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Radiotherapy Protocol of Central Neurocytoma for Resource-limited Settings in the Absence of Official Guidelines: A Case Report and Review of the Literature

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Abstract

BACKGROUND: Central neurocytoma (CN) is one of the rarest brain tumors which can cause considerable threats to the patient. Studies and trials regarding its treatment are scarce, and no official guidelines are dedicated to this disease. The main principle of treatment generally consists of surgery and radiotherapy. The choice of radiotherapy is divided into conventional fractionated radiotherapy and stereotactic radiosurgery (SRS). However, access to SRS in developing countries such as Indonesia is still limited.

AIM: We report a case delineating the timeline and process of treatment in CN with a review of the literature.

METHODS: We report the case of a 29-year-old woman with a solid inhomogeneous mass (AP 5.63 × CC 5.36 × LL 5.16 cm) in the right ventricle, attached to the septum pellucidum, as displayed on the magnetic resonance imaging (MRI). The patient had been vomiting for the past three weeks and presented with bidirectional horizontal nystagmus.

RESULTS: Cognitive evaluation with Montreal Cognitive Assessment (MoCA-Ina) demonstrated a mild cognitive impairment. Biopsy was performed, and pathology analysis revealed some cells with fibrillary background and some with a honeycomb-like appearance. The immunohistochemistry staining showed positive results with synaptophysin and neuronal nuclear protein. According to the WHO classification of the central nervous system tumors, the profile favored CN Grade II. Subtotal resection (STR) was performed to reduce the tumor mass, which was measured with MRI 2-month post-surgery (AP 4.09 × CC 3.01 × LL 4.13 cm) and then followed by an external radiation program. Using intensity modulated radiation therapy (IMRT), a total dose of 54 Gy was given in 27 fractions, with the average planning target volume of 54.3 Gy. There was a minuscule reduction in tumor mass as seen in post-radiotherapy MRI (AP 4.00 × CC 3.86 × LL 3.63 cm). After the last session and at the 18-month follow-up, the patient did not have any complaints or abnormalities during clinical assessment. Reevaluation using MoCA-Ina showed an improved cognitive function.

CONCLUSIONS: In line with recent evidence, we demonstrated that STR followed by IMRT with the dosage of 54 Gy in 27 fractions was a feasible treatment strategy for CN that resulted in cognitive improvement, with no side effects.

Introduction

Central neurocytoma (CN) is among the rarest brain tumors and has an incidence rate of <1% of all central nervous system (CNS) neoplasms [1]. Initially described by Hassoun and colleagues in 1982 [2], CN is considered a benign neoplasm classified as WHO Grade II [3]. Although benign, the mass effect caused by the tumor Neurocytoma can lead to hydrocephalus due to intraventricular mass obstructing the cerebrospinal fluid system [4], which can be fatal if left untreated.

Treatment for CN generally consists of surgical resection followed by radiotherapy. Consensus or official guidelines for CN are non-existent; therefore, recent treatment choice is often individualized while guided by existing evidence. The surgical resection methods include gross total resection (GTR) and subtotal resection (STR), and the method of radiotherapy is usually divided into conventional fractionated radiotherapy (CFRT) and stereotactic radiosurgery (SRS). A study in 2019 reported a glaring disparity in SRT availability in different continents, with Asia having 19-time more people per unit ratio than North America [5]. In Indonesia, a country with a population of around 270 million, only five hospitals can perform stereotactic surgery [6]. Therefore, there is a necessity for reports regarding the treatment of CN. We report a case delineating the timeline and process of treatment in CN with a review of the literature.

Case Report

We report a 29-year-old woman who complained of a progressively worsening severe headache. She had been vomiting for the past three weeks, and there was no history of seizures or neurological deficits. The patient had no other significant medical history. On referral to a neurologist, a further examination was performed, and bidirectional horizontal nystagmus was noticed. Montreal Cognitive Assessment – Indonesian version (MoCA-Ina) resulted in a score of 25 points which signifies a mild cognitive impairment, particularly in the memory domain.

Surgery and biopsy

A cranial magnetic resonance imaging (MRI) demonstrated a heterogeneous solid mass with multiple calcifications in the right ventricle attached to the septum pellucidum, pushing against the cerebellum and third ventricle (Figure 1). This situation caused both left midline shifting and obstructive hydrocephalus. STR was then performed to reduce the mass and alleviate the symptoms of heightened intracranial pressure. Several issues were underlying the decision to choose STR rather than GTR. A transcortical approach from the keen point was chosen, from which the microscope could not visualize the tumor mass on the anterior side. Furthermore, in the middle of the operation, the surgeon could identify the septal vein; thus, continuing to operate would pose further risk to the patient.

A histopathological evaluation followed the surgery. The preparation from intraventricular biopsy revealed tumor fragments (volume ± 20 ccs), with the largest piece measuring 1.5 cm, while the smallest one was 0.2 cm. The fragments were composed of round cells with a diffuse hypercellular arrangement. Some cells had a fibrillary background, while the rest displayed a honeycomb-like appearance. The cells appeared monomorphic and isomorphic with round nuclei and speckled chromatin. However, mitotic structures were not observed. Histochemical analysis of glial fibrillary acidic protein was positive on the glial cells present. Synaptophysin was diffusely positive, and neuronal nuclear antigen (NeuN) was positive for some tumor cells. Meanwhile, epithelial membrane antigen (EMA), CD117, and cytokeratin were negative. Histopathologic and immunohistochemical profiles leaned toward CN Grade II of the WHO CNS tumors classification [3].

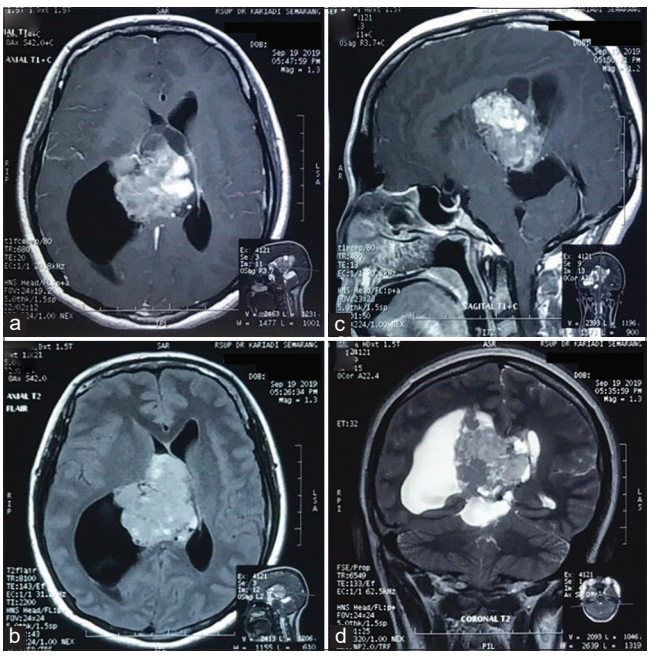

Figure 1: Pre-operative magnetic resonance imaging (A and C: T1+C; B: T2 Flair; D: T2) demonstrated an inhomogeneous intraventricular mass in the right lateral ventricle (AP 5.63 × CC 5.36 × LL 5.16 cm) attached to septum pellucidum with minimal intratumoral bleeding, cerebellar herniation, and signs of an increased intracranial pressure

Radiotherapy

At the 2-month follow-up after surgery, MRI showed a residual mass (Figure 2). The patient was sent to the radiotherapy unit to undergo an external radiation program. Radiotherapy was given with a total dose of 54 Gy in 27 fractions using intensity modulated radiation therapy (IMRT) (Figure 3). In planning, the dose-volume histogram (DVH) showed that all organs at risk were still within the safe limits of radiation tolerance (Figure 4), and the average dose of the planning target volume (PTV) was 54.3 Gy (Table 1). Chemotherapy was not included in the treatment plan. Afterward, tumor size was evaluated using MRI 3 months after radiotherapy was completed (Figure 5). The results showed a reduction in tumor mass compared to the pre-radiotherapy MRI in January 2020.

Outcome and follow-up

Subsequently, the patient did not have any complaints. No acute side effects were found on the physical examination, as described in the RTOG acute radiation morbidity scoring criteria. At the 18-month follow-up after radiotherapy, the patient did not express any complaints. No long-term side effects of radiotherapy as described in the RTOG late radiation morbidity scoring scheme or any neurological deficit were found on the physical examination. Cognitive reevaluation using the MoCA-Ina score revealed a normal result of 28 points,

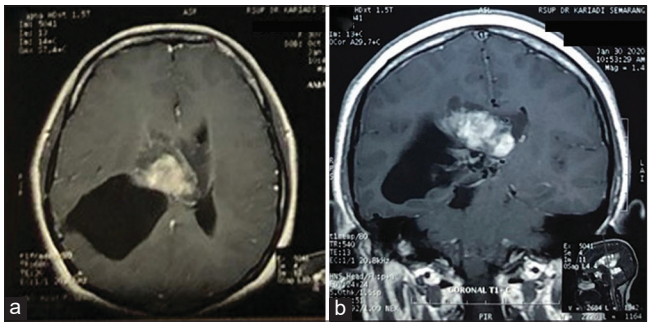

Figure 2: Post-operative cranial magnetic resonance imaging in T1 sequence with contrast (A: Axial; B: Coronal) demonstrated the remaining mass (AP 4.09 × CC 3.01 × LL 4.13 cm) after STR

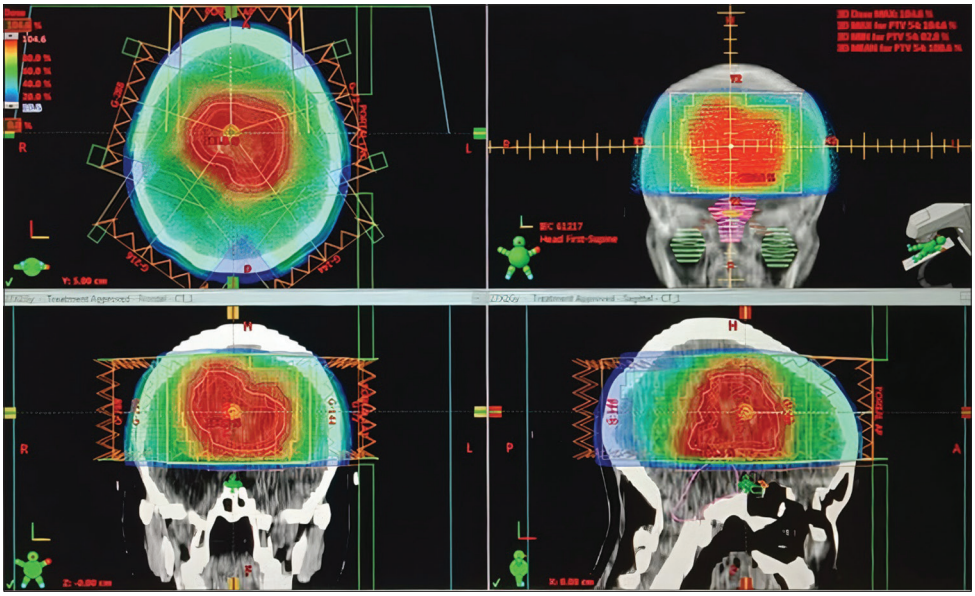

Figure 3: Three-dimensional planning with intensity-modulated radiation therapy (IMRT)

having improved from her previous assessment. The patient is continuously being followed up every six months.

Discussion

CN often occurs in young adults but can also be found in other age groups [7]. The National Cancer Database (2004–2015) collected the data of 223,404 patients diagnosed with primary brain tumors and 868 patients diagnosed using biopsy-proven neurocytoma. The mean age at diagnosis was 31 years, and there was an equal distribution between males (49.5%) and females (50.5%). The location of the tumors was spread among intraventricular tumors (622 [72%]), outside the ventricles (168 [19%]), and overlapped or not specific (78 [9%]) [8]. The same study also concluded that patient age ($p < 0.001$), WHO grade ($p < 0.001$), and medical comorbidity scores ($p = 0.002$) were associated independently with overall survival (OS). The clinical symptoms depend on the tumor location. These include headaches, seizures, nausea, vomiting, vision or gaze problems, imbalance, or decreased consciousness [9]. Patients with CN may clinically present with signs of increased intracranial pressure and obstructive hydrocephalus due to the tumor location, which frequently resides in the intraventricular foramen area [9], [10]. Obstructive hydrocephalus was found in our patient due to the tumor attached to the septum pellucidum, thus pushing the third ventricle. Our patient presented with a headache and bidirectional horizontal nystagmus, which has been reported can be caused by obstructive hydrocephalus [11].

Radiologic studies, including specific computed tomography (CT) scan and MRI, were chosen as the initial option for diagnosis and tumor localization [10], [12]. CN illustration on CT scans typically appears as an iso- to hyper-dense or mixed dense mass commonly found within the lateral ventricles, close to the septum pellucidum, and foramen of Monro [12], [13]. Hypodense

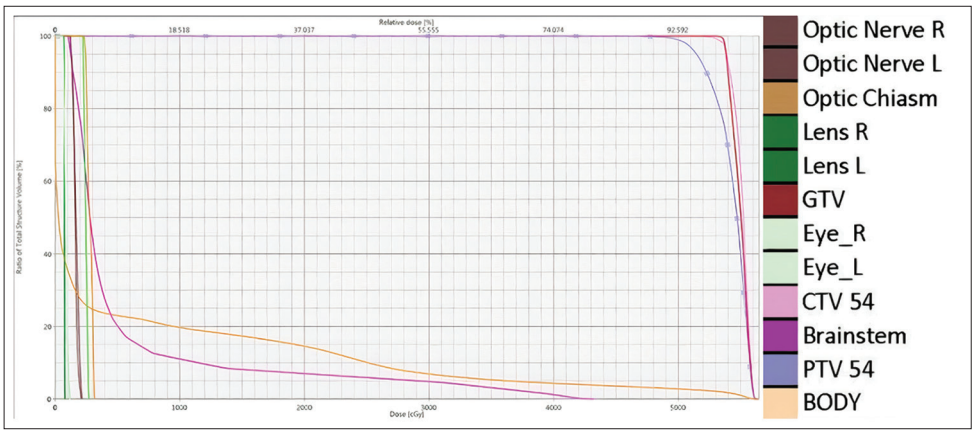

Figure 4: Dose and relative dose plotted in a graph against the ratio of total structure volume (%) with the structures labeled in color in correspondence to the graph

Table 1: Dose statistics of the external beam planning

Structure	Plan	Volume (cm^2)	Dose Cover (%)	Sampling Cover (%)	Min. Dose (cGy)	Max. Dose (cGy)	Mean dose (cGy)
Optic Nerve R	27 × 2 Gy	0.2	100.0	100.3	121.4	209.9	159.5
Optic Nerve L	27 × 2 Gy	0.5	100.0	99.8	117.6	221.0	168.2
Optic Chiasm	27 × 2 Gy	0.3	100.0	99.2	227.7	321.0	277.8
Lens R	27 × 2 Gy	0.1	100.0	100.1	68.1	78.7	73.4
Lens L	27 × 2 Gy	0.1	100.0	101.4	68.8	81.3	75.0
GTV*	27 × 2 Gy	51.1	100.0	100.0	5304.1	5635.2	5494.1
Eye R	27 × 2 Gy	7.7	100.0	100.0	61.00	122.2	85.3
Eye L	27 × 2 Gy	8.8	100.0	100.0	57.00	128.7	84.1
CTV† 54	27 × 2 Gy	105.3	100.0	100.1	5163.2	5647.7	5509.3
Brainstem	27 × 2 Gy	22.9	100.0	99.9	100.6	4326.3	553.7
PTV†+ 54	27 × 2 Gy	178.7	100.0	100.1	4470.8	5467.7	5431.8
Body	27 × 2 Gy	7018.3	100.0	100.6	0.0	5467.7	634.0

*Gross tumor volume; †Clinical target volume; †+Planning target volume.

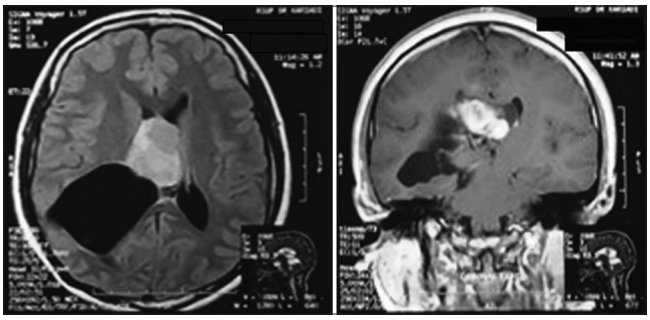

Figure 5: Magnetic resonance imaging 3-month post-radiotherapy (T2: left; T1+C: Right) demonstrated a slight reduction in mass (AP 4.00 × CC 3.86 × LL 3.63 cm)

areas correlated to cystic degeneration usually give a heterogeneous appearance to the tumor [13], [14]. MR imaging may illustrate heterogeneous isointense or slightly hypointense masses on T1-weighted and isointense to hyperintense on T2-weighted imaging [1], [12], [13], [14]. Histologically, CN is composed of monomorphic tumor cells with regular-round nuclei and a scant eosinophilic or clear cytoplasm appearing in an area of fibrillary stroma or neuropils [15]. There may be a calcification, small unremarkable nucleoli ("fried egg" appearance), and long capillary-sized vessels [9]. It is most likely derived from the subependymal neural progenitor cells [16], [17]. In immunohistochemistry, the presence of synaptophysin indicates neuronal cells and is considered a classic marker for CN. Neuronal nuclei (NeuN) also suggest the neuronal nature of the tumor and can serve as a reliable marker. EMA may differentiate CN from other types of CNS neoplasm. It is typically expressed in epithelial and ependymal cells; thus, its positivity can indicate ependymoma [18].

GTR is generally recommended as the primary therapy due to the minimal chance of recurrence [19]. A couple of single-center retrospective studies demonstrated a significantly longer OS and progression-free survival (PFS) in complete GTR compared to STR [4], [20]. However, radiotherapy is beneficial when complete surgical resection cannot be achieved due to difficult access to the tumor location or other complicated situations [10], [21], [22], [23]. Tumor resectability depends on the tumor size, location, the extent of the lesion, adherence to critical structure, and the surgeon's experience [21]. In the scenario where STR is performed, adjuvant radiotherapy has shown to significantly improve local control (LC), PFS, and prolong survival [19], [20], [24]. Interestingly, a systematic review in 2014 did not find significant difference in LC (93% vs. 88%, p = 0.40), OS (98% vs. 90%, p = 0.05), recurrence (RR = 0.57, 95% CI: 0.21–1.57), and risk of mortality (RR = 0.23, 95% CI: 0.05–1.05) between SRS and CFRT [25]. One international multicenter analysis in 2021 also could not find a significant difference in OS and PFS between different resections (p = 0.4) and radiation techniques (3D-Conformal Radiotherapy vs. IMRT, p = 1) [24]. Another systematic review in 2020 demonstrated that the different resections combined with adjuvant radiotherapy mainly affected the recurrence rate, not OS [26].

Regarding optimal dose, one meta-analysis in 2003 reviewed various radiotherapy dose regimes for CN after STR. The author found that the 5-year LC for equivalent dose in 2-Gy fractions was significantly (p = 0.0066) improved (98% vs. 69%) in higher doses (i.e., 54.0–62.2) compared to lower doses (i.e., 40.0–53.6 Gy). The 10-year LC in higher and lower doses was 89% versus 65% [27]. Another systematic review of radiotherapy doses using SRS and conventional radiotherapy (cRT) mentioned that the mean marginal (peripheral) dose of the SRS subgroup was 14.9 Gy (SD = 3.2; range 9–25 Gy) while the cRT subgroup was 53.0 Gy (SD 11.52; range 20–84 Gy). Meanwhile, the 5-year LC proportion among the SRS and cRT subgroup was 93% and 88%, respectively [23]. Further investigation of optimal dosage was continued by the aforementioned multicenter analysis, which stated that doses higher than 54 Gy were not associated with better clinical outcomes (p = 0.05) [24].

Conclusions

CN is a benign tumor that may cause serious and fatal complications. Surgical resection followed by radiotherapy is the mainstay of its treatment. If GTR cannot be performed, STR followed by radiotherapy can be done to ensure a good outcome. In resource-limited settings where SRS is not readily accessible, using CFRT such as IMRT can achieve comparable results

without lowering treatment outcomes. The optimal dose of CFRT in CN seems to be at 54 Gy, where in our case, it did not cause any side effects and improved cognition at the 3-month follow-up.

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