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Original Article

Assessment of Clinical and Neurological Alterations Before Radiation Therapy in Children With Malignant Brain Tumours

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Abstract

Aim: Young patients with a brain tumour (BT) show neurocognitive alterations as both consequences of the tumour and of the treatments received. In this paper we present the basal analysis of a patient's series, correlating tumour localisation, symptoms, neurological/endocrinological impairments, surgery/ies ± chemotherapy, and cognitive assessments at the time of enrolment before focal-radiotherapy (RT).

Methods: Sixty-six children eligible for focal RT underwent a neurocognitive assessment. The demographic, pathological and clinical variables with MRI morphological scans, where different kinds of damage scores were defined, were analysed.

Results: The patientssmedian age was 8 years; the most frequent tumour was ependymoma (41%), and supratentorial (71%) was the prevalent site. All but 2 children (with germ cell tumours), had received surgery and 32 chemotherapy courses before irradiation. Ad-hoc scores for neurological deficits, endocrine alterations and structural abnormalities were created and applied. Patients with infratentorial tumours locations showed the highest score of neurological damage while endocrine alterations were more serious in patients with craniopharyngioma and germ cell tumours of the sellar region and ventricular system. The median number of damaged areas was equal to 2 for each child. Neurological deficit scores were not associated with hydrocephalus and surgery/ies received, unlike endocrine deficits. Tumour site, length of symptoms and endocrine alterations were found to be associated with cognitive impairment.

Conclusion: The pre-radiation evaluations highlighted that damages develop already prior to focal-RT. Specific scores may quantify damages that are generated by multiple factors that need to be considered over time after irradiation.

Key words: Brain tumours; children; neuro-cognitive disabilities; neurosurgery; radiotherapy

Introduction

A wide range of risk factors associated with late-onset neurocognitive sequelae in survivors of childhood brain tumours (BTs) has been highlighted, including the tumour itself and its effects on surrounding tissues through infiltration and pressure, which may lead to hydrocephalus [1–6]. Additional factors include younger age at diagnosis, extent, number and

Abbreviations: BT, brain tumours; RT, radiotherapy; MRI, magnetic resonance imaging; FSIQ, full scale intelligence quotient; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; PSI, processing speed index; WM, working memory; L, left hemisphere; R, right hemisphere; IQR, interquartile range.

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complications of surgical resections, duration of follow-up, and radiation therapy (RT) treatments, particularly the field sizes and doses used [7,8]. More recently, outcome has also been correlated with returns to school, rehabilitation, and sport activities [9–11]. RT is an indispensable tool for treatment of the vast majority of paediatric BT, and radiation-induced brain injuries have been described more frequently in the last twenty years due to the efficacy of treatment protocols with improvement in life expectancy [12].

In order to assess the unwanted effects of RT over time, a longitudinal study was conducted focusing on its specific role, if possible distinguishing its effects from those caused by the tumour itself, surgery/ies, chemotherapy and any other contributor to the final results.

A complete picture of the patients' basal situation could in fact contribute to clarifying the role of each source of damage and to studying their inter-relationship. This effort will allow an improved understanding of the future results in longitudinal analyses.

Specific indicators of deficits according to different clinical aspects, morphological, neurological and endocrinological, were created and standardised to introduce sharable scores in paediatric oncology literature.

It is extremely well known in fact how endocrine and metabolic disabilities can be acquired and evolve during time after adjuvant treatments [13], with nearly 50% of patients suffering from one or several abnormal hormonal secretion and function, but less is reported about a patient's situation at diagnosis or after surgery ± chemotherapy alone [14,15].

The location of the tumour and the extent of the surgical cavity [16] are other risk factors for neurocognitive decline and neuropsychological morbidity, as damage to different parts of the brain is associated with diverse types and levels of cognitive impairment [2–6,17].

Moreover, children with BT have an increased risk of sensorineural damage, including compromised visual, auditory, sensory and motor function, as well as seizures, correlated to injuries from the tumour [18]. Tumours arising in the cerebral hemispheres may result in a wide range of higher-order cognitive difficulties, while infratentorial tumours have been associated with procedural memory and motor deficits [19]. The cerebellum is, however, not only constituted by wide associative areas mainly involved in motor coordination and execution, but is an integrative centre for higher emotional and cognitive functions, including language, also in the developing brain [20]. The bilateral cerebellar participation in the linguistic system has been confirmed by studies on children with cerebellar tumours (either side), showing impairment in several cognitive functions such as verbal fluency and expressive language [21].

Magnetic resonance imaging (MRI) was only used to determine structural abnormalities and abnormal signal intensities in the tumour regions in a small number of papers [22,23], but a more precise tumour region description has not yet consistently been found to predict neuropsychological outcomes.

Shortman *et al.* [24] suggested that hydrocephalus is associated with early cognitive impairment, a finding in keeping with data from recent long-term follow-up studies [25–27]. A "basal" neurocognitive evaluation before the commencement of focal RT, but after surgery, when performed, may be a starting point for distinguishing subsequent abnormalities due to RT and for highlighting original brain disabilities as a result of the tumour itself, surgery, chemotherapy, and child developmental processes.

This work reports on: i) the identification of the existing prefocal RT alterations (neurological, endocrine, morphological, and neurocognitive) and their relationship with the patients' demographical and medical history; ii) the relationship between neurocognitive outcome and morphological alterations of different brain areas. The aim was to highlight those areas more likely to play a crucial role in cognitive problems after having taken into account the pre-existing damage and individual variability. We initially developed three distinct ad-hoc scores—targeting endocrine, neurological, and morphological alterations—that can be quickly adopted and validated in future cohort descriptions.

Materials and Methods

Sixty-six consecutive children with BT who were candidates to receive focal RT (including whole ventricular system when indicated) in our Institute were enrolled between 2014 and 2021. The institutional Review Board of Fondazione IRCCS Istituto Nazionale dei Tumori approved the study on December 17, 2017, and written consents were obtained from all participants and their legal guardians. Patients with high-grade glioma were excluded from this protocol, as their poor prognosis would have hindered the possibility of subsequent assessments. Before RT (Interquartile range (IQR): 23 days before or 8 days after the start of RT), each patient underwent a neurocognitive assessment based on standardised age-appropriate tests (Supplemental Table S1). A database including demographical and clinical variables, gender, age at the time of diagnosis, at the time of RT, and at the time of neurocognitive testing, surgery, hydrocephalus, duration of symptoms, intensive rehabilitation if performed, MRI diffusion tensor imaging (DTI) exam, tumour site, histology, fields and total RT prescribed doses, chemotherapy regimen containing ± neurotoxic drugs, endocrine disabilities, and neurological deficits, was implemented. Specifically, information about any neurological deficits and any endocrine alterations at baseline such as hypocorticism, hypothyroidism, growth hormone (GH) deficiency, panhypopituitarism, electrolyte alterations, polyuria, polydipsia and premature puberty, metabolic, alterations, and hyponutrition or obesity was collected for each patient.

In evaluating the chemotherapy regimens administered prior to radiation therapy, we classified platinum derivatives, vincristine, methotrexate, bevacizumab, and high-dose thiotepa as neurotoxic agents, as opposed to etoposide

and temozolomide, which were considered to have a lower neurotoxic potential [28].

MRI data were acquired on a Philips Achieva 3T with a 32-channel head coil. MRI scans included T1- and T2-weighted images. Starting from information collected in the dataset or MRI morphological scans, ad-hoc original scores were created in order to better describe each patient's status regarding neurological deficits, endocrine, and structural alterations.

Batteries of tests were administered to the children by two trained pediatric clinical psychologists (MCO and PG). Depending on the children's age, a different number of completed tests could be administered to patients (see Supplemental material). Neurocognitive assessments were based on standardised tests with well-defined means and standard deviations indicating the level of impairment and enabling a comparison of performances at different ages. In accordance with the standardised scores present in each test manual, raw scores were corrected according to patient age and classified in a binary outcome ("impaired"/"non-impaired") for the purposes of the analyses. An additional dataset was created with the values obtained as the outcome of each neurocognitive test submitted to the patients. Statistical methods are reported in the Supplemental material.

Results

Patients Characteristics

The patients' clinical status is shown in Table 1. Of the 66 patients, 42% were female, the median age was 8.4 years (IQR: 4.8–13.5 years), 27% were under 5 years old. The IQR of patients' symptoms duration ranged from 2 to 12 months, with a median of 3 months.

The longest median time to diagnosis was observed for suprasellar tumours (30 months, IQR 12–60) compared to tumours originating in the supratentorial ventricular system (12 months, IQR 2–35), and temporal lobes or pineal regions (2 months, IQR 1–2). The longest median time to diagnosis was reported in patients aged 12–18 years (6 months, IQR: 2–10).

Table 1
Characteristics of patients included in the study

Variable	n (N=66)	%
Sex		
Female	28	42.42
Male	38	57.58
Age, years		
0–5	18	27.27
5–10	20	30.30
10–15	16	24.24
15–20	7	10.61
≥20	5	7.58
Tumour site (i)		
Infratentorial	19	28.79
Supratentorial	47	71.21
Tumour site (ii)		
Infratentorial	19	28.79
Frontal lobes	13	19.70
Parietal lobes	6	9.09
Temporal lobes	2	3.03
Pineal region	3	4.55
Sellar region	10	15.15
Ventricular system	13	19.70
Tumour type		
Craniopharyngioma	7	10.61
Ependymoma	28	42.42
Germinoma	15	22.73
High-grade gliomas	5	7.58
S-embryonal tumours	5	7.58
Pineal tumours	3	4.55
Other	3	4.55
Hydrocephalus		
No	33	50.00
Yes	33	50.00
Surgery		
Complete resection	29	43.94
Partial resection	32	48.48
Biopsy	3	4.55
No surgery	2	3.03
Number of surgeries		
0	2	3.03
1	33	50.00
2	16	24.24
3: (>2)	15	22.73
Chemotherapy pre-RT		
No	34	51.52
Yes	32	48.48
Prescribed dose (Gy)		
30.6	7	10.61
36	8	12.12
50.4	1	1.52
54	22	33.33
59.4	22	33.33
67.4	6	9.09
Radiotherapy technique		
Conformal	2	3.03
Proton	3	4.55
VMAT	60	90.91
VMAT + Boost	1	1.52
Neurotoxic drugs		
Bevacizumab	1	1.52
Platinum derivatives ± others	32	48.48
Vincristine	2	3.03
None	31	46.97
Intensive rehabilitation		
No	54	81.82
Yes	12	18.18
	Median	***IQR***
Duration of symptoms (months)	3	2–12
Age (years)	8.4	4.8–13.5
Time interval from 1st surgery to RT	4.1	2.5–7.1

(*continued on next page*)

Table 1 (*continued*)

IQR: Interquartile range.

Overall, the most frequent tumour site was supratentorial (71.2%), represented by frontal lobes and ventricular system in 19.7%; infratentorial tumours accounted for 28.79 %. As far as histological subtypes, ependymoma, and germinoma represented more than 65% of all the tumours.

Fifty per cent of the patients had hydrocephalus, 43.9% (n = 24) had undergone a complete surgical removal, while only two had not undergone any surgery and 31 patients had more than one excision. Supplemental Figure S1 depicts the relationship between surgical outcome and hydrocephalus.

Of the 66 total patients, 32 underwent chemotherapy before RT, and the percentages receiving the neurotoxic agents vs those with a lower neurotoxic potential were similar (48.5% and 47.0%, respectively). Less than 20% patients had undergone intensive rehabilitation therapy in a specific unit after surgery and before receiving adjuvant treatment.

Morphological Damage Score

To quantify the structural alterations, an expert neuroradiologist (AE) evaluated the severity of gross anatomical and signal abnormality of the cortical and subcortical regions in both hemispheres, blind to patients' diagnosis, using a qualitative scale. Structural abnormalities were assessed across supratentorial regions (bilateral frontal, temporal, parietal, occipital, insular, cingulate), using the USCLobes atlas [29] as a reference for guidance, and in the brainstem, basal nuclei, and cerebellum. The morphological damage score was assigned as follows: score 0 (normal appearance), score 1 (mild anatomical damage and signal abnormality), score 2 (moderate anatomical damage and/or signal abnormality), score 3 (recognisable but distorted morphology and/or severe signal abnormality) and score 4 (severe anatomical damage, and intense, pervasive hyperintensity) [30,31]. A score for each hemisphere was assigned for symmetrical brain regions. Coherently, the ventricular system was evaluated as score 0 (normal size), score 1 (mild enlargement), score 2 (moderate enlargement) and score 3 (severe enlargement). Figure 1A reports morphological damage scores within a patient for each region. The median number of damaged areas in each child was 2 (IQR: 2−3), and no child had a score of 4. The duration of symptoms did not correlate with the number of damaged areas. In each patient, the maximum number of regions with a score of 2 or 3 was 5 and 3, respectively. There were nineteen scores of 3 counted among 13 patients. Only one child had more than 50% (n = 13/18) of areas with damages, whereas 7 patients had all scores equal to 0.

Each region was considered non-normal (score >0) in at least one patient, whereas 10 regions were scored as 3 in at least one patient (Figure 1B). Quantitatively, the most frequently damaged areas were ventricular, with enlargement (n = 17), brainstem (n = 17), and right (R) frontal lobe (n = 16), while qualitatively, it was the left (L) temporal (75.0% of score 3) and L frontal (41.7% with score 3) lobes. On the contrary, the least quantitatively damaged areas were the R insula (n = 3), R occipital, L temporal, and L occipital regions (n = 4), although 33.3% of R insula has a score of 3.

Neurological Deficit Score

Each patient received a neurological score based on the number of concomitant deficits: score 0 (no deficit), score 1 (one cranial nerve deficit or ataxia or pyramidal syndrome), score 2 (i.e. two cranial nerve deficits or one nerve plus ataxia), score 3 (multiple deficits), score 4 (coma or psychosis without clear neurological deficits or posterior fossa syndrome) and score 5 (multiple deficits plus coma or psychosis).

In addition, a qualitative classification considered the type of impaired activity, whereby each patient belonged to one of these classes: no deficits, visual or ocular motility deficits, sensory and motor deficits ± epilepsy, cerebellar deficits, life-threatening complex deficits, or mental deficits.

Figure 2A illustrates the distribution of neurological deficit scores across the various activity impairment categories in the 66 children studied. Among the participants, 19 (28.8%) exhibited no deficits, while 21 (31.8%) were classified with a score of 1, with 67% of these patients experiencing visual acuity or ocular motility impairments. Additionally, 15 patients (22.7%) received a score of 3, nearly all of whom (93.3%) had sensory and motor deficits, often accompanied by epilepsy. Four patients with a score of four or more had life-threatening complex deficits.

The highest scores were observed in the youngest children, particularly in the 0−5 age group, where 50% of the patients had a score of at least 3 (Figure 2B).

By focussing on the tumour sites (Figure 2C), we observed that all the patients with a pineal tumour had a score of 1 (3/3), while the highest percentage of patients with scores >1 had posterior fossa tumours (68.4%). The 4 patients with the highest scores (4 or 5) had tumours in the posterior fossa, in the sellar region, or in temporal lobes; all of them had hydrocephalus. Patients with symptoms duration shorter than 12 months showed higher percentages of severe neurological deficits (Figure 2D). The number of patients with neurological deficits appeared to be independent by hydrocephalus, as well as surgery and chemotherapy administered (Figure 2E−G).

Endocrine Alterations Score

To quantify the endocrine alterations, an expert paediatric oncologist (MM) harmonised the data and categorised them according to the type and the amount of alterations: (i) score 1 for only one deficit present at the time of patient referral, (ii) score 2 for two deficits, (iii) score 3 for three

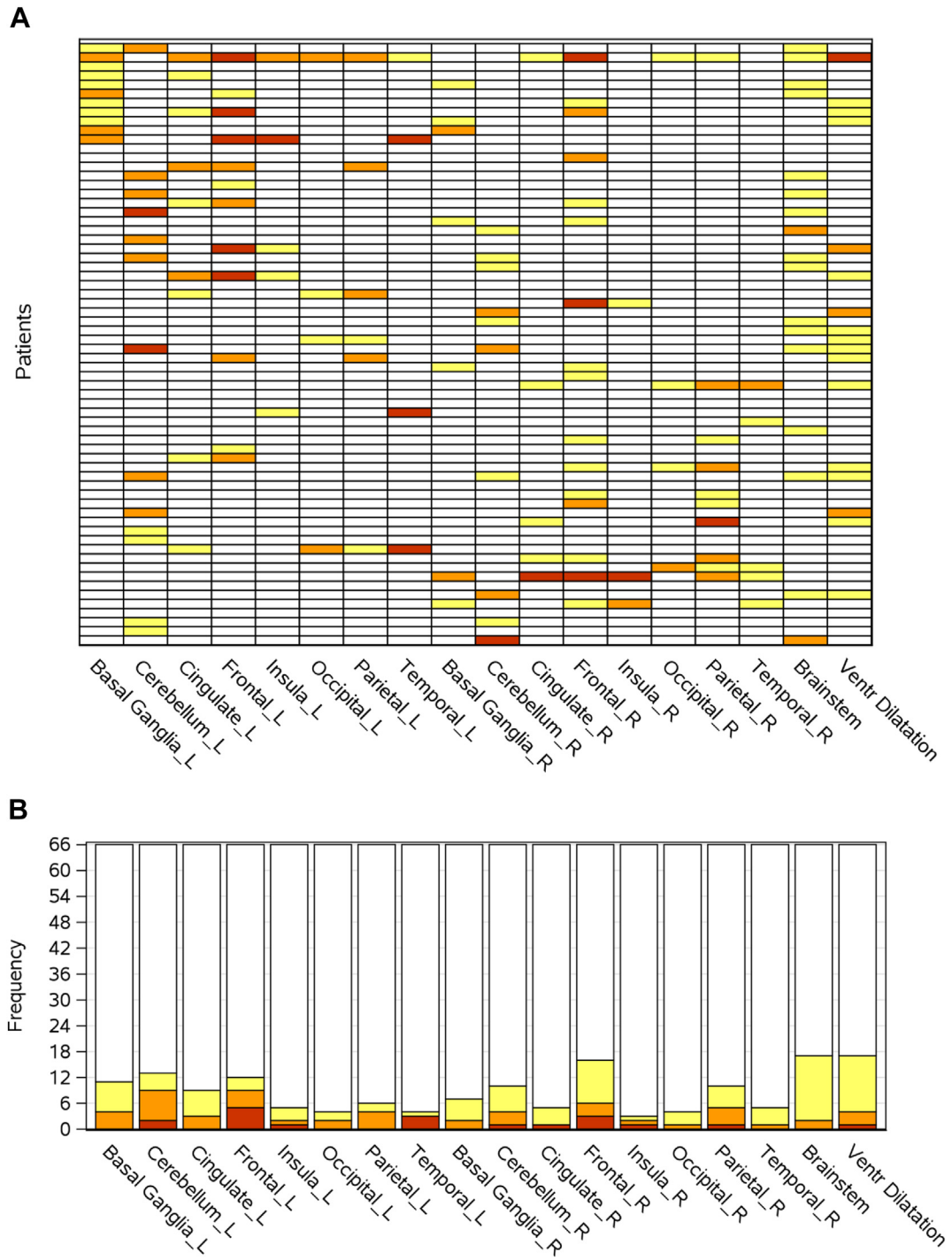

Fig 1. Morphological damage scores in each brain region.

A, Heatmap displaying the morphological damage scores across patients and brain regions. The x-axis shows the brain regions (L: left or R: right) according to the atlas, and each row represents one patient. Each cell is coloured based on the morphological damage score, with a gradient ranging from white (score = 0, no damage) to dark red (score = 3, severe damage). The legend indicates the colour scale corresponding to the damage scores.

B, Stacked bar plot showing the frequency of patients with a specific damage score in each brain region of the atlas. The x-axis shows the brain regions (L: left or R: right) according to the atlas. The bars are colour-coded to represent the severity of the damage, with a gradient from white (score = 0, no damage) to dark red (score = 3, severe damage). Each bar reflects the distribution of damage levels for each region across the patient cohort.

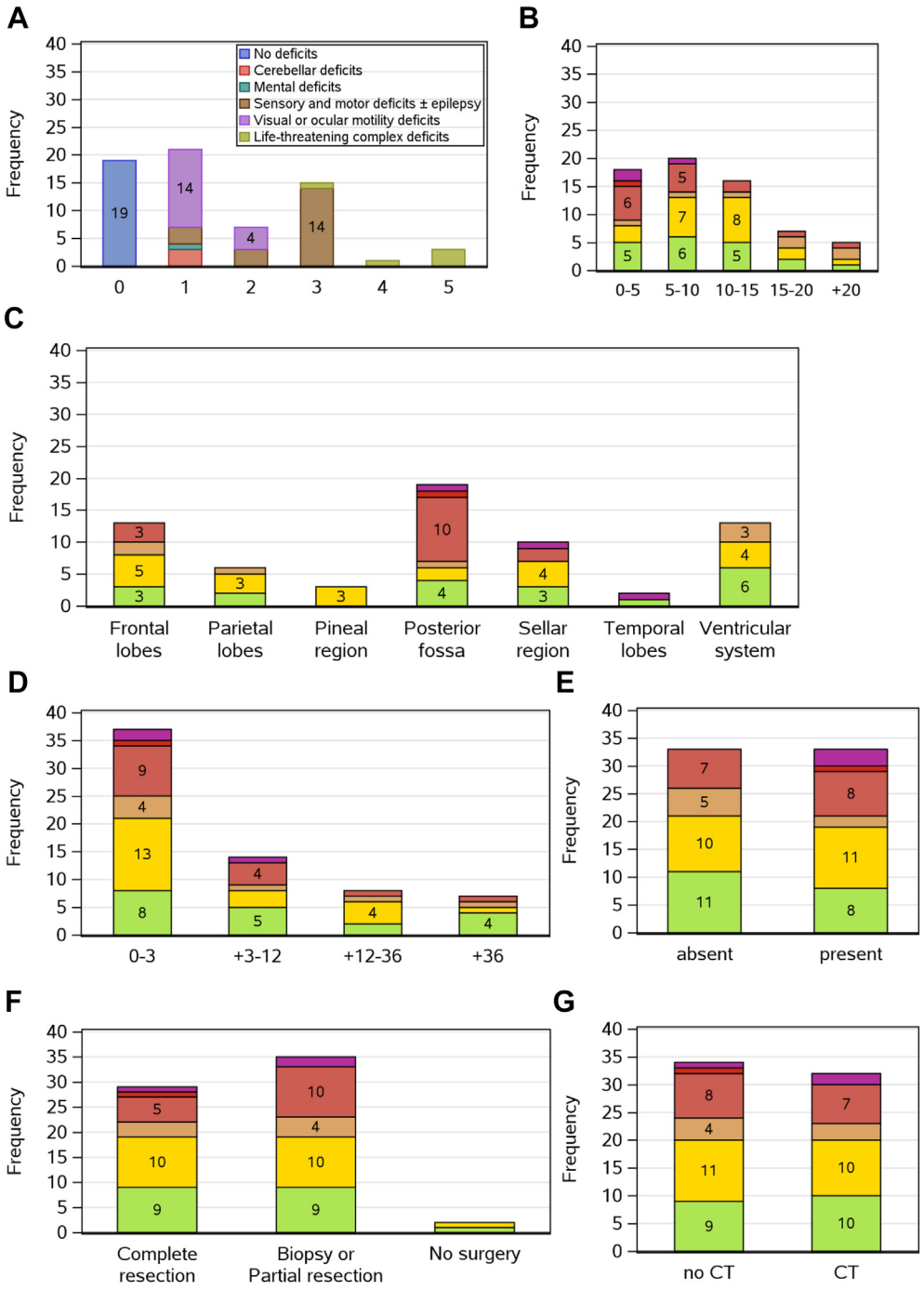

Fig 2. Neurological deficits score evaluation.
A, Bar plot showing the distribution of patients by neurological deficits score and type of deficit. The x-axis represents the scores, while the y-axis indicates the number of patients with each score. Bars are coloured to represent different types of deficits. The numbers within the bars indicate the frequency of patients in each category.
B-G, Bar plots showing the frequency of patients across different categories of the investigated clinical variable (B, ages in years, C, tumour site, D, months of symptoms, E, hydrocephalus, F, surgery, G, chemotherapy). The y-axis represents the number of patients in each category. The colours of the bars represent the different neurological deficit scores: 0 (green, no deficit), 1 (yellow), 2 (light orange), 3 (dark orange), 4 (red), and 5 (purple). The numbers within the bars indicate the frequency of patients in each category.

deficits, (iv) score 4 for panhypopituitarism, (v) score 5 for pan hypopituitarism and other deficits (i.e. salt-wasting syndrome, obesity, hyperprolactinemia, osteopenia, etc). Score 0 was assigned to patients with no endocrine alterations.

Figure 3A represents the distribution of the endocrine alterations score. The majority of patients had no endocrine alterations (68.2%), and about 26% of patients had a score of 4 or 5. Panhypopituitarism was the most prevalent alteration.

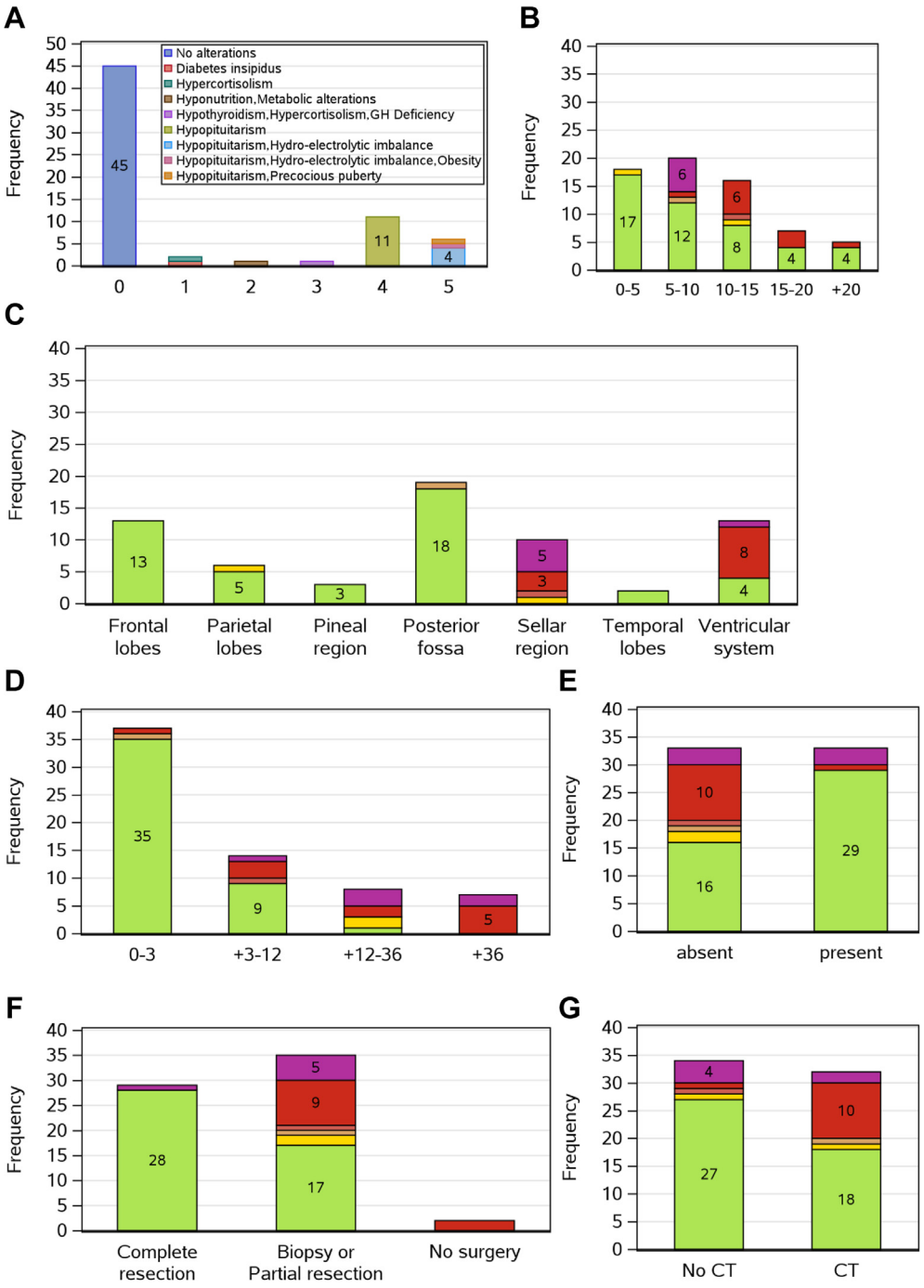

Fig 3. Endocrine alterations score evaluation.
A, Bar plot showing the distribution of patients by endocrine alterations score and type of alteration. The x-axis represents the scores, while the y-axis indicates the number of patients with each score. Bar colour represents different types of alterations. The numbers within the bars indicate the frequency of patients in each category.
B–G, Bar plot showing the frequency of patients across different categories of the investigated clinical variables (B, ages in years, C, tumour site, D, months of symptoms, E, hydrocephalus, F, surgery, G, chemotherapy). The y-axis represents the number of patients in each category. The colours of the bars represent the different endocrine alterations scores: 0 (green, no deficit), 1 (yellow), 2 (light orange), 3 (dark orange), 4 (red), and 5 (purple). The numbers within the bars indicate the frequency of patients in each category.

The age of the patients was associated with the endocrine alterations score ($p = 0.027$), the most severe endocrine disruptions were found in children of school age, where they were observed for 35% or more of patients (35% in 5–10 years, 37.5% in 10–15 years, 42% in 15–20 years), Figure 3B.

With regard to the relationship between endocrine alterations and tumour sites ($p \leq 0.001$), Figure 3C shows that

all patients with a tumour in the sellar region had an alteration (score >0 in 10/10). Moreover, the sellar region and ventricular system were the only two tumour sites including patients with endocrine alterations score >2. In patients who reported symptoms lasting more than one year, less than 1% showed no signs of endocrine disruption (Figure 3D).

Almost 88% and 48% of patients had no endocrine alterations among those with and without hydrocephalus, respectively ($p = 0.001$, Figure 3E). The 6 patients with the maximum score of 5, however, were equally represented in the two groups. Only one patient of the 29 who underwent a complete surgical resection had a score other than zero, as shown in Figure 3F. The presence of endocrinopathies was not associated with the use of chemotherapy ($p = 0.064$, Figure 3G).

Inter-rater Reliability of Neurological and Endocrinological Scores

As regards the inter-rater reliability of the endocrinological alteration and neurological deficit scores, reproducibility between other two paediatric oncologists and the reference values according to the proposed scores classification criteria by MM were evaluated as described in statistical analysis (see Supplemental material). Weighted Kappa (K_w) values for endocrine alterations score were slightly higher in comparison to those related to the neurological ones, but all were satisfactory $K_w > 0.9$ (Supplemental Table S2).

Neurocognitive Damage

FSIQ, verbal intelligent quotient (VIQ), and performance intelligent quotient (PIQ) were computed in more than 70% of patients. Figure 4A shows the number of patients with an impaired/nonimpaired score according to the standardised threshold for each cognitive subtest (Supplemental Table S1). Full-Scale Intelligence Quotient (FSQI) had the higher percentage of impaired results (35.7%) while the PIQ the lowest (22.6%). With regard to the derived indexes, processing speed index (PSI) had higher impaired results than working memory (WM) (40.9% vs 28.2%). In particular, the cognitive index results are shown in Supplemental Figure S2 in conjunction with the patients' clinical variables. No significant differences were found in patient' ages between those with or without impaired scores; however, we observed a higher proportion of patients with infratentorial tumours among those with impaired verbal IQ ($p = 0.048$, Figure 4B). Patients who achieved better results in the FSIQ reported having symptoms that lasted less than 12 months ($p = 0.003$) and a similar trend was observed for the PIQ ($p = 0.060$, Figure 4C). All patients with an endocrine alteration score of 5 belonged to the impaired FSIQ group, while most patients with a non-impaired FSIQ did not have endocrine alterations ($p = 0.038$, Figure 4D). The distributions of hydrocephalus, extent of surgery, chemotherapy, and neurological deficit scores did not show any clear differences among the patients with and without impaired results (Supplemental Figure S2).

Neurocognitive Damage and Structural Alterations

Neurocognitive damage in each patient was analysed alongside the morphological damage scores across cortical and subcortical regions. The left basal ganglia and left frontal regions were the areas with the proportion of patients with structural damage that differed between those who obtained impaired and nonimpaired results, as highlighted by the most relevant cases in Figure 4E. For example, only 2 out of 34 patients (<10%) with nonimpaired FSIQ had damage in the left basal ganglia region, while 7 out of 19 patients (37%) with impaired FSIQ had damage in this region ($p = 0.007$).

Discussion

Neurotoxic effects due to RT typically become fully apparent between 2 and 5 years after treatment completion and are often associated with significant and chronic impairments in various domains, including physical, medical, social, emotional, behavioural, and neurocognitive functioning. Notably, it is estimated that 40%–100% of paediatric brain tumour survivors experience cognitive deficits related to the tumour and/or its treatment [32–34].

The primary objective of this research, at the time it was conceived, was to investigate late radiation damage following focal RT for childhood BT, establishing the relationship between brain tissue damage, radiation dose levels, and neurocognitive outcomes, and to determine the tolerance doses for the most sensitive areas of the developing brain, which could then be used as dose constraints in RT treatment planning..

For these complex aims, an initial description of the basal situation of the 66 patients recruited in this observational trial was required and is reported here as a first step of this complex project.

Besides the administered batteries of neurocognitive tests, new parameters were introduced in this study in order to create reproducible scores.

A score of endocrinological alterations and neurological deficits already present at diagnosis and correlated to the tumour damage and/or to the necessary surgical procedures, were defined. Similarly, the morphological damage also received a score. These semiquantitative measures allowed the correlations at baseline (i.e. before RT) and will be used in the follow-up after RT. The development of neurocognitive dysfunction influenced by a variety of host and treatment factors, in fact, often increases over time.

By examining 54/66 cases treated with heterogeneous surgical approaches, the infratentorial site was found to be associated with VIQ impairment [35], and higher FIQ correlated with a shorter symptoms history. A similar trend was also observed for PIQ, despite a similar neurological deficit score. Additionally, endocrinological status was a significant factor in IQ impairment: all patients with a

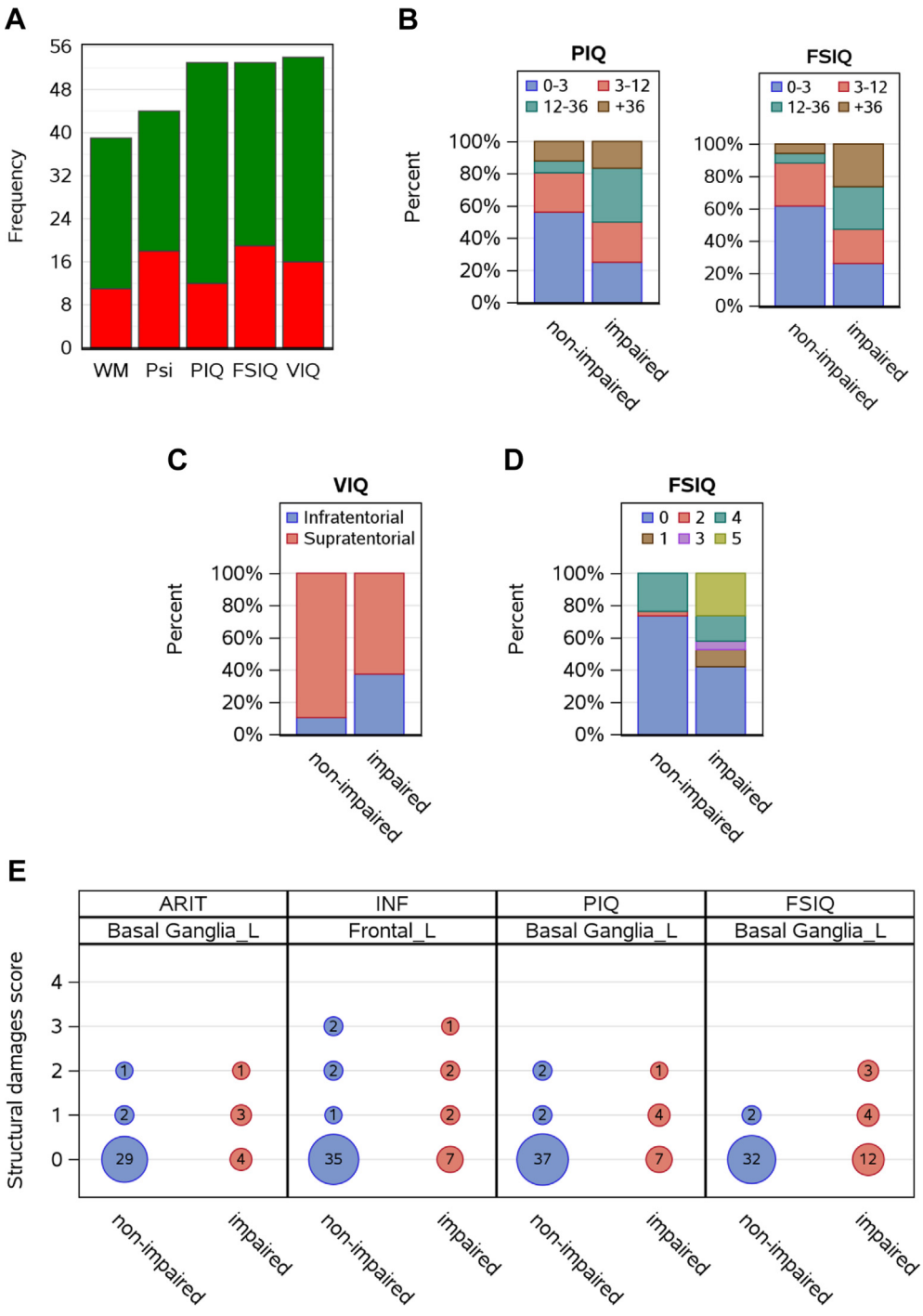

Fig 4. Neurocognitive test evaluation.
A, Bar plot showing the frequency of patients across different cognitive aggregate indexes (see Supplemental Table S1). The colours of the bars represent the different outcome of the indexes: nonimpaired (green) or impaired (red).
B-D, Bar plot showing the distributions (%) of clinical variables (B, months of symptoms, C, tumour site, D, endocrine alterations score) across cognitive outcomes ('impaired' or 'nonimpaired') for the most relevant combinations of cognitive indexes and clinical variables.
E, Bubble plots representing the ROI's morphological damage score and the outcomes of specific cognitive evaluation. The panels report the structural damage score (from 0 to 4) into the left basal ganglia, left frontal region in relation to the outcome of arithmetic (ARIT) and information (INF) subevaluations or the performance IQ (PIQ) and full scale IQ (FISQ) (see Supplemental Table S1). The numbers within the bubbles indicate the frequency of patients for each combination.

severe neurological deficit (score of 5) had IQ impairment, while most patients with an endocrinological score 0 demonstrated normal IQ levels. Obviously, the majority of patients with endocrinological alterations had tumours in the suprasellar and third ventricular regions. The issue of the correlation of cognitive impairment with endocrine risk factors has already been reported and is considered an important modifiable factor for preventing further deterioration [36]. The long-term detrimental effect of hydrocephalus is already well known [37]. In our series, the extent and number of surgeries, the presence of neurological deficits—observed in over 70% of patients—and the effects of chemotherapy [38,39] did not significantly impact on neurocognitive outcomes shortly after diagnosis. In contrast, the morphological damage was correlated with the neurocognitive outcome, as shown by the impact of the basal ganglia on FSIQ. Among previous papers, all related to presurgical status [2–6], not all authors found neurocognitive alterations in the presurgical phase even when comparing patients with a control group [4], thus partly explaining what we have found as a cumulative effect of tumours and surgical acts.

The most compromised areas were those of praxic skills and memory, followed by the executive functions and attention. The impairment of praxic skills is easily understandable as these abilities are strongly influenced by executive functions, which include planning, programming, and other higher cognitive skills such as memory and attention, as demonstrated by numerous authors [2,4,6,40–44]; however, at the same time we cannot exclude a possible impact of the tumour on the motor systems of the brain. Moreover, we found that the nondominant hand, assembly, and recall tasks from the Purdue Pegboard and the Rey Complex Figure tests showed the highest percentage of impaired scores, exceeding 40%. We hypothesise that the decline in nondominant hand and assembly test from the Purdue Pegboard suggests that the subject's cognitive resources are more intensively used to exercise the dominant hand, renouncing the ability to develop the skills related to the less important hand, just as happens for other cognitive domains [1,45,46] and in accordance with clinical practice, in which we observe a great investment in the use of the dominant hand. It can be assumed that the reason for the decline is not the loss of skills, but the failure to learn and acquire new skills at the age-appropriate rate, resulting in relatively lower functioning compared to what is expected for age. Despite its noteworthy findings, the present study has several limitations. The sample is highly variable in terms of age, tumour type and site, surgical approaches, length of symptoms, neurological and endocrinological deficits already present, making it challenging to interpret the specific relationships between these factors and cognitive functioning. Additionally, the small sample size limited the ability to conduct group comparisons of neurocognitive functioning based on distinct demographic factors or tumour characteristics. Future studies should involve multiple sites to recruit larger, more diverse samples, enabling systematic analysis of these effects and providing more robust conclusions. The hypothetical reversibility of certain conditions, such as space-occupying lesions, hydrocephalus, visual loss, hearing impairment, or neuroendocrine dysfunction, will needs a future evaluation as the original project implied.

The original scores developed in the current study to assess morphological, endocrinological, and neurological deficits are a true novelty and could be easily reproduced in other studies, as also shown by the results obtained from the evaluation of inter-rater reliability among three paediatric oncologists. In the upcoming report on this series, which will include the effects of RT and the cumulative impact of previously described factors over time, the utility of these scores will be further validated.

A similar series carefully assessed prior to receiving focal RT for various malignant BT was, however, never reported by literature with so many details. Other papers have in fact describe neuropsychological testing in BT patients before surgical or subsequent treatments commence with correlation of sites, symptoms and their duration, neurological deficits and hydrocephalus, but never included specific morphological, neurological and endocrine scores [47]. The findings revealed an unexpectedly high incidence of impairments across all examined areas.

In addition to monitoring these patients over time, all available clinical and social resources must be leveraged from the very beginning of each patient's journey to significantly enhance their care and support [48–51].

Ethics

Institutional Review Board of Fondazione IRCCS Istituto Nazionale dei Tumori approved the study on December 17, 2017.

Author contribution

ML, MM, AE, PV, PG, EP contributed to the manuscript conception and design. Material preparation and data collection were performed by AE, GP, CC, SM, AN, FS, EP, MCO, VB, ES, DP, RL, LM, SV, GP, PV, EP, MM; analysis was performed by ML and PV. The first draft of the manuscript was written by ML, MM and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Maura Massimino reports financial support was provided by Associazione Italiana per la Ricerca sul Cancro. Maura Massimino reports a relationship with

AIRC that includes: funding grants. No other activities if there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Consent to participate

Written consents were obtained from all participants and their legal guardians.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2025.103872.

References

[1] Mulhern RK, Merchant TE, Gajjar A, Reddick WE, Kun LE. Late neurocognitive sequelae in survivors of brain tumors in childhood. *Lancet Oncol* 2004;5(7):399–408. https://doi.org/10.1016/S1470-2045(04)01507-4.

[2] Irestorm E, Perrin S, Tonning IO. Pretreatment Cognition in Patients Diagnosed With Pediatric Brain Tumors. *Pediatr Neurol* 2018;79:28–33. https://doi.org/10.1016/j.pediatrneurol.2017.11.008.

[3] van Kessel E, Baumfalk AE, van Zandvoort MJE, Robe PA, Snijders TJ. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a systematic review of neurocognitive functioning prior to anti-tumor treatment. *J Neurooncol* 2017;134(1):9–18. https://doi.org/10.1007/s11060-017-2503-z.

[4] Varela M, Liakopoulou M, Alexiou GA, Pitsouni D, Alevizopoulos GA. Presurgical neuropsychological and behavioral evaluation of children with posterior fossa tumors. *J Neurosurg Pediatr* 2011;8(6):548–553. https://doi.org/10.3171/2011.8.PEDS11223.

[5] Thigpen JC, Pearson M, Robinson KE, Andreotti C, Dunbar JP, Watson KH, *et al*. Presurgical assessment of cognitive function in pediatric brain tumor patients: feasibility and initial findings. *Neurooncol Pract* 2016;3(4):261–267. https://doi.org/10.1093/nop/npv066.

[6] Di Rocco C, Chieffo D, Pettorini BL, Massimi L, Caldarelli M, Tamburrini G. Preoperative and postoperative neurological, neuropsychological and behavioral impairment in children with posterior cranial fossa astrocytomas and medulloblastomas: the role of the tumor and the impact of the surgical treatment. *Childs Nerv Syst* 2010;26(9):1173–1188. https://doi.org/10.1007/s00381-010-1166-2.

[7] Ajithkumar T, Price S, Horan G, Burke A, Jefferies S. Prevention of radiotherapy-induced neurocognitive dysfunction in survivors of pediatric brain tumours: the potential role of modern imaging and radiotherapy techniques. *Lancet Oncol* 2017;18:e91–e100. https://doi.org/10.1016/S1470-2045(17)30030-X.

[8] Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD. Radiation-induced brain injury: A review. *Front Oncol* 2012;2:73. https://doi.org/10.3389/fonc.2012.00073.

[9] Piscione PJ, Bouffet E, Timmons B, Courneya KS, Tetzlaff D, Schneiderman JE, *et al*. Exercise training improves physical function and fitness in long-term pediatric brain tumor survivors treated with cranial irradiation. *Eur J Cancer* 2017;80:63–72. https://doi.org/10.1016/j.ejca.2017.04.020.

[10] Schrieff-Elson LE, Thomas KGF, Rohlwink UK. Pediatric Traumatic Brain Injury: Outcomes and Rehabilitation. In: Di Rocco C, Pang D, Rutka J, editors. *Textbook of pediatric neurosurgery*. Cham: Springer; 2017. p. 1–28. https://doi.org/10.1007/978-3-319-31512-6_150-1.

[11] Glaser AW, Nik Abdul Rashid N, CL U, Walker DA. School behaviour and health status after central nervous system tumours in childhood. *Br J Cancer* 1997;76(5):643–650. https://doi.org/10.1038/bjc.1997.439.

[12] Koustenis E, Hernaiz Driever P, De Sonneville L, Rueckriegel SM. Executive function deficits in pediatric cerebellar tumor survivors. *Eur J Pediatr Neurol* 2016;20(1):25–37. https://doi.org/10.1016/j.ejpn.2015.11.001.

[13] Clement SC, Schouten-van Meeteren AYN, Boot AM, Claahsen-van der Grinten HL, Granzen B, Sen Han K, *et al*. Prevalence and risk factors of early endocrine disorders in childhood brain tumor survivors: A nationwide, multicenter study. *J Clin Oncol* 2016;34(36):4362–4370. https://doi.org/10.1200/JCO.2016.67.5025.

[14] Bajwa SJ, Haldar R. Endocrinological disorders affecting neurosurgical patients: An intensivists perspective. *Indian J Endocrinol Metab* 2014;18(6):778–783. https://doi.org/10.4103/2230-8210.140240.

[15] Merchant TE, Williams T, Smith JM, Rose SR, Danish RK, Burghen GA, *et al*. Preirradiation endocrinopathies in pediatric brain tumor patients determined by dynamic tests of endocrine function. *Int J Radiat Oncol Biol Phys* 2002;54(1):45–50. https://doi.org/10.1016/s0360-3016(02)02888-2.

[16] Sahrizan NSA, Manan HA, Abdul Hamid H, Abdullah JM, Yahya N. Functional Alteration in the Brain Due to Tumor Invasion in Pediatric Patients: A Systematic Review. *Cancers* 2023;15(7):2168. https://doi.org/10.3390/cancers15072168.

[17] Corti C, Urgesi C, Massimino M, Gandola L, Bardoni A, Poggi G. Effects of supratentorial and infratentorial tumor location on cognitive functioning of children with brain tumor. *Child's Nervous Syst* 2020;36(3):513–524. https://doi.org/10.1007/s00381-019-04434-3.

[18] Packer RJ, Meadows AT, Rorke LB, Goldwein JL, D'Angio G. Long-term sequelae of cancer treatment on the central nervous system in childhood. *Med Pediatr Oncol* 1987;15(5):241–253. https://doi.org/10.1002/mpo.2950150505.

[19] Quintero-Gallego EA, Gómez CM, Vaquero Casares E, Márquez J, Pérez-Santamaría FJ. Declarative and procedural learning in children and adolescents with posterior fossa tumours. *Behav Brain Funct* 2006;2:9. https://doi.org/10.1186/1744-9081-2-9.

[20] Riva D, Taddei M, Ghielmetti F, Erbetta A, Bulgheroni S. Language Cerebro-cerebellar Reorganization in Children After Surgery of Right Cerebellar Astrocytoma: a fMRI Study. *Cerebellum* 2019;18(4):791–806. https://doi.org/10.1007/s12311-019-01039-z.

[21] Riva D, Giorgi C. The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. *Brain* 2000;123(5):1051–1061. https://doi.org/10.1093/brain/123.5.1051.

[22] Peterson RK, Ng R, Ludwig NN, Jacobson LA. Tumor region associated with specific processing speed outcomes. *Pediatr*

Blood Cancer 2023;70(3):e30167. https://doi.org/10.1002/pbc.30167.
[23] Iuvone L, Peruzzi L, Colosimo C, Tamburrini G, Caldarelli M, Di Rocco C, *et al*. Pretreatment neuropsychological deficits in children with brain tumors. *Neuro Oncol* 2011;13(5):517–524. https://doi.org/10.1093/neuonc/nor013.
[24] Shortman RI, Lowis SP, Penn A, McCarter RJ, Hunt LP, Brown CC, *et al*. Cognitive function in children with brain tumors in the first year after diagnosis compared to healthy matched controls. *Pediatr Blood Cancer* 2014;61(3):464–472. https://doi.org/10.1002/pbc.24746.
[25] Hardy KK, Bonner MJ, Willard VW, Watral MA, Gururangan S. Hydrocephalus as a possible additional contributor to cognitive outcome in survivors of pediatric medulloblastoma. *Psychooncology* 2008;17(11):1157–1161. https://doi.org/10.1002/pon.1349.
[26] Reimers TS, Ehrenfels S, Mortensen EL, Schmiegelow M, Sønderkaer S, Carstensen H, *et al*. Cognitive deficits in long-term survivors of childhood brain tumors: Identification of predictive factors. *Med Pediatr Oncol* 2003;40(1):26–34. https://doi.org/10.1002/mpo.10211.
[27] Aarsen FK, Van Dongen HR, Paquier PF, Van Mourik M, Catsman-Berrevoets CE. Long-term sequelae in children after cerebellar astrocytoma surgery. *Neurology* 2004;62(8):1311–1316. https://doi.org/10.1212/01.wnl.0000120549.77188.36.
[28] Was H, Borkowska A, Bagues A, Tu L, Liu JYH, Lu Z, *et al*. Mechanisms of Chemotherapy-Induced Neurotoxicity. *Front Pharmacol* 2022;13:750507. https://doi.org/10.3389/fphar.2022.750507.
[29] Joshi AA, Choi S, Liu Y, Chong M, Sonkar G, Gonzalez-Martinez J, *et al*. A hybrid high-resolution anatomical MRI atlas with sub-parcellation of cortical gyri using resting fMRI. *J Neurosci Methods* 2022;374:109566. https://doi.org/10.1016/j.jneumeth.2022.109566.
[30] Rosazza C, Andronache A, Sattin D, Bruzzone MG, Marotta G, Nigri A, *et al*. Multimodal study of default-mode network integrity in disorders of consciousness. *Ann Neurol* 2016;79(5):841–853. https://doi.org/10.1002/ana.24634.
[31] Vanden Berghe S, Cappelle S, De Keyzer F, Peeters R, Coursier K, Depotter A, *et al*. Qualitative and quantitative analysis of diffusion-weighted brain MR imaging in comatose survivors after cardiac arrest. *Neuroradiology* 2020;62(11):1361–1369. https://doi.org/10.1007/s00234-020-02460-6.
[32] Armstrong GT, Liu Q, Yasui Y, Huang S, Ness KK, Leisenring W, *et al*. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2009;101(13):946–958. https://doi.org/10.1093/jnci/djp148.
[33] Turner CD, Chordas CA, Liptak CC, Rey-Casserly C, Delaney BL, Ullrich NJ, *et al*. Medical, psychological, cognitive and educational late-effects in pediatric low-grade glioma survivors treated with surgery only. *Pediatr Blood Cancer* 2009;53(3):417–423. https://doi.org/10.1002/pbc.22081.
[34] Moore 3rd BD. Neurocognitive outcomes in survivors of childhood cancer. *J Pediatr Psychol* 2005;30(1):51–63. https://doi.org/10.1093/jpepsy/jsi016.
[35] Levisohn L, Cronin-Golomb A, Schmahmann JD. Neuropsychological consequences of cerebellar tumour resection in children: Cerebellar cognitive affective syndrome in a paediatric population. *Brain* 2000;123(5):1041–1050. https://doi.org/10.1093/brain/123.5.104136.
[36] Moon JH. Endocrine Risk Factors for Cognitive Impairment. *Endocrinol Metab* 2016;31(2):185–192. https://doi.org/10.3803/EnM.2016.31.2.185.
[37] Erickson K, Baron IS, Fantie BD. Neuropsychological Functioning in Early Hydrocephalus: Review From a Developmental Perspective. *Child Neuropsychol* 2001;7(4):199–229. https://doi.org/10.1076/chin.7.4.199.8737.
[38] Kulkarni AV, Donnelly R, Mabbott DJ, Widjaja E. Relationship between ventricular size, white matter injury, and neurocognition in children with stable, treated hydrocephalus. *J Neurosurg Pediatr* 2015;16(3):267–274. https://doi.org/10.3171/2015.1.PEDS14597.
[39] Ullrich NJ, Embry L. Neurocognitive dysfunction in survivors of childhood brain tumors. *Semin Pediatr Neurol* 2012;19(1):35–42. https://doi.org/10.1016/j.spen.2012.02.014.
[40] Lehtonen A, Howie E, Trump D, Huson SM. Behaviour in children with neurofibromatosis type 1: Cognition, executive function, attention, emotion, and social competence. *Dev Med Child Neurol* 2013;55(2):111–125. https://doi.org/10.1111/j.1469-8749.2012.04399.x.
[41] Remigereau C, Roy A, Costini O, Barbarot S, Bru M, Le Gall D. Praxis skills and executive function in children with neurofibromatosis type 1. *Appl Neuropsychol Child* 2018;7(3):224–234. https://doi.org/10.1080/21622965.2017.1295856.
[42] Pratt ML, Leonard HC, Adeyinka H, Hill EL. The effect of motor load on planning and inhibition in developmental coordination disorder. *Res Dev Disabil* 2014;35(7):1579–1587. https://doi.org/10.1016/j.ridd.2014.04.008.
[43] Ruddock S, Piek J, Sugden D, Morris S, Hyde C, Caeyenberghs K, *et al*. Coupling online control and inhibitory systems in children with Developmental Coordination Disorder: Goal-directed reaching. *Res Dev Disabil* 2015;36C:244–255. https://doi.org/10.1016/j.ridd.2014.10.013.
[44] Bergqvist M, Möller MC, Björklund M, Borg J, Palmcrantz S. The impact of visuospatial and executive function on activity performance and outcome after robotic or conventional gait training, long-term after stroke-as part of a randomized controlled trial. *PLoS One* 2023;18(3):e0281212. https://doi.org/10.1371/journal.pone.0281212.
[45] Palmer SL, Goloubeva O, Reddick WE, Glass JO, Gajjar A, Kun L, *et al*. Patterns of intellectual development among survivors of pediatric medulloblastoma: a longitudinal analysis. *J Clin Oncol* 2001;19(8):2302–2308. https://doi.org/10.1200/JCO.2001.19.8.2302.
[46] Saury JM, Emanuelson I. Cognitive consequences of the treatment of medulloblastoma among children. *Pediatr Neurol* 2011;44(1):21–30. https://doi.org/10.1016/j.pediatrneurol.2010.07.004.
[47] Margelisch K, Studer M, Ritter BC, Steinlin M, Leibundgut K, Heinks T. Cognitive dysfunction in children with brain tumors at diagnosis. *Pediatr Blood Cancer* 2015;62(10):1805–1812. https://doi.org/10.1002/pbc.25596.
[48] Claude F, Ubertini G, Szinnai G. Endocrine Disorders in Children with Brain Tumors: At Diagnosis, after Surgery, Radiotherapy and Chemotherapy. *Children* 2022;9(11):1617. https://doi.org/10.3390/children9111617.
[49] Philip PA, Ayyangar R, Vanderbilt J, Gaebler-Spira DJ. Rehabilitation outcome in children after treatment of primary brain tumor. *Arch Phys Med Rehabil* 1994;75(1):36–39.
[50] Day AM, Slomine BS, Salama C, Quinton TL, Suskauer SJ, Salorio CF. Functional Gains in Children Receiving Inpatient Rehabilitation After Brain Tumor Resection. *Arch Phys Med Rehabil* 2021;102(11):2134–2140. https://doi.org/10.1016/j.apmr.2021.05.001.
[51] Lim AN, Lange BJ, King AA. Rehabilitation for survivors of pediatric brain tumors: our work has just begun. *Future Neurol* 2009;5(1):135–146. https://doi.org/10.2217/fnl.09.65.