Child's Nervous System (2021) 37:871–878
https://doi.org/10.1007/s00381-020-04944-5

ORIGINAL ARTICLE

The rationale and development of a CyberKnife© registry for pediatric patients with CNS lesions

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Received: 11 August 2020 / Accepted: 23 October 2020 / Published online: 10 November 2020

Abstract

Background CyberKnife© Radiosurgery (CKRS) is a recognized treatment concept for CNS lesions in adults due to its high precision and efficacy beside a high patient comfort. However, scientific evidence for this treatment modality in pediatric patients is scarce. A dedicated registry was designed to document CyberKnife© procedures in children, aiming to test the hypothesis that it is safe and efficient for the treatment of CNS lesions.

Methods The CyberKnife© registry is designed as a retrospective and prospective multicenter observational study (German Clinical Trials Register (https://www.drks.de), DRKS-ID 00016973). Patient recruitment will be ongoing throughout a 5-year period and includes collection of demographic, treatment, clinical, and imaging data. Follow-up results will be monitored for 10 years. All data will be registered in a centralized electronic database at the Charité-Universitätsmedizin. The primary endpoint is stable disease for benign and vascular lesions at 5 years of follow-up and local tumor control for malign lesions at 1- and 2-year follow-up. Secondary endpoints are radiation toxicity, side effects, and neurocognitive development.

Conclusion The CyberKnife© registry intends to generate scientific evidence for all treatment- and outcome-related aspects in pediatric patients with treated CNS lesions. The registry may define safety and efficacy of CKRS in children and serve as a basis for future clinical trials, inter-methodological comparisons and changes of treatment algorithms.

Keywords CNS lesions · pediatric · CyberKnife · frameless image-guided robotic radiosurgery · radiosurgery

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00381-020-04944-5.

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Abbreviations

APRO Arbeitsgemeinschaft für pädiatrische Radioonkologie (Working group for Pediatric Radiation Oncology)
CKRS CyberKnife radiosurgery
CNS Central nervous system
DGN Deutsche Gesellschaft für Neurologie (German Society of Neurology)
MRI Magnet resonance imaging

Background

Frameless image-guided robotic radiosurgery, i.e., CyberKnife© (Accuray Incorporated, Sunnyvale, CA) Radiosurgery (CKRS), is a well-established treatment concept for high precision radiotherapy of circumscribed lesions in adults, either as adjuvant treatment to surgical resection or as primary treatment for CNS lesions not amenable to surgery [1]. It demonstrated safety and efficiency with a therapeutic profile comprising a broad spectrum of distinct CNS lesions, which can be treated with single-fraction or hypo-fractionated irradiation [2–7]. Beside the high technical accuracy, which is comparable to that of frame-based systems, its high patient comfort facilitated its frequent application and represents one of its most important advantages [8–10]. Other advantages are high tumor control, low morbidity and toxicity, as well as repeatability for recurrent tumors [7, 11–15]. External radiation therapy, notably conformal radiotherapy, has been and is still the standard of care in the complex treatment of pediatric brain tumors despite the risk of long-term side effects [16–21]. Moreover, vascular CNS lesions have eventually evolved as one of the main indications for frame-based systems in children [22–28]. Image-guided robotic radiosurgery has been intensely evaluated in adult patients and proven to be beneficial in multiple pathological conditions within the CNS. Pediatric patients, however, present with a distinct subset of entities and are more susceptible to the type of treatment than adults. Therefore, they are expected to show a different profile of indications, outcomes, and long-term side effects after radiation therapy and CKRS treatment, respectively [29]. There are only few reports on CKRS application in children and equally few including children in adult case series [30–37]. All of them were generated from retrospectively collected data and did not include significant case numbers compared to adult case series nor assess long-term outcomes. Moreover, they did not provide substantial data for deriving indication standards with respect to entities, timing of CKRS treatment, and previous therapies. Although they demonstrate overall favorable results, there remains a substantial lack of clinical evidence opposing the routine use of CKRS for defined pediatric entities. In addition, in most countries, CKRS treatment is only available in few centers. These limitations reflect the rationale to establish a registry that systematically monitors CKRS treatments in children with CNS lesions. The Pediatric CyberKnife© Registry is expected to test the hypothesis that CKRS treatment in this patient subgroup is safe and efficient and to provide a structured overview for treatment indications and entity-specific protocols. Beyond the clinical rationale, there is a substantial rationale for publishing the establishment and format of the registry. We aim to generate awareness of this treatment form in children with CNS lesions and to highlight the knowledge gap, which requires increase of contributors on an international level.

Methods

The Pediatric CyberKnife© Registry is an observational retrospective and prospective multicenter study, with one coordinating center at the Charité-Universitätsmedizin Berlin and ten other contributing centers in Germany (Fig. 1). The study was approved by the ethics committee of the Charité-Universitätsmedizin Berlin, Germany as well as by the APRO (Working group for Pediatric Radiation Oncology as part of the German Society of Radiation Oncology). Additional registration was obtained at the German Clinical Trials Register (https://www.drks.de), DRKS-ID 00016973. The intended aims of the registry are summarized in Table 1.

Patient recruitment

The patient recruitment and follow-up is provided on a local level at each site and related to the locally performed treatments. The patients recruited for the registry must meet the following inclusion criteria:

- Patient age ≤ 18 years
- Documented diagnosis of CNS lesion (including CNS metastases) in MRI or CT
- Local tumor or vascular board approval for CKRS treatment
- Informed consent (by the legal representative and patient, when possible with respect to his/her age)
- Obtained or planned CKRS treatment

There are no exclusion criteria except missing consent of the legal representatives or the patient if applicable with respect to age.

Data collection

The data collection is performed retro- and prospectively. Data storage is centralized at the coordinating center at the Charité-Universitätsmedizin Berlin. A pseudonymization is applied according to the local data safety protocols and data are filed in a customized digital database, established at the

Table 1 Summarizes the defined aims of the Pediatric CyberKnife© Registry

Main goals	Specifications
Comprehensive data collection	Nationwide documentation of every patient < 18, who has undergone CKRS for any kind of CNS lesion (including CNS metastases)
	Demographics, Diagnosis, previous therapies
Outcome monitoring	Peri- and post-interventional outcome monitoring including clinical and neurological changes, local tumor control, progression free survival, cognitive changes (neuropsychological evaluations) and radiation toxicity to monitor patients
Definition of treatment indications	• Analyses of entity-specific treatment responses and comparative outcome analyses
	• Definition of optimal time points for CKRS treatments and interference with previous therapies
Protocol development	Technical specification of entity-related CKRS treatment protocols (fractions, isodose lines, repetitive treatments)
Generation of substudies	Generation of secondary study protocols for comparative and inter-methodical outcome analysis (including different radiation types and surgical procedures)
Outlook	• Linkage of the registry to interdisciplinary treatment networks (GPOH)
	• Validation of developed CRKS treatment protocols within the German Society of Radiation Oncology
	• International expansion of the registry

Charité-Universitätsmedizin Berlin, using the commercial software FileMaker Pro© (FileMaker Inc., Santa Clara, CA). The multi-dimensional database system is integrated into the network infrastructure of the coordinating center and allows automated data import and export within programmed scripts [38]. The database was approved by the data protection and safety board of the Charité-Universitätsmedizin. Data management, quality, and safety will be monitored by the corresponding responsible institutions throughout the study. Two dedicated data collection forms will be used to record the initial treatment (treatment form) and the follow-up visits, scheduled at 3, 6, 12 months, and yearly after treatment (follow up form). The data collection forms include the following information (Supplement Information: Figures 1and 2):

A Treatment form:

- Demographic data and institution
- Diagnosis (imaging and/or histopathology)
- Clinical and neurological status (assessed according to the guidelines of the German Society of Neurology, DGN)
- Previous treatments (surgery, radiation, chemotherapy)
- CKRS treatment: date(s), fractions, treatment parameters (treatment volumes, tumor doses and the prescribed percentages of isodose lines)
- Steroid medication

B Follow-up form:

- Number and date of follow-up
- Clinical and neurological status (assessed according to the guidelines of the German Society of Neurology, DGN)
- Complications after CKRS treatment (causative and unrelated)
- Additional treatments for complications
- Radiological follow up results (MRI +/- contrast; vascular-supported imaging)

The study protocol includes monitoring of neuropsychological outcome at 1, 2, 5, and 10 years after CKRS treatment. The evaluations will be performed by a dedicated neuropsychologist in the corresponding oncological treatment center, using standardized tests (Wechsler intelligence scale for children and Wechsler memory test) according to the patient's age. A flow diagram including all study visits is illustrated in Fig. 2.

Outcome measures

The primary endpoint is stable disease for benign and vascular lesions at 5 years of follow-up and local tumor control for malign lesions local at 1- and 2-year follow-up. Accordingly, rates of local and distant failure as well as the progression free survival will be determined. These will be assessed via imaging, MRI +/− contrast for benign and malignant brain tumors as well as metastases and vascular supported imaging for vascular lesions, respectively. Measurable disease will be determined according to the recommendations of the Response Assessment in Neuro-Oncology (RANO) group [39, 40]. Radiographic assessment of the treatment outcome is defined as followed: complete response (CR): disappearance of the whole tumor, partial response (PR): at least a 30% decrease in tumor volume compared to baseline, minor response (MR): decrease of tumor volume up to 30% compared

Fig. 1 Illustration of the nationwide distribution of CyberKnife© centers in Germany participating in the registry. The figure was generated using the free online tool available at https://www.mixmaps.de

to baseline, stable disease (SD): unchanged tumor volume, progressive disease (PD): increase of the overall tumor volume of at least 20% or tumor growth of at least 5 mm. Local control (LC) is defined as no radiographic evidence of PD. Distant failure is defined as occurrence of any new lesions beyond the index lesion.

Secondary endpoints are radiation toxicity, side effects, and long-term effects, such as impairment of neurocognitive development. They will be assessed at early and late timepoints during the follow-up in order to derive comprehensive outcomes after CKRS treatment.

Sample size calculation

The sample size calculation for the study is based on a preliminary retrospective survey among the 11 contributing centers. This is because entity incidences are not representative for calculating eventual CKRS numbers due to the HIT protocols, which are applied for the standardized treatment of CNS tumors and due to the novelty of the CKRS treatment in children. The retrospective survey allowed inclusion of 95 children, being treated with CKRS treatment within the last 7 years. According to the extrapolated treatment incidence based on the retrospective survey, we assume an additional prospective recruitment period of five years for achieving the intended total of 150–200 patients. From a statistical standpoint, these numbers were used for preliminary test calculations and confirmed to be sufficient for future multivariate analysis with regard to other treatment modalities and subgrouping. The occurrence of side effects and complications, which is defined as change of the clinical/neurological status before and after intervention, will be divided to separate results in clinical/neurological status deterioration or no deterioration. The sample size calculation will be adjusted according to the assumed number of clinical/neurological status deterioration in both groups according to results of less than 10% reported in adult cohorts [2, 7, 41].

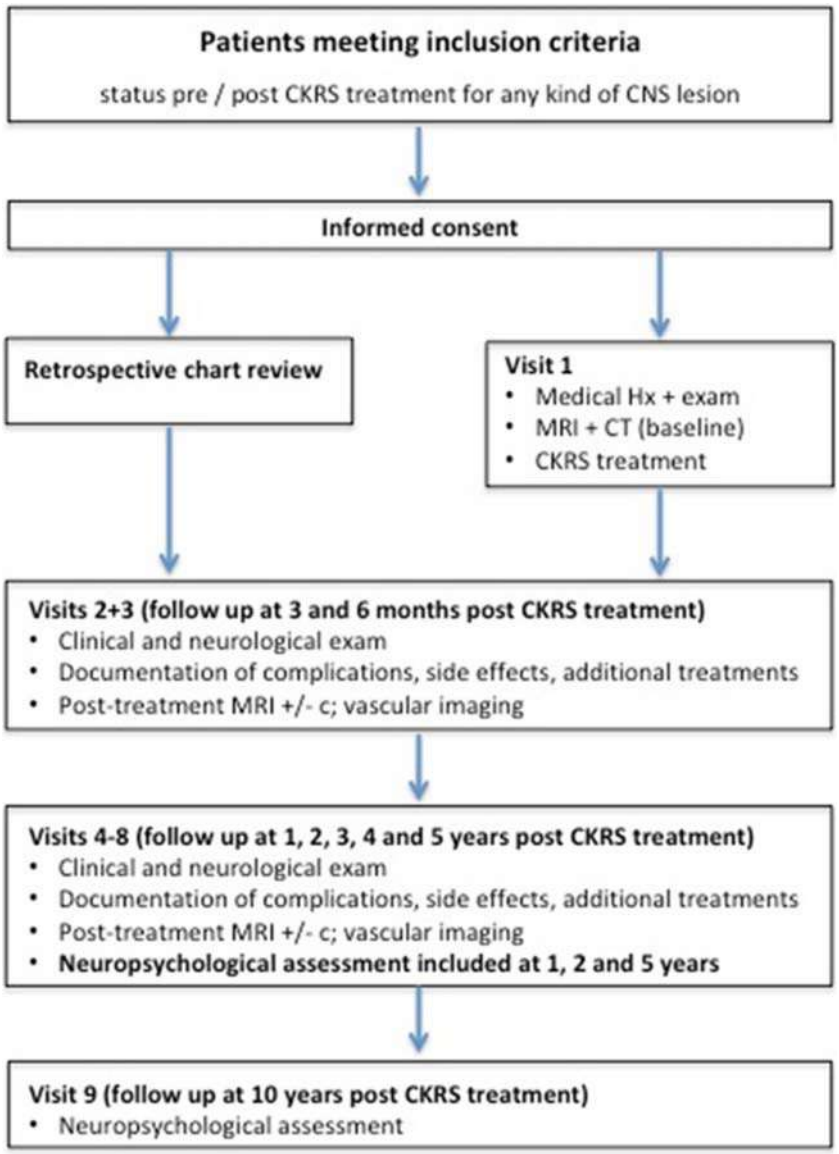

Fig. 2 Flow diagram outlining the schedule of treatment and follow up visits included in the study protocol

Statistical analysis

The rates of stable disease and local tumor control, as well as of progression-free survival will be calculated using the Kaplan–Meier method. In a second step, age-matched control groups of conventionally irradiated patients from a pre-existing internal database will be used to calculate differences between pairs of Kaplan–Meier curves using the log-rank test. Values of $p < .05$ will be considered to be statistically significant. Interference of diagnosis and distinct previous treatments will be analyzed using a multivariate logistic regression model.

Radiation toxicities will be evaluated with the Common Terminology Criteria for Adverse Events version 4.0. Substantial clinical data on acute side effects and complications after CKRS treatment do not exist in pediatric patients, yet. Thus, a detection of the clinical/neurological status change of more than 5% by the intervention is considered to be clinically relevant. Therefore, in a comparative analysis with age-matched control groups (same diagnosis, no treatment), the Fisher's exact test will be used with a significance level of 5% (two-tailed) with power of 80%, requiring a total of 110 patients per group. To detect possible confounders related to baseline values, co-morbidities and center would be tested for statistical significance, by using a Logistic regression with a p value < 0.05 considered as significant.

Discussion

Availability and indications for CKRS treatment in the pediatric population are rare and need precise evaluation,

especially in light of its favorable results in adults and its potential in a patient population with high susceptibility for the choice of treatment (frame-based versus no frame). The Pediatric CyberKnife© Registry represents the first registry that focuses on CKRS treatment for CNS lesions in the pediatric population and was initiated as a nationwide, multicenter registry. It is considered to fill the gap of deficient scientific evidence by bundling patient data, focusing on CKRS treatment and outcome parameters. The main goal of the registry is to inform about entity-specific treatment results as well as late radiation effects and related morbidities. Moreover, it aims to generate nationwide treatment guidelines in order to step up from local tumor and vascular board decisions. As such, the study protocol was developed on the basis of the most recent CKRS treatment and follow-up standards in adults supplemented by cognitive function assessment. This is for evaluating potential long-term effects of the radiation in developing children. The variables included in the protocol were chosen with respect to reliability and practicability in a multicenter setting reflecting the major aims of the registry: assessment of feasibility, safety, and efficacy in pediatric patients. The boundaries of this registry were initially set to the treatment modality of CKRS, the CNS, and the pediatric population. However, there are other treatment forms, such as Gamma Knife radiosurgery or proton beam radiation, which are equally limited in this subpopulation and who may benefit from a pre-existing platform for parallel data collection. Other future implications of the registry might be its expansion on an international level, involving more participating centers and thereby increasing case numbers as well as the degree of evidence and experience. All of these processes may alter the format and the scope of the registry in the future, requiring integration in an interdisciplinary network, such as the German Society of Radiation Oncology and the German Society for Pediatric Oncology and Hematology in order to increase its impact. Points for discussion are limitations of the registry, which are mainly related to its observational study type and the comprehensive lack of standardized CKRS treatment protocols for any of the observed entities, which might generate additional confounders within the registry. However, these limitations are just as much present in current clinical practice as they are in the registry and therefore are object of the current investigation.

Conclusions

The development and initiation of the Pediatric CyberKnife© Registry plays an essential role in evaluating a novel non-invasive treatment form in pediatric CNS lesions with a suspected similarly low morbidity profile as observed in adults. Eventually, it will serve as a basis for future clinical trials, inter-methodological comparisons, and changes of treatment algorithms.

Acknowledgments We thank Karin Dieckmann at the Department of Radiotherapy, Medical University, Beate Timmermann at the Clinic for Particle Therapy, University Hospital Essen, Germany and Ralf-Dieter Kortmann at the Department of Radiation Therapy, University of Leipzig, Germany for conducting the external review of the study protocol during the annual meeting of the Working group for Pediatric Radiation Oncology. We thank John Adler and Michael S.B. Edwards at the Department of Neurosurgery, Stanford University School of Medicine, Stanford, California, USA for their supportive advice, encouragement and methodical review.

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Author's contributions LNL developed the protocol, set up the multicenter cooperation and wrote the manuscript. AG and JD gave advice on study protocol and provided corrections for the manuscript. PV and VB supervised the study. MK was the main contributor in developing the study protocol and created the study-specific database.

Funding The study was not funded. The authors report no conflict of interest concerning the methods used in this study or the findings specified in this paper.

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflicts of interest There are no conflicts of interest or competing interests to report by any of the authors.

Ethics approval and consent to participate An ethics approval for this registry study was obtained by the ethics committee of the Charité – Universitätsmedizin in Berlin in January 2018 (EA2_232_17). All CyberKnife Centers in Germany gave written consent for participation in the study according to the described protocol. The study was registered at the German Clinical Trials Register (https://www.drks.de), DRKS-ID 00016973.

Consent for publication All authors reviewed the final manuscript and gave consent for publication in Child's Nervous System.

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