GMJ 2024;35:161-167

DOI: http://dx.doi.org/10.12996/gmj.2023.3762

Retrospective Analysis of the Factors Affecting Recurrence, Survival, and Effect of Hippocampus Radiotherapy Doses on Neurocognitive Functions in Patients Diagnosed with Glioblastoma Multiforme

Glioblastoma Multiforme Tanısıyla Tedavi Edilen Hastalarda Nüks, Sağkalımı Etkileyen Faktörlerin ve Hipokampus Radyoterapi Dozlarının Nörobilişsel Fonksiyonlara Etkisinin Retrospektif Analizi

Sevilcan İnan[1], Öznur Dönmez Tutanç[1], Hülya Ertaş[2], Fatih Aydemir[3], Burcu Caner[4], Turgay Toksoy[5], Pınar Çona[6]

[1]University of Health Sciences Türkiye, Bursa City Hospital, Clinic of Radiation Oncology, Bursa, Türkiye
[2]University of Health Sciences Türkiye, Bursa City Hospital, Clinic of Medical Oncology, Bursa, Türkiye
[3]University of Health Sciences Türkiye, Bursa City Hospital, Clinic of Neurosurgery, Bursa, Türkiye
[4]Bursa Uludağ University Faculty of Medicine, Department of Medical Oncology, Bursa, Türkiye
[5]Ali Osman Sönmez Oncology Hospital, Clinic of Medical Physics, Bursa, Türkiye
[6]University of Health Sciences Türkiye, Bursa City Hospital, Medical Physics, Clinic of Radiation Oncology, Bursa, Türkiye

ABSTRACT

Objective: This study aimed to evaluate radiotherapy (RT) doses, RT effects on neurocognitive functions, and possible factors that may affect recurrence or death in patients with glioblastoma multiforme (GBM).

Methods: The data of 21 patients with GBM were retrospectively analyzed. RT treatment plans and doses and hippocampus ipsilateral and contralateral doses were recorded. The Mini-Mental State Examination (MMSE) is used to assess neurocognitive functions. The time of recurrence and death, if any, of the patients was recorded. Factors such as gender, age, patient performance status, tumor size, tumor localization, type of surgery, and time between surgery and RT were analyzed to determine any effect on the risk of recurrence or death.

Results: The median planning target volume dose was 59.86 gray (Gy). The maximum ipsilateral hippocampus dose was 51.85 Gy, and the maximum contralateral hippocampus dose was 46.25 Gy. With the MMSE, 3 of 4 patients had cognitive impairment. At the end of follow-up, 16 patients had recurrence and died. The median disease-free survival was 10 months [95% confidence interval (CI): 5.7-14.2], and the median overall survival was 24 months (95% CI: 16.0-31.9). Only poor performance status increased the risk of recurrence (hazard ratio: 4.31, 95% CI: 1.26-14.70, p=0.02).

ÖZ

Amaç: Bu çalışmada glioblastoma multiforme (GBM) tanılı hastalarda radyoterapi (RT) dozları ve RT'nin nörobilişsel etkileri ile nüks veya ölümü etkileyebilecek olası faktörlerin değerlendirilmesi amaçlanmıştır.

Yöntemler: GBM tanılı 21 hastanın verilerini retrospektif olarak inceledik. RT tedavi plan ve dozları ile hipokampus ipsilateral ve kontralateral dozları kaydedildi. Nörobilişsel işlevleri değerlendirmek için Mini-Mental Durum Muayenesi (MMDM) yapıldı. Hastaların varsa nüks ve ölüm zamanları kaydedildi. Yaş, cinsiyet, hasta performans durumu, tümör boyutu, cerrahi tipi, tümör lokalizasyonu ve cerrahi ile RT arasındaki süre gibi faktörlerin nüks veya ölüm riski üzerindeki etkisini belirlemek için analiz yapıldı.

Bulgular: Hastaların medyan planlama tedavi volümü dozu 59,86 gray (Gy) idi. Maksimum ipsilateral hipokampus dozu 51,85 Gy ve maksimum kontralateral hipokampus dozu 46,25 Gy idi. MMDM ile 4 hastanın 3'ünde bilişsel işlev bozukluğu vardı. İzlem sonunda 16 hastada nüks ve ölüm saptandı. Medyan hastalıksız sağkalım 10 aydı [%95 güven aralığı (GA): 5,7-14,2], medyan genel sağkalım 24 aydı (%95 GA: 16,0-31,9). Sadece kötü performans durumunun nüks riskini artırdığı saptandı (tehlike oranı: 4,31, %95 GA: 1,26-14,70, p=0,02).

Address for Correspondence/Yazışma Adresi: Burcu Caner MD, Bursa Uludağ University Faculty of Medicine, Department of Medical Oncology, Bursa, Türkiye
E-mail / E-posta: drburcucaner@gmail.com
ORCID ID: orcid.org/0000-0003-1591-3323

Received/Geliş Tarihi: 12.12.2022
Accepted/Kabul Tarihi: 08.05.2023

ABSTRACT

Conclusion: Because hippocampus shielding was not performed, our hippocampus doses were high. Hippocampal-sparing RT is essential for the preservation of neurocognitive functions. The increased risk of recurrence in patients with poor performance status is possibly related to treatment dose reduction, delay, or discontinuation.

Keywords: Glioblastoma, radiotherapy, hippocampus, cognitive dysfunction

ÖZ

Sonuç: Hipokampus koruması yapılmadığı için hipokampus dozlarımız yüksekti. Hipokampal koruyucu RT, nörobilişsel işlevlerin korunması için gereklidir. Performans durumu kötü olan hastalarda artmış nüks riski, muhtemelen tedavi dozunun azaltılması, tedavinin geciktirilmesi veya kesilmesi ile ilişkilidir.

Anahtar Sözcükler: Glioblastoma, radyoterapi, hipokampus, bilişsel bozukluk

INTRODUCTION

Primary brain tumors constitute approximately 2% of all cancers. In adults, glioblastoma multiforme (GBM) and grade 3 anaplastic astrocytoma (AA) are the two most common histological types (1,2). GBM, the most common and aggressive primary malignant intracranial tumor in adults, accounts for 50-60% of all astrocytic tumors. The patients are usually between 45 and 70 years of age. Diagnosis in childhood is rare. The male/female ratio is approximately 1.5/1 (3-5).

GBM is an infiltrating tumor located in the cerebral hemisphere. It is commonly at the borders of the parietal, occipital, and frontal lobes. They usually occupy more than one functional brain region because of their diffuse and deep localization, which is one of the main factors that make surgery difficult. They can also be localized outside the cerebral hemispheres. Almost half of brainstem glial tumors exhibit high malignancy characteristics. Furthermore, approximately 10% of GBMs are not deeply localized and may mimic cerebral metastases by localizing on the white-gray matter border (6-9).

The standard treatment is the Stupp protocol, which involves surgical resection of the tumor, followed by regional radiotherapy (RT) with concurrent temozolomide (TMZ) chemotherapy and six adjuvant cycles of TMZ (10). A randomized phase III study revealed that RT and TMZ combination prolongs survival in GBM. In this study, 573 patients were randomized to receive RT only or RT concurrent with TMZ, followed by adjuvant TMZ. RT was administered in 30 fractions [2 gray (Gy)/day] totaling 60 Gy. Concurrent TMZ was administered at a dose of 75 mg/m^2/day continuously during RT, including weekends. Adjuvant TMZ was initiated 28 days after the completion of RT and was administered for 6 cycles (150-200 mg/m^2/day, on 1-5 days every 28 days). In this study, the median overall survival (OS) was 12 months in the RT-alone arm and 15 months in the RT-TMZ arm. The 2-year survival rates were 10% and 26%, respectively. The median disease-free survival (DFS) was 5 months and 6.9 months. The 1- and 2-year DFS rates were 9% and 2% in the RT-alone arm and 27% and 11% in the RT-TMZ arm ($p<0.0001$). In this phase III study, the RT-TMZ combination demonstrated a remarkable improvement in survival (11).

In a phase II study by Athanassiou et al. (12), among 110 patients, RT alone (60 Gy) was compared with RT-TMZ treatment. The results of the study favored the combined treatment arm: the median DFS was 5.2 months vs. 10.8 months; the 1-year DFS rates were 7.7% vs. 36.6%; the median OS was 7.7 months vs. 13.4 months; and the 1-year OS rates were 15.7% vs. 56.3%, respectively. Toxicity was mostly hematological, and 1 patient was reported to have died due to febrile neutropenia.

The hippocampus plays an important role in emotional learning and memory consolidation (13,14). Whole-brain RT can lead to various side effects, such as the development of cerebellar and neurocognitive dysfunctions and impaired short-term memory and learning ability (15,16). Interruption of neurogenesis in the subgranular region can lead to memory impairment (17,18). The function of the hippocampus is negatively affected by radiation. Therefore, improving techniques to protect the hippocampus from radiation is vital. Dosimetric studies performed with intensity-modulated radiotherapy (IMRT) or tomotherapy in the literature show promise.

In our study, we evaluated RT doses and hippocampal neurocognitive effects in patients with GBM treated with the Stupp protocol. We also evaluated treatment tolerance, disease-free and OS times, and possible factors that may affect recurrence or death.

MATERIALS AND METHODS

In our study, we retrospectively evaluated 21 patients treated with a histologically confirmed diagnosis of GBM between April 2015 and October 2020. Inclusion criteria were as follows: being over 17 years of age, having Eastern Cooperative Oncology Group (ECOG) performance score ≤3, and having normal bone marrow, renal, and liver function (defined as hemoglobin ≥10 g/dL, thrombocyte count ≥100,000/µL, absolute neutrophil count ≥1,500/µL; serum creatinine level <1.5 mg/dL; alanine aminotransferase and aspartate aminotransferase levels <2.5 times the upper limit of normal, total bilirubin <1.5 times the upper limit of normal). Patients with poor medical condition due to other comorbidities or infections were excluded from the study.

The treatment protocol was TMZ concurrent RT with a median of 60 Gy (2 Gy-60 Gy) with standard 6 mV photon energy applied according to the Stupp protocol. In RT, we used VMAT and IMRT techniques in 30 fractions as planning target volume 1 (PTV1)=GTV+2 cm=40 Gy, PTV2=GTV+1 cm=60 Gy as standard. TMZ was administered concurrently with RT as 75 mg/m^2/day throughout RT; and it was administered 150-200 mg/m^2/day, on 1-5 days every 28 days for 6 cycles, following.

When evaluating neurocognitive functions, we first drew the hippocampus retrospectively to determine RT doses. We further evaluated the ipsilateral and contralateral hippocampus doses. Subsequently, the Mini-Mental State Examination (MMSE) was performed on 4 alive patients in the outpatient setting. The MMSE evaluates orientation, registration (short-term memory), recall, attention and calculation, language, and the ability to understand and follow verbal and written commands. A score equal to or

greater than 24 indicates normal cognition. Scores below 24 indicate cognitive impairment (19-23 points: mild, 10-18 points: moderate, ≤9 points: severe impairment). The MMSE test was obtained from the internet (19).

Disease recurrence and death data were obtained from patient files. DFS was defined as the length of time between the end of primary treatment for cancer and the time of disease recurrence or death. OS was defined as the length of time from GBM diagnosis to death.

This study was conducted in accordance with the Declaration of Helsinki. Ethics committee approval was obtained from the Bursa City Hospital Institutional Clinical Research Ethics Committee for the study (approval number: 2019-KAEK-140, 2021-19/7, date: 20.10.2021).

Statistical Analysis

Statistical analysis was performed using SPSS software version 28.0 (IBM Corp., Armonk, NY, USA). The variables' distribution is evaluated using the Shapiro-Wilk test, and the variables are given as median (minimum-maximum) values and frequency values. Categorical variables were compared using the chi-square test and Fisher's exact test. The Kaplan-Meier test, with comparisons made with the log-rank test, was used for survival analyses. Cox regression analysis was used to evaluate possible factors on the risk of recurrence and death. A p-value <0.05 is considered statistically significant.

RESULTS

Twenty-one patients were involved in the study. After the median follow-up period of 66 months, the median DFS was 10 months [95% confidence interval (CI): 5.7-14.2 months] and the median OS was 24 months (95% CI: 16.0-31.9 months). The patients' clinical characteristics are given in Table 1.

We administered TMZ to 21 patients concomitantly with RT. 4 patients could not complete RT because of ECOG performance status deterioration. Two patients died during RT. TMZ-induced pancytopenia developed in one patient, which required treatment delay. In the first-month control MRI after RT, 2 patients had residual/recurrent mass images and were referred for surgery. Adjuvant TMZ could not be administered to 5 patients because of ECOG performance status deterioration. In 1 patient, the dose was reduced by 10% because of grade 2 thrombocytopenia. Four patients had recurrence on adjuvant treatment. Three of them were referred for surgery. One patient underwent reirradiation and was administered second-line chemotherapy following. Seventeen of 21 patients who died during the follow-up period, 4 patients remained alive.

In the statistical analysis, we examined the factors that may alter the risk of recurrence or death. Upon evaluation for the risk of recurrence, being older than 50 years of age, being male, having poor ECOG performance score, smaller tumor size, total excision, tumors on right cerebral hemisphere or non-frontal location, and the interval between surgery and RT being more than 4 weeks were found as factors increasing the risk, with only poor ECOG performance score being statistically significant (p=0.02). Factors increasing the risk of death were the same as those for the risk of recurrence, except that having a left cerebral tumor seemed to increase the risk of death, and none of the factors were statistically significant. The Cox regression analysis results are given in Tables 2, 3.

RT critical organ doses are given in Table 4. We further examined the ipsilateral and contralateral hippocampus doses of 19 patients. The median ipsilateral maximum hippocampus dose was 61.21 Gy (minimum-maximum: 26.53-63.06), and the median contralateral maximum hippocampus dose was 48.01 Gy (minimum-maximum: 16.03-62.89). The ipsilateral and contralateral hippocampus doses are given in Table 5.

In our evaluation of 4 living patients with MMSE, we found 1 patient with normal cognitive function, one with mild cognitive function, one with moderate cognitive function, and one with severe cognitive dysfunction. The MMSE is shown in Figure 1.

DISCUSSION

In high-grade astrocytomas, the 5-year survival after treatment with surgery and RT is less than 10-20%; the median OS is 27 months in AA and 8 months in GBM (20).

The treatment of GBM consists of surgery, followed by RT and chemotherapy. Chemotherapy has been used in GBM treatment

Table 1. Clinical characteristics of the patients

	Number (%)
Age	
<50 years	5 (24%)
≥50 years	16 (76%)
Gender	
Male	17 (81%)
Female	4 (19%)
ECOG* performance score	
ECOG 0, 1	12 (57%)
ECOG 2, 3	9 (43%)
Location of the tumor	
Temporal	3 (14%)
Frontal	6 (28%)
Parietal	5 (24%)
Temporaparietal	2 (10%)
Temporooccipital	1 (5%)
Frontoparietal	3 (14%)
Parietooccipital	1 (5%)
Tumor size	
<4 cm	6 (29%)
≥4 cm	15 (71%)
Surgery	
Total excision	18 (85%)
Subtotal excision	3 (15%)
Surgery-radiotherapy interval	
<4 weeks	3 (14%)
≥4 weeks	18 (86%)

*ECOG: Eastern Cooperative Oncology Group.

since the 1970s. Nitrosoureas are alkylating agents and are the oldest drugs used in the treatment of central nervous system malignancies. Carmustine (BCNU) is still one of the most effective chemotherapeutics, with a response rate of approximately 40%. In recent years, TMZ, a second-generation alkylating agent, has been used in GBM and AA and has been found to be as effective as BCNU, and has been included in standard post-RT treatment protocols (21,22). In a multicenter study, in 525 patients with recurrent GBM,

Table 2. Cox regression analysis of factors for recurrence

		Univariate analysis		
		HR	**95% CI**	**p-value**
Age	<50 years (R) vs. ≥50 years	3.11	0.82-11.72	0.09
Gender	Female (R) vs. male	1.11	0.24-5.00	0.88
ECOG	ECOG score 0, 1 (R) vs. ECOG score 2, 3	4.31	1.26-14.70	0.02
Tumor size	<4 cm (R) vs. >4 cm	0.83	0.25-2.66	0.75
Surgery	Total excision (R) vs. subtotal excision	0.70	0.15-3.18	0.65
Location of the tumor	Left cerebral (R) vs. right cerebral	1.01	0.34-3.00	0.97
Location of the tumor	Frontal (R) vs. others	1.36	0.48-3.83	0.55
Surgery-radiotherapy interval	<4 weeks (R) vs. ≥4 weeks	4.34	0.56-33.10	0.15

HR: Hazard ratio, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group.

Table 3. Cox regression analysis of factors for death

		Univariate analysis		
		HR	**95% CI**	**p-value**
Age	<50 years (R) vs. ≥50 years	1.55	0.43-5.50	0.49
Gender	Female (R) vs. Male	1.91	0.42-8.68	0.39
ECOG	ECOG score 0, 1 (R) vs. ECOG score 2, 3	382.87	0.28-512995.00	0.10
Tumor size	<4 cm (R) vs. >4 cm	0.68	0.20-2.24	0.53
Surgery	Total excision (R) vs. subtotal excision	0.52	0.11-2.35	0.39
Location of the tumor	Left cerebral (R) vs. right cerebral	0.79	0.26-2.35	0.67
Location of the tumor	Frontal (R) vs. others	1.87	0.64-5.51	0.25
Surgery-radiotherapy interval	<4 weeks (R) vs. ≥4 weeks	2.46	0.32-18.98	0.38

HR: Hazard ratio, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group.

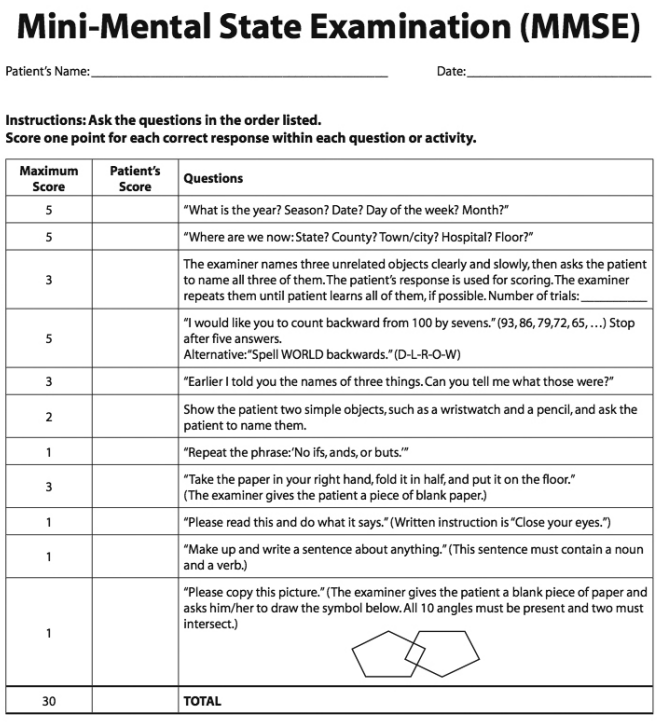
Table 4. Critical organ radiation doses during radiotherapy

	Median dose (minimum-maximum) (gray)
PTV V95* dose	59.86 (57.90-60.55)
PTV** dose	60.67 (60.00-61.40)
Right lens maximum dose	3.35 (1.35-8.41)
Left lens maximum dose	2.90 (0.88-6.95)
Right eye maximum dose	17.17 (5.30-55.00)
Left eye maximum dose	17.25 (1.76-49.08)
Right optic nerve maximum dose	18.28 (1.66-54.39)
Left optic nerve maximum dose	20.20 (1.10-54.42)
Optic chiasm maximum dose	31.45 (1.68-54.25)
Whole brain maximum dose	62.78 (55.78-65.24)
Brain stem maximum dose	46.72 (2.55-60.87)

*PTV V95: Planning target volume enclosed by 95% isodose, **PTV: Planning target volume.

Table 5. Ipsilateral and contralateral hippocampus radiation doses (gray)

Mean dose ipsilateral	Maximum dose ipsilateral	Mean contralateral dose	Maximum dose contralateral
60.29	62.25	29.05	39.78
52.17	56.78	32.41	34.39
40.11	56.30	19.87	32.05
47.58	61.21	26.82	46.25
56.88	61.58	36.19	54.32
58.41	61.48	42.84	62.89
45.70	50.93	30.41	48.01
58.26	61.60	33.25	40.50
44.28	60.94	30.85	58.48
49.72	62.07	20.92	35.71
60.12	62.61	38.88	53.76
11.86	26.53	8.67	20.05
60.91	63.06	36.07	49.56
15.2	47.07	15.87	48.51
6.82	42.49	3.11	16.03
19.85	49.51	16.3	36.32
60.99	62.28	40.22	57.31
57.35	62.45	29.91	55.1
51.85	60.57	29.91	55.1



Mini-Mental State Examination (MMSE)

Patient's Name:_____ Date:_____

Instructions: Ask the questions in the order listed.
Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79,72, 65, ...) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.)
30		**TOTAL**

Figure 1. Mini-Mental State Examination.

with TMZ, a 6-month DFS rate of 46% and a 12-month OS rate of 24% were observed (23).

TMZ is a per oral applied, rapidly absorbed agent and shows nearly 100% bioavailability. TMZ can cross the blood– brain barrier and reach effective concentrations in the central nervous system, with a cerebrospinal fluid/plasma ratio of approximately 30-40% (24). TMZ improves the quality of life and prolongs DFS and OS (25). In older studies, the median OS was around 1-1.5 years. However, with improvements in cancer care, some patients with GBM have an OS of nearly 2 years. For example, in the GEINO 14-01 trial published in 2020, the median OS of patients who received 6 months of adjuvant TMZ was 23.3 months (26). Similarly, in a study comparing different RT techniques, the median OS of patients was around 18-25 months (27). In our study, the patients' median DFS was 10 months, and the median OS was 24 months, which is consistent with recent data. In contrast, isocitrate dehydrogenase 1 (IDH1) mutation and O6-methylguanine-DNA methyltransferase (MGMT) methylation are known prognostic factors for GBM. The OS of class 1 patients (class 1=MGMT methylated/IDH1 mutant or MGMT methylated/IDH1 wild type/Gross Total Resection/Karnofsky Performance Status ≥90) reaches 67 months (28). The mutation status of our patients is unknown. The longer OS in our study could be the result of the high MGMT methylated percentage of patients in the study group.

While administering RT to the patients, we tried to keep our PTV 95 (PTV enclosed by the 95% isodose) and risk organs within the RTOG 0933 range, as shown in Table 2. However, we did not draw the hippocampus. In recent studies, it has been reported that deficits in learning and memory, especially in patients receiving whole-brain RT, are associated with the radiation-affected hippocampus (29,30). In a study using linac-based IMRT with hippocampus sparing for whole-brain RT, Gondi et al. (31) reported that they delivered 30 Gy to the whole brain. They determined the shape of the hippocampus and created hippocampal avoidance zones using a volumetric expansion of 5 mm around the hippocampus. According to their results, the maximum dose received by the hippocampus was 15.3 Gy, whereas the mean dose was 7.8 Gy. They reported that modern IMRT techniques provide hippocampus preservation with acceptable target coverage and homogeneity (31). According to RTOG 0933, the hippocampus maximum dose should be ≤16 Gy. Because we did not perform hippocampus protection, our hippocampus RT doses were high.

While it is possible to protect both hippocampi in whole brain RT, it is difficult to protect the same side of the hippocampus in tumors to which higher doses are administered, such as GBM. Wee et al. (32) showed that hippocampus preservation does not increase the risk of relapse.

Study Limitations

One of the major limitations of this study is the limited number of patients. Statistical significance could not be reached for the factors of disease recurrence or death. In addition, the genetic profile of patients for prognostic changes is unknown. The retrospective design of the study is another limitation. MMSE could not be performed on all patients because 16 patients included had already died at the time of evaluation.

CONCLUSION

In our study, the Stuppe protocol for the treatment of GBM was well tolerated. Because we did not preserve the hippocampus during RT, our patients showed loss of neurocognitive functions. We have thereby understood that we should pay more attention to protecting at least the opposite hippocampus according to the tumor location.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Bursa City Hospital Institutional Clinical Research Ethics Committee for the study (approval number: 2019-KAEK-140, 2021-19/7, date: 20.10.2021).

Informed Consent: Prospective study.

Authorship Contributions

Surgical and Medical Practices: S.İ., Ö.D.T., H.E., F.A., T.T., P.Ç. Concept: S.İ., Ö.D.T., H.E., Design: S.İ., Ö.D.T., H.E., B.C., Data Collection or Processing: S.İ., Ö.D.T., H.E., F.A., T.T., P.Ç., Analysis or Interpretation: B.C., Ö.D.T., Literature Search: S.İ., Ö.D.T., B.C., Writing: S.İ., Ö.D.T., B.C.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Kleihues P, Burger PC, Scheithauer BW. The new WHO classification of brain tumours. Brain Pathol 1993; 3: 255-68.
2. Burger PC, Vogel FS, Green SB, Strike TA. Glioblastoma multiforme and anaplastic astrocytoma. Pathologic criteria and prognostic implications. Cancer 1985; 56: 1106-11.
3. Karlsson UL, Leibel SA, Wallner K, Davis LW, Brady LW. Brain. Philadelphia; 2004; 28: 791-838.
4. Levin VA, Leibel SA, Gutin PH: Neoplasms of the central nervous system. In: DeVita VT Jr, Hellmar S, Rosenberg SA, (eds): Cancer: Principles and Practice of Oncology. 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001; p. 2100-2160.
5. Kleihues P, Cavenee WK, International Agency for Research on Cancer. Pathology and Genetics of Tumours of the Nervous System. Lyon, France: International Agency for Research on Cancer, 2000.
6. Ringertz N. Grading of gliomas. Acta Pathol Microbiol Scand 1950; 27: 51-64.
7. Michelsen JJ, New PF. Brain tumour and pregnancy. J Neurol Neurosurg Psychiatry 1969; 32: 305-7.
8. Burger PC, Green SB. Patient age, histologic features, and length of survival in patients with glioblastoma multiforme. Cancer 1987; 59: 1617-25.
9. DAVIS L, MARTIN J, et al. A study of 211 patients with verified glioblastoma multiforme. J Neurosurg 1949; 6: 33-44.
10. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005; 352: 987-96.
11. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5- year analysis of the EORTC-NCIC trial. Lancet Oncol 2009; 10: 459-66.
12. Athanassiou H, Synodinou M, Maragoudakis E, Paraskevaidis M, Verigos C, Misailidou D, et al. Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. J Clin Oncol 2005; 23: 2372-7.
13. Marsh JC, Gielda BT, Herskovic AM, Wendt JA, Turian JV. Sparing of the hippocampus and limbic circuit during whole brain radiation therapy: A dosimetric study using helical tomotherapy. J Med Imaging Radiat Oncol 2010; 54: 375-82.
14. Raineki C, Holman PJ, Debiec J, Bugg M, Beasley A, Sullivan RM. Functional emergence of the hippocampus in context fear learning in infant rats. Hippocampus 2010; 20: 1037-46.
15. De Angelis LM, Delattre JY, Posner JB. Radiation induced dementia in patients cured of brain metastases. Neurology 1989; 39: 789-96.
16. Roman DD, Sperduto PW. Neuropsychological effects of cranial radiation: current knowledge and future directions. Int J Radiat Oncol Biol Phys 1995; 31: 983-98.
17. Jeneson A, Mauldin KN, Hopkins RO, Squire LR. The role of the hippocampus in retaining relational information across short delays: the importance of memory load. Learn Mem 2011; 18: 301-5.
18. Hamilton GF, Murawski NJ, St Cyr SA, Jablonski SA, Schiffino FL, Stanton ME, et al. Neonatal alcohol exposure disrupts hippocampal neurogenesis and contextual fear conditioning in adult rats. Brain Res 2011; 1412: 88-101.
19. Mini-Mental State Examination (MMSE), https://medworksmedia.com/product/mini-mental-state-examination-mmse. (Accessed 01.11.2022).
20. Sherman CD. UICC Klinik onkoloji. 4. Baskı, Ankara: Başbakanlık Basımevi, 1990.
21. Karadeniz AN, Frazer I. Erişkin Yaş Oligodendrogliomalı Hastalarda Kombine Tedavi ve Radyoterapi Sonuçları. Türk Onkoloji Dergisi 1987; 3: 605-11.
22. Levin VA, Silver P, Hannigan J, Wara WM, Gutin PH, Davis RL, et al. Superiority of post-radiotherapy adjuvant chemotherapy with CCNU, procarbazine, and vincristine (PCV) over BCNU for anaplastic gliomas: NCOG 6G61 final report. Int J Radiat Oncol Biol Phys 1990; 18: 321-4.
23. Newlands ES, Foster T, Zaknoen S. Phase I study of temozolamide (TMZ) combined with procarbazine (PCB) in patients with gliomas. Br J Cancer 2003; 89: 248-25.
24. Brada M, Hoang-Xuan K, Rampling R, Dietrich PY, Dirix LY, Macdonald D, et al. Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. Ann Oncol 2001; 12: 259-66.
25. Stupp R, Dietrich PY, Ostermann Kraljevic S, Pica A, Maillard I, Maeder P, et al. Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. J Clin Oncol 2002; 20: 1375-82.
26. Balana C, Vaz MA, Sepúlveda JM, Mesia C, del Barco S, Pineda E, et al. A phase II randomized, multicenter, open-label trial of continuing adjuvant temozolomide beyond six cycles in patients with glioblastoma (GEINO 14–01). Neuro Oncol 2020; 22: 1851.
27. Mallick S, Kunhiparambath H, Gupta S, Benson R, Sharma S, Laviraj MA, et al. Hypofractionated accelerated radiotherapy (HART) with concurrent and adjuvant temozolomide in newly diagnosed glioblastoma: a phase II randomized trial (HART-GBM trial. J Neurooncol 2018; 140: 75-82.
28. Wee CW, Kim E, Kim N, Kim IA, Kim TM, Kim YJ, et al. Novel recursive partitioning analysis classifcation for newly diagnosed glioblastoma: a multi-institutional study highlighting the MGMT promoter methylation and IDH1 gene mutation status. Radiother Oncol 2017;

123: 106-11.

29. Yung WK, Albright RE, Olson J, Fredericks R, Fink K, Prados MD, et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. Br J Cancer 2000; 83: 588-93.
30. Monje ML, Mizumatsu S, Fike JR, Palmer TD. Irradiation induces neural precursor-cell dysfunction. Nat Med 2002; 8: 955-62.
31. Gondi V, Tolakanahalli R, Mehta MP, Tewatia D, Rowley H, Kuo JS, et al. Hippocampal-sparing whole-brain radiotherapy: a "how-to" technique using helical tomotherapy and linear accelerator-based intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2010; 78: 1244-52.
32. Wee CW, Kim KS, Kim CY, Han JH, Kim YJ, Kim IA. Feasibility of hippocampus-sparing VMAT for newly diagnosed glioblastoma treated by chemoradiation: pattern of failure analysis. Radiat Oncol 2020; 15: 98.