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Original article

Imaging biomarkers of outcome after radiotherapy for pediatric ependymoma

Fatima Tensaouti [a,*], Anne Ducassou [b], Léonor Chaltiel [c], Annick Sevely [d], Stéphanie Bolle [e], Laetitia Padovani [f], Anais Jouin [g], Claire Alapetite [h], Stéphane Supiot [i], Aymeri Huchet [j], Valérie Bernier [k], Line Claude [l], Christine Kerr [m], Elisabeth Le Prisé [n], Anne-Isabelle Bertozzi-Salamon [o], Samuel Liceaga [a], Jean Albert Lotterie [p,a], Patrice Péran [a], Anne Laprie [a,b], On behalf of the radiotherapy committee of the French Society for Childhood Cancer (SFCE)

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

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ABSTRACT

Background and purpose: Ependymoma is the third most common brain tumor in children. Radiation therapy (RT) is systematically administered after maximum surgical resection, utilizing recent advances in radiation delivery. Imaging can make a significant contribution to improving treatment outcome. This prompted us to look for significant preoperative and postoperative imaging markers for survival.

Material and methods: We undertook a national retrospective review of 121 patients who had undergone resection followed by RT. Preoperative tumor volumes on T1 and FLAIR images were delineated, together with postoperative hyperintense volumes on FLAIR images. Overall survival (OS) and disease-free survival (DFS) analyses included clinical data and volumes extracted from images.

Results: After a median follow-up of 38.5 months, 80.2% of patients were alive, but 39.7% had experienced at least one event. Statistically significant differences between patients with and without postoperative FLAIR abnormalities were found for both DFS (71.9% vs. 40.3%; $p = 0.006$) and OS (93.7% vs. 72.4%; $p = 0.023$) in the univariate analyses, and for OS ($p = 0.049$) in the multivariate analyses.

Conclusions: Postoperative FLAIR hyperintensities are a negative prognostic factor for intracranial ependymoma and may be a surrogate for residual disease. They could therefore prove helpful in patients' surgical and radiotherapeutic management.

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Ependymoma is the third most common type of brain tumor in children [1]. Radiotherapy (RT) is systematically delivered after maximum surgical resection, which can include second- and even third-look surgery. Chemotherapy is currently only used to delay radiation in infants and very young children [2, 1, 3], but open children's oncology group trials have randomized patients to better understand the potential benefits of chemotherapy [4, 5], and in the ongoing European SIOP trial (NCT00004224), post-RT maintenance chemotherapy is randomized in patients with residual disease. Ependymoma is treated in a curative setting and benefits from the most recent advances in RT techniques, such as IMRT [6], proton therapy [7], and additional boosts of stereotactic fractionated RT in the case of unresectable residual tumor [8]. Ensuring accurate RT targeting of residual tumor and optimizing RT ballistics and dose are both heavily reliant on imaging quality.

MRI is the mainstay technique for assessing intracranial ependymoma. It can delineate both the extent of the tumor and its growth pattern, owing to its soft-tissue contrast and the complementary information yielded by T1- and T2/fluid-attenuated inversion recovery (FLAIR)-weighted sequences.

The appearance of intracranial ependymomas has been described in detail in the literature [9]. The lesions are character-

* 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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ized by uneven and heterogeneous enhancement and by a constant FLAIR/T2 hypersignal. However, the role of imaging characteristics in predicting the survival of patients with intracranial ependymomas has only been reported in a few studies [10], including a recent one, conducted by our team, that focused on diffusion and perfusion MRI in a series of 60 patients [11].

In a recent prospective trial, gross residual tumor was assessed on postoperative MRI, on the sequence where it could best be appreciated, judging from its preoperative MRI features: T1 sequence with gadolinium enhancement, T2, or (most frequently) FLAIR [8].

Extent of resection (ER) is still used as a measure of surgical success in all brain tumor [12], but does not provide a direct indication of the residual tumor burden that must be resolved by RT and chemotherapy treatment. The biological impact of ER depends on preoperative tumor volume, as an almost complete resection of a large tumor may leave behind a larger tumor mass than a subtotal resection of a small tumor. Although there has been some research on gliomas [13], no study has yet assessed the relationship between postoperative FLAIR volumes in ependymoma, which may include infiltrating tumor cells, and clinical outcomes. Furthermore, no study has yet reported an analysis combining clinical, imaging and biological data to identify the most relevant biomarker for ependymoma. There is an urgent need to combine efforts to understand the response of this tumor type to treatment and avoid relapses, 70% of which occur in the tumor bed [6, 14].

We hypothesized that residual FLAIR abnormalities are a surrogate for residual tumor, and can thus serve as markers for outcome after RT.

Material and methods

Patient selection

A total of 202 patients who had been diagnosed with intracranial ependymomas between 2000 and 2013 were included in the Pediatric Ependymoma Photons, Protons and Imaging (PEPPI) study [11], a large retrospective French study approved by the national French ethics committee and the French data protection authority (CNIL) [6]. Inclusion criteria included the presence of histologically proven, localized, intracranial ependymoma, age at diagnosis ≤25 years, and adjuvant RT treatment. We retrieved the patients' clinical and imaging data, and carefully reviewed all the pathological reports. Tumor grade was determined using standard WHO criteria. Where the presence or absence of anaplasia was not clearly stated, a central review was carried out. A total of 121 patients had MRI imaging available that included T1-, post-contrast (PC)-T1- and FLAIR-weighted imaging (WI). None of these patients had received RT or chemotherapy beforehand. All patients underwent image acquisition before RT and less than 48 h after surgery. Table 1 summarizes the characteristics of the patients included in this study.

Table 1
Patients' characteristics.

Variable	Patients (N = 121)
Age (years)	
Median (range)	4 (1.0–22.0)
Sex	
Male	71 (58.7%)
Female	50 (41.3%)
Tumor location	
Infratentorial	85 (70.2%)
Supratentorial	36 (29.8%)
Tumor grade	
II	46 (38.0%)
III	75 (62.0%)
Resection	
Subtotal resection (STR)	18 (14.9%)
Gross total resection (GTR)	103 (85.1%)
Dose (Gy)	
≤54	43 (35.5%)
>54	78 (64.5%)
Chemotherapy	
Yes	36 (29.8%)
No	85 (70.2%)
Patterns of failure	
No failure	73 (60.3%)
Local failure	30 (24.8%)
Distant failure	14 (11.6%)
Local and distant failure	4 (3.3%)

Data imaging

Imaging was performed with different (GE/Philips/Siemens) 1.5T (79.62% of the cohort) and 3T scanners. Quantitative volumetric analysis of pre- and postoperative MR data was carried out on T1-, PC-T1- and T2/FLAIR-WI images.

Data processing and imaging characteristics

Preoperative tumor volume (PRTV) on PC-T1-WI, PRTV on FLAIR-WI, postoperative hyperintense volume on FLAIR-WI (POHVF), and postoperative contrast enhancement volume on PC-T1 imaging were manually delineated by a radiation oncologist specializing in pediatrics (AD) and double-checked by a team composed of a radiation oncologist specializing in pediatrics (AL) and a pediatric neuroradiologist (AS) (Fig. 1). All the FLAIR imaging data were rigidly coregistered to the PC-T1-WI using mutual information as an objective function and simplex as an optimizer [15]. The FLAIR imaging was coregistrered to the post-contrast T1WI in order to precisely locate the residue and correct some spatiotemporal differences between these two sequences. This allowed us to avoid contouring nonparenchymal FLAIR hyperintensities and define other components (e.g., blood) inside the cavity resection. All automatic coregistrations were visually verified and validated. Coregistration and volume delineation were performed with Sisyphe, an in-house neuroimaging software toolbox [16]. Postoperative tumor volume on FLAIR-WI was scored as absent or present.

Statistical analysis

Data were subjected to the usual statistical analyses. Variables included tumor volume extracted from the MRI data, sex, ER (gross total resection (GTR) vs. subtotal resection (STR)), histological grading, tumor location (infratentorial vs. supratentorial) and RT dose (≤54 Gy vs. >54 Gy).

Qualitative variables were summarized as frequencies and percentages for each category, and continuous variables as medians and ranges.

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, with the following first-event definitions: local relapse, distant relapse, or death for DFS; and death for OS. Relapse was defined as *local* if a new contrast enhancement lay within the operative tumor site (bed tumor). If not, it was defined as *distant*.

Patients who did not present any event were right-censored at the time of their final follow-up. Univariate analyses were performed using the log-rank test for categorical variables.

Cox proportional hazards models were used for multivariate analyses and expressed as hazard ratios (HRs) with 95% confidence

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