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Original article

Neuroendocrine late effects after tailored photon radiotherapy for children with low grade gliomas: Long term correlation with tumour and treatment parameters

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ABSTRACT

Purpose: To evaluate neuroendocrine late effects in paediatric patients with low grade glioma (LGG) who underwent radiotherapy.

Methods and material: We performed a retrospective evaluation of 40 children with LGG treated from July 2002 to January 2015 with external radiotherapy. Tumour locations were cerebral hemisphere ($n = 2$); posterior fossa ($n = 15$); hypothalamic–pituitary axis (HPA, $n = 15$); spine ($n = 5$). Three patients presented a diffuse disease. We looked for a correlation between endocrine toxicity and tumour and treatment parameters. The impact of some clinical and demographic factors on endocrinal and neuro toxicity was evaluated using the log-rank test.

Results: The median follow-up was 52 months (range: 2–151). Median age at irradiation was 6. The dose to the HPA was significantly associated with endocrine toxicity (P value = 0.0190). Patients who received chemotherapy before radiotherapy and younger patients, showed worse performance status and lower IQ. The 5-year overall survival (OS) and progression free survival (PFS) rates were 94% and 73.7%, respectively.

Conclusion: Radiotherapy showed excellent OS and PFS rates and acceptable late neuroendocrine toxicity profile in this population of LGG patients treated over a period of 13 years. In our experience, the dose to the HPA was predictive of the risk of late endocrine toxicity.

Low grade gliomas (LGG) are relatively slow-growing primary brain tumours with a very heterogeneous clinical behaviour [1,2], they are the most common brain tumours in childhood (up to 35% of central nervous system malignancies in children) [3]. Surgery remains the gold standard in the treatment of this disease and radical resection is the most important prognostic factor to obtain a durable progression free survival (PFS) and overall survival (OS) [4]. Optimal therapeutic strategy for patients presenting non-resectable tumours or those that underwent non-radical resection remains a controversial issue. Indeed, the concerns regarding the toxicity of therapy often outweigh the benefits of delaying tumour progression. Chemotherapy is recommended for young children to delay irradiation in order to minimize risk for late effects [5]. When combined with chemotherapy, radiotherapy (RT) obtains very interesting 5-year PFS rates of up to more than 80% and durable disease control in a significant proportion of paediatric cases [6–8]. This effectiveness should be evaluated looking also at the risk of late toxicity effects, such as neurocognitive or neuroendocrine deficits and vasculopathies. This is likely the result of a complex interaction between the tumour, individual patients' characteristics and treatment features [9]. The length of the follow up after the treatment also influences the results [9–11]. Aim of this study was to evaluate the neuroendocrine toxicities of paediatric patients with LGG who underwent standard photon radiotherapy delivered with conformal radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT). We also analysed and reported whether the risk of toxicity was related to some clinical of therapeutic features.

Materials and methods

Population

We retrospectively evaluated all the children consecutively treated in our department with a diagnosis of LGG. All histologic

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subtypes were included. All patients having received a surgery and/or chemotherapy before RT have been retrospectively analysed for OS and PFS. Patients who presented spinal disease or with evidence of neuro-endocrine deficiency prior RT have been excluded in the analysis of neuro-endocrinal toxicity. For each patient, both parents signed informed consent.

Radiotherapy technique and volumes

All patients received 3DCRT or IMRT to their primary tumour. The RT technique was chosen according to the tumour site: IMRT was delivered if the tumour was very near to organs at risk (OARs), while 3DCRT was preferred in all other localizations to reduce integral low dose. 3DCRT was delivered using a 6–15 MV linear accelerator (Varian Clinac 2100 CD) equipped with Multileaf collimator and on-board Imaging and IMRT using helical tomotherapy (Hi-ART Accuray Incorporated, Sunnyvale, Ca, USA). Patients were immobilized with a 3-point thermoplastic mask (Orfit industries, Jericko, NY, USA). A simulation CT scan with 2.5 mm slices was obtained and then it was co-registered with magnetic resonance imaging (MRI) using a rigid co-registration protocol, in order to delineate the target volume and OARs. Target volume definitions followed ICRU Report 62 recommendations. The gross tumour volume (GTV) included the tumour bed +/− residual tumour; clinical target volume (CTV) included GTV with an added margin of 0.5 mm; the planning target volume (PTV) included CTV surrounded by an additional symmetric margin of 0.3 mm. Patients with leptomeningeal dissemination received a cranio-spinal irradiation (CSI). RT dose was prescribed according to tumour site: gliomas located next to brainstem, hypothalamic–pituitary axis (HPA), cerebral hemisphere received 54 Gy (2 Gy/fraction), while those located at the spinal level received 50 Gy (2 Gy/fraction). Patients presenting a diffuse disease received 36 Gy (2 Gy/fraction) on craniospinal axis + a boost of 13 Gy on the LGG bed. Cumulative and differential dose–volume histograms were calculated for OARs like pituitary gland, left and right lobe temporal, left and right hippocampus (HPC, considered as a single OAR), and total brain. The HPC was manually contoured in according to the method of Gondi et al. Constraints for the OARs are reported in Table 1.

Table 1
Dose constraints of OARs recommended for radiotherapy planning.

OARs	Dose constraints
Optic chiasm & optic pathways	Dmax < 54 Gy V60 < 1%
Lobe temporal	Dmax < 60 Gy Dmean < 16 Gy
Hippocampus	D40 $\leq$ 7.3 Gy
Hypothalamus	Dmax $\leq$ 16 Gy
Pituitary gland	Dmax $\leq$ 54 Gy LH-FSH < 40 Gy TSH < 40 Gy ADH < 40 Gy PRL < 40 Gy GH < 25 Gy
Spine	Dmax < 46 Gy
Brain Stem	Dmax < 54 Gy

Endpoints

The endocrine and neurocognitive toxicities were the primary outcomes. The endocrine toxicity was evaluated as presence/absent and by lowering of specific neuro-hormone values. Neurotoxicity was evaluated using the intelligence quotient (IQ) values.

Toxicity evaluation

All patients received at Pediatric Neuro-Oncology Department regular follow-up evaluations for cerebrovascular disease, endocrinopathy, and neurocognitive disorders. Clinical evaluations and tests were performed by specialists before RT and every 6 months after the end of the RT.

Endocrine toxicity

We evaluated the HPA function at baseline and during the follow-up. Test performed to evaluated endocrine deficiency were summarized in Supplementary material.

Patients with intracranial tumour were included in the dose–response analysis of the incidence of overall endocrinopathy. Patients were categorized in 3 groups according to dose received by HPA as follows: high, intermediate and low risk if mean dose to HPA was >40 Gy, between 12 and 40 Gy and <12 Gy, respectively. The incidence of endocrinopathy was also stratified according to tumour location (HPA *versus* other) and median age (>6 years *versus* $\leq$6 years).

Neurocognitive toxicity

Neurocognitive outcomes were assessed before RT and during the follow-up using a battery of neurocognitive tests, differentiated for age and including an IQ and Wechsler Individual Achievement Test reading and spelling in order to assess global intellectual functioning, memory, social–emotional adjustment.

Statistical analysis

Continuous variables are given as means and standard deviations, whereas categorical variables as number and/or percentage of subjects.

Endocrine toxicity baseline differences among the HPA dose, the tumour location, the chemotherapy and the age were tested using Fisher's Exact. The impact of the HPA dose, the tumour location, the chemotherapy and the age on the risk to have endocrinal toxicity was assessed by the log-rank test and then, the Kaplan–Meier curves were depicted. Moreover, the impact of the mentioned covariates on the 4 specific toxicities (growth hormone – GH, adrenocorticotropic hormone – ACTH, thyroid-stimulating hormone – TSH, gonadotropins release hormone – GnRH), were also evaluated using again the log-rank test. The association between HPA dose and tumour location was evaluated using Fisher's Exact test. Subgroup analysis was performed comparing endocrine toxicity for tumour location. The rationale for this subgroup analysis was based on clinical evidence that tumour location is strictly linked to endocrine toxicity.

To investigate the association of the neurotoxicity with the demographic and clinical characteristics a univariate analysis was performed using the linear regression model and the Likelihood Ratio test was used as a test of statistical significance.

A Kaplan–Meier analysis with log-rank significance testing was performed to depict OS and PFS among groups. Data from patients who were lost to follow-up were censored at the time of the last available appointment. Owing to the small sample size of this study multivariate analysis was not performed for any outcomes.

Adjustments for multiple testing were done using the Bonferroni testing procedure. Differences, with a P value less than 0.05, were selected as significant and data were acquired and analysed in R v3.4.0 software environment [12]. Finally, to determine whether the study had adequate power a post-hoc power analysis was computed using cox regression where endocrine toxicity and continuous HPA values were the dependent and independent variable, respectively.

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