TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2023;38(1):22–28
doi: 10.5505/tjo.2022.3710

ORIGINAL ARTICLE

Radiation Therapy after Complete or Incomplete Resection of Central Neurocytomas: The Experience of Single Center

Meltem DAĞDELEN,[1] Rahşan KEMERDERE,[2] Merve ŞAHİN,[1] Mehmet Yiğit AKGÜN,[3] Ecem DEMİR,[1] Cumhur YILDIRIM,[1] Songül KARAÇAM,[1] Günay CAN,[4] Nil ÇOMUNOĞLU,[5] Ali Metin KAFADAR,[2] Ömer Erol UZEL[1]

[1]Department of Radiation Oncology, Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul-*Türkiye*
[2]Department of Neurosurgery, Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul-*Türkiye*
[3]Department of Neurosurgery, Kırıkkale Provincial Health Directorate Yüksek İhtisas Hospital, Kırıkkale-*Türkiye*
[4]Department of Public Health, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, İstanbul-*Türkiye*
[5]Department of Pathology, Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul-*Türkiye*

OBJECTIVE

The objective of the study was to evaluate the outcomes of central neurocytoma treatments.

METHODS

Between 2003 and 2019, 23 post-operative patients with central neurocytoma were included in the study. According to the World Health Organization (WHO) 2021 classification, 14 patients were classified as atypical neurocytoma. Gross total resection was performed in 12 patients whereas subtotal resection (STR) was performed in ten patients and eight patients had residual disease. In total, 13 patients received radiotherapy (RT), nine of whom were irradiated postoperatively, and four patients were irradiated after relapse. Recurrence and progression-free survival (PFS) of each subgroup were presented.

RESULTS

The median follow-up was 59 months (15–262 months). The 5-year overall survival (OS) was 89.3% and PFS was 83.4%. During follow-up in total three patients died; two patients had disease progression-related death, and one patient died because of his comorbidities. Comparing the outcome of RT group and the observation group; there was no recurrence in the radiotherapy group, but three recurrences or progression were detected in the observation arm. There was no statistical significance (p=0.257) due to the low number of patients in this subgroup. Patients with extraventricular tumors received postoperative radiotherapy; however, patients had recurrences and died due to disease progression. Furthermore, there was no statistical significance (p=1.00) when the operation type was evaluated. In terms of histopathology, recurrence or progression was observed in two patients with typical CN and one patient with atypical histology, which was not statistically significant (p=0.247).

CONCLUSION

All treatment modalities were applied in our cohort, but due to the small number of patients, the significance of any modality could not be demonstrated. However, the prognosis of the patients with extraventricular pathology was very poor and two patients died due to the disease.

Keywords: Central neurocytoma; extraventricular; radiotherapy; surgery; treatment modalities.

Received: June 27, 2022
Revised: September 21, 2022
Accepted: October 09, 2022
Online: November 16, 2022

Accessible online at:
www.onkder.org

Dr. Meltem DAĞDELEN
İstanbul Üniversitesi-Cerrahpaşa,
Cerrahpaşa Tıp Fakültesi,
Radyasyon Onkolojisi Anabilim Dalı,
İstanbul-Türkiye
E-mail: meltem.dagdelen@iuc.edu.tr

INTRODUCTION

Central neurocytoma (CN) is a rare brain tumor, which is usually located in the lateral ventricle.[1] Macroscopically CN cells consist of round, calcified lesions; whereas, microscopically the lesions consist of round cells with intercellular fibrilar zones and rosette-like structures. Immunohistochemical staining of synaptophysin is used to diagnose and differentiate. The presence of mitosis and necrosis is very rare. The cell with round nuclei and spread out thin chromatin are detected on electron microscopy.[2] Before the WHO 2016 classification, pathological differentiation into typical-atypical CN was determined according to mitotic activity, vascular proliferation, and focal necrosis rates; however, the WHO 2016 classifications are based on Ki67 levels.[3]

The gold standard treatment is surgery. Gross total resection (GTR) provides an advantage over subtotal resection (STR) in overall survival (OS) and progression-free survival (PFS).[4,5] Post-operative therapy is controversial. After a comprehensive review of available data, adjuvant radiotherapy (RT) increased PFS but had no benefit OS.[6–10] RT treatment volumes and doses are also controversial and differ greatly among clinics. Our study retrospectively analyzed the follow-up status and survival of 23 post-operative CN patients with and without RT.

MATERIALS AND METHODS

Study Population

We performed a retrospective analysis with an appropriate Local Ethics Committee approval (Approval Date and Number: 14.01.2021 A-09). Between 2003 and 2019, records of patients were screened who underwent surgery for brain tumors and 23 patients with CN were included. Before the WHO 2016 classification, pathological differentiation into typical-atypical CN was determined according to mitotic activity, vascular proliferation, and focal necrosis rates; however, the WHO 2016 and 2021 CN classifications are based on Ki67 levels.[11] Pathology pieces of all patients were reassessed by a senior neuropathologist according to the new classification.

Surgery

According to the localization and extension of the tumor, the CN operation was performed through an interhemispheric or transcortical approach. The lateral ventricle of the related side, where the main bulk of the tumor is located, was reached through anterior callosotomy in all interhemispheric cases. The transcortical route was performed through the middle frontal gyrus. The tumor was extracted with the Cavitron Ultrasonic Surgical Aspirator following the normal ependymal lining. The tumor's main determinant of total resection was the invasion of diencephalic and vascular structures (thalamostriate and internal cerebral veins). A combined approach (interhemispheric and transcortical) was used for total resection to remove the hidden part of the residual tumor on the superior wall of the lateral ventricle in the same session. For intra-axial extraventricular cases, transcortical resection was used according to the site of lesions. The external ventricular drainage system was placed in the ventricular cavity at the end of the surgery. The same craniotomy was used in recurrent cases.

RT Indication and Volume

For CN; RT indications are STR, atypical histology, and extraventricular location. Furthermore, the opinion on surgery about the quality of resection is considered in multidisciplinary councils.

During simulation computed tomography (CT), the patients were immobilized with a thermoplastic head and shoulder mask in a supine position. The non-contrast CT was obtained with a 2.5 mm slice thickness from the head to the first cervical vertebra on a GE Lightspeed 16 CT scanner. Organs at risk and target volumes were contoured according to the Radiation Therapy Oncology Group guidelines.

On magnetic resonance images (MRI), CN appears hyperintense in T2 FLAIR images, and contrast enhancement in T1 images. So for determining the irradiation volume, MRI were fused with simulation CT images to better visualize the Gross Tumor Volume using T1 and T2 FLAIR images. For the microscopic disease coverage, clinical target volume (CTV) is determined by contouring the whole lateral ventricles. Planning target volume is created by giving a 3–5 mm margin for daily set-up errors.

For the tumors located in ventricles, a boost to the operation bed was added. CTV was delineated with a margin of 1–2 cm to the operation bed in the extraventricular frontal lesion and 54 Gy was implemented with External Beam Radiotherapy. After the STR of the cerebellar tumor, stereotactic radiosurgery (SRS) was applied to the residue in 1 patient (13 Gy). Treatment modalities are described in Table 1.

Follow-up

Patients who were observed or were treated with RT after surgical treatment was followed up with physical and neurological examination, and cranial MRI every 3 months for the first 2 years, every 6 months between 2 and 5 years, and annually after 5 years.

Turk J Oncol 2023;38(1):22–28
doi: 10.5505/tjo.2022.3710

Table 1 Patients' characteristics

	n	%
Age (Median+range)	26 (12–41)	
Gender		
Male	12	52.2
Female	11	47.8
Resection type		
GTR	12	52.2
STR	10	43.4
Biopsy	1	4.3
Fractionation		
Conventional	12	52.2
SRS	1	4.3
Radiation treatment		
Postoperative after progression/definitive		
Postoperative adjuvant	9	39.1
Location		
Ventricular	21	91.3
Extraventricular	2	8.7
Pathology		
Typical neurocytoma	8	34.7
Atypical neurocytoma	15	65.2

GTR: Gross total resection; STR: Subtotal resection; SRS: Stereotactic radiosurgery

Statistical Analysis

PFS was determined as the time from operation to progression according to the RANO. The Kaplan–Meier survival analysis was performed for OS and PFS. Age, histopathological features, and Ki67 levels were evaluated in univariate analyzes. SPSS version 21 (IBM Corp. Armonk, NY) computer software was used for statistical analysis, and $p<0.05$ was accepted for statistical significance.

RESULTS

We identified 23 patients with the diagnosis of CN. The characteristics of the patients are in Table 1. The median age was 26 (range 12–41) and 12 (52%) patients were male. Twenty patients had tumors located at lateral ventricles, one patient's was at the third ventricle, and two patients had extraventricular tumors (frontal lobe and cerebellum). For the surgical routes; the interhemispheric was used in 14 cases, transcortical route in seven, combined route in one patient, and endoscopic biopsy was performed for one patient whose tumor was located on the posterior wall of the third ventricle. In 15 of the 23 patients, the lateral ventricle was reached from the right side; whereas the frontal horn of the left lateral ventricle was entered in seven patients. For a cerebellar tumor, suboccipital craniotomy was the entry route. In one patient, the right frontal subcortical extra-ventricular lesion was removed totally through a cortical window.

GTR was performed in 12 patients (52%) whereas STR was performed in 10 (46%) patients and eight patients had a median residual disease of 1.7 cc (range: 0.3–3.5 cc). Since the study spans many years, post-operative MRI's of two patients were not available; only eight residual volume values were reported. After the re-evaluation median Ki67 level of our study was 4 (range: 1–10). One patient was diagnosed by a stereotactic biopsy and treated with only RT. In total, 13 patients received RT, nine of whom were irradiated postoperatively, and four patients were irradiated after relapse. The median dose was 54 Gy ((Prescribed dose ranged from 45 to 54 Gy in 1,8 to 2 Gy fractions with 6MV). After 45 Gy to the lateral ventricle and operation bed, 9 Gy a boost to the operation bed was added. After the STR of the cerebellar tumor, 13 Gy SRS was given to the residue in one patient. Six patients undergoing GTR and four patients undergoing STR continue to be followed up without recurrence, and the median follow-up period was 75.3 months (27–130 months). The treatment of the patients is in shown Figure 1.

The median follow-up was 59 months (7–262 months). The 5-year OS was 89.3% and PFS was 83.4% (Figs. 2, 3). Three patients died. The cause of death was disease progression in two patients and unknown in one. Progression was detected in five patients. There were three recurrences after GTR and two progressions of residue after STR (Fig. 4). After progression all patients received RT, 3 of them were reoperated before irradiation. One patient with a history of STR could not be re-operated and only received RT treatment.

When patients which have intraventricular tumors were analyzed, comparing the outcome of RT group and the observation group; there was no recurrence in the radiotherapy group, but three recurrences or progression were detected in the observation arm. There was no statistical significance ($p=0.257$) due to the low number of patients in this subgroup. Furthermore, there was no significance detected when the operation type was evaluated ($p=1.00$). Recurrence or progression was observed in two patients with typical CN histology and one patient with atypical histology ($p=0.247$) (Fig. 5). Ki 67, age, and gender were also found to have no statistically significant relations with progression and recurrence ($p=1.00$, $p=1.00$, and $p=1.00$, respectively).

For the patients who had extraventricular tumors; although radiotherapy was given after GTR, recurrence

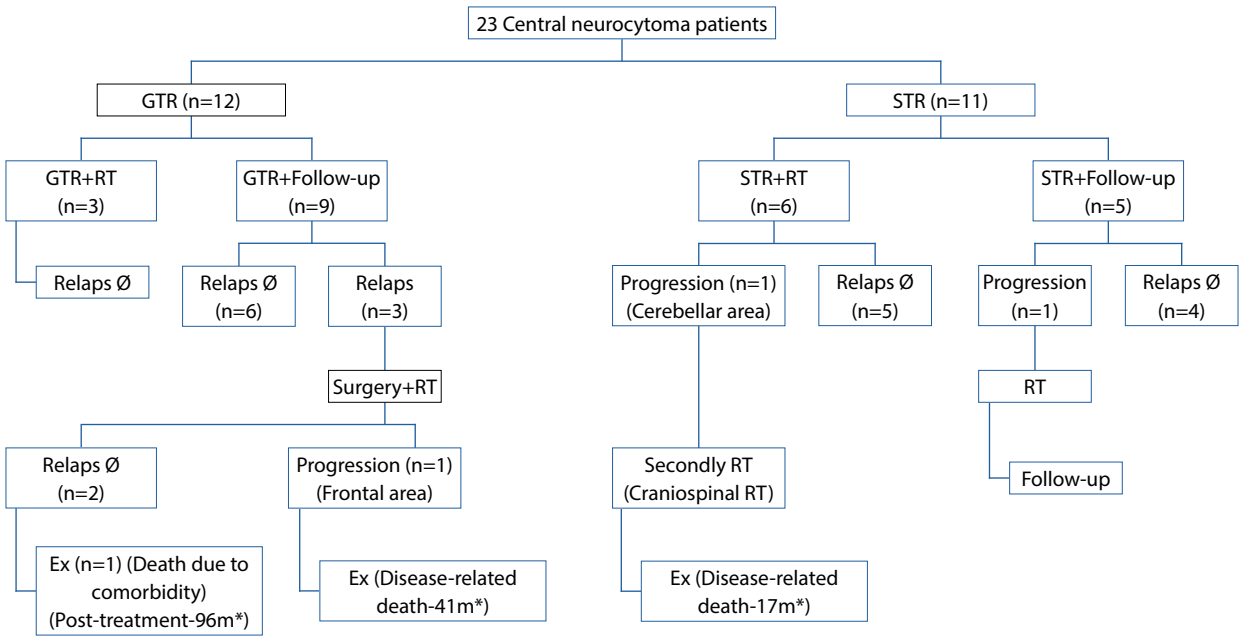

Fig. 1. The treatment of the patients.
*: This calculation is made between surgery time and death time. GTR: Gross total resection; STR: Subtotal resection; RT: Radiotherapy

was observed in the patient with frontal CN. The patient, who underwent surgery in both recurrences, was administered four cycles of chemotherapy after the last surgery. The chemotherapy regimen data are unknown. Soft tissue and bone metastases were detected during the interim evaluation. The patient died due to disease progression while receiving chemotherapy treatment. On the other hand, the patient with cerebellar tumor was treated with Gamma-Knife postoperatively; nonetheless, after recurring with craniospinal seeding, he received craniospinal RT. The prescribed radiation dose for this patient was 46 Gy in 23 fractions. He died 6 months after the treatment.

Patterns of dissemination of patients who relapsed were analyzed. In all patients who relapsed after GTR, the recurrence was in the primary tumor site. While recurrence was detected through spinal dissemination in one patient who underwent STR, the other patient's tumor progressed through the 3rd ventricle to the 4th ventricle. No serious acute or chronic side effects were found in both arms. The most common toxicities were observed as partial alopecia, fatigue, and skin reaction. After irradiation neurocognitive tests were not performed, because pre-operative neurocognitive data were missing and the evaluation would be ineffective. However, no clinically obvious neurocognitive deterioration was observed during their follow-up.

DISCUSSION

Surgery is the most important treatment option for CN and one of the prognostic factors.[12] GTR has a statistically significant improvement in OS and local control compared to STR.[4,5,13] However, Byun et al.[14] could not find any statistical significance for local control between STR and GTR. In our study, three patients with GTR treated by RT had no recurrence, whereas three out of nine patients who had GTR without RT recurred. Two patients with STR had progression: the one with cerebellar tumor underwent RT before progression and the other patient underwent RT after progression. In the light of the discussion above, GTR is an important prognostic factor; however, we did not find any statistical significance when compared to STR.

Another prognostic factor is being pathologically atypical-typical.[15] Having an atypical feature is a poor prognostic factor in local control and OS.[14] Before the WHO 2016, pathological differentiation into typical-atypical was made according to mitotic activity, vascular proliferation, and focal necrosis rates; however, the WHO 2016 guidelines are made based on Ki67 levels.[3] After the re-evaluation of the pathology specimen according to the WHO 2016 classification, 14 patients were classified as atypical neurocytomas. When the two groups were compared in terms of atypia, no

Turk J Oncol 2023;38(1):22–28
doi: 10.5505/tjo.2022.3710

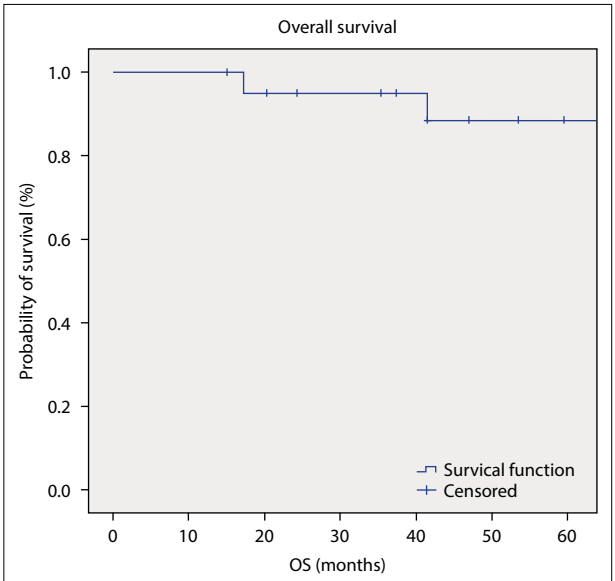

Fig. 2. Overall survival.

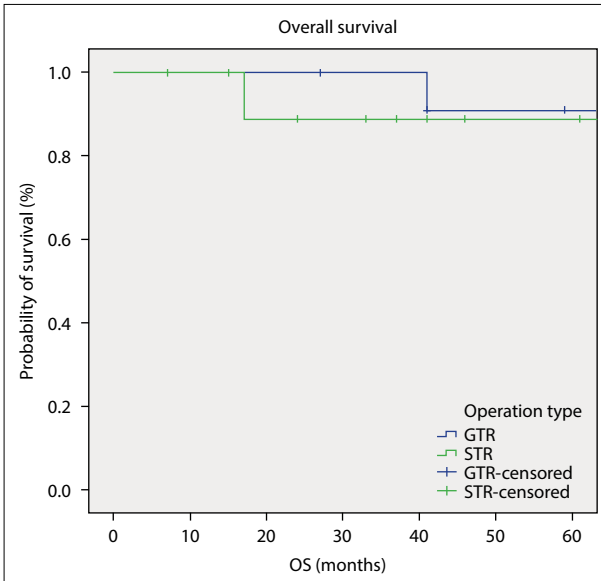

Fig. 4. Kaplan-Meier curves of each subgroup.
GTR: Gross total resection; STR: Subtotal resection.

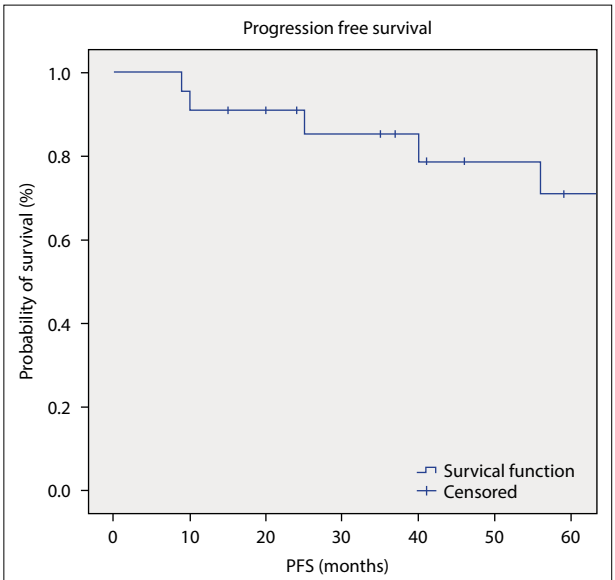

Fig. 3. Progression-free survival.

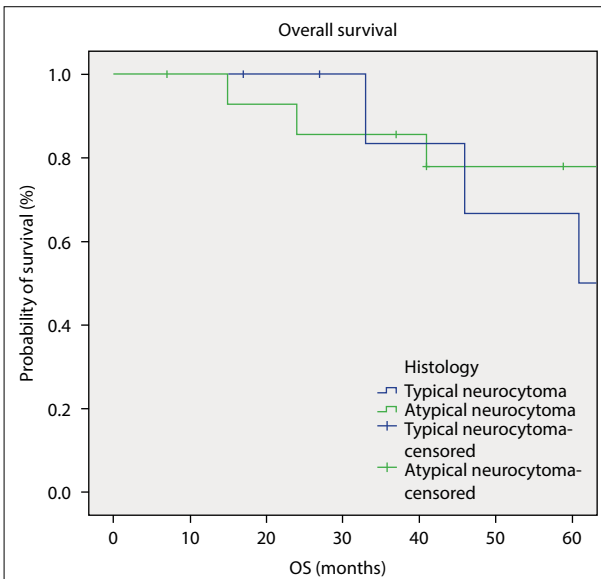

Fig. 5. Kaplan-Meier curves of each histology.

statistically significant difference was observed. In some studies, published before the WHO 2016 guidelines, a proliferation index such as Ki 67 or MIB L1 was reported to be prognostic for CN. Ki67> 2% was associated with a worse prognosis.[8,14,16] Another study also showed that Ki 67>4% had a poor prognosis.[17,18] In the recent article, the main risk factors for recurrence have demonstrated the presence of residual disease and the Ki-67 index of over 5%.[19] However, in our study, no relationship was found between Ki67.

In the literature, it is stated that RT provides a statistically significant benefit in local control, yet its effectiveness has not been demonstrated in OS.[5,20,21] For the optimal dose of RT in typical neurocytomas, 50 Gy after STR has been sufficient.[22] Again, in another study by Rades et al.,[20] the benefit of RT over 54 Gy could not be shown. In this context, 50 or 54 Gy is recommended as the optimum RT dose.[23] In these studies the treatment volume is planned by giving a 2 cm margin to the operation site, such as a low-grade

glial tumor.[23] However, recent data support 1 cm as a margin for low-grade glial tumor CTV. In our study, all lateral ventricles were considered as CTV. Since the study spans many year, multidisciplinary decisions have evolved into coverage of whole lateral ventricles, the tumor originates mainly from the lateral ventricle and there is a possibility of intraventricular relapse. For contouring post-operative tumor bed, CTV is delineated with a margin of 1–2 cm to the operation bed which generally covers whole lateral ventricules. Because these lesions are not encapsulated, the resectable tumors cannot be removed totally with surgery. So that, a boost dose to the primary tumor was given.

In terms of tumor localization, extraventricular localization is rare in CNs, mostly located in the lateral ventricle. The other most common extraventricular sites for CN are 46% frontal, 23% parietal, 14% temporal, and 11% occipital. In the retrospective evaluation made by Brat et al.,[24] recurrences are seen only after STR, and the presence of atypical features was associated with poor prognosis. In our study, two recurrences were observed: The first was a typical cerebellar CN with STR, and the other was an atypical frontal CN with GTR. Post-recurrence distant metastasis was observed in both cases. Bone and soft tissue metastasis were detected in the patient with the frontal location and, chemotherapy (CT) was administered after a second relapse. Soft tissue and bone metastases were detected during the interim evaluation after chemotherapy. Chemotherapy as adjuvant therapy is still controversial in the literature.[1] A limited number of case reports have discussed adjuvant or salvage chemotherapy. A variety of chemotherapeutics and regimens have been used, often based on a different initial diagnosis. In the literature, some series were treated with salvage chemotherapy because of the presence of metastases. These small sample size studies reported that chemotherapy reduced 25–60% of tumor volume.[10] As a result, chemotherapy was part of the treatment strategy. Craniospinal spread was observed in the patient with the cerebellar location. In a case report about craniospinal seeding, chemotherapy has been used.[25] However, in literature the evidence level of chemotherapy is not strong, so that in our patient we administered craniospinal RT without chemotherapy.

When RT-related side effects were evaluated, radionecrosis due to RT was shown in two studies Alan,[26,27] yet no Grade 3 chronic side effects were observed in our study. The negative neurocognitive effects of brain irradiation are observed in patients who had whole-brain irradiation or prophylactic cranial irradiation, which is used in brain metastases, medulloblastoma, and leukemias. The neurocognitive decline is the main reason for omitting or delaying radiotherapy in LGGs.[28] Besides RT, it was shown that also tumor progression harmed neurocognitive functions. However, neurocognitive testing was not performed because of no baseline data on the patients' neurocognitive status.

Limitations

In this study, which is limited to a small sample, comparisons of treatment methods cannot be made, and it is a retrospective study. Its strength is that it is a single-center and the application of all treatment methods. Although the small number of patients seems to be a disadvantage in terms of statistical analysis, there is a reasonable number of patients in terms of CN cases.

CONCLUSION

All treatment modalities were applied in the study, but due to the small number of patients, the significance of any modality could not be demonstrated. Apart from this, two extraventricular neurocytomas were treated and followed in our study. Recurrence and metastasis were detected in two patients, and two patients died because of the disease.

Peer-review: Externally peer-reviewed.

Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (no: A-09, date: 14/01/2021).

Financial Support: None declared.

Authorship contributions: Concept – M.D., Ö.E.U.; Design – R.K., M.Ş.; Supervision – M.Y.A., A.M.K.; Funding – N.Ç., C.Y.; Materials – N.Ç., C.Y., E.D., S.K.; Data collection and/or processing – G.C., M.Y.A.; Data analysis and/or interpretation – G.C., S.K.; Literature search – R.K., M.D.; Writing – M.D., E.D., M.Ş.; Critical review – Ö.E.U., A.M.K.

REFERENCES

1. Choudhari KA, Kaliaperumal C, Jain A, Sarkar C, Soo MY, Rades D, et al. Central neurocytoma: a multi-disciplinary review. Br J Neurosurg 2009;23(6):585–95.
2. Hassoun J, Söylemezoglu F, Gambarelli D, Figarella-Branger D, von Ammon K, Kleihues P. Central neurocytoma: a synopsis of clinical and histological features. Brain Pathol 1993;3(3):297–306.

Turk J Oncol 2023;38(1):22–28
doi: 10.5505/tjo.2022.3710

3. Diamandis P, Aldape K. World Health Organization 2016 classification of central nervous system tumors. Neurol Clin 2018;36(3):439–47.
4. Hallock A, Hamilton B, Ang LC, Tay KY, Meygesi JF, Fisher BJ, et al. Neurocytomas: long-term experience of a single institution. Neuro Oncol 2011;13(9):943–9.
5. Rades D, Schild SE. Treatment recommendations for the various subgroups of neurocytomas. J Neurooncol 2006;77(3):305–9.
6. Kim DG, Kim JS, Chi JG, Park SH, Jung HW, Choi KS, et al. Central neurocytoma: proliferative potential and biological behavior. J Neurosurg 1996;84(5):742–7.
7. Tomura N, Hirano H, Watanabe O, Watarai J, Itoh Y, Mineura K, et al. Central neurocytoma with clinically malignant behavior. AJNR Am J Neuroradiol 1997;18(6):1175–8.
8. Mackenzie IR. Central neurocytoma: histologic atypia, proliferation potential, and clinical outcome. Cancer 1999;85(7):1606–10.
9. Rades D, Fehlauer F, Schild SE. Treatment of atypical neurocytomas. Cancer 2004;100(4):814–7.
10. Leenstra JL, Rodriguez FJ, Frechette CM, Giannini C, Stafford SL, Pollock BE, et al. Central neurocytoma: management recommendations based on a 35-year experience. Int J Radiat Oncol Biol Phys 2007;67(4):1145–54.
11. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO classification of tumors of the central nervous system: A summary. Neuro Oncol 2021;23(8):1231–51.
12. Wang M, Zhou P, Zhang S, Liu X, Lv L, Wang Z, et al. Clinical features, treatment, and long-term outcomes of central neurocytoma: A 20-year experience at a single center. World Neurosurg 2018;109:e59–e66.
13. Vasiljevic A, François P, Loundou A, Fèvre-Montange M, Jouvet A, Roche PH, et al. Prognostic factors in central neurocytomas: a multicenter study of 71 cases. Am J Surg Pathol 2012;36(2):220–7
14. Byun J, Hong SH, Yoon MJ, Kwon SM, Cho YH, Kim JH, et al. Prognosis and treatment outcomes of central neurocytomas: clinical interrogation based on a single center experience. J Neurooncol 2018;140(3):669–77.
15. Söylemezoglu F, Scheithauer BW, Esteve J, Kleihues P. Atypical central neurocytoma. J Neuropathol Exp Neurol 1997;56(5):551–6.
16. Schmidt MH, Gottfried ON, von Koch CS, Chang SM, McDermott MW. Central neurocytoma: a review. J Neurooncol 2004;66(3):377–84.
17. Kaur G, Kane AJ, Sughrue ME, Oh M, Safaee M, Sun M, et al. MIB-1 labeling index predicts recurrence in intraventricular central neurocytomas. J Clin Neurosci 2013;20(1):89–93.
18. Imber BS, Braunstein SE, Wu FY, Nabavizadeh N, Boehling N, Weinberg VK, et al. Clinical outcome and prognostic factors for central neurocytoma: Twenty year institutional experience. J Neurooncol 2016;126(1):193–200.
19. Konovalov A, Maryashev S, Pitskhelauri D, Siomin V, Golanov A, Dalechina A. The last decade's experience of management of central neurocytomas: Treatment strategies and new options. Surg Neurol Int 2021;12:336.
20. Rades D, Fehlauer F, Ikezaki K, Schild SE. Dose-effect relationship for radiotherapy after incomplete resection of atypical neurocytomas. Radiother Oncol 2005;74(1):67–9.
21. Samhouri L, Meheissen MAM, Ibrahimi AKH, Al-Mousa A, Zeineddin M, Elkerm Y, et al. Impact of adjuvant radiotherapy in patients with central neurocytoma: a multicentric international analysis. Cancers (Basel) 2021;13(17):4308.
22. Rades D, Schild SE. Is 50 Gy sufficient to achieve long-term local control after incomplete resection of typical neurocytomas? Strahlenther Onkol 2006;182(7):415–8.
23. Rades D, Schild SE, Ikezaki K, Fehlauer F. Defining the optimal dose of radiation after incomplete resection of central neurocytomas. Int J Radiat Oncol Biol Phys 2003;55(2):373–7.
24. Brat DJ, Scheithauer BW, Eberhart CG, Burger PC. Extraventricular neurocytomas: Pathologic features and clinical outcome. Am J Surg Pathol 2001;25(10):1252–60.
25. Ando K, Ishikura R, Morikawa T, Nakao N, Ikeda J, Matsumoto T, et al. Central neurocytoma with craniospinal dissemination. Magn Reson Med Sci 2002;1(3):179–82.
26. Paek SH, Han JH, Kim JW, Park CK, Jung HW, Park SH, et al. Long-term outcome of conventional radiation therapy for central neurocytoma. J Neurooncol 2008;90(1):25–30.
27. Chen YD, Li WB, Feng J, Qiu XG. Long-term outcomes of adjuvant radiotherapy after surgical resection of central neurocytoma. Radiat Oncol 2014;9:242.
28. Surma-aho O, Niemelä M, Vilkki J, Kouri M, Brander A, Salonen O, et al. Adverse long-term effects of brain radiotherapy in adult low-grade glioma patients. Neurology 2001;56(10):1285–90.