time of their last follow-up. Univariate analyses were performed using the log-rank test for categorical variables.

The competing risks method was used to analyze the pattern of recurrence for locoregional and distant metastatic events. Comparisons of cumulative incidences between groups were performed using Gray's test.

All reported *p*-values were two-sided. For all statistical tests, differences were considered significant at the 5% level. Statistical analyses were performed using the STATA 13.0 software (StataCorp LP, College Station, TX).

Results

With a median follow-up among survivors of 53.8 months (95% CI [47.0, 63.5]) and an OS rate of 71.4% (95% CI [63.1, 78.2]) at 5 years, 84 (41.6%) patients presented with relapse. The DFS rate was 50.4% [42.2, 58.0] at 5 years. 35% of 202 patients included in this study had received chemotherapy. Thirty-eight patients presenting with relapse or death had received chemotherapy, in 97.4% it was prior to Radiotherapy. Topographic analysis of relapse showed that 50 (59.5%) patients had a local relapse in the radiation field, six (7.1%) in the edge of field, six (7.1%) locoregional outside the field, 10 (11.9%) in the spine, five (6.0%) supratentorial and seven (8. 3%) local and distant. The interval of margin was [0.5–2] for CTV (median = 1 cm) and [0.3–2.5] for PTV (median = 0.5 cm).

Table 1 describes the characteristics of the group of patients with relapse and the one without relapse.

Regarding local failures, we could verify the treatment plans of 33 RP, whose MRI relapse exams and initial treatment DICOM RT data were available. Six (18.2%) of them had undergone subtotal resection, and 9% had a Grade II tumor. The median dose was 59.4 Gy [50.4–59.4].

Sixteen of these 33 RP had been treated with 3D conformal radiation therapy (CRT-3D; 48.5%), 14 (42.4%) with IMRT (5 arctherapy, 7 IMRT, 2 tomotherapy) and 5 with proton therapy (15%).

Figs. 2 and 3 provide examples of two patients who presented with local relapse 15 months (Fig. 2) and 12 months (Fig. 3) after gross total resection and RT, and were classified as having a tumor bed failure. Analysis of the local failure showed that all relapses were in the higher dose regions of the radiation field. Median volume of relapse was 1.25 cc [0.11–27], and these volumes of relapse received a median dose of 57.8 Gy [50.0–61.7]. Two of the three patients whose PTV was defined in the relapse site before RT, relapsed in the initial tumor bed, which was found to have not